smoking history and other factors have been accepted as the most appropriate tool for initial diabetes mellitus screening [28–30]. The use of such a risk score might also be feasible for initial screening, although its value has yet to be established in the Japanese population.

In our study, HRs for CVD mortality were higher in participants in the higher normal blood glucose group than in those in the lower normal group. Furthermore, a statistically significant positive linear relationship was observed within normal glucose levels. The HRs for CVD mortality seemed to increase linearly when we divided normal CBG (<7.77 mmol/l) into quintiles. We considered the relationship between CBG and CVD risk as continuous, rather than being determined by a threshold. Thus, similarly to blood pressure [31–33], lower CBG may yield lower CVD mortality rates, as some epidemiological studies have shown in meta-analyses with fasting blood glucose [34] or in other studies with OGTT [9, 35].

From a public health perspective, these results suggest that there is a certain impact on excess risk of CVD death, even when serum blood glucose increases mildly, without reaching the borderline high CBG level. In our study, the number of participants with higher normal glucose was much greater than that for those with borderline high CBG and high CBG. As a population strategy, lifestyle modifications such as body weight reduction, smoking cessation and an increase in physical activity may be effective, less intensive ways to improve a higher normal glucose level [36]. Other strategies such as adequate medication and/or intensive lifestyle modifications might reduce the risk of CVD mortality for individuals with borderline high CBG or high CBG.

The present study has a number of limitations. First, since it was based on blood glucose level measurement on one occasion only, the results might include a regression dilution bias, possibly attenuating the association between CBG and long-term mortality [37]. Second, since we used death as an endpoint, we only estimated fatal CVD and did not include non-fatal cases. Third, since we had no information on fasting blood glucose levels or post load glucose obtained by OGTT results, we were unable to compare the predictive power of the different methods for assessing blood glucose levels. Finally, socioeconomic status might have affected our results, but we were unable to adjust for this factor owing to a lack of relevant information. In conclusion, CBG predicted CHD and CVD mortality in a Japanese population regardless of time since last meal. Even within the normal range, raised CBG levels were related to an elevated risk of CHD and CVD mortality in Japanese. Thus, CBG could be an alternative to fasting blood glucose or OGTT, in situations where it is unrealistic to ask all patients to fast, as in population screening for CVD risk factors, which requires higher participation rates.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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Low-Risk Profile for Cardiovascular Disease and Mortality in Japanese

Takako Yamamoto, MD*; Yasuyuki Nakamura, MD**; Atsushi Hozawa, MD*; Tomonori Okamura, MD*; Takashi Kadowaki, MD*; Takehito Hayakawa, PhD†; Yoshitaka Murakami, PhD*; Yoshikuni Kita, PhD*; Akira Okayama, MD††; Robert D. Abbott, PhD*,‡; Hirotsugu Ueshima, MD*
for the NIPPON DATA80 Research Group‡‡

Background Some studies focusing on low-risk profiles for cardiovascular disease have been reported in Western countries. Yet, few reports have examined, with substantial longevity, the low-risk profile for cardiovascular disease in the Japanese population. This study examines whether having a favorable risk factor profile yields lower all-cause mortality and whether the proportion of those with a low-risk profile is larger in the Japanese population.

Methods and Results A total of 8,339 men and women aged 30–69 years without a history of cardiovascular diseases for 19 years, who had participated in the 1980 National Survey on Circulatory Disorders after being randomly selected from throughout Japan, were followed. Low risk was defined as having all of the following baseline characteristics: blood pressure (BP) <120/80 mmHg; no antihypertensive medication; serum cholesterol 160–240 mg/dl (4.14–6.22 mmol/L); no history of diabetes; and non-smoker. The long-term mortality of the low-risk group was compared with that of others using the Cox proportional hazard model. The prevalence of low risk was 9.4% of all participants. The multivariate-adjusted hazard ratios for low-risk individuals compared with others were as follows: 0.33 (95% confidence intervals (CI), 0.15–0.74) for cardiovascular disease and 0.63 (95% CI, 0.46–0.88) for all-cause mortality. The most attributable risk factor for all-cause mortality was high BP (≥120/80 mmHg).

Conclusion Japanese individuals with favorable cardiovascular disease risk profiles had lower mortality from cardiovascular disease and all-causes than those without. (*Circ J* 2008; **72:** 545–550)

Key Words: Cardiovascular diseases; Mortality; Risk factors

Recently, studies focusing on the low-risk profile for cardiovascular disease (CVD); that is, having all the optimal CVD risk profiles, such as lower blood pressure (BP), optimal total cholesterol (TC), no diabetes, non-smoker and so on, have been reported in Western countries[1–7] These studies usually showed that participants with a low-risk CVD profile had a lower all-cause mortality than others.

Japan has the longest lifespan in the world. Beyond the very low infant mortality rate, some reasons might explain this. Crude mortality due to coronary heart disease in Japan is one-third that of the United States[8–11] The age-adjusted stroke mortality rate in Japan has decreased markedly during the past few decades and the it is now approaching that in Western societies[12] This lower CVD mortality rate might partly explain why the Japanese have such a longer life span compared with the rest of the world[12] To understand the lower CVD and all-cause mortality rate in the Japanese population, it should be of interest to know whether they have a more prevalent low-risk profile. Yet, to date, few reports have examined the prevalence of a low-risk CVD profile and the relationship between a low-risk profile and mortality in Japan. Therefore, in the present study we analyzed data accumulated over a period of 19 years from a representative cohort of the general Japanese population to clarify: (1) whether having a favorable risk factor profile yields lower all-cause mortality, as well as CVD mortality; (2) whether the prevalence of a low-risk profile is larger among Japanese than among Western populations; and (3) which CVD risk factors are mostly attributable to all-cause death in Japanese.

Methods

Participants

This cohort participated in the 1980 National Survey on Circulatory Disorders[8] A total of 10,546 individuals (4,640 men and 5,906 women; aged 30 years), who were selected randomly from 300 health districts throughout Japan, participated in the survey, which comprised a medical history, physical examinations, blood tests and a self-administered

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**Department of Health Science, Shiga University of Medical Science, Otsu, **Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, †Department of Hygiene & Preventive Medicine, School of Medicine, Fukushima Medical University, Fukushima, ††Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan and ‡Division of Biostatistics and Epidemiology, University of Virginia School of Medicine, Charlottesville, VA, USA*
‡‡For a list of the investigators and members of the NIPPON DATA80 Research Group, please see Appendix of Okumura et al[20]
Mailing address: Takako Yamamoto, MD, Department of Health Science, Shiga University of Medical Science, Seta Tukinowa-cho, Otsu 520-2192, Japan. E-mail: takako11@belle.shiga-med.ac.jp

Table 1 Baseline Characteristics of the Study Participants (Comprising 3,658 Men and 4,681 Women Aged 30–69 Years in 1980), Low-Risk Group and Others, NIPPON DATA80

Characteristics	*Low-risk group**	*Others*	*p value*
No. participants (%)	*784 (9.4)*	*7,555 (90.6)*	
Age (years)	*43.0±9.6*	*48.5±11*	*<0.01*
Male (%)	*13.9*	*47.0*	*<0.01*
BMI (kg/m²)	*21.9±2.9*	*22.9±3.1*	*<0.01*
SBP (mmHg)	*109±6.7*	*137±20*	*<0.01*
DBP (mmHg)	*67.7±6.3*	*82.7±12*	*<0.01*
Serum cholesterol (mmol/L)	*4.92±0.51*	*4.88±0.90*	*NS*
Serum glucose (mmol/L)	*5.12±0.95*	*5.59±1.71*	*<0.01*
Current smoker (%)	*0*	*37.0*	

**Low-risk was defined as having all of the following at base line: SBP <120 mmHg and DBP <80 mmHg; receiving no antihypertensive treatment; 4.14 mmol/L <serum total cholesterol concentration <6.22 mmol/L; non-fasting serum glucose concentration <11.1 mmol/L, or fasting serum glucose concentration <7.0 mmol/L; no history of diabetes, myocardial infarction, stroke and angina; and current non-smoker.*

Values are presented as the means±SD or frequencies. P values were tested by t-test or chi-squared test.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

SI conversion factors: to convert glucose to millimoles per liter, multiply by 0.0551; cholesterol to millimoles per liter, multiply by 0.0259.

lifestyle questionnaire. The cohort was followed until 1999 (NIPPON DATA80).[13–16] The overall population aged 30 years in the 300 participating health districts was 13,771. Therefore, the participation rate of the survey was 76.6% before exclusion for the following reasons: missing information on the baseline survey (n=76); lost to follow up (n=989); age ≥70 years (n=950); any individual with a history of myocardial infarction, stroke or angina pectoris (n=192). We analyzed data from the remaining 8,339 individuals (3,658 men and 4,681 women).

