Serum Uric Acid and Risk of Stroke and Its Types: the Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

The role of serum uric acid as a predictor of stroke remained controversial among general Japanese population. We conducted a prospective cohort study of 5235 men and 8185 women residents aged 40–79 years at baseline between 1985 and 1994, initially free from stroke, coronary heart disease and under medication for hyperuricemia or gout, in four Japanese communities. Cox proportional hazards models were used to estimate sex-specific hazard ratios of stroke and its types in relation to serum uric acid levels. During a median follow-up of 23.1 years, we determined 1018 (488 men and 530 women) incident stroke, including 222 (99 and 123) intraparenchymal hemorrhages, 113 (33 and 80) subarachnoid hemorrhages and 667 (347 and 320) ischemic strokes. After adjustment for age, community and known cardiovascular risk factors, the multivariable hazard ratios (95%CIs) for the highest versus lowest quintiles of serum uric acid were 1.45 (1.07–1.96) for total stroke, 1.20 (0.65–2.20) for intraparenchymal hemorrhage, 1.46 (0.69–3.09) for subarachnoid hemorrhage and 1.61 (1.07–2.41) for ischemic stroke in women. The corresponding multivariable hazard ratios (95%CIs) in men were 1.02 (0.74–1.35), 0.83 (0.40–1.72), 1.19 (0.38–3.75) and 1.00 (0.70–1.41). Furthermore, those positive associations with risks of total and ischemic strokes in women were more evident in non-users of antihypertensive medication rather than the users. In conclusion, elevated serum uric acid levels are independent predictors for total stroke in women, but not in men. The positive association in women was mostly attributable to ischemic stroke, and more

pronounced among non-users or users of antihypertensive medication.

Key words: stroke; stroke types; serum uric acid; follow-up study; epidemiology

Introduction

Uric acid is the end product of purine catabolism, and it is positively associated with known cardiovascular risk factors, e.g., obesity, dyslipidemia, impaired glucose tolerance, chronic kidney disease and hypertension.[1–3] Elevated serum uric acid levels could stimulate the renin–angiotensin system and restrain release of endothelial nitric oxide, contributing to pre–glomerular arteriolosclerosis and increasing blood pressure.[4–6] Furthermore, elevated serum uric acid levels were reported as indicators of oxidative stress due to its compensatory mechanism against oxidative stress resulted from atherosclerosis and aging.[7] A recent meta-analysis of 13 cohort studies showed that serum uric acid levels were positively associated with risk of stroke in both sexes, whereas this association trended to be nonlinear in men.[8] European prospective cohort studies reported consistent results to support predictive roles of serum uric acid on risk of stroke,[9–13] but findings from American[14–15] and Asian cohort studies[16–20] remained controversial.

Elevated serum uric acid levels are regularly observed among hypertensive patients with antihypertensive medication use, especially diuretic use.[21] The Atherosclerosis Risk in Communities (ARIC) study found that serum uric acid levels were positively associated with risk of ischemic stroke in non-users of diuretic, but not in the users,[15] suggests that diuretic-

inducted elevated serum uric acid levels were not predictor of risk of ischemic stroke. Based on prior studies, we hypothesized that elevated serum uric acid levels are independent predictor of risk of stroke among general Japanese population, and these associations are mainly observed in subjects without antihypertensive medication use.

Methods

Study Population

The present study is part of the Circulatory Risk in Communities Study (CIRCS), a prospective community-based study of cardiovascular disease among general Japanese population since 1963.[22, 23] The surveyed population included 5442 men and 8279 women aged 40–79 years who participated in annual health checkups with the examination of serum uric acid between 1985 and 1994. The subjects were enrolled from four communities: Ikawa town (a rural community in Akita Prefecture in northwestern Japan), the Minami-Takayasu district in Yao City (a southwestern suburb in Osaka Prefecture), Noichi town (a rural community in Kochi Prefecture in southwestern Japan), and Kyowa town (a rural community in Ibaraki Prefecture in central Japan). The baseline surveys were conducted in 1985–1990, 1985–1994, 1985–1990 and 1985–1991, respectively. After the exclusion of subjects who had a history of stroke or coronary heart disease (162 men and 92 women), and used medication for hyperuricemia or gout (45 men and 2 women) at baseline, 5235 men and 8185 women were eligible for this

analysis. Subjects were followed to determine the incident stroke and its types until the end of 2010 for Noichi, 2011 for Kyowa, and 2013 for Ikawa and Yao. Informed consent was obtained from the community representatives rather than each subjects because the present study is a secondary use of existing data for public health practice on cardiovascular disease prevention in local communities. Ethical approval of the CIRCS study has been admitted by the Ethics Committee of the Osaka Center for Cancer and Cardiovascular Disease Prevention and of Osaka University.

