Table 3 Baseline Characteristics According to Risk Group Among 4,144 Men and 5,318 Women (NIPPON DATA80: 1980–1994)

	Risk 0	Risk 1–2	Risk 3–4	p (χ^2 or ANOVA)
Men (N=4,144) (% prevalence)	655 (15.8)	2,950 (71.2)	539 (13.0)	
Age (years)	43.7±10.8	51.4±13.2	52.8±13.0	<0.0001
BMI (kg/m^2)	21.4±2.3	22.3±2.7	24.8±3.3	<0.0001
SBP (mmHg)	117±8	141±20	149±18	<0.0001
DBP (mmHg)	73±7	85±12	90±12	<0.0001
BG (mg/dl)	112±12	130±37	157±50	<0.0001
TC (mg/dl)	168±19	184±31	221±28	<0.0001
Smoking (%)	65.5	64.2	55.3	0.0002
Drinking (%)	73.0	75.2	73.5	0.405
Women (N=5,318) (% prevalence)	1,124 (21.1)	3,303 (62.1)	891 (16.8)	
Age (years)	41.5±9.8	52.0±13.1	58.3±11.5	<0.0001
BMI (kg/m^2)	21.3±2.3	22.7±3.0	25.6±4.0	<0.0001
SBP (mmHg)	115±8	134±20	151±20	<0.0001
DBP (mmHg)	71±8	81±11	87±12	<0.0001
BG (mg/dl)	112±11	128±31	154±46	<0.0001
TC (mg/dl)	167±20	190±32	223±29	<0.0001
Smoking (%)	10.0	8.6	8.2	0.291
Drinking (%)	24.8	18.7	17.7	<0.0001

Data are % or mean ± SD.
ANOVA, analysis of variance. Other abbreviations see in Tables 1,2.

Table 4 Hazard Ratios of CHD and Stroke Mortality According to Risk Group Among 4,144 Men and 5,318 Women (NIPPON DATA80: 1980–1994)

	Men				Women			
	Risk 0	Risk 1–2	Risk 3–4	Trend p	Risk 0	Risk 1–2	Risk 3–4	Trend p
Subgroup N	655	2,950	539		1,124	3,303	891	
CHD, N	1	33	8		3	31	10	
/1,000 PY	0.1	0.9	1.2		0.1	0.4	1.7	
HR*	1	3.51 (0.47–26.1)	8.04 (1.03–62.6)	0.0002	1	1.04 (0.31–3.46)	0.75 (0.20–2.78)	0.66
Stroke, N	3	85	30		6	71	31	
/1,000 PY	0.3	2.2	4.4		0.3	0.9	5.1	
HR*	1	2.64 (0.83–8.39)	5.06 (1.53–16.7)	<0.0001	1	1.24 (0.53–2.88)	1.27 (0.52–3.08)	0.53

Hazard ratios (95% confidence interval) are shown.
HR: age, cigarette smoking and alcohol intake were entered as covariates for multivariate analyses.*
/1,000 PY, per 1,000 person-years. Other abbreviations see in Table 2.

trends across risk groups were conducted by assigning an ordinal value to each number risk (0 to 4) and modeling this as a continuous variable in separate Cox proportional hazard models.

All p values were two-tailed, and $p<0.05$ was considered significant. Data are presented as means ± SDs unless stated otherwise.

Results

Principal Components

The results of principal component analysis of the risk factors are shown in Table 1. In men, a 2-component solution explained 60% of the common variance in the data set. The component has large positive loadings (≥0.40) for 3 of the 5 risk factor components, and the second has large positive loadings for 2 of the 5 risk factor components. One component, BMI, shows overlap. In women, a one-component solution explained 40% of the common variance in the data set. The component has large positive loadings for 4 of the 5 risk factors. In both men and women, loadings for glucose were not large.

Cutoff Values for Risk Components

The obtained categorical cutoff values for the risk components by heuristic analyses were BMI: 27 kg/m^2, blood glucose=130 mg/dl, total cholesterol=200 mg/dl, and SBP/DBP=130/85 mmHg for men. Table 2 shows the results of heuristic analyses in men to obtain the cutoff values for the risk components. Only the results of 3 representative categorical values for each component are shown. The prevalence of the risk 3–4 group in %, hazard ratios and p values for CHD and stroke mortality are shown. It can be seen that selecting the cutoff values for the 4 components satisfied prognostic significance for both CHD and stroke mortality in men.

We did not have appropriate cut-offs for the women; therefore, we used the same cut-offs as for the men.

Baseline Characteristics

The baseline characteristics for men and women in each risk group are shown in Table 3. Age was significantly greater in the higher risk groups for men and women. Smoking was less in the higher risk groups for men and drinking was less in the higher risk groups for women. BMI, SBP, DBP, blood glucose and total cholesterol were significantly higher in the higher risk groups by definition.

If the high risk group is defined here as those who have 3 or 4 risk components, its prevalence was 13.0% for men and 16.8% for women.

Combined Risks and Outcome: Multivariate Cox Analyses

Case number, unadjusted mortality per 1,000 person-years, and hazard ratios of CHD, and stroke mortality by multivariate Cox analyses adjusted for age, smoking and drinking are shown in Table 4 for both men and women. In men, for those in the risk 3–4 group, the hazard ratio of CHD was 8.04 and that of stroke was 5.06, in comparison with the risk 0 group. Both trends were significant (trend $p<0.0001$ and 0.0002). Men in the risk 1–2 group carried intermediate risks for CHD and stroke.

However, in women, no significant trend was noted for CHD or stroke mortality, probably because of lower mortality.

Discussion

This prospective population-based cohort study in Japan reports an association of the high-risk group with CHD and stroke mortality. The previously proposed cut-off values for cardiovascular risk factors cannot be applied to non-Western populations because, for instance, the average BMI and waist circumference for Asians are smaller.[5–9,17–20] Several studies in Asians report that for the definition of obesity in Asians the cutoff value for BMI is 23 kg/m^2 and for waist circumference is 90 cm for men and 80 cm for women.[20,21]

In the present study, we selected hypertension, hypercholesterolemia, hyperglycemia and obesity as the components of the combined cardiovascular risk, and the cutoff values for each of these were determined heuristically using Cox analyses of CHD and stroke mortality. By the present definition, the prevalence of the high-risk group with 3 or more risk factors was 13.0% for Japanese men and 16.8% for women in 1980. Although CHD mortality in Japan is relatively low in comparison with that of the Western population, the impact of the combined risk factors on CHD mortality in men was significant, with a multivariate adjusted hazard ratio of 8.04.

The lack of prognostic significance of the combined cardiovascular risk in women in the present study is probably due to a lower incidence of CHD and stroke compared with men.

Study Limitations

The method of obtaining the categorical cutoff values for the risk components and the method of evaluating the prognostic significance of the newly obtained diagnostic criteria of the combined risks were the same, namely Cox analyses. This may appear to be a circular tautology. However, the second Cox analysis was applied merely to show the magnitude of the prognostic significance of the criteria. Applying these criteria to a different population or to the same study with a longer follow-up may be needed in the future to verify this method. Another method of obtaining the cutoff values may be to apply the recursive partitioning method.[26,27] This method may be quite valuable in handling variables that are independent of each other, such as handling gene expression data for tumor and cell classification,[27] but may not be useful when the variables are confounded by each other, such as blood pressure, BMI, total cholesterol concentrations, blood glucose and age, as in the present study. In fact, trial use of this method for the present data resulted in impractical cutoff values, with one variable having different values that appeared at more than 2 ranches of the tree.

The results of principal component analysis in this study suggest clustering of 4 of the 5 components (BMI, SBP, DBP, total cholesterol and non-fasting glucose) except for 1 component, non-fasting glucose. This may be due to the fact that we did not have fasting glucose data. We also need more variables, such as HDL-cholesterol, triglyceride concentrations, an index of insulin resistance, and inflammation markers, to examine the clustering and to find the primary unifying underlying abnormality of the clustered risk factors, as performed in recent studies.[28,29]

Non-fasting blood samples were used in the present study, and direct measurement of HDL-cholesterol was not performed. Therefore, we did not have measurements for fasting blood glucose, triglycerides or HDL-cholesterol, which are other important components of metabolic syndrome. Furthermore, waist circumference measurements will be required in future studies.

We used mortality data as endpoints, which might have led to misclassification of the causes of death. However, it has been reported that the death-certificate diagnosis of stroke and cancer in Japan is quite accurate,[30,31] although it has also been reported that most cases of sudden cardiac death tend to be described on Japanese death certificates as "coronary heart disease", "heart failure" or "unknown cause".[32,33] Furthermore, mortality statistics for coronary heart disease by the end of 1994 may have been underestimated using ICD9, since deaths coded as "heart failure" may hide certain coronary events.[32–35]

Conclusion

Cutoff values for cardiovascular risk factors have been obtained and the defined high-risk group with combined risk factors is important risk for Japanese men.

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References

1. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; **295:** 180–189.
2. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37:** 1595–1607.
3. Meigs JB, D'Agostino RBS, Wilson PW, Cupples LA, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome: The Framingham Offspring Study. *Diabetes* 1997; **46:** 1594–1600.
4. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation* 2004; **109:** 42–46.
5. Liese AD, Mayer-Davis EJ, Haffner SM. Development of the multiple metabolic syndrome: An epidemiologic perspective. *Epidemiol Rev* 1998; **20:** 157–172.
6. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285:** 2486–2497.
7. Alberti KG, Zimmet PZ. Definition, diagnosis, and classification of diabetes mellitus and its complications 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation.

