Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2006;22:409–415
DOI: 10.1159/000094860

Received: February 20, 2006
Accepted: April 13, 2006
Published online: August 4, 2006

Body Mass Index and Risk of Stroke Mortality among a Random Sample of Japanese Adults: 19-Year Follow-Up of NIPPON DATA80

Izumi Oki[a] Yosikazu Nakamura[a] Tomonori Okamura[b] Akira Okayama[c]
Takehito Hayakawa[d] Yoshikuni Kita[b] Hirotsugu Ueshima[b]
NIPPON DATA80 Research Group

[a]Department of Public Health, Jichi Medical University, Tochigi; [b]Department of Health Science, Shiga University of Medical Science, Shiga; [c]Department of Preventive Cardiology, National Cardiovascular Center, Osaka, and [d]Department of Public Health, Shimane University School of Medicine, Shimane, Japan

Key Words
Body mass index · Stroke mortality · Cerebral infarction · Intracerebral hemorrhage · Obesity

Abstract
Background: The relationship between body mass index (BMI) and stroke mortality remains unclear. The aim of the present study was to elucidate the relationship between BMI and stroke death in a representative cohort of Japanese men and women. ***Methods:*** We analyzed a database of 9,526 men and women aged 30 years and older who were randomly selected throughout Japan in 1980. These individuals had no history of stroke and were followed for 19 years. Hazard ratios (HR) and their 95% confidence intervals (CI) of deaths due to total stroke, cerebral infarction, and intracerebral hemorrhage were examined using Cox's proportional hazards regression models of BMI levels. ***Results:*** A U-shaped association between BMI and cerebral infarction mortality was observed. Participants with the highest BMI category (BMI ≥ 30.0) showed a significantly highest HR for cerebral infarction (HR 2.46, 95% CI 1.01–5.99). The excess risk at the lower extreme of the BMI was confined to men. These associations did not change after excluding deaths occurring in the first 2 years of follow-up. ***Conclusions:*** In the Japanese general population, a U-shaped association between BMI and cerebral infarction mortality was found and the excess risk at the lower extreme of the BMI was confined to men.

Members of the NIPPON DATA80 Research Group are listed in the appendix.

Introduction

Although high body mass index (BMI) is well recognized as a risk factor for coronary heart disease, data on the association between BMI and stroke mortality remain limited. Obesity was categorized as a 'less well documented or potentially modifiable risk factor' in the guideline statement for health professionals from the Stroke Council of the American Heart Association [1]. Several studies have found a positive association between obesity and the risk of fatal and nonfatal stroke, particularly ischemic stroke [2–8]. Others have suggested a U-

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/06/0226–0409$23.50/0

Accessible online at:
www.karger.com/ced

Izumi Oki
Department of Public Health, Jichi Medical University
3311-1 Yakushiji Shimotsukeshi
Tochigi 329-0498 (Japan)
Tel. +81 285 58 7338, Fax +81 285 44 7217, E-Mail i-oki@jichi.ac.jp

shaped association, with individuals at either extreme of the BMI distribution at high risk [9, 10].

Most large-scale epidemiological studies have been conducted on western populations in which the criteria for obesity are different from those for Asian populations. Furthermore, few long-term follow-up studies have been conducted on Asian populations. Among Japanese men and women, the mean BMI is much lower than that of western countries [11]. However, Asian populations tend to have a higher percentage of body fat at any given BMI [12]. In Japan, the mean BMI has increased steadily over the last several decades [13, 14]. Clearly, the obesity epidemic is not restricted to western countries, and increases in mean BMI often occur at a faster rate in Asian countries than in western countries.

In the present study, we examined the relationship between BMI and deaths due to total stroke, cerebral infarction, and intracerebral hemorrhage during 19 years of follow-up of men and women in a nationally representative cohort of the Japanese population.

Subjects and Methods

Populations

The present study was based on the National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged conducted in 1980 (NIPPON DATA80). The details of the NIPPON DATA80 have been reported previously [15, 16].

The subjects of this cohort were participants in the National Survey on Circulatory Disorders in 1980. A total of 10,546 community-dwelling individuals (4,640 men and 5,906 women) aged 30 years and over from 300 randomly selected districts participated in the survey in 1980. This cohort of subjects was followed until 1999. As the overall population aged 30 years and over was 13,771 in the surveyed districts, the participation rate in the study was 76.6%. From the total of 10,546 participants, 1,020 were excluded for the following reasons: failure to follow-up (n = 870), past history of stroke (n = 117), and some missing data in survey (n = 33). Finally, data from 9,526 participants (4,171 men and 5,355 women) were used for the analyses.

Baseline Variables

The standardized procedures used in the National Survey on Circulatory Disorders in 1980 have been described elsewhere [15–17]. Staff members of the local public health centers in the respective districts carried out the examinations in community centers. Body weight was measured with participants wearing light clothes without shoes. The height of each participant was measured without shoes by a stadiometer. Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants. Nonfasting blood samples were drawn and centrifuged within 60 min of collection. Frozen serum was sent to the Osaka Medical Center for Health Science and Promotion, Osaka, Japan. At the laboratory, serum total cholesterol was measured using the Lieberman-Burchard direct method. Blood sugar was measured using a cupric-neocuproine method. A Technicon SMA 1260 (Technicon Instruments, Tarrytown, N.Y., USA) was used for these measurements.

Baseline information on hypertension, history of stroke and coronary heart disease, and smoking and alcohol drinking habits were obtained from a self-administered questionnaire. Individuals who indicated a history of hypertension were asked whether they were using antihypertensive agents or not. Subjects were asked to indicate whether they were current smokers, had quit smoking, or had never smoked. For alcohol drinking habits, subjects were asked to indicate whether they were nondrinkers, ex-drinkers, occasional drinkers, or everyday drinkers. Subjects were qualified as current drinkers if the response was occasional drinker or everyday drinker.

Follow-Up and Outcome Definitions

Subjects who died during the follow-up period were identified by local public health centers. Vital statistics for determining causes of death were obtained from the Management and Coordination Agency of the Government of Japan. The underlying causes of death for the National Vital Statistics were coded according to the 9th International Classification of Diseases for data regarding deaths until the end of 1994 and the 10th International Classification of Diseases for data regarding deaths from the beginning of 1995 [16].

The research protocol of the present study was approved by the Ethics Committee of Shiga University of Medical Science, Japan.

Statistical Analysis

Cox's proportional hazards regression models were used to examine the relationships between BMI and mortality. To determine the relationship between BMI and stroke mortality, BMI was entered as a categorical variable [11, 18]. Increasing levels of BMI were investigated using five BMI categories: <18.5, 18.5–22.9, 23.0–24.9, 25.0–29.9, and ≥30.0. These categories mirror WHO categories except normal category. The WHO normal category (18.5–24.9) was divided into two because the majority of the study population and events fell into that particular category. We selected the third category (23.0–24.9) as a reference. Furthermore, Cox's proportional hazard analyses were performed after excluding subjects who died within the initial 2 years of the follow-up period in order to rule out the possibility that subjects with subclinical diseases, such as cancer and chronic inflammatory disease, might have affected baseline BMI and the relationship with final outcome. Men and women were analyzed comprehensively. Smoking status, alcohol drinking can be confounded in BMI and mortality association; these variables were included in the model as well as age and sex. Blood pressure, serum total cholesterol, and glucose are considered in part to be a biological consequence of obesity, these variables were also adjusted in further analysis. Stratified analyses were performed by sex. All analyses were carried out using SAS version 8.02 for Windows (SAS Institute, Cary, N.C., USA).

Table 1. Baseline characteristics by category of BMI of 9,526 Japanese men and women aged 30 years and over in 1980, NIPPON DATA80

	BMI				
	<18.5	18.5–22.9	23.0–24.9	25.0–29.9	≥30.0
Men					
Number	273	2,194	902	765	37
Age, years	57.0 ± 16.0	50.7 ± 13.3	49.3 ± 12.4	48.5 ± 11.5	49.7 ± 12.6
Systolic blood pressure, mm Hg	137.3 ± 24.7	136.8 ± 21.0	139.6 ± 19.9	141.6 ± 19.4	143.1 ± 23.2
Diastolic blood pressure, mm Hg	79.5 ± 11.2	81.9 ± 12.2	84.8 ± 11.6	87.6 ± 12.2	91.2 ± 13.9
Serum total cholesterol, mmol/l	4.5 ± 0.7	4.7 ± 0.8	4.9 ± 0.9	5.1 ± 0.9	5.3 ± 1.0
Serum glucose, mmol/l	7.3 ± 2.0	7.2 ± 2.1	7.3 ± 2.3	7.3 ± 1.9	8.3 ± 2.5
Medication (antihypertension), %	9.2	8.0	10.2	13.6	16.2
Current smoker, %	68.9	65.5	61.8	56.3	48.7
Current drinker, %	63.0	75.0	77.1	75.0	62.2
Deaths from total stroke, n (n/TPY)	20 (5.02)	97 (2.63)	22 (1.41)	24 (1.78)	2 (3.26)
Deaths from cerebral infarction, n (n/TPY)	17 (4.26)	58 (1.57)	11 (0.70)	14 (1.04)	1 (1.63)
Deaths from intracerebral hemorrhage, n (n/TPY)	3 (0.75)	23 (0.62)	6 (0.38)	6 (0.45)	1 (1.63)
Women					
Number	381	2,620	1,135	1,056	163
Age, years	53.3 ± 15.0	49.6 ± 13.6	51.0 ± 12.9	52.4 ± 12.1	53.4 ± 12.2
Systolic blood pressure, mm Hg	128.7 ± 20.4	130.3 ± 20.5	135.3 ± 20.7	141.4 ± 21.9	146.7 ± 22.6
Diastolic blood pressure, mm Hg	75.6 ± 12.1	77.5 ± 11.3	80.6 ± 11.4	83.8 ± 11.4	88.5 ± 13.5
Serum total cholesterol, mmol/l	4.7 ± 0.8	4.8 ± 0.9	5.0 ± 0.9	5.1 ± 0.9	5.4 ± 0.9
Serum glucose, mmol/l	7.2 ± 1.9	7.0 ± 1.7	7.2 ± 1.8	7.4 ± 2.2	7.6 ± 1.8
Medication (antihypertension), %	5.8	7.9	12.6	18.8	31.9
Current smoker, %	16.3	8.5	7.7	8.7	5.5
Current drinker, %	16.3	21.8	19.9	16.7	17.2
Deaths from total stroke, n (n/TPY)	12 (1.91)	70 (1.52)	33 (1.65)	31 (1.67)	8 (2.82)
Deaths from cerebral infarction, n (n/TPY)	7 (1.11)	35 (0.76)	17 (0.85)	17 (0.92)	5 (1.76)
Deaths from intracerebral hemorrhage, n (n/TPY)	3 (0.48)	15 (0.32)	7 (0.35)	4 (0.22)	2 (0.70)

TPY = Total person-years follow-up (/1,000 person-years).

