Serum Albumin and Risks of Stroke and Its Subtypes: The Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

Background: Few studies have investigated the association between serum albumin levels and the risk of stroke subtypes among the general Japanese population.

Methods and Results: In this study, 5,071 men and 7,969 women aged 40–74 years, initially free from stroke, coronary artery disease, and kidney and hepatic failure, and residing in 4 Japanese communities completed a baseline risk factor survey between 1985 and 1994. During the 24-year follow-up, 528 men and 553 women experienced stroke. In the entire study cohort, multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) of total stroke, ischemic stroke, and intracerebral hemorrhage for the lowest vs. highest quartiles of serum albumin were 1.45 (1.18–1.77), 1.52 (1.17–1.97), and 1.57 (1.04–2.37), respectively. In men, multivariable HRs (95% CIs) for total stroke, ischemic stroke, and intracerebral hemorrhage in the lowest vs. highest serum albumin quartile were 1.44 (1.07–1.92), 1.48 (1.03–2.11) and 1.71 (0.92–3.18), respectively, whereas in women they were 1.50 (1.13–1.99), 1.63 (1.11–2.39), and 1.56 (0.89–2.74), respectively. Similar inverse associations were observed for each of the ischemic stroke subtypes, but not for subarachnoid hemorrhage.

Conclusions: Low serum albumin levels were associated with an increased risk of total stroke, ischemic stroke, ischemic stroke subtypes, and intracerebral hemorrhage.

Introduction

Albumin, the most abundant protein in human blood plasma, has essential physiologic effects in maintaining health. Albumin is a multifunctional protein that modulates the colloid osmotic pressure between the blood vessels and tissues, and binds and transports various endogenous molecules (e.g., free fatty acids, hormones, bilirubin, and metal ions) and some medications. The synthesis of albumin is adversely affected by poor nutritional status and chronic inflammation.[1] Albumin is considered an antioxidant because of its ligand-binding and free radical-scavenging properties.[2] Furthermore, albumin has been reported to exert anticoagulant actions and inhibitory effects on platelet function.[3] Numerous Western and Asian cohort studies have reported that low serum albumin concentrations are independent risk factors of all-cause and cardiovascular mortality in the general population.[4–9] Several Western cohort studies further reported an inverse association between serum albumin concentrations and the risk of total and ischemic strokes;[10–12] in one of these studies, which examined the risks of ischemic stroke subtypes, low serum albumin concentrations were found to be associated with an increased risk of cardioembolic and cryptogenic ischemic stroke.[12] Stroke is a dominant subtype of cardiovascular disease in most Asian countries.[13] However, few Asian cohort studies have investigated associations between serum albumin concentrations and the risk of stroke and stroke subtypes.

The aim of the present study was to examine associations between serum albumin

concentrations and the risk of stroke and stroke subtypes among middle-aged Japanese men and women. We hypothesized that low serum albumin concentrations were associated with an increased risk of stroke and stroke subtypes, independent of serum total cholesterol concentrations and other traditional cardiovascular risk factors.

Methods

Study Population

This study is part of the Circulatory Risk in Communities Study (CIRCS), an ongoing dynamic community cohort study of cardiovascular disease in the general Japanese population ongoing since 1963.[14,15] The study population was comprised of 5,263 men and 8,081 women community residents aged 40−74 years who participated in annual health checkups. The participants were enrolled from 4 communities: Ikawa (a rural community in Akita Prefecture in northwestern Japan), Minami-Takayasu (a suburb in Osaka Prefecture in mid-western Japan), Noichi (a rural community in Kochi Prefecture in western Japan), and Kyowa (a rural community in Ibaraki Prefecture in mid-eastern Japan). Baseline surveys were conducted in these 4 communities in 1985−1990, 1985−1994, 1985−1990 and 1985−1991, respectively. Individuals who had a history of stroke, coronary artery disease, hepatic failure, kidney failure, or were undergoing hemodialysis

at baseline (193 men, 111 women) were excluded. This left 5,071 men and 7,969 women available for the present analysis. Informed consent was obtained from community representatives because this study was a secondary use of existing data from the cardiovascular disease prevention program in Japanese communities. Ethics approval was obtained from the ethics committees of the Osaka Center for Cancer and Cardiovascular Disease Prevention (Reference no. 29-Ethics-2) and Osaka University (Reference no. 14285-6).

Follow-up and Ascertainment of Cases

Participants were followed up to determine incident stroke, and its subtypes, occurring by the end of 2010 for Noichi, 2014 for Kyowa, 2016 for Yao, and 2017 for Ikawa. Follow-up was terminated at the first incident stroke, exit from the community, or death; 1,020 (8%) participants moved out from the communities and 4,633 (36%) died. The median follow-up period was 24 years.