Diabetes Med 1998; **15:** 539–553.
8. Kim MH, Kim MK, Choi BY, Shin YJ. Prevalence of the metabolic syndrome and its association with cardiovascular diseases in Korea. *J Korean Med Sci* 2004; **19:** 195–201.
9. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004; **27:** 1182–1186.
10. Fujimoto WY, Bergstrom RW, Boyko EJ, Chen KW, Kahn SE, Leonetti DL, et al. Preventing diabetes: Applying pathophysiological and epidemiological evidence. *Br J Nutr* 2000; **84**(Suppl 2): S173–S176.
11. Hayakawa T, Okayama A, Ueshima H, Kita Y, Choudhury SR, Tamaki J. Prevalence on impaired activities of daily living and impact of stroke and lower limb fracture on it in Japanese elderly people. *Cerebrovasc Dis Prev* 2000; **3:** 187–194.
12. Sakata K, Hashimoto T, Ueshima H, Okayama A. Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980–1994 (National Integrated Projects for Prospective Observation of Non-communicable Diseases and its Trend in the Aged). *Eur J Epidemiol* 2001; **17:** 46–48.
13. Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H. What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med* 2003; **253:** 169–180.
14. Japanese Ministry of Health and Welfare. National survey on circulatory disorders. Tokyo: Japan Heart Foundation, 1982 (in Japanese).
15. Myers GL, Kimberly MM, Waymack PP, Smith SJ, Cooper GR, Sampson EJ. A reference method laboratory network for cholesterol: A model for standardization and improvement of clinical laboratory measurements. *Clin Chem* 2000; **46:** 1762–1772.
16. Bittner D, McCleary M. The cupric-phenanthroline chelate in the determination of monosaccharides in whole blood. *Am J Clin Pathol* 1963; **40:** 423–424.
17. Yoon YS, Oh SW, Baik HW, Park HS, Kim WY. Alcohol consumption and the metabolic syndrome in Korean adults: The 1998 Korean National Health and Nutrition Examination Survey. *Am J Clin Nutr* 2004; **80:** 217–224.
18. Nakamura Y, Amamoto K, Tamaki S, Okamura T, Tsujita Y, Ueno Y, et al. Genetic variation in aldehyde dehydrogenase 2 and the effect of alcohol consumption on cholesterol levels. *Atherosclerosis* 2002; **164:** 171–177.
19. Nakamura Y, Okamura T, Tamaki S, Kadowaki T, Hayakawa T, Kita Y, et al. Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: NIPPON DATA80, 1980–94. *Am J Clin Nutr* 2004; **80:** 58–63.
20. Snehalatha C, Viswanathan V, Ramachandran A. Cutoff values for normal anthropometric variables in Asian Indian adults. *Diabetes Care* 2003; **26:** 1380–1384.
21. World Health Organization. Obesity: Preventing and managing the global epidemic: Report of a WHO consultation. WHO Tech Rep Ser 2000; **894:** 1–53.
22. Ogawa K, Numano M, Iizuka M, Yanagisawa A, Yoshino H, Ishikawa K, et al. Angiographic and coronary risk factor analyses of Japanese patients with ischemic heart disease before age 40, a multicenter cooperative study. *Jpn Circ J* 1996; **60:** 822–830.
23. Nakamura T, Tsubono Y, Kameda-Takemura K, Funakoshi T, Yamashita S, Hisamichi S, et al. Magnitude of sustained multiple risk factors for ischemic heart disease in Japanese employees: A case–control study. *Jpn Circ J* 2001; **65:** 11–17.
24. Yanase M, Takatsu F, Tagawa T, Kato T, Arai K, Koyasu M, et al. Insulin resistance and fasting hyperinsulinemia are risk factors for new cardiovascular events in patients with prior coronary artery disease and normal glucose tolerance. *Circ J* 2004; **681:** 47–52.
25. Zhang H, Tamakoshi K, Yatsuya H, Murata C, Wada K, Otsuka R, et al. Long-term body weight fluctuation is associated with metabolic syndrome independent of current body mass index among Japanese men. *Circ J* 2005; **69:** 13–18.
26. Zhang H, Bracken MB. Tree-based risk factor analysis of preterm delivery and small-for-gestational-age birth. *Am J Epidemiol* 1995; **141:** 70–78.
27. Zhang H, Yu CY, Singer B. Cell and tumor classification using gene expression data: Construction of forests. *Proc Natl Acad Sci USA* 2003; **100:** 4168–4172.
28. Sakkinen PA, Wahl P, Cushman M, Lewis MR, Tracy RP. Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome. *Am J Epidemiol* 2000; **152:** 897–907.
29. Hanley AJ, Karter AJ, Festa A, D'Agostino R Jr, Wagenknecht LE, Savage P, et al. Insulin Resistance Atherosclerosis Study: Factor analysis of metabolic syndrome using directly measured insulin sensitivity. *Diabetes* 2002; **51:** 2642–2647.
30. Hasuo Y, Ueda K, Kiyohara Y, Wada J, Kawano H, Kato I, et al. Accuracy of diagnosis on death certificates for underlying causes of death in a long-term autopsy-based population study in Hisayama, Japan; with special reference to cardiovascular diseases. *J Clin Epidemiol* 1989; **42:** 577–584.
31. Ron E, Carter R, Jablon S, Mabuchi K. Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. *Epidemiology* 1994; **5:** 48–56.
32. Saito I, Folsom AR, Aono H, Ozawa H, Ikebe T, Yamashita T. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. *Int J Epidemiol* 2000; **29:** 837–844.
33. Saito I, Ozawa H, Aono H, Ikebe T, Yamashita T. Change of the number of heart disease deaths according to the revision of the death certificates in Oita city. *Nippon Koshu Eisei Zasshi* 1997; **44:** 874–879 (in Japanese).
34. Tokashiki T, Muratani A, Kimura Y, Muratani H, Fukiyama K. Sudden death in the general population in Okinawa: Incidence and causes of death. *Jpn Circ J* 1999; **63:** 37–42.
35. Baba S, Ozawa H, Sakai Y, Terao A, Konishi M, Tatara K. Heart disease deaths in a Japanese urban area evaluated by clinical and police records. *Circulation* 1994; **89:** 109–115.

γGTPと循環器疾患死亡の関連-NIPPON DATA90-

Gamma-Glutamyltransferase predicts cardiovascular death among Japanese women. Atherosclerosis. 2006 in press

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【背景】 近年、γGTPの有用性について論じられている。γGTPが飲酒と独立した循環器疾患の危険因子であることが、いくつかの研究において示されている。しかしながら非飲酒者集団においてもγGTPが循環器疾患の危険因子であるかについて調べた論文は少ない。日本人女性は飲酒率が低いことで知られているので非飲酒者集団における検討を行うのに適している。

【方法】 NIPPON DATA90の対象者のうち、γGTP測定が実施され、肝機能異常、脳心血管疾患の既往歴がなく、追跡可能、かつ必要な交絡要因を備えた男性2724名、女性4122名の追跡調査を実施した。追跡期間は9.6年間であり、期間中、男性83名、女性82名の脳卒中死亡が観察された。γGTPと循環器疾患死亡の関連は交絡要因を調整したコックス比例ハザードモデルを用いて計算した。

【結果】 現在飲酒者は男性で59%、女性で7%であった。女性では多変量調整後のハザード比は基準群（γGTP 1-12 U/L）と比べて高値群（γGTP 50 U/L以上）で2.88（95%信頼区間 1.14-7.28）と有意な高値を示した。非飲酒者において連続変量（対数変換）で関連を検討しても関連は有意であった(ハザード比 1.62 、95%信頼区間 1.11-2.37)。一方、男性では有意な関連は認められなかった。

【結論】 γGTPは飲酒者の少ない日本人女性において循環器疾患との強い正の関連を示した。これはγGTPが飲酒のマーカーのみならず循環器疾患の危険因子であることを強く示唆する結果である。高γ-GTPに対する介入、治療の必要性について更なる研究が必要である。

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γ-Glutamyltransferase predicts cardiovascular death among Japanese women

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Abstract

The clinical importance of γ-glutamyltransferase (GGT) has recently been debated. Although some studies have suggested that the relationship between GGT and cardiovascular disease (CVD) mortality is independent of alcohol consumption, *to our knowledge* no studies have reported the relationship between GGT and CVD mortality in never-drinker subgroups. Since Japanese women are known to have a lower prevalence of alcohol consumption, we examined whether GGT predicts CVD mortality in never-drinkers. We followed 2724 Japanese men and 4122 Japanese women without prior CVD or liver dysfunction for 9.6 years and observed 83 and 82 CVD deaths, respectively. Current alcohol drinkers comprised 59% of men and 7% of women. Among women, the multiple adjusted hazard ratio (HR) for CVD mortality compared with the reference group (GGT: 1–12 U/L) was 2.88 (95% confidence interval (CI), 1.14–7.28) for the elevated group (GGT ≥ 50 U/L). This positive relationship was unchanged in the never-drinkers subgroup (HR for log-transformed continuous GGT, 1.62 (95% CI, 1.11–2.37)). No significant relationships were observed in men. GGT displays a strong positive association with CVD mortality among Japanese women, for whom the prevalence of ever-drinkers is very low. Exploring the significance and biological mechanisms of GGT might provide useful insights into CVD prevention.