Results

The mean (± standard deviation) baseline BMI in our entire study population was 22.7 (± 3.2), with means of 22.5 (± 2.9) observed for men and 22.9 (± 3.4) for women. Table 1 shows the mean and prevalence of the baseline characteristics and unadjusted numbers of deaths due to stroke by BMI categories. Death rates are shown per 1,000 person-years. Mean values for systolic blood pressure, diastolic blood pressure, serum total cholesterol, and use of antihypertension agents in both sexes were higher in higher BMI categories. In contrast, the proportion of current smokers was higher in lower BMI categories.

Total population time observed was 164,457 person-years, and the mean follow-up period was 17.3 years. During the follow-up period, 319 deaths due to stroke were observed, including 182 cerebral infarctions, 70 intracerebral hemorrhages and 67 other types of stroke (subarachnoid hemorrhage and unclassified). The relationships among baseline BMI categories and deaths due to total stroke, cerebral infarction, and intracerebral hemorrhage are shown in table 2. A U-shaped association between BMI and cerebral infarction mortality was observed. In both men and women, the highest BMI category (≥30.0) showed the highest hazard ratio, although it did not reach statistical significance. We observed statistically significant elevation when men and women were combined. The excess risk in the lower extreme of the BMI distribution was confined to men. For total stroke mortality, pattern of association was similar to that of cerebral infarction; however, no statistically significant association was observed in the model adjusted for age, smoking, and alcohol drinking.

To exclude the influence of preexisting disease, deaths during the first 2 years of the follow-up period were excluded from the analysis. There were 25 deaths due to total stroke, including 10 cerebral infarctions and 5 intracerebral hemorrhages during the first 2-year follow-up period. After excluding such deaths, similar trends were observed.

Discussion

We found a U-shaped association between BMI and cerebral infarction mortality, the excess risk in the lower extreme of the BMI distribution was confined to men. The U-shaped association did not change after excluding deaths in the first 2 years of follow-up. The strengths of the present study are as follows: (1) the analysis of randomly selected subjects representative of the Japanese population; (2) a high participation rate (76.6%); (3) the direct collection of height, weight and biological markers from all participants; (4) a long follow-up period (19 years). Although previous cohort studies have been conducted in selected geographic areas of Japan, no follow-up studies have been conducted on a randomly selected sample throughout Japanese population. Furthermore, while several large cohort studies [10] have collected data by means of interviews, in the present study, staff members of local public health centers measured height and weight, and blood samples received from all participants were accurately measured. In Japan, a national prevention program for all Japanese residents (examination of health care under the health care law for the aged) has been in place since 1983; thus, the baseline data in the present study was not influenced by that intervention.

Some prospective studies have shown an increased risk for stroke with increasing BMI, particularly cerebral infarction [2–8]. Several studies also suggested that abdominal obesity, rather than general obesity, is associated

Table 2. Relationship between BMI and death due to total stroke, cerebral infarction, and intracerebral hemorrhage in 9,526 Japanese men and women aged 30 years and over, as determined at the 19-year follow-up of NIPPON DATA80

BMI	Stroke				Cerebral infarction			
	adjusted for age, smoking and alcohol		fully adjusted[a]		adjusted for age, smoking and alcohol		fully adjusted[a]	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Men and women[b]								
<18.5	1.14 (0.73, 1.77)	0.56	1.36 (0.87, 2.12)	0.18	1.57 (0.90, 2.73)	0.11	1.85 (1.05, 3.26)	0.03
18.5–22.9	1.21 (0.89, 1.64)	0.23	1.28 (0.94, 1.74)	0.12	1.28 (0.84, 1.96)	0.25	1.36 (0.88, 2.09)	0.17
23.0–24.9	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
25.0–29.9	1.22 (0.84, 1.78)	0.29	1.17 (0.80, 1.71)	0.41	1.43 (0.86, 2.39)	0.17	1.41 (0.84, 2.36)	0.20
≥30.0	1.94 (0.98, 3.82)	0.06	1.87 (0.95, 3.69)	0.07	2.46 (1.01, 5.99)	0.05	2.49 (1.02, 6.10)	0.05
Men								
<18.5	1.64 (0.89, 3.03)	0.11	1.90 (1.02, 3.53)	0.04	2.64 (1.22, 5.70)	0.01	3.07 (1.41, 6.68)	<0.01
18.5–22.9	1.58 (0.99, 2.51)	0.05	1.61 (1.01, 2.57)	0.05	1.85 (0.97, 3.53)	0.06	1.87 (0.98, 3.58)	0.06
23.0–24.9	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
25.0–29.9	1.62 (0.91, 2.90)	0.10	1.57 (0.88, 2.80)	0.13	2.02 (0.91, 4.45)	0.08	1.91 (0.86, 4.22)	0.11
≥30.0	3.60 (0.84, 15.36)	0.08	3.71 (0.87, 15.88)	0.08	4.59 (0.59, 35.75)	0.15	4.73 (0.61, 36.94)	0.14
Women								
<18.5	0.79 (0.40, 1.55)	0.50	0.99 (0.50, 1.96)	0.98	0.92 (0.37, 2.26)	0.85	1.12 (0.45, 2.81)	0.81
18.5–22.9	0.95 (0.63, 1.44)	0.81	1.06 (0.70, 1.62)	0.79	0.91 (0.51, 1.63)	0.76	1.03 (0.57, 1.88)	0.92
23.0–24.9	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
25.0–29.9	0.97 (0.59, 1.58)	0.89	0.93 (0.56, 1.52)	0.76	1.04 (0.53, 2.05)	0.90	1.05 (0.53, 2.09)	0.88
≥30.0	1.47 (0.68, 3.17)	0.33	1.44 (0.66, 3.13)	0.36	1.72 (0.63, 4.68)	0.29	1.85 (0.68, 5.09)	0.23

HR = Hazard ratio; CI = confidence interval.
[a] Adjusted for, age, smoking, alcohol, systolic blood pressure, serum cholesterol level, and serum glucose level.
[b] Adjusted for sex.

with an increased risk for stroke [19]. Obesity is a strong risk factor for the development of hypertension [20], diabetes [21], and hypercholesteremia [22]. It has been well established that metabolic syndrome, due to visceral fat accumulation, is a strong risk factor in ischemic stroke [22, 23]. In the present study, participants in the highest BMI group may have had more risk factors related to metabolic syndrome but were not included in the baseline survey. For example, a large proportion of obese individuals have higher visceral fat accumulation than nonobese individuals, which is a key factor of metabolic syndrome [22]. As we did not measure serum high-density lipoprotein cholesterol, triglyceride levels, or the homeostasis model assessment index, we need to adjust for or assess these factors in a further study.

One of the possible explanations for excess risk in men in the lower extreme of the BMI distribution was due to case fatality. Mortality was the only endpoint outcome in the present study; thus, results were not affected by non-fatal cerebral infarction. Kimura et al. [24], reported that the case fatality rate was 6.9% in patients with ischemic stroke and transient ischemic attack. Also Kiyohara et al. [25], reported that lower BMI was a significant risk factor for death after stroke.

Observational studies of body weight and mortality are susceptible to methodological problems, including failure to control for weight loss due to subclinical disease and the unhealthy biological effects of heavy smoking [26]. For deaths due to cerebral infarction, a U-shaped association was observed between BMI and hazard ratio among men; however no such association was observed among women. Mean BMI among women increased with increasing age. In contrast, among men, mean BMI increased in the 40s and 50s, but decreased with increasing age. The effect of age may have influenced the pattern of association even after adjusting the models for age. It is difficult to control the above-mentioned 'reverse-causal' effect and confounding factors in a cohort study. Thus, the relation between low BMI and mortality should be interpreted with caution.

The present study has several limitations. First, for detecting statistically significant relationships between BMI and mortality, especially for BMI ≥ 30.0, the sample size was not large enough. The prevalence of obesity (BMI ≥ 30.0) in Japanese adults is quite low compared with data from western populations [11]. In the present study, subjects with BMI ≥ 30.0 account for only 0.9% of men and 3.0% of women. Second, we used National Vital Statistics on the underlying causes of death, which are based on death certificates issued by medical practitioners, as endpoints. Stroke subtypes may lead to misclassification on death certificates. However, since the 1980s, the use of CT scans on stroke patients has been widespread among local Japanese hospitals [27]. Therefore, we believe the diagnoses of stroke subtypes on death certificates to be sufficiently accurate.