Details regarding endpoint determination have been described in previous reports of CIRCS.[14,15] Stroke surveillance was performed during the whole follow-up period. Information for candidate cases of stroke was ascertained from multiple sources, such as death certificates, national insurance claims, annual household questionnaires, annual cardiovascular risk surveys, and reports by either local physicians, public health nurses, or health volunteers. The diagnosis of stroke was further confirmed: all living patients with a suspected stroke were telephoned, visited,

or invited to take part in a face-to-face survey during their annual health checkups. In addition, medical records were obtained from local clinics and hospitals. In the case of death, medical histories were obtained from families and/or attending physicians, and relevant medical records were reviewed. Stroke was defined as a focal neurological disorder with rapid in onset that persisted at least 24 h or until death. Stroke subtypes, including intracerebral and subarachnoid hemorrhage, ischemic stroke (lacunar infarction, large artery occlusive infarction, embolic infarction and unclassified infarction), were classified on the basis of computed tomography (CT) and magnetic resonance imaging (MRI) findings. For diagnosed cases of stroke without brain imaging, stroke subtypes were classified as ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and unclassified stroke according to clinical criteria.[16] Lacunar infarction was diagnosed as 1 or multiple infarctions involving focal, small, and deep areas based on the presence of lacunar syndrome and/or brain imaging, without cerebral cortical or cerebellar impairment. Large artery occlusive infarction was diagnosed as infarction involving the cortical artery regions in the cerebrum and cerebellum (cortex and subcortical areas) based on the presence of cortical signs and/or brain imaging. Embolic infarction was defined as cerebral infarction caused by emboli from extracranial sources. When an embolic source was present in the medical record and brain imaging supported the diagnosis, those infarctions were considered as embolic infarctions. Unclassified infarction included those cases of ischemic stroke that failed to meet the

criteria for lacunar infarction, large artery occlusive infarction, or embolic infarction because of a lack of brain imaging to confirm the diagnosis. CT or MRI findings were available for 94% of stroke cases in this analysis. The final diagnoses were made by a panel of 2−4 experienced physician epidemiologists who were blinded to the data from the risk factor survey using the same diagnostic criteria for stroke.

Baseline Examination

Blood was drawn from seated subjects into plain, siliconized glass tubes, and the serum was separated within 30 min. Serum albumin was measured using the bromocresol green method. Serum total cholesterol was measured using the direct Lieberman-Burchard method from 1984 to August 31, 1986 and the enzymatic method from September 1, 1986 to 1994. Serum triglycerides were measured using the fluorometric method from 1984 to August 31, 1986, the enzymatic method from September 1, 1986 to July 22, 1993, and the enzymatic method for free glycerol from July 23, 1993 to 1994. Serum glucose was measured using the cupric-neocuproine method from 1984 to August 31, 1986, the hexokinase method from September 1, 1986 to July 22, 1993, and the glucokinase method from July 23, 1993 to 1994. Serum glucose concentrations (mmol/L) measured by the cupric-neocuproine method were adjusted using the following linear regression formula: serum glucose concentrations (mg/dL) $\times$ 0.0474 + 0.541. All measurements were

performed at the Osaka Medical Central for Cancer and Cardiovascular Disease, an international member of the US National Cholesterol Reference Method Laboratory Network (CRMLN).[17,18] During health checkups, subjects' height (in stockinged feet) and weight (in light clothing) were measured. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m^2). Trained observers interviewed participants to determine smoking status, the number of cigarettes smoked per day, usual weekly intake of alcohol (evaluated using the unit "go", a traditional Japanese unit of volume corresponding to 23 g ethanol), and medication use. Menopausal status was ascertained in women, with no menstruation for more than 6 months defined as a postmenopausal status. Systolic and diastolic blood pressure (SBP/DBP) in the right arm were measured by trained physicians using standard mercury sphygmomanometers and unified epidemiological methods.19 Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg and/or the use of antihypertensive medication. Diabetes was defined as fasting glucose levels ≥ 7.0 mmol/L and/or non-fasting glucose levels ≥ 11.1 mmol/L and/or the use of medication for diabetes.

Statistical Analyses

Analyses of covariance (ANCOVAs) were used to compare differences in sex-specific, age- and community-adjusted mean values or the prevalence of baseline characteristics according to serum

albumin quartiles. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence interval (CIs) of stroke and its subtypes for each quartile and 1 standard deviation (SD) decrease in serum albumin (0.3 g/dL in all participants, 0.3 g/dL in men and 0.2 g/dL in women). Median values for each serum albumin quartile were using to test the trend of associations with the risk of stroke and its subtypes.