Endpoint Determination

National Vital Statistics was used to clarify the cause of death. In accordance with Japan's Family Registration Law, all death certificates issued by physicians are forwarded to the Ministry of Health and Welfare via public health centers in the district of residence. The underlying causes of death were coded according to the 9th and 10th revisions of the International Classification of Diseases for the National Vital Statistics. We confirmed death in each health district by computer matching data from the National Vital Statistics with district, gender, and dates of birth and death as key codes. Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, Government of Japan. Ethical approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Baseline and Biochemical Examinations

The baseline surveys were conducted by public health centers. Baseline BP was measured by trained observers using a standard mercury sphygmomanometer affixed to the right arm of seated participants who had rested for 5 min. Height in stockinged feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). Results of a self-administered questionnaire that included questions about participants' smoking habits, alcohol consumption, current health status and medical history were obtained. Non-fasting or fasting (at least 5 h after the last meal) blood samples were centrifuged at room temperature for 15 min at 1,500 g and within 60 min of collection, and then stored at −70°C. Serum TC concentration was analyzed at a single laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan), using a sequential auto analyzer (SMA12; Technicon, Tarrytown, NY, USA) and the Lieberman–Burchard direct method. This laboratory is a member of the Cholesterol Reference Method Laboratory Network, and the precision and accuracy of serum cholesterol measurements have been certified in the Lipid Standardization Program, administered by the Centers for Disease Control and Prevention, Atlanta.[17] Serum glucose concentrations measured by the cupric neocuproline method were converted into the values used in the hexokinase method.[18] The cohort was divided into the categories 'low risk' and 'other'. Low risk was defined as having the following characteristics at the time of the baseline survey: BP <120/80 mmHg, a level categorized as normal by the JNC 7;[19] no antihypertension medication; TC 160–240 mg/dl (4.14–6.22 mmol/L); non-fasting serum glucose <200 mg/dl (11.1 mmol/L) or fasting serum glucose <126 mg/dl (7.0 mmol/L); no history of diabetes; and not currently smoking. Although other papers define TC <200 mg/dl (5.18 mmol/L) as low risk for CVD,[1,2,5–7] we defined TC as low risk because low TC (ie, <160 mg/dl (4.14 mmol/L)) is associated with increased risk of cerebral hemorrhage,[13,20,21] and risk for CVD is not increased significantly at TC levels between 200 and 240 mg/dl (5.18–6.22 mmol/L) in Japan.[13]

Statistical Analysis

All statistical analyses were performed using SAS version 8.02 for WINDOWS (SAS Institute Inc, Cary, NC, USA). Men and women were first analyzed separately and then together. We used the chi-squared and t-test to compare dichotomous and continuous variables, respectively. The age-adjusted and multivariate-adjusted hazard ratios (HR) for all-cause and cause-specific mortality were calculated using a Cox proportional hazard model. For multivariate analyses, age, gender, BMI and frequency of alcohol consumption (ie, occasional, daily or none) were entered as covariates. The significance of an interaction between gender and low-risk status for all-cause and cause-specific mortality was tested using an interaction term for the continuous and categorical variables in a multivariate-adjusted model. All p-values were 2-tailed and $p<0.05$ was considered significant. Data are presented as the means±SD unless otherwise stated.

Table 2 Number of Deaths and Hazard Ratios (95% CI) for Low-Risk Group and Others of Major Causes of Death, Men and Women Combined, NIPPON DATA80, 1980–1999

Causes of death	*Low-risk group** (N=784)*	*Others** (N=7,555)*
All cause		
No. deaths (/TPY)	*39 (2.6)*	*1,101 (8.0)*
Age-adjusted HR (95%CI)	*0.65 (0.47–0.90)*	*1.00*
*Multivariate-adjusted HR**	*0.63 (0.46–0.87)*	*1.00*
Cardiovascular disease		
No. deaths (/TPY)	*6 (0.4)*	*339 (2.5)*
Age-adjusted HR (95%CI)	*0.33 (0.15–0.74)*	*1.00*
*Multivariate-adjusted HR**	*0.33 (0.15–0.74)*	*1.00*
Cancer		
No. of deaths (/TPY)	*21 (1.4)*	*431 (3.1)*
Age-adjusted HR (95%CI)	*0.89 (0.57–1.39)*	*1.00*
*Multivariate-adjusted HR**	*0.90 (0.57–1.40)*	*1.00*

**Adjusted for age, gender, BMI and alcohol consumption.*
***For definitions of 'low-risk 'and 'others', see footnotes of Table 1.*
CI, confidence intervals; /TPY, 1,000 person-years; HR, hazard ratio of low-risk group compared with others. Other abbreviation see in Table 1.

We also calculated the population-attributable fraction for all-cause death among the risk factors by the formula[22]:

[Proportion of cases exposed to risk factor× (Adjusted HR−1)/Adjusted HR].

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the 2 categories of participants. Those with a low risk accounted for 9.4% of the total and contained a higher proportion of women. The mean values for age, BMI, systolic BP (SBP), diastolic BP (DBP) and glucose concentrations differed significantly between the 2 groups.

Mortality by Cause, Low Risk vs Other

Among 109 low-risk men and 675 low-risk women, 9 (all-cause mortality rate, 4.6/1,000 person-years) and 30 (all-cause mortality rate, 2.4/1,000 person-years) died, respectively. These all-cause mortality rates in low-risk participants were lower than those in others (10.4/1,000 person-years in others men and 6.1/1,000 person-years in others women). For both men and women, the multivariate-adjusted HRs (95% confidence intervals (CI)) for all-cause death in low-risk individuals were significantly lower than those in the other group; HR=0.47 (0.24–0.90) in men and HR=0.73 (0.50–1.06) in women. As we did not find any significant relationship between gender and low-risk profile for mortalities (p=0.17 for all-cause and p=0.58 for CVD death), we combined the data from men and women in the analyses that followed.

Table 2 shows the number of deaths, age-adjusted rates per 1,000 person-years and the HR of low-risk individuals for all-cause and cause-specific mortality. Crude mortality rates per 1,000 person-years for CVD were 0.4 and 2.5 among the low risk and the other group, respectively. Similarly, all-cause mortality per 1,000 person-years was 2.6 for low risk and 8.0 for the other group. The multivariate-adjusted HRs for CVD death and all-cause death in low-risk individuals were significantly lower than for those in the other group; HR=0.33 (95% CI, 0.15–0.74) for CVD mortality and 0.63 (0.46–0.88) for all-cause mortality. The frequency of deaths due to stroke was only 1 in 784 low-risk individuals (0.1 per 1,000 person-years), but was 154 in 7,555 of the other group (1.1 per 1,000 person-years). Although the risk of cancer mortality was also slightly lower in low-risk individuals (HR=0.90; 0.57–1.40), the difference was not statistically significant.

Population-Attributable Risk of CVD Risk Factors for All-Cause Mortality

Table 3 shows multivariate-adjusted HRs for all-cause death according to major CVD risk factors and their population-attributable risk fractions (%). The proportion of cases exposed to non-normal BP, currently smoking were 91.8%, 46.6%, 30.1% and 9.4% of all deaths, respectively. The HRs for high BP, smoking, diabetes, serum cholesterol and all-cause mortality were 1.40 (1.13–1.74), 1.51 (95% CI, 1.31–1.74), 1.20 (1.06–1.37) and 1.81 (1.48–2.22), respectively. Accordingly, the population-attributable risk ratios for all-cause mortality were 26.2%, 15.7%, 5.1% and 4.2% for high BP, smoking, non-optimal serum cholesterol and diabetes, respectively. When we calculated the population-attributable risk fraction for each gender, the population-attributable risk ratios for all-cause death in men were 20.8%, 20.5%, 5.0% and 4.5% for high BP, smoking, non-optimal serum cholesterol and diabetes, respectively, and were 31.8%, 6.0%, 5.6% and 3.2% in women, respectively.

Discussion

We found that only a few middle-aged adults had a low-risk profile for CVD. We also found that participants with a low-risk profile had a lower risk not only for CVD mortality but also for all-cause mortality. Moreover, among the major CVD risk factors, we discovered that the population-attributable risk for all-cause death was highest for high BP, followed by smoking.