In conclusion, a U-shaped association between BMI and cerebral infarction mortality was found. The excess risk at the lower extreme of the BMI distribution was confined to men.

Intracerebral hemorrhage			
adjusted for age, smoking and alcohol		fully adjusted[a]	
HR (95% CI)	p value	HR (95% CI)	p value
1.02 (0.38, 2.72)	0.97	1.23 (0.46, 3.29)	0.69
1.19 (0.63, 2.24)	0.58	1.26 (0.67, 2.37)	0.48
1.00 (reference)		1.00 (reference)	
0.91 (0.40, 2.08)	0.83	0.83 (0.36, 1.91)	0.66
2.57 (0.72, 9.13)	0.14	2.31 (0.65, 8.26)	0.20
0.92 (0.23, 3.74)	0.91	1.00 (0.24, 4.12)	1.00
1.40 (0.57, 3.44)	0.47	1.37 (0.55, 3.40)	0.50
1.00 (reference)		1.00 (reference)	
1.39 (0.45, 4.34)	0.57	1.36 (0.44, 4.23)	0.60
5.75 (0.69, 48.10)	0.11	6.61 (0.79, 55.65)	0.08
1.06 (0.27, 4.18)	0.94	1.55 (0.39, 6.24)	0.54
0.99 (0.40, 2.42)	0.97	1.19 (0.48, 2.95)	0.71
1.00 (reference)		1.00 (reference)	
0.58 (0.17, 1.99)	0.39	0.50 (0.15, 1.72)	0.27
1.79 (0.37, 8.63)	0.47	1.47 (0.30, 7.25)	0.63

Appendix

The NIPPON DATA80 Research Group

Chairman. Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Consultants. Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido), Teruo Omae (Health C&C Center Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hos-

pital, Nakatsu, Oita), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi).

Research Members. Akira Okayama (Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka), Kazunori Kodama, Fumiyoshi Kasagi (Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga), Takehito Hayakawa, Shinichi Tanihara (Department of Public Health, School of Medicine, Shimane University, Izumo, Shimane), Shigeyuki Saito (Second Department of Internal Medicine School of Medicine, Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate), Yosikazu Nakamura (Department of Health Science Division of Epidemiology and Community Health, Jichi Medical School, Minami Kawachi, Tochigi), Fumihiko Kakuno (Hikone Public Health Center, Hikone, Shiga).

Research Associate Members. 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), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako, Saitama), Sohel R. Choudhury, (National Heart Foundation Hospital and Research Institute, Dhaka, Bangladesh), Yutaka Kiyohara (Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Fukuoka), Minoru Iida (Kansai University of Welfare Sciences, Kashihara, Kashiwara Osaka), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama).

Acknowledgements

This study was supported by the grant-in-aid of the Ministry of Health and Welfare under the auspices of Japanese Association for Cerebro-cardiovascular Disease Control, the Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare and a Health and Labor Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-Chouju-046, H14-Chouju-003, H17-Chouju-012).

References

1 Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, Hademenos G, Hill M, Howard G, Howard VJ, Jacobs B, Levine SR, Mosca L, Sacco RL, Sherman DG, Wolf PA, del Zoppo GJ: Primary prevention of ischemic stroke: a statement for healthcare professionals from the stroke council of the American Heart Association. Stroke 2001; 32:280–299.

2 Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE: Body mass index and the risk of stroke in men. Arch Intern Med 2002;162:2557–2562.

3 Abbott RD, Behrens GR, Sharp DS, Rodriguez BL, Burchfiel CM, Ross GW, Yano K, Curb JD: Body mass index and thromboembolic stroke in nonsmoking men in older middle age: the Honolulu Heart Program. Stroke 1994;25:2370–2376.

4 Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, Buring JE: Prospective study of body mass index and risk of stroke in apparently healthy women. Circulation 2005;111:1992–1998.

5 Rexrode KM, Hennekens CH, Willett WC, Colditz GA, Stampfer MJ, Rich-Edwards JW, Speizer FE, Manson JE: A prospective study of body mass index, weight change, and risk of stroke in women. JAMA 1997;277:1539–1545.

6 Jood K, Jern C, Wilhelmsen L, Rosengren A: Body mass index in mid-life is associated with a first stroke in men: a prospective population study over 28 years. Stroke 2004;35: 2764–2769.

7 Song YM, Sung J, Davey Smith G, Ebrahim S: Body mass index and ischemic and hemorrhagic stroke: a prospective study in Korean men. Stroke 2004;35:831–836.

8 Ni Mhurchu C, Rodgers A, Pan WH, Gu DF, Woodward M: Body mass index and cardiovascular disease in the Asia-Pacific region: an overview of 33 cohorts involving 310,000 participants. Int J Epidemiol 2004;33:751–758.

9 Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Wada Y, Inaba Y, Tamakoshi A: Body mass index and mortality from cardiovascular disease among Japanese men and women: the JACC study. Stroke 2005;36: 1377–1382.

10 de Freitas GR, Bogousslavsky J: Primary stroke prevention. Eur J Neurol 2001;8:1–15.

11 World Health Organization: Obesity: Preventing and Managing the Global Epidemic. WHO Technical Report Series No 894. WHO, Geneva, 2000.

12 Deurenberg P, Deurenberg-Yap M, Guricci S: Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. Obes Rev 2002;3:141–146.

13 Yoshiike N, Seino F, Tajima S, Arai Y, Kawano M, Furuhata T, Inoue S: Twenty-year changes in the prevalence of overweight in Japanese adults: the national nutrition survey 1976–95. Obes Rev 2002;3:183–190.

14 Liu L, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Ueshima H: Changes in body mass index and its relationships to other cardiovascular risk factors among Japanese population: results from the 1980 and 1990 national cardiovascular surveys in Japan. J Epidemiol 1999;9:63–74.

15 Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, Okamura T, Minowa M, Iimura O; NIPPON DATA80 Research Group: Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. Stroke 2004;35:1836–1841.

16 Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Elliot P, Ueshima H; for the NIPPON DATA80 Research Group: Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. Am Heart J 2004;147:1024–1032.

17 Ministry of Health and Welfare: National Survey on Circulatory Disorders 1980. Tokyo, Japan Heart Foundation, 1982.

18 Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity: New criteria for 'obesity disease' in Japan. Circ J 2002;66:987–992.

19 Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC: Body size and fat distribution as predictors of stroke among US men. Am J Epidemiol 1996;144:1143–1150.
20 Stamler J: Epidemiologic findings on body mass and blood pressure in adults. Ann Epidemiol 1991;1:347–362.
21 Kahn BB, Flier JS: Obesity and insulin resistance. J Clin Invest 2000;106:473–481.
22 Matsuzawa Y, Shimomura I, Nakamura T, Keno Y, Kotani K, Tokunaga K: Pathophysiology and pathogenesis of visceral fat obesity. Obes Res 1995;3(suppl 2):187S–194S.
23 Horlick L: Dyslipidemia and metabolic factors in the genesis of heart attack and stroke. Health Rep 1994;6:94–99.
24 Kimura K, Kazui S, Minematsu K, Yamaguchi T; for the Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC): Analysis of 16,922 patients with acute ischemic stroke and transient ischemic attack in Japan. Cerebrovasc Dis 2004;18:47–56.
25 Kiyohara Y, Kubo M, Kato I, Tanizaki Y, Tanaka K, Okubo K, Nakamura H, Iida M: Ten-year prognosis of stroke and risk factors for death in a Japanese community: the Hisayama study. Stroke 2003;34:2343–2347.
26 Willett WC, Dietz WH, Colditz GA: Guidelines for healthy weight. N Engl J Med 1999; 341:427–434.
27 Statistics and Information Department, Ministry of Health and Welfare: Health and Welfare Statistics in Japan. Tokyo, Health and Welfare Statistics Association, 1993.

Circ J 2006; **70:** 960–964

Combined Cardiovascular Risk Factors and Outcome
— NIPPON DATA80, 1980–1994 —

Yasuyuki Nakamura, MD; Takako Yamamoto, MD*; Tomonori Okamura, MD*; Takashi Kadowaki, MD*; Takehito Hayakawa, PhD**; Yoshikuni Kita, PhD*; Shigeyuki Saitoh, MD†; Akira Okayama, MD††; Hirotsugu Ueshima, MD*; for the NIPPON DATA 80 Research Group

Background To examine the prognostic significance of the high-risk group with combined cardiovascular risk factors in the Japanese, we analyzed the relationship between the high-risk group with combined risks and coronary heart disease (CHD) and stroke mortality using the NIPPON DATA80 database.
Methods and Results At baseline in 1980, those of age ≥30 years were randomly selected and 4,144 men and 5,318 women without CHD and/or stroke at baseline were followed for 14 years. The cutoff values for risk components obtained heuristically by Cox analysis were hypertension (systolic ≥130, or diastolic ≥85 mmHg, or on antihypertensive drugs), hypercholesterolemia (total cholesterol ≥200 mg/dl), hyperglycemia (≥130 mg/dl, or self-reported diabetes) and obesity (body mass index ≥27 kg/m^2). Subjects were divided into 3 groups (0, 1–2 and 3–4 risks). Compared with those men in the risk 0 group, the hazard ratios in men in the risk 3–4 for CHD mortality was 8.04 (95% confidence interval: 1.03–62.6), and the stroke mortality was 5.06 (1.53–16.7). In women, no statistically significant difference was found due to a lesser number of events.
Conclusion The high-risk group with combined risk factors is important risk for Japanese men. (*Circ J* 2006; **70:** 960–964)