Ascertainment of Cases

The previous CIRCS study has reported the details of endpoint determination.[22, 23] Candidate cases of stroke were obtained from various information sources of death certificates, national insurance claims, annual household questionnaires, annual cardiovascular risk surveys, and reports by either local physicians, public health nurses, or health volunteers. To confirm the diagnosis, all living suspected stroke cases were phoned, visited or invited to take part in risk factor surveys, or alternatively, a medical history was obtained from their families. Furthermore, medical records in the local clinics and hospitals were reviewed. In the case of death, histories from families and/or attending physicians were obtained and medical records were reviewed. Stroke was defined as a focal neurological disorder which contained rapid in onset and lasted at least 24h or until death. Stroke subtypes were classified as intraparenchymal hemorrhage,

subarachnoid hemorrhage, and ischemic stroke (large-artery occlusive infarction, lacunar infarction or others) primarily by using CT or MRI,[24] which were available for 93.8% of stroke cases. The same diagnostic criteria of incident stroke and its types were used in all communities throughout the whole study period.

Baseline Examination

For all subjects, blood samples were drawn in seated position, stored in plain, siliconized glass tubes, centrifuged and its sera was separated within 30 minutes. Blood test had two time changes in methodology and measurement instrument during the baseline on September 1, 1986 and on July 22, 1993. Serum uric acid was firstly measured with the phosphotungstic acid method using SMA-6/60 automatic analyzer (Technicon, Tarrytown, NY, USA), then the uricase method using SMAC automatic analyzer (Technicon), and same method suing Autoanalyzer 7250 (Hitachi Medical Corp., Ibaraki, Japan). Serum glucose was measured with the cupric-neocuproine method using SMA-6/60, the hexokinase method using SMAC and the glucokinase method using Autoanalyzer 7250. The values of serum glucose (mmol/L) measured using the cupric-neocuproine method were adjusted by using a linear regression formula: serum glucose concentrations (mg/dL) × 0.0474 + 0.541. Serum creatinine was measured originally with the non-compensated kinetic Jaffe method using SMA-6/60, SMAC and Autoanalyzer 7250 on different periods, and converted to a contiguous value with the

enzymatic method by minus 0.2 mg/dL.[25] These 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).[26, 27]

An interview was conducted by trained observers to ascertain the smoking status, number of cigarettes smoked per day, the usual weekly intake of alcohol evaluated by units of "go" (a traditional Japanese unit of volume corresponding to 23g of ethanol), and the use of medication for hypertension or diabetes mellitus. In women, menopausal status was ascertained and postmenopausal status was defined by the end of menstruation for more than 6 months. Height in stocking feet and weight in light clothing were measured during health checkups, and body mass index was calculated as weight (kg) divided by the square of height (m^2). Systolic and diastolic blood pressure in right arm were measured using standard mercury sphygmomanometers.[28] Diabetes mellitus was defined as a fasting glucose level of ≥7.0 mmol/L, or a non-fasting glucose level of ≥11.1 mmol/L or use of medication for diabetes mellitus. Estimated glomerular filtration rate (eGFR) was calculated using a standardized formula from the Japan Society of Nephrology Chronic Kidney Disease Initiative Guidelines: eGFR (ml/min per 1.73m^2) = 194 × (serum creatinine [enzyme method])$^{-1.094}$ × (age)$^{-0.287}$ × (0.739 in women).[29] Atrial fibrillation was diagnosed using the standard 12-lead electrocardiogram.

Statistical Analyses

In view of the different levels of serum uric acid between men and women, sex-specific analyses were performed at the present study. Age- and community-adjusted mean values or the prevalence of baseline characteristics were compared according to quintiles of serum uric acid using the analyses of covariance. Cox proportional hazards models were used to calculate sex-specific hazard ratios with 95% confidence intervals (CIs) of stroke and its types according to quintiles of serum uric acid and 1 standard deviation (SD) increment of serum uric acid (1.3 mg/dL in men and 1.0 mg/dL in women).