One of the previous studies based on 5 large cohorts studies, involving a 16-year follow-up study of Multiple Risk Factor Intervention Trial (MRFIT) and a 22-year follow-up study of Chicago Heart Association Detection Project in Industry[5] showed that long-term mortality rates for individuals with favorable CVD risk factor profiles in youth and middle age were much lower than those of individuals having at least one of the risk factors. They defined low risk as serum cholesterol level <200 mg/dl (<5.17 mmol/L), BP ≤120/80 mmHg and currently non-smoking. In that study, low-risk individuals comprised only 4.8–9.9% and the age-

Table 3 Population-Attributable Risk of Major Cardiovascular Disease Risk Factors for All-Cause Death, NIPPON DATA80, 1980–1999

Risk factors	*No. deaths (%)*	*Multivariate-adjusted HR† (95%CI)*	*Population-attributable risk*
Men and women			
*High BP**			
Normal BP	*94 (8.2%)*	*1.00*	
Non-normotensive	*1,046 (91.8%)*	*1.40 (1.13–1.74)*	*26.2%*
Smoking			
Non-smoker	*609 (53.4%)*	*1.00*	
Current smoker	*531 (46.6%)*	*1.51 (1.31–1.74)*	*15.7%*
Serum cholesterol			
*Optimal****	*796 (69.9%)*	*1.00*	
Non-optimal	*344 (30.1%)*	*1.20 (1.06–1.37)*	*5.1%*
*Diabetes***			
Non-diabetic	*1,032 (90.6%)*	*1.00*	
Diabetic	*108 (9.4%)*	*1.81 (1.48–2.22)*	*4.2%*
Men			
*High BP**			
Normal BP	*51 (7.7%)*	*1.00*	
Non-normotensive	*613 (92.3%)*	*1.29 (0.97–1.72)*	*20.8%*
Smoking			
Non-smoker	*199 (30.0%)*	*1.00*	
Current smoker	*465 (70.0%)*	*1.41 (1.19–1.67)*	*20.5%*
Serum cholesterol			
*Optimal****	*456 (68.7%)*	*1.00*	
Non-optimal	*208 (31.3%)*	*1.17 (0.99–1.37)*	*4.5%*
*Diabetes***			
Non-diabetic	*590 (88.9%)*	*1.00*	
Diabetic	*74 (11.1%)*	*1.82 (1.49–2.23)*	*5.0%*
Women			
*High BP**			
Normal BP	*43 (9.0%)*	*1.00*	
Non-normotensive	*433 (91.0%)*	*1.54 (1.11–2.12)*	*31.8%*
Smoking			
Non-smoker	*410 (86.1%)*	*1.00*	
Current smoker	*66 (13.9%)*	*1.76 (1.35–2.29)*	*6.0%*
Serum cholesterol			
*Optimal****	*340 (71.4%)*	*1.00*	
Non-optimal	*136 (28.6%)*	*1.24 (1.02–1.51)*	*5.6%*
*Diabetes***			
Non-diabetic	*442 (92.9%)*	*1.00*	
Diabetic	*34 (7.1%)*	*1.83 (1.29–2.60)*	*3.2%*

**High BP (ie, non-normotensive) was defined as SBP ≥120 mmHg, DBP ≥80 mmHg or receiving antihypertensive treatment.*
***Diabetes was defined as non-fasting serum glucose ≥11.1 mmol/L or fasting serum glucose ≥7.0 mmol/L or history of diabetes.*
****Optimal was defined as serum cholesterol 4.14–6.22 mmol/L.*
†Adjusted for age, gender, smoking, hypertension, diabetes, serum cholesterol, BMI and alcohol consumption status.
HR, hazard ratio; BP, blood pressure. Other abbreviations see in Tables 1,2.

adjusted relative risks ranged from 0.42 to 0.60 for all-cause mortality and from 0.15 to 0.28 for CVD mortality, respectively! Another previous study that also investigated low-risk profiles is that by Daviglus and colleagues, who studied 7,302 women (aged 18–39 years) without prior CHD or major electrocardiographic abnormalities, screened between 1967 and 1973, for the Chicago Heart Association Detection Project in Industry[5] They found that only 20% met all the criteria for low-risk profile, which they defined as: TC <200 mg/dl; BP ≤120/80 mmHg; BMI <25 kg/m^2; no anti-hypertensive or cholesterol-lowering medication; no diabetes; and no smoking. They also showed the multivariate-adjusted all-cause relative risk for low-risk women was 0.19 compared with women with 2 or more high-risk factors[5] Giampaoli and colleagues' conducted a 10-year follow-up study of Italian participants aged 35–69 years from 12 population samples[6] They defined low risk as having all of the following applied at baseline: SBP <120 mmHg; DBP <80 mmHg; receiving no hypertensive drug treatment; serum TC <5.17 mmol/L (<200 mg/dl); BMI, <25.0 kg/m^2; non-smoker; and no diabetes. They found that all the factors could be applied to only 3.5% of women and 1.6% of men[6] Lloyd-Jones et al studied all Framingham Heart Study participants who were free of CVD at 50 years of age[7] They found that only 3.2% of men and 4.5% of women had all the optimal factors; that is, TC <4.65 mmol/L (<180 mg/dl), BP <120/<80 mmHg, non-smoker and non-diabetic[7]

When our results for relative risk of low-risk profile for all-cause mortality are compared with those of Stamler et al[1] whose study used similar criteria and compared the risk of low-risk profile with all others as we did, our results are somewhat modest. Various reasons could explain these discrepancies, which will now be considered. Since we used the low-risk profile for CVD mortality in these studies, the proportion of CVD deaths in all deaths can explain the discrepancy. The World Health Organization's Health Statistics and Health Information Systems[9] displays a table regarding numbers and rates of registered deaths. In 2000 in Japan, death due to diseases of the circulatory system (ICD10: I00-I99) accounted for 27.5% of all deaths in men

and 35.3% of all deaths in women? Corresponding values for the same year in the USA was 37.2% for all-cause mortality in men and 41.1% in women? Moreover, mortality rates in Japan due to stroke, which occurs in relatively older individuals, are still higher than those due to CHD, which results in death among younger individuals[8] Another reason could be that most Japanese men are likely to have been smokers in the past[8] whereas men who have never smoked might have had a health condition in their youth, such as tuberculosis or asthma. Thus, relatively weaker men might be included in the 'low risk' group. However, as we did not obtain information about participants' histories of non-CVDs, we can't confirm this speculation.

Although the definition we used was different, the proportion of individuals with a low-risk profile in the present study was mostly similar to that of other studies (3–10%)[1,2,6,7] except for the report by Daviglus et al[5] which studied younger women. Since the prevalence of a low-risk profile was similar to that of other studies and the relative risk of a low-risk profile for all-cause and CVD mortality is rather modest in Japan, Japanese longevity might not be fully explained by a low-risk profile; that is, additional factors might affect the lower CVD risk in Japan. A recent study by Sekikawa et al has found that middle-aged Japanese men have a lower prevalence of coronary artery calcification than middle-aged men in the USA despite having similar levels of BP and low-density lipoprotein-cholesterol, and a higher incidence of diabetes and smoking[23] They also suggested that factors other than the classical major factors are involved in risk for CVD. Thus, an investigation of factors that affect a lower CVD risk in Japan, such as green tea consumption, fish consumption or others, should be encouraged![14,24,25]

We assessed the magnitude of the CVD risk factors for all-cause mortality. The criteria for each risk factor were the same as those used to define low-risk status. Among those participants with a low-risk profile in the present study, a few with diabetes had the highest HRs for all-cause death, whereas many with high BP, as defined by JNC 7, had a modest HR for all-cause death. As a result, high BP had the highest population-attributable risk fraction for all-cause death, followed by smoking, serum cholesterol, and diabetes for both men and women. Although the population-attributable fraction was not very high, the prevalence of diabetes is increasing steadily, where the prevalence in 2003 (6.9%) was almost double that in 1980 (3.8%). Taking this into consideration, diabetes should have more impact in the future. A distinct difference between men and women was observed regarding the impact of smoking on all-cause mortality. In men, smoking caused a high population risk, being at the same level as high BP, whereas in women smoking contributed much less to population risk compared with high BP. Apparently, this is because the prevalence of smoking is quite different between men and women (men, 64.8%; women, 8.8%) at the baseline survey.

The present study has some methodological limitations. First, we measured risk factors only once at baseline, so we did not have any information about the status of the participants or changes in lifestyle. Second, we used the original definition of a low-risk profile for serum cholesterol. Thus, direct comparisons between the present study and other Western studies are quite difficult. However, as shown in our previous studies, participants whose serum cholesterol level was between 160 and 240 mg/dl (4.14–6.22 mmol/L) had the lowest CVD mortality risk, which might be because Japanese have not been exposed to a high lipid diet for as long as populations in Western countries, especially at the baseline examination of the study. Hence, our approach should be appropriate for the Japanese population.

In conclusion, the benefit of having a low-risk status is apparent in Japan. Individuals with low CVD risk have lower mortality rates due to all-causes and CVD. The most attributable risk factor for all-cause mortality was high BP. Thus, we reconfirmed the importance of maintaining lower BP as a public health strategy, as well as to stop or never start smoking, and maintain modest levels of TC, as well as lower serum glucose levels.

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Appendix

Author Affiliations: Department of Health Science, Shiga University of Medical Science (Drs Yamamoto, Hozawa, Okamura, Kadowaki, Ueshima; PhDs Murakami, Kita); Cardiovascular Epidemiology, Kyoto Women's University (Dr Nakamura); Department of Public Health Science, Shimane University School of Medicine (PhD Hayakawa); Department of Preventive Cardiology, National Cardiovascular Center (Dr Okayama); Division of Biostatistics and Epidemiology, University of Virginia School of Medicine (PhD Abbott).