Key Words: Cohort study; Coronary heart disease; Risk factors; Stroke

Cardiovascular risk factors, such as dyslipidemia, hypertension, hyperglycemia and obesity, are consistent and common but largely undertreated and undercontrolled in many countries,[1] although it is known that these risk factors often cluster together.[2,3] This clustering is now considered to be the "metabolic syndrome", which is closely related to insulin resistance.[3,4] Cutoff values for cardiovascular risk factors have beene derived either empirically or from the results of cross-sectional studies,[3,5–7] but ideally, such cutoff values should be derived from the data of longitudinal cohort studies, so that risk factors have prognostic implications. Furthermore, the cutoff values for these risk factors and the prognostic significance of combined risk factors have not yet been reported in Asian populations, where coronary heart disease (CHD) mortality and obesity are relatively rare, but susceptibility to diabetes mellitus has been reported to be higher.[8–10] The individual cutoff values should be determined for different populations, so to examine the prognostic significance of the high-risk group with combined risk factors we analyzed the relationship between combined cardiovascular risk factors and CHD and stroke mortality using the database of the National Integrated Project for Prospective Observation of Noncommunicable Diseases and Its Trends in the Aged, 1980 (NIPPON DATA80), which includes more than 10,000 subjects in Japan who were followed for 14 years.[11–13]

(Received January 10, 2006; revised manuscript received April 27, 2006; accepted May 25, 2006)
*Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, *Department of Health Science, Shiga University of Medical Science, Otsu, **Department of Epidemiology, Shimane University, Faculty of Medicine, Izumo, †Department of Medicine, Sapporo School of Medicine, Sapporo, ††Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan*
Investigators and members of the research group are listed in the appendix of reference 13.
Mailing address: Yasuyuki Nakamura, MD, Cardiovascular Epidemiology, Kyoto Women's University, 35 Imakumano, Kitahiyoshicho, Higashiyama-ku, Kyoto 605-8501, Japan. E-mail: nakamury@kyoto-wu.ac.jp

Methods

Subjects

The subjects in this cohort were participants in the 1980 National Survey on Circulatory Disorders;[14] the detailed methods of the NIPPON DATA80 have been described previously;[13] but are summarized here. A total of 10,546 community-based subjects aged ≥30 years in 300 randomly selected health districts throughout Japan participated in the survey, which consisted of a medical history, physical examinations, blood tests and a self-administered questionnaire on lifestyle. The cohort was followed until 1994.[11–13] To clarify the causes of death, we used the National Vital Statistics.

Of the 10,546 subjects, a total of 1,084 were excluded for the following reasons: past history of CHD or stroke (n=166), missing information on the baseline survey (n=48), lost to follow-up (n=870). We analyzed the remaining 9,462 subjects (4,144 men, 5,318 women). Ethical approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Biochemical and Baseline Examinations

The baseline surveys were conducted by public health centers. Systolic and diastolic blood pressures (SBP, DBP)

Table 1 Results of Principal Component Analysis Among 3,820 Men and 4,857 Women Not Taking Medication (NIPPON DATA80: 1980–1994)

	Men		Women
	Factor 1	Factor 2	Factor 1
Variables			
BMI	0.44	0.65	0.50
SBP	0.84	−0.37	0.86
DBP	0.88	−0.18	0.85
Total cholesterol	0.33	0.72	0.44
Glucose	0.24	−0.25	0.31
Total variance	0.37	0.23	0.40
Cumulative variance	0.37	0.60	0.40

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

were measured by trained operators using a standard mercury sphygmomanometer on the subjects' right arm while the subjects were seated and after they had rested for more than 5 min. Height in stockinged feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m).

A lifestyle survey was carried out using a self-administered questionnaire. Non-fasting blood samples were drawn and centrifuged within 60 min of collection, and then stored at −70°C until analysis. Total cholesterol was analyzed in a sequential auto-analyzer (SMA12/60; Technicon, Tarrytown, NY, USA) at a single laboratory (Osaka Medical Center for Health Science and Promotion), which is a member of the Cholesterol Reference Method Laboratory Network[15] The serum concentration of glucose was measured using the cupric-neocuproline method[16]

Combined Cardiovascular Risk Factors

The previous cutoff values used for the definition of metabolic syndrome[6,7] were not applied in the present study for the following reasons. Waist girth was not measured during the baseline examinations in 1980. The modified WHO definition uses BMI ≥30 kg/m^2 as a criteria for abdominal obesity, but because the average BMI for Japanese adult men and women is around 23 kg/m^2, there are very few subjects whose BMI is more than 30 kg/m^2.[17–20] Non-fasting blood samples were used in the present study, and direct measurement of high density lipoprotein (HDL) cholesterol was not performed. Therefore, we selected 4 components of the combined risk factors, namely, obesity, hyperglycemia, hypercholesterolemia and hypertension. The cutoff value for each component was determined heuristically using the mortality data described below. We considered those who were on antihypertensive medication as having hypertension, and those who with self-reported diabetes mellitus as having hyperglycemia. We then divided the study subjects into 3 groups: risk 0 for subjects who had none of the above components, risk 1–2 for subjects who had 1 or 2 of the components, and risk 3–4 for subjects who had 3 or 4 of the above components.

Statistical Analyses

SAS version 8.02 for WINDOWS (SAS Institute Inc, Cary, NC, USA) was used throughout the analyses. Men and women were analyzed separately. The chi-square test was used to compare dichotomous variables. To compare the means among the 3 groups, one-way analysis of variance was used.

Table 2 Results of Heuristic Analysis in Men to Obtain the Cutoff Values for Risk Components Among 4,144 Men (NIPPON DATA80: 1980–1994)

	Risk 3–4 (%)	CHD HR (p)	Stroke HR (p)
BMI (kg/m^2)			
26	*15*	*6.94 (0.064)*	*4.77 (0.010)*
27	*13*	*8.04 (0.046)*	*5.06 (0.008)*
28	*11.5*	*9.17 (0.035)*	*5.26 (0.007)*
BG (mg/dl)			
120	*17.5*	*6.12 (0.081)*	*4.43 (0.042)*
130	*13*	*8.04 (0.046)*	*5.06 (0.008)*
140	*10*	*7.11 (0.068)*	*4.33 (0.007)*
TC (mg/dl)			
180	*20*	*2.39 (0.144)*	*4.80 (0.131)*
200	*13*	*8.04 (0.046)*	*5.06 (0.008)*
220	*7.8*	*10.29 (0.028)*	*5.24 (0.008)*
SBP/DBP (mmHg)			
120/80	*14.9*	*>50 (0.986)*	*4.56 (0.137)*
130/85	*13*	*8.04 (0.046)*	*5.06 (0.008)*
140/90	*10.3*	*3.20 (0.053)*	*4.51 (0.002)*

Fixing the values of 3 components, value of the 4th component was varied categorically and the Cox analyses were performed. Hazard ratios (HR) with p values for CHD and stroke mortality were compared. The risk 0 group was used as the reference group. The Cox analyses were repeated until the lowest cutoff value for each component that had a prognostic significance for CHD and/or stroke mortality was obtained. The obtained cutoff values were BMI=27 kg/m^2, BG=130 mg/dl, TC=200 mg/dl, SBP/DBP=130/85 mmHg for men. Risk 3–4= subjects who had 3 or 4 of the risk (risks are: hypertension: SBP ≥130 mmHg, or DBP ≥85 mmHg, or on anti-hypertensive drugs; hypercholesterolemia: TC ≥200 mg/dl; hyperglycemia: BG ≥130 mg/dl or self-reported diabetes mellitus; obesity: BMI ≥27 kg/m^2).
CHD, coronary heart disease; BG, blood glucose; TC, total cholesterol. Other abbreviations see in Table 1.

Principal component analysis was conducted using the FACTOR procedure of SAS in order to examine clustering. Subjects who were taking antihypertensive, antidiabetic or cholesterol-lowering medications were excluded from this principal component analysis. The number of components to be retained was based on eigenvalue criteria (≥1.0). The resulting factor pattern was interpreted using factor loadings of ≥0.40.

The multivariate-adjusted hazard ratios for CHD, and stroke mortality were calculated using the Cox proportional hazard model, including age, cigarette smoking (currently smoking or not), and alcohol intake (drinkers or non-drinkers) as covariates. The risk 0 group was used as the reference group. The cutoff values for each of the 4 components were determined heuristically using the Cox analyses on CHD and stroke mortality. Namely, fixing the values of 3 components, the value of the 4th component was categorically varied and the Cox analyses were performed. The Cox analyses were repeated until we found the lowest cutoff value for each component that had prognostic significance for CHD and/or stroke mortality. The entered values for each component were BMI: from 25 to 30 kg/m^2 with 1 kg/m^2 increments; blood glucose: from 100 to 160 mg/dl with 10 mg/dl increments; total cholesterol: from 180 to 260 mg/dl with 20 mg/dl increments; SBP/DBP: 120/80, 130/85 and 140/90 mmHg. Because most of the analyses in women did not yield cutoff values that had prognostic significance, the cutoff values for men were applied in the analyses of women.

Hazard ratios for the association of CHD and stroke mortality with the component conditions were analyzed by the Cox proportional hazard model as above. Tests of linear

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.

Acknowledgments

This study was supported by a grant-in-aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebrocardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare.

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. Albertti 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.

Circ J 2006; **70:** 370–375

Effect of Conventional Risk Factors for Excess Cardiovascular Death in Men

— NIPPON DATA80 —

Junko Tamaki, MD; Hirotsugu Ueshima, MD*; Takehito Hayakawa, MD**; Sohel Reza Choudhury, MD†; Kazunori Kodama, MD††; Yoshikuni Kita, PhD*; Akira Okayama, MD‡; for the NIPPON DATA80 Research Group‡‡

Background The present study examined how sex differences in conventional risk factors for cardiovascular disease (CVD), especially smoking, account for excess male mortality from CVD in Japan.

