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Letter to the Editor

Association of Hypertension and Subclinical Organ Damage With Mortality Due to Stroke and Its Subtypes

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Dear Sir:

The relationship between hypertension and cardiovascular diseases has been consistently observed,[1-4] as has the relationship between cardiovascular diseases and hypertensive organ damage, indicated by electrocardiographic (ECG) changes, funduscopic changes, and chronic kidney disease.[5] However, few studies have comprehensively examined such risk factors for stroke. We sought to elucidate the association between risk factors assessed during screening examinations, including markers of hypertensive subclinical organ damage, and the risk of mortality attributed to total stroke and its subtypes, including subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke, in Japanese residents.

The Ibaraki Prefectural Health Study comprised participants aged 40–79 years who underwent a health checkup in 1993 for health education and policymaking purposes.[6] The 93,651 enrolled participants were followed up until 2016. Markers of hypertensive subclinical organ damage were defined as follows: funduscopic changes (Keith-Wagener-Barker classification ≥grade 1), resting ECG ST-T changes diagnosed by well-trained physicians, proteinuria ≥1+, and low estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. We calculated the population attributable fraction (PAF) to assess the contribution of each risk factor to mortality due to stroke or its subtypes, the hazard ratio (HR) of mortality due to stroke and its subtypes associated with four types of subclinical organ damage, with and without hypertension, and the trend across categories based on the count of subclinical organ damage markers, using Cox proportional hazard models. Detailed methods are provided in Supplementary Methods. The protocol of the Ibaraki Prefectural Health Study was approved by the Ethics Committees of Ibaraki Prefecture (R5-1) and the University of Tsukuba (1628-4). Informed consent was obtained from community representatives to conduct this epidemiological study.

During a 23.1-year median follow-up, there were 3,858 deaths due to total stroke, including 490 from subarachnoid hemorrhage, 905 from intracerebral hemorrhage, and 2,397 from ischemic stroke. Table 1 shows the age-adjusted means and prevalence of baseline characteristics of the patients who died due to stroke and its subtypes and of those who remained stroke-free. Compared with non-cases, those who died from total stroke had a significantly higher prevalence of hypertension, ECG ST-T changes, funduscopic changes, proteinuria, and low eGFR. Similar trends were observed for stroke subtypes. As shown in Table 2 and Supplementary Table 1, atrial fibrillation was strongly associated with the risk of mortality due to total stroke, intracerebral hemorrhage, and ischemic stroke. Current smoking status

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Table 1. Age-adjusted baseline characteristics of participants developing stroke or its subtypes and of participants remaining free of stroke