The first HR model was adjusted for age, sex, and community, whereas the second was adjusted for age, sex, community, and serum total cholesterol (mmol/L). The full multivariable model was further adjusted for sex-specific quartiles of BMI (kg/m^2), cigarette smoking status (never, former, and current [1−19 or 20 cigarette/day]), alcohol intake status (never, former, and current [<23, 23−45, ≥46 g ethanol/day]), SBP (mmHg), antihypertensive medication use (no or yes), sex-specific quartiles of serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT), sex-specific quartiles of serum triglycerides (mmol/L), atrial fibrillation (no or yes), diabetes (no or yes), and menopausal status (pre- or post-menopausal) in women. We evaluated the effect of the interaction between sex and serum albumin concentrations on the risk of total stroke and its subtypes using a cross-product term of sex (0 or 1) and serum albumin concentrations (continuous) for this model.

All statistical analyses were performed using SAS System for Windows version 9.4 (SAS Institute, Cary, NC, USA) and 2-tailed $P<0.05$ was considered significant.

Results

Table 1 lists sex-specific, age- and community-adjusted mean values or the prevalence of traditional cardiovascular risk factors at baseline according to serum albumin quartiles. A significant inverse association between age and serum albumin concentrations was observed in both sexes, and this association was stronger in men than in women. Serum albumin concentrations were positively associated with SBP and DBP, the use of antihypertensive medication, and serum total cholesterol and triglycerides concentrations in both sexes, as well as BMI in men, but inversely associated with the prevalence of current smoking and ethanol intake in men. Serum albumin concentrations were positively associated with the prevalence of diabetes and postmenopausal status in women. With regard to biomarkers of liver disease, serum albumin concentrations were positively associated with serum GOT and GPT in women, but tended to be inversely associated with both these biomarkers in men.

During the median 24-year follow-up, totaling 288,770 person-years, there were 1,081 cases of incident stroke (528 in men, 553 in women). The observed stroke subtypes included 719 ischemic strokes (383 in men, 336 in women), 229 intracerebral hemorrhages (102 in men, 127 in women), 116 subarachnoid hemorrhages (34 in men, 82 in women), and 17 unclassified strokes (9 in men, 8 in women). Ischemic stroke subtypes included 325 lacunar infarctions (182 in men, 143

in women), 72 large artery occlusive infarctions (33 in men, 39 in women), 120 embolic infarctions (61 in men, 59 in women), and 202 unclassified infarctions (107 in men, 95 in women).

Table 2 lists the multivariable HRs for total stroke, ischemic stroke, and intracerebral and subarachnoid hemorrhages in all participants. Low serum albumin concentrations tended to be associated with increased age-, sex- and community-adjusted risks of total stroke, ischemic stroke, and intracerebral hemorrhage, but not subarachnoid hemorrhage. After adjustment for serum total cholesterol, these associations did not change materially. However, these associations were strengthened and became statistically significant after further adjustment for SBP and the use of antihypertensive medication. After adjustment for other conventional cardiovascular risk factors, these associations remained significant. The multivariable HRs of total stroke, ischemic stroke, and intracerebral hemorrhage for the lowest vs. highest quartile of serum albumin in all participants were 1.45 (95% CI 1.18−1.77; P trend <0.001), 1.52 (95% CI 1.17−1.97; P trend=0.002), and 1.57 (95% CI 1.04−2.37; P trend=0.03), respectively. The multivariable HRs (95% CIs) of total stroke, ischemic stroke, and intracerebral hemorrhage for a 1-SD decrease in serum albumin concentrations were 1.14 (1.08−1.22), 1.16 (1.08−1.26) and 1.17 (1.02−1.33), respectively. Sex-specific HRs for total stroke and its subtypes are listed in Table 3. Inverse associations between serum albumin concentrations and the risk of total and ischemic strokes were similarly observed in men and women, with no sex interaction (P interaction=0.33 for total stroke and P

interaction=0.40 for ischemic stroke). Low serum albumin concentrations trended to be associated with increased risk of intracerebral hemorrhage in both men and women, and no association was observed for risk of subarachnoid hemorrhage in either sex.

When we examined ischemic stroke subtypes, low serum albumin concentrations were associated with an increased risk of lacunar infarction in the total study cohort; the multivariable HR for the lowest vs. highest quartile of serum albumin was 1.82 (95% CI 1.24−2.67; Pt rend=0.002), whereas that for a 1-SD decrease in serum albumin concentrations was 1.18 (95% CI 1.06−1.33). In addition, a 1-SD decrease in serum albumin concentrations was associated with an increased risk of large artery occlusive and embolic infarctions, with multivariable HRs (95% CIs) of 1.26 (1.00 − 1.60) and 1.24 (1.03 − 1.48), respectively (Supplementary Table 1). Inverse associations with serum albumin concentrations were similarly observed for lacunar infarction, primarily in men, and for large artery occlusive and embolic infarctions in women (Supplementary Table 2).

