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Association between the geriatric nutritional risk index and the risk of stroke in elderly patients with hypertension: A longitudinal and cohort study

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Objective: We aimed to investigate the association between the GNRI and the risk of stroke in elderly patients with hypertension.

Methods: A total of 5312 elderly hypertensive patients free of history of stroke were included. Multivariate Cox models were used to calculate hazard ratios (HRs) and their 95% confidence intervals (CIs) for stroke and its subtypes.

Results: The average time of follow-up was 3.8 years, and the median time was 3.2 years. We identified 640 individuals with stroke, of whom 526 had an ischemic stroke (IS) and 114 had a hemorrhagic stroke (HS). After adjusting for confounding variables, compared with participants in the lowest quartile of the GNRI, those in the third and fourth quartiles were associated with a decreased risk of stroke (adjusted HR 0.72, 95% CI 0.58–0.90, and adjusted HR 0.58, 95% CI 0.46–0.74, respectively, P for trend < 0.001). Similar results were found for IS and HS. Moreover, there were L-shaped associations of GNRI with new-onset HS (P for non-linearity = 0.034). Multiple sensitivity analyses and stratified analyses did not materially change the results.

Conclusions: In summary, we found that a lower GNRI was associated with a higher risk of incident stroke in elderly hypertensive patients. Additional prospective data collection is required to confirm our findings.

KEYWORDS

geriatric nutritional risk index, stroke, elderly, hypertension, longitudinal cohort

Introduction

Stroke, including ischemic stroke (IS) and hemorrhagic stroke (HS), is the leading cause of the global burden of disease (1). China has the highest burden of strokes in the world (2). There are still 250 million new instances of stroke each year in China, and that number is rising, even though the incidence and frequency of stroke have decreased globally (3). Hypertension has now been identified as the primary variable risk factor for stroke (4). Several large epidemiological surveys in China have shown that more than 50% of people over 60 years of age have hypertension (5). Therefore, identifying the residual risk of stroke and early risk stratification in elderly patients with hypertension is essential to more effectively tailoring risk reduction strategies.

Malnutrition is associated with a poor clinical prognosis in patients with various diseases (6). According to studies, malnutrition is significantly linked to increased levels of inflammatory response, arterial calcification, and atherosclerosis progression, which raises the possibility that it plays a key role in the emergence of cardiovascular disease (7, 8). The geriatric nutritional risk index (GNRI) is a simple, well-established nutrition assessment tool that uses serum albumin and body mass index (BMI) (9). Recent studies have shown that GNRI is associated with the development of atherosclerosis and an increased risk of cardiovascular mortality in older patients (10, 11). However, studies on GNRI as a predictor of new-onset stroke are still limited. Until now, only one cohort study has reported lower GNRI in hemodialysis patients as an independent risk factor for cerebral infarction and hemorrhage, and it is unclear whether this effect can be extended to older patients with hypertension (10). Therefore, GNRI may have important clinical implications for stroke risk stratification in hypertensive patients. In addition, the status of the dose-response relationship between GNRI and the risk of stroke and its subtypes in elderly hypertensive patients is uncertain.

Therefore, the present study is based on a cohort study aiming to investigate the association between GNRI and the risk of stroke and its subtypes in elderly hypertensive patients and to characterize the nature of the dose-response relationship.

Materials and methods

Study population

We conducted a cohort study at the People's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang, China. All patients were either older than 60 years of age and were recruited between January 1, 2010, and December 31, 2021. First, we excluded patients who had <6 months of followup or had the outcome at baseline. Second, we further excluded individuals with missing data on body height, body weight, or serum albumin level. Third, we excluded participants with severe wasting diseases (e.g., malignancy, autoimmune diseases, severe hepatic disease, and severe renal insufficiency). Finally, this left a final study population of 5,312 patients. Participant flow is shown in Figure 1. A comparison of baseline characteristics for in- and excluded participants are presented in Supplementary Table S1. This study was approved by the ethics committee of the People's Hospital of Xinjiang Uygur Autonomous Region (No. KY2021031901). A waiver of informed consent was granted due to the retrospective data collection. The study was reported as per the STROBE statement for observational cohort studies (12).

Covariate collection and definitions

Data were abstracted electronically from the patient's medical records, including demographic characteristics, diagnoses according to the International Classification of Diseases 10th Revision (ICD-10), prescribed medications, and laboratory reports. Weight, height, heart rate, and blood pressure (BP) were measured using standard protocols. The BMI (kg/m²) was computed from the measured weight and height. Smoking status included categories of current smokers and non-smokers. Participants are classified as current drinkers and non-smokers. Blood samples were drawn after an overnight fast. The participants' prior medical histories were evaluated 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. To quantify the burden of comorbidities, the Charlson Comorbidity Index (CCI) was calculated as described previously (13). Prescription claims within the last year before the baseline defined concomitant medications. The list of concomitant medications included in the study is shown in Supplementary Table S2. The GNRI formula used was as follows: $GNRI = (1.489 \times albumin, g/l) +$ $(41.7 \times \text{present/ideal body weight})$. Ideal weight was calculated using the Lorenz formulas: For males: height - 100 - [(height -150)/4]. For females: height - 100 - [(height - 150)/2.5] (14).

Follow-up and outcome measures

The primary outcome was the first occurrence of stroke (ischemic or hemorrhagic), either nonfatal or fatal. Secondary outcomes included the first ischemic stroke and the first hemorrhagic stroke. Methods of determination of incident stroke are described in the Supplementary material. Outcomes of events since participants enrolled in the study were determined through medical records, patient and family interview, contact with local disease and death registries, or access to the database of basic medical insurance. These data





sources are linked using an individual national identification number assigned to each Chinese person for life. This number is replaced by a series number when provided for personal data analysis to anonymize the individual participant's data. Patients were followed from the date of enrollment to the end of the observation period, defined as the date of the last follow-up visit, the date of the first appearance of any study outcome, the date of death, or the end of the study period (December 31, 2021).

Statistical analysis

Details of the missing covariates are shown in Supplementary Table S3. Missing values of covariates (all

covariates were missing in <6%) were imputed using multiple imputations by chained equations. Characteristics of study participants were expressed by GNRI quartiles. For differences in cumulative incidence between groups, we used Kaplan-Meier curves and the log-rank test. The multicollinearity test suggested that the variance inflation factors of all variables were less than five, confirming that the regression model was not affected by multicollinearity. The hazard ratio (HR) estimates and 95% confidence intervals (CI) were determined by the Cox regression models. Tests for non-linear associations were performed using restricted cubic spline regressions. We also performed subgroup analyses stratified by potential confounders. Sensitivity analyses were undertaken to evaluate the robustness of the results. First, to minimize the chance of reverse causation, we excluded events that occurred within 1 or 3 years after the baseline visit. Second, sensitivity analysis determined whether event risks remained stable after accounting for competing risks. Third, participants with CCI ≥ 2 were excluded to reduce confounding factors caused by associated comorbidity. Fourth, participants with atrial fibrillation were excluded. Lastly, to evaluate potential unmeasured confounding, we calculated E-values. Further analysis details are provided in the Supplementary material. Statistical analyses were performed using R software, version 4.1.1. Two-sided P-values <0.05 were considered statistically significant.