	Men					Women				
	Total stroke (n=1,620)	Subarachnoid hemorrhage (n=124)	Intracerebral hemorrhage (n=377)	Ischemic stroke (n=1,093)	Noncases (n=30,194)	Total stroke (n=2,238)	Subarachnoid hemorrhage (n=366)	Intracerebral hemorrhage (n=528)	Ischemic stroke (n=1,304)	Noncases (n=59,599)
Age* (yr)	67.3§	62.5‡	65.2§	68.6§	60.2	67.9§	64.5§	66.2§	69.4§	57.7
Systolic BP (mm Hg)	141.3§	138.7	141.2‡	141.7§	136.2	139.7§	140.1§	139.4‡	139.8	131.8
Diastolic BP (mm Hg)	81.6‡	81.1	82.7§	81.2	80.9	79.4†	81.1§	80.4§	78.5‡	77.7
Hypertension (%)	69.5§	58.9	66.8‡	71.5§	54.9	69.5§	66.7§	64.8‡	72.5§	44.9
Non HDL-C (mg/dL)	136.5†	135.5	132.8§	138.2	140.8	155.2§	153.3†	151.4§	157.2§	151.0
Low (%)	8.3‡	10.5‡	10.6§	7.1	5.9	2.0‡	2.5	2.1	1.8‡	2.7
High (%)	17.8	16.1	17.5	18.3	20.4	35.0§	33.6	30.5§	37.3‡	30.2
HDL-C (mg/dL)	53.2	53.2	54.4‡	52.6	52.4	55.3	55.8	55.4	55.2	56.8
Low HDL-C (%)	18.3	19.4	17.8	18.6	18.7	12.4	11.8	11.4†	12.8	9.0
Hypertriglyceridemia (%)	10.0	9.7	9.8	10.0	13.6	9.7‡	9.3	10.4	9.3‡	9.6
Hyperglycemia (%)	26.7‡	27.4	26.3	26.5†	21.9	17.3	11.2‡	16.5	19.5‡	12.6
Atrial fibrillation (%)	3.0§	0.0	2.4†	3.7§	1.0	2.2§	0.6	1.3†	3.1§	0.3
BMI (kg/m^2)	22.9†	22.8	22.6§	22.9	23.3	23.8	23.5†	23.8	23.8	23.6
Body weight										
Over (%)	23.6	25.0	22.0†	24.1	28.5	34.6	30.6	34.7	35.4	31.4
Under (%)	5.7	4.8	7.7‡	5.1	4.2	5.5‡	4.9	4.6	5.9‡	3.8
Smoking status										
Past (%)	26.8§	17.7‡	26.0†	28.2‡	27.4	0.7	1.1	0.4	0.7	0.7
Current (%)	50.9§	61.3‡	54.9‡	47.9	50.4	4.6‡	6.8‡	4.7	3.8	4.8
Drinking status										
Past (%)	7.4	8.1	6.6	7.5	5.6	0.3	0.6	0.2	0.3	0.2
Current (%)	61.1	61.3	61.5	60.9	65.6	6.5	6.8‡	5.1	6.8	9.6
ECG ST-T changes (%)	2.9‡	1.6	1.3	3.7§	1.4	4.9§	4.6‡	4.0†	5.1§	1.8
Funduscopic changes (%)	42.6§	36.3†	37.4‡	44.7§	26.0	43.1§	39.1‡	40.5‡	45.5‡	22.8
Proteinuria (%)	4.1	4.8	3.5	4.0	3.3	3.1‡	3.3	2.7	3.3†	1.8
Low eGFR (%)	11.4†	8.1	11.4†	11.3	5.8	15.6§	9.3	13.8†	18.1‡	5.5

Values are means or prevalence, adjusted for age.
BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate.
*Unadjusted; †P<0.1; ‡P<0.05; §P<0.001 (difference from noncases).

was significantly associated with mortality due to subarachnoid hemorrhage. In contrast, the PAF of mortality from total stroke was the highest for hypertension (21%). A similar tendency was observed for mortality due to subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke (23%, 18%, and 23%, respectively). Among hypertensive patients (Table 3 and Supplementary Table 2), mortality from total stroke was significantly associated with all four markers when compared with non-hypertensive individuals without subclinical organ damage: multivariable HR (95% confidence interval [CI]) were 2.45 (2.05–2.94) for ECG ST-T changes, 1.82 (1.66–2.00) for funduscopic changes, 1.78 (1.46–2.17) for proteinuria, and 1.78 (1.58–2.01) for low eGFR. Although funduscopic changes, proteinuria, and low eGFR were associated with stroke mortality, even among non-hypertensive individuals, each multivariable HR was lower than that among hypertensive patients. In addition, the number of markers was linearly associated with the risk of mortality from stroke and stroke type in individuals with hypertension. Notably, these results were generally similar when analyzed separately for men and women.

Our results highlight the association of hypertension and subclinical organ damage with mortality due to stroke and its subtypes. The PAF for hypertension of total stroke death (approximately 20%) was consistent with that in the other Asia-Pacific regions.[7] Despite notable regional variations in the impact of hypertension on fatal stroke risk, globally, hypertension was consistently the leading risk factor with the highest PAF for cardiovascular mortality, especially for stroke.[1] It is noteworthy that