Keywords: γ-Glutamyltransferase; Alcohol drinking; Cardiovascular diseases; Prospective studies; Japanese

1. Background

Serum γ-glutamyltransferase (GGT) is a well-known enzyme marker of alcohol consumption and liver disease [1]. However, several recent epidemiological studies have revealed that GGT is a marker of oxidative stress [2], and is associated with several cardiovascular risk factors [3,4]. Furthermore, GGT is predictive of future hypertension, diabetes, stroke and coronary heart disease (CHD) [5–12]. However, most studies investigating relationships between GGT and stroke, CHD and cardiovascular disease (CVD) mortality [9–13] have either not adjusted for alcohol consumption, since GGT was used as a marker of alcohol consumption [10,11] or did not obtain baseline alcohol information [12]. Although GGT might represent an important and independent risk factor for CVD [9,13], little evidence has suggested whether GGT itself is predictive of CVD disease or merely a marker of alcohol consumption. As the prevalence of alcohol drinking and smoking are very

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low in Japanese women, particularly in middle to older age, analysis of such individuals should clarify whether GGT levels are predictive of CVD mortality even in never-drinkers.

Our a priori hypothesis was that GGT would predict CVD even in never-drinkers. To test this, we analyzed 9.6-year follow-up data from the National Survey on Circulatory Disorders, Japan, which was initiated in 1990.

2. Methods and population

2.1. Population

Cohort studies of the National Survey on Circulatory Disorders, Japan, were called the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA). NIPPON DATA comprised two cohort studies. Baseline surveys were performed in 1980 and 1990 (NIPPON DATA80 and NIPPON DATA90) [14–16]. The present study analyzed data from NIPPON DATA90 [15,16] as the baseline survey from NIPPON DATA80 did not include any measurement of serum GGT levels. A total of 8384 community residents (3504 men, 4880 women; ≥30-years-old) from 300 randomly selected districts participated in the survey and were followed until November 15, 2000. The overall population of ≥30-years-old in all districts was 10,956, and the participation rate in this survey was 76.5%. Accordingly, these participants were thought to be representative of the Japanese population [16]. Of the 8384 participants, 1538 were excluded for the following reasons: no baseline GGT measurement ($n=662$), glutamic-oxaloacetic transaminase (GOT) level ≥50 U/L, glutamic pyruvic transaminase (GPT) level ≥50 U/L ($n=519$), history of coronary heart disease or stroke ($n=209$), no measurement of confounding factors ($n=3$) and participants for whom follow-up information could not be obtained because of incomplete residential access information at the first survey ($n=145$). The remaining 6846 participants (2724 men, 4122 women) were included in the analysis.

2.2. Follow-up survey

Underlying causes of death for the National Vital Statistics were coded according to the 9th International Classification of Disease (ICD-9) for deaths occurring up to the end of 1994 and according to the 10th International Classification of Disease (ICD-10) for deaths occurring from the beginning of 1995. Details of the classification used in the present study have been described elsewhere [14]. Permission to use National Vital Statistics was obtained from the Management and Coordination Agency of the Japanese Government. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12–18, 2000).

2.3. Baseline examination

Non-fasting blood samples were obtained and serum was separated and centrifuged soon after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. All samples were shipped to the same laboratory (SRL, Tokyo, Japan) for blood measurements.

GGT was measured using 3-carboxyl-4-nitroanilide substrate methods. GOT and GPT were measured using ultraviolet methods. Serum total-cholesterol and triglycerides (TG) were measured enzymatically. High-density lipoprotein cholesterol (HDL-C) was measured by the precipitation method using heparin-calcium. Lipid measurements were standardized using the Lipids Standardization Program from the Centers for Disease Control/National Heart, Lung and Blood Institute [17]. Plasma glucose was also measured enzymatically. Diabetes was defined as serum glucose ≥200 mg/dL and/or self-reported history of diabetes. Baseline blood pressures (BP) were measured by trained observers using a standard mercury sphygmomanometer on the right arm of the seated subject. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Public health nurses obtained information on smoking, use of antihypertensive agents and medical histories. For alcohol consumption, public health nurses categorized participants into the following drinking habit categories based on questioning: never-drinkers, ex-drinkers, current drinkers. Current drinkers were defined as drinking ≥3 days/week and consuming ≥1 *gou* per drinking occasion. If the participant was a current drinker, the nurse also asked them the amount of alcohol consumption using *gou*, the traditional Japanese unit of sake, per drinking occasion. For *sake*, 1 *gou* (180 mL) is equivalent to 23 g of alcohol, which is also approximately two measures of whisky (70 mL) or one bottle of beer (633 mL) in terms of alcohol content. Habitual exercise was defined as: (1) exercise ≥2 days/week; (2) duration of exercise per exercise session ≥30 min; (3) continuing the habit for ≥1 year. If participants answered that they did not have any exercise habit, the nurse asked whether exercise was unable to be performed due to health reasons.

2.4. Statistical analysis

To examine associations between GGT and CVD mortality, GGT levels were classified into four groups. These groups were defined as follows: reference, 1–12 U/L; moderate, 13–24 U/L; moderate high, 25–49 U/L; elevated, ≥50 U/L. Basic characteristics were compared among GGT groups using means for continuous variables and percentages for dichotomous variables. As the distribution of TG was positively skewed, geometric mean (antilogarithm of the log-transformed mean) was used instead of arithmetic mean.

Crude mortality rates were estimated among groups. Multivariate-adjusted hazard ratio (HR) and 95% confidence intervals (CI) were also estimated among groups. Cox proportional hazard modeling was used to estimate adjusted

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HR of CVD mortality. Models were constructed separately for men and women. The reference GGT group was treated as a reference group. Adjustment for confounding factors was performed using three different approaches in this study. First, we adjusted for age only (Model 1). Second, we included other possible confounding factors as follows: age, HDL-C, total-cholesterol, TG (log-transformed), BMI (<18.5, 18.5–24.9 or ≥25), smoking status (never-smoker, ex-smoker or current smoker), drinking status (never-drinker, ex-drinker and current drinker), GOT, GPT and exercise habit (Model 2). For men, we further categorized current smoking and current drinking into two categories each. Cigarette smoking was classified as 1–20 cigarettes/day or ≥21 cigarettes/day. Current drinking was classified as equal to drinking 1 *gou* (23 g of alcohol) per occasion and 2 *gou* or more. Systolic BP, antihypertensive medication and diabetes were not included in Model 2. Since GGT is known to predict future hypertension and diabetes [5–8], adjusting for BP and diabetes might represent an over-adjustment. We therefore created another model (Model 3) using the same factors as Model 2 with the addition of systolic BP, use of antihypertensive medication and diabetes. In each model, the HR of CVD mortality was also estimated using continuous serum GGT values. When GGT levels were used as continuous variables, log-transformed values were used because GGT level is skewed. Values of $P < 0.05$ were considered statistically significant. SAS software (Version 9.1) was used for analyses.

3. Results

Median GGT level was 27 U/L (interquartile range, 18–43 U/L) for men and 14 U/L (interquartile range, 11–21 U/L) for women. Proportions of current, ex- and never-drinkers were 59, 7 and 35% for men and 7, 1 and 93% for women, respectively. Table 1 shows baseline characteristics for study participants according to GGT level. GGT levels were higher in men than in women. For men, mean age was lower in higher GGT groups. Conversely, mean age was higher in GGT groups for women. Mean HDL level was lower in higher GGT groups in women, while no association was observed in men. Otherwise, determinants of GGT were similar in men and women, comprising higher BMI,

Table 1
Mean and prevalence of baseline characteristics stratified by γ-glutamyltransferase (GGT) level at the baseline survey in 1990, NIPPON DATA90

	Men				Women			
	Reference 1–12[a]	Moderate 13–24[a]	Moderate high 25–49[a]	Elevated 50–468[a]	Reference 1–12[a]	Moderate 13–24[a]	Moderate high 25–49[a]	Elevated 50–295[a]
N	183	937	913	691	1538	1812	593	179
Age (years)	57.0	54.5	52.9	51.1	49.8	52.4	55.2	56.0
BMI (kg/m^2)	20.9	21.9	23.1	23.8	22.0	22.9	23.9	23.9
Total-cholesterol (mg/dL)	177.6	191.2	202.5	206.1	197.9	208.1	219.4	221.4
HDL-cholesterol (mg/dL)	50.1	50.3	50.3	51.9	58.0	56.8	56.0	54.5
Triglyceride* (mg/dL)	4.5	4.6	4.9	5.0	4.5	4.7	4.8	5.0
GOT (U/L)	20.2	21.5	23.9	27.1	18.6	20.6	23.4	27.3
GPT (U/L)	15.1	18.3	23.2	28.8	13.8	17.2	23.2	28.1
Systolic BP (mmHg)	131.0	134.8	137.5	142.2	128.7	134.2	138.5	141.0
Diastolic BP (mmHg)	78.9	80.9	83.6	87.2	76.8	80.0	82.2	84.1
Use of antihypertensive medication (mmHg)	7.1	11.1	14.8	13.5	9.2	15.8	25.3	22.9
Diabetes (%)	6.0	5.2	5.5	9.0	2.1	4.0	9.8	10.6
Smoking								
Never (%)	26.8	24.1	21.0	14.8	91.0	87.9	85.3	86.0
Ex-smoker (%)	25.7	23.5	24.0	22.0	2.7	2.4	1.9	2.8
Current (≤1–20 cigarettes/day, %)	15.9	16.7	16.0	14.2	4.9	6.8	7.4	6.7
Current (≥21cigarettes/day, %)	31.7	35.8	39.0	49.1	1.4	3.0	5.4	4.5
Drinking								
Never (%)	61.2	49.2	32.5	12.3	96.0	92.0	88.9	81.0
Ex-drinker (%)	6.6	7.3	5.3	4.3	0.6	1.2	0.8	0.6
Current (=22.8 g per one occasion, %)	24.0	29.7	32.0	31.0	3.0	5.9	7.4	11.2
Current (>22.8 g per one occasion, %)	8.2	13.9	30.2	52.4	0.5	1.0	2.9	7.3
Habitual exercise (not exercising due to ill health, %)	7.1	4.8	4.5	3.3	5.7	6.4	8.3	10.1
Habitual exercise (not exercising for reasons other than ill health, %)	68.9	72.3	71.7	76.1	77.0	74.5	71.0	70.4
Habitual exercise (yes, %)	24.0	23.0	23.8	20.6	17.4	19.1	20.7	19.6

N, numbers of participants; BMI, body mass index; HDL, high-density lipoprotein; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BP, blood pressure; '*', log-transformed; participants were not fasting when the blood samples were drawn.
[a] GGT (U/L).