The initial hazard ratio model was adjusted for age and community, while multivariable model added body mass index (sex-specific quartiles), cigarette smoking status (never, former, and current 1-19 or 20 cigarettes per day), alcohol intake status (never, former, and current < 23, 23–45, ≥46 g ethanol per day), systolic blood pressure (mmHg), antihypertensive medication use (no or yes), atrial fibrillation (no or yes), serum total cholesterol (mmol/L), serum triglycerides (sex-specific quartiles), estimated glomerular filtration rate (sex-specific quartiles), and diabetes mellitus (no or yes), and menopausal status (pre- or post-menopause) in women. To assess whether antihypertensive medication-induced changes of serum uric acid modified these associations, we conducted a subgroup analysis and stratified subjects by using of antihypertensive medication or not.

SAS System (version 9.4; SAS Inc, Cary, NC) was used in all statistical analyses. P values

<0.05 were defined as statistically significant with two-tailed statistical tests.

Results

Table 1 shows sex-specific, age- and community-adjusted mean values or the prevalence of known cardiovascular risk factors at baseline according to serum uric acid quintiles. Subjects with elevated serum uric acid levels were older in women but similar in men. In both sexes, serum uric acid levels were positively associated with body mass index, systolic and diastolic blood pressure, the prevalence of antihypertensive medication use, serum total cholesterol, triglyceride and ethanol intake, and inversely associated with estimated glomerular filtration rate. Serum uric acid levels were positively associated with the prevalence of postmenopausal status in women. In addition, serum uric acid levels were positively associated with the prevalence of current smokers in women, but inversely in men. Subjects with higher serum uric acid levels had the higher prevalence of atrial fibrillation and the lower prevalence of diabetes mellitus in men, but the similar prevalence of them in women.

During the median 23.1 years follow-up totaling 275,535 person-years, 1018 (488 men and 530 women) cases of incident stroke, which included 222 (99 men and 123 women) intraparenchymal hemorrhages, 113 (33 men and 80 women) subarachnoid hemorrhages and 667 (347 men and 320 women) ischemic strokes, were documented.

Table 2 lists sex-specific, age- and community-adjusted and multivariable hazard ratios of total stroke, intraparenchymal hemorrhage, subarachnoid hemorrhage and ischemic stroke

according to serum uric acid quintiles. After adjustment for age, community and main cardiovascular risk factors, the multivariable hazard ratios (95%CIs) of total stroke for the highest versus lowest quintile of serum uric acid was 1.02 (0.74–1.35), P for trend = 0.89 in men and 1.45 (1.07–1.96), P for trend = 0.007 in women. The multivariable hazard ratios (95%CIs) of total stroke for 1 SD increment of serum uric acid was 1.02 (0.92–1.13) in men and 1.12 (1.03–1.22) in women. The positive association was confined to women, and the sex interaction was statistically significance (P for interaction < 0.05). When stratified by age, the association with risk of total stroke in women did not vary; the multivariable hazard ratios (95%CIs) for 1 SD increment of serum uric acid was 1.17 (0.99-1.38) for ages of 40–54 years, and 1.12 (1.01-1.25) for ages of 55–79 years (data not shown in Table). In women, serum uric acid levels were positively associated with risk of ischemic stroke, but not of intraparenchymal hemorrhage or subarachnoid hemorrhage. The multivariable hazard ratios (95%CIs) of ischemic stroke, intraparenchymal hemorrhage and subarachnoid hemorrhage stroke for the highest versus lowest quintiles of serum uric acid were 1.61 (1.07–2.41); P for trend = 0.07, 1.20 (0.65–2.20); P for trend = 0.18 and 1.46 (0.69–3.09); P for trend = 0.15, respectively. In men, no positive associations were observed and the corresponding multivariable hazard ratios (95%CIs) were 1.00 (0.70–1.41); P for trend = 0.94, 0.83 (0.40–1.72); P for trend = 0.83 and 1.19 (0.38–3.75); P for trend = 0.27.