Table 2. Hazard ratios and population attributable fractions of total stroke

	No. at risk	Person-years	No. of cases	Crude incidence, per 1,000 person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)*	PAF (%) (95% CI)
Hypertension	46,010	873,269	2,682	3.1	1.42 (1.32–1.52)	1.45 (1.35–1.55)	21 (17–25)
Non HDL-C							
Low	3,559	65,492	179	2.7	1.55 (1.33–1.80)	1.49 (1.28–1.74)	2 (1–2)
High	25,216	50,2764	1,071	2.1	0.96 (0.90–1.04)	0.97 (0.90–1.05)	-
Low HDL-C	11,608	222,267	574	2.6	1.12 (1.02–1.22)	1.15 (1.05–1.27)	2 (1–3)
Hypertriglyceridemia	10,167	203,174	379	1.9	0.93 (0.84–1.03)	0.90 (0.81–1.01)	-
Hyperglycemia	14,916	278,868	820	2.9	1.23 (1.14–1.33)	1.19 (1.10–1.29)	3 (2–5)
Atrial fibrillation	565	8,067	99	12.3	3.35 (2.74–4.09)	3.39 (2.77–4.15)	2 (1–2)
Body weight							
Over	28,472	572,126	1,158	2.0	1.01 (0.94–1.08)	0.97 (0.90–1.04)	-
Under	3,730	64,479	216	3.3	1.30 (1.13–1.49)	1.31 (1.14–1.51)	1 (1–2)
Smoking status							
Past	9,141	168,988	449	2.7	0.94 (0.82–1.07)	0.92 (0.81–1.05)	-
Current	19,005	348,949	927	2.7	1.37 (1.24–1.53)	1.34 (1.21–1.49)	6 (4–8)
Drinking status							
Past	1,927	30,727	127	4.1	1.15 (0.95–1.39)	1.09 (0.90–1.32)	-
Current	26,649	512,905	1,136	2.2	1.06 (0.97–1.16)	1.00 (0.91–1.09)	-

PAF was calculated only when the HR with adjustment for age and sex was significant (P<0.05).
HR, hazard ratio; CI, confidence interval; PAF, population attributable fraction; HDL-C, high-density lipoprotein cholesterol; CI, confidence interval.
*Adjusted for age, sex, hypertension, low non HDL-C, high non HDL-C, low HDL-C, hypertriglyceridemia, hyperglycemia, atrial fibrillation, body weight, and smoking and drinking status.

these markers were also associated with the risk of stroke mortality among non-hypertensive individuals, although the magnitude of association was smaller than that among hypertensive individuals. Our previous study showed that mild hypertensive retinopathy was associated with a higher risk of stroke mortality, regardless of the presence of hypertension,[8] and the present study extended these findings by showing that the association was also applicable to other types of subclinical organ damage with a longer follow-up. Subclinical organ damage may reflect masked, borderline, or past hypertension. Thus, screening for these markers may be useful for non-hypertensive individuals to assess the future risk of stroke mortality.

This is the first study to examine the association of hypertension and subclinical organ damage with the risk of mortality due to stroke and its subtypes in Asia. Large-scale cohort settings allowed for the analysis of stroke type and hypertension status. However, this study had several limitations. First, the study population was limited to Japanese individuals; therefore, generalizability should be considered with caution. However, evidence based on the population, including the high incidence of stroke, could provide a reference for other countries affected by stroke epidemics. Second, because participation in health checkups was voluntary, the healthy participant effect was unavoidable. Furthermore, we used data for each risk factor measured only at baseline. During a follow-up period of >20 years, participants characteristics, such as blood pressure, may have changed due to lifestyle modifications or treatment conditions. This may have weakened the association with stroke mortality owing to dilution bias. Finally, owing to its observational nature, this study could not prove that controlling hypertension could prevent stroke. Rather, it highlights the importance of screening for cardiovascular risk factors, including hypertension-related organ damage.

In conclusion, we found significant associations between hypertension, along with markers of subclinical organ damage, and stroke mortality. Screening examinations including hypertensive markers may contribute to the prevention of mortality from any type of stroke in normotensive and hypertensive patients.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.01683.

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Table 3. Hazard ratios of stroke and its subtypes according to the markers of subclinical organ damage and the number of them among hypertensive individuals among hypertensive and nonhypertensive individuals