Methods and Results In a 14-year follow-up study, causes of death were ascertained among 10,546 Japanese aged 30 years or older at the baseline. The proportion of the excess male risk of CVD explained by the differences in risk factors was estimated as $(HR_0-HR_1)/(HR_0-1)$, where HR_0 is the age-adjusted hazard ratio (men vs women) and HR_1 is the age and risk factor-adjusted hazard ratio. The age-adjusted male:female ratios were 1.60 (95% confidence interval (CI), 1.32–1.94) for CVD, 1.75 (95% CI, 1.33–2.30) for stroke, and 1.55 (95% CI, 0.97–2.49) for coronary heart disease. The proportion of excess male risk of CVD explained by smoking was 46% and excess risk explained by all risk factors including smoking was 36%. In men, drinking habits decreased the excess risk of CVD. Except for the association between drinking habits and CVD, the impact of the hazard ratios of conventional risk factors had no sex difference.

Conclusions Smoking contributes substantially to excess male mortality from CVD when the smoking rates vary substantially by sex. (*Circ J* 2006; **70:** 370–375)

Key Words: Cardiovascular disease; Cohort study; Japan; Risk factor; Sex difference; Smoking

The decrease in mortality from cardiovascular disease (CVD) over the past 35 years in Japan has significantly contributed to the longevity of its people[1]. The mortality rate from stroke has decreased since 1965, and mortality from coronary heart disease (CHD) has not risen since 1970[2]. Declining CVD mortality might be attributed to declines in blood pressure[2,3]. Myocardial infarction and coronary death were lower compared with those from Western reports[4]. However, CVD continues to be a major cause of death in Japan[1].

International studies have reported an excess in male mortality for CVD[5,6]. In addition, explanations for how sex differences in conventional risk factors for CVD account for that excess have been investigated[7–9]. However, it is not yet understood how conventional risk factors contribute to sex differences in CVD in Asian countries[10]. Likewise, as benefits of smoking cessation for patients with acute myocardial infraction[11] sex differences in smoking should be investigated. Smoking rates substantially vary by sex in Japan and in other Asian countries, such as China, Singapore, and the Republic of Korea[12,13] and are much greater than in Western countries[13]. In 2002, the smoking rate was 43.3% for Japanese men and 10.2% for Japanese women[12].

In the current study, we investigated how sex differences in conventional risk factors for CVDs, especially differences in smoking, explain the excess in male deaths from CVD in Japan. We used a 14-year follow-up study consisting of a representative sample of Japanese subjects.

(Received October 26, 2005; revised manuscript received January 12, 2006; accepted January 27, 2006)

*Department of Public Health, Kinki University School of Medicine, Osaka-sayama, *Department of Health Science, Shiga University of Medical Science, Otsu, **Department of Public Health, Shimane University Faculty of Medicine, Izumo, Japan, †Department of Community Medicine, School of Medical Sciences Universiti Sains Malaysia, Kota Bharu, Malaysia, ††Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima and ‡Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan*

‡‡Investigators of the research group are listed in Appendix 1.

Mailing address: Junko Tamaki, MD, Department of Public Health, Kinki University School of Medicine, 377-2 Onohigasi, Osaka-sayama 589-8511, Japan. E-mail: jtamaki@med.kindai.ac.jp

Methods

Setting and Follow-up Study

NIPPON DATA80 (National Integrated Projects for Prospective Observation of Non-communicable Disease And its Trends in the Aged) is a 14-year follow-up study, whose baseline survey was conducted in 1980 as the National Cardiovascular Survey[14]. Sampling procedures have been reported in detail elsewhere[15–17]. In the National Cardiovascular Survey, people in 300 districts across Japan were selected by random sampling of all residents aged 30 years or older and were then invited to participate in the survey. The survey was conducted during November 1980, with 10,897 subjects (response rate=79.1%). Of the total subjects, 10,546 with complete information on age, sex, and blood pressure at the baseline were defined as the cohort.

In 1994, the NIPPON DATA80 research group conducted a follow-up study. The vital status of subjects was determined by reviewing registration records linked to their present address from local public health centers in 1994.

Table 1 Distribution of Mean and Prevalence (%) of Risk Factors at Baseline Survey in 1980 for Men and Women Aged 30–89 Years, NIPPON DATA80 (N=8,938)

	Men (n=3,976)		Women (n=4,962)	
*Age (years)**				
30–39 (%)	*26.6*		*26.8*	
40–49	*27.4*		*26.2*	
50–59	*22.6*		*23.2*	
60–69	*14.4*		*15.2*	
70–79	*7.7*		*7.2*	
80–89	*1.2*		*1.5*	
<50 years old	*Mean*	*SD*	*Mean*	*SD*
*Systolic blood pressure†,** (mmHg)*	*131.5*	*(16.9)*	*125.0*	*(16.6)*
*Diastolic blood pressure†,** (mmHg)*	*81.8*	*(11.9)*	*76.7*	*(11.2)*
≥50 years old				
*Systolic blood pressure†,** (mmHg)*	*145.8*	*(21.9)*	*142.8*	*(22.9)*
*Diastolic blood pressure†,** (mmHg)*	*85.3*	*(12.4)*	*82.5*	*(11.9)*
All ages				
*Body mass index (kg/m²)‡,***	*22.5*	*(2.9)*	*22.8*	*(3.4)*
*Serum cholesterol (mg/dl)†,***	*186.2*	*(32.7)*	*190.2*	*(33.9)*
*Serum glucose (mg/dl)†,***	*130.7*	*(38.3)*	*129.1*	*(34.0)*
Hypertension,‡,** %*	*49.3*		*39.9*	
Obesity,§,** %*	*19.3*		*22.3*	
High cholesterol,‖,** %*	*15.0*		*18.4*	
Diabetes mellitus,¶,** %*	*6.8*		*4.0*	
Cigarette smoking history,** %*				
Current	*63.6*		*8.7*	
Former	*18.1*		*2.1*	
Never	*18.2*		*89.1*	
Drinking habit,** %*				
Daily	*48.4*		*2.9*	
Occasionally	*26.5*		*17.0*	
Former	*5.1*		*1.3*	
Never	*19.9*		*78.6*	

*SD, standard deviation; SI conversion factors, to convert milligrams per deciliter to millimoles per liter, multiply by 0.0259. *Chi-square test was used to compare between both genders. †Comparisons of mean values between both genders were performed by using a t-test. ‡Hypertension was defined as a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg, or on antihypertensive drug. §Obesity was defined by a body mass index ≥25.0 kg/m². ‖High cholesterol was defined as total cholesterol ≥220 mg/dl (5.7 mmol/L). ¶Diabetes mellitus was defined as a casual blood glucose ≥200 mg/dl, or with a present history of diabetes mellitus. **p<0.05.*

When a subject's change of residence was detected in registration records, we requested registration records in the cities or towns where they were currently living. The details, including date of death, of subjects who had died were taken from registration records. The underlying causes of death were derived from the National Vital Statistics. By matching the area code of the place of death, sex, date of birth, and date of death using data from mortality statistics in Japan, the underlying cause of death was determined. Thus, we could identify the cause of death for 99.5% of 1,327 deceased subjects. Using NIPPON DATA80, this follow-up study ascertained the vital status of 9,638 (91.4% of the original 10,546 subjects).

Study Population

Of the 10,546 subjects initially examined in 1980, those excluded from the present study were aged over 90 years and had a history of CVD in the baseline data. After exclusion criteria were applied, 4,347 men and 5,440 women aged between 30 and 89 years without CVD at baseline were identified. Among these subjects, 3,976 (91.5%) of men and 4,962 (91.2%) of women were followed up; these 8,938 subjects were used for the analyses in the current study.

Study Variables and Mortality

The method of risk factor measurement used in the baseline survey of 1980 has been described elsewhere[13,15,16] Briefly, standardized measures were made of blood pressure, height, weight, and serum total cholesterol. Data on drinking and smoking habits and history of diseases were obtained from a self-administered questionnaire. Drinking status was classified as never, formerly, occasionally, or daily. Data on smoking habits were obtained by asking subjects to note whether they were a 'non-', 'current-', or 'ex-' smoker, and, in the case of smokers, recorded the number of cigarettes smoked per day.

Hypertension was defined as a systolic blood pressure (SBP) of 140 mmHg or greater and/or a diastolic blood pressure (DBP) of 90 mmHg or greater, or the regular use of an antihypertensive drug. Hypercholesterolemia was defined as total cholesterol of 220 mg/dl (5.7 mmol/L) or greater. The criteria for diabetes mellitus in these analyses were defined as a casual blood glucose level of 200 mg/dl or greater, or with a current history of diabetes mellitus. Obesity was defined by a body mass index equal to or greater than 25.0 kg/m².

Causes of death were classified according to the International Classification of Diseases, Ninth Revision (ICD-9). CVD deaths were those assigned ICD codes 390 to 459, which include CHD (codes 410–414) and stroke (codes 430–438). Permission to use the National Cardiovascular Survey in 1980 and vital statistics for determining causes of death were obtained from the Management and Coordination Agency, Government of Japan.