Results

Baseline characteristics

As illustrated in the flow chart (Figure 1), a total of 5312 participants were included in the current study. The average age of the study population was 66.5 years (SD 4.8). The GNRI was approximately normally distributed (Figure 2). Baseline characteristics of the study participants by GNRI quartiles are

Characteristics	GNRI quartiles						
	Quartile 1	Quartile 2	Quartile 3	Quartile 4			
	(≤94.33)	(94.34–103.17)	(103.18-119.61)	(≥119.63)			
No. of participants	1327	1329	1328	1328			
Age, years	66.17 ± 4.70	66.67 ± 4.87	66.69 ± 4.82	66.43 ± 4.78	0.316		
Male, <i>n</i> (%)	624 (47.02%)	732 (55.08%)	692 (52.11%)	696 (52.41%)	< 0.001		
Current smoker, n (%)	396 (29.84%)	423 (31.83%)	381 (28.69%)	385 (28.99%)	0.283		
Current drinker, <i>n</i> (%)	339 (25.55%)	381 (28.67%)	329 (24.77%)	353 (26.58%)	0.119		
Duration of hypertension, years					< 0.001		
<5	789 (59.46%)	1065 (80.14%)	972 (73.19%)	1044 (78.61%)			
5-9	167 (12.58%)	71 (5.34%)	185 (13.93%)	183 (13.78%)			
≥ 10	371 (27.96%)	193 (14.52%)	171 (12.88%)	101 (7.61%)			
Heart rate, bpm	80.37 ± 9.73	80.51 ± 10.07	80.37 ± 9.80	80.50 ± 9.73	0.970		
SBP, mmHg	144.12 ± 20.62	143.28 ± 20.49	143.73 ± 20.52	143.92 ± 19.54	0.738		
DBP, mmHg	89.02 ± 14.52	88.68 ± 13.92	88.89 ± 14.18	88.91 ± 14.21	0.940		
BMI, kg/m ²	24.31 ± 3.30	24.41 ± 3.34	24.35 ± 3.32	24.19 ± 3.34	0.355		
Comorbid conditions, n (%)							
Dyslipidemia	858 (64.66%)	807 (60.72%)	778 (58.58%)	787 (59.26%)	< 0.001		
Atrial fibrillation	26 (1.96%)	27 (2.03%)	33 (2.48%)	40 (3.01%)	0.255		
Coronary heart disease	215 (16.20%)	233 (17.53%)	218 (16.42%)	225 (16.94%)	0.799		
Diabetes	358 (26.98%)	371 (27.92%)	385 (28.99%)	362 (27.26%)	0.662		
Charlson comorbidity index					0.139		
0	617 (46.50%)	579 (43.57%)	631 (47.52%)	594 (44.73%)			
1	391 (29.46%)	380 (28.59%)	347 (26.13%)	387 (29.14%)			
≥2	319 (24.04%)	370 (27.84%)	350 (26.36%)	347 (26.13%)			
Laboratory tests							
ALT, U/L	24.17 (15.00-35.59)	24.42 (15.75-35.07)	24.41 (15.93-35.63)	24.62 (14.50-35.90)	0.685		
AST, U/L	21.00 (16.00-28.27)	21.40 (16.00-27.71)	21.21 (16.00-28.45)	21.37 (16.00-28.17)	0.929		
GGT, U/L	27.79 (17.04-41.51)	28.00 (17.89-40.40)	29.05 (18.08-42.49)	28.68 (17.45-41.48)	0.230		
Cr, µmol/L	69.92 ± 22.48	69.08 ± 21.63	70.05 ± 22.25	69.62 ± 22.86	0.686		
UA, μmol/L	334.05 ± 91.20	334.06 ± 90.17	333.41 ± 91.31	331.81 ± 90.97	0.910		
BUN, mmol/L	5.26 ± 1.51	5.28 ± 1.51	5.28 ± 1.51	5.33 ± 1.54	0.712		
TC, mmol/L	4.61 ± 0.96	4.58 ± 0.96	4.51 ± 0.96	4.47 ± 0.99	0.005		
TG, mmol/L	1.69 (1.12-2.48)	1.60 (1.08-2.32)	1.64 (1.15-2.49)	1.56 (1.08-2.32)	0.016		
HDL-C, mmol/L	1.04 ± 0.27	1.07 ± 0.26	1.15 ± 0.26	1.19 ± 0.27	0.006		
LDL-C, mmol/L	2.88 ± 0.81	2.77 ± 0.80	2.73 ± 0.80	2.70 ± 0.83	0.009		
HbA1c, %	6.21 ± 1.08	6.20 ± 1.06	6.13 ± 1.05	6.10 ± 1.03	0.014		
FPG, mmol/L	5.20 ± 1.35	5.23 ± 1.37	5.27 ± 1.48	5.22 ± 1.42	0.621		
Hcy, µmol/L	15.11 ± 6.36	15.15 ± 6.23	15.24 ± 6.28	15.12 ± 6.41	0.949		
Concomitant medications, n (%)							
Statins	652 (49.13%)	626 (47.10%)	585 (44.05%)	559 (42.09%)	< 0.001		
Aspirin	955 (71.97%)	930 (69.98%)	903 (68.00%)	858 (64.61%)	< 0.001		
ACEI/ARB	928 (69.93%)	937 (70.50%)	963 (72.52%)	923 (69.50%)	0.333		
Beta-blocker	461 (34.74%)	463 (34.84%)	490 (36.90%)	487 (36.67%)	0.509		
Calcium channel blockers	1036 (78.07%)	1023 (76.98%)	1077 (81.10%)	1048 (78.92%)	0.064		
Diuretics	296 (22.31%)	290 (21.82%)	331 (24.92%)	288 (21.69%)	0.156		
Insulin	126 (9.50%)	134 (10.08%)	132 (9.94%)	125 (9.41%)	0.921		
Oral antidiabetic agents	222 (16.73%)	229 (17.23%)	249 (18.75%)	235 (17.70%)	0.565		

TABLE 1 Baseline characteristics stratified across quartiles of GNRI.

GNRI, metabolic score for insulin resistance; 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.



shown in Table 1. Participants with a lower GNRI tended to be women, have a higher duration of hypertension, a higher prevalence of dyslipidemia, take more statins and aspirin, have higher HbA1c, TC, TG, and LDL-C levels, and have lower HDL-C compared with participants in the quartile 4 group.

Association between GNRI and total stroke and its subtypes

The average time of follow-up was 3.8 years, and the median time was 3.2 years. We identified 640 individuals with stroke, of which 526 had IS and 114 had HS. The Kaplan-Meier curve showed that participants in the quartile 1 group had a higher risk of total stroke, IS instead of HS than those in other groups (log-rank test, P < 0.001, Figure 3A; P = 0.001, Figure 3B; P = 0.001, Figure 3C). Overall, there was a significant inverse association of GNRI with the risk of first total stroke (Figure 4A) (per SD increment; full adjusted HR: 0.80; 95% CI: 0.73, 0.87). Consistently, when GNRI was assessed as quartiles, the full adjusted HRs of first stroke for participants in quartile 2, quartile 3, and quartile 4 were 0.94 (95% CI: 0.77, 1.15), 0.72 (95% CI: 0.58, 0.90), and 0.58 (95% CI: 0.46, 0.74) respectively, compared with those in quartile 1 (P for trend <0.001) (Table 2). Similarly, a significant inverse association between GNRI and both IS and HS (Figure 4). Moreover, there were L-shaped associations of GNRI with new-onset HS (P for non-linearity = 0.034). Sensitivity analyses were conducted to verify the



robustness of the reported findings. The results of sensitivity analyses were similar to those observed in the main analysis (Supplementary Tables S4–S9 and Supplementary Figure S1 in the Supplement).

Stratified analyses

Stratified analyses were performed to assess the association of GNRI (per SD increment) with total stroke and its subtypes, as provided in Figure 5. No interaction was found between subgroup variables and the association of GNRI with the risk of total stroke. Similar results were found for IS and HS.