Author Contributions: Dr Yamamoto had full access to all of the study's data and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study Concept and Design: Yamamoto, Ueshima, Nakamura, Hozawa, Okamura, Hayakawa, Kadowaki, Murakami, Okayama.
Acquisition of Data: Ueshima, Okamura, Kita, Hayakawa, Kadowaki.
Analysis and interpretation of data: Yamamoto, Nakamura, Hozawa, Okamura, Kadowaki, Hayakawa, Kita, Murakami, Abbott, Ueshima.
Drafting of the Manuscript: Yamamoto, Nakamura, Hozawa, Okamura, Kita, Hayakawa, Kadowaki, Murakami, Okayama, Ueshima.
Critical Revision of the Manuscript for Important Intellectual Content: Ueshima, Okamura, Hozawa, Murakami, Abbott, Hayakawa, Kadowaki, Kita.
Statistical Analysis: Yamamoto, Nakamura, Hozawa, Murakami, Okamura, Hayakawa, Kita, Kadowaki, Okayama, Ueshima.
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Study Supervision: Ueshima, Nakamura, Okamura, Hozawa, Murakami, Kadowaki, Hayakawa, Kita.
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nature publishing group

Relationship Between BMI and All-cause Mortality in Japan: NIPPON DATA80

Atsushi Hozawa[1], Tomonori Okamura[2], Izumi Oki[3], Yoshitaka Murakami[1], Takashi Kadowaki[1], Koshi Nakamura[1], Naomi Miyamatsu[4], Takehito Hayakawa[5], Yoshikuni Kita[1], Yosikazu Nakamura[6], Yasuyuki Nakamura[7], Robert D. Abbott[1,8], Akira Okayama[9] and Hirotsugu Ueshima[1]; NIPPON DATA80 Study Group.

As body composition in Asian populations is largely different from Western populations, a healthy BMI could also differ between the two populations. Thus, further study is needed to determine whether a healthy BMI in Asians should be lower than Western populations, as recommended by the World Health Organization (WHO). We investigated the relationship between BMI and mortality in a sample of 8,924 Japanese men and women without stroke or heart disease. During 19 years of follow-up, 1,718 deaths were observed. We found a U-shaped relationship between BMI and fatal events. Risk of total mortality was highest in participants with BMI <18.5 kg/m² and lowest in participants with BMI 23.0–24.9 kg/m². These findings persisted even after excluding the first 5 years of follow-up with a focus on healthy participants who never smoked, were aged <70 years, and had total cholesterol (TC) levels ≥4.1 mmol/l (*N* = 3712). For both the full sample and healthy participants, all-cause mortality risk did not differ between BMI ranges 21.0–22.9 and 23.0–24.9 kg/m². Our findings do not support the recent WHO implications that BMIs <23.0 kg/m² is healthy for Asians. Therefore, further studies are needed to identify an optimal BMI range for Asia.

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Body composition in Asia is largely different from Western populations. Some reports have indicated that Asian populations tend to have a higher ratio of body fat at any given body mass index (BMI) (1,2). Furthermore, recent studies have suggested that the area of visceral fat is wider among Japanese than in Western individuals with a similar girth (3). Thus, whether it is appropriate to apply Western guidelines to define obesity in Asian populations is uncertain. The World Health Organization (WHO) recommends that optimal BMI should be lower in Asian vs. Western populations (4).

On the other hand, several prospective studies conducted in Japan and in other Asian countries have suggested that not only obese, but also underweight individuals have a high risk of all-cause mortality (5–9). Several explanations have been proposed to explain how being underweight is associated with all-cause mortality, such as (i) the effect of heavy smoking on weight loss (5,10–12); (ii) the effect of age (older participants are relatively leaner than those who are middle aged) (10,12,13); (iii) total cholesterol (TC) is lower in leaner individuals and low TC effects hemorrhagic stroke, cancer, and liver diseases (14–17); (iv) weight loss is often associated with subclinical diseases (5–15, 17, 18).

To diminish the impact of these effects on the relationship between BMI and mortality and to understand whether or not Japanese should have a lower optimal BMI than Westerners as proposed by the WHO, we examined the association between BMI and death from all causes and from cardiovascular disease (CVD) in a restricted sample of healthy Japanese individuals who were <70 years of age, who had never smoked, whose TC levels were not particularly low, and who survived for at least 5 years. To our knowledge, the association between BMI and mortality in such a restricted healthy sample has not been described previously.

MATERIALS AND METHODS

The subjects in this cohort study were participants in the Japanese National Cardiovascular Survey of 1980, which was conducted together with the annual National Nutrition Survey that used a similar method and questionnaire. The standardized procedures used in this survey have been described elsewhere (14,15). All household members 30 years of age (up to 92 years) (*N* = 13,771) were surveyed in 300 randomly selected census tracts throughout Japan.

A total of 10,546 individuals (76.6% of 13,771) 30 years of age or older completed the 1980 baseline examination (NIPPON DATA80) (14,15). Among these, we excluded 2 individuals for whom information about height was not available, 755 participants with a history of CVD (16),

[1]Department of Health Science, Shiga University of Medical Science, Otsu, Japan; [2]Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan; [3]Tochigi Cancer Center, Utsonomiya, Japan; [4]Department of Clinical Nursing, Shiga University of Medical Science, Otsu, Japan; [5]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan; [6]Department of Public Health, Jichi Medical University, Shimotsuke, Japan; [7]Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, Japan; [8]Division of Biostatistics and Epidemiology, University of Virginia School of Medicine, Charlottesville, Virginia, USA; [9]Japan Anti-Tuberculosis Association, Tokyo, Japan. Correspondence: Atsushi Hozawa (hozawa-thk@umin.ac.jp)

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who did not have complete information about confounding factors, and 849 participants who could not be followed up because of incomplete residential access information after the first survey. Consequently, we analyzed 8,924 participants (3,969 men and 4,955 women).

As reported previously (14,15), we identified the participants who had died by computer matching data from Japanese National Vital Statistics records, using area, gender, date of birth, and death as key codes. We obtained permission to use the National Vital Statistics records from the Management and Coordination Agency of the Government of Japan. Approval was further granted from the Institutional Review Board of Shiga University of Medical Science (nos. 12–18, 2000).

To examine the relationship between BMI and death due to all causes and CVD, participants were divided into seven BMI categories: BMI <18.5, 18.5–20.9, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, and ≥30 kg/m². The distributions of baseline characteristics across BMI groups were gender- and age-adjusted using analysis of covariance and logistic regression.

We estimated the relative hazards (RHs) and the 95% confidence intervals for all-cause and CVD mortality between the BMI strata using the Cox proportional hazards regression model. There were no apparent reasons to suggest that the proportionality assumption was inappropriate. We considered the group with BMI 23.0–24.9 kg/m² as a reference. For the entire cohort, we used two models to estimate the RHs: (i) adjusted for age, gender, smoking, and alcohol consumption, and (ii) adjusted for the same factors, plus systolic blood pressure, use of antihypertensive medication, TC, and diabetes. Diabetes was defined as a nonfasting glucose value ≥11.1 mmol/l (≥200 mg/dl) or a self-reported history of diabetes (19).

To diminish the effects of confounding due to age, smoking, TC, and pre- or coexisting disease on mortality, we analyzed the data after removing the first 5 years of follow-up among those who had never smoked, who were <70 years of age, and who had TC ≥4.1 mmol/l (15). All *P* values were based on a two-sided level of significance. Data were analyzed using SAS software (version 9.1; SAS Institute, Cary, NC).

RESULTS

Table 1 shows the age- and gender-adjusted relationship between BMI and several CVD risk factors. Systolic, diastolic blood pressure, and TC were increased with increasing BMI. Similarly, adjusted percentages for antihypertensive medication or having diabetes also increased with increasing BMI. In contrast, the age-adjusted percent of current smokers declined as BMI increased. These findings were similar in both men and women (data not shown).

After 19 years of follow-up, there were 1,718 deaths, among which 607 were due to CVD. Because of the limited number of obese individuals, we combined BMI categories 27.0–29.9 kg/m² and ≥30 kg/m² into one group for the following analyses.

Figure 1a shows the RHs of all-cause mortality across the BMI groups, in which a U-shaped relationship between BMI and fatal events is apparent after adjusting for age, gender, smoking, and alcohol consumption status (model 1). The RHs for all-cause mortality was higher in the underweight (model 1, RH = 1.39; 95% confidence interval = 1.16–1.67), compared with the reference group. Adjustment for blood pressure, antihypertensive medication, TC, and diabetes did not alter this finding (data not shown). The RHs for all-cause and CVD mortality (Figure 1b) was the lowest in the participants with BMI between 23 and 25 kg/m². As the relationship between BMI and all-cause and CVD mortality was similar between men and women (data not shown), we analyzed men and women together in the following analyses.