Discussion

The present prospective community-based study of 5,071 Japanese men and 7,969 women community residents aged 40 − 74 years found that low serum albumin concentrations were associated with increased risks of total stroke, ischemic stroke, ischemic stroke subtypes, and

intracerebral hemorrhage, but not subarachnoid hemorrhage, after adjustment for serum total cholesterol, SBP, the use of antihypertensive medication, and other conventional cardiovascular risk factors.

The inverse associations between serum albumin concentrations and the of total and ischemic strokes in the present study are consistent with results reported in previous studies. The First National Health and Nutrition Examination Survey (NHANES I) of 4,157 US Whites and 740 Blacks aged 45－74 years with 9－16 years of follow-up reported that serum albumin concentrations were inversely associated with the risk of incident total and non-hemorrhagic strokes; with multivariable HRs (95% CIs) of total and non-hemorrhagic strokes for the highest (>4.4 g/dL) vs. lowest (<4.2 g/dL) tertiles of serum albumin being 0.59 (0.37−0.93) and 0.58 (0.36−0.93), respectively, in participants aged 45−64 years and 0.74 (0.57−0.94) and 0.72 (0.55−0.94), respectively, in those aged 65−74 years.[10] The British Regional Heart Study (BRHS) of 7,690 British men aged 40−59 years with a 16.8-year follow-up reported a similar inverse association, with a multivariable HR (95% CI) of incident total stroke for the highest (≥4.7 g/dL) vs. lowest (<4.3 g/dL) quartiles of serum albumin of 0.63 (0.44−0.89).[11]

The Northern Manhattan Study of 2,986 American men and women aged ≥40 years with a 12-year follow-up period investigated the associations of serum albumin concentrations with risks of incident ischemic stroke subtypes.[12] That study found that low serum albumin was

associated with increased risks of cardioembolic and cryptogenic ischemic strokes, with the multivariable HRs (95% CIs) for the lowest (2.7−4.2 g/dL) vs. highest (4.6−5.5 g/dL) tertiles of serum albumin being 0.60 (0.24−1.52) for lacunar infarction (n=65), 1.36 (0.73−2.55) for large artery occlusive infarction (n=35), 1.92 (1.10−3.34) for cardioembolic infarction (n=92), and 2.59 (1.21−5.53) for cryptogenic ischemic stroke (n=55).[12] The Northern Manhattan Study did not provide data on intracerebral and subarachnoid hemorrhages. Cryptogenic ischemic stroke is considered a subtype of ischemic stroke; it does not have a well-defined etiology, with possible mechanisms including occult paroxysmal atrial fibrillation and other atrial cardiopathies, paradoxical embolism through a patent foramen ovale, and substenotic atherosclerosis, among others.[20] However, this stroke subtype was not considered in the present study because of the difficulties associated with the consistent detection and diagnosis of cryptogenic ischemic stroke.

Several potential mechanisms underlying the inverse relationship between serum albumin concentrations and the risk of ischemic stroke have been proposed. First, low serum albumin concentrations are indicators of moderate to severe malnutrition. Second, low serum albumin concentrations are an indication of inflammation: inflammatory activation of macrophages and other immune system cells produces more cytokines (e.g., interleukin-1, interleukin-6 and tumor necrosis factor-α), causing protein synthesis in the liver to switch from albumin to other acute-phase proteins.[21] Third, albumin has antioxidant effects by binding copper,

iron, and other cationic ligands, inhibiting the generation of reactive oxygen species.[22,23] Albumin also has indirect antioxidant effects by binding bilirubin, with the albumin-bound bilirubin protecting against oxidative damage caused by low-density lipoprotein cholesterol.[24] Fourth, albumin plays an important role in anticoagulation by binding antithrombin4 and its inhibitory effects on platelet aggregation.[25,26]

To the best of our best knowledge, this study is the first to find an excess risk of intracerebral hemorrhage associated with low serum albumin concentrations (<4.3 g/dL) after adjustment for traditional cardiovascular risk factors. The plausibility of this excess risk has been reported elsewhere. Low serum albumin concentrations were associated with low animal protein intake.[27] Both the Nurses' Health Study cohort study of 85,764 American women aged 34–59 years[28] and the Hisayama Study of 2,400 Japanese men and women aged 40–79 years[29] showed that low animal protein intake was associated with an increased risk of intracerebral hemorrhage, with the multivariable HRs (95% CI) for the highest vs. lowest quantiles of animal protein intake of 0.32 (95% CI 0.10–1.00; Ptrend=0.04) and 0.47 (95% CI 0.23–0.96; Ptrend=0.03), respectively.