	No. at risk	Person-years	No. of cases	Crude incidence, per 1,000 person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)*
Nonhypertensive individuals without subclinical organ damage	39,338	820,199	730	0.9	1.00	1.00
Nonhypertensive individuals with						
ECG ST-T changes	433	8,055	23	2.9	1.54 (1.02–2.33)	1.51 (1.00–2.28)
Funduscopic changes	6,511	123,399	363	2.9	1.36 (1.20–1.55)	1.36 (1.20–1.54)
Proteinuria	596	11,024	26	2.4	1.64 (1.11–2.42)	1.62 (1.10–2.39)
Low eGFR	1,532	26,037	108	4.1	1.28 (1.05–1.56)	1.26 (1.03–1.54)
Hypertensive individuals with						
ECG ST-T changes	1,241	21,278	134	6.3	2.50 (2.09–3.00)	2.45 (2.05–2.94)
Funduscopic changes	16,567	298,931	1,292	4.3	1.78 (1.62–1.95)	1.82 (1.66–2.00)
Proteinuria	1,616	26,419	109	4.1	1.83 (1.50–2.22)	1.78 (1.46–2.17)
Low eGFR	4,055	65,209	426	6.5	1.78 (1.58–2.00)	1.78 (1.58–2.01)
No. of subclinical organ damage markers†						
0	26,066	516,439	1,110	2.1	1.37 (1.24–1.50)	1.41 (1.28–1.55)
1	16,784	307,041	1,233	4.0	1.77 (1.61–1.95)	1.83 (1.66–2.01)
2	2,804	44,812	292	6.5	2.17 (1.89–2.50)	2.21 (1.91–2.55)
3+	356	4,977	47	9.4	3.19 (2.37–4.30)	3.09 (2.29–4.18)
HR for an increase of 1 category number					1.30 (1.23–1.37)	1.29 (1.23–1.37)

HR, hazard ratio; CI, confidence interval; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol.
*Adjusted for age, sex, low non HDL-C, high non HDL-C, low HDL-C, hypertriglyceridemia, hyperglycemia, atrial fibrillation, body weight, and smoking and drinking status; †Indicates the number of subclinical organ damage markers with hypertension comprising ECG ST-T changes, funduscopic changes, proteinuria, or low eGFR. Groups with 3 or more markers were included in groups with 2 markers only when they comprised fewer than 10 cases.

pan (H20-Junkankitou [Seishuu]-Ippan-013, H23-Junkankitou [Seishuu]-Ippan-005, H26-Junkankitou [Seisaku]-Ippan-001, H29-Junkankitou [Seishuu]-Ippan-003, JP20FA1002 and JP-23FA1006), and the Japan Society for the Promotion of Science Kakenhi grant numbers JP17H04121 and JP21H03194.

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: KA, KY. Study design: KA, KY. Methodology: KA, KY, TS, HI, FI. Data collection: KY, TS, FI. Investigation: all authors. Statistical analysis: KA. Writing—original draft: KA. Writing—review & editing: KY, TS, TK, HI, FI. Funding acquisition: KY, TS, HI. Approval of final manuscript: all authors.

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Supplementary Methods

Study cohort

Ibaraki Prefecture is located in the mid-eastern region of Japan, northeast of Tokyo, with a population of approximately 28 million people. The area consists of urban, rural, and predominantly agricultural regions and included 87 municipalities as of 1993. To better understand the relationship between risk factors and disease, the Ibaraki Prefectural Government launched a community-based large cohort study called the Ibaraki Prefectural Health Study. This initiative aimed to support health education and inform policymaking.

The study cohort consisted of residents aged 40 to 79 years who participated in a health checkup offered by their local municipality in 1993. At the time, all residents over 40 were eligible for these checkups as part of the local health care program under the health care system for the elderly. A total of 97,043 participants from 38 municipalities (as of 1993) were initially involved in the study. Of these, 3,025 participants were excluded due to incomplete health checkup data (n=2,106) or a history of stroke (n=919). Additionally, individuals with unknown causes of death (n=33) were excluded at the end of the follow-up period.

Ultimately, 93,651 participants (31,814 men and 61,837 women) were included in the study. The participants were followed until December 31, 2016, using data from death certificates.

Baseline measurements

During the health checkups, participants' height (measured with socks on) and weight (measured while wearing light clothing) were recorded. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Blood pressure was measured by a trained observer using a standard mercury sphygmomanometer. Blood samples were collected from participants in a seated position, with approximately 83% of the samples drawn in a non-fasting state (<8 h since the last meal), as fasting was not required at baseline.