Incremental predictive value of GNRI

As illustrated in Table 3, according to C-statistic, risk prediction was improved by adding the GNRI to established risk factors (C-statistic increased from 0.613 to 0.648, P < 0.001). Moreover, according to continuous NRI and IDI, the GNRI significantly improved risk discrimination for total stroke [continuous NRI (95% CI): 0.118 (0.066–0.172), P

< 0.001; IDI (95% CI): 0.017 (0.009–0.029), P < 0.001]. Furthermore, the DCA for the different models is shown in Supplementary Figure S2. The decision curves show that using a combination of GNRI features to predict total stroke increases the net benefit more than using established risk factors alone. Similar results were observed in IS and HS.

Discussion

This study investigated the relationship between GNRI and incident stroke in elderly hypertensive patients. The findings revealed that the risk of stroke was significantly associated with baseline GNRI after adjusting for multiple confounders. In addition, a significant L-shaped dose-response relationship between GNRI and the risk of incident HS was observed, indicating a rapid increase in the risk of HS when GNRI was below 103. These findings were reliable in subgroup and multiple sensitivity analyses. Overall, the present study revealed that low CNRI was associated with a higher risk of incident stroke. To our knowledge, this is the first study to show an association between GNRI and the risk of incident stroke in a large retrospective cohort.

Exposure	Unadjusted	Model 1	Model 2	Model 3 HR (95% CI)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)		
Total stroke					
Per SD increment	0.81 (0.74, 0.87)	0.79 (0.73, 0.86)	0.80 (0.73, 0.87)	0.80 (0.73, 0.87)	
Quartiles					
Q1	Ref	Ref	Ref	Ref	
Q2	1.00 (0.82, 1.22)	0.95 (0.78, 1.16)	0.94 (0.77, 1.16)	0.94 (0.77, 1.15)	
Q3	0.74 (0.60, 0.92)	0.71 (0.57, 0.88)	0.72 (0.58, 0.90)	0.72 (0.58, 0.90)	
Q4	0.60 (0.48, 0.76)	0.58 (0.46, 0.73)	0.58 (0.46, 0.74)	0.58 (0.46, 0.74)	
P for trend	< 0.001	< 0.001	< 0.001	< 0.001	
Ischemic stroke					
Per SD increment	0.85 (0.78, 0.93)	0.84 (0.77, 0.92)	0.84 (0.77, 0.92)	0.84 (0.76, 0.91)	
Quartiles					
Q1	Ref	Ref	Ref	Ref	
Q2	1.07 (0.86, 1.34)	1.02 (0.81, 1.27)	1.00 (0.80, 1.26)	1.00 (0.80, 1.25)	
Q3	0.79 (0.62, 1.00)	0.75 (0.59, 0.96)	0.76 (0.59, 0.96)	0.75 (0.59, 0.96)	
Q4	0.69 (0.54, 0.88)	0.66 (0.51, 0.84)	0.65 (0.51, 0.84)	0.65 (0.50, 0.84)	
P for trend	< 0.001	< 0.001	< 0.001	< 0.001	
Hemorrhagic stroke					
Per SD increment	0.61 (0.50, 0.75)	0.61 (0.49, 0.75)	0.64 (0.52, 0.79)	0.64 (0.52, 0.79)	
Quartiles					
Q1	Ref	Ref	Ref	Ref	
Q2	0.76 (0.48, 1.20)	0.75 (0.47, 1.19)	0.78 (0.49, 1.24)	0.77 (0.48, 1.22)	
Q3	0.54 (0.33, 0.89)	0.54 (0.33, 0.89)	0.58 (0.35, 0.96)	0.57 (0.35, 0.95)	
Q4	0.34 (0.19, 0.61)	0.33 (0.19, 0.60)	0.38 (0.21, 0.69)	0.38 (0.21, 0.69)	
P for trend	<0.001	<0.001	0.001	0.001	

TABLE 2 Association between GNRI and the incidence of outcomes.

Model 1: adjusted for age, sex, BMI, heart rate, SBP, DBP, duration of hypertension, smoking, and drinking status.

Model 2: model 1 plus comorbid conditions.

Model 3: model 2 plus laboratory tests and concomitant medications.

SD, standard deviation; HR, hazard ratio; CI, confidence interval. Other abbreviations as presented in Table 1.

Aging is a condition that affects all people. One of the most susceptible demographics and one that is more likely to experience nutritional issues is the elderly (15). Similarly, malnutrition is an important independent risk factor for stroke, as is hypertension (16-19). In contrast to other clinical variables, nutritional status is a modifiable risk factor that physicians can act on. Therefore, appropriate tools are needed to assess the nutritional status of elderly patients with hypertension and to identify patients at risk to reduce their risk of stroke. Among multiple proxies of nutritional status, serum albumin levels and BMI are often used to evaluate nutritional status (20, 21). Hypoalbuminemia has been linked to acute and chronic inflammation, low BMI may be a sign of malnutrition, and both conditions may be a result of the loss of muscle and adipose tissue (22). In the general population, hypoalbuminemia and higher BMI have been reported as independent risk factors for stroke (23-26). Systemic edema, hepatic failure, and inflammation all have a negative influence on serum albumin levels. The status of body fluids also impacts body weight

(27, 28). Consequently, assessing nutritional risk and prognosis solely based on albumin or BMI may not be sufficient. Simple hematological data (serum albumin) and anthropometric data can be used to compute the GNRI, a simplified form of the nutritional risk index (including height and weight) (14, 15). These indicators are readily available and can reduce information bias. Because of its objective nature, GNRI overcomes the problems of traditional nutrition indicators, including subjective issues such as mini-nutritional assessments (29). And GNRI correlates well with malnutrition-inflammation scores and has been regarded as one of the gold standards for nutritional assessment of elderly patients with chronic diseases (10, 30). There is evidence that patients with chronic illnesses, including chronic hemodialysis and peripheral vascular disease, have a lower GNRI (31-35). The results of Xiong et al. demonstrated that low GNRI levels were a strong predictor of cardiovascular and cerebrovascular events in patients with CKD (36). GNRI has also been reported to predict cardiovascular events, including cardiovascular disease mortality, in patients