Serum total cholesterol, which, like albumin, is synthesized in the liver, is another useful indicator of nutritional status. Accordingly, serum albumin concentrations were positively associated with serum total cholesterol in the baseline surveys, but the association of serum albumin concentrations with the risk of total stroke or its subtypes did not change materially after

adjustment for serum total cholesterol concentrations. In addition, serum albumin concentrations were positively associated with baseline SBP and DBP, as well as the use of antihypertensive medication, which is consistent with the findings of a previous study.[30] After further adjustment for SBP and the use of antihypertensive medication, the inverse associations between serum albumin concentrations and the risk of total stroke or its subtypes strengthened and became statistically significant.

The strength of the present study is its large-scale prospective cohort design with a median follow-up of 24 years, so that sufficient cases of stroke were collected to investigate sex-specific associations between serum albumin concentrations and the risk of stroke and its subtypes. However, the study does have some limitations. First, the single measurement of serum albumin at the time of the baseline survey could bias the association towards nil, such that the real associations would be greater than those we found. Second, the number of cases of large artery occlusive and embolic infarctions was relatively small, so that further follow-up is needed to confirm our results regarding ischemic stroke subtypes. Third, other inflammatory markers (e.g., C-reactive protein and leukocyte counts) were not considered because of limited data.

In conclusion, low serum albumin concentrations were associated with an increased risk of total stroke, ischemic stroke, ischemic stroke subtypes, and intracerebral hemorrhage, but not subarachnoid hemorrhage.

Appendix

The CIRCS Investigators

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Competing Interest

None declared.

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Table1. Baseline characteristics of participants according to quartiles of serum albumin.

	Serum albumin quartiles				P for
	Q1 (low)	Q2	Q3	Q4 (high)	difference
Men					
No. at risk	988	1328	1488	1267	
Range of serum albumin, g/dL	2.6–4.2	4.3–4.4	4.5–4.6	4.7–5.6	
Median serum albumin, g/dL	4.1	4.4	4.5	4.8	
Age, year	59.6 (0.3)	56.5 (0.2)	53.5 (0.2)	50.1 (0.2)	<0.001
Body mass index, kg/m^2	22.4 (0.1)	23.0 (0.1)	23.3 (0.1)	23.5 (0.1)	<0.001
Systolic blood pressure, mmHg	130.5 (0.6)	131.7 (0.5)	134.5 (0.5)	137.1 (0.5)	<0.001
Diastolic blood pressure, mmHg	79.1 (0.4)	80.5 (0.3)	83.4 (0.3)	85.0 (0.3)	<0.001
Antihypertensive medication use, %	11.4	11.4	13.8	18.0	<0.001
Serum total cholesterol, mmol/L	4.55 (0.03)	4.76 (0.02)	4.97 (0.02)	5.21 (0.02)	<0.001
Serum triglyceride, mmol/L	1.52 (0.04)	1.70 (0.04)	1.84 (0.04)	2.08 (0.04)	<0.001
Serum glutamic-oxaloacetic transaminase (GOT), IU/L	33.3 (0.7)	28.7 (0.6)	29.0 (0.6)	30.8 (0.6)	0.01
Serum glutamic-pyruvic transaminase (GPT), IU/L	34.3 (1.0)	30.8 (0.8)	32.2 (0.8)	33.8 (0.9)	0.03
Diabetes mellitus, %	8.4	7.8	8.1	10.0	0.21
Atrial fibrillation, %	1.5	1.0	0.8	1.1	0.47
Current smokers, %	64.4	64.8	59.3	56.3	0.004
Ethanol intake, g/day	32.1 (0.9)	29.5 (0.8)	28.4 (0.7)	28.7 (0.8)	0.01
Women					
No. at risk	1601	2418	2431	1519	
Range of serum albumin, g/dL	3.4–4.2	4.3–4.4	4.5–4.6	4.7–5.3	
Median serum albumin, g/dL	4.2	4.4	4.5	4.8	
Age, year	55.3 (0.2)	54.0 (0.2)	53.8 (0.2)	53.5 (0.2)	<0.001
Body mass index, kg/m^2	23.3 (0.1)	23.3 (0.1)	23.5 (0.1)	23.5 (0.1)	0.09
Systolic blood pressure, mmHg	127.6 (0.4)	130.3 (0.4)	132.3 (0.4)	135.4 (0.5)	<0.001
Diastolic blood pressure, mmHg	76.1 (0.3)	78.2 (0.2)	79.5 (0.2)	81.5 (0.3)	<0.001
Antihypertensive medication use, %	10.9	13.6	14.7	19.2	<0.001
Serum total cholesterol, mmol/L	4.87 (0.02)	5.09 (0.02)	5.31 (0.02)	5.54 (0.02)	<0.001
Serum triglyceride, mmol/L	1.38 (0.03)	1.47 (0.02)	1.56 (0.02)	1.74 (0.03)	<0.001
Serum glutamic-oxaloacetic transaminase (GOT), IU/L	23.5 (0.3)	23.5 (0.2)	24.1 (0.2)	25.2 (0.3)	<0.001
Serum glutamic-pyruvic transaminase (GPT), IU/L	22.6 (0.5)	22.2 (0.4)	22.9 (0.4)	24.3 (0.5)	0.007
Diabetes mellitus, %	3.6	3.7	5.5	4.9	0.008
Atrial fibrillation, %	0.4	0.5	0.2	0.2	0.19
Current smokers, %	8.0	7.5	8.5	10.0	0.40
Ethanol intake, g/day	1.6 (0.2)	1.5 (0.1)	1.3 (0.1)	1.4 (0.2)	0.68
Postmenopausal, %	57.8	61.4	64.6	67.3	<0.001

