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).

Supplementary References

1. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis* 2010;56:32-38.
2. Walsh JB. Hypertensive retinopathy. Description, classification, and prognosis. *Ophthalmology* 1982;89:1127-1131.
3. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;31:1281-1357.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206-1252.
5. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; Guideline Development Group. Management of hypertension: summary of NICE guidance. *BMJ* 2011;343:d4891.
6. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med* 2004;351:2310-2317.
7. Ohira T, Iso H, Imano H, Kitamura A, Sato S, Nakagawa Y, et al. Prospective study of major and minor ST-T abnormalities and risk of stroke among Japanese. *Stroke* 2003;34:e250-e253.
8. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikemiya Y, Takishita S. Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* 2003;41:1341-1345.
9. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med* 2005;142:342-351.
10. Appel LJ, Wright JT Jr, Greene T, Agodoa LY, Astor BC, Bakris GL, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;363:918-929.
11. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). *Kidney Int* 2005;67:2089-2100.
12. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998;88:15-19.

 https://doi.org/10.5853/jos.2024.01683