Serum triglyceride levels were determined using enzymatic methods, while high-density lipoprotein cholesterol (HDL-C) levels were measured using the phosphotungstic acid magnesium method. Plasma glucose levels were assessed using the glucose oxidase electrode method, and serum creatinine levels were measured using the Jaffe method. The serum creatinine values were adjusted to align with enzymatic methods using the following equation: serum creatinine by enzyme method (mg/dL)=1.0085× serum creatinine by the Jaffe method (mg/dL) - 0.265. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese version of the Chronic Kidney Disease Epidemiology Collaboration equation.[1]

A standard 12-lead electrocardiogram (ECG) was performed while participants were lying in a relaxed position. Experienced physicians evaluated the ECG signals. Urinalysis was conducted using a dipstick to assess hematuria, glycosuria, and proteinuria, with urine samples collected freshly and spontaneously. Retinal photographs were taken of one eye (usually the right eye) using a non-mydriatic fundus camera after 5 minutes of darkness adaptation. Hypertensive retinopathy was assessed by trained physicians and examiners using the Keith-Wagener-Barker classification system.[2] Electrocardiographic diagnoses were also conducted by trained physicians.

Face-to-face interviews gathered information on participants' smoking and drinking habits, medical history, and treatments for stroke, heart disease, hypertension, dyslipidemia, and diabetes mellitus.

There are potential subclinical organ damages to be considered in the management of hypertension.[3-5] Of these, we selected the following four markers because they could be noninvasively assessed during health checkups. Funduscopic changes, including retinal microvascular abnormalities, are considered useful indicators that reflect the development of hypertension.[6] Resting ECG ST-T changes may reflect end-organ defects of long-term hypertension.[7] Elevated blood pressure leads to the progression of chronic kidney disease,[8-10] which can be detected by proteinuria and low eGFR.[11]

Follow-up surveillance

The participants were followed until the end of 2016 to track either relocation from the community or death. Information on the date of relocation or death was obtained from local governments. Death registrations were managed by the Ministry of Health, Labor and Welfare, with the underlying causes of death coded for the National Vital Statistics using the International Classification of Diseases and Related Health Problems (ICD), 9th revision (1993–1994) and 10th revision (1995–2016).

Deaths from total stroke were identified using ICD-9 codes 430–438 and ICD-10 codes I60–I69. Subarachnoid hemorrhage was classified under ICD-9 code 430 and ICD-10 codes I60 and I69.0. Intracerebral hemorrhage was identified using ICD-9 codes 431–432 and ICD-10 codes I61 and I69.1. Ischemic stroke was classified under ICD-9 codes 433–434 and 437.7 and ICD-10 codes I63 and I69.3.

Statistical analysis

Analysis of covariance or logistic regression analysis was used to compare age-adjusted mean values and the prevalence of baseline health checkup parameters (1993) between participants who died from stroke or its subtypes and those who remained stroke-

free. Cox proportional hazards models were employed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for cause-specific mortality. The reference group consisted of individuals without each respective risk factor.

Person-years were calculated by summing the duration of individual follow-up until the time of death, relocation from the community, or the end of the follow-up period, whichever occurred first. In the first model for HR calculations, adjustments were made for age and sex. In the second, multivariable-adjusted model, additional adjustments were made for the following factors: hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or current use of antihypertensive drugs), low non-HDL-C (<2.33 mmol/L), high non-HDL-C (≥4.40 mmol/L or current use of cholesterol-lowering drugs), low HDL-C (<1.03 mmol/L), hypertriglyceridemia (fasting serum triglycerides ≥1.69 mmol/L or non-fasting serum triglycerides ≥2.82 mmol/L), hyperglycemia (fasting serum glucose ≥6.11 mmol/L, non-fasting serum glucose ≥7.77 mmol/L, or current use of antidiabetic drugs), atrial fibrillation (diagnosed by trained physicians), overweight (BMI ≥25), underweight (BMI <18.5), past smoking, current smoking, past drinking, and current drinking status.

The population attributable fraction (PAF) was calculated to evaluate the contribution of each risk factor to mortality from stroke and its subtypes, using the standard formula: PAF=prop×(HR−1)/HR, where prop is the proportion of cases in each category, and HR is the multivariable HR for the category.[12] The study also examined the risk of mortality from stroke and its subtypes associated with four subclinical organ damage markers, both with and without hypertension. Non-hypertensive participants without subclinical organ damage served as the reference group. Trend tests were conducted across categories based on the number of subclinical organ damage markers (0, 1, 2, 3, or more). Groups with three or more markers were included in the two-marker group if they consisted of fewer than 10 cases.