Values were presented as means (standard errors) or proportions, adjusted for age and community.

Table 2. Hazard ratios (HRs, 95% CIs) of total stroke and its subtypes according to quartiles of serum albumin in total participants.

	Serum albumin quartiles				P for trend	1 SD decrease*
	Q1 (low)	Q2	Q3	Q4 (low)		
No. at risk	2589	3746	3919	2786		
Person-years	53,084	82,818	88,380	64,488		
Total stroke						
No. of events	261	314	309	197		
Age-, sex-, community-adjusted HR (95% CI)	1.16 (0.96–1.40)	1.04 (0.87–1.24)	1.03 (0.86–1.23)	1.00	0.12	1.07 (1.01–1.13)
Multivariable HR[1] (95% CI)	1.17 (0.96–1.43)	1.05 (0.87–1.26)	1.03 (0.86–1.23)	1.00	0.10	1.08 (1.01–1.14)
Multivariable HR[2] (95% CI)	1.37 (1.12–1.67)	1.15 (0.96–1.39)	1.10 (0.92–1.32)	1.00	0.002	1.13 (1.06–1.20)
Multivariable HR[3] (95% CI)	1.45 (1.18–1.77)	1.19 (0.99–1.44)	1.13 (0.94–1.35)	1.00	<0.001	1.14 (1.08–1.22)
Ischemic stroke						
No. of events	165	228	213	113		
Age-, sex-, community-adjusted HR (95% CI)	1.18 (0.92–1.51)	1.26 (1.00–1.58)	1.20 (0.96–1.51)	1.00	0.22	1.08 (1.00–1.16)
Multivariable HR[1] (95% CI)	1.24 (0.96–1.60)	1.30 (1.03–1.64)	1.22 (0.97–1.54)	1.00	0.11	1.10 (1.02–1.19)
Multivariable HR[2] (95% CI)	1.44 (1.12–1.87)	1.43 (1.13–1.80)	1.30 (1.04–1.64)	1.00	0.005	1.15 (1.07–1.24)
Multivariable HR[3] (95% CI)	1.52 (1.17–1.97)	1.45 (1.15–1.84)	1.34 (1.06–1.69)	1.00	0.002	1.16 (1.08–1.26)
Intracerebral hemorrhage						
No. of events	66	54	61	48		
Age-, sex-, community-adjusted HR (95% CI)	1.30 (0.88–1.91)	0.77 (0.52–1.13)	0.85 (0.58–1.25)	1.00	0.17	1.10 (0.97–1.25)
Multivariable HR[1] (95% CI)	1.20 (0.81–1.80)	0.73 (0.49–1.09)	0.83 (0.57–1.22)	1.00	0.32	1.08 (0.95–1.23)
Multivariable HR[2] (95% CI)	1.40 (0.94–2.10)	0.81 (0.54–1.21)	0.89 (0.60–1.30)	1.00	0.09	1.13 (0.99–1.29)
Multivariable HR[3] (95% CI)	1.57 (1.04–2.37)	0.88 (0.59–1.32)	0.93 (0.63–1.36)	1.00	0.03	1.17 (1.02–1.33)
Subarachnoid hemorrhage						
No. of events	24	29	30	33		
Age-, sex-, community-adjusted HR (95% CI)	0.77 (0.45–1.32)	0.62 (0.38–1.03)	0.62 (0.38–1.02)	1.00	0.28	0.93 (0.78–1.10)
Multivariable HR[1] (95% CI)	0.75 (0.43–1.31)	0.61 (0.37–1.02)	0.62 (0.37–1.01)	1.00	0.25	0.92 (0.77–1.09)
Multivariable HR[2] (95% CI)	0.89 (0.50–1.56)	0.69 (0.41–1.15)	0.66 (0.40–1.09)	1.00	0.57	0.97 (0.81–1.15)
Multivariable HR[3] (95% CI)	0.94 (0.53–1.67)	0.72 (0.43–1.22)	0.70 (0.42–1.15)	1.00	0.73	0.98 (0.82–1.17)

*1 SD decrease of serum albumin was 0.3 g/dL.

