Table 2 Person-Years, Numbers of Deaths and Age-Adjusted Mortality Rate (per 100,000 Person-Years) and RR for Stroke Death, Cardiovascular Death and All-Cause Death by 19-Year Follow-up of NIPPON DATA80

	Non-AF	AF	RR (95%CI)
Men and women			
Total number	9,423	60	
Person-years	162,980	699	
Stroke death	308 (115)	10 (342)	2.51 (1.37–4.62)
Cardiovascular death	674 (249)	24 (1,342)	2.76 (1.87–4.08)
All-cause death	1,878 (713)	41 (2,173)	1.87 (1.38–16.2)
Men			
Total number	4,127	27	
Person-years	69,915	356	
Stroke death	163 (156)	2 (227)	0.99 (0.25–3.98)
Cardiovascular death	343 (328)	5 (366)	1.24 (0.51–2.99)
All-cause death	1,014 (983)	15 (1,429)	1.37 (0.82–2.27)
Women			
Total number	5,296	33	
Person-years	93,065	343	
Stroke death	145 (100)	8 (689)	5.43 (2.89–10.2)
Cardiovascular death	331 (217)	19 (5,711)	5.41 (3.59–8.15)
All-cause death	864 (587)	26 (6,398)	4.59 (2.19–37.7)

Data are number of deaths (age-adjusted mortality rates) and RR (95%CI).
Direct age adjustment was performed based on the Japan standard population of 1985.
Age-adjusted RR and 95%CI were estimated by the Mantel-Haenszel procedure.
RR, relative risks; CI, confidence intervals. Other abbreviation see in Table 1.

Registration Law, 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. From 1980 to 1994 the underlying causes of death were coded according to the International Classification of Diseases (ICD) 9th Revision and from 1995 to 1999 were coded according to the ICD 10th Revision.

We confirmed deaths by computer matching of data from the Vital Statistics, using area, sex, dates of birth and death as key codes[16] Death from stroke was defined as ICD 9 code numbers 430–438 or ICD 10 code numbers I60–I69. Death from cardiovascular disease was defined as ICD 9 code numbers 390–459 or ICD 10 code numbers I00–I99.

Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, the Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 12-18, 2000).

Statistical Analysis

Student's t-test was used to test differences of several parameters between 2 groups. The chi-square test was used to compare the frequencies among the categories. Age-adjusted mortality rates were calculated by the direct method using the Japanese standard population of 1985. Age-adjusted relative risks and 95% confidence intervals were calculated using the Mantel-Haenszel procedure. Multivariate adjusted relative risks attributable to AF for all-cause mortality and cause-specific mortality were calculated using Cox's proportional hazard model with adjustments for age, SBP, BMI, serum TC levels, plasma glucose levels, presence of valvular heart disease or LVH on ECG, current smoking and regular drinking. All probability values were 2-tailed, and values less than 0.05 were considered to be statistically significant. The Statistical Package for Social Sciences (SPSS Japan Inc version 11.0 Tokyo, Japan) was used for the analyses.

Results

The prevalence of AF was 0.64% in this study (0.65% among men and 0.62% among women). Table 1 shows the baseline characteristics of participants with AF (AF group) and those without AF (non-AF group). Mean ages in the male and female AF groups (63.4 years and 68.8 years, respectively) were significantly higher than those in the non-AF groups (50.6 years and 50.3 years, respectively). In women, mean SBP and the percentages of participants with LVH or HT in the AF group were significantly higher than those in the non-AF group (SBP: 145.2 vs 133.9; LVH: 15.2% vs 4.8%; HT: 69.7% vs 41.4%). The proportion of subjects with valvular heart disease in the AF groups was significantly higher than in the non-AF group in both men and women (11.1% vs 0.5% in men; 18.2% vs 0.6% in women). Prevalence of current smokers in the male AF group was significantly lower than in the male non-AF group (37.0% vs 63.3%).

Table 2 shows the results of age-adjusted mortality rates based on the Japan standard population of 1985 (per 100,000 person-years) and relative risks for stroke death, cardiovascular death and all-cause death. The observed person-years were 163,679. A total of 1,919 deaths occurred during this period (1,878 in the non-AF group and 41 in the AF group). Age-adjusted mortality rates in both sexes were 713 in the non-AF group and 2,173 in the AF group. Age-adjusted relative risks in both sexes attributable to AF for stroke death, cardiovascular death and all-cause death were 2.51, 2.76 and 1.87, respectively.

Among men, age-adjusted mortality rates were 983 in the non-AF group, 1,429 in the AF group. Age-adjusted relative risks attributable to AF for stroke death, cardiovascular death and all-cause death were 0.99, 1.24 and 1.37, respectively (NS).

On the other hand, age-adjusted relative risks attributable to AF for stroke death, cardiovascular death and all-cause death among women were 5.43, 5.41 and 4.59, respectively (all p values <0.05).

Table 3 shows the results of Cox's regression analysis

Table 3 Multivariate Adjusted RR (95% CI) Attributable to AF by Cox's Regression Analysis, NIPPON DATA80, 19-Year Follow-up

	All participants RR (95%CI)	<65 years RR (95%CI)	≥65 years RR (95%CI)
Men and women	9,483 (60†)	7,922 (24†)	1,561 (36†)
Stroke death	2.69 (1.42–5.10)	14.7 (4.59–47.2)	1.93 (0.90–4.14)
CVD death	2.76 (1.81–4.20)	9.63 (4.30–21.6)	2.06 (1.26–3.39)
All-cause death	1.88 (1.37–2.58)	4.00 (2.21–7.25)	1.47 (1.01–2.13)
Men	4,154 (27†)	3,477 (12†)	677 (15†)
Stroke death	1.27 (0.31–5.18)	9.31 (1.24–70.1)	0.67 (0.09–4.85)
CVD death	1.38 (0.56–3.43)	3.44 (0.47–25.0)	1.09 (0.39–3.05)
All-cause death	1.39 (0.82–2.35)	2.83 (1.05–7.63)	1.10 (0.59–2.05)
Women	5,329 (33†)	4,445 (12†)	863 (21†)
Stroke death	3.75 (1.80–7.82)	19.0 (4.41–82.1)	2.83 (1.21–6.60)
CVD death	3.96 (2.46–6.37)	10.8 (3.80–30.9)	2.87 (1.62–5.08)
All-cause death	2.28 (1.53–3.38)	5.00 (2.16–11.6)	1.73 (1.07–2.78)

Data are multivariate adjusted RR (95%CI).
Multivariate adjusted RR (exponential β) and 95%CI were estimated by Cox's regression analysis after adjusting for age, body mass index, systolic blood pressure, blood glucose level, total cholesterol level, history of valvular heart disease, existence of left ventricular hypertrophy, regular drinking and current smoking status.
†Number of participants with atrial fibrillation.
CVD, cardiovascular disease. Other abbreviation see in Tables 1,2.

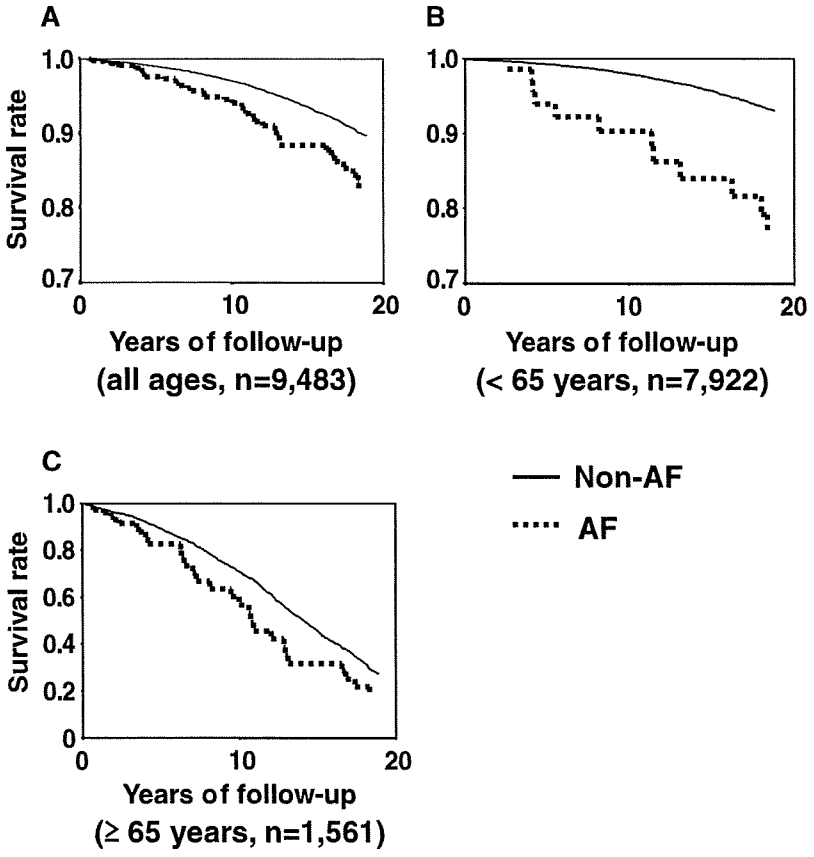

Fig 1. Cox's regression survival curves for subjects with and without atrial fibrillation (AF) in the 19-year follow-up of NIPPON DATA80. Survival curves were determined by Cox's regression analysis stratified by existence of AF after adjusting for age, body mass index, systolic blood pressure, blood glucose level, total cholesterol level, history of valvular heart disease, existence of left ventricular hypertrophy, regular drinking, and current smoking status. Cox's regression curves for (A) subjects of all ages, (B) subjects aged 64 years or younger, (C) subjects aged 65 years or older.

with adjustments for other risk factors. At all ages, multivariate adjusted relative risks for both sexes attributable to AF for stroke death, cardiovascular death and all-cause death were 2.69, 2.76 and 1.88, respectively (all p values <0.05). These were 1.27, 1.38 and 1.39 among men (NS) and 3.75, 3.96 and 2.28 among women (all p values <0.05). Among persons aged 64 years or younger, relative risks for stroke death, cardiovascular death and all-cause death attributable to AF were higher than among participants of all ages. Relative risks for stroke death were notably high in both men and women. Among persons aged 65 years or older, relative risks for death from each cause were lower than among participants of all ages.

Fig 1 shows the Cox's regression survival curves for subjects with or without AF. The survival curve in the AF group was below that in the non-AF group (Fig 1A). The difference between survival rates in the AF group and the non-AF group was more evident among persons aged 64

years or younger (Fig 1B), with the difference being somewhat vague among persons aged 65 years or older (Fig 1C).