Table 2 Age-Adjusted Death Rate, and Hazard Ratio of Men and Women for Cardiovascular Diseases NIPPON DATA80, 1980–1994 (N=8,938)

	Cardiovascular disease		*Stroke*		*Coronary heart disease*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
Number of deaths	217	196	111	91	36	33
*Crude death rate**	419	295	214	137	69	50
Age-adjusted death rate†	344	218	176	102	56	36
Age-adjusted men/women ratio‡	1.60		1.75		1.55	
95%confidence interval	(1.32–1.94)		(1.33–2.30)		(0.97–2.49)	

**Crude death rate per 100,000 person-years of observation.*
†Age-adjusted death rate per 100,000 person-years of observation, adjusted by direct methods to the population of Japan who were 30–89 years old in 1985 for the 5-year age groups.
‡Age-adjusted hazard ratio for men vs women.

Table 3 Hazard Ratio and Proportion of Excess Risk in Men Associated With the Difference of Risk Factors in Each Model, NIPPON DATA80, 1980–1994

Risk factors included in the model	*Cardiovascular disease*			*Stroke*			*Coronary heart disease*		
	*HR**	*(95%CI)*	*Excess risk† %*	*HR**	*(95%CI)*	*Excess risk† %*	*HR**	*(95%CI)*	*Excess risk† %*
Age, sex	1.61	(1.32–1.95)		1.77	(1.34–2.33)		1.56	(0.97–2.50)	
Age, sex, HT‡	1.59	(1.31–1.93)	3.6	1.74	(1.31–2.29)	4.0	1.56	(0.97–2.50)	–0.4
Age, sex, obesity§	1.63	(1.34–1.98)	–3.3	1.79	(1.35–2.36)	–2.9	1.60	(0.99–2.58)	–7.6
Age, sex, high cholesterol‖	1.60	(1.31–1.94)	1.7	1.76	(1.33–2.33)	1.5	1.63	(1.01–2.62)	–13.0
Age, sex, DM¶	1.55	(1.28–1.88)	9.2	1.74	(1.32–2.30)	3.7	1.50	(0.93–2.41)	10.3
Age, sex, current smoker	1.33	(1.06–1.66)	46.2	1.49	(1.08–2.06)	36.0	1.23	(0.70–2.15)	59.3
*Age, sex, current drinker***	1.75	(1.41–2.19)	–24.4	1.69	(1.23–2.33)	10.3	1.72	(0.996–2.98)	–29.5
Age, sex, HT, obesity, high cholesterol DM, current smoker, current drinker	1.39	(1.08–1.79)	36.4	1.41	(0.98–2.02)	46.8	1.34	(0.71–2.51)	39.3

**Hazard ratio of men vs women. Hazard ratio and 95%confidence interval determined by Cox proportional hazard regression. †Proportion of excess risk in men defined as (HR0–HR1)/(HR0–1); HR0=age-adjusted hazard ratio of men vs women; HR1=age-, and risk factor-adjusted hazard ratio of men vs women. HR0=1.61, 1.77, and 1.56, for CVD, stroke, and coronary heart disease, respectively. ‡Hypertension was defined as a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg, or on antihypertensive drug. §Obesity was defined by a body mass index ≥25.0 kg/m². ‖High cholesterol was defined as total cholesterol ≥220 mg/dl (5.7 mmol/L). ¶Diabetes mellitus was defined as a casual blood glucose ≥200 mg/dl, or with a present history of diabetes mellitus. **Current drinker was defined as subjects who drink occasionally or daily.*
HR, hazard ratio; CI, confidence interval; HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Statistical Analysis

Chi-square tests were used to compare the risk-factor distribution, and the t-test was used to compare the mean of continuous variables between women and men. The age-adjusted death rate was calculated by direct methods with the 1985 model population of Japan as the standard population. Cox proportional hazard models were used to calculate age and multivariate-adjusted hazard ratios and corresponding 95% confidence intervals (CI) of CVD deaths for each risk factor. The assumption that the hazard ratio of the primary exposure remained constant over time for each risk factor was confirmed by Cox regression with time-dependent covariates.

To examine how the sex differences in the risk factors explain the excess CVD risk in men, a model with sex as an independent variable was built with data including both males and females, to which the other risk factors were added to the model as used by Jousilahti et al[9] The proportion of the excess CVD risk in men that was explained by the sex differences in the risk factors was estimated as follows. The differences in CVD hazard ratios of men vs women before and after adjustment for risk factors was divided by the denominator that subtracted background risk from hazard ratio (men vs women) as [(HR0–HR1)/(HR0–1), where HR0 is age-adjusted hazard ratio (men vs women), HR1 is age, and risk factor-adjusted hazard ratio][9]

We tested for differences in the hazard ratio of CVD between both males and females by including interaction terms between sex and risk factor in the proportional hazard model. The percentage change in modifiable risk with each change or each 10-unit change was calculated by Cox proportional hazard models. Analyses were calculated using the software SPSS 10.0J for Windows (SPSS10.0J for Windows, Standard Version, SPSS, 2000).

The Ethics Committee of Shiga University of Medical Science, Japan, approved the research protocol of the study.

Results

Baseline Characteristics

The distribution of mean and prevalence of risk factors at the baseline of 8,938 subjects is shown in Table 1. Average age at baseline was 50.0±12.9 (mean±standard deviation (SD)) years for men and 50.2±13.1 years for women. The means of SBP and DBP, body mass index, and serum cholesterol were lower in men than in women, and higher for serum glucose ($p<0.05$).

Statistically significant differences by sex were found in proportions of current smokers (men, 63.6%; women, 8.7%) and current drinkers (men, 74.9%; women, 19.9%). The prevalence of hypertension and diabetes mellitus was higher in men, and the prevalence of obesity and hypercholesterolemia was higher in women. Average blood pressures of those who took antihypertensive drug were SBP 159±20.1 mmHg (mean±SD), DBP 92.5±11.9 mmHg in

men, and SBP 158.0±21.6 mmHg (mean±SD), DBP 89.9±12.8 mmHg in women.

CVD Mortality

The mean (±SD) follow-up periods were 13.0±2.7 years for men and 13.7±2.2 years for women. There were 51,851 person-years of follow-up in the men, and 66,336 person-years in the women. The mean (±SD) of ages at CVD death were 75.5±11.4 years old in men and 78.2±10.4 years old for women. The mean age at CVD death in women was older than that among men ($p<0.05$). The mean (±SD) of ages at stroke death were 76.4±10.7 years old for men and 77.3±11.2 years old for women, those at CHD death were 71.9±13.3 years old for men and 77.3±10.0 years old for women. The mean age at CHD death in women was older than that in men ($p<0.05$).

Table 2 shows age-adjusted death rates and the hazard ratio of men compared with women for CVD. When adjusted for age, men were 1.60 (95% CI, 1.32–1.94) times more likely to die from CVD than women, and 1.75 (95% CI, 1.33–2.30) times more likely to die from stroke.

Excess Male CVD Risk Explained by the Differences in Risk Factors

Table 3 shows risk in men relative to women, and the proportion of excess risk in men which was explained by the sex difference in risk factor for each model. The age-adjusted hazard ratios for men vs women were 1.61 (95% CI, 1.32–1.95) for CVD, 1.77 (95% CI, 1.34–2.33) for stroke, and 1.56 (95% CI, 0.97–2.50) for CHD. The sex difference in smoking explained the largest proportion of risk factor-associated CVD and stroke deaths. As for CVD death, the sex difference in current drinking was negatively associated with excess deaths of men. Overall, 36% of the excess deaths of men from CVD were associated with the gender difference in all risk factors added to the model, and 46% for stroke.

As a result of testing for sex differences in the hazard ratio of risk factors by including interaction terms between sex and risk factor in the proportional hazard model, interactions between risk factors and sex were not statistically significant in the model of developing CVD, stroke, and CHD, with the exception of the interaction between current drinking and sex in the model of developing CVD (data not shown).

Total Mortality and Excess Male Risk Explained by the Differences in Risk Factors

Numbers of total deaths were 606 for men and 506 for women. When adjusted for age, men were 1.70 (95% CI, 1.51–1.92) times more likely to die for total death. The sex difference in smoking explained 25.5% of the excess total deaths of men. Overall, 25% of the excess total deaths of men were associated with the sex difference in all risk factors; hypertension, obesity, high cholesterol, diabetes mellitus, current smoker, and current drinker (data not shown).

Effect of Risk Factors for CVD in Men and Women

The associations between risk factors and deaths from CVD in men and women are shown in Table 4. In multivariate analysis, hazard ratios of CVD for current smokers were 1.49 in men, and 1.56 in women. Hypertension and diabetes mellitus were also statistically significant risk factors for CVD in both men and women. Hazard ratios of

Table 4 Hazard Ratio of Cardiovascular Disease, Stroke, and Coronary Heart Disease for Men and Women, NIPPON DATA80, 1980–1994 (N=8,938)

Risk factors		Cardiovascular disease				Stroke		Coronary heart disease	
		Death no.	Crude death rate*	Hazard ratio (95% confidence interval)†					
				Men	Women	Men	Women	Men	Women
Hypertension‡	No	51	189						
	Yes	166	666	1.64 (1.18–2.28)	1.54 (1.08–2.19)	1.86 (1.15–3.01)	2.63 (1.46–4.74)	1.20 (0.57–2.54)	0.83 (0.39–1.77)
Obesity§	No	180	433						
	Yes	37	361	1.15 (0.79–1.66)	1.01 (0.73–1.41)	1.21 (0.73–2.01)	0.95 (0.59–1.53)	1.44 (0.63–3.25)	1.04 (0.46–2.36)
High cholesterol‖	No	186	424						
	Yes	31	389	0.97 (0.66–1.43)	0.88 (0.63–1.23)	0.84 (0.48–1.48)	0.92 (0.57–1.49)	2.21 (1.04–4.67)	0.9 (0.42–2.07)
Diabetes mellitus¶	No	179	369						
	Yes	37	1,118	1.56 (1.09–2.24)	1.98 (1.28–3.07)	1.17 (0.68–2.03)	1.78 (0.92–3.44)	1.58 (0.64–3.88)	2.65 (1.02–6.88)
Current smoker	No	78	417						
	Yes	139	420	1.49 (1.12–1.98)	1.56 (1.04–2.35)	1.40 (0.94–2.08)	1.52 (0.84–2.77)	1.97 (0.93–4.18)	1.29 (0.44–3.75)
Current drinker**	No	96	772						
	Yes	120	305	0.63 (0.46–0.85)	1.2 (0.81–1.76)	0.88 (0.57–1.36)	1.31 (0.75–2.27)	0.51 (0.25–1.06)	1.25 (0.51–3.08)

*Per 100,000 person-years. †Risk without each risk factor is defined as 1 for reference, hazard ratio and 95% confidence interval determined by Cox proportional hazards regression where the model included all 6 risk factors, age, and ex-drinker or not. ‡Hypertension was defined as a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg, or on antihypertensive drug. §Obesity was defined by a body mass index ≥25.0 kg/m². ‖High cholesterol was defined as total cholesterol ≥220 mg/dl (5.7 mmol/L). ¶Diabetes mellitus was defined as a casual blood glucose ≥200 mg/dl, or with a present history of diabetes mellitus. **Current drinker was defined as subjects who drink occasionally or daily.