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Table 2
Relative hazards (95% confidence interval (CI)) for CVD mortality according to γ-glutamyltransferase (GGT) level in women

	Reference 1–12[b]	Moderate 13–24[b]	Moderate high 25–49[b]	Elevated 50–295[b]	Continuous[a]
Person-years	14982	17548	5682	1707	39918
N of CVD mortality	27	32	17	6	82
CVD mortality rate/1000 person-years	1.80	1.82	2.99	3.52	2.05
Model 1	1	1.10 (0.66–1.84)	1.59 (0.86–2.93)	2.20 (0.90–5.40)	1.50 (1.06–2.12)
Model 2	1	1.17 (0.69–1.98)	1.86 (0.98–3.53)	2.88 (1.14–7.28)	1.71 (1.18–2.47)
Model 3	1	1.16 (0.68–1.98)	1.89 (0.95–3.75)	2.97 (1.06–8.34)	1.73 (1.13–2.63)

NIPPON DATA90, 1990–2000. *N*, numbers of participants; HDL, high-density lipoprotein; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BP, blood pressure; Model 1, adjusted for age; Model 2, adjusted for age, alcohol consumption (never, past and current), cigarette smoking (never, past and current), HDL-cholesterol, total-cholesterol, triglyceride*, GOT, GPT, body mass index (<18.5, 18.5–24.9 and ≥25 kg/m^2) and habitual exercise (yes, not exercising for reasons other than ill health, not exercising due to ill health); Model 3, Model 2 + systolic BP, use of antihypertensive medication and diabetes.
[a] Log-transformed.
[b] GGT (U/L).

total-cholesterol, log-transformed TG, GOT, GPT, systolic and diastolic BP, use of antihypertensive medication and prevalence of diabetes in higher GGT groups. Prevalence of never-drinkers and never-smokers was lower in higher GGT groups. For men, the prevalence of current drinkers was >80% in the highest GGT groups. Conversely, for women, the prevalence of current drinkers was <20% even in the highest GGT groups.

Table 2 shows follow-up information and risk of GGT for CVD mortality in women. From a total of 39,918 person-years, 82 CVD deaths were observed (stroke, $n=38$; CHD, $n=12$; other heart disease, $n=27$; other CVD, $n=5$). CVD mortality rates according to GGT category were 1.80/1000 person-years for the reference group, 1.82/1000 person-years for moderate, 2.99/1000 person-years for moderate-high and 3.52/1000 person-years for elevated. Compared with the reference group, multivariate adjusted HRs (Model 2) were significantly higher in the elevated category (HR, 2.88; 95% CI, 1.14–7.28). These findings were unchanged when quartiles of GGT were used. These positive significant relationships between GGT and CVD mortality were also apparent when log-transformed GGT level was used as a continuous variable (HR, 1.71; 95% CI, 1.18–2.47). These relationships were unchanged even after adjusting for systolic BP, use of antihypertensive medication and diabetes (Model 3). A significant relationship was also identified between GGT and CVD mortality among never-drinkers (HR, 1.62; 95% CI, 1.11–2.37; Model 2). These results were unchanged when we excluded the few subjects with very high GGT (GGT ≥100 U/L). The relationship between GGT and overall mortality in women (274 deaths) was also investigated. Overall mortality was significantly increased in elevated category (Model 2) (HR, 2.07; 95% CI, 1.20–3.59) compared with the reference category. Positive significant relationships between log-transformed continuous GGT and overall mortality were also observed (HR, 1.36; 95% CI, 1.10–1.68).

Table 3 shows the relationship between GGT level and CVD mortality among men. During 25,830 person-years, we observed 83 CVD mortality cases (stroke, $n=29$; CHD, $n=23$; other heart disease, $n=26$; other CVD, $n=5$). In contrast to women, no significant associations were observed. This is true even after adjusting for alcohol consumption using more detailed definitions. Analysis of the small number of never-drinker men revealed no significant findings (HR of log-transformed continuous GGT with CVD mortality, 0.58 (95% CI, 0.29–1.13). No significant association was identi-

Table 3
Relative hazards (95% confidence interval (CI)) for CVD mortality according to γ-glutamyltransferase (GGT) level in men

	Reference 1–12[b]	Moderate 13–24[b]	Moderate high 25–49[b]	Elevated 50–468[b]	Continuous[a]
Person-years	1651	8787	8706	6687	25830
N of CVD mortality	10	39	24	10	83
CVD mortality rate/1000 person-years	6.06	4.44	2.76	1.50	3.21
Model 1	1	1.03 (0.51–2.06)	0.77 (0.37–1.61)	0.61 (0.25–1.49)	0.80 (0.58–1.09)
Model 2	1	1.14 (0.56–2.35)	0.95 (0.43–2.10)	0.87 (0.33–2.33)	0.95 (0.67–1.36)
Model 3	1	0.99 (0.48–2.04)	0.77 (0.34–1.76)	0.84 (0.30–2.39)	0.93 (0.62–1.41)

NIPPON DATA90 1990–2000. *N*, numbers of participants; HDL, high-density lipoprotein; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BP, blood pressure; Model 1, adjusted for age; Model 2, adjusted for age, alcohol consumption (never, past, 1 go, 2 go or more), cigarette smoking (never, past, current: ≤1–20 cigarettes/day and current: ≥21cigarettes/day), HDL-cholesterol, total-cholesterol, triglyceride*, GOT, GPT, body mass index (<18.5, 18.5–24.9 and ≥25 kg/m^2) and habitual exercise (yes, not exercising for reasons other than ill health, not exercising due to ill health); Model 3, Model 2 + systolic BP, use of antihypertensive medication and diabetes.
[a] Log-transformed.
[b] GGT (U/L).

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fied between log-transformed continuous GGT and overall mortality (292 deaths) in men (HR, 1.14; 95% CI, 0.95–1.37).

4. Discussion

This prospective study tested the hypothesis that GGT would predict CVD mortality even in never-drinkers in the Japanese population. For Japanese women, for whom the prevalence of drinking is very low, GGT was independently and positively associated with CVD mortality. In contrast, we did not identify any relationship between GGT and CVD mortality among Japanese men, for whom the prevalence of smoking and drinking is high.

The strengths of the present study are as follows: (1) study participants were selected randomly from a representative sample of the Japanese population with a high participation rate (76.5%); (2) because most Japanese women at that time did not drink (93% in this study), the effects of alcohol consumption did not need to be considered; (3) we excluded participants who might have potential liver dysfunction such as chronic hepatitis, that is high GOT or GPT, to focus on the risks associated with GGT.

Previous studies have reported a positive significant relationship between GGT and CVD incidence or mortality [9–13]. However, such studies have typically used GGT as a marker of alcohol consumption [10–12], and thus did not adjust for alcohol consumption. However, findings using self-reported alcohol consumption and CVD mortality differ from findings using GGT, with the former showing a U- or J-shaped relationship and the latter showing a linear relationship [12]. A Finnish study that directly compared relationships between self-reported alcohol consumption and stroke incidence with the relationship between GGT and stroke showed that stroke incidence was not predicted by self-reported alcohol consumption, but was strongly predicted by GGT [10]. These findings suggest that GGT is not only a marker of alcohol consumption, but also has an independent role in CVD mortality. Findings from a British study showed that GGT predicts ischemic heart disease independent of alcohol consumption or other factors relating to GGT, supporting this finding [9]. Similarly, a recent report confirmed a positive relationship between GGT and coronary events after adjusting for alcohol consumption, with positive relationships observed for both <20 and ≥20 g/day [13]. However, to the best of our knowledge, no studies have investigated the pathological importance of GGT among never-drinkers and our study of Japanese women might be the first to clarify that GGT predicts CVD mortality in never-drinkers.

Other mechanisms are considered to explain the relationship between GGT and CVD. First, GGT is known to be increased in participants with high TG, cholesterol and glucose levels [3,4]. However, adjusting for these factors did not attenuate the relationship in the present study. Second, recent experimental work has reported that active GGT is present in atherosclerotic plaques of coronary and cerebral arteries [18,19]. GGT could thus be considered as a marker of subclinical atherosclerosis. Third, recent epidemiological studies have reported that GGT level is inversely associated with antioxidant levels [2]. The Coronary Artery Risk Development in Young Adults Study reported that GGT level within the normal range is inversely associated with serum carotenoid levels [20], and positively associated with future F2-isoprostane [7]. Following these study series, several epidemiological investigations have confirmed these findings, such as NHANES III [21] and various Japanese studies [22,23]. GGT is thus thought to be a marker of oxidative stress and enhanced lipid oxidization can be more enhanced in participants with high GGT than in those with lower GGT. Although the biological mechanisms remain unclear, some experimental evidence indicates that GGT is directly involved in the generation of reactive oxygen species under physiological conditions [2].