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bit 2320 - 0.36 0.310/7.0.050 Area 0.222 0.0200.050 bit 0.430.031.030 0.430.031.030 0.430.031.030 0.430.031.030 0.430.031.030 0.430.031.030 0.430.031.030 0.430.031.030 0.440.031.030 0.440.031.030 0.430.031.030 0.440.031.030 0.440.031.030 0.430.031.030 0.440.031.030 0.430.031.030 0.440.031.030 0.440.031.030 0.430.031.030 0.440.031.030 0.430.031.030 0.440.031.030 0.430.031.030 0.440.031.030 0.440.031.030 0.430.031.030 0.440.031.030.030 0.4	lo	2082		9	0.80(0.71,0.91)	No	2082	1		0.86(0.75,0.98)
Attrait life/illation State O.316 State O.327 O.03023 (00) hardson comprisidity index 0.322 0.700 (50.08) </td <td>es</td> <td>3230</td> <td>1 - - -</td> <td>•</td> <td>0.81(0.73,0.90)</td> <td>Yes</td> <td>3230</td> <td>1-</td> <td></td> <td>0.85(0.75,0.95)</td>	es	3230	1 - - -	•	0.81(0.73,0.90)	Yes	3230	1-		0.85(0.75,0.95)
un de la de	trial fibrillation			0.316		Atrial fibrillation			0.222	
Bankson comorbidity index 4 20 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	5186	1		0.81(0.75,0.88)	No	5186	1 - 1		0.86(0.79,0.94)
naminison connorbidity modes 22 100 000000000000000000000000000000000000	es	126			0.63(0.39,1.03)	Yes	126		0.040	0.63(0.39,1.03)
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	harlson comorbidity index	0.404		0.532	0 77(0 00 0 00)	Charlson comorbidity inde	X		0.818	0.00/0.70.0.04)
2 1 136 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		2421			0.77(0.68,0.86)	0	2421			0.83(0.73,0.94)
Component pleat disease ses Component disease ses	2	1386			0.83(0.72,0.99)	≥2	1386			0.86(0.73,1.04)
0. 0.11 0	oronary heart disease	1000		0.862	0.00(0.71,0.97)	Coronary heart disease	1300		0.425	0.00(0.73,1.03)
a a b a b a b a b a b a b a b a b a b a	0	4421	1.001	0.002	0.81(0.74 0.88)	No	4421	1.0	0.720	0.87(0.78.0.95)
biabetes biabet	es	891	1 - B	-	0.79(0.66,0.95)	Yes	891	1		0.79(0.65.0.96)
b 0 3 3 3 5 1 1 7 7 1 1 1 1 1 1 1 2 0 1 1 1 1 1 1 1 1 1 1 1	Diabetes	1001000		0.296	,,,	Diabetes			0.076	,
bis of the second secon	10	3836	1.4	•	0.83(0.75,0.91)	No	3836	1.00		0.89(0.81,0.99)
inc.king status 0.88 0.780 (72.087) 0.810 (70.094) 0.810 (70.094) Vict.ment 1985 0.810 (70.094) 0.810 (70.094) 0.800 (70.094) Vict.ment 1985 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) Vict.ment 1992 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) Vict.ment 1992 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) Vict.ment 1992 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) Vict.ment 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) Vist.ment 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) Vist.ment 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) 0.800 (70.094) Vist.mitinitizizizi	/es	1476	1 - - 1		0.75(0.64,0.88)	Yes	1476	1-8-1		0.75(0.63,0.89)
do current 1960	Smoking status			0.588		Smoking status		I	0.834	
Current 1985 0.58(07.2.097) Current 1985 0.776 0.88(07.2.097) Victorent 3910 0.776 0.88(07.2.097) Not current 3910 0.776 0.88(07.1.089) Victorent 3910 0.776 0.88(07.0.987) Not current 3910 0.776 0.88(07.1.089) Victorent 1000 0.776 0.88(07.0.987) Not current 3910 0.776 0.88(07.1.089) Victorent 1000 0.776 0.88(07.0.987) Not current 3910 0.98(07.1.089) Victorent 1000 0.997 Not current 3910 0.997 Not current 3910 0.997 Standard 0.997 0.997 0.990 0.113 0.50(0.40.071) 0.50(0.40.071) 0.50(0.40.076) 0.50(0.40	lot current	3727	1 · · · · ·		0.79(0.72,0.87)	Not current	3727	1.00.00		0.85(0.76,0.94)
Oriching status Oriching s	Current	1585		•••	0.83(0.72,0.97)	Current	1585	1 		0.86(0.73,1.02)
dicurrent 3910 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Drinking status			0.711		Drinking status			0.776	
Juliant 1402	Not current	3910			0.81(0.74,0.89)	Not current	3910	1		0.86(0.77,0.95)
To prove the kindport of Kind Streams of Kindport of Kind Streams of Kindport of Kind Streams of Kindport of Kindp	Jurrent	1402			0.79(0.67,0.92)	Current	1402			0.83(0.71,0.98)
Table 2744 0 0.60(0.450.89) ige 0.113 0.80(0.450.89) 70 years 1423 0 0.80(0.54,123) Mint 0.80(0.54,123) 0.80(0.50,08) 24 kg/m² 276 0 0.56(0.40,0.76) 24 kg/m² 276 0 0.56(0.50,08) Variation of hypertension 0.89(0.50,08) 0.80(0.28,128) 10 years 837 0 0.56(0.41,0.77) 10 years 0.330 0.56(0.40,0.78) 10 years 0.330 0.56(0.40,0.8) Ysilpidemia 0.56(0.41,0.77) 0.56(0.40,0.8) 10 years 0.330 0.56(0.40,0.8) Ysilpidemia 0.502 0.56(0.40,0.8) 10 years 0.56(0.41,0.77) 10 years 1.36 0.570 10 years 0.56(0.40,0.78) 10 years 0.56(0.40,0.78) 12 years 0.56(0.40,0.78) 13 years 0.570 10 years 0.56(0.40,0.78) 10 years 0.56(0.40,0.73) 12 years 0.58(0.60,73) 13 years	C Subgroup I	He Number	Lower risl	k Higher risk stroke <u>P (interactior</u> 0 937	ı) Hazard Ratio(95% CI)			Lower risk	Higher risk	
Alale 2744 1 0 000,045,0.80) 70 years 3889 1 0.56(0,44,0.71) 70 years 123 0.56(0,40,0.76) 24 kg/m ² 276 0.418 24 kg/m ² 276 0.69(0,50,0.85) Duration of hypertension 0.690 0.50(0,31,0.89) 10 years 380 0 0.50(0,20,1.28) 10 years 330 0 0.50(0,20,1.28) 10 years 330 0 0.50(0,20,1.28) 10 years 330 0 0.50(0,30,0.69) ystilpidemia 0.50(0,30,0.69) 0.50(0,40,0.76) 10 years 1366 0 0.50(0,40,0.78) 10 years 1366 0 0.50(0,40,0.78) 10 years 0.506(0,40,0.78) 0.50(0,40,0.89) 10 years 0.50(0,40,0.78) 0.50(0,40,0.78) 10 years 0.50(0,40,0.78) 0.50(0,40,0.78) 10 years 0.50(0,40,0.78) 0.70(0,47,1.80) 10 years 0.50(0,40,0.73) 0.50(0,40,0.73) 10 years 0.50(0,40,73) 0.50(0,40,73) <td< td=""><td>C Subgroup I Gender</td><td>He Number</td><td>Lower risl</td><td>k Higher risk troke <u>P (interactior</u> 0.937</td><td>ı) Hazard Ratio(95% CI)</td><td></td><td></td><td>Lower risk</td><td>Higher risk</td><td></td></td<>	C Subgroup I Gender	He Number	Lower risl	k Higher risk troke <u>P (interactior</u> 0.937	ı) Hazard Ratio(95% CI)			Lower risk	Higher risk	
Age 0.113 70 years 1423 0.50(0.44.0.71) 70 years 1423 0.82(0.54,123) 24 kg/m ² 2576 0.610 24 kg/m ² 2576 0.65(0.40.0.76) 24 kg/m ² 2576 0.65(0.40.0.76) 24 kg/m ² 2576 0.65(0.40.0.76) 25 years 606 0.70(0.53.0.85) 10 years 380 0.502 10 years 380 0.502 ystip/demia 0.56(0.41.0.77) 86 0.502 10 years 105 0.502 10 years 1050 0.50(0.410.07) 10 years 1050 0.50(0.410.07) 10 years 1050 0.50(0.40.0.5) 10 years 1050 0.70(0.450.0.50) 10 years 1050 0.70(0.490.0.99) 10 years 0.58(0.40.0.73) 10 years 0.58(0.40.0.70) 10 years 0.58(0.40.0.70) 10 years 0.58(0.40.0.70) 10 years 0.58(0.40.0.70) </td <td>C Subgroup I Sender Female</td> <td>He Number 2568</td> <td>Lower risi</td> <td>k Higher risk stroke <u>P (interactior</u> 0.937</td> <td>1<u>) Hazard Ratio(95% CI)</u> 0.61(0.45,0.83)</td> <td></td> <td></td> <td>Lower risk</td> <td>Higher risk</td> <td></td>	C Subgroup I Sender Female	He Number 2568	Lower risi	k Higher risk stroke <u>P (interactior</u> 0.937	1 <u>) Hazard Ratio(95% CI)</u> 0.61(0.45,0.83)			Lower risk	Higher risk	