Figure 1 also shows the results after excluding the first 5 years of follow-up and restricting the sample to those who never smoked, were <70 years of age, and whose TC level was ≥4.1 mmol/l. Risk for both all-cause (Figure 1c) and CVD mortality (Figure 1d) was not attenuated in underweight individuals. The risk increased in participants with BMI ≥25 kg/m² and seemed more apparent in this restricted sample of healthy participants than in the entire population. For all-cause mortality, even in this restricted sample

Table 1 Age-, gender-adjusted baseline characteristics of several risk factors across BMI categories. NIPPON DATA80,1980

	BMI < 18.5	18.5 ≤ BMI < 21	21 ≤ BMI < 23	23 ≤ BMI < 25	25 ≤ BMI < 27	27 ≤ BMI < 30	30 ≤ BMI	*P* for trend
Male + Female (*N*)	604	2,209	2,348	1,891	1,073	615	184	
Age (years) (Mean (s.d.))	54.1 (15.5)	49.6 (13.8)	49.7 (12.8)	49.7 (12.5)	50.1 (11.8)	50.8 (12.2)	52.5 (12.4)	0.36
Gender (% female) (% (*N*))	58.3% (352)	53.9% (1,191)	53.7% (1,261)	55.2% (1,043)	53.3% (572)	62.8% (386)	81.5% (150)	<0.01
Systolic BP (mm Hg) (mean*(s.d.))	129.0 (22.2)	131.2 (20.8)	134.9 (20.6)	137.1 (20.3)	140.4 (20.1)	142.4 (22.2)	145.0 (23.1)	<0.01*
Diastolic BP (mm Hg) (mean*(s.d.))	76.4 (12.0)	78.0 (11.7)	80.8 (11.9)	82.5 (11.7)	84.7 (11.3)	86.4 (12.8)	89.3 (13.8)	<0.01*
Total cholesterol (mmol/l) (mean*(s.d.))	4.51 (0.72)	4.63 (0.81)	4.81 (0.83)	4.94 (0.88)	5.07 (0.86)	5.09 (0.88)	5.24 (0.91)	<0.01*
Hypertensive drugs (%* (no. of yes))	4.3% (39)	5.3% (118)	9.1% (205)	11.3% (201)	15.6% (159)	15.1% (93)	24.4% (50)	<0.01*
Diabetes (%* (no. of yes))	5.1% (38)	4.4% (99)	4.3% (98)	5.8% (105)	6.0% (62)	8.4% (49)	10.7% (18)	<0.01*
Current smoking (%* (no. of yes))	40.9% (233)	35.6% (805)	32.7% (794)	31.7% (605)	29.0% (325)	31.1% (168)	26.4% (26)	<0.01*
Current alcohol drinking (%* (no. of yes))	19.2% (109)	23.2% (527)	25.2% (614)	24.5% (468)	20.6% (231)	19.0% (100)	17.1% (15)	0.09*

N, numbers of participants.
*Adjusted for age and gender.

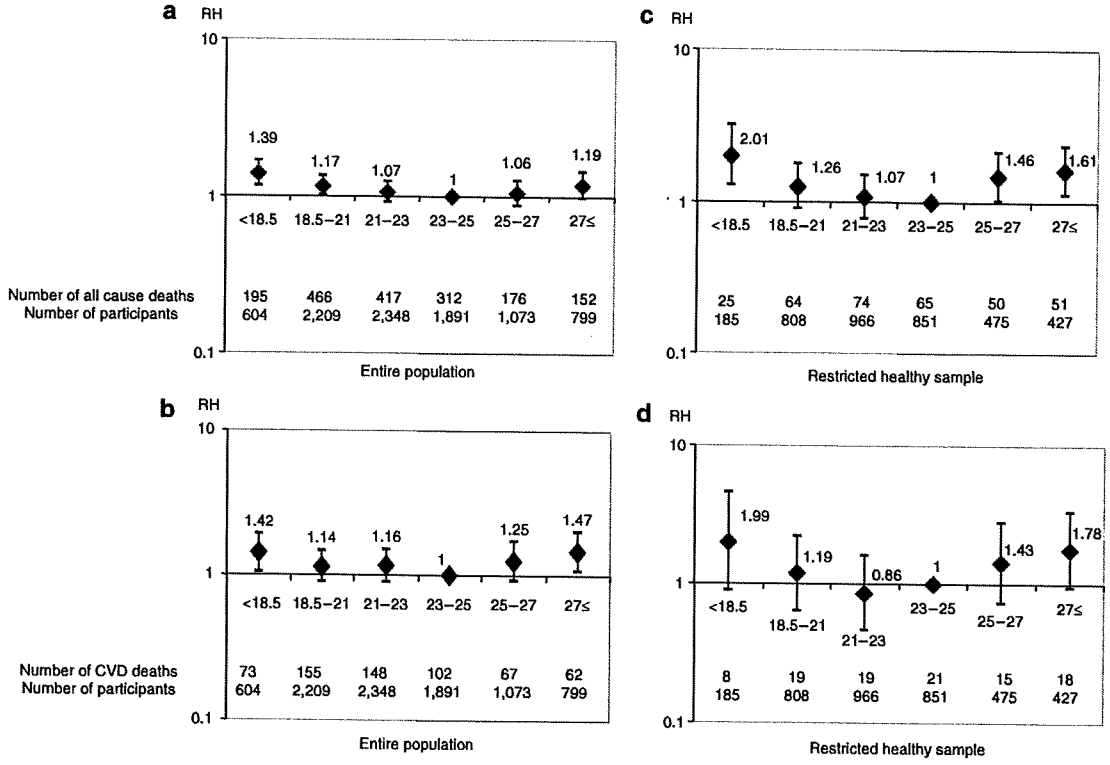

Figure 1 Relationship of BMI with death from all causes and cardiovascular disease (CVD) in the unrestricted and restricted sample of healthy individuals. (**a**) Relationship between BMI categories and all-cause mortality in the unrestricted sample. (**b**) Relationship between BMI categories and CVD mortality in the unrestricted sample. (**c**) Relationship between BMI categories and all-cause mortality in the restricted sample of healthy individuals. (**d**) Relationship between BMI categories and all-cause mortality in the restricted sample of healthy individuals. RHs: relative hazards are adjusted for age, gender, smoking (never, past, current; 1–20, 21–40, or ±41 cigarettes/day), and alcohol consumption (never, past, occasional, and daily). The BMI range from ≥23 to <25 kg/m² is used as a reference for comparison with other BMI strata. Diamonds and numbers above diamonds represented RHs. Bars = 95% confidence intervals for the corresponding RHs. The restricted sample of a healthy individuals is defined as participants who had never smoked, were <70 years of age, had TC γ4.1 mmol/l, and who could be followed up for >5 years.

of healthy participants, those with BMI between 23 and 25 kg/m² had the lowest risk of all-cause mortality. The risk of death due to CVD was also similar in this group to that of the group whose BMI was between 21 and 22.9 kg/m².

DISCUSSION

The results of this study show that the lowest relative risk for all-cause mortality was associated with a BMI between 23.0 and 24.9 kg/m². This range was also unchanged when analyses were limited to participants who had never smoked, were <70 years of age, had TC ≥4.1 mmol/l, and who could be followed up for at least 5 years.

Several factors might modify the relationship between BMI and all-cause mortality, especially for lower BMI levels. The effect of weight loss due to smoking (5,10–12), higher age (10,12,13), low TC (14–16,20), and subclinical conditions which can coexist in underweight individuals (5–15,17,18) might explain the higher mortality in lean participants. However, when we restricted our analyses to participants <70 years of age, who never smoked, had TC ≥4.1 mmol/l, and who could be followed up for at least 5 years, the relationship between higher all-cause mortality and being underweight persisted. The data also show that those with a BMI between 23 and 25 kg/m² in this restricted sample of healthy individuals had the lowest risk of all-cause mortality. Thus, we conclude that higher mortality among lean participants cannot be fully explained by the above mentioned factors. The relationship between BMI and CVD mortality was also similar to associations with all-cause mortality. This was consistent with a recent study of Korean men and women who did not have self-reported atherosclerotic CVD, cancer, liver disease, diabetes, or respiratory diseases at baseline (5).

As the WHO defines a healthy BMI as <23 kg/m² in Asian individuals (4), data regarding optimal BMI for all-cause mortality in Asia is of interest. For Western populations, a healthy BMI is defined as <25 kg/m². Our study does not support the notion that a lower BMI cutoff value in Asian vs. Western populations is warranted because all-cause mortality risk does not appear to differ between BMI ranges from 18.5 to 22.9 and from 23.0 to 24.9 kg/m². Our findings further suggest that risk of death may be highest in individuals with a BMI <18.5 kg/m², even for those who fell in our restricted healthy sample. We believe that additional studies are needed to properly identify an optimal BMI range for Asian populations that is associated with maximum longevity.

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DISCLOSURE

The authors declared no conflict of interest.

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APPENDIX

NIPPON DATA80, 90: "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, Japan).

Consultant: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido, Japan), Teruo Omae (Health C&C Center, Hisayama, Kasuya, Fukuoka, Japan), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita, Japan), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama, Japan), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi, Japan).

Participating researchers: Akira Okayama (The First Institute of Health Service, Japan Anti-Tuberculosis Association, Chyioda-ku, Tokyo, Japan), Kazunori Kodama, Fumiyoshi Kasagi (Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Hiroshima, Japan), Tomonori Okamura (Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka, Japan), Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga, Japan), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Fukushima, Japan), Shinichi Tanihara (Department of Hygiene and Preventive Medicine, Fukuoka University School of Medicine, Fukuoka, Fukuoka, Japan), Shigeyuki Saito (Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate, Japan), Yosikazu Nakamura (Department of Public Health, Jichi Medical University School of Medicine, Shimotsuke, Tochigi, Japan), Fumihiko Kakuno (Higashiomi Public Health Center, Higashiomi, Shiga, Japan).