All statistical tests were two-sided, and *P*-values <0.05 were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA).

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Supplementary Table 1. Hazard ratios and population attributable fractions of stroke subtypes

	No. at risk	Person-years	No. of cases	Crude incidence, per 1,000 person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)*	PAF (%) (95% CI)
Subarachnoid hemorrhage							
Hypertension	46,010	873,269	317	0.4	1.45 (1.19–1.75)	1.54 (1.26–1.87)	23 (12–32)
Non HDL-C							
Low	3,559	65,492	22	0.3	1.72 (1.11–2.66)	1.65 (1.06–2.56)	2 (0–4)
High	25,216	502,764	143	0.3	0.94 (0.77–1.15)	0.96 (0.78–1.17)	-
Low HDL-C	11,608	222,267	67	0.3	1.14 (0.88–1.48)	1.19 (0.91–1.56)	-
Hypertriglyceridemia	10,167	203,174	46	0.2	0.82 (0.61–1.11)	0.83 (0.60–1.15)	-
Hyperglycemia	14,916	278,868	75	0.3	0.93 (0.73–1.20)	0.91 (0.71–1.17)	-
Atrial fibrillation	565	8,067	2	0.2	0.73 (0.18–2.94)	0.74 (0.19–2.99)	-
Body weight							
Over	28,472	572,126	143	0.2	0.89 (0.73–1.09)	0.86 (0.70–1.06)	-
Under	3,730	64,479	24	0.4	1.21 (0.80–1.84)	1.19 (0.78–1.81)	-
Smoking status							
Past	9,141	168,988	26	0.2	0.84 (0.52–1.36)	0.85 (0.52–1.38)	-
Current	19,005	348,949	101	0.3	1.83 (1.34–2.49)	1.84 (1.34–2.53)	9 (4–14)
Drinking status							
Past	1,927	30,727	12	0.4	1.49 (0.80–2.75)	1.52 (0.82–2.82)	-
Current	26,649	512,905	101	0.2	0.97 (0.73–1.28)	0.89 (0.67–1.18)	-
Intracerebral hemorrhage							
Hypertension	46,010	873,269	594	0.7	1.32 (1.14–1.51)	1.37 (1.18–1.58)	18 (9–25)
Non HDL-C							
Low	3,559	65,492	51	0.8	1.79 (1.35–2.39)	1.74 (1.30–2.33)	2 (1–4)
High	25,216	502,764	227	0.5	0.85 (0.73–0.99)	0.85 (0.72–0.99)	-4 (-9–0)
Low HDL-C	11,608	222,267	127	0.6	1.05 (0.87–1.26)	1.07 (0.88–1.31)	-
Hypertriglyceridemia	10,167	203,174	92	0.5	0.96 (0.78–1.18)	0.98 (0.78–1.23)	-
Hyperglycemia	14,916	278,868	186	0.7	1.20 (1.02–1.41)	1.17 (1.00–1.38)	3 (0–6)
Atrial fibrillation	565	8,067	16	2.0	2.51 (1.53–4.11)	2.56 (1.56–4.21)	1 (0–2)
Body weight							
Over	28,472	572,126	266	0.5	0.97 (0.84–1.12)	0.96 (0.83–1.12)	-
Under	3,730	64,479	53	0.8	1.42 (1.07–1.88)	1.36 (1.02–1.81)	2 (0–3)
Smoking status							
Past	9,141	168,988	100	0.6	1.00 (0.76–1.31)	1.01 (0.77–1.34)	-
Current	19,005	348,949	232	0.7	1.52 (1.23–1.89)	1.52 (1.22–1.89)	9 (4–13)
Drinking status							
Past	1,927	30,727	26	0.8	0.99 (0.65–1.50)	0.95 (0.63–1.44)	-
Current	26,649	512,905	259	0.5	0.93 (0.77–1.12)	0.85 (0.70–1.02)	-
Ischemic stroke							
Hypertension	46,010	873,269	1,726	2.0	1.48 (1.35–1.62)	1.48 (1.35–1.63)	23 (18–28)
Non HDL-C							
Low	3,559	65,492	102	1.6	1.40 (1.15–1.72)	1.36 (1.11–1.66)	1 (0–2)
High	25,216	502,764	686	1.4	1.03 (0.94–1.13)	1.04 (0.95–1.14)	-
Low HDL-C	11,608	222,267	370	1.7	1.14 (1.02–1.28)	1.19 (1.06–1.33)	2 (1–4)
Hypertriglyceridemia	10,167	203,174	230	1.1	0.96 (0.84–1.09)	0.88 (0.76–1.02)	-
Hyperglycemia	14,916	278,868	544	2.0	1.32 (1.20–1.45)	1.26 (1.14–1.39)	5 (3–7)