Discussion

This study shows that AF contributes to stroke mortality, cardiovascular mortality and all-cause mortality in both sexes of the Japanese general population, especially the young generation (<65 years old). Although the prognosis of AF has been reported for Westerners, the extent to which AF contributes to mortality in the Japanese general population has not been fully elucidated. Some researchers tried to reveal the difference in Japanese subjects between the prognosis of patients with sustained AF and that of patients without AF after cardioversion; however, those studies did not determine whether AF contributes to mortality in Japanese people[18,19] Moreover, the difference in mortality attributable to AF in elderly and middle-aged people has not been addressed in a representative Japanese general population until now.

The framingham Heart Study showed that AF contributed to an increase in stroke incidence, even in elderly people[20] and so careful attention is needed to interpret the result that suggested a low relative risk for mortality attributable to AF among elderly persons in the present study. Because the prevalence of AF has been reported to be less than 1% among Japanese persons aged less than 70 years,[14] participants aged less than 65 years at the time of registration would be less likely to develop AF and elderly persons more likely to develop AF during the follow-up period. This would attenuate the relative risk for death from each cause attributable to AF among the elderly.

The present study also showed obvious sex difference in the risk for death from each cause attributable to AF. A significant interaction between AF and sex certainly exists. In the Framingham Heart Study, AF was no longer significantly associated with increased mortality among men after elimination of 30-day mortality, in contrast to the results for women[21] Other studies also showed that AF was a greater risk for mortality in women than in men[22–24] In a recent study the greater risk for ischemic stroke attributable to AF in women than in men was also confirmed, as well as the risk for mortality[25] The reason why a sex difference exists in the relationship between AF and mortality and in the relationship between AF and ischemic stroke is unknown.

We estimated age-adjusted mortality rates using direct age adjustment based on the Japanese standard population of 1985. All-cause mortality in female participants with AF exceeded 6,000 per 100,000 person-years, which seems to be an overestimation of the actual status, although the relative risk determined by using the Mantel-Haenszel procedure was similar to the multivariate adjusted relative risk estimated by Cox's regression analysis. The small number of subjects with AF, especially in the female younger generation, may have distorted the results and caused overestimation of the mortality rate. Analysis of a small number of subjects with AF may also lack robustness, because a different result would be obtained if several cases had other outcomes.

Study Limitations

Since the original survey in 1980 was not designed for a prospective study, retrospective analyses of the data have several limitations. Risk factors were only observed once at baseline and changes in lifestyle or risk factor levels were not considered. The risk attributable to risk factors may have been underestimated and confounding effects of risk factors may not have been fully adjusted. Assessment of relative risks attributable to AF for mortality analyzed by the presence of AF based on a single recording of ECG at baseline does not take into account subsequent development of AF and, therefore, tolerates underestimation of the relative risks. A follow-up study of the incident cases is preferable for estimating the actual risks for mortality attributable to diseases such as AF, which have an age-dependent prevalence. Paroxysmal AF can not be always detected by a single recording of ECG, so the lack of cases of paroxysmal AF results in underestimation of the relative risks for mortality attributable to AF. Lack of information on the history of anticoagulant therapy also seems to be a study limitation.

Persons with AF may have impaired cardiac function and therefore already have developed asymptomatic organic heart disease. Although we estimated the mortality risk after adjusting for other risk factors, including presence of valvular heart disease or LVH, this analytical procedure may not have been fully adjusted for the effect of heart failure on prognosis.

We estimated the relative risks for mortality attributable to AF using data from the Vital Statistics, but we did not estimate relative risks for cardiovascular morbidity attributable to AF. AF is an important predisposing factor for both heart failure[26] and hospital admission[27] Whether AF affects cardiovascular morbidity among Japanese people remains to be determined.

Despite its several limitations, this study has some strong points. One is the representative Japanese population randomly selected from throughout Japan in the 1980s. Therefore, the total mortality rate and cause-specific mortality rate in this study should be considered as representing the actual status of Japanese adults living in the 1980s and may reflect results from the era before anticoagulant therapy became widespread. Another strong point of this study is the high follow-up rate despite a long follow-up period. There were 163,679 person-years and the mean follow-up period exceeded 17.

Conclusions

AF affects stroke mortality, cardiovascular mortality and all-cause mortality in the Japanese general population. Careful attention should therefore be paid to persons with AF in order to prevent future cardiovascular events.

Acknowledgments

This study was conducted under the auspices of the Japanese Association for Cerebro-Cardiovascular Disease Control and funded by a research grant from the Ministry of Health and Welfare, Japan (7A-2 and H11-Choju-046).

References

1. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154:** 1449–1457.
2. Lin H, Wolf P, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation: The Framingham Study. *Stroke* 1996; **27:** 1760–1764.
3. Stewart S, Murphy N, Walker A, McGuire A, McMurray J. Cost of an emerging epidemic: An economic analysis of atrial fibrillation in the UK. *Heart* 2004; **90:** 286–292.
4. Wolf P, Abbott R, Kannel W. Atrial fibrillation: A major contributor to stroke in the elderly: The Framingham Study. *Arch Intern Med*

1987; **147:** 1561–1564.
5. Tsang TS, Petty GW, Barnes ME, O'Fallon WM, Bailey KR, Wiebers DO, et al. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: Changes over three decades. *J Am Coll Cardiol* 2003; **42:** 93–100.
6. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; **285:** 2370–2375.
7. Kannel W, Wolf P, Benjamin E, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population-based estimates. *Am J Cardiol* 1998; **82:** 2N–9N.
8. Friberg J, Scharling H, Gadsboll N, Jensen G. Sex-specific increase in the prevalence of atrial fibrillation (The Copenhagen City Heart Study). *Am J Cardiol* 2003; **92:** 1419–1423.
9. Ministry of Health, Labour and Welfare. Patient survey 1999. Tokyo: The Ministry, 2001.
10. Ministry of Health, Labour and Welfare. Vital statistics of Japan 2003. Tokyo: The Ministry, 2005.
11. Labarthe D. Epidemiology and prevention of cardiovascular diseases. Gaithersburg, MD: Aspen Publishers, 1998.
12. American Heart Association. Heart disease and stroke statistics 2004 update. Dallas, TX: AHA, 2004.
13. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: The Hisayama study. *Stroke* 2000; **31:** 2616–2622.
14. Ohsawa M, Okayama A, Sakata K, Kato K, Itai K, Onoda T, et al. Rapid increase in estimated number of persons with atrial fibrillation in Japan: An analysis from National Surveys on Cardiovascular Diseases in 1980, 1990 and 2000. *J Epidemiol* 2005; **15:** 194–196.
15. Ministry of Health and Welfare Japan. National survey on circulatory disorders 1980. Tokyo: The Ministry, 1983.
16. Iida M, Ueda K, Okayama A, Kodama K, Sawai K, Shibata S, et al; Nippon Data 80 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.
17. Ueshima H, Choudhury S, 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.
18. Koitabashi T, Inomata T, Niwano S, Nishii M, Takeuchi I, Nakano H, et al. Paroxysmal atrial fibrillation coincident with cardiac decompensation is a predictor of poor prognosis in chronic heart failure. *Circ J* 2005; **69:** 823–830.
19. Fujiki A, Sakamoto T, Iwamoto J, Nishida K, Nagasawa H, Mizumaki K, et al. Pharmacological cardioversion of persistent atrial fibrillation with and without a history of drug-resistant paroxysmal atrial fibrillation. *Circ J* 2006; **70:** 1138–1141.
20. Wolf P, Abbott R, Kannel W. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991; **22:** 983–988.
21. Benjamin E, Wolf P, D'Agostino R, Silbershatz H, Kannel W, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. *Circulation* 1998; **98:** 946–952.
22. Kannel W, Abbott R, Savage D, McNamara P. Epidemiologic features of chronic atrial fibrillation: The Framingham study. *N Engl J Med* 1982; **306:** 1018–1022.
23. Flegel K, Shipley M, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. *Lancet* 1987; **1:** 526–529.
24. Lake F, Cullen K, de Klerk N, McCall M, Rosman D. Atrial fibrillation and mortality in an elderly population. *Aust NZ J Med* 1989; **19:** 321–326.
25. Fang M, Singer D, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: The AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005; **112:** 1687–1691.
26. Dries D, Exner D, Gersh B, Domanski M, Waclawiw M, Stevenson L. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A retrospective analysis of the SOLVD trials: Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* 1998; **32:** 695–703.
27. Stewart S, MacIntyre K, MacLeod M, Bailey A, Capewell S, McMurray J. Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986–1996. *Eur Heart J* 2001; **22:** 693–701.

Appendix 1

The NIPPON DATA80 Research Group

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

Consultants: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo), Teruo Omae (National Cardiovascular Center, Suita), Kazuo Ueda (School of Health Science, Kyusyu University, Fukuoka), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya).

Research Members: Akira Okayama (Department of Preventive Cardiology, National Cardiovascular Center, Suita), Kazunori Kodama, Fumiyoshi Kasagi (Radiation Effects Research Foundation, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu), Shigeyuki Saito (Internal Medicine II, Cardiology and Nephrology, Sapporo Medical University, Sapporo), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Morioka), Takehito Hayakawa, Shinichi Tanihara (Department of Public Health, School of Medicine, Shimane University, Izumo), Yoshikazu Nakamura (Department of Public Health, Jichi Medical School, Minamikawachi), Hiroshi Horibe (Keisen Clinic, Akashi), Masumi Minowa (Department of Epidemiology, National Institute of Public Health, Wako).

Research Associate Members: Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano and members of 300 public health centers in Japan, Minoru Iida (Kansai University of Welfare Science, Osaka), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public health, Wako), Sohel R Choundhury (Department of Community Medicine, School of Medical Sciences University Sains Malaysia), Yutaka Kiyohara (Department of Medicine and Clinical Science, Kyusyu University, Fukuoka), Tsutomu Hashimoto (Wakayama Red Cross Blood Center, Wakayama), Atsushi Terao (Hikone Public Health Center, Hikone), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Saitama).