CVD of current male drinkers were 0.63 (with statistical significance), but had no statistical significance for women. For stroke, only high blood pressure was a statistically significant risk factor for both men and women. For coronary heart disease, high cholesterol was a statistically significant risk factor for men, and diabetes mellitus was a statistically significant risk factor for women.

Omitted from Table 4, the observed percentage changes in risk for CVD death with each change in risk factors, a 10 mmHg increase in SBP, 10 mg/dl increase in casual glucose, and smoking, are expected to increase risk by 15.7%, 4.5%, and 50.9% in men, and 8.6%, 5.0%, and 58.9% in women, with statistical significance, respectively. Current drinking is expected to decrease the risk of CVD by 39.1%, a statistical significant value in men, but not in women.

Discussion

In this nationally representative study in Japan, we found that the major determinant of the sex difference in CVD death was the difference in smoking, which explained nearly half of the excess CVD deaths of men. However, the sex difference in the conventional risk factors, including smoking, explained only one-third of the excess CVD deaths of men. The smaller proportion of excess risk explained by all risk factors other than smoking could be attributed to the preventive effect of alcohol intake for CHD[18] Except for drinking, the hazard ratio for CVD did not differ significantly between men and women.

Our study as well as previous studies[10,19,20] found no sex difference in the hazard ratio for CVD of smoking[10,19,20] A previous analysis of 40 cohort studies[20] found no sex difference in the hazard ratio for stroke from smoking, although a meta-analysis found a slightly increased risk in women[21] A review noted no sex difference in the hazard ratio for CHD from smoking[8] In contrast, an analysis of 40 cohort studies found that women tend to have a higher hazard ratio for CHD from smoking[20] These analyses suggest that the hazard ratio of smoking for CVD is not affected or is increased slightly in women. Thus, the excess of CVD deaths in males explained by sex differences in smoking could be attributed mainly to sex differences in the prevalence of smoking.

Sex differences in all of the conventional risk factors explained about one-third of male excess deaths for CVD in our study. A prospective cohort study also showed that differences in conventional risk factors for CVD explained half of the excess CHD deaths in men in Finland, although drinking habits were not included[9] These data indicate that excess mortality in men can be modified by lifestyle changes.

Study Limitations

One limitation of our study is that we could not follow cardiovascular events during follow-up from the baseline study in 1980, as this study was conducted as a retrospective cohort study in 1994. Another limitation of our study is the potential misclassification of subjects because we examined CVD risk status only at baseline. Using a single measurement to estimate the effect of risk factors can cause regression-dilution bias[22] and our data might have underestimated the risk factors. Another possible limitation is the potential sex difference when tracking CVD risk factors over time, although a previous 16-year follow-up study found no major sex differences[23] Other limitations of our study are the inclusion of frequency of drinking to estimate alcohol consumption, the inability to measure a dose effect of smoking, and the inclusion of casual blood glucose concentration, which might have underestimated the prevalence of diabetes or impaired glucose tolerance because these require measurement of fasting glucose concentration or a glucose challenge test. Additionally, we have not investigated the sex differences in the effect of smoking stratified by cigarettes per day for CVD, although men who smoked more than 20 cigarettes per day would have a higher risk for stroke and CHD death than those who smoked 1 to 20 cigarettes per day[10] That is because our primary purpose was to investigate the effect of sex differences in smoking rates for CVD, and a goal of the intervention relating to smoking would be smoking cessation rather than reducing the numbers of cigarettes per day.

In our sample, the sex difference in smoking represented the largest proportion of risk factor-associated CVD deaths. Sex differences in smoking rates might also explain the large sex differences in CVD deaths in other Asian countries, such as China, Singapore, and the Republic of Korea, where smoking rates vary widely by sex and age-standardized death rates for CVD are higher than in Japan[13,24] However, the female smoking rate has been increasing in these countries, and further studies are needed to evaluate whether the recent increase in smoking rates in women reduces the sex differences in CVD mortality using follow-up data classified according to the ICD-10.

We found sex differences in mortality and risk factors for CVD. Focusing on the risk factors for CVD rather than individual diseases such as stroke or CHD might clarify the total effect of risk factors for CVD, including heart failure and other causes. In particular, heart failure as a cause of death was officially recorded more frequently during the follow-up period in Japan, where the ICD-9 was used until 1994.

Conclusion

In conclusion, our findings from a nationally representative cohort study in Japan indicate that differences in smoking among men and women explain half of the sex differences in CVD deaths. All conventional risk factors for CVD including smoking explained about one-third of the sex difference in CVD deaths. Hence, excess deaths among men from CVD are not inevitable and can be avoided through interventions. In particular, smoking contributes substantially to excess male CVD deaths in areas where the smoking rate is much higher in men than in women.

Acknowledgments

This study was supported by the grant-in-aid of the Ministry of Health and Welfare under the auspices of Japanese Association for Cerebrocardiovascular Disease Control, the Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labour and Welfare and a Health and Labour Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-Chouju-046, H14-Chouju-003).

References

1. Ministry of Health, Labor & Welfare. Vital statistics of Japan 2003. Tokyo: Health and Welfare Statistics Association, 2005: 188–189 (in Japanese).
2. Ueshima H, Tatara K, Asakura S. Declining mortality from ischemic heart disease and change in coronary risk factors in Japan, 1956–1980. *Am J Epidemiol* 1987; **125:** 62–72.

3. Ueshima H. Changes in dietary habits, cardiovascular risk factors and mortality in Japan. *Acta Cardiol* 1990; **8:** 647–655.
4. Hirobe K, Terai T, Fujioka S, Goto K, Dohi S; 3M-Study Project Committee of the Japan Association of Occupational Physicians "San-yu-kai". Morbidity of myocardial infraction multicenter study in Japan (3M Study): Study design and event rates for myocardial infraction and coronary death by age category in Japanese workers. *Circ J* 2005; **69:** 767–773.
5. Lawlor DA, Ebrahim S, Davey Smith G. Sex matters: Secular and geographical trends in sex differences in coronary heart disease mortality. *BMJ* 2001; **323:** 541–545.
6. Khaw KT. Epidemiology of stroke. *J Neurol Neurosurg Psychiatry* 1996; **61:** 333–338.
7. Janghorbani M, Hedley AJ, Jones RB, Zhianpour M, Gilmour WH. Gender differential in all-cause and cardiovascular disease mortality. *Int J Epidemiol* 1993; **22:** 1056–1063.
8. Price JF, Fowkes FG. Risk factors and the sex differential in coronary artery disease. *Epidemiology* 1997; **8:** 584–591.
9. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: A prospective follow-up study of 14786 middle-aged men and women in Finland. *Circulation* 1999; **99:** 1165–1172.
10. Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, et al. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke* 2004; **35:** 1836–1841.
11. Kinjo K, Sato H, Sakata Y, Nakatani D, Mizuno H, Shimizu M, et al. Impact of smoking status on long-term mortality in patients with acute myocardial infraction. *Circ J* 2005; **69:** 7–12.
12. The Study Circle for Health and Nutrition Information, Ministry of Health, Labor and Welfare. The National Nutrition Survey in Japan, 2002. Tokyo: Daiichi Shuppan; 2004; 124 (in Japanese).
13. Mackay J, Eriksen M. The tobacco atlas. Geneva: World Health Organaization: 2002; 94–100.
14. Ministry of Health and Welfare. National Survey on Circulatory Disorders 1980. Tokyo: Japan Heart Foundation; 1982, 1–8 (in Japanese).
15. Ueshima H on behalf of the NIPPON DATA80 research group. NIPPON DATA: A follow-up study of National Survey on Cardiovascular Disease in 1980. *Japanese Journal of Cardiovascular Disease Prevention* 1997; **31:** 231–237.
16. Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H, et al. What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med* 2003; **253:** 169–180.
17. NIPPON DATA80 Research Group. Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese–NIPPON DATA80. *J Hum Hypertens* 2003; **17:** 851–857.
18. McElduff P, Dobson AJ. How much alcohol and how often? Population based case-control study of alcohol consumption and risk of a major coronary event. *BMJ* 1997; **314:** 1159–1164.
19. Marang-van de Mheen PJ, Smith GD, Hart CL, Hole DJ. Are women more sensitive to smoking than men? Findings from the Renfrew and Paisley study. *Int J Epidemiol* 2001; **30:** 787–792.
20. Asia Pacific Cohort Studies Collaboration. Smoking, quitting, and the risk of cardiovascular disease among women and men in the Asia-Pacific region. *Int J Epidemiol* 2005; **34:** 1036–1045.
21. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ* 1989; **298:** 789–794.
22. Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischemic heart disease in observational studies: Data from the BUPA study. *BMJ* 1994; **308:** 363–366.
23. Wilsgaard T, Jacobsen BK, Schirmer H, Thune I, Lochen ML, Njolstad I, et al. Tracking of cardiovascular risk factors: The Tromso study, 1979–1995. *Am J Epidemiol* 2001; **154:** 418–426.
24. World Health Organization. 9. Noncommunicable diseases, including mental health. Strengthening surveillance for noncommunicable diseases. http://www.wpro.who.int/pdf/rcm51/rd/bhcp-4a.pdf

Appendix 1

List of the NIPPON DATA80 Research group

NIPPON DATA80: "National Integrated Projects for Prospective Observation of Non-communicable Diseases And its Trends in the Aged"

Chairman: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Consultants: 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, Koshigata, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi).