70 years 3889 0 0.50(0.40,07) 3M1 0.418 0.418 24 kg/m² 275 0.60(0.50,0.80) Dutation of hypertension 0.50(0.40,0.76) 5 years 380 0.60(0.50,0.80) 10 years 380 0.60(0.50,0.80) ysiphiptiona 0.50(0.40,0.76) ysiphiptiona 0.50(0.40,0.76) ysiphiptiona 0.50(0.28,0.28) ysiphiptiona 0.50(0.40,0.76) 6s 0.282 0.50(0.40,0.76) rist al fibrillation 0.500 10 years 320 0.500 10 years 0.516 0.500.50,0.80) ysiphiptiona 0.500 0.500.50,0.80) 10 years 320 0.500 10 years 0.516 0.500.50,0.60) 10 years 0.516 0.500.760,0.50,0.50) 10 years 0.516 0.500.760,0.50,0.50) 10 years 0.516 0.500.040,0.70) 10 years 0.516 0.510,0.60,0.70) 12 years 0.580 0.510,0.60,0.70) 12 years 0.580 <	C Subgroup I Gender emale Aale	He Number 2568 2744	Lower risi	k Higher risk stroke <u>P (interactior</u> 0.937	1) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80)			Lower risk	Higher risk	
Vial Vial 0.418 0.55(0.40,076) 24 kg/m ² 276 0.418 0.55(0.40,076) 22 kg/m ² 278 0.69(0.50,0.86) Duration of hypertension 0.692 5 years 606 0.59(0.28,1.28) DyslipIdemia 0.502 Vial 0.59(0.28,1.28) DyslipIdemia 0.502 Vial 0.59(0.28,1.28) DyslipIdemia 0.502 Vial 0.59(0.41,0.77) Vial 0.59(0.41,0.77) Vial 0.502 Vial 0.61(0.50,0.76) Yeas 126 Vial 0.51(0.50,0.60) Vial 0.51(0.50,0.60) Vial 0.51(0.50,0.60) Vial 0.52 Vial 0.52 Vial 0.52 Vial 0.51(0.50,0.60) Vial 0.51(0.50,0.60) Vial 0.52 Vial 0.52 Vial 0.52 Vial 0.52 Vial 0.58(0.46,0.73) Vial <t< td=""><td>C Subgroup I Sender emale Aale Sge 20</td><td>He <u>Number</u> 2568 2744 2880</td><td>Lower risl</td><td>k Higher risk troke P (interaction 0.937 0.113</td><td> i) Hazard Ratio(95% Ci) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.65(0.44,0.74) </td><td></td><td></td><td>Lower risk</td><td>Higher risk</td><td></td></t<>	C Subgroup I Sender emale Aale Sge 20	He <u>Number</u> 2568 2744 2880	Lower risl	k Higher risk troke P (interaction 0.937 0.113	 i) Hazard Ratio(95% Ci) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.65(0.44,0.74) 			Lower risk	Higher risk	
224 kg/m² 2576 0 0.560 0.050 24 kg/m² 2736 0.692 0.660 0.650 5 years 3370 0 0.592 0.580 10 years 036 0.592 0.580 0.590 ysight/demia 0.592 0.590 0.590 0.590 10 years 036 0.691 0.590 0.590 ysight/demia 0.592 0.560 0.590 0.590 10 years 0320 0 0.650 0.590 ysight/demia 0.592 0.560 0.590 0.590 Ytrial fibrillation NA 0.610 0.610 0.610 Ysight/demia 0.510 0.510 0.510 0.510 0.510 Ytrial fibrillation NA 0.510	C Subgroup I Sender emale Aale gge 70 years - 70 years	He 2568 2744 3889 1423	Lower risk	k Higher risk stroke <u>P (interactior</u> 0.937 0.113	 h) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.870(5.41,23) 			Lower risk	Higher risk	
24 2 m² 273 273 0.660.50.0.860 Duration of hypertension 0.692 0.670.53.0.850 59 years 606 0.570.53.0.850 19 years 606 0.560.241.0.890 19 years 836 0.652 Valid Identia 0.560.241.0.77) 6s 3230 0.650.260.980 Valid Identia 0.560.41.0.77) 6s 3230 0.670.53.0.85) Valid Identia 0.650.49.0.85) Valid Identia 0.650.49.0.85) Valid Identia 0.650.49.0.85) Valid Identia 0.671.047.1.08) 272 136 0.771.047.1.08) 273 0.550 0.571.047.1.08) 274 0.580.48.0.73) 6a 3836 0.678 6a 0.580.48.0.73) 70 0.680(0.47,0.76) 70 0.680(0.47,0.76) 70 0.680(0.47,0.76) 70 0.680(0.47,0.76) 70 0.680(0.47,0.76) 70 0.680(0.47,0.76) 70 0.680(0.47,0.76) 70	C Subgroup I Sender Sender Jale Age 470 years 300 years 300 years 300 years 300 years	He 2568 2744 3889 1423	Lower risk	k Higher risk troke <u>P (interactior</u> 0.937 0.113	 h) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 			Lower risk	Higher risk	
Duration of hypertension 0.692 is years 360 0.67(0.53.0.65) is years 360 0.50(2.3.1.28) yspilpidemia 0.502 0.50(2.3.1.28) is yaars 0.66(0.41,0.77) yspilpidemia 0.502 is yaars 0.66(0.49,0.85) Atria fibrillation NA is yaars 0.60(0.50,0.76) is yaars 0.50(2.3.05) Atria fibrillation 0.50(2.3.0.69) is yaars 0.50(0.36,0.69) is yaars 0.50(0.36,0.69) is yaars 0.50(0.40,0.73) is yaars 0.50(0.41,0.76) yaars 0.50(0.41,0.0) yaars 0.50(0.41,0.0) yaars 0.50(0.41,0.0) yaars 0.558 yaars 0.558	C Subgroup I Sender Female Aale Age 70 years 70 years 3MI 24 ko/m ²	He 2568 2744 3889 1423 2576	Lower risk	k Higher risk troke P (interaction 0.937 0.113	a) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76)			Lower risk	Higher risk	
5 years 3870 0 0.77(0.53.0.85) + 9 years 606 0.57(0.53.0.85) ysilpidemia 0.570(2.31.0.89) ysilpidemia 0.50(2.81.28) ysilpidemia 0.50(2.81.28) ysilpidemia 0.50(0.41.0.77) és 3230 0 hadron 5186 0.55(0.41.0.77) és 126 0.56(0.41.0.77) fes 126 0.57(0.53.0.65) /balton 5186 0.57 /balton 0.61(0.50.0.76) fes 126 0.57(0.47.108) /calton 0.58(0.46,0.73) /baltons 0.58(0.46,0.70) /baltons 0.58(0.46,0.70) /baltons 0.66(0.44,1.00) /baltons 0.58(0.40,0.	C Subgroup I Sender Female Aale 70 years 70 years 50MI 24 kg/m ² 24 kg/m ²	Her 2568 2744 3889 1423 2576 2736	Lower risk	k Higher risk troke P (interaction 0.937 0.113	 hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 			Lower risk	Higher risk	
9-9 yaars 606 0 0.53(0.31,0.89) 9 yaars 836 0.59(0.28,1.28) 0 yaars 836 0.59(0.28,1.28) 0 yaars 202 0.502 bis 202 0.502 yaars 0.505 0.502 bis 202 0.50(0.49,0.05) Ytrial fibrillation NA 0.61(0.50,0.76) Yaarson comorbidity index 0.279 100 1005 0.279 22 1385 0.221 0 0.201 0.50(0.46,0.73) Yaarson comorbidity index 0.221 12 0.381 0.50(0.46,0.73) 23 1385 0.321 0 0.530(0.42,0.70) Yasson 0.54(0.42,0.70) Yasson 0.578 0.60(0.47,0.76) 0.66(0.44,1.00) Orinking status 0.66(0.44,1.00) Out current 3910 0.91 Variant 100 0.59 Variant 0.000 Variant 0.000 Variant 0.67(0.54,0.84)	C Subgroup 1 Sender Female Aale Syge 70 years 70 years 3MI 2:24 kg/m ² 2:24 kg/m ² 2:24 kg/m ²	Her 2568 2744 3889 1423 2576 2736	Lower risk	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692	 b) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 			Lower risk	Higher risk	
10 years 836 0 0.500 (28,1.28) io 2082 0.502 io 3230 0.502 io 550 (39,0.85) Vital fibrillation 0.502 io 5180 0.61(0.50,0.76) ios 126 0.500 (36,0.69) charlson comorbidity index 0.279 ios 1386 0.500 (36,0.69) ios 1386 0.500 (36,0.69) ios 1386 0.500 (36,0.69) ios 0.421 (0.70) ios 0.580 (46,0.73) ios 0.580 (46,0.73) ios 0.836 ios 0.610 (56,1.17) ios 0.624 (42,0.70) ios 0.630 (47,0.76) iorrent 327 0.658 iot current 310 0.51 iot current 310 0.580 iot current	C Sender emale fale yge 70 years 70 years 3MI 24 kg/m ² 24 kg/m ² Duration of hypertension 5 years	Her 2568 2744 3889 1423 2576 2736 3870	Lower risi	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692	 a) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 			Lower risk	Higher risk	