Eur J Epidemiol (2007) 22:691–698
DOI 10.1007/s10654-007-9168-4

CARDIOVASCULAR DISEASE

The proportion of individuals with obesity-induced hypertension among total hypertensives in a general Japanese population: NIPPON DATA80, 90

Koshi Nakamura · Tomonori Okamura · Takehito Hayakawa · Atsushi Hozawa · Takashi Kadowaki · Yoshitaka Murakami · Yoshikuni Kita · Akira Okayama · Hirotsugu Ueshima · for the NIPPON DATA80, 90 Research Group

Received: 13 March 2007 / Accepted: 9 July 2007 / Published online: 7 August 2007

Abstract The increased prevalence of obesity in Japan may contribute to the high prevalence of hypertension in Japan. In the present study, we calculated the odds ratio for hypertension in obesity (body mass index (BMI) $\geq$ 25.0 kg/m^2) using data from independent nationwide surveys conducted in 1980 and 1990. We estimated the percentage of hypertensives whose condition was due to obesity among total hypertensives in the general Japanese population. In the 1980 survey, 18.8% of 4,623 male participants were obese and 50.4% were hypertensive, whereas 22.6% of 5,893 female participants were obese and 41.1% were hypertensive. For both sexes, obese participants had a higher odds ratio for hypertension than non-obese participants (BMI < 25.0 kg/m^2), and there was a significant dose–response relationship between BMI and the odds ratio for hypertension. Among all hypertensives, the percentage whose hypertension was due to obesity in 1980 and 1990 was 11.4% (95% confidence interval (CI): 4.7–17.7%) and 15.3% (95% CI: 6.8–23.1%) for men and 19.3% (95% CI: 12.1–25.9%) and 22.3% (95% CI: 14.6–29.3%) for women, respectively. Approximately 80–90% of individuals with obesity-induced hypertension were in the 25.0 $\leq$ BMI < 30.0 kg/m^2 category for both sexes in each year. In conclusion, we found that obesity-induced hypertension as a proportion of total hypertension increased between 1980 and 1990 for both sexes. Obesity now is playing a more important role in the high prevalence of hypertension in Japan than it was before.

Keywords Obesity · Body mass index · Hypertension · Japan

NIPPON DATA80, 90 Research Group—Members of the Research Group are listed in the Appendix.

K. Nakamura (✉) · T. Okamura · A. Hozawa · T. Kadowaki · Y. Murakami · Y. Kita · H. Ueshima
Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu City, Shiga 520-2192, Japan
e-mail: ksnkmr@belle.shiga-med.ac.jp

T. Hayakawa
Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima City, Fukushima, Japan

A. Okayama
The First Institute of Health Service, Japan Anti-Tuberculosis Association, Chiyoda-ku, Tokyo, Japan

Introduction

The high prevalence of hypertension in Japan has been mainly attributed to both high sodium [1–5] and high alcohol intake, at least among men [2, 4, 6–8]. The mean body mass index (BMI) in the Japanese population in 1960 was less than 22 kg/m^2 [2, 9], far lower than that in the Western population (approximately 25 kg/m^2) [10]. Thus, obesity was not a significant factor in hypertension for the Japanese population at that time. However, the mean BMI of the Japanese population increased significantly over subsequent decades [2, 9, 11]. As a result, obesity may now be playing a more important role in the high prevalence of hypertension in Japan than it was before [2, 4, 11–14]. Therefore, it is important to clarify how much obesity is contributing to the high prevalence of hypertension in Japan.

In the present study, we measured and compared the proportion of individuals with obesity-induced hypertension among total hypertensives in both 1980 and 1990 in populations selected randomly from the overall Japanese population.

Population and methods

Study design and participants

NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged) is a series of cohort studies conducted by the National Survey on Circulatory Disorders, Japan. The details of these cohort studies have been previously reported [15–20]. In the present study, we analyzed baseline data from NIPPON DATA80 (data from the Third National Survey on Circulatory Disorders, Japan in 1980) and NIPPON DATA90 (data from the Fourth National Survey on Circulatory Disorders, Japan in 1990). The 1980 and 1990 surveys were conducted in independent populations, which comprise different participants.

In the 1980 survey, a total of 10,546 community residents (4,640 men and 5,906 women; ≥ 30 years old) participated from 300 randomly selected districts. The overall population aged 30 and over in all districts was 13,771, and the participation rate in this survey was 76.6%. Of the 10,546 participants, 30 were excluded due to missing information in the baseline survey. The remaining 10,516 participants (4,623 men and 5,893 women) were included in the analysis.

Similarly, in the 1990 survey, a total of 8,384 residents (3,504 men and 4,880 women; ≥ 30 years old) participated, comprising 76.5% of 10,956 residents aged 30 and over. Of the 8,384 participants, 122 were excluded due to missing information in the baseline survey. The remaining 8,262 participants (3,454 men and 4,808 women) were included in the analysis. Accordingly, the participants in these surveys were thought to be representative of the Japanese population.

The present study was approved by the Institutional Review Board of Shiga University of Medical Science for Ethical Issues (No.12–18, 2000).

Examination

In both surveys, body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Obesity was defined as a BMI $\geq$ 25.0 kg/m^2 [22]. In order to estimate the proportion of individuals with obesity-induced hypertension among total hypertensive participants in the study populations, the participants were classified into two categories: "BMI < 25.0 (kg/m^2)" and "BMI $\geq$ 25.0 (kg/m^2)". Additionally, in order to investigate the details of the corresponding proportion, obese participants were stratified into two further categories: "25.0 $\leq$ BMI < 30.0 (kg/m^2)" and "BMI $\geq$ 30.0 (kg/m^2)". These ranges were in accordance with the obesity classification system of the Japan Society for the Study of Obesity [21] and that of the World Health Organization [22].

Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a sufficient period of rest. Information on use of anti-hypertensive agents was obtained by public health nurses. According to the Seventh Report of the Joint National Committee [23], hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg, a diastolic blood pressure $\geq$ 90 mmHg, the use of anti-hypertensive agents, or any combination of these. Alcohol drinking and smoking habits were also assessed by interviews with public health nurses.

Statistical analysis

Initially, we analyzed data from the 1980 and 1990 surveys using one-way analysis of variance or a Chi-square test to compare baseline risk characteristics among the different BMI categories. Next, we calculated the prevalence of hypertension in each of two BMI categories ("BMI < 25.0 (kg/m^2)" and "BMI $\geq$ 25.0 (kg/m^2)") in 1980 and 1990. Using a logistic regression model, the significance of an interaction between hypertension, obesity and sex was tested using an interaction term for the categorical variables (2 categories for sex, and 3 categories for BMI). The odds ratio for hypertension in each BMI category was calculated with BMI < 25.0 serving as a reference. Age (continuous variable), alcohol drinking habit (never, ex- or current drinker, using two dummy variables with never serving as a reference) and smoking habit (never, ex- or current smoker, using two dummy variables with never serving as a reference) were included in the regression models as potential confounding variables. We calculated the percentage of individuals with obesity-induced hypertension among total hypertensives in 1980 and 1990 using the following equation: [prevalence of obesity among hypertensives $\times$ (odds ratio $-$ 1)]/odds ratio [24]. The 95% confidence interval (CI) for the corresponding proportion was calculated using the formula proposed by Greenland [25]. Finally, in order to investigate the details of the corresponding proportion, we analyzed the data using the above equation after classifying the participants into three BMI categories ("BMI < 25.0 (kg/m^2)", "25.0 $\leq$ BMI < 30.0 (kg/m^2)" and "BMI $\geq$ 30.0 (kg/m^2)").

The statistical analysis was performed using SPSS 14.0J for Windows (SPSS Japan Inc., Tokyo, Japan). P values were two-sided, and values of $p < 0.05$ were considered statistically significant.

Results

For the 1980 survey, the mean values or proportions of risk characteristics for male and female participants grouped

according to their BMI are summarized in Table 1. Of the 4,623 male participants (mean age, 49.9 years old; mean body height, 162.2 cm; mean body weight, 59.3 kg; mean BMI, 22.5 kg/m^2), 18.8% were obese and 50.4% were hypertensive, whereas 22.6% of the 5,893 female participants (mean age, 50.1 years old; mean body height, 150.1 cm; mean body weight, 51.5 kg; mean BMI, 22.8 kg/m^2) were obese and 41.1% were hypertensive. For both sexes, there were little differences in the mean values of body height among the three BMI categories, although there were large differences in the mean values of body weight. For men, the mean values of age in the two obese categories were lower than in the non-obese category, whereas for women, the mean values of age in the two obese categories were higher than in the non-obese category.

In the 1980 survey, there was no interaction of hypertension with obesity and sex ($p = 0.14$). For both sexes, an obese participant with a BMI $\geq$ 25.0 kg/m^2 had a higher prevalence of hypertension (60.2% vs. 48.1% for men, and 58.7% vs. 35.9% for women) and a significantly higher odds ratio for hypertension (2.03; 95% CI: 1.73–2.39 for men, and 2.57; 95% CI: 2.24–2.96 for women), as compared to a non-obese participant with a BMI < 25.0 kg/m^2. The proportion of individuals with obesity-induced hypertension among total hypertensives was estimated to be 11.4% (95% CI: 4.7–17.7%) for men and 19.3% (95% CI: 12.1–25.9%) for women (the results described above are not shown in the Table). There was a dose–response relationship between BMI and odds ratio for hypertension in both sexes (Table 2). Table 2 shows the percentage of individuals with obesity-induced hypertension among total hypertensives in each of the further stratified BMI categories. The proportion of individuals with obesity-induced hypertension was much higher in the 25.0 $\leq$ BMI < 30.0 (kg/m^2) category than in the BMI $\geq$ 30.0 (kg/m^2) category for both sexes.

For the 1990 survey, the mean values or proportions of risk characteristics for male and female participants grouped according to their BMI are summarized in Table 1. Of the 3,454 male participants (mean age, 53.3 years old; mean body height, 163.6 cm; mean body weight, 61.6 kg; mean BMI, 23.0 kg/m^2), 23.7% were obese and 49.8% were hypertensive, whereas 23.8% of the 4,808 female participants (mean age, 52.7 years old; mean body height, 151.2 cm; mean body weight, 52.2 kg; mean BMI, 22.8 kg/m^2) were obese and 43.1% were hypertensive. Similar to the 1980 survey, there was little difference in the mean values of body height among the three BMI categories for both sexes, although there were significant differences in the mean values of body weight. Furthermore, for men, the mean values of age in the two obese categories were lower than that in the non-obese category, whereas for women, the mean values of age in the two obese categories were higher than that in the non-obese category.