Research Members: Akira Okayama (Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka), Kazunori Kodama, Fumiyoshi Kasagi (Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga), Takehito Hayakawa, Shinichi Tanihara (Department of Public Health, School of Medicine, Shimane University, Izumo, Shimane), Shigeyuki Saito (Second Department of Internal Medicine School of Medicine, Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate), Yosikazu Nakamura (Department of Health Science Division of Epidemiology and Community Health, Jichi Medical School, Minami Kawachi, Tochigi), Fumihiko Kakuno (Hikone Public Health Center, Hikone, Shiga).

Research Associate Members: 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), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako, Saitama), Sohel R. Choudhury (National Heart Foundation Hospital & Research Institute, Dhaka, Bangladesh), Yutaka Kiyohara (Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyusyu University, Fukuoka, Fukuoka), Minoru Iida (Kansai University of Welfare Sciences, Kashiwara, Osaka), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama).

ELSEVIER

Atherosclerosis 190 (2007) 216–223

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort

Tomonori Okamura[a,*], Hideo Tanaka[b], Naomi Miyamatsu[c], Takehito Hayakawa[d], Takashi Kadowaki[a], Yoshikuni Kita[a], Yasuyuki Nakamura[e], Akira Okayama[f], Hirotsugu Ueshima[a], for the NIPPON DATA80 research group[1]

[a] *Department of Health Science, Shiga University of Medical Science, Shiga, Japan*
[b] *Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan*
[c] *Department of Clinical Nursing, Shiga University of Medical Science, Shiga, Japan*
[d] *Department of Public Health, Shimane University School of Medicine, Shimane, Japan*
[e] *Cardiovascular Epidemiology, Faculty of Home Economics, Kyoto Womens's University, Kyoto, Japan*
[f] *Department of Preventive Cardiology, National Cardiovascular Center, Osaka, Japan*

Received 29 August 2005; received in revised form 4 January 2006; accepted 25 January 2006
Available online 10 March 2006

Abstract

No study has shown a positive relationship between hypercholesterolemia and all-cause mortality in the Japanese population. Therefore, a cohort study of 17.3 years' duration was conducted on 9216 participants aged 30 years or older, selected randomly from throughout Japan. In both the lowest (<4.14 mmol/L, 160 mg/dl) and highest (≥6.71 mmol/L, 260 mg/dl) total cholesterol (TC) groups, there was a positive association between TC and risk of all-cause mortality (hazard ratio (HR) 1.19; 95% confidence interval (CI), 1.03–1.37 and 1.36 (95% CI, 1.05–1.77), respectively). The lowest TC group had an increased risk of liver disease (HR 3.03; 95% CI, 1.70–5.43), whereas the highest TC group had an increased risk of coronary heart disease (HR 3.81; 95% CI, 1.70–5.43). After exclusion of deaths due to liver disease during the entire follow-up period and all-cause deaths within the first 5 years of follow-up, the increased HR in the lowest TC group disappeared (HR 1.05; 95% CI, 0.89–1.24). Although the cut-off point seemed to be higher than that for Western populations, hypercholesterolemia was shown to be positively associated with all-cause mortality in Japan.

Keywords: Cholesterol; All-cause mortality; Liver disease; Cohort studies; Risk factors

* Corresponding author at: Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan. Tel.: +81 77 548 2191; fax: +81 77 543 9732.
E-mail address: tokamura@belle.shiga-med.ac.jp (T. Okamura).

[1] Members of the NIPPON DATA80 Research group are listed in [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; Okamura T, Hayakawa T, Kadowaki T, et al. Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. Am Heart J 2004;147:1024–32; Ueshima H, Choudhury SR, Okayama A, et al. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. Stroke 2004;35:1836–41; Okamura T, Hayakawa T, Kadowaki T, et al. A combination of serum low albumin and above-average cholesterol level was associated with excess mortality. J Clin Epidemiol 2004;57:1188–95; Nakamura Y, Okamura T, Tamaki S, et al. Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80). Am J Clin Nutr 2004;80:58–63; Miyamatsu N, Kadowaki T, Okamura T, et al. Different effects of blood pressure on mortality from stroke subtypes depending on BMI levels: a 19-year cohort study in the Japanese general population, NIPPON DATA80. J Hum Hypertens 2005;19:285–91; Nakamura Y, Ueshima H, Okamura T, et al. Association between fish consumption and all-cause and cause-specific mortality in Japan: NIPPON DATA80, 1980–1999. Am J Med 2005;118:239–45].

0021-9150/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2006.01.024

1. Introduction

The causal relationship between high levels of serum total cholesterol (TC) and coronary heart disease is well established. Several studies in Western populations have shown clearly that a high cholesterol concentration contributes to an increased risk of all-cause mortality [1–4]. However, to our knowledge, a positive relationship between high serum levels of TC and all-cause mortality has not been reported in Asian populations [5–8].

Recent prospective studies in Japan have shown, however, that low serum TC is a predictive marker for deaths due to liver cancer in community residents [8] and for liver cancer in blood donor who are positive for antibodies to the hepatitis C virus [9]. Accordingly, the relationship between TC and all-cause mortality may be affected by liver diseases in the Japanese population, which is known to have a higher mortality from chronic liver diseases and liver cancer compared with Western populations [10].

Therefore, our a priori hypothesis was that serum TC may be associated positively with all-cause mortality in Japanese residents, but that this relationship may be modified by mortality from liver disease. In order to investigate the validity of this hypothesis, we carried out a 17.3-year cohort study to investigate the relationship between serum TC and all-cause and/or liver disease mortality.

2. Methods

2.1. Populations

A total of 10,546 community dwellers (4640 men and 5906 women), aged 30 years and over, from 300 districts participated in the National Cardiovascular Survey in 1980. These districts were randomly selected throughout Japan to avoid regional bias. In other words, this survey covered all 47 prefectures of Japan according to census population in 1980.

These participants were followed until 1999. As the overall population aged ≥30 in the surveyed districts numbered 13,771, the number of participants was 10,546 (participation rate) 76.6%). The present study extended the follow-up period of NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980), the details of which have been reported previously [8,11–16]. Of the 10,546 participants, a total of 1330 were excluded for the following reasons: past history of coronary heart disease or stroke ($n=280$), missing information at the baseline survey ($n=180$), and lost to follow-up ($n=870$). We then analyzed the data from the remaining 9216 participants (4035 men and 5181 women). There was no significant difference in the mean TC between the participants lost to follow-up and those in the study.

2.2. Endpoint determination

As reported previously, [8,11–16] we confirmed those participants who had died in each area by computer matching of data from the National Vital Statistics, using the area, gender, date of birth and death as key codes. In order to clarify the cause of death, we used the National Vital Statistics. In Japan, all death certificates issued by medical doctors are forwarded centrally to the Ministry of Health and Welfare via the public health centers in the area of residency. The underlying cause of death for the National Vital Statistics was coded according to the Ninth International Classification of Disease (ICD-9) until the end of 1994 and from the beginning of 1995 by the 10th International Classification of Disease (ICD-10) by specialists for coding in the Ministry of Health and Welfare. In our analyses, liver cancer (ICD-9 code: 155, 199.1; ICD-10 code: C22) and non-cancer liver disease (ICD-9 code: 70, 570–573; ICD-10 code: B15–B19, K70–K77) were combined into a single category (death due to liver disease).

Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (Nos. 12–18, 2000).

2.3. Baseline examination

Non-fasting blood samples were drawn and centrifuged within 60 min of collection. Serum total cholesterol and albumin were analyzed using an auto analyzer (SMA12/60; Technicon, Tarrytown, USA) at one central laboratory (Present name: Osaka Medical Center for Health Science and Promotion). Since April 1975, the precision and accuracy of the cholesterol measurements in the laboratory have been certified by the CDC-NHLBI Lipid Standardization Program of the Center for Disease Control and Prevention (CDC), Atlanta, Georgia [17].

Baseline blood pressures were measured on the right arm of seated participants by trained observers using a standard mercury sphygmomanometer. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents, or any combination of these findings. Serum glucose was measured by the cupric-neocuproine method. Diabetes was defined as a non-fasting serum glucose ≥11.1 mmol/L, a history of diabetes, or both. Height in stocking feet and weight in light clothing were measured. Public health nurses obtained information on smoking, drinking and medical history.

2.4. Statistical analysis

We set the cut-off points for serum TC based on the combination of clinical criteria. First, we defined 4.14 mmol/L (160 mg/dl), 5.18 mmol/L (200 mg/dl) and 6.21 mmol/L (240 mg/dl) of serum TC as cut-off points according to the