Supplementary Table 1. Continued

	No. at risk	Person-years	No. of cases	Crude incidence, per 1,000 person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)*	PAF (%) (95% CI)
Atrial fibrillation	565	8,067	80	9.9	3.96 (3.16–4.96)	3.98 (3.18–4.99)	2 (2–3)
Body weight							
Over	28,472	572,126	725	1.3	1.05 (0.96–1.15)	0.99 (0.91–1.09)	-
Under	3,730	64,479	133	2.1	1.24 (1.04–1.48)	1.30 (1.09–1.55)	1 (0–2)
Smoking status							
Past	9,141	168,988	317	1.9	0.91 (0.78–1.06)	0.88 (0.76–1.03)	-
Current	19,005	348,949	574	1.6	1.25 (1.10–1.43)	1.22 (1.07–1.39)	4 (1–7)
Drinking status							
Past	1,927	30,727	86	2.8	1.13 (0.90–1.43)	1.04 (0.82–1.31)	-
Current	26,649	512,905	755	1.5	1.12 (1.01–1.25)	1.07 (0.96–1.20)	2 (-1–5)

PAF was calculated only when the HR with adjustment for age and sex was significant (P<0.05).
HR, hazard ratio; CI, confidence interval; PAF, population attributable fraction; HDL-C, high-density lipoprotein cholesterol.
*Adjusted for age, sex, hypertension, low non HDL-C, high non HDL-C, low HDL-C, hypertriglyceridemia, hyperglycemia, atrial fibrillation, body weight, and smoking and drinking status.

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Supplementary Table 2. Hazard ratios of stroke subtypes according to the markers of subclinical organ damage and the number of them among hypertensive individuals among hypertensive and nonhypertensive individuals