We next conducted a subgroup analysis, stratified by use of antihypertensive medication or

not, and the results are summarized in Table 3. In women, serum uric acid levels were positively associated with risk of total and ischemic strokes in non-users of antihypertensive medication, but not in the users, although the interaction with antihypertensive medication was not statistically significant (P for interaction = 0.87); the multivariable hazard ratios (95%CIs) for the highest versus lowest quintiles of serum uric acid was 1.46 (1.02–2.09); P for trend = 0.02 for total stroke, and 1.62 (1.00–2.63); P for trend = 0.12 for ischemic stroke in non-users of antihypertensive medication. The multivariable hazard ratios (95%CIs) for 1 SD increment of serum uric acid was 1.11 (1.00–1.24) for total stroke, and 1.06 (0.91–1.22) for ischemic stroke in non-users of antihypertensive medication. In men, no positive associations with the highest versus lowest quintiles of serum uric acid or 1 SD increment of serum uric acid were observed for total or ischemic stroke in either non-users or users of antihypertensive medication.

Discussion

In this prospective community-based study of 5235 men and 8185 women aged 40–79 years, we found that serum uric acid levels were positively associated with risk of total stroke in women, but not in men. The positive association in women was mostly attributable to ischemic stroke, and more pronounced among non-users or users of antihypertensive medication.

A recent meta-analysis of 12 prospective cohort and 1 nested case-control studies showed the positive associations of serum uric acid with risk of stroke in both sexes; the summary of relative risks (95% CIs) of stroke for a 1 mg/dL increment of serum uric acid were 1.10 (1.05–

1.14) in men, and 1.11 (1.09–1.13) in women. In that meta-analysis, a dose-response association was found in women (P for nonlinear trend = 0.51). However, the association of serum uric acid with risk of stroke trended to be nonlinear in men (P for nonlinear trend < 0.001), and the risk of stroke increased significantly and steeply when values of serum uric acid exceeded 6 mg/dL.[8]

Although European perspective cohort studies consistently found the positive associations of serum uric acid levels with risk of stroke,[9–13] findings from Asian studies remained inconsistent.[16–20] The Chin-Shan Community Cardiovascular Cohort Study of 1703 Taiwan men and 1899 women aged 35 years or older with 11-year follow-up reported that plasma uric acid was positively associated with risk of incident stroke; the multivariable hazard ratios (95%CIs) of 1 mg/dL increment of plasma uric acid were 1.13 (0.88–1.46) in men, and 1.32 (1.00–1.73) in women.[16] A 2-year follow-up study of 61,304 Japanese men and 94,018 women aged 40–73 years reported J-shaped associations of serum uric acid levels with risk of self-reported non-fatal stroke; the multivariable odds ratios (95%CIs) for the highest (≥7.1 mg/dL in men and ≥5.5 mg/dL in women) versus third quintiles (5.7–6.2 mg/dL in men and 4.4–4.8 mg/dL in women) of serum uric acid was 1.26 (1.04–1.54) in men, and 1.24 (1.00–1.48) in women.[17] However, the NIPPON DATA 80 study of 3596 Japanese men and 4576 women aged 30 years or older with 14-year follow-up and the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Study of 15,628 Japanese men and

20,685 women aged 35–89 years with 441,771 person-years of follow-up reported that serum uric acid levels were not associated with risk of stroke mortality in either sex.[18, 19] Another 9-year follow-up study of 22,698 Korean men aged 30–77 years reported no association with risk of stroke mortality.[20]

These associations of serum uric acid levels with risk of stroke trended to be non-linear. The NIPPON DATA 80 study reported the multivariable hazard ratios (95%CIs) of total stroke for each quartiles of serum uric acid were 0.84 (0.45-1.59), 0.66 (0.33-1.33) and 1.71 (0.92-3.17) in men, and 1.40 (0.54-3.63), 0.95 (0.37-2.45) and 1.12 (0.46-2.74) in women, respectively.[18] The EPOCH-JAPAN study reported the corresponding multivariable hazard ratios (95%CIs) for each quintiles of serum uric acid were 0.83 (0.58-1.18), 0.77 (0.52-1.13), 0.77 (0.52-1.13) and 1.19 (0.84-1.68) in men, and 1.27 (0.90-2.01), 0.98 (0.62-1.54), 1.05 (0.67-1.64) and 1.46 (0.98-2.19) in women.[19] Men had higher serum uric acid levels than women, even than postmenopausal women. The absence of association of serum uric acid levels with risk of stroke in the present study in men could be due to the antioxidant effect of serum uric acid. Furthermore, our study found J-shaped associations with risks of subarachnoid hemorrhage and ischemic stroke in men, and intraparenchymal and subarachnoid hemorrhage in women, which could be influenced in part by the antioxidant effect.