Participating research associates: Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano, Takahisa Kawamoto and members of 300 Public Health Centers in Japan, Masumi Minowa (Faculty of Humanities, Seitoku University, Matsudo, Chiba, Japan), Minoru Iida (Kansai University of Welfare Sciences, Kashiwara, Osaka, Japan), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa, Japan), Shigemichi Tanaka (Department of Cardiology, Cardiovascular Center, Teine Keijinkai, Sapporo, Hokkaido, Japan), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga, Japan), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako, Saitama, Japan), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo, Japan), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama, Japan).

Original Article

Relationships between Family Histories of Stroke and of Hypertension and Stroke Mortality: NIPPON DATA80, 1980–1999

Aya KADOTA[1,2], Tomonori OKAMURA[3], Atsushi HOZAWA[4], Takashi KADOWAKI[1], Yoshitaka MURAKAMI[1], Takchito HAYAKAWA[5], Yoshikuni KITA[1], Akira OKAYAMA[6], Yasuyuki NAKAMURA[7], and Hirotsugu UESHIMA[1], for the NIPPON DATA80 Research Group*

A family history of stroke seems to be related with increased risk of stroke although the relationship is not always significant. Increased risk of stroke is strongly associated with hypertension, which might be also associated with family history. However, investigations into the relationship between family history of hypertension and stroke mortality are scarce. We investigated whether a family history of stroke and that of hypertension evaluated using a simple questionnaire could predict stroke mortality in Japanese. We obtained parental histories of stroke and of hypertension from 8,037 randomly selected general Japanese without history of cardiovascular disease and followed them for 19 years. The multivariate adjusted hazard ratios (HRs) for total stroke mortality, intra-cerebral hemorrhage mortality and for cerebral infarction mortality according to family history were estimated using the Cox proportional hazards model. The prevalences of family histories of stroke and of hypertension were 20.6% and 31.1%, respectively. A family history of stroke was not related to total stroke mortality, intra-cerebral hemorrhage mortality or to cerebral infarction mortality. Meanwhile, a family history of hypertension was positively related to total stroke mortality among women aged less than 60 years and men aged 60 or more years (women: HR=3.41, 95% confidence interval [CI]: 1.49–7.81; men: HR=1.50, 95% CI: 1.00–2.24) even after adjustment for systolic blood pressure. In conclusion, a family history of stroke could not predict total stroke mortality. However, a family history of hypertension might predict an increased risk for total stroke. (*Hypertens Res* 2008; 31: 1525–1531)

Key Words: **family history, stroke, hypertension, stroke mortality, epidemiology**

From the [1]Department of Health Science and [2]Department of Internal Medicine, Shiga University of Medical Science, Otsu, Japan; [3]Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan; [4]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; [5]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan; [6]The First Institute of Health Service, Japan Anti-Tuberculosis Association, Tokyo, Japan; and [7]Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, Japan.

*Members of the Research Group are listed in the reference 6.

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Address for Reprints: Aya Kadota, M.D., Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu 520–2192, Japan. E-mail: ayakd@belle.shiga-med.ac.jp

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Introduction

One of the simplest ways to determine whether individuals have a potential genetic risk for diseases, even in developing countries, is to collect information about their family history. The 2002 American Heart Association guidelines for primary prevention of cardiovascular disease and stroke recommend regularly updating family histories for coronary heart disease (*1*).

Stroke is strongly affected by hypertension, which may also be associated with family history (*2*). Thus, knowledge of the family history of hypertension might also provide potential predictability for stroke. Nevertheless, the relationship between stroke mortality and a family history of stroke and of hypertension remains unclear except for the relationship between subarachnoid hemorrhage and a family history(*3*, *4*).

Although stroke mortality and incidence has remained still higher in Japan than in Western countries (*5*), very few prospective studies have examined the association between family history and stroke mortality in the general Japanese population. NIPPON DATA80 is a large cohort study of individuals selected randomly from all over Japan who were followed up for 19 years. We investigated whether a simple questionnaire about family histories of stroke and of hypertension could predict stroke mortality among the general Japanese population.

Methods

Population

Cohort studies of the National Survey on Circulatory Disorders, Japan, are referred to as NIPPON DATA (National Integrated Project for Prospective Observation of Noncommunicable Disease and its Trends in the Aged). The present study analyzed data from NIPPON DATA80, in which baseline surveys were performed in 1980. Details of this cohort have been reported elsewhere (*6*).

A total of 10,546 residents (4,640 men and 5,906 women, aged ≥30 years) from 300 randomly selected districts participated in the survey and were followed up until November 1999. The overall population of residents over 30 years of age in all districts was 13,771, and the participation rate in the survey was 76.6%. Accordingly, these participants were considered to be representative of the Japanese population. Of the 10,546 participants, 2,509 were excluded due to incomplete residential access information at the first survey (n=908), a history of coronary heart disease or stroke (n=697), or missing information in baseline survey (n=904). The present study analyzed data from the remaining 8,037 participants (3,586 men and 4,451 women). The prevalences of family histories of stroke and of hypertension did not differ between those who were followed up and those who were not.

Follow-Up Survey

The underlying causes of death in the National Vital Statistics which we obtained from the Ministry of Health, Labour and Welfare were coded according to the 9th International Classification of Diseases (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the start of 1995 until the end of 1999. The details of these classifications are described elsewhere (*1*). Codes 430–438 in ICD-9 and I60–I69 in ICD-10 were defined as death from total stroke, which included death from cerebral infarction (codes 433, 434, 437.7a and 7b in ICD-9, I61 and I69.1 in ICD-10) and from intra-cerebral hemorrhage (codes 431–432 in ICD-9, I63 and I69.3 in ICD-10).

The Management and Coordination Agency of the Government of Japan provided permission to use the National Vital Statistics and the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000) approved this study.

Baseline Examination

Public health nurses obtained information about parental family histories of stroke and of hypertension (none, both parents, only paternal, only maternal). We defined a participant as "family history positive" if he or she reported that one parent had such a history. Public health nurses also obtained information about smoking, alcohol consumption, and medical history. Trained observers obtained baseline blood pressure values using a standard mercury sphygmomanometer placed on the right arm of seated participants. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Non-fasting blood samples were obtained at the baseline survey. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to a central laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan) for blood measurements. Plasma glucose was measured using the cupric-neocuproine method and converted to the value of the glucose oxidase method (*7*). Total cholesterol was also measured enzymatically as standardized by the Centers for Disease Control/National Heart, Lung, and Blood Institute (CDC-NHLBI) Lipids Standardization Program (*8*).

We defined high blood pressure as systolic blood pressure of ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the administration of antihypertensive agents, or any combination of these. We divided participants into five categories of smokers (never-smoked; ex-smoker; current smoker, <21 cigarettes/d, ≥21 cigarettes/d and ≥41 cigarettes/d) and four categories of drinking (never-drinker; ex-drinker; current drinker, occasionally and daily).

Table 1. Means and Prevalence of Baseline Characteristics of 3,586 Men and 4,451 Women Aged 30 Years and Older (NIPPON DATA80, 1980)