To date, most studies have shown a positive association between GGT and CVD mortality or CVD incidence in both men and women [9–13]. However, our findings are inconsistent in this regard. We considered that we did not find a positive association between GGT and CVD mortality in men because of the difficulty in controlling for the effects of alcohol consumption, and reverse causality may be present. Participants who had problems with health or liver conditions might display reduced alcohol consumption. Conversely, participants might drink more when they have less concern for their health. However, we could not find any significant results even in the few male participants without any drinking history. Thus, the lack of relationship between GGT and CVD mortality in Japanese men might not be fully explained by the confounding to alcohol consumption. Further studies should be needed to clarify whether a relation of GGT with CVD mortality is observed in Japanese men.

Some methodological limitations were present in this study. Since we did not have incidence data, the possibility exists that GGT does not predict CVD incidence, but instead represents a marker of prognosis after the CVD event. However, relationships between risk factors and CVD mortality and CVD incidence are usually similar. We thus did not consider this limitation as critical. Second, we had only 83 and 82 cases of CVD mortality for women and men, respectively, and thus could not analyze cause-specific relationships between GGT and CVD mortality.

In conclusion, GGT displays a strong positive association with CVD mortality among Japanese women, for whom the prevalence of ever-drinkers is very low. Exploring the significance and biological mechanisms of GGT might provide useful insights into CVD prevention.

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Appendix A

List of the NIPPON DATA90 Research group:

NIPPON DATA90: "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged".
Chairman: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).
Consultant: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido), Teruo Omae (Health C&C Center, Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi).
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References

[1] Teschke R, Brand A, Strohmeyer G. Induction of hepatic microsomal γ-glutamyltransferase activity following chronic alcohol consumption. Biochem Biophys Res Commun 1977;75:718–24.
[2] Lee DH, Blomhoff R, Jacobs DR. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Rad Res 2004:38:535–9.
[3] Sakuta H, Suzuki T, Yasuda H, Ito T. Gamma-glutamyl transferase and metabolic risk factors for cardiovascular disease. Intern Med 2005;44(6):538–41.
[4] Kim DJ, Noh JH, Cho NH, et al. Serum gamma-glutamyltransferase within its normal concentration range is related to the presence of diabetes and cardiovascular risk factors. Diab Med 2005;22:1134–40.
[5] Lee DH, Ha MH, Kim JH, et al. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. Diabetologia 2003;46:359–64.
[6] Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. Diabetes Care 1998;21:732–7.
[7] Lee DH, Jacobs DR, Gross M, et al. γ-Glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Clin Chem 2003;49:1358–66.
[8] Nakanishi N, Suzuki K, Tatara K. Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care 2004;27:1427–32.
[9] Wannamethee G, Ebrahim S, Shaper A. γ-Glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. Am J Epidemiol 1995;142:699–708.
[10] Jousilahti P, Rastenyte D, Tuomilehto J. Serum γ-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. Stroke 2000;31:1851–5.
[11] Bots ML, Salonen JT, Elwood PC, et al. Gamma-glutamyltransferase and risk of stroke: the EUROSTROKE project. J Epidemiol Commun Health 2002;56(Suppl. 1):i25–9.
[12] Ruttmann E, Brant LJ, Concin H, et al., Vorarlberg Health Monitoring and Promotion Program Study Group. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005;112:2130–7.
[13] Meisinger C, Doring A, Schneider A, Lowel H, For The KORA Study Group. Serum gamma-glutamyltransferase is a predictor of incident coronary events in apparently healthy men from the general population. Atherosclerosis 2006;(February (14)) [Epub ahead of print].
[14] Okamura T, Kadowaki T, Hayakawa T, et al. What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003;253:169–80.
[15] Okamura T, Hayakawa T, Kadowaki T, et al., NIPPON DATA90 Research Group. The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. Atherosclerosis 2006;184:143–50.
[16] Nakamura K, Okamura T, Hayakawa T, et al. NIPPON DATA90 Research Group: Electrocardiogram screening for left high R-wave predicts cardiovascular death in a Japanese community-based population. Hypertens Res 2006;29:353–60.
[17] Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL cholesterol by the US Cholesterol Reference Method Laboratory Network. J Atheroscler Thromb 2003;10:145–53.

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[18] Paolicchi A, Emdin M, Ghliozeni E, et al. Images in cardiovascular medicine. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. Circulation 2004;109:1440.
[19] Pompella A, Emdin M, Passino C, Paolicchi A. The significance of serum gamma-glutamyltransferase in cardiovascular diseases. Clin Chem Lab Med 2004;42:1085–91.
[20] Lee DH, Gross MD, Jacobs Jr DR, Cardiovascular Risk Development in Young Adults Study. Association of serum carotenoids and tocopherols with gamma-glutamyltransferase: the Cardiovascular Risk Development in Young Adults (CARDIA) Study. Clin Chem 2004;50:582–8.
[21] Lim JS, Yang JH, Chun BY, et al. Is serum gamma-glutamyltransferase inversely associated with serum antioxidants as a marker of oxidative stress? Free Rad Biol Med 2004;37:1018–23.
[22] Yamada J, Tomiyama H, Yambe M. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. Atherosclerosis 2006 [Epub ahead of print].
[23] Sugiura M, Nakamura M, Ikoma Y, et al. High serum carotenoids are inversely associated with serum gamma-glutamyltransferase in alcohol drinkers within normal liver function. J Epidemiol 2005;15:180–6.

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身長と脳卒中の関連-NIPPON DATA80-

Relation of adult height with stroke mortality in Japan: NIPPON DATA80. Stroke. 2007 Jan;38(1):22-6.
Hozawa A, Murakami Y, Okamura T, Kadowaki T, Nakamura K, Hayakawa T, Kita Y, Nakamura Y, Okayama A, Ueshima H; The NIPPON DATA80 Research Group.

【背景】 わが国における年齢調整脳卒中死亡率は1950年から1970年にかけて世界で最も高い水準であった。しかしながら1965年以降劇的な減少を続けている。
それと平行して日本人の平均身長は伸び続けてきた。これは特に幼少時における栄養状態の改善によるものと考えられる。したがって高血圧の管理の向上のみならず、身長に代表される成育環境の要因の変化も脳卒中死亡の減少につながった可能性がある。諸外国からはいくつか身長と脳卒中の関連についての報告がなされているが、わが国での研究はない。本研究では特に幼少時の成育環境要因の指標となりうる身長と脳卒中の関連が種々の危険因子と独立して観察されるかについて検討を行った。

【方法】 NIPPON DATA80の対象者のうち、脳心血管疾患の既往歴がなく、追跡可能、かつ必要な交絡要因（年齢、体重、収縮期血圧、降圧剤内服の有無、糖尿病、総コレステロール、喫煙、飲酒）を備えた男性3,969名、女性4,955の追跡調査を実施した。追跡期間は19年間であり、期間中、男性158名、女性132名の脳卒中死亡が観察された。身長と脳卒中の関連は交絡要因を調整したコックス比例ハザードモデルを用いて計算した。

【結果】 身長は年齢と強い逆相関を示した。粗解析では男女ともに身長が高ければ高いほど脳卒中死亡が少ないという負の関連を示した。しかし男性においてはこの負の関連は年齢を調整することによって有意ではなくなった（多重補正後身長5cm上昇あたりの脳卒中死亡のハザード比（95%信頼区間）： 0.92（0.79-1.08））。一方、女性ではこの負の関連は年齢を調整した後も有意であり、この関連は種々の調整要因を調整しても不変であった（多重補正後身長5cm上昇あたりの脳卒中死亡のハザード比（95%信頼区間）： 0.77（0.64-0.91）。さらに年齢による効果修飾の可能性を考慮して年代層別に層別化解析を行ったが、女性についてはほとんどの年齢階級で負の関連が観察された。

【結論】 欧米の報告と同様に日本人女性においても身長と脳卒中の負の関連が認められた。日本人の脳卒中死亡減少の背景には高血圧の管理の向上に加えて身長の上昇を指標とする幼少時の成育環境要因の変容が影響を与えている可能性がある。

Relation of Adult Height With Stroke Mortality in Japan
NIPPON DATA80

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Background and Purpose—The age-adjusted stroke mortality rate in Japan was the highest in the world from 1950 to the 1970s, but it started to dramatically decrease after 1965. In addition to improved management of high blood pressure, the increase in average height might also contribute to this reduction. The present study investigates whether height is an independent risk for stroke mortality in Japan.

Methods—Among participants of the National Survey on Cardiovascular Diseases in 1980 who were randomly selected from the Japanese population, we followed up 3969 and 4955 Japanese men and women without prior cardiovascular disease for a maximum of 19 years and observed 158 and 132 stroke deaths.

Results—Height was inversely correlated with age and with crude stroke mortality. The relationship was attenuated in men when we adjusted for age or other possible confounders (multivariate adjusted relative hazards of a 5-cm increase of height for stroke mortality: 0.92, 95% CI: 0.79 to 1.08). For women, the inverse relationship (relative hazard: 0.77: 95% CI: 0.64 to 0.91) remained after multivariate adjustment. These relationships persisted when we stratified participants by age.