Antihypertensive medication, such as diuretic, β-blocker, angiotensin converting enzyme inhibitor and non-losartan angiotensin II receptor blocker have an effect of increasing blood

uric acid concentrations, while other medication, such as calcium channel blocker and losartan, have an opposite effect in hypertensive patients.[21] The Atherosclerosis Risk in Communities (ARIC) study of 13,413 American men and women aged 45–64 years with a 12.6-year follow-up reported a positive association of serum uric acid levels with risk of ischemic stroke in non-users of diuretic, but not in the users; the multivariable hazard ratios (95%CIs) of ischemic stroke for the highest (≥6.9 mg/dL) versus lowest quartile (≤4.8 mg/dL) of serum uric acid were 1.49 (1.00–2.23) in non-users of diuretic, and 0.73 (0.40–1.34) in the users.[15] In Japan during the 1980s, calcium channel blocker and angiotensin converting enzyme inhibitor were approved by the Ministry of Health, Labour and Welfare, and selected as first choice drugs of hypertension treatment.[30] Those drugs were likely to induce decreased or elevated serum uric acid levels and could weak the association of serum uric acid levels with risk of stroke.

The potential mechanisms underlying the positive association of elevated uric acid levels with risk of stroke remains uncertain, although several possibilities have been proposed. First, elevated uric acid levels were associated with increased mean platelet volume,[31] vascular endothelial function,[32] vascular smooth muscle cell proliferation and inflammation,[33] thereby increasing the risk of ischemic stroke. Second, uric acid-induced microvascular injury, e.g., vascular smooth muscle cell proliferation, could lead to pre-glomerular vascular disease and elevated blood pressure.[4–6] Animal studies found that once microvascular injury occurred, hypertension turned to salt-driven and was independent of uric acid,[34] while uric acid continued

to cause pre-glomerular vascular disease even under diuretic treatment.[35] These findings suggested that uric acid-induced microvascular disease other than hypertension may account for the increased risk of stroke. Third, uric acid has a powerful free radical scavenging capacity against oxidative stress.[36] A nested case-control study of 150 cases with elevated carotid intimal-medial thickness and 150 age-sex-matched controls within the ARIC study cohort showed that atherosclerosis cases had higher oxygen radical absorbance capacities than controls, and this difference was explained mostly by higher serum uric acid levels.[7] Such a protective effect might mark the positive association of serum uric acid levels with risk of stroke in men partly due to the higher serum uric acid levels compared to those in women.

As for strengths of our study, we used incident cases of stroke and its types as the target endpoint because serum uric acid may be more directly associated with it rather than fatal outcome. In addition, we analyzed these associations stratified by antihypertensive medication use or not, which allowed us to investigate these sex-specific associations among subjects with pharmacologically inducted hyperuricemia.

Our study has several potential limitations. The single measurement of serum uric acid at baseline would make the association bias toward to null due to the random measurement variations. Therefore, the real association would be greater than that we reported. We have no data of use of diuretic or other type-specific antihypertensive medication, so we could not investigate the impact of medication-induced elevated or decreased serum uric acid levels on

risk of stroke.

In conclusion, elevated serum uric acid levels are independent predictors for total stroke in women, but not in men of general Japanese population. The positive association in women was mostly attributable to ischemic stroke, and more pronounced among non-users or users of antihypertensive medication.

Appendix

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Competing Interest

None declared.

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Table 1. Baseline characteristics of subjects according to quintiles of serum uric acid.