Baseline risk characteristics	Family history							
	Men				Women			
	Stroke		Hypertension		Stroke		Hypertension	
	No	Yes	No	Yes	No	Yes	No	Yes
A: Age less than 60								
Number of participants	2,199	559	1,183	875	2,676	719	2,348	1,047
Family history of stroke (%)	0.0	100.0	14.4	32.8*	0.0	100.0	14.8	35.4*
Age (years)	44.47±8.43	44.47±8.44	44.34±8.46	44.73±8.38	44.54±8.62	44.49±8.48	44.63±8.65	44.30±8.45
BMI (kg/m^2)	22.81±2.80	22.62±2.77	22.80±2.78	22.72±2.81	22.86±3.27	22.82±3.34	22.82±3.25	22.91±3.38
SBP (mmHg)	134.52±18.70	134.63±18.39	134.06±18.79	135.59±18.26	129.24±19.15	129.18±19.11	129.35±19.07	128.97±19.29
DBP (mmHg)	83.21±12.13	82.56±12.41	82.78±12.03	83.72±12.50	78.27±11.64	79.28±11.67	78.22±11.36	79.07±12.27
Total cholesterol (mg/dL)	188.15±33.31	185.77±32.23	187.67±32.96	187.66±33.41	187.28±32.69	186.42±35.06	186.81±32.52	187.76±34.69
Blood glucose (mg/dL)	100.34±32.17	98.73±25.33	99.52±29.61	101.07±33.52	98.17±26.65	96.06±19.53	98.63±27.77	95.70±18.56
High blood pressure (%)	35.1	37.6	34.5	37.9	25.1	26.6	25.2	25.9
Medication for hypertension (%)	7.1	6.8	7.3	6.5	7.8	9.0	7.7	8.9
Drinking (%)								
Non-drinker	21.8	19.3	21.6	20.7	78.4	78.4	77.8	79.9
Occasional-drinker	29.1	27.4	29.3	27.8	19.0	19.2	19.3	18.4
Current-drinker	49.1	53.3	49.1	51.5	2.6	2.4	2.9	1.7
Smoking (%)								
Non-smoker	33.7	34.7	33.4	35.2	92.0	91.8	92.4	91.1
Current smoker (<21 cigarettes/d)	37.2	35.8	38.0	34.7	7.3	7.4	7.0	8.0
Current smoker (≥21 cigarettes/d)	29.1	29.5	28.6	30.1	0.7	0.8	0.6	0.9
B: Age 60 and more								
Number of participants	654	174	559	269	852	204	749	307
Family history of stroke (%)	0.0	100.0	15.0	33.5*	0.0	100.0	15.1	29.6*
Age (years)	69.06±6.35	68.54±6.04	68.67±6.05	69.12±6.75	68.71±6.29	69.01±6.87	68.66±6.20	69.03±6.87
BMI (kg/m^2)	21.78±2.91	21.77±3.09	21.74±2.90	21.86±3.03	22.77±3.54	22.78±3.53	22.79±3.54	22.74±3.51
SBP (mmHg)	150.24±20.87	150.22±20.94	150.32±22.49	150.06±22.45	147.32±22.59	144.85±22.61	147.64±22.78	144.88±22.09
DBP (mmHg)	85.12±12.67	84.89±11.64	84.81±12.33	85.61±12.72	82.65±12.32	81.53±11.86	82.58±12.33	82.06±12.03
Total cholesterol (mg/dL)	182.57±31.72	185.70±32.46	184.39±31.98	180.81±31.60	201.52±34.43	195.63±30.05	200.90±33.00	199.12±35.36
Blood glucose (mg/dL)	111.50±40.45	106.04±28.31	110.28±40.45	110.50±33.36	110.04±35.33	110.88±31.05	109.86±33.53	111.03±36.91
High blood pressure (%)	67.4	72.4	67.8	69.9	63.6	61.8	64.9	59.3
Medication for hypertension (%)	26.9	31.0	26.7	30.1	29.1	30.4	29.9	28.0
Drinking (%)								
Non-drinker	35.9	32.8	36.3	33.1	84.6	82.8	84.6	83.4
Occasional-drinker	20.6	17.2	18.8	22.3	11.3	12.7	11.2	12.4
Current-drinker	43.4	50.0	44.9	44.6	4.1	4.5	4.2	4.2
Smoking (%)								
Non-smoker	43.3	48.3	44.5	43.9	88.7	91.2	89.2	89.3
Current smoker (<21 cigarettes/d)	45.3	40.2	44.7	43.1	10.3	8.3	9.9	10.1
Current smoker (≥21 cigarettes/d)	11.4	11.5	10.8	13.0	1.0	0.5	0.9	0.6

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. High blood pressure was defined as SBP≥140 mmHg and/or DBP≥90 mmHg and/or medication. "Non-drinker" represents never-drinker and ex-drinker. "Non-smoker" represents never-smoked and ex-smoker. *$p<0.05$.

Statistical Analysis

Continuous variables were compared using the analysis of variance and dichotomized variables were compared using the χ^2-test to determine differences in the baseline characteristics according to family history categories. The multivariate adjusted hazard ratios (HRs) of stroke mortality were estimated by three Cox proportional hazards models with the following adjustments: Model 1, age; Model 2, age, total cholesterol, blood glucose, smoking, and drinking category; Model 3, systolic blood pressure was added to Model 2. All confidence intervals were estimated at the 95% level. All statistical tests were two-sided and significance was defined as $p<0.05$. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 11.0J, Tokyo, Japan) was used to perform all analyses.

Results

The prevalences of family histories of stroke and of hypertension were 20.6 and 31.1%, respectively. Table 1 shows the baseline characteristics of the study participants stratified by gender and age according to family histories. In both gender- and age-specific groups, participants with a family history of hypertension more often had a family history of stroke. We did not find any significant difference according to family history in mean values of age, BMI, blood pressure, total cholesterol, or blood glucose. In addition, the prevalences of hypertension, frequency of medication for hypertension, smoking, or alcohol consumption did not significantly differ.

Total person-years of follow-up were 140,340 and the mean follow-up period was 17.5 years. During this period, 1,570 participants died of all causes and 261 participants died of total stroke (152 of ischemic stroke, 58 of intra-cerebral hemorrhagic stroke and 51 of other conditions).

Table 2 shows gender specific analyses. The number of stroke deaths, multiple adjusted HRs and 95% confidence intervals (CIs) for stroke mortality according to family histories of stroke and of hypertension are listed. A family history of stroke was not related to stroke mortality in either gender. A family history of hypertension was positively and significantly related to cerebral infarction mortality in men (Table 2; total stroke, Model 2: HR=1.38, 95% CI: 0.97–1.96, cerebral infarction, Model 2: HR=1.68, 95% CI: 1.08–2.60). On the other hand, a family history of hypertension did not predict stroke mortality in women.

Table 3 shows gender- and age-group-specific analyses. A family history of stroke was not related to stroke mortality in either gender or any age specific group. A family history of hypertension did not relate to total stroke mortality in younger men aged <60 years but significantly increased total stroke mortality in elderly men aged ≥60 years (Table 3: men B; Model 2: HR=1.52, 95% CI: 1.02–2.27). Conversely, in women, a family history of hypertension significantly increased total stroke mortality in younger group aged <60 years (Table 3: women A; Model 2: HR=3.06, 95% CI: 1.37–6.86). Among elderly women aged ≥60 years, we did not find any relationship between family history of hypertension and stroke mortality (Table 3: women B). We calculated all HRs using the three models and found that adjustment for systolic blood pressure did not alter these findings.

Discussion

The present study found that a family history of stroke could not predict stroke mortality in the general Japanese population. However, a family history of hypertension significantly related to stroke mortality among elderly men aged 60 or more years and younger women aged less than 60 years.

In previous epidemiologic investigations including studies of twins and the Framingham Study, a family history of stroke seemed to increase the risk of stroke although some studies did not find a significant relationship (*4*, *9–16*). Floßmann *et al.* systematically reviewed the genetic epidemiology of ischemic stroke. Their meta-analyses identified a positive family history of stroke as a moderate risk factor for ischemic stroke in both case-control (odds ratio [OR]: 1.76; 95% CI, 1.7–1.9) and cohort (OR: 1.3; 95% CI, 1.2–1.5) studies (*4*). Although possible confounding factors were not adjusted for, a prospective Japanese study showed that a family history of stroke increased the risk of intra-cerebral hemorrhage but not of cerebral infarction (*11*). Based on these findings, the American Heart Association/American Stroke Association Stroke Council noted that both paternal and maternal histories of stroke are associated with increased risk of stroke through many mechanisms, including 1) genetic heritability of stroke risk factors, 2) inheritance of susceptibility to the effects of such risk factors, 3) familial sharing of cultural/environmental and lifestyle factors, and 4) interaction between genetic and environmental factors (*3*).

On the bases of this information, we initially postulated that participants with a family history of stroke might have higher blood pressure, other unfavorable risk factors and consequently a higher HR for stroke mortality than those without such a family history. However, we did not identify any significant associations. One possible explanation for the absence of a relationship between family history of stroke and stroke mortality might be the very high historical stroke mortality rate in Japan. Although the genetic pool of Japanese has not changed, the age-adjusted stroke mortality rate has significantly decreased during the past half-century (*17*). This suggests that environmental factors in the past, such as especially higher salt intake which lead to increased blood pressure or malnutrition, strongly contributed to the stroke incidence, especially that of cerebral hemorrhage (*18*). Furthermore, since infectious disease was frequent cause of death during the lifetimes of respondents' parents, there were also some possibilities that a positive family history of stroke in the present study included the parents who were afflicted with stroke because they simply lived longer. Thus, a family his-

Table 2. Multiple Adjusted Hazard Ratios and 95% Confidence Intervals According to the Family History by Gender in 3,586 Men and 4,451 Women Aged 30 Years and Older (NIPPON DATA80, 1980–1999)

	Family history							
	Men				Women			
	Stroke		Hypertension		Stroke		Hypertension	
	No	Yes	No	Yes	No	Yes	No	Yes
Number of participants	2,853	733	2,442	1,144	3,528	923	3,097	1,354
Person-years	48,805	12,550	41,926	19,378	62,799	16,237	55,044	23,992
All stroke								
Number of death	115	24	85	54	95	27	82	40
HR (95% CI)*	1.00	0.70 (0.45–1.10)	1.00	1.40 (0.99–1.99)	1.00	1.27 (0.82–1.95)	1.00	1.11 (0.75–1.62)
HR (95% CI)**	1.00	0.73 (0.47–1.15)	1.00	1.38 (0.97–1.96)	1.00	1.32 (0.85–2.04)	1.00	1.08 (0.73–1.59)
HR (95% CI)***	1.00	0.73 (0.47–1.15)	1.00	1.36 (0.96–1.93)	1.00	1.38 (0.89–2.14)	1.00	1.13 (0.77–1.66)
Intra-cerebral hemorrhage								
Number of death	28	6	22	12	18	6	13	11
HR (95% CI)*	1.00	0.77 (0.31–1.88)	1.00	1.19 (0.58–2.44)	1.00	1.26 (0.49–3.23)	1.00	1.93 (0.85–4.37)
HR (95% CI)**	1.00	0.77 (0.31–1.90)	1.00	1.16 (0.56–2.39)	1.00	1.36 (0.52–3.51)	1.00	1.87 (0.82–4.26)
HR (95% CI)***	1.00	0.78 (0.32–1.94)	1.00	1.13 (0.55–2.32)	1.00	1.47 (0.57–3.82)	1.00	1.82 (0.80–4.18)
Cerebral infarction								
Number of death	72	14	49	37	52	14	49	17
HR (95% CI)*	1.00	0.61 (0.34–1.10)	1.00	1.69 (1.10–2.61)	1.00	1.35 (0.74–2.45)	1.00	0.76 (0.44–1.33)
HR (95% CI)**	1.00	0.64 (0.35–1.15)	1.00	1.68 (1.08–2.60)	1.00	1.41 (0.78–2.57)	1.00	0.74 (0.42–1.29)
HR (95% CI)***	1.00	0.63 (0.35–1.14)	1.00	1.65 (1.07–2.56)	1.00	1.48 (0.81–2.69)	1.00	0.77 (0.44–1.36)