Conclusions—Height is inversely related to stroke mortality and the relationship is statistically significant among Japanese women. (***Stroke*. 2007;38:22-26.**)

Key Words: height ■ Japanese ■ mortality ■ prospective studies ■ stroke

Age-adjusted stroke mortality rate in Japan was the highest in the world from the 1950 to the 1970s[1,2] and twice as high as that in the West at that time.[1,2] However, age-adjusted stroke mortality in Japanese started decreasing dramatically after 1970. The rate was 175.8 per million in 1970 and 104.7 per million in 2001[1] among urban Japanese.[3] A reduction in blood pressure (BP) and improved BP management are believed to be main factors in decreasing the incidence of stroke.[4]

The average height of Japanese people has simultaneously increased. The mean height at age 30 to 39 was lower in men and women born between 1936 and 1945 (163.8 cm for men and 152.7 cm for women) than between 1961 to 1970 (170.6 cm for men and 157.6 cm for women).[5] Several previous studies,[6–16] but not all,[17] have reported that height is inversely related to stroke mortality. Therefore, increment of average height might be also associated with reduction of Japanese stroke mortality. However, no studies have been reported in Japanese and also in other Asians, excluding one article.[16]

To investigate whether height is an independent risk factor for stroke mortality, we performed prospective studies of a representative population of Japanese individuals.

Methods

The subjects of this cohort study were the participants in the National Cardiovascular Survey of 1980 that was conducted together with the National Nutrition Survey that is annually implemented using a similar method and a questionnaire. The standardized procedures used in this survey have been described elsewhere.[18–20] All household members aged 30 years or older (up to 92 years) were surveyed in 300 census tracts that were randomly selected throughout Japan. The baseline survey included medical examinations, blood pressure measurements, blood tests, and a self-administered questionnaire about lifestyle. Trained staff at local health centers in the respective districts performed the examinations in community centers. A history of illnesses, including heart disease, stroke, and diabetes, as well as smoking and drinking habits were obtained from the questionnaire. Height and weight were measured when the subjects wore light clothing and no shoes. Subjects were asked to note whether they were current smokers, had quit smoking, or had never smoked, and smokers were asked to note the number of cigarettes smoked each day. Similarly, subjects were asked to answer whether they had never consumed alcohol, did so in the past, occasionally or regularly (daily) do so. Blood pressure was measured using a standard sphygmomanometer to obtain systolic and diastolic BP. Nonfasting blood samples were collected. The measurement precision and accuracy of the assay for serum total cholesterol (TC) was certified by the Lipid Standardization Program administered by the Centers for Disease Control and Prevention. Diabetes was defined as a nonfasting glucose value ≥200 mg/dL or a self-reported history of diabetes.[21]

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A total of 10 546 individuals aged 30 years or older for whom complete baseline information regarding age, gender, and BP was complete in the 1980 data set was defined as the cohort (NIPPON DATA80).[18–20] From these, we excluded two who did not have information about height; 755 with a history of stroke (N=117), coronary heart disease (N=163), or other heart disease (N=475); 16 who did not have complete information about confounding factors; and 849 participants who could not follow up because of incomplete residential access information after first survey. Consequently, we analyzed 8924 participants (3969 men and 4955 women). There was no significant difference in the mean age-adjusted height between the participants lost to follow up and those in the study.

As reported previously,[18–20] we confirmed the participants who had died in each area by computer-matching data from the National Vital Statistics using area, gender, date of birth, and death as key codes. We then clarified causes of death using the National Vital Statistics. All death certificates issued by medical doctors in Japan are forwarded to a central database at the Ministry of Health and Welfare through public health centers in the area of residence.

The underlying causes of death for Japan's National Vital Statistics were to be coded according to the International Classification of Diseases, 9th Revision (ICD-9) by the close of 1994 and to the International Classification of Diseases, 10th Revision (ICD-10) from the beginning of 1995. Codes of 430 to 438 in ICD-9 and I60–I69 in ICD-10 were defined as death from total strokes, which included death from cerebral infarction (codes 433, 434, 437.7a, 7b in ICD-9, I61 and I69.1 in ICD-10) and from cerebral hemorrhage (codes of 431 to 432 in ICD-9, I63 and I69.3 in ICD-10). Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency of the Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

To examine the association between height and stroke mortality, participants were divided into quartiles. We compared the basic characteristics among height quartiles by mean as continuous variable and percentages as dichotomous variables. We also analyzed the crude and age-adjusted relationship between height and stroke risk factors. Pearson correlation coefficient was used for the crude analysis of continuous variables (systolic BP and TC), and the slope of the regression coefficient was used for age-adjusted analysis. As for the dichotomous variables (diabetes, current smoking, and daily drinking), OR estimated by logistic regression used both crude and age-adjusted analyses. The units of change in height were set at five centimeters in the logistic regression mentioned previously.

We estimated the relative hazards (RH) and the 95% CIs of height for stroke mortality using the Cox proportional hazard model. Because the average height of men and women is quite different, we separately analyzed men and women. We treated the lowest height quartile as a reference group. We used three models to estimate RH, namely crude, age-adjusted, and multivariate adjusted models. The multivariate adjusted model included the following possible confounding factors: age, body weight, systolic BP, use of antihypertensive medication, diabetes, TC, smoking category (never smoked; exsmoker; current smoker 1 to 20 cigarettes per day, 21 to 40, or 41+ cigarettes per day), and alcohol consumption category (never, past, occasional, and daily). We also analyzed relation of continuous height increase per 5-cm increase with stroke mortality. To investigate age-specific differences in the effect of height on stroke mortality, we established five age groups (30 to 49, 50 to 59, 60 to 69, 70 to 79, and 80 over) and performed age-specific analysis in each by Cox regression. A probability value of <0.05 was considered significant. SAS software (version 9.1) was used for analyses. To estimate the RH observed in previous estimates of RH per height reduction, we calculated the reciprocal of the RH to estimate the RH per height increase.

Results

The mean age and height of the study participants were 50.0 (SD: 13.0) years and 162.3 (SD: 6.7) cm for men and 50.2 (SD: 13.1) years and 150.1 (SD: 6.1) cm for women.

Taller participants were younger than smaller individuals (Table 1). Correlations between height and age were close both in men ($r=-0.44$, $P<0.01$) and in women ($r=-0.52$, $P<0.01$). Mean systolic BP levels and the prevalence of diabetes were lower in taller participants. The mean TC level was higher in taller men. Conversely, the mean TC level was higher in smaller women. These characteristics were mostly attenuated after adjusting for age (Table 2).

TABLE 1. Risk Factors for Stroke by Body Height Levels, NIPPON DATA80, 1980

	Men				Women			
Height Category	−157.9	158.0 to 162.3	162.4 to 166.6	166.7+	−146.1	146.2 to 150.2	150.3 to 154.1	154.2+
N	982	998	983	1006	1223	1228	1257	1247
Mean height, cm	153.7	160.2	164.4	170.6	142.1	148.4	152.2	157.5
Age, years	57.9	51.9	47.6	42.8	60.0	51.3	46.7	43.1
Weight, kg	52.5	57.8	61.4	65.8	47.0	50.5	52.9	55.4
Systolic BP, mm Hg	142.3	139.8	136.9	133.4	141.0	135.0	130.1	127.6
Diabetes, %	9%	7%	7%	5%	6%	4%	3%	3%
TC, mg/dL	184.3	185.2	188.1	187.2	196.1	191.9	188.8	184.1
Smoking								
Never	21%	17%	18%	16%	89%	89%	90%	88%
Past	18%	19%	18%	17%	2%	2%	2%	2%
Current 1 to 20 cigarettes/day, %	43%	42%	37%	33%	8%	8%	8%	9%
Current 21 to 40 cigarettes/day, %	15%	18%	24%	27%	1%	0%	1%	1%
Current 41+ cigarettes/day, %	2%	3%	4%	6%	0%	0%	0%	0%
Drinking								
Never	23%	20%	19%	17%	82%	77%	80%	75%
Past	7%	6%	4%	3%	2%	1%	1%	1%
Occasional	22%	27%	28%	29%	13%	18%	17%	20%
Daily	47%	47%	48%	51%	3%	3%	2%	3%

TABLE 2. Relation of 5-cm Increase in Height With Stroke Risk Factors, NIPPON DATA80, 1980

	Crude		Age-Adjusted		Crude		Age-Adjusted	
	r	*P*	Slope	*P*	r	*P*	Slope	*P*
Systolic BP	−0.17	<0.01	0.19	0.45	−0.24	<0.01	0.24	0.34
TC	0.03	0.04	0.40	0.36	−0.13	<0.01	0.94	0.03
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Diabetes	0.88	0.81 to 0.97	1.08	0.97 to 1.20	0.77	0.69 to 0.87	1.08	0.94 to 1.23
Current smoking	1.08	1.03 to 1.13	1.02	0.96 to 1.07	1.06	0.98 to 1.15	1.13	1.03 to 1.25
Daily drinking	1.03	0.98 to 1.08	1.01	0.96 to 1.06	0.98	0.85 to 1.12	1.08	0.92 to 1.26

After 19.0 years of follow up, 158 (97 ischemic, 37 hemorrhagic, and 24 unidentified) men and 132 (69 ischemic, 26 hemorrhagic, and 37 unidentified) women died of stroke. Table 3 shows that the crude stroke mortality rates were highest in the lowest height quartile and gradually decreased as the category increased both in men and in women.

Adjustment for age largely attenuated the inverse relationship and this relationship between height and stroke mortality in men was not statistically significant (RH of stroke mortality for 5-cm height increase, 0.90; 95% CI, 0.79 to 1.03). However, the inverse relationship between height and stroke mortality remained significant for women. This relationship was also unchanged after adjusting for other possible confounding factors (RH of stroke mortality for 5-cm height increase: 0.77; 95% CI, 0.64 to 0.91).