tysing termina USAU io 2082 io 2082 io 0.56(0.41,0.7) is 0.65(0.49,0.85) thriaf fibrillation NA io 5186 io 0.61(0.50,0.76) iss 126 charlson comorbidity index 0.279 iss 126 iss 126 iss 0.50(0.41,0.7) iss 0.21 iss 0.221 iss 0.221 iss 0.50(0.36,0.69) iss 0.50 iss 0.50 iss 0.50 iss 0.50(0.41,0.73) iss 0.321 iss 0.540(0.42,0.70) iss 0.540(0.42,0.70) iss 0.610 iss 0.670 iss 0.600(0.47,0.76) iss 0.660(0.41,0.00) binking status 0.670 iss 0.567 is	C Subgroup // Sender female tale Vge 70 years 70 years SMI 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 5 years -5 years -9 years	Her 2568 2744 3889 1423 2576 2736 3870 606	Lower risi	k Higher risk ttroke <u>P (interaction</u> 0.937 0.113 0.418 0.692	 a) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 			Lower risk	Higher risk	
Composition 2020 Composition 000(000000000000000000000000000000000	C Subgroup Sender iemale Atale Gge 70 years 70 years 30 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 29 years 10 years 10 years	Her 2568 2744 3889 1423 2576 2736 3870 606 836	Lower risk	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692	 h) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.42(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.59(0.28,1.28) 			Lower risk	Higher risk	
Atrial fibrillation NA Output Description io 5186 0.61(0.50,0.76) iss 126 0.61(0.50,0.76) charlson comorbidity index 0.279 2421 0.70(0.47,1.08) 1505 0.70(0.49,0.99) Coronary heart disease 0.321 io 4421 0.58(0.46,0.73) iss 891 0.58(0.46,0.73) iss 891 0.54(0.42,0.70) isso 0.616 0.81(0.56,1.17) iolo 3836 0.610 iolo 3836 0.66(0.44,1.00) iorrent 3727 0.660(0.44,1.00) iorrent 3727 0.058 iot current 3920 0.670 iot current 3920 0.058 iot current 3920 0.058 iot current 3920 0.058 iot current 3920 0.58(0.67(0.54,0.84)) iverent 1402 0.058 iot current 3910 0.15 iverent 150 0.058 iot current 3910 0.54(0.42,0.70) iverent 3010 0.058 iot current 3910 0.058(0.67(0.54,0.84)) iverent <td>C Subgroup 1 Sender Finale Male System 70 years 70 years 8MI 24 kg/m² 24 kg/m² 24 kg/m² 24 kg/m² 10 years -9 years 10 years</td> <td>Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082</td> <td>Lower risl</td> <td>k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692</td> <td> b) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.56(0.24,1.28) 0.56(0.41,0.71) </td> <td></td> <td></td> <td>Lower risk</td> <td>Higher risk</td> <td></td>	C Subgroup 1 Sender Finale Male System 70 years 70 years 8MI 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 10 years -9 years 10 years	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082	Lower risl	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692	 b) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.56(0.24,1.28) 0.56(0.41,0.71) 			Lower risk	Higher risk	
lo 5186 0 0.61(0.50,0.76) les 126 0.279 Charlson comorbidity index 2421 0 0 0.279 1505 0 0 0.279 1505 0 0 0.279 2007 nary heart disease 0.321 0.58(0.46,0.73) les 811 0 0 0.84 0.61(0.50,0.76) 0.68 0.77(0.47,1.08) 0.68 0.61(7) 100 0.86 0 0.77(0.47,1.08) 0.68 0.61(7) 100 0.86 0 0.61(7) 100 0.86 0 0.678 100 0.076 0.678 0.66(0.47,0.76) 0.66(0.41,100) 0.71king status 100 0.058 0.66(0.41,100) 0.71king status 0.058 0.66(0.41,100) 0.71king status 0.058 0.66(0.41,100) 0.71king status 0.058 0.66(0.41,100) 0.71king status 0.058 0.66(0.41,100) 0.71king status 0.058 0.67(0.54,0.84) 0.74(0.54,0.84) 0.75(0	C Subgroup // Sender emale fale Vge 70 years 70 years SMI -24 kg/m ² -24 kg/m ² -24 kg/m ² -24 kg/m ² -34	He 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230	Lower risl	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692	 h) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.53(0.51,0.89) 0.59(0.28,1.28) 0.56(0.41,0.77) 0.65(0.49,0.87) 			Lower risk	Higher risk	
Yes 126 thardson comorbidity index 0.279 100 2421 0.50(0.36,0.69) 1505 0.71(0.47,1.08) 12 1386 0.70(0.49,0.99) Coronary heart disease 0.321 100 4421 0.58(0.46,0.73) 13babets 0.70(0.47,1.26) 13babets 0.81(0.56,1.7) 16s 1476 0.81(0.56,1.7) 100 1585 0.660(0.47,0.76) 101 current 1727 0.600 102 current 327 0.610 104 current 1585 0.660(0.47,0.76) 104 current 327 0.658 105 current 327 0.610 104 current 310 0.67(0.54,0.84) 104 current 390 0.810 105 current 391 0.670 104 current 390 0.670 105 current 390 0.80 105 current 1490 0.810 105 current 0.380 105 current 0.580 105 current 0.380	C Subgroup I Sender emale faile 70 years 70 years 24 kg/m ² 24 kg/m ² 29 years 5 years 10 years 29 years 10 years 20 yslipidemia 10 6 5 set xtrial fibrillation	He 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230	Lower risk	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.113 0.418 0.692 0.502 NA	 a) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.59(0.28,1.28) 0.56(0.41,0.77) 0.65(0.49,0.85) 			Lower risk	Higher risk	
Charlson comorbidity index 0.279 2421 0.710 1505 0.710 2 1366 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 2 0.700 3 0.600 3 0.600 4 0.600 4 0.600 4 0.600 4 0.600 4 0.600 4 0.600 4 0.600 4 0.600 4 0.600 4 0.600 4 0.600 4 0.610 4 0.620 4 0.800 4 0.800 4 0.800 4 0.800 4 0.800 4 0.800 4 0.800 4 0.800 <tr< td=""><td>C Subgroup 1 Sender emaile tale (ge 70 years 70 years 24 kg/m² 24 kg/m² 24 kg/m² 24 kg/m² 24 kg/m² 24 kg/m² 10 years 5 years 10 years 10</td><td>Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186</td><td>Lower risl</td><td>k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692 </td><td> h) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.53(0.31,0.89) 0.59(0.28,1.28) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) </td><td></td><td></td><td>Lower risk</td><td>Higher risk</td><td></td></tr<>	C Subgroup 1 Sender emaile tale (ge 70 years 70 years 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 10 years 5 years 10	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186	Lower risl	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692 	 h) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.53(0.31,0.89) 0.59(0.28,1.28) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 			Lower risk	Higher risk	
2421 0.50(0.36,0.69) 1505 0.71(0.47,1.08) 2 1386 0.70(0.49,0.99) coronary heart disease 0.321 io 4421 0.07(0.47,1.26) jabetes 0.77(0.47,1.26) jabetes 0.084 io 3836 0.61(0.42,0.70) es 1476 0.65(0.46,0.73) io current 3727 0.678 lot current 3727 0.60(0.47,0.76) virrent 155 0.658 lot current 3910 0.658 lot current 3910 1.5 virrent 1402 0.38(0.22,0.67) Higher risk Higher risk	C budgroup I bender emale lale tge 70 years 70 years 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 10 years 5 years 10 years by apars 10 years by apars 10 years by apars by apars 10 years by apars by apars	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186 126	Lower risi	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692 	 a) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.59(0.28,1.28) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 			Lower risk	Higher risk	