HR, hazard ratio; CI, confidence interval. Estimated by Cox proportional hazard model adjusted for: *age (Model 1); **age, blood glucose, total cholesterol, smoking habits and drinking habits (Model 2); and ***age, systolic blood pressure, blood glucose, total cholesterol, smoking habits and drinking habits (Model 3).

Table 3. Multiple Adjusted Hazard Ratios and 95% Confidence Intervals According to the Family History by Gender and Age Specific Group in 3,586 Men and 4,451 Women Aged 30 Years and Older (NIPPON DATA80, 1980–1999)

	Family history							
	Men				Women			
	Stroke		Hypertension		Stroke		Hypertension	
	No	Yes	No	Yes	No	Yes	No	Yes
A: Age less than 60								
Number of participants	2,199	559	1,883	875	2,676	719	2,348	1,047
Person-years	40,085	10,144	34,412	15,817	49,918	13,300	43,811	19,407
All stroke								
Number of death	26	8	22	12	20	5	11	14
HR (95% CI)*	1.00	1.19 (0.53–2.69)	1.00	1.10 (0.54–2.27)	1.00	0.74 (0.27–2.00)	1.00	3.18 (1.42–7.11)
HR (95% CI)**	1.00	1.30 (0.57–2.96)	1.00	1.03 (0.50–2.14)	1.00	0.72 (0.26–1.95)	1.00	3.06 (1.37–6.86)
HR (95% CI)***	1.00	1.31 (0.57–3.00)	1.00	1.04 (0.50–2.16)	1.00	0.65 (0.24–1.78)	1.00	3.41 (1.49–7.81)
B: Age 60 and more								
Number of participants	654	174	559	269	852	204	749	307
Person-years	8,720	2,355	7,514	3,561	12,881	2,937	11,233	4,585
All stroke								
Number of death	89	16	63	42	75	22	71	26
HR (95% CI)*	1.00	0.58 (0.34–1.00)	1.00	1.50 (1.01–2.23)	1.00	1.42 (0.88–2.30)	1.00	0.81 (0.52–1.28)
HR (95% CI)**	1.00	0.58 (0.34–1.01)	1.00	1.52 (1.02–2.27)	1.00	1.54 (0.95–2.50)	1.00	0.76 (0.48–1.20)
HR (95% CI)***	1.00	0.58 (0.34–1.00)	1.00	1.50 (1.00–2.24)	1.00	1.57 (0.97–2.57)	1.00	0.77 (0.49–1.23)

HR, hazard ratio; CI, confidence interval. Estimated by Cox proportional hazard model adjusted for: *age (Model 1); **age, blood glucose, total cholesterol, smoking habits and drinking habits (Model 2); and ***age, systolic blood pressure, blood glucose, total cholesterol, smoking habits and drinking habits (Model 3).

tory of stroke assessed using the reports to a simple questionnaire in the present study could not predict stroke mortality in Japan. Differentiation of family history of stroke and age of stroke onset among afflicted parents might be important to understand the influence of a family history of stroke on stroke mortality (*16*).

Hypertension is one of the main risk factors for stroke, which is also supposed to be affected by family history (*2*, *19*). Several genetic epidemiologic studies have revealed that gene polymorphisms are related to hypertension (*19–21*). Some studies have also found an aggregation of hypertension and stroke in family histories and medical histories, suggesting a close association between these diseases (*22*, *23*). We also found an aggregation of both diseases in family histories in the present study. However, studies on the relationship between a family history of hypertension and stroke mortality are still scarce and the results are not concordant. Floßmann *et al.* mentioned the difficulty of diagnosing family history of hypertension in the past in their review (*4*). Okada *et al.* reported the prevalence of family history of hypertension was 5.4% (224/4,186) in 1976 (*11*), which was much lower than that observed in the present study. Recall for parental hypertension may be difficult to confirm because of less frequent opportunity for measuring blood pressure or different criteria of hypertension when their parents were young and alive and of so-called "recall bias." Thus, further study should be warranted. In our present findings, we observed the relationship between family history of hypertension and stroke mortality was evident with a significant HR greater than 3.0 among younger women than elder women and men. This suggests that some genetic influences are involved in the pathogenesis of hypertension and stroke (*14*, *15*), although HR of elder men was around 1.5 with statistical significance. We primarily hypothesized that the relation between family history of hypertension and stroke mortality was stronger in younger than that in elderly because the effect of environmental cardiovascular risk factors might be evident in the elderly and numbers of risk factors would increase with age (*24*), which attenuated the effect of family history due to genetic background. This hypothesis is consistent with our findings for women. Since the awareness of hypertension was reported to be lower in men than in women (*25*), lower accuracy of family history of hypertension in men might have lead to the low HR in younger men.

In conclusion, a simple questionnaire designed to assess a family history of stroke could not be an index of potential genetic risk predicting stroke mortality in this study. More specific information with regard to parental history of stroke or more specific genetic exploration might be required to assess the genetic risk of stroke mortality. Whereas a family history of hypertension obtained from a simple questionnaire might have the potential to predict an increased risk of total stroke mortality. For individuals who reported family history of hypertension, other cardiovascular risk factors and the risk factors for future hypertension such as salt intake (*26*), should be managed to prevent stroke.

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Original Article

Prognostic Value of Q Wave for Cardiovascular Death in a 19-Year Prospective Study of the Japanese General Population

Aya Higashiyama[1, 2], Atsushi Hozawa[3], Yoshitaka Murakami[1], Tomonori Okamura[2], Makoto Watanabe[2], Yasuyuki Nakamura[4], Takehito Hayakawa[5], Takashi Kadowaki[1], Yoshikuni Kita[1], Akira Okayama[6], and Hirotsugu Ueshima[1] for the NIPPON DATA80 Research Group[7]

[1]Department of Health Science, Shiga University of Medical Science, Ostu, Japan
[2]Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan
[3]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[4]Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, Japan
[5]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan
[6]The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo, Japan
[7]Members of the Research Group are listed in the Appendix

Aim: Little is known about the prognostic value of q wave abnormality for cardiovascular disease (CVD) on a resting electrocardiogram (ECG) of the Japanese general population with an extremely low incidence of myocardial infarction.
Methods: We followed 8,339 participants without a past and present history of CVD for 19 years. The multivariate-adjusted hazard ratio (HR) of q wave abnormality for CVD mortality was estimated by the Cox proportional hazards model.
Results: The multivariate-adjusted HR of composite findings of moderate or severe q wave abnormality was 1.75 (95% confidence interval (CI): 0.97–3.17) for mortality due to CVD and 2.97 (95%CI: 1.43–6.16) due to heart diseases. The multivariate-adjusted HR of mild abnormality for mortality from heart diseases was 1.95 (95%CI: 1.00–3.81). The relationship between moderate or severe abnormalities and mortality from CVD was unchanged when participants with ST-T changes and high amplitude R waves were excluded and when participants were divided by the presence of major CVD risk factors such as hypertension. Q wave abnormality was not associated with the risk of stroke.
Conclusion: Moderate or severe q wave abnormalities are prominent and important predictors of mortality due to CVD and heart disease in the Japanese general population without CVD history.

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Key words; Hazard ratio, Cardiovascular diseases, Heart diseases, Cohort study

Introduction

Resting electrocardiogram (ECG) abnormalities such as q or ST-T wave abnormality classified by the Minnesota code (MC) have consistently been associated with an increased risk of all-cause mortality and CVD death, with most studies reporting a doubled relative risk[1-3].

Q wave in resting ECG is considered a sign of old myocardial infarction[4]. Previous studies have assessed the risk of q wave abnormality among the general population[1, 2, 5, 6]; however, little is known about the prevalence or prognostic value of q wave abnormality in the non-Western general population, such as Japanese, with an extremely low incidence of myocardial infarction.

Address for correspondence: Aya Higashiyama, Preventive Cardiology, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka, 565-8565, Japan
E-mail: ahigashi@hsp.ncvc.go.jp
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