We also observed an inverse relationship between height and ischemic stroke in men and in women (multivariate adjusted RH [95% CI] for 5-cm height increase: men, 0.92 [0.75 to 1.13]; women, 0.66 [0.51 to 0.84]). Height was also inversely related to cerebral hemorrhage in men, but not in women among whom 26 had cerebral hemorrhage (multivariate adjusted RH [95% CI] for 5-cm height increase: men, 0.85 [0.62 to 1.16]; women, 1.05 [0.70 to 1.55]).

Because the correlations between age and height were highly significant for both men and women, we analyzed the relationship between height and stroke mortality according to age category (Table 4). The age-specific analyses of men produced inconsistent findings. However, height and stroke mortality in women were closely and inversely related (range of RH: 0.63 to 0.78) except for the age category 60 to 69 years (RH=1.16).

No relationship between height and heart disease, cancer, and total mortality was determined (RH and 95% CI of mortality for 5-cm height increase for men—heart disease: 1.03 [0.87 to 1.21]; cancer: 1.09 [0.98 to 1.22]; total mortality: 1.02 [0.95 to 1.08]) and that for women (heart disease: 1.07 [0.91 to 1.27]; cancer: 1.07 [0.93 to 1.23]; and total mortality: 1.02 [0.95 to 1.10]).

Discussion

The present study uncovered a close inverse relationship between height and stroke mortality in women. We also

TABLE 3. RH and 95% CI of Stroke Mortality According to Height Level, NIPPON DATA80, 1980 to 1999

Men					
Category of height (cm)	−157.9	158.0 to 162.3	162.4 to 166.6	166.7+	5-cm increase in height
Person-years	15 162	16 927	17 321	18 112	67 522
Stroke mortality	74	42	28	14	158
Stroke mortality rate per 1000 person-years	4.88	2.48	1.62	0.77	2.34
Crude RH (95% CI)	1	0.50 (0.34 to 0.72)	0.32 (0.21 to 0.49)	0.15 (0.09 to 0.27)	0.63 (0.58 to 0.69)
Age-adjusted RH (95% CI)	1	0.79 (0.54 to 1.15)	0.91 (0.58 to 1.42)	0.81 (0.45 to 1.47)	0.90 (0.79 to 1.03)
Multiple adjusted RH (95% CI)	1	0.79 (0.53 to 1.18)	1.03 (0.63 to 1.66)	1.02 (0.52 to 1.97)	0.92 (0.79 to 1.08)
Women					
Category of height (cm)	−146.1	146.2 to 150.2	150.3 to 154.1	154.2+	5-cm increase in height
Person-years	19 869	21 866	22 798	22 907	87 441
Stroke mortality	80	32	12	8	132
Stroke mortality rate per 1000 person-years	4.03	1.46	0.53	0.35	1.51
Crude RH (95% CI)	1	0.36 (0.24 to 0.54)	0.13 (0.07 to 0.24)	0.09 (0.04 to 0.18)	0.43 (0.38 to 0.49)
Age-adjusted RH (95% CI)	1	0.91 (0.59 to 1.39)	0.58 (0.31 to 1.10)	0.65 (0.30 to 1.41)	0.81 (0.70 to 0.95)
Multiple adjusted RH (95% CI)	1	0.88 (0.57 to 1.36)	0.66 (0.34 to 1.27)	0.73 (0.33 to 1.62)	0.77 (0.64 to 0.91)

Multiple adjusted: adjusted for age, weight, systolic BP, diabetes, TC, antihypertensive drug, smoking (never, past, current 1 to 20, 21 to 40, 41+ cigarettes/day), drinking (never, past, occasional, and daily).

TABLE 4. Age Group-Specific RH and 95% CI of 5-cm Increase of Height for Stroke Mortality, NIPPON DATA80, 1980 to 1999

	No. of Participants	Stroke Mortality	RH*
Men			
Age group			
30 to 49	2142	10	0.76 (0.43 to 1.30)
50 to 59	900	28	1.09 (0.73 to 1.64)
60 to 69	571	51	0.88 (0.68 to 1.14)
70 to 79	307	59	1.01 (0.79 to 1.31)
80+	50	10	0.26 (0.07 to 1.07)
Women			
Age group			
30 to 49	2627	10	0.78 (0.39 to 1.57)
50 to 59	1149	16	0.65 (0.38 to 1.12)
60 to 69	752	35	1.16 (0.81 to 1.65)
70 to 79	355	55	0.70 (0.54 to 0.91)
80+	73	16	0.63 (0.33 to 1.22)

*Adjusted for age, weight, systolic BP, diabetes, TC, antihypertensive drug, smoking (never, past, current 1 to 20, 21 to 40, 41+ cigarettes/day), drinking (never, past, occasional, and daily).

observed an inverse but nonsignificant relationship between these two parameters in men.

The strengths of this study were as follows: (1) Japanese participants, (2) long follow up, and (3) separate analysis of age groups.

Several others have reported that height is inversely related to stroke mortality or incidence.[6–17] Except for one follow-up study of an American nurse,[17] height is consistently inversely related to stroke mortality and incidence. The range of RH per 5-cm increase was 0.84 to 0.93 for men and 0.74 to 0.90 for women.[6,10,14,16] Similarly, the range of RH per 10-cm increase was 0.76 to 0.84 for men and 0.83 for women.[11,12,15] These data were consistent with of ours, that is, the RH values per 5-cm increase were 0.92 (not significant) for men and 0.77 for women. The only study reported from Asia showed that the RH for stroke mortalities per 5-cm increase in height was 0.93 (95% CI: 0.88 to 0.98) in men,[16] but there no data available for women.

To understand why height relates to stroke mortality, several explanations should be considered. First, because height is closely correlated with age, the possibility of an age effect cannot be excluded. However, we considered that the age or cohort effect did not fully explain the relationship between height and stroke mortality for the following reasons. Age adjustment did not fully attenuate the inverse relationship between height and stroke mortality in women and the association was inverse in most age categories of women. Second, height might relate to the classic stroke disease risk factors. However, our analyses did not identify a clear, statistically significant relationship between height and systolic BP, TC, diabetes, smoking, and drinking status after adjusting for age. Furthermore, adjusting these variables did not fully attenuate the relationship between height and stroke mortality in women. Third, because height is a function of both genetic and environmental factors, the relationship between height with stroke should be considered from two viewpoints. A recent study has shown an inverse relationship between height and mortality attributable to coronary heart disease, even within monozygotic discordant twins, and the authors concluded that the inverse relationship between height and coronary heart disease mortality can be explained by environmental factors.[22] Of course, because their study focused on mortality attributable to coronary heart disease and not stroke, heredity, which relates to height itself, might affect stroke mortality. Further studies are required to clarify whether heredity itself affects the relationship between height and stroke. From the environmental viewpoint, an anthropologic measure such as height is one surrogate measure of childhood development. Throughout the fetal period and childhood, environmental factors such as nutrition, infection, and socioeconomic circumstance deeply influence development.[23] Several, but not all, studies have shown that adverse socioeconomic conditions early in life are related to stroke mortality.[24] Although height itself might be a risk for cardiovascular disease, we considered height as a surrogate measure of childhood development. Thus, although its contribution would be smaller than improved BP control or management, increasing height might partly contribute to the decrease in stroke mortality among Japanese over the past four decades, at least for women.

We observed no significant relationship between height and stroke mortality among men, which is inconsistent with previous findings. Although our results did not reach statistical significance, the RH was similar to those of a Korean study (RH=0.93 observed; 1263 stroke mortality).[16] Thus, the inverse relationship between height and stroke mortality might not be very close in men and our study might not be sufficiently sensitive to detect it. A larger and longer follow-up study might be required to clarify this issue.

This study has several limitations. Because we did not have any information on socioeconomic status of the participants in this study, we could not adjust for socioeconomic status at baseline. However, all Japanese are covered by health insurance, which allows to access to all potential treatment. Therefore, treatment for participants of lower and higher socioeconomic status should not significantly differ and thus cannot explain the inverse relationship. We also did not have information on childhood socioeconomic status, which is more likely to affect adult height. Therefore, although we considered height as a surrogate measure of childhood development, we could not clarify whether the inverse relation between height and stroke mortality could be fully explained by childhood socioeconomic status. Second, because we did not have incidence data, height might not predict stroke incidence, but only be a marker of prognosis after a stroke event. However, the relationships between risk factors and stroke mortality and cardiovascular disease incidence were similar. Therefore, we did not consider this limitation critical.

Height is inversely related to stroke mortality and the relationship was statistically significant in women. Thus, the decreasing trend in stroke mortality among the Japanese population might be partly explained by an increase in height

attributable to improved socioeconomic circumstances during fetal, childhood, and adolescent periods.

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Disclosures

None.