	Serum uric acid quintiles					P for
	Q1 (low)	Q2	Q3	Q4	Q5 (high)	difference
Men						
No. at risk	1062	1085	1107	930	1051	
Range of serum uric acid, mg/dL	0.7–4.6	4.7–5.3	5.4–5.9	6.0–6.6	6.7–11.2	
Median serum uric acid, mg/dL	4.1	5.0	5.6	6.3	7.2	
Age, year	56.7 (0.3)	55.8 (0.3)	53.8 (0.3)	55.2 (0.3)	55.2 (0.3)	<0.001
Body mass index, kg/m^2	22.1 (0.1)	22.5 (0.1)	23.0 (0.1)	23.5 (0.1)	23.9 (0.1)	<0.001
Systolic blood pressure, mmHg	131.4 (0.6)	131.7 (0.5)	133.3 (0.5)	135.3 (0.6)	137.8 (0.6)	<0.001
Diastolic blood pressure, mmHg	79.5 (0.4)	80.8 (0.3)	81.6 (0.3)	83.3 (0.4)	85.2 (0.4)	<0.001
Antihypertensive medication use, %	10.4	9.3	11.2	16.0	22.7	<0.001
Atrial fibrillation, %	1.0	0.9	0.7	0.8	2.2	0.006
Serum total cholesterol, mmol/L	4.74 (0.03)	4.84 (0.03)	4.85 (0.03)	4.95 (0.03)	5.05 (0.03)	<0.001
Triglyceride, mmol/L	1.50 (0.04)	1.61 (0.04)	1.74 (0.04)	1.90 (0.04)	2.21 (0.04)	<0.001
eGFR, ml/min per 1.73 mm^2	88.4 (0.5)	85.9 (0.5)	81.9 (0.5)	78.8 (0.6)	73.5 (0.5)	<0.001
Diabetes mellitus, %	10.0	7.8	8.0	7.4	7.2	<0.001
Current smokers, %	65.6	65.9	60.2	53.1	56.1	<0.001
Ethanol intake, g/day	28.0 (0.9)	27.9 (0.8)	27.6 (0.8)	29.8 (0.9)	33.2 (0.9)	<0.001
Women						
No. at risk	1699	1614	1638	1548	1686	
Range of serum uric acid, mg/dL	0.7–3.5	3.6–4.0	4.1–4.5	4.6–5.1	5.2–10.3	
Median serum uric acid, mg/dL	3.2	3.8	4.3	4.8	5.7	
Age, year	51.4 (0.2)	52.8 (0.2)	54.1 (0.2)	56.2 (0.2)	58.8 (0.2)	<0.001
Body mass index, kg/m^2	22.4 (0.1)	22.8 (0.1)	23.3 (0.1)	23.7 (0.1)	24.8 (0.1)	<0.001
Systolic blood pressure, mmHg	129.0 (0.4)	130.2 (0.4)	131.2 (0.4)	132.6 (0.4)	135.3 (0.4)	<0.001
Diastolic blood pressure, mmHg	76.3 (0.3)	77.4 (0.3)	78.8 (0.3)	79.6 (0.3)	81.7 (0.3)	<0.001
Antihypertensive medication use, %	8.6	11.4	13.1	15.1	28.2	<0.001
Atrial fibrillation, %	0.5	0.6	0.3	0.2	0.4	0.54
Serum total cholesterol, mmol/L	5.00 (0.02)	5.12 (0.02)	5.18 (0.02)	5.28 (0.02)	5.45 (0.02)	<0.001
Triglyceride, mmol/L	1.27 (0.02)	1.38 (0.02)	1.50 (0.02)	1.65 (0.03)	1.92 (0.03)	<0.001
eGFR, ml/min per 1.73 mm^2	94.7 (0.5)	88.1 (0.5)	85.5 (0.5)	82.2 (0.5)	75.7 (0.5)	<0.001
Diabetes mellitus, %	4.9	3.9	4.8	4.4	4.6	0.63
Current smokers, %	6.0	8.6	7.9	8.3	11.3	0.03
Ethanol intake, g/day	1.1 (0.2)	1.0 (0.2)	1.4 (0.2)	1.8 (0.2)	1.7 (0.2)	0.006
Postmenopausal, %	58.8	61.7	63.6	66.2	68.2	<0.001

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

eGFR, estimated glomerular filtration rate.

Table 2. Age–, community–adjusted and multivariable hazard ratios (HRs, 95%CIs) of total stroke and its types according to quintiles of serum uric acid.