Q1: 2.6–4.2 g/dl, Q2: 4.3–4.4 g/dl, Q3: 4.5–4.6 g/dl, Q4:4.7–5.6 g/dl.

[1] adjusted further for serum total cholesterol.

[2] adjusted further for systolic blood pressure and antihypertensive medication use.

[3] adjusted further for body mass index, cigarette smoking status, alcohol intake status, serum triglyceride, serum glutamic-oxaloacetic transaminase (GOT), serum glutamic-pyruvic transaminase (GPT), atrial fibrillation and diabetes mellitus.

Table 3. Sex-specific hazard ratios* (HRs, 95% CIs) of total stroke and its subtypes according to quartiles of serum albumin.

	Serum albumin quartiles				P for trend	1 SD decrease†
	Q1 (low)	Q2	Q3	Q4 (high)		
Men						
No. at risk	988	1328	1488	1267		
Person-years	17,767	27,019	31,741	28,457		
Total stroke						
No. of events	126	149	146	107		
Age- and community-adjusted HR (95%	1.14 (0.86–1.50)	1.03 (0.80–1.33)	0.99 (0.77–1.28)	1.00	0.34	1.09 (0.98–1.21)
Multivariable HR[1] (95% CI)	1.19 (0.90–1.59)	1.06 (0.82–1.38)	1.01 (0.79–1.31)	1.00	0.21	1.12 (1.00–1.25)
Multivariable HR[2] (95% CI)	1.40 (1.05-1.86)	1.18 (0.91-1.53)	1.09 (0.84-1.40)	1.00	0.02	1.18 (1.06-1.32)
Multivariable HR[3] (95% CI)	1.44 (1.07–1.92)	1.18 (0.91–1.54)	1.11 (0.86–1.43)	1.00	0.01	1.19 (1.07–1.33)
Ischemic stroke						
No. of events	86	124	107	66		
Age- and community-adjusted HR (95%	1.13 (0.80–1.59)	1.29 (0.95–1.75)	1.13 (0.83–1.54)	1.00	0.46	1.09 (0.97–1.24)
Multivariable HR[1] (95% CI)	1.21 (0.85–1.72)	1.35 (0.99–1.84)	1.16 (0.85–1.58)	1.00	0.26	1.13 (0.99–1.29)
Multivariable HR[2] (95% CI)	1.39 (0.98-1.99)	1.47 (1.08-2.02)	1.24 (0.90-1.69)	1.00	0.05	1.19 (1.05-1.35)
Multivariable HR[3] (95% CI)	1.48 (1.03–2.11)	1.49 (1.09–2.04)	1.30 (0.95–1.78)	1.00	0.03	1.21 (1.06–1.37)
Intracerebral hemorrhage						
No. of events	29	18	30	25		
Age- and community-adjusted HR (95%	1.41 (0.78–2.53)	0.63 (0.34–1.18)	0.96 (0.56–1.65)	1.00	0.33	1.13 (0.88–1.43)
Multivariable HR[1] (95% CI)	1.43 (0.78–2.63)	0.64 (0.34–1.20)	0.97 (0.56–1.67)	1.00	0.31	1.14 (0.88–1.46)
Multivariable HR[2] (95% CI)	1.74 (0.94-3.20)	0.73 (0.39-1.39)	1.05 (0.61-1.80)	1.00	0.10	1.22 (0.96-1.56)
Multivariable HR[3] (95% CI)	1.71 (0.92–3.18)	0.72 (0.38–1.37)	1.01 (0.59–1.75)	1.00	0.12	1.23 (0.96–1.58)
Subarachnoid hemorrhage						
No. of events	7	6	8	13		
Age- and community-adjusted HR (95%	0.93 (0.34–2.53)	0.51 (0.19–1.36)	0.56 (0.23–1.36)	1.00	0.61	0.93 (0.61–1.42)
Multivariable HR[1] (95% CI)	0.83 (0.29–2.35)	0.47 (0.17–1.30)	0.53 (0.22–1.31)	1.00	0.50	0.89 (0.57–1.38)
Multivariable HR[2] (95% CI)	1.02 (0.36-2.91)	0.56 (0.20-1.57)	0.58 (0.23-1.42)	1.00	0.79	0.98 (0.64-1.52)
Multivariable HR[3] (95% CI)	1.02 (0.35–3.02)	0.60 (0.21–1.67)	0.61 (0.24–1.52)	1.00	0.80	0.98 (0.60–1.53)
Women						
No. at risk	1601	2418	2431	1519		
Person-years	35,318	55,799	56,638	36,031		
Total stroke						
No. of events	135	165	163	90		
Age- and community-adjusted HR (95%	1.27 (0.97–1.67)	1.11 (0.86–1.44)	1.10 (0.85–1.42)	1.00	0.08	1.08 (1.00–1.16)
Multivariable HR[1] (95% CI)	1.23 (0.93–1.63)	1.09 (0.84–1.41)	1.08 (0.84–1.40)	1.00	0.14	1.07 (0.99–1.15)