In the 1990 survey as well as the 1980 survey, there was no interaction of hypertension with obesity and sex ($p = 0.31$). For both sexes, an obese participant with a BMI $\geq$ 25.0 kg/m^2 had a higher prevalence of hypertension (60.3% vs. 46.6% for men, and 63.3% vs. 36.9% for women) and a significantly higher odds ratio for hypertension (2.15; 95% CI: 1.81–2.56 for men, and 2.77; 95% CI: 2.37–3.23 for women), as compared to a non-obese participant with a BMI < 25.0 kg/m^2. The proportion of individuals with obesity-induced hypertension among total hypertensives was estimated to be 15.3% (95% CI: 6.8–23.1%) for men and 22.3% (95% CI: 14.6–29.3%) for women (the results described above are not shown in the Table). There was a dose–response relationship between BMI and odds ratio for hypertension in both sexes (Table 2). Table 2 shows the percentage of individuals with obesity-induced hypertension among total hypertensives stratified further into a number of BMI categories. The proportion of individuals with obesity-induced hypertension was much higher in the 25.0 $\leq$ BMI < 30.0 (kg/m^2) category than in the BMI $\geq$ 30.0 (kg/m^2) category for both sexes.

Discussion

In the present study, we demonstrated the increased proportion of individuals with obesity-induced hypertension (BMI $\geq$ 25.0 kg/m^2) among total hypertensives over a decade between 1980 and 1990 for both sexes. Only data from a nationwide random sampling survey such as ours is able to generate a reliable estimate of the prevalence of obesity and hypertension in the whole Japanese population and the proportion of individuals with obesity-induced hypertension among total hypertensives in Japan, which is a major strength of the present study.

Obesity is associated with the development of hypertension [26–32]. Mechanisms of the development of hypertension among obese individuals include hyperinsulinemia, insulin-induced sodium retention and increased sympathetic tone [32]. Previously, Takashima [33] reported that 9.4% of middle-aged male hypertensives in a corporation in Japan had obesity-induced hypertension (BMI $\geq$ 25.0 kg/m^2) in a cross-sectional study in 1980. Our result is fairly consistent with this finding. For Western populations, with a higher mean BMI compared to Japanese and other Asian populations [34], obesity is generally defined as a BMI $\geq$ 30.0 kg/m^2, and a condition of 25.0 $\leq$ BMI < 30.0 kg/m^2 is regarded as overweight [22]. However, here, we compared our results with results from

Table 1 Baseline risk characteristics in 1980 and 1990 of Japanese participants based on sex and body mass index: NIPPON DATA80, 90

	Men				Women			
	Body mass index (BMI) (kg/m^2)				Body mass index (BMI) (kg/m^2)			
	BMI < 25.0	25.0 ≤ BMI < 30.0	30.0 ≤ BMI		BMI < 25.0	25.0 ≤ BMI < 30.0	30.0 ≤ BMI	
In 1980								
Number of participants (percentage)	3,758	830	42		4,565	1,155	176	
	(81.2)	(17.9)	(0.9)		(77.4)	(19.6)	(3.0)	
Age (years)	50.4 ± 13.7	47.9 ± 11.6	48.0 ± 12.5	*	49.5 ± 13.7	51.9 ± 12.3	52.6 ± 12.3	*
Body height (cm)	162.1 ± 6.8	162.8 ± 6.2	161.6 ± 9.1	*	150.4 ± 6.2	149.3 ± 5.7	148.7 ± 6.0	*
Body weight (kg)	56.6 ± 7.3	70.6 ± 6.2	81.7 ± 7.7	*	48.6 ± 6.1	60.0 ± 5.2	71.6 ± 8.3	*
Body mass index (kg/m^2)	21.5 ± 2.0	26.6 ± 1.2	31.3 ± 1.7	*	21.4 ± 2.1	26.9 ± 1.3	32.3 ± 2.2	*
Alcohol drinking habit								*
Ex-drinker (%)	5.9	5.4	4.8		1.6	2.0	2.3	
Current daily drinker (%)	74.1	75.3	66.7		21.3	17.0	17.0	
Smoking habit				*				
Ex-smoker (%)	18.4	20.0	31.0		2.3	2.7	3.4	
Current smoker (%)	64.7	56.2	50.0		10.0	10.0	5.1	
Systolic blood pressure (mmHg)	137.6 ± 21.2	141.6 ± 19.7	143.0 ± 22.5	*	131.4 ± 20.9	141.5 ± 22.2	146.9 ± 22. 3	*
Diastolic blood pressure (mmHg)	82.6 ± 12.1	87.6 ± 12.5	90.9 ± 13.5	*	78.1 ± 11.7	83.8 ± 11.5	88.9 ± 13.5	*
Use of anti-hypertensive agents (%)	9.8	13.5	14.3	*	9.2	19.3	31.8	*
In1990								
Number of participants (percentage)	2,636	758	60		3,666	999	143	
	(76.3)	(21.9)	(1.7)		(76.2%)	(20.8)	(3.0)	
Age (years)	53.8 ± 14.0	51.8 ± 12.6	49.5 ± 12.4	*	51.8 ± 14.3	55.9 ± 12.8	55.3 ± 12.7	*
Body height (cm)	163.5 ± 6.9	164.1 ± 6.6	164.8 ± 6.6	*	151.6 ± 6.6	150.0 ± 6.4	150.0 ± 6.0	*
Body weight (kg)	58.2 ± 7.5	71.7 ± 6.5	86.5 ± 9.6	*	49.3 ± 6.2	60.3 ± 5.8	72.0 ± 7.3	*
Body mass index (kg/m^2)	21.7 ± 2.1	26.6 ± 1.2	31.8 ± 2.3	*	21.4 ± 2.1	26.8 ± 1.3	31.9 ± 1.9	*
Alcohol drinking habit								
Ex-drinker (%)	7.2	6.7	5.0		1.1	1.0	0.7	
Current daily drinker (%)	56.9	60.7	58.3		6.9	5.1	6.3	
Smoking habit								
Ex-smoker (%)	23.1	25.7	30.0		2.7	2.7	2.8	
Current smoker (%)	55.6	54.1	45.0		9.4	9.2	13.3	
Systolic blood pressure (mmHg)	136.6 ± 20.3	140.6 ± 18.2	148.9 ± 19.2	*	131.0 ± 20.2	141.3 ± 20.0	148.7 ± 22. 9	*
Diastolic blood pressure (mmHg)	82.4 ± 11.4	86.9 ± 11.4	91.9 ± 10.2	*	77.8 ± 11.2	84.6 ± 11.6	87.5 ± 13.8	*
Use of anti-hypertensive agents (%)	11.7	16.0	25.0	*	12.5	25.2	32.2	*

Values indicate the mean ± SD or the % of participants in that category

Mean values or proportions were compared among the three BMI categories by one way analysis of variance or a Chi square test;* statistical significance ($p < 0.05$)

Table 2 Prevalence of hypertension, odds ratio for hypertension in obesity, and proportion of individuals with obesity-induced hypertension among total hypertensives in 1980 and 1990 grouped by sex and body mass index: NIPPON DATA80, 90

Body mass index (BMI) (kg/m^2)	Number of participants (percentage)	Hypertension			Obesity-induced hypertension among total hypertensives (%)
		Cases	Prevalence (%)	Adjusted odds ratio (95% confidence interval)	
In 1980					
Men					
BMI < 25.0	3,752 (81.2)	1,806	48.1	1.00	
25.0 ≤ BMI < 30.0	829 (17.9)	497	60.0	2.01 (1.70–2.37)*	10.7
30.0 ≤ BMI	42 (0.9)	27	64.3	2.63 (1.34–5.20)*	0.7
Women					
BMI < 25.0	4,562 (77.4)	1,640	35.9	1.00	
25.0 ≤ BMI < 30.0	1,155 (19.6)	660	57.1	2.40 (2.07–2.78)*	15.9
30.0 ≤ BMI	176 (3.0)	121	68.8	4.17 (2.92–5.95)*	3.8
In 1990					
Men					
BMI < 25.0	2,636 (76.3)	1,228	46.6	1.00	
25.0 ≤ BMI < 30.0	758 (21.9)	450	59.4	2.04 (1.70–2.44)*	13.3
30.0 ≤ BMI	60 (1.7)	43	71.7	4.59 (2.50–8.42)*	2.0
Women					
BMI < 25.0	3,666 (76.2)	1,351	36.9	1.00	
25.0 ≤ BMI < 30.0	999 (20.8)	621	62.2	2.6 (2.20–3.05)*	18.4
30.0 ≤ BMI	143 (3.0)	102	71.3	4.5 (3.00–6.80)*	3.8

Obesity was defined as a body mass index ≥ 25.0 kg/m^2, and 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

Odds ratios were calculated by a logistic regression model adjusted for age, alcohol drinking habit and smoking habit; * statistical significance ($p < 0.05$), vs. BMI < 25.0

a study, which measured the proportion of individuals with hypertension due to the same BMI level as ours (BMI 25.0 kg/m^2) among total hypertensives in a Western country. Wilson et al. [27] reported that 26% of male hypertensives and 28% of female hypertensives in a population in the United States had hypertension which was attributed to BMI $\geq$ 25.0 kg/m^2 in a 44-year follow-up study from 1948. Consequently, the proportion of individuals with hypertension due to BMI $\geq$ 25.0 kg/m^2 among total hypertensives in Japan should be lower than the corresponding proportion in the United States.

The number of Japanese participants with 25.0 $\leq$ BMI < 30.0 kg/m^2 was approximately eight times greater than that with BMI $\geq$ 30.0 kg/m^2 for both sexes in the present study. Approximately 80–90% of the Japanese participants with hypertension due to BMI $\geq$ 25.0 kg/m^2 were in the 25.0 $\leq$ BMI < 30.0 kg/m^2 category for both sexes. Japanese in the 25.0 $\leq$ BMI < 30.0 kg/m^2 category contributed more significantly to the high prevalence of hypertension in Japan rather than Japanese with BMI 30.0 kg/m^2. Therefore, in order to reduce the prevalence of hypertension in Japan, more attention should be paid to Japanese in the 25.0 $\leq$ BMI < 30.0 kg/m^2 category who account for the majority of the obese in the Japanese population (BMI $\geq$ 25.0 kg/m^2) [35–38]. However, according to Wilson's study [27], in the United States, approximately 60–70% of individuals with hypertension due to BMI $\geq$ 25.0 kg/m^2 could be attributed to the 25.0 $\leq$ BMI < 30.0 kg/m^2 category, whereas approximately 30–40% could be attributed to the BMI $\geq$ 30.0 kg/m^2 category.