	No. at risk	Person-years	No. of cases	Crude incidence, per 1,000 person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)*
Subarachnoid hemorrhage						
Nonhypertensive individuals without subclinical organ damage	39,338	820,199	116	0.1	1.00	1.00
Nonhypertensive individuals with						
ECG ST-T changes	433	8,055	7	0.9	3.73 (1.75–7.95)	3.85 (1.80–8.21)
Funduscopic changes	6,511	123,399	44	0.4	1.46 (1.03–2.08)	1.48 (1.04–2.10)
Proteinuria	596	11,024	6	0.5	3.10 (1.37–6.99)	3.16 (1.40–7.14)
Low eGFR	1,532	26,037	10	0.4	1.17 (0.61–2.23)	1.18 (0.62–2.25)
Hypertensive individuals with						
ECG ST-T changes	1,241	21,278	12	0.6	2.00 (1.11–3.61)	2.17 (1.20–3.92)
Funduscopic changes	16,567	298,931	144	0.5	1.86 (1.44–2.40)	2.00 (1.55–2.59)
Proteinuria	1,616	26,419	12	0.5	1.97 (1.09–3.55)	2.17 (1.20–3.93)
Low eGFR	4,055	65,209	34	0.5	1.45 (0.99–2.14)	1.54 (1.05–2.28)
No. of subclinical organ damage markers†						
0	26,066	516,439	147	0.3	1.48 (1.15–1.90)	1.58 (1.23–2.04)
1	16,784	307,041	140	0.5	1.89 (1.45–2.46)	2.04 (1.56–2.68)
2+	3,160	49,789	30	0.6	2.12 (1.39–3.24)	2.33 (1.52–3.58)
HR for an increase of 1 category number					1.23 (1.04–1.45)	1.25 (1.06–1.48)
Intracerebral hemorrhage						
Nonhypertensive individuals without subclinical organ damage	39,338	820,199	204	0.2	1.00	1.00
Nonhypertensive individuals with						
ECG ST-T changes	433	8,055	4	0.5	1.11 (0.42–2.99)	1.10 (0.41–2.96)
Funduscopic changes	6,511	123,399	84	0.7	1.33 (1.03–1.71)	1.32 (1.03–1.71)
Proteinuria	596	11,024	9	0.8	2.25 (1.16–4.37)	2.26 (1.16–4.39)
Low eGFR	1,532	26,037	28	1.1	1.56 (1.05–2.32)	1.58 (1.06–2.34)
Hypertensive individuals with						
ECG ST-T changes	1,241	21,278	22	1.0	1.77 (1.15–2.73)	1.79 (1.16–2.78)
Funduscopic changes	16,567	298,931	271	0.9	1.60 (1.33–1.93)	1.67 (1.39–2.02)
Proteinuria	1,616	26,419	18	0.7	1.29 (0.80–2.09)	1.32 (0.81–2.13)
Low eGFR	4,055	65,209	88	1.3	1.78 (1.38–2.28)	1.84 (1.43–2.38)
No. of subclinical organ damage markers†						
0	26,066	516,439	269	0.5	1.33 (1.10–1.60)	1.38 (1.15–1.67)
1	16,784	307,041	257	0.8	1.61 (1.32–1.95)	1.68 (1.38–2.05)
2+	3,160	49,789	68	1.4	2.13 (1.60–2.85)	2.23 (1.66–2.98)
HR for an increase of 1 category number					1.26 (1.12–1.42)	1.26 (1.12–1.42)
Ischemic stroke						
Nonhypertensive individuals without subclinical organ damage	39,338	820,199	396	0.5	1.00	1.00
Nonhypertensive individuals with						
ECG ST-T changes	433	8,055	11	1.4	1.21 (0.66–2.19)	1.16 (0.64–2.11)
Funduscopic changes	6,511	123,399	229	1.9	1.40 (1.19–1.64)	1.39 (1.18–1.63)
Proteinuria	596	11,024	11	1.0	1.15 (0.64–2.09)	1.11 (0.61–2.02)
Low eGFR	1,532	26,037	67	2.6	1.18 (0.92–1.53)	1.15 (0.89–1.49)

Supplementary Table 2. Continued

	No. at risk	Person-years	No. of cases	Crude incidence, per 1,000 person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)*
Hypertensive individuals with						
ECG ST-T changes	1,241	21,278	96	4.5	2.86 (2.31–3.55)	2.72 (2.19–3.37)
Funduscopic changes	16,567	298,931	853	2.9	1.87 (1.66–2.11)	1.89 (1.67–2.13)
Proteinuria	1,616	26,419	76	2.9	1.96 (1.54–2.49)	1.84 (1.44–2.34)
Low eGFR	4,055	65,209	292	4.5	1.78 (1.54–2.06)	1.74 (1.50–2.01)
No. of subclinical organ damage markers†						
0	26,066	516,439	679	1.3	1.41 (1.24–1.60)	1.43 (1.26–1.62)
1	16,784	307,041	818	2.7	1.86 (1.65–2.11)	1.89 (1.66–2.14)
2	2,804	44,812	190	4.2	2.10 (1.76–2.51)	2.07 (1.73–2.49)
3+	356	4,977	39	7.8	3.88 (2.78–5.41)	3.60 (2.58–5.04)
HR for an increase of 1 category number					1.31 (1.23–1.40)	1.29 (1.21–1.38)

Groups with 3 or more markers were included in groups with 2 markers only when they comprised fewer than 10 cases.
HR, hazard ratio; CI, confidence interval; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol.
*Adjusted for age, sex, low non HDL-C, high non HDL-C, low HDL-C, hypertriglyceridemia, hyperglycemia, atrial fibrillation, body weight, and smoking and drinking status; †Indicates the number of subclinical organ damage markers with hypertension comprising ECG ST-T changes, funduscopic changes, proteinuria, or low eGFR.

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