Multivariable HR[2] (95% CI)	1.44 (1.09-1.91)	1.20 (0.92-1.56)	1.16 (0.89-1.50)	1.00	0.01	1.11 (1.03-1.20)
Multivariable HR[3] (95% CI)	1.50 (1.13–1.99)	1.22 (0.94–1.59)	1.18 (0.91–1.53)	1.00	0.005	1.12 (1.04–1.20)
Ischemic stroke						
No. of events	79	104	106	47		
Age- and community-adjusted HR (95% CI)	1.34 (0.93–1.94)	1.30 (0.92–1.84)	1.34 (0.95–1.89)	1.00	0.16	1.08 (0.99–1.19)
Multivariable HR[1] (95% CI)	1.36 (0.93–1.99)	1.31 (0.93–1.87)	1.34 (0.95–1.90)	1.00	0.15	1.09 (0.99–1.20)
Multivariable HR[2] (95% CI)	1.61 (1.10-2.36)	1.46 (1.03-2.08)	1.44 (1.02-2.03)	1.00	0.02	1.14 (1.04-1.25)
Multivariable HR[3] (95% CI)	1.63 (1.11–2.39)	1.45 (1.02–2.07)	1.44 (1.02–2.04)	1.00	0.02	1.13 (1.03–1.24)
Intracerebral hemorrhage						
No. of events	37	36	31	23		
Age- and community-adjusted HR (95%	1.41 (0.83–2.40)	0.97 (0.57–1.64)	0.83 (0.48–1.42)	1.00	0.13	1.13 (0.97–1.31)
Multivariable HR[1] (95% CI)	1.20 (0.69–2.08)	0.88 (0.51–1.49)	0.79 (0.46–1.35)	1.00	0.37	1.07 (0.92–1.25)
Multivariable HR[2] (95% CI)	1.36 (0.78-2.37)	0.95 (0.56-1.63)	0.83 (0.48-1.43)	1.00	0.19	1.11 (0.95-1.30)
Multivariable HR[3] (95% CI)	1.56 (0.89–2.74)	1.03 (0.60–1.78)	0.88 (0.51–1.52)	1.00	0.08	1.15 (0.99–1.35)
Subarachnoid hemorrhage						
No. of events	17	23	22	20		
Age- and community-adjusted HR (95%	0.84 (0.43–1.62)	0.74 (0.41–1.35)	0.69 (0.38–1.27)	1.00	0.59	0.95 (0.79–1.15)
Multivariable HR[1] (95% CI)	0.81 (0.41–1.60)	0.73 (0.39–1.34)	0.69 (0.37–1.26)	1.00	0.55	0.94 (0.78–1.14)
Multivariable HR[2] (95% CI)	0.96 (0.48-1.90)	0.81 (0.44-1.49)	0.74 (0.40-1.36)	1.00	0.88	0.99 (0.82-1.20)
Multivariable HR[3] (95% CI)	0.99 (0.50–1.98)	0.82 (0.44–1.52)	0.77 (0.42–1.42)	1.00	0.95	0.99 (0.82–1.21)

*P values for sex interaction were 0.33 for all stroke, 0.39 for intracerebral hemorrhage, 0.58 for subarachnoid hemorrhage and 0.40 for ischemic stroke.

†1 SD decrease of serum albumin was 0.3 g/dL in men, 0.2 g/dL in women.

Q1: 2.6–4.2 g/dl, Q2: 4.3–4.4 g/dl, Q3: 4.5–4.6 g/dl, Q4:4.7–5.6 g/dl in men; Q1: 3.4–4.2 g/dl, Q2: 4.3–4.4 g/dl, Q3: 4.5–4.6 g/dl, Q4: 4.7–5.3 g/dl in women.

[1] adjusted further for serum total cholesterol.

[2] adjusted further for systolic blood pressure and antihypertensive medication use.

[3] adjusted further for body mass index, cigarette smoking status, alcohol intake status, serum triglyceride, serum glutamic-oxaloacetic transaminase (GOT), serum glutamic-pyruvic transaminase (GPT), atrial fibrillation and diabetes mellitus.