The prevalence of hypertension among Japanese has remained unchanged from 1980 to 1990 (approximately 50% for men and 40% for women). However, the proportion of individuals with obesity-induced hypertension among total hypertensives in Japan increased, as the prevalence of obesity among Japanese has increased. As for the increased prevalence of obesity, it is notable that the mean body weight remarkably increased between 1980 and 1990, although the mean body height also somewhat increased. High sodium intake has been a more important factor for hypertension in the Japanese population, compared to Western populations [1–5]. Some previous studies suggest the mean value of sodium intake in the Japanese population has remained unchanged or slightly decreased between 1980 and 1990this is lower than in the mid-1970s or beforē[1–5, 39], although we could not confirm such a trend by using this data because of lack of information on sodium intake. Furthermore, high alcohol intake also has been important among Japanese men, although the prevalence of drinkers among Japanese women is very low [2, 4, 6–8]. We confirmed the decreased prevalence of current daily drinkers among men over the decade using this data (74.3% in 1980 and 57.7% in 1990). These findings possible imply that high sodium and alcohol intake play a less important role in the high prevalence of hypertension in Japan than it did before. Therefore, we propose that the increased prevalence of obesity has compensated for reduced sodium and alcohol intake with regards to the high prevalence of hypertension in Japan. Moreover, we assume that the pandemic of obesity in Japan may have affected not only the prevalence of hypertension but also the prevalence of other obesity-related cardiovascular risks (e.g., type 2 diabetes) in Japan [29, 31, 40].

BMI is a widely used surrogate measurement of total body fat [41]. Recently, obesity has been quantified not only by BMI but also by other anthropometric parameters (e.g., waist circumference, fat distribution). However, other anthropometric parameters were not available in the present study. Sakurai et al. [42] suggested that among four anthropometric parameters of obesity (i.e., BMI, waist circumference, waist-to-hip ratio, and waist-to-height ratio), BMI has the strongest association with blood pressure and the prevalence of hypertension for middle-aged Japanese women. Additionally, there is little difference among the four anthropometric parameters in the strength of association with blood pressure or the prevalence of hypertension for middle-aged Japanese men, although BMI is ranked third among these four parameters [42]. Therefore, our results for the proportion of individuals with obesity-induced hypertension quantified by BMI among total hypertensives in Japan are reasonable.

The present study has some limitations. First, our results were estimated by using cross-sectional data in which reverse causality is occasionally observed. For example, the participants with obesity-induced hypertension may have attempted to reduce their body weight prior to the surveys, and this would results in a decreased prevalence of obesity in the study population. However, blood pressure levels also might have decreased after body weight reduction among the participants with obesity-induced hypertension [36–38]. Therefore, our results may show the prevalence of obesity and hypertension in the study population on the basis of the well-established causality between obesity and hypertension [26–32]. Finally, blood pressure-related social factors (e.g., stress, irregular lifestyle) and dietary factors (e.g., sodium intake, potassium intake) were not available in the present study. Especially, adjustment for sodium intake is significant to assess the risk for hypertension among Japanese because of its importance [1–5]. However, in addition to the trend of unchanged or slightly decreased sodium intake among Japanese between 1980 and 1990 [3–5, 39], Mikawa et al. [13] observed there was little difference in the sodium/potassium intake ratio between obese and non-obese Japanese in 1985. Consequently, the lack of adjustment for

sodium intake perhaps may have little impact on the result of increased proportion of hypertensives due to obesity over the decade.

In conclusion, Japan has witnessed a progressive rise in the proportion of individuals with obesity-induced hypertension among total hypertensives between 1980 and 1990 in both sexes. Obesity now plays a more important role in the high prevalence of hypertension in Japan than it did before. In order to reduce the proportion of individuals with obesity-induced hypertension among total hypertensives in Japan, an appropriate strategy to encourage the population to adopt healthy dietary habits and to increase their physical activity should be considered.

Acknowledgements We are grateful to all members of the Japanese Association of Public Health Center Directors and all staff of the public health centers that cooperated with the present study. The present study was supported by a Grant-in-Aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-cardiovascular Disease Control, a 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, H17-chouju-012, H19-chouju-ippan-014).

Appendix

List of the NIPPON DATA80, 90 Research group.

NIPPON DATA80, 90: "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged."

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

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

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

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

References

1. Dahl LK. Possible role of salt intake in the development of essential hypertension. Int J Epidemiol 2005;34:967–72.
2. Ueshima H, Tatara K, Asakura S, Okamoto M. Declining trends in blood pressure level and the prevalence of hypertension, and changes in related factors in Japan, 1956–1980. J Chronic Dis 1987;40:137–47.
3. INTERSALT Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. BMJ 1988;297:319–28.
4. Hashimoto T, Fujita Y, Ueshima H, Kagamimori S, Kasamatsu T, Morioka S, et al. Urinary sodium and potassium excretion, body mass index, alcohol intake and blood pressure in three Japanese populations. J Hum Hypertens 1989;3:315–21.
5. Nakagawa H, Morikawa Y, Okayama A, Fujita Y, Yoshida Y, Mikawa K, et al. Trends in blood pressure and urinary sodium and potassium excretion in Japan: reinvestigation in the 8th year after the Intersalt Study. J Hum Hypertens 1999;13:735–41.
6. Marmot MG, Elliott P, Shipley MJ, Dyer AR, Ueshima H, Beevers DG, et al. Alcohol and blood pressure: the INTERSALT study. BMJ 1994;308:1263–7.
7. Klag MJ, Moore RD, Whelton PK, Sakai Y, Comstock GW. Alcohol consumption and blood pressure: a comparison of native Japanese to American men. J Clin Epidemiol 1990;43:1407–14.
8. Ueshima H, Ozawa H, Baba S, Nakamoto Y, Omae T, Shimamoto T, et al. Alcohol drinking and high blood pressure: data from a 1980 national cardiovascular survey of Japan. J Clin Epidemiol 1992;45:667–73.
9. Inoue S. Prevalence and secular trends of obesity in Japan. Nippon Rinsho 2002;60(Suppl 8):119–27 (in Japanese).

10. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. JAMA 1994;272:205–11.
11. 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;9:163–74.
12. Kanazawa M, Yoshiike N, Osaka T, Numba Y, Zimmet P, Inoue S. Criteria and classification of obesity in Japan and Asia-Oceania. Asia Pac J Clin Nutr 2002;11(Suppl 8):S732–7.
13. Mikawa K, Ueshima H, Hashimoto T, Fujita Y, Naruse Y, Nakagawa H, et al. An INTERSALT study investigation: relationship between body mass index and blood pressure in the combined populations of three local centres in Japan. J Hum Hypertens 1994;8:101–5.
14. Hori Y, Toyoshima H, Kondo T, Tamakoshi K, Yatsuya H, Zhu S, et al. Gender and age differences in lifestyle factors related to hypertension in middle-aged civil service employees. J Epidemiol 2003;13:38–47.
15. Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Elliott P, et al. NIPPONDATA80 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;147:1024–32.
16. Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H. The NIPPON DATA80 Research Group. Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). J Hypertens 2006;24:459–62.
17. Oki I, Nakamura Y, Okamura T, Okayama A, Hayakawa T, Kita Y, et al. Body Mass Index and risk of stroke mortality among a random sample of Japanese adults: 19-year follow-up of NIPPON DATA80. Cerebrovasc Dis 2006;22:409–15.
18. Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Ueshima H. NIPPON DATA90 Research Group. The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. Atherosclerosis 2006;184:143–50.
19. Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, et al. NIPPON DATA90 Research Group: electrocardiogram screening for left high R-wave predicts cardiovascular death in a Japanese community-based population. Hypertens Res 2006;29:353–60 (errata: Hypertens Res 2006;29:833).
20. Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Ohnishi H, et al. The NIPPON DATA90 Research Group. Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. Circ J 2006;70:954–9.
21. The 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;66:987–92.
22. World Health Organization. Obesity. Preventing and managing the global endemic. WHO Technical Report Series no 894. Geneva: WHO; 2000.
23. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. National High Blood Pressure Education Program Coordinating Committee.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–72 (errata: JAMA 2003;290:197).
24. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15–9.
25. Greenland S. Re: "Confidence limits made easy: interval estimation using a substitution method". Am J Epidemiol 1999;149:884–6.
26. Kannel WB, Brand N, Skinner JJ Jr, Dawber TR, McNamara PM. The relation of adiposity to blood pressure and development of hypertension. The Framingham study. Ann Intern Med 1967;67:48–59.
27. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 2002;162:1867–72.
28. Kawabe H, Shibata H, Hirose H, Tsujioka M, Saito I, Saruta T. Determinants for the development of hypertension in adolescents. A 6-year follow-up. J Hypertens 2000;18:1557–61.
29. Yamagishi K, Hosoda T, Sairenchi T, Mori K, Tomita H, Nishimura A, et al. Body mass index and subsequent risk of hypertension, diabetes and hypercholesterolemia in a population-based sample of Japanese. Nippon Koshu Eisei Zasshi 2003;50:1050–7 (in Japanese).
30. Droyvold WB, Midthjell K, Nilsen TI, Holmen J. Change in body mass index and its impact on blood pressure: a prospective population study. Int J Obes 2005;29:650–5.
31. Ishikawa-Takata K, Ohta T, Moritaki K, Gotou T, Inoue S. Obesity, weight change and risks for hypertension, diabetes and hypercholesterolemia in Japanese men. Eur J Clin Nutr 2002;56:601–7.
32. Berchtold P, Sims EA, Horton ES, Berger M. Obesity and hypertension: epidemiology, mechanisms, treatment. Biomed Pharmacother 1983;37:251–8.
33. Takashima Y. Population attributable risk percent (PAR) of obesity in essential hypertension. Nippon Eiseigaku Zasshi 1985;39:914–23 (in Japanese).
34. Zhou BF, Stamler J, Dennis B, Moag-Stahlberg A, Okuda N, Robertson C, et al. INTERMAP Research Group. Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTERMAP study. J Hum Hypertens 2003;17:623–30.
35. Dyer AR, Elliott P. The INTERSALT study: relations of body mass index to blood pressure. J Hum Hypertens 1989;3:299–308.
36. Schotte DE, Stunkard AJ. The effects of weight reduction on blood pressure in 301 obese patients. Arch Intern Med 1990;150:1701–4.
37. Jones DW. Body weight and blood pressure. Effects of weight reduction on hypertension. Am J Hypertens 1996;9:50s–4s.
38. Hirose H, Saito I, Tsujioka M, Kawabe H, Saruta T. Effects of body weight control on changes in blood pressure: three-year follow-up study in young Japanese individuals. Hypertens Res 2000;23:421–6.
39. The Study Circle for Health and Nutrition Information. The national nutrition survey in Japan, 2002. Tokyo: Daiichi-Shuppan; 2004. p. 182 (in Japanese).
40. Yoshiike N. An increasing trend in the prevalence of diabetes mellitus in Japan. In: The 116th Japanese Association of Medical Sciences Symposium Report: Recent Topics on Diabetes Mellitus. Tokyo: The Japanese Association of Medical Sciences; 2000. p. 6–12 (in Japanese).
41. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Am J Clin Nutr 1998;68:899–917.
42. Sakurai M, Miura K, Takamura T, Ota T, Ishizaki M, Morikawa Y, et al. Gender differences in the association between anthropometric indices of obesity and blood pressure in Japanese. Hypertens Res 2006;29:75–80.