	Serum uric acid quintiles					P for trend	1SD increment[§]
	Q1 (low)	Q2	Q3	Q4	Q5 (high)		
Men							
No. at risk	1062	1085	1107	930	1051		
Person-years	19,919	21,252	22,034	17,857	19,799		
Total stroke							
No. of events	96	102	91	97	102		
Age- and community-adjusted HR (95%CI)	1.00	1.03 (0.78–1.37)	1.00 (0.75–1.33)	1.22 (0.92–1.62)	1.22 (0.92–1.62)	0.08	1.10 (1.01−1.21)
Multivariable HR (95%CI)	1.00	1.03 (0.78–1.36)	0.95 (0.71–1.27)	1.10 (0.82–1.48)	1.02 (0.74–1.35)	0.89	1.02 (0.92−1.13)
Intraparenchymal hemorrhage							
No. of events	19	21	23	21	15		
Age- and community-adjusted HR (95%CI)	1.00	1.07 (0.57–1.98)	1.24 (0.67–2.29)	1.36 (0.73–2.54)	0.91 (0.46–1.81)	0.92	0.99 (0.80−1.22)
Multivariable HR (95%CI)	1.00	1.06 (0.57–1.98)	1.23 (0.66–2.29)	1.26 (0.67–2.41)	0.83 (0.40–1.72)	0.83	0.95 (0.75−1.19)
Subarachnoid hemorrhage							
No. of events	7	4	5	10	7		
Age- and community-adjusted HR (95%CI)	1.00	0.52 (0.15–1.77)	0.63 (0.20–1.99)	1.59 (0.60–4.20)	1.03 (0.36–2.96)	0.40	1.17 (0.82–1.69)
Multivariable HR (95%CI)	1.00	0.53 (0.15–1.83)	0.66 (0.20–2.13)	1.96 (0.70–5.47)	1.19 (0.38–3.75)	0.27	1.22 (0.83–1.80)
Ischemic stroke							
No. of events	69	74	62	65	77		
Age- and community-adjusted HR (95%CI)	1.00	1.05 (0.76–1.46)	0.96 (0.68–1.36)	1.13 (0.80–1.59)	1.29 (0.93–1.80)	0.11	1.13 (1.01−1.26)
Multivariable HR (95%CI)	1.00	1.04 (0.74–1.45)	0.89 (0.63–1.26)	1.01 (0.71–1.44)	1.00 (0.70–1.41)	0.94	1.02 (0.91−1.15)
Women							
No. at risk	1699	1614	1638	1548	1686		
Person-years	37,083	35,060	35,780	32,845	33,905		
Total stroke							
No. of events	75	80	105	104	166		
Age- and community-adjusted HR (95%CI)	1.00	1.05 (0.76–1.44)	1.24 (0.92–1.67)	1.20 (0.89–1.62)	1.61 (1.22–2.13)	<0.001	1.17 (1.08−1.26)
Multivariable HR (95%CI)	1.00	1.02 (0.74–1.40)	1.20 (0.89–1.63)	1.15 (0.84–1.56)	1.45 (1.07–1.96)	0.007	1.12 (1.03–1.22)
Intraparenchymal hemorrhage							
No. of events	22	14	21	30	36		
Age- and community-adjusted HR (95%CI)	1.00	0.64 (0.33–1.26)	0.88 (0.48–1.60)	1.25 (0.71–2.18)	1.28 (0.74–2.20)	0.08	1.21 (1.03−1.42)
Multivariable HR (95%CI)	1.00	0.64 (0.32–1.25)	0.86 (0.47–1.59)	1.22 (0.68–2.18)	1.20 (0.65–2.20)	0.18	1.19 (0.99−1.42)
Subarachnoid hemorrhage							
No. of events	13	11	13	15	28		
Age- and community-adjusted HR (95%CI)	1.00	0.87 (0.39–1.94)	0.97 (0.45–2.09)	1.14 (0.54–2.42)	1.89 (0.96–3.73)	0.02	1.25 (1.01−1.54)
Multivariable HR (95%CI)	1.00	0.81 (0.36–1.81)	0.85 (0.39–1.86)	0.99 (0.45–2.15)	1.46 (0.69–3.09)	0.15	1.15 (0.90–1.45)
Ischemic stroke							
No. of events	39	55	70	55	101		
Age- and community-adjusted HR (95%CI)	1.00	1.36 (0.90–2.05)	1.54 (1.04–2.28)	1.16 (0.77–1.76)	1.77 (1.21–2.58)	0.008	1.11 (1.00–1.23)
Multivariable HR (95%CI)	1.00	1.33 (0.88–2.02)	1.52 (1.02–2.26)	1.12 (0.73–1.72)	1.61 (1.07–2.41)	0.07	1.06 (0.95–1.18)

[§]1 SD increment of serum uric acid was 1.3 mg/dL in men and 1.0 mg/dL in women.

Q1: 0.7–4.6 mg/dL, Q2: 4.7–5.3 mg/dL, Q3: 5.4–5.9 mg/dL, Q4:6.0–6.6 mg/dL, Q5: 6.7–11.2 mg/dL in men; Q1: 0.7–3.5 mg/dL, Q2: 3.6–4.0 mg/dL, Q3: 4.1–4.5 mg/dL, Q4: 4.6–5.1 mg/dL, Q5: 5.2–10.3 mg/dL in women.