References

1. Vital statistics (Chapter 2). In: *Journal of Health and Welfare Statistics*. 2003;50:40–64. Tokyo: Health and Welfare Statistics Association, Tokyo [in Japanese].
2. Ueshima H. Changes in dietary habits, cardiovascular risk factors and mortality in Japan. *Acta Cardiol*. 1990;45:311–327.
3. Kitamura A, Iso H, Iida M, Naito Y, Sato S, Jacobs DR, Nakamura M, Shimamoto T, Komachi Y. Trends in the incidence of coronary heart disease and stroke and the prevalence of cardiovascular risk factors among Japanese men from 1963 to 1994. *Am J Med*. 2002;112:104–109.
4. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. *Stroke*. 2003;34:2349–2354.
5. *The National Health and Nutrition Survey in Japan*. Tokyo: Daiichi Syuppan Publisher, 2003 [in Japanese].
6. Njolstad I, Arnesen E, Lund-Larsen PG. Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women. A 14-year follow-up of the Finnmark Study. *Circulation*. 1996;94:2877–2882.
7. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Adult height, stroke, and coronary heart disease. *Am J Epidemiol*. 1998;148:1069–1076.
8. Parker DR, Lapane KL, Lasater TM, Carleton RA. Short stature and cardiovascular disease among men and women from two southeastern New England communities. *Int J Epidemiol*. 1998;27:970–975.
9. Hart CL, Hole DJ, Smith GD. Risk factors and 20-year stroke mortality in men and women in the Renfrew/Paisley study in Scotland. *Stroke*. 1999;30:1999–2007.
10. Jousilahti P, Tuomilehto J, Vartiainen E, Eriksson J, Puska P. Relation of adult height to cause-specific and total mortality: a prospective follow-up study of 31 199 middle-aged men and women in Finland. *Am J Epidemiol*. 2000;151:1112–1120.
11. Davey Smith G, Hart C, Upton M, Hole D, Gillis C, Watt G, Hawthorne V. Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. *J Epidemiol Community Health*. 2000;54:97–103.
12. McCarron P, Greenwood R, Ebrahim S, Elwood P, Smith GD. Adult height is inversely associated with ischaemic stroke. The Caerphilly and Speedwell collaborative studies. *J Epidemiol Community Health*. 2000; 54:239–240.
13. McCarron P, Hart CL, Hole D, Smith GD. The relation between adult height and haemorrhagic and ischaemic stroke in the Renfrew/Paisley study. *J Epidemiol Community Health*. 2001;55:404–405.
14. Goldbourt U, Tanne D. Body height is associated with decreased long-term stroke but not coronary heart disease mortality? *Stroke*. 2002; 33:743–748.
15. McCarron P, Okasha M, McEwen J, Smith GD. Height in young adulthood and risk of death from cardiorespiratory disease: a prospective study of male former students of Glasgow University, Scotland. *Am J Epidemiol*. 2002;155:683–687.
16. Song YM, Smith GD, Sung J. Adult height and cause-specific mortality: a large prospective study of South Korean men. *Am J Epidemiol*. 2003; 158:479–485.
17. Rich-Edwards JW, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Speizer FE, Hennekens CH. Height and the risk of cardiovascular disease in women. *Am J Epidemiol*. 1995;142:909–917.
18. Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H, for Nippon Data80 Research Group. What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med*. 2003;253:169–180.
19. Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, Okamura T, Minowa M, Iimura O. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke*. 2004;35: 1836–1841.
20. Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, Nakamura Y, Okayama A, Ueshima H, for the NIPPON DATA80 Research Group. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis*. 2006; Mar 8 [Epub ahead of print].
21. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2005;28:S37–42.
22. Silventoinen K, Zdravkovic S, Skytthe A, McCarron P, Herskind AM, Koskenvuo M, de Faire U, Pedersen N, Christensen K, Kaprio J; GenomEUtwin Project. Association between height and coronary heart disease mortality: a prospective study of 35 000 twin pairs. *Am J Epidemiol*. 2006;163:615–621.
23. Miura K, Nakagawa H, Greenland P. Invited commentary: height–cardiovascular disease relation: where to go from here? *Am J Epidemiol*. 2002;155:688–689.
24. Galobardes B, Smith GD, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. *Ann Epidemiol*. 2006;16:91–104.

自己申告による高血圧既往歴は、循環器疾患死亡を予測するか？
－NIPPON DATA80 19年追跡における実測血圧値との比較－

東山綾、寶澤　篤、村上義孝、門脇崇、喜多義邦、岡村智教、上島弘嗣（滋賀医科大学福祉保健医学）、早川岳人（島根医科大学公衆衛生学）、岡山明（国立循環器病センター循環器予防健診部）

（背景と目的）血圧実測値に基づいて判定された高血圧は、循環器疾患の重要な危険因子であることは周知の通りである。自己申告に基づく高血圧既往歴は、血圧に関する情報として容易に得ることができ、実測により判定された高血圧に対して、ある程度の感度と特異度を有することが知られている。よって、自己申告による高血圧既往歴も循環器疾患死亡を予測する可能性があるが、自己申告による高血圧既往歴と循環器疾患の関連については、ほとんど検討がなされていない。本研究ではこれらの関連について明らかにすることを目的とした。

（方法）1980年循環器疾患基礎調査の対象者のうち、循環器疾患既往のない30歳から59歳の男女6,427人を19年間追跡した。高血圧既往歴は、保健婦により聴取された。1980年当時の高血圧判定基準に基づき、対象者を実測値もしくは内服薬の有無により、高血圧有り・無しの2群に分け、高血圧の有無に関する既往歴の感度、特異度を算出した。循環器疾患及び脳卒中、脳梗塞、脳出血、冠動脈疾患による死亡についての高血圧既往歴のハザード比を、コックス比例ハザードモデルにて算出した。その際調整因子として、性、年齢、糖尿病既往歴、BMI、血清総コレステロール値、喫煙及び飲酒習慣の有無を用いた。全対象を実測収縮期血圧値20mmHgごとのカテゴリーで分割し、各々で年齢調整循環器疾患死亡率を算出してプロットし、更に高血圧既往歴有り群の年齢調整循環器疾患死亡率を算出して、高血圧既往歴のリスクが、実測値何mmHgのリスクに相当するかを検討した。

（結果）高血圧既往歴の、実測等に基づき判定された高血圧に対する感度は、男性52%、女性65%であり、特異度は男女とも95%であった。男女統合で、上記の調整因子を用いて算出された既往歴のハザード比は、循環器疾患死亡において2.49（95%CI:1.72-3.61）、脳卒中死亡3.22（95%CI:1.88-5.53）、脳梗塞死亡3.50（95%CI:1.56-7.87）、脳出血死亡3.20（95%CI:1.13-9.06）、冠動脈疾患死亡1.53（95%CI:0.67-3.47）であった。既往歴の有無と高血圧の有無により、対象を4群に分け、既往歴・高血圧共に無しの群のハザード比を1とした場合のハザード比は、既往歴無し高血圧有り群で2.69（95%CI:1.60-4.54）、既往歴有り高血圧有り群で2.68（95%CI:1.50-4.76）、既往歴有り高血圧無し群で2.09（95%CI:1.03-4.24）であった。更に同じモデルに、実測収縮期血圧値を調整因子として投入した所、各ハザード比の有意性は消失したが、傾向は残存していた。高血圧既往歴有りの群の年齢調整循環器疾患死亡率は千人年あたり2.3であり、この値は収縮期血圧160-179mmHgの群の年齢調整循環器疾患死亡率に相当していた。

（結論）高血圧既往歴は、実測高血圧者の約半数をスクリーニングすることができ、また循環器疾患死亡と有意な関連がみられた。この結果から、地域住民に対し継続的に血圧測定を施行することが困難な場合などに、高血圧スクリーニングの一手段として、自己申告による高血圧既往歴が有用である可能性が示唆された。

Does self-reported history of hypertension predict cardiovascular death? -Comparison with BP measurement in a 19- year prospective study-

Running Title: History of hypertension and CVD mortality in Japan

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【Abstract】

(Objective) Hypertension as assessed by blood pressure (BP) measurement is one of the most important risk factors for cardiovascular diseases (CVD). Self-reported history of hypertension (self-reported HT) is an easy way to obtain information on BP and is known to have a certain sensitivity and high specificity for HT confirmed by BP measurement (confirmative HT). Thus, it might predict CVD mortality, but few studies have reported on this relationship. (Methods) We followed 6,427 participants aged 30-59 years without a history of CVD for 19 years. The multivariate-adjusted hazard ratio (HR) of CVD mortality was estimated by the Cox proportional hazard model. (Results) The sensitivity and specificity of self-reported HT for confirmative HT were 52-65% and 95%, respectively. The multivariate-adjusted HR of self-reported HT for CVD death was 2.49 (95% confidence interval (CI): 1.72-3.61). Compared to participants with neither self-reported HT nor confirmative HT, those with confirmative HT showed a consistently higher HR for CVD mortality. Self-reported HT without confirmative HT was also significantly related to CVD mortality (HR=2.10, 95% CI=1.04-4.26). These tendencies were unchanged when we further adjusted for systolic BP level. The age-adjusted mortality rate of individuals with self-reported HT corresponded to the age-adjusted mortality rate of individuals whose systolic BP was 160-179 mmHg. (Conclusions) Self-reported HT could screen half of the participants for confirmative HT and was significantly associated with CVD mortality. These results indicate that self-reported HT can be a useful tool to screen for individuals with high BP if it is hard to perform BP measurements continuously among all members of a community.

【Condensed Abstract】

To understand the importance of self-reported history of hypertension (self-reported HT), we followed 6,427 participants without cardiovascular diseases (CVD) for 19 years. The sensitivity and specificity of self-reported HT for hypertension as assessed by blood pressure (BP) measurement were 52-65% and 95%, respectively. The multivariate-adjusted HR of self-reported HT for CVD death was 2.49 (95% CI: 1.72-3.61). The age-adjusted mortality rate of individuals with self-reported HT corresponded to the age-adjusted mortality rate of individuals whose systolic BP was 160-179 mmHg. These results indicate that self-reported HT can be a useful tool to screen for individuals with high BP.

【Key Words】

self-reported history of hypertension, cardiovascular diseases, cohort study, hazard ratio