Original Article

Joint Impact of Smoking and Hypertension on Cardiovascular Disease and All-Cause Mortality in Japan: NIPPON DATA80, a 19-Year Follow-Up

Atsushi HOZAWA[1], Tomonori OKAMURA[1], Yoshitaka MURAKAMI[1], Takashi KADOWAKI[1], Koshi NAKAMURA[1], Takehito HAYAKAWA[2], Yoshikuni KITA[1], Yasuyuki NAKAMURA[3], Robert D. ABBOTT[1,5], Akira OKAYAMA[4], and Hirotsugu UESHIMA[1], the NIPPON DATA80 Research Group

Hypertension and smoking are major risk factors for death due to cardiovascular disease (CVD). These attributions for CVD mortality should be higher in the countries where obesity-related conditions are uncommon. However, the joint effect of these risk factors on CVD and all-cause mortality have not been described. We followed a representative 8,912 Japanese men and women without a history of stroke and heart disease. Participants were categorized into 4 groups as follows: a group of individuals who neither smoked nor had hypertension (HT), a group of current smokers, a group with HT, and a group of current smokers with HT. We further calculated population-attributable fractions (PAF) of CVD and all-cause mortality based on relative hazards assessed by proportional hazard regression models. After 19 years of follow-up, we observed 313 and 291 CVD and 948 and 766 all-cause deaths for men and women, respectively. The PAF of CVD mortality due to smoking or HT were 35.1% for men and 22.1% for women. The PAF of CVD mortality was higher in participants <60 years of age (57.4% for men and 40.7% for women) *vs.* those who were older (26.3% for men and 18.1% for women). Aggressive attempts to discourage smoking and to curb HT could yield large health benefits in Japan and throughout Asia, particularly for those aged <60 years. Efforts to warn about the adverse consequence of HT and smoking during adolescence and youth could yield the greatest health benefits, since positive behaviors adopted early are more easily continued into middle adulthood and later life. (*Hypertens Res* 2007; 30: 1169–1175)

***Key Words*: hypertension, smoking, population attributable fraction, epidemiology, prospective studies**

From the [1]Department of Health Science, Shiga University of Medical Science, Otsu, Japan; [2]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan; [3]Department of Cardiovascular Epidemiology, Faculty of Home Economics, Kyoto Women's University, Kyoto, Japan; [4]Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan; and [5]University of Virginia School of Medicine, Charlottesville, USA.

This study was supported by a Grant-in-Aid from the Ministry of Health, Labour 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, Labour and Welfare of Japan, and a Health and Labour Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-chouju-046, H14-chouju-003, and H17, 18-chouju-012). One of the authors (R.D.A.) was supported by the Japan Society for the Promotion of Science (JSPS) through the JSPS Invitation Fellowship Program for Research in Japan.

Address for Reprints: Atsushi Hozawa, M.D., Ph.D., Department of Health Science, Shiga University of Medical Science, SetaTsukinowa-cho, Otsu 520–2192, Japan. E-mail: ahozawa@belle.shiga-med.ac.jp

Received April 23, 2007; Accepted in revised form July 3, 2007.

Introduction

Hypertension (HT) is one of the strongest risk factors for cardiovascular disease (CVD) (*1*). Smoking is also an important risk factor for CVD mortality (*2*). The prevalence of smoking and HT in Japan (*3*, *4*) and in other Asian countries is excessive (*5–9*). Thus, the impact of HT and smoking on CVD mortality should be high in Japanese and throughout Asia.

Although several studies have described the higher population-attributable risk fraction (PAF) of CVD due to HT alone or smoking alone in Japan (*10*, *11*) and in other Asian populations (*8*, *9*), the numbers of CVD and all-cause deaths that could jointly be explained by HT and smoking in Japan have not been examined. Understanding the joint contribution of HT and smoking to CVD could help guide Japan and other Asian countries in formulating programs that warn of the adverse consequences of these risk factors, particularly in areas where obesity-related conditions are relatively uncommon (*12*).

In addition, since previous studies have suggested that the relative risk of smoking alone or HT alone on CVD mortality is stronger in younger than in older individuals (*10*, *11*), the combined impact of HT and smoking on CVD and all-cause mortality might also differ by age group.

Therefore, to describe the amount of CVD and all-cause mortality that could be explained by current smoking and HT in Japan, we calculated the age-specific joint impact of smoking and HT on CVD and all-cause mortality using a representative national survey with a high follow-up rate.

Methods

Study Participants

The subjects of this cohort study participated in the National Cardiovascular Survey of 1980. The standardized procedures used in that survey have been described elsewhere (*13*). All household members ≥30 years of age were surveyed in 300 census tracts that were randomly selected throughout Japan.

The number of individuals selected was 13,771. Among these, 10,546 individuals had completed baseline information regarding age, gender, and blood pressure (BP). The sample comprised the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged (NIPPON DATA80) (*4*, *13–15*). Thus, 76.6% of the overall population was available for analysis. From this sample, we excluded participants with a history of stroke (N=117), coronary heart disease (N=163) or other heart diseases (N=475). An additional 32 were excluded who lacked data on BP, glucose, cholesterol, and smoking and drinking habits. There were 847 participants who were excluded because they had missing residential information and mortality follow-up. The final sample thus included 8,912 participants (3,963 men and 4,949 women). Compared to those not excluded (N=8,912), the excluded group due to loss to follow-up was younger (self-reported age: 46.3 years *vs.* 49.6 years) and less likely to smoke cigarettes (33% *vs.* 39%). These differences, however, appeared to be modest. There were no differences with respect to gender (women comprised 56% of both groups) or age-adjusted BP.

Data Collection

The baseline survey included medical examinations, BP measurements, blood tests, and a self-administered questionnaire about lifestyle. Trained staff at local health centers in the respective districts performed the examinations in community centers. A history of heart disease, stroke and diabetes, as well as smoking and drinking habits was obtained from the questionnaire. Height and weight were measured with the subjects wearing light clothing and no shoes. The subjects were asked to note whether they were current smokers, had quit smoking, or had never smoked, and smokers were asked to note the number of cigarettes smoked each day. We treated ex-smokers and those who had never smoked as nonsmokers in this study. Single measurements of systolic and diastolic BP (SBP and DBP) were obtained after a 5 min rest by trained public health nurses at each public health center using a standard mercury sphygmomanometer. HT was defined as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medication (*1*). Non-fasting blood samples were collected. The precision and accuracy of the assay for measuring serum total cholesterol (TC) were certified by the Lipid Standardization Program administered by the Centers for Disease Control and Prevention, Atlanta, USA (*16*). Diabetes was defined as a serum glucose value ≥200 mg/dL or a self-reported history of diabetes. For alcohol consumption, subjects were asked whether they were never drinkers, past drinkers, occasional drinkers, or regularly drinkers on a daily basis.

Follow-Up Survey

NIPPON DATA80 has completed follow-up surveys until 1999. The underlying causes of death were coded for the Japanese National Vital Statistics according to the 9th International Classification of Disease (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the beginning of 1995. Details of the classification used in the present study have been described elsewhere (*13*). Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency of the Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Statistical Analysis

To examine the association of the combined effects of smok-

Table 1. Baseline Characteristics According to the Combination of Blood Pressure and Smoking Status: NIPPON DATA80, 1980, Japan

Characteristics	Younger (age <60 years)					Older (age ≥60 years)				
	Normotensive		Hypertensive			Normotensive		Hypertensive		
	Non-smoker	Current smoker	Non-smoker	Current smoker	*p*-value*	Non-smoker	Current smoker	Non-smoker	Current smoker	*p*-value*
Men										
N	580	1,178	450	829		90	161	320	355	
Age	42.6	42.2	46.7	47.2	<0.01	68.9	67.5	69.9	68.1	<0.01
BMI (kg/m^2)	22.6	22.1	23.7	23.2	<0.01	21.4	20.9	22.5	21.6	<0.01
Diabetes (%)	4	4	6	8	<0.01	8	11	9	15	0.054
Total cholesterol (mg/dL)	186.8	183.3	196.7	188.5	<0.01	184.3	176.5	187.0	180.6	<0.01
Drinking status										
Never (%)	24	19	19	12	<0.01	33	34	26	22	<0.01
Past (%)	5	4	3	3		16	7	11	8	
Occasional (%)	36	29	30	22		27	19	20	17	
Daily (%)	35	48	48	63		24	40	43	52	
Women										
N	2,403	216	1,060	92		312	41	741	84	
Age	42.3	42.1	49.4	48.8	<0.01	67.4	67.1	69.1	69.1	<0.01
BMI (kg/m^2)	22.3	21.9	24.1	24.0	<0.01	21.8	21.7	23.4	22.1	<0.01
Diabetes (%)	1	1	6	4	<0.01	10	10	8	8	0.92
Total cholesterol (mg/dL)	182.5	185.6	195.8	199.7	<0.01	199.6	190.6	202.4	197.6	<0.01
Drinking status										
Never (%)	79	46	84	48	<0.01	81	71	84	67	<0.01
Past (%)	1	5	1	3		1	5	2	5	
Occasional (%)	19	36	13	35		15	15	10	19	
Daily (%)	2	13	2	14		2	10	4	10	

N, number of participants; BMI, body mass index; non-smoker, never smoked and ex-smoker. *Test by analysis of variance for continuous variable and χ^2 test for categorical variables.

ing and HT on mortality, participants were categorized as: 1) neither smokers nor HT, 2) smokers only, 3) HT only, and 4) smoker with HT. We compared basic characteristics among the four groups using means for continuous variables and percentages for dichotomous variables. We separately analyzed men and women and those <60 years and ≥60 years of age. We estimated the multivariate adjusted relative hazards (RH) and the 95% confidence intervals (95% CI) for the effect of the combination of smoking and HT on CVD and on all-cause mortality using Cox proportional hazard models. We treated those who were neither smokers nor HT as a reference group. The multivariate adjusted model included the following possible confounding factors: age, body mass index, diabetes, TC, and alcohol consumption category (never, past, occasional, and daily). We also calculated the PAF of CVD and all-cause mortality due to the combination of smoking and HT using methods described elsewhere (*17*). The PAF was also recalculated for comparison with other Japanese studies (*4*, *10*).