Multivariable hazard ratio adjusted for age, community, body mass index, cigarette smoking status, alcohol intake status, systolic blood pressure, atrial fibrillation, serum total cholesterol, serum triglycerides, estimated glomerular filtration rate, diabetes mellitus, antihypertensive medication use, and in women, menopausal status.

Table 3. Multivariable hazard ratios (HRs, 95%CIs) of total and ischemic strokes according to quintiles of serum uric acid, stratified by antihypertensive medication use or not.

	Antihypertensive medication non-user							Antihypertensive medication user							
	Serum uric acid quintiles					P for trend	1 SD increment[§]	Serum uric acid quintiles					P for trend	1 SD increment[§]	P for interaction[¶]
	Q1 (low)	Q2	Q3	Q4	Q5 (high)			Q1 (low)	Q2	Q3	Q4	Q5 (high)			
Men															
No. of risk	932	976	1001	783	819			130	109	106	147	232			
Person-years	18,032	19,502	20,313	15,360	16,094			1,887	1,750	1,720	2,496	3,705			
Total stroke															
No. of events	73	83	75	74	59			24	19	16	23	43			
Multivariable HR (95%CI)	1.00	1.09 (0.79-1.50)	1.03 (0.74-1.43)	1.22 (0.87-1.71)	0.93 (0.65-1.35)	0.97	1.01(0.90-1.12)	1.00	0.80 (0.43-1.52)	0.74 (0.38-1.48)	0.81 (0.45-1.48)	1.04 (0.60-1.79)	0.73	1.05 (0.87-1.29)	0.98
Ischemic stroke															
No. of events	54	60	50	46	41			16	14	12	19	36			
Multivariable HR (95%CI)	1.00	1.08 (0.74-1.56)	0.92 (0.62-1.37)	1.01 (0.68-1.52)	0.85 (0.55-1.31)	0.44	0.97 (0.85-1.11)	1.00	0.89 (0.41-1.91)	0.83 (0.38-1.80)	1.00 (0.50-2.01)	1.31 (0.69-2.46)	0.36	1.15 (0.92-1.43)	0.32
Women															
No. of risk	1596	1456	1433	1298	1149			103	158	205	250	537			
Person-years	35,203	31,939	31,667	27,917	24,028			1,881	3,121	4,113	4,929	9,877			
Total stroke															
No. of events	63	62	83	78	89			12	18	22	26	77			
Multivariable HR (95%CI)	1.00	1.00 (0.70-1.42)	1.30 (0.93-1.82)	1.17 (0.83-1.66)	1.46 (1.02-2.09)	0.02	1.11 (1.00-1.24)	1.00	0.96 (0.46-2.03)	0.86 (0.42-1.76)	0.87 (0.42-1.77)	1.23 (0.64-2.36)	0.16	1.15 (0.97-1.37)	0.87
Ischemic stroke															
No. of events	32	41	56	41	52			7	14	14	14	49			
Multivariable HR (95%CI)	1.00	1.28 (0.80-2.05)	1.74 (1.12-2.70)	1.16 (0.72-1.88)	1.62 (1.00-2.63)	0.12	1.06 (0.91-1.22)	1.00	1.49 (0.59-3.80)	1.05 (0.41-2.67)	0.88 (0.34-2.29)	1.55 (0.66-3.65)	0.23	1.09 (0.87-1.35)	0.95

[§]1 SD increment of serum uric acid was 1.2 mg/dL in men and 1.0 mg/dL in women of antihypertensive medication non-user, and 1.5 mg/dL in men and 1.2 mg/dL in women of antihypertensive medication user.

[¶]The P value means an interaction of antihypertensive medication use and serum uric acid levels on risk of each event.

Q1: 0.7–4.6 mg/dL, Q2: 4.7–5.3 mg/dL, Q3: 5.4–5.9 mg/dL, Q4:6.0–6.6 mg/dL, Q5: 6.7–11.2 mg/dL in men; Q1: 0.7–3.5 mg/dL, Q2: 3.6–4.0 mg/dL, Q3: 4.4–4.5 mg/dL, Q4: 4.6–5.1 mg/dL, Q5: 5.2–10.3 mg/dL in women.

Multivariable hazard ratio adjusted for age, community, body mass index, cigarette smoking status, alcohol intake status, systolic blood pressure, atrial fibrillation, serum total cholesterol, serum triglycerides, estimated glomerular filtration rate (eGFR), diabetes mellitus and in women, menopausal status.