1505 1 0.71(0.47, 1.08) 2 1366 0.70(0.49, 0.99) formary heart disease 0.321 0.58(0.46, 0.73) 6s 4421 0 0.58(0.46, 0.73) 9abetes 0.77(0.47, 1.26) 10 3836 0 9abetes 0.844 10 3836 0.54(0.42, 0.70) es 0.54(0.42, 0.70) es 0.678 10 current 3727 0.660(0.47, 0.76) vurrent 1585 0.66(0.44, 1.00) virturent 1402 0.58 10 current 3910 0.55 10 current 3910 0.58 10 current 3910 0.67(0.54, 0.84) 10 rurent 1402 0.88(0.22, 0.67) 10 surrent of ONRI 1.50 increment of ONRI Lower risk Higher risk	C sender emale tale tale tale tale 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 10 years 9 years 10 years 10 years years 10 years to years 10 years to years 10 years	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186 126	Lower risi	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.113 0.418 0.692 0.502 NA 0.279	 a) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.59(0.28,1.28) 0.56(0.41,0.77) 0.66(0.50,0.76) 0.61(0.50,0.76) 			Lower risk	Higher risk	
12 1386 1 0.70(0.49,0.99) Jornary heart disease 0.321 0.58(0.46,0.73) is 831 0.58(0.46,0.73) is 0.54(0.42,0.70) is 0.670 is 0.670 is 0.60(0.47,0.76) jurrent 3727 0.658 iot current 3727 0.058 iot current 3910 0.58(0.67(0.54,0.84)) jurrent 1402 0.58(0.48,100) is is 0.38(0.22,0.67) if HR per each ISD increment of ONRI Is Lower risk Higher risk	C Subgroup Sender Hale Gge 70 years 30 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 25 kg/m ² 20 years 30 30 30 kg/m ² 30 years 30 years 3	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186 126 2421	Lower risi	k Higher risk troke P (interaction 0.937 0.113 0.418 0.692 0.502 NA 0.279	b) Hazard Ratio(95% Cl) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 0.50(0.36,0.69)			Lower risk	Higher risk	
Constrained inserts C.321 io 4421 0.58(0.46,0.73) iss 891	C Subgroup I Sender emaile falle type 70 years 50 years 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 25 years -0 years	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186 126 2421 1505	Lower risi	k Higher risk troke <u>P (interaction</u> 0.937 0.113 0.418 0.692 0.502 NA 0.279	 a) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 0.50(0.36,0.69) 0.71(0.47,1.08) 			Lower risk	Higher risk	
obs 142 0 0.00(400,473) Ses 851 0.084 Jabetes 0.084 Jo 3836 0 Ses 1476 0.54(0.42,0.70) Smoking status 0.678 Jourrent 3727 0 Jourrent 3727 0 Jourrent 3727 0 Jurrent 1585 0.66(0.44,1.00) Jrinking status 0.058 Jourrent 3910 0 Jurrent 1402 0.38(0.22,0.67) HR per each 150 increment of ONNI Lower risk Higher risk Higher risk	C Subgroup Sender emale fale Vge 70 years 70 years 3MI 24 kg/m ² 24 kg/m ² 25 years 10 years years 10 years years 10 years years 10 years 5 years 10 yea	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186 126 2421 1505 1386	Lower risk	k Higher risk troke P (interaction 0.937 0.113 0.418 0.692 0.502 NA 0.279	 h) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.53(0.51,0.89) 0.59(0.28,1.28) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 0.50(0.36,0.69) 0.71(0.47,1.08) 0.70(0.49,0.99) 			Lower risk	Higher risk	
Jobetes 0.084 0.10(4, 11, 10, 2) Job 3836 0.084 0.54(0.42, 0.70) @s 1476 0.81(0.56, 1.17) iot current 3727 0.058 Jurrent 1585 0.66(0.44, 1.00) Drinking status 0.058 Iot current 3910 Jurrent 1402 Iot current 3910 Jurrent 0.058 Iot current 0.058 Lower risk Higher risk	C Subgroup Sender female Male Nge 70 years 300 24 kg/m ² 24 kg/m ² 25 years 300 5 years 300 5 years 300 5 years 5 years 5 years 5 years 10 years 5 years 10 years 5 years 10 y	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186 126 2421 1505 1386 4424	Lower risi	k Higher risk troke P (interaction 0.937 0.113 0.418 0.692 0.502 NA 0.279 0.321	 a) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.59(0.28,1.28) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 0.50(0.36,0.69) 0.71(0.47,1.08) 0.70(0.49,0.99) 0.56(0.46,0.72) 			Lower risk	Higher risk	
lo 3836 0.54(0.42,0.70) és 1476 0.81(0.56,1.17) ömoking status 0.678 öl current 3727 0.60(0.47,0.76) varrent 1585 0.66(0.44,1.00) prinking status 0.058 öl current 3910 0.55 0.66(0.44,1.00) prinking status 0.058 0.058 0.81(0.22,0.67) Burrent 1402 1402 1.5 His per seat. 15D increment of ONNI Lower risk Higher risk	C Subgroup 1 Sender emaile falle Vge 70 years SMI 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 20 varis of hypertension 5 years -9 years -	Her 2568 2744 3889 1423 2576 2736 2736 3870 606 836 2082 3230 5186 126 2421 1505 1386 1453 1453 1453 1454 1455 1456 1455 1456 1457	Lower risi	k Higher risk troke P (interaction 0.937 0.113 0.418 0.692 	 a) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.59(0.28,1.28) 0.66(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 0.50(0.36,0.69) 0.71(0.47,1.08) 0.70(0.49,0.99) 0.58(0.46,0.73) 0.70(0.47,1.26) 			Lower risk	Higher risk	
les 1476 0.81(0.56, 1.17) imoking status 0.678 lot current 3727 urrent 1585 of current 0.678 lot current 0.670 imoking status 0.670 lot current 0.910 urrent 0.958 lot current 0.910 iment 1402 iment 0.38(0.22,0.67) iment 1.5 HR per each 1.50 increment of MIN Lower risk Higher risk	C sender emale tale tge 70 years 70 years 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 24 kg/m ² 10 years 10 years 10 years 10 years 10 years trial fibrillation to es trial fibrillation to es to	Her 2568 2744 3889 1423 2576 2736 3870 606 836 2082 3230 5186 126 2421 1505 1386 4421 891	Lower risk	k Higher risk troke P (Interaction 0.937 0.113 0.113 0.418 0.692 0.502 NA 0.279 0.321	h) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.56(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 0.61(0.50,0.76) 0.50(0.36,0.69) 0.71(0.47,1.08) 0.70(0.49,0.99) 0.58(0.46,0.73) 0.77(0.47,1.26)			Lower risk	Higher risk	
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lot current: 3727 Urrent: 155 Urrent: 3910 Urrent: 3910 Urrent: 3910 Urrent: 3910 Urrent: 1402 Urrent: 1402 Urrent: 1402 Urrent: 1402 Urrent: 1402 Urrent: 15 HR Pare tesh 150 Increment of ONRI Lower risk Higher risk	C bildgroup I bender emale lale Gge 70 years MI 24 kg/m ² 24 kg/m ² 25 years 10 years bysipidemia to bes trial fibrillation lo es trial fibrillation lo es bilder 2 2 bilder 2	Her 2568 2744 3889 1423 2576 2736 2756 2736 3870 606 836 2082 3230 5186 126 2421 1505 1386 4421 891 3836	Lower risi morrhagic s	k Higher risk troke P (interaction 0.937 0.113 0.418 0.692 0.502 NA 0.279 0.321	 h) Hazard Ratio(95% CI) 0.61(0.45,0.83) 0.60(0.45,0.80) 0.56(0.44,0.71) 0.82(0.54,1.23) 0.55(0.40,0.76) 0.66(0.50,0.86) 0.67(0.53,0.85) 0.53(0.31,0.89) 0.56(0.24,1.28) 0.66(0.41,0.77) 0.65(0.49,0.85) 0.61(0.50,0.76) 0.50(0.36,0.69) 0.71(0.47,1.08) 0.70(0.49,0.99) 0.58(0.46,0.73) 0.77(0.47,1.26) 0.54(0.42,0.70) 0.81(0.56,1.17) 			Lower risk	Higher risk	
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with heart failure (37). Furthermore, a study by Anzaki et al. (38) showed that low GNRI levels were associated with all-cause mortality and major adverse cardiovascular events after elective percutaneous coronary intervention (PCI). Cheng et al. (11)