Results

Baseline Characteristics

The mean age±SD was 50.0±13.0 years for men and 50.2±13.1 years for women. The prevalence of HT was 49.3% for men and 40.0% for women. The prevalence of current smoking was 63.7% for men and 8.8% for women. Table 1 shows the baseline characteristics according for each of the four smoking and HT groups. For both men and women, the hypertensive groups were older, more obese, more likely to have diabetes, more likely to have higher TC levels, and more likely to consume alcohol on a daily basis than the normotensive groups. The differences were statistically significant. Male current smokers were leaner, had lower TC levels, and were more likely to consume alcohol on a daily basis than male nonsmokers. Female current smokers were more likely to consume alcohol and to have a lower body mass index than female nonsmokers. No other differences in risk factors were found to be significant.

Table 2. Relative Hazard (RH) and 95% Confidence Interval (CI) for Cardiovascular Disease (CVD) or All Cause Mortality According to the Combination of Blood Pressure (BP) and Smoking Status by Age Group: NIPPON DATA80, 1980–1999

	Younger (age <60 years)					Older (age ≥60 years)				
	Normotensive		Hypertensive			Normotensive		Hypertensive		
	Non-smoker	Current	Non-smoker	Current	Total	Non-smoker	Current	Non-smoker	Current	Total
Men										
Person-year	10,623	21,437	8,232	14,692	54,984	1,295	2,260	4,165	4,708	12,428
CVD death	6	19	13	51	89	17	29	78	100	224
CVD mortality rate (per 1,000 person-years)	0.6	0.9	1.6	3.5	1.6	13.1	12.8	18.7	21.2	18.0
RH (95% CI) for CVD mortality*	1	1.58 (0.63–3.97)	1.96 (0.73–5.22)	3.86 (1.62–9.19)		1	1.02 (0.56–1.87)	1.27 (0.74–2.17)	1.72 (1.02–2.89)	
Excess CVD death		7.0	6.4	37.8	51.1		0.7	16.4	41.8	58.9
PAF for CVD death (%)		7.8	7.1	42.4	57.4		0.3	7.3	18.6	26.3
All cause death	40	115	50	143	348	47	99	209	245	600
All cause mortality rate (per 1,000 person-years)	3.8	5.4	6.1	9.7	6.3	36.3	43.8	50.2	52.0	48.3
RH (95% CI) for all cause mortality*	1	1.40 (0.98–2.01)	1.21 (0.79–1.84)	1.69 (1.17–2.42)		1	1.24 (0.87–1.76)	1.32 (0.95–1.82)	1.47 (1.07–2.02)	
Excess all cause death		33.0	8.5	58.1	99.6		18.9	50.2	78.3	147.4
PAF for all cause death (%)		9.5	2.4	16.7	28.6		3.2	8.4	13.1	24.6
Women										
Person-year	44,630	3,990	19,427	1,656	69,703	4,947	601	10,971	1,133	17,652
CVD death	16	3	28	5	52	49	3	160	27	239
CVD mortality rate (per 1,000 person-years)	0.4	0.8	1.4	3.0	0.7	9.9	5.0	14.6	23.8	13.5
RH (95% CI) for CVD mortality*	1	2.58 (0.75–8.93)	2.19 (1.13–4.22)	5.88 (2.07–16.72)		1	0.46 (0.14–1.48)	1.23 (0.88–1.71)	2.01 (1.25–3.23)	
Excess CVD death		1.8	15.2	4.1	21.2		0.0	29.6	13.6	43.2
PAF for CVD death (%)		3.5	29.2	8.0	40.7		0.0	12.4	5.7	18.1
All cause death	100	13	85	10	208	117	19	373	49	558
All cause mortality rate (per 1,000 person-years)	2.2	3.3	4.4	6.0	3.0	23.7	31.6	34.0	43.2	31.6
RH (95% CI) for all cause mortality*	1	1.63 (0.90–2.94)	1.07 (0.79–1.47)	1.77 (0.91–3.46)		1	1.23 (0.75–2.01)	1.28 (1.03–1.59)	1.61 (1.15–2.26)	
Excess all cause death		5.0	5.8	4.4	15.2		3.5	80.7	18.6	102.9
PAF for all cause death (%)		2.4	2.8	2.1	7.3		0.6	14.5	3.3	18.4

PAF, population attributable fraction; non-smoker, never smoked and ex-smoker. *Adjusted for age, body mass index, diabetes, total cholesterol, and drinking status.

Follow-Up Data

There were 67,412 and 87,355 person-years of follow-up in men and women, respectively (up to 19 years per person). During this time, a total of 948 men and 766 women died, and 313 and 291 of these deaths were due to CVD, respectively.

In this study, we combined never smokers and ex-smokers into one category because of the small number of ex-smokers. In addition, the risk factor–adjusted RH for deaths due to CVD for ex-smokers *vs.* never smokers was nearly one (RH=1.09 for men and RH=1.18 for women). This was also true for all-cause deaths (RH=1.14 for men and RH=1.18 for women).

Since CVD mortality in smokers with HT was higher in those <60 years of age than in those ≥60 years (p for interaction: <0.01 for men and 0.03 for women), we analyzed these groups separately. Table 2 further shows that the age-stratified joint impact of smoking and HT on CVD mortality was stronger in participants <60 years old *vs.* participants who were older.

For younger men, the risk factor–adjusted RH for CVD mortality was significantly higher in smokers with HT *vs.* the reference value (RH=3.86; 95% CI: 1.62–9.19). This value tended to be higher, but not significantly so, in the smoking only (RH=1.58; 95% CI: 0.63–3.97) and HT only (RH=1.96; 95% CI: 0.73–5.22) groups. Compared to the reference group, the risk factor–adjusted RH for CVD mortality among younger women was significantly higher in smokers with HT (RH=5.88; 95% CI: 2.07–16.72) and participants with HT only (RH=2.19; 95% CI: 1.13–4.22). The PAFs of CVD mortality in the smoking only, HT only, and smoking with HT groups were 7.8%, 7.1%, and 42.4%, respectively. Smoking and HT accounted for 57.4% of CVD deaths among younger men. Smoking and HT also accounted for 40.7% of CVD deaths among younger women. These proportions were higher than those observed in older participants (26.3% in men and 16.6% in women). However, the number of excess CVD deaths due to smoking and HT among men were similar between the younger and older subgroups (51.1 for younger and 58.9 for older male participants). In contrast, the excess deaths due to CVD among young women was half that in those who were older (21.2 for younger and 43.2 for older female participants). The overall sum of excess CVD deaths (PAF) due to smoking and HT was 110.0 (35.1%) for men and 64.4 (22.1%) for women.

Similar to the CVD findings, the risk factor–adjusted RH for all-cause mortality was higher in the smoking only, HT only, and smoking plus HT groups than in the group with neither factor. The PAFs of all-cause mortality due to smoking combined with HT were 28.6% for younger men, 24.6% for older men, 7.3% for younger women, and 18.4% for older women. The sum of the excess of all-cause deaths (PAF) due to smoking and HT were 247.0 (26.1%) for men and 118.1 (15.4%) for women.

Discussion

Evidence suggests that smoking and HT account for a large proportion of CVD and all-cause mortality in Japan. In the present report, although the number of excess CVD deaths due to smoking and HT were similar between younger and older men, the PAF was more than double in those who were younger. The number of excess deaths due to CVD among young women was half the number among older women. Because of the exceptionally high RHs, the PAF was also more than doubled in those who were younger. These findings confirm the importance of discouraging smoking and eliminating HT. They further suggest that aggressive attempts to warn about the adverse consequences of smoking and HT at an early age could yield significant health benefits in Japan, particular for those <60 years. Similar findings may also apply to other Asian countries where smoking and HT are highly prevalent.

It is well known that smoking has an important effect on CVD and all cause mortality in Japan (*4*, *10*). The NIPPON DATA80 (*4*) showed that the PAF of CVD mortality due to smoking was 27.5% for men and 5.0% for women, while the PAF for all-cause mortality was 15.0% for men and 4.0% for women. These values were similar to those of Iso *et al.* (*10*), who found that 23.5% and 6.0% of CVD mortality could be explained by smoking status. Other Japanese studies have also reported similar values for the PAF for all-cause mortality (*18–20*) due to smoking (range of PAF: 22–34% for men and 0–5% for women), and other Asian studies have yielded PAFs that are comparable to those in Japan (*8*).

Similarly, HT is also a potent CVD risk factor (*9*, *11*, *13*, *21*). However, few studies have described the PAF of CVD deaths due to HT defined as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medication in Japan (*9*). A few studies have described the PAF for CVD death due to non-optimal BP (SBP ≥120 mmHg or DBP ≥80 mmHg or current use of antihypertensive medication) (*11*, *14*). These studies found that the PAF of non-optimal BP was very high. Thus, both HT and smoking definitely contribute to a large proportion of CVD or all-cause deaths. These findings should be applied to other Asian populations, most of which have a high prevalence of smoking and HT and few obesity-related CVD risk factors, such as diabetes or hypercholesterolemia (*4–6*). In fact, a recent study has reported that a large fraction of CVD was attributable to HT (*9*).

However, the joint impact of smoking and HT on CVD and all-cause mortality is relatively unknown. Since Rothman described that the sum of disease attributable to various causes in reality has no upper limit (*22*), simple addition of these PAFs might not express the true contributions of the risk factors. Thus, it makes sense that the PAF should be calculated using a combination of smoking and HT when trying to determine their joint impact.

We found that the PAF for CVD mortality was higher in

younger than in older populations. This is consistent with previous findings. Iso *et al.* reported that excess CVD mortality associated with cigarette smoking is more evident in middle-age (40–64 years of age) than in the elderly (65–79 years) (*10*). Sairenchi *et al.* also reported that the PAF for CVD mortality due to non-optimal BP is higher in younger than in elderly persons (*11*). Although we could not conclude why the PAF for CVD mortality was higher in the younger than in the older population in the present work, this difference might be partly explained by an age-related increase in the risk for CVD in nonsmoking elderly individuals without HT; the crude CVD mortality rate in nonsmoking elderly participants without HT was more than 20 times as large as that in nonsmoking younger persons without HT. The PAF is defined by both RH and the prevalence. Since the prevalence of HT was greater in older than in younger participants, the difference in the PAF for CVD mortality between younger and older participants observed in our study could be explained by the higher RH in the younger participants. Thus, earlier intervention to discourage smoking and warn against the hazard of HT should have a greater benefit in those who are young, with continued carry-over into later life. Similar interventions in the elderly are also important, because the number of excess CVD deaths due to smoking and HT were higher among those aged 60 or older *vs.* those who were younger.

The strength of our study was the use of a representative population with a high response rate and long follow-up period. Thus, our results could be applicable to the entire Japanese population. The study also has several limitations that should be considered. First, these data were based on participants who lived 25 years ago. Since Japanese lifestyles have recently undergone dramatic changes, it may be that these data are less applicable today. However, the 2003 National Health and Nutrition Survey in Japan showed that the prevalence of current smoking among younger men (30–59 years) has remained high (54.4–56.8%) and that the prevalence is increasing among younger women (10.7–18.1%). These values were also rather high when compared with the sample in the present study (*23*). The prevalence of HT remained similarly high in the 2003 survey (10.1% for the age group of 30–39 years, 30.8% for 40–49 years, 36.4% for 50–59 years, 52.4% for 60–69 years and 57.5% for those aged ≥70 years, with men and women combined) (*23*). Thus, the prevalence of both smoking and HT continues to be a major public health problem, and developing intervention strategies to warn of the adverse health consequence of smoking and HT should be a top priority. Secondly, we defined HT as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medications. Therefore, our results might underestimate the true PAF due to HT compared with other studies that used optimal BP levels (SBP <120 mmHg and DBP <80 mmHg) as a reference. Furthermore, since we obtained only single BP values for each participant, some measurement error may have occurred. Such error could have resulted in conservative findings. Finally, we combined never and ex-smokers into one category because of the small number of deaths that were observed in the ex-smoker group, particularly among those who were young. Although combining never and ex-smokers into a single group could have resulted in an underestimation of the impact of smoking on our PAFs, this may not have been the case in this instance because, after adjusting for risk factors, the rate of all-cause and CVD mortality were nearly identical in never and ex-smokers.

In conclusion, our results suggest that eliminating two major CVD risk factors, namely, smoking and HT, would prevent 35% of CVD deaths in men and 22% of CVD deaths in women. Moreover, eliminating these factors would prevent 26% of all-cause deaths in men and 15% of all cause deaths in women. Intervention programs that discourage smoking and warn of the adverse consequences of HT in adolescence might eventually yield the greatest health benefits for men and women <60 years of age, since the increased capacity for healthy behaviors would be carried over into later life. It seems likely that the benefits from initial intervention programs as early in life as possible will increase longevity, not just in Japan, but throughout Asia.

Acknowledgements

The authors thank all members of the Japanese Association of Public Health Center Directors and all staff of the public health centers that cooperated with this study.

References

1. Chobanian AV, Bakris GL, Black HR, *et al*, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
2. U.S. Department of Health and Human Services: The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
3. The Fifth National Survey of Cardiovascular Diseases. Tokyo, Chuo-Hoki Publisher, 2003 (in Japanese).
4. Ueshima H, Choudhury SR, Okayama A, *et al*: Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke* 2004; **35**: 1836–1841.
5. Ko M, Kim MT, Nam JJ: Assessing risk factors of coronary heart disease and its risk prediction among Korean adults: the 2001 Korea National Health and Nutrition Examination Survey. *Int J Cardiol* 2006; **110**: 184–190.
6. Wang L, Kong L, Wu F, Bai Y, Burton R: Preventing chronic diseases in China. *Lancet* 2005; **366**: 1821–1824.
7. Ueshima H, Zhang XH, Choudhury SR: Epidemiology of hypertension in China and Japan. *J Hum Hypertens* 2000; **14**: 765–769.

8. Martiniuk AL, Lee CM, Lam TH, *et al*, Asia Pacific Cohort Studies Collaboration: The fraction of ischaemic heart disease and stroke attributable to smoking in the WHO Western Pacific and South-East Asian regions. *Tob Control* 2006; **15**: 181–188.
9. Martiniuk AL, Lee CM, Lawes CM, *et al*, for the Asia-Pacific Cohort Studies Collaboration: Hypertension: its prevalence and population-attributable fraction for mortality from cardiovascular disease in the Asia-Pacific region. *J Hypertens* 2007; **25**: 73–79.
10. Iso H, Date C, Yamamoto A, *et al*, JACC Study Group: Smoking cessation and mortality from cardiovascular disease among Japanese men and women: the JACC Study. *Am J Epidemiol* 2005; **161**: 170–179.
11. Sairenchi T, Iso H, Irie F, *et al*: Age-specific relationship between blood pressure and the risk of total and cardiovascular mortality in Japanese men and women. *Hypertens Res* 2005; **28**: 901–919.
12. WHO Technical Report Series 894, Obesity: Preventing and Managing the Global Epidemic. Part I. The Problem of Overweight and Obesity. Geneva, World Health Organization, 2000, pp 6–37.
13. Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H, Nippon Data80 Research Group: What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med* 2003; **253**: 169–180.
14. Iida M, Ueda K, Okayama A, *et al*, Nippon Data 80 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 data 80. *J Hum Hypertens* 2003; **17**: 851–857.
15. Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H, The NIPPON DATA80 Research Group: Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). *J Hypertens* 2006; **24**: 459–462.
16. Nakamura M, Sato S, Shimamoto T: Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. *J Athroscler Thromb* 2003; **10**: 145–153.
17. Rockhill B, Newman B, Weinberg C: Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88**: 15–19.
18. Hozawa A, Ohkubo T, Yamaguchi J, *et al*: Cigarette smoking and mortality in Japan: the Miyagi Cohort Study. *J Epidemiol* 2004; **14**: S12–S17.
19. Hara M, Sobue T, Sasaki S, Tsugane S: Smoking and risk of premature death among middle-aged Japanese: ten-year follow-up of the Japan Public Health Center–based prospective study on cancer and cardiovascular diseases (JPHC Study) cohort I. *Jpn J Cancer Res* 2002; **93**: 6–14.
20. Uno F, Ishikawa S, Nakamura Y, *et al*: Smoking and risk of all-cause mortality: the Jichi Medical School (JMS) Cohort Study. *J Epidemiol* 2005; **15**: 173–179.
21. Arima H, Tanizaki Y, Kiyohara Y, *et al*: Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. *Arch Intern Med* 2003; **163**: 361–366.
22. Rothman KJ: Epidemiology—An Introduction—. New York, Oxford University Press, 2002.
23. The National Health and Nutrition Survey in Japan. Tokyo, Daiichi Syuppan Publisher, 2003, Japan (in Japanese).

Published by Oxford University Press on behalf of the International Epidemiological Association

International Journal of Epidemiology 2007;36:1060–1067
doi:10.1093/ije/dym169

CARDIOVASCULAR DISEASE

Is weak association between cigarette smoking and cardiovascular disease mortality observed in Japan explained by low total cholesterol?—NIPPON DATA80

Atsushi Hozawa,[1]* Tomonori Okamura,[1] Takashi Kadowaki,[1] Yoshitaka Murakami,[1] Koshi Nakamura,[1] Takehito Hayakawa,[2] Yoshikuni Kita,[1] Yasuyuki Nakamura,[3] Akira Okayama[4] and Hirotsugu Ueshima for NIPPON DATA80 Research group[†]

Accepted 24 July 2007

Background An international comparison has indicated that the association between smoking and cardiovascular disease (CVD) differs according to total cholesterol (TC) levels. However, little has been published about the relationship between smoking and CVD mortality among populations with various cholesterol levels.

Methods We calculated the adjusted relative hazard (RH) of smoking for CVD mortality among 8912 Japanese individuals without a history of stroke or heart disease, who were separated according to TC levels of ⩾5.40, 4.81–5.39, 4.26–4.80 and <4.25 mmol/l into groups Q4, Q3, Q2 and Q1, respectively. The *P*-values for multiple interactions between TC and smoking status for CVD mortality were calculated using TC as a continuous variable, dichotomized smoking status (never vs current), and by including cross-product terms in the regression models.

Results After 19 years of follow-up, 313 men and 291 women died of CVD. The RH of CVD mortality among men who currently smoked compared with those who never smoked was increased with higher TC (RH = 2.36 in Q4) and decreased in those with lower TC (RH = 0.85 in Q1) (interaction, $P < 0.01$). The profiles for coronary heart disease (CHD) mortality and ischaemic CVD (composite endpoint of CHD and ischaemic stroke) in men and for ischaemic CVD mortality in women were identical. The interaction might be explained by a biological mechanism and by frailty of those who have never smoked with lower TC.

Conclusions Counteractive measures should be implemented against smoking targeted towards Japanese with elevated TC levels.

Keywords Cigarette smoking, total cholesterol, cardiovascular diseases, interaction, prospective studies, Japan

Cigarette smoking is a known risk factor for both coronary heart disease (CHD) and stroke.[1] However, although the rate of cigarette smoking is high among Japanese men, mortality from ischaemic heart disease is strikingly lower than that in the USA.[2,3] Smoking is thus considered a weaker CHD risk factor in Japan than in Western countries.[4,5] However, cigarette smoking is closely related to CHD among Japanese immigrants living in Hawaii.[4] Thus, the between-population difference in CHD might be explained not by ethnicity but by environmental factors. Similar to Japan, the Seven Countries Study showed

[1] Department of Health Science, Shiga University of Medical Science, Shiga, Japan.
[2] Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan.
[3] Cardiovascular Epidemiology, Faculty of Home Economics, Kyoto Women's University, Kyoto, Japan.
[4] Department of Preventive Cardiology, National Cardiovascular Center, Osaka, Japan.
[†] Members of the NIPPON DATA Research Group are listed in the Appendix.
* Corresponding author. Department of Health Science, Shiga University of Medical Science, SetaTsukinowa -cho, Otsu 520-2192, Shiga, Japan. E-mail: ahozawa@belle.shiga-med.ac.jp