shown that in patients with chronic coronary artery occlusion (CTO) following PCI, the GNRI score at admission was a reliable predictor of adverse cardiovascular events. The prediction of cardiovascular events following PCI in patients with CTO was

	C-Statistic	P-value	cNRI	P-value	IDI	P-value
	Estimate (95% CI)		Estimate (95% CI)		Estimate (95% CI)	
Total stroke						
Established risk factors	0.613 (0.590-0.636)		Reference		Reference	
Established risk factors + GNRI	0.648 (0.625-0.672)	< 0.001	0.118 (0.066-0.172)	< 0.001	0.017 (0.009-0.029)	< 0.001
Ischemic stroke						
Established risk factors	0.638 (0.612-0.663)		Reference		Reference	
Established risk factors + GNRI	0.658 (0.632-0.683)	0.005	0.096 (0.044-0.160)	< 0.001	0.012 (0.005-0.021)	0.033
Hemorrhagic stroke						
Established risk factors	0.673 (0.625-0.721)		Reference		Reference	
Established risk factors + GNRI	0.718 (0.670-0.766)	0.017	0.190 (0.057-0.311)	0.007	0.014 (0.005-0.052)	< 0.001

TABLE 3 Incremental predictive value of GNRI.

The established risk factorsl included age, sex, heart rate, duration of hypertension, SBP, DBP, smoking status, drinking status, comorbid conditions, and laboratory tests.

DI, integrated discrimination improvement; cNRI, continuous net reclassification improvement. Other abbreviations as presented in Table 1.

greatly enhanced by including the GNRI score into existing risk prediction algorithms (11). Elderly patients with hypertension are prone to multiple chronic diseases and may focus more on the primary disease, but nutritional support is mostly neglected. Our findings suggest that physicians may incorporate the identification of nutritional status into their daily practice. From prior research and the findings of the current study, we suggest that modestly increasing calorie and protein intake in malnourished elderly patients with hypertension may reduce the risk of stroke (39, 40). Further prospective intervention trials are needed to establish causality.

Although the underlying mechanisms remain unclear, there are some possible explanations. Oxidative stress and inflammation play key roles in the pathogenesis of stroke (41). First, serum albumin is a multifunctional protein that exerts neuroprotective effects in ischemic strokes, such as resisting antioxidants and reducing erythrocyte pressure levels (42, 43). According to Dziedzic et al. (43) stroke patients with decreased serum albumin levels had worse prognoses. Low albumin levels significantly enhanced the probability of recurrence in stroke patients and were related with poor outcome in all stroke subtypes (43, 44). Second, another potential mechanism may be attributed to the inflammatory response. According to a number of studies, inflammation frequently fosters a catabolic state that increases protein breakdown and slows protein synthesis, resulting in malnutrition and a decrease in GNRI (45). Additionally, it has been proven in the past that malnutrition is associated with higher than normal levels of inflammatory markers (46). Lower albumin levels are a result of the catabolic cytokines, muscle catabolism, and hunger suppression that are linked to chronic inflammatory disorders (47, 48). As a result, inflammation may be a key relationship between dietary status and the risk of cardiovascular disease (49). Severe malnutrition is

closely associated with high levels of inflammation, and inflammation can increase the burden of atherosclerosis (50). At the same time, the inflammatory response reduces albumin synthesis, further inducing malnutrition (51). There may be a positive feedback loop between inflammation, malnutrition, immune defense, and adverse events, resulting in a vicious cycle. Therefore, the link between these three entities is also described as the malnutrition-inflammation-atherosclerosis syndrome (52, 53).

The strengths of this study lie in the novelty, the long observational period, and the well-characterized participants. Despite the aforementioned merits, several limitations of the present study merit discussion. First, it was observational and cannot establish causation. Second, the time-dependent changes of GNRI during the follow-up period were not assessed. Third, we didn't examine the predictive value of GNRI against more thorough nutrition evaluations. Despite adjustment for major confounding factors, the risk of residual unmeasured confounding remains possible. Finally, this study is limited to China and needs to be replicated in other different populations. Given the limitations inherent in this study, these results should be interpreted with caution but warrant further investigation in subsequent studies.

Conclusion

In summary, we demonstrated that a lower GNRI was associated with a higher risk of incident stroke in elderly hypertensive patients. In addition, a significant L-shaped dose-response relationship between GNRI and the risk of incident HS was observed. Additional prospective data collection is required to confirm our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by People's Hospital of Xinjiang Uygur Autonomous Region. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

XC and JHu analyzed the data and wrote the manuscript. JHo, QZ, MW, YD, and WY helped with copyediting. XC and NL audited the data. SL, JHu, and XC conducted research. NL had primary responsibility for the final content of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/ fnut.2022.1048206/full#supplementary-material

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