drome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care* 28: 385–390, 2005
26. Ford ES: Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 28:1769–1778, 2005
27. Takeuchi H, Saitoh S, Takagi S, Ohnishi H, Ohhata J, Isobe T, Shimamoto K: Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program-Adult Treatment Panel III to Japanese men—the Tannno and Sobetsu Study. *Hypertens Res* 28:203–208, 2005
28. Katzmarzyk PT, Janssen I, Ross R, Church TS, Blair SN: The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. *Diabetes Care* 29:404–409, 2006
29. Yoon YS, Lee ES, Park C, Lee S, Oh SW: The new definition of metabolic syndrome by the International Diabetes Federation is less likely to identify metabolically abnormal but non-obese individuals than the definition by the revised National Cholesterol Education Program: the Korea NHANES Study. *Int J Obes (Lond)* 31:528–534, 2007
30. Ohnishi H, Saitoh S, Takagi S, Katoh N, Chiba Y, Akasaka H, Nakamura Y, Shimamoto K: Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population. *Diabetes Care* 29:1128–1129, 2006

ELSEVIER

Social Science & Medicine 65 (2007) 822–832

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

Urban–rural difference in stroke mortality from a 19-year cohort study of the Japanese general population: NIPPON DATA80

Nobuo Nishi[a,*], Hiromi Sugiyama[a], Fumiyoshi Kasagi[a], Kazunori Kodama[a], Takehito Hayakawa[b], Kazuo Ueda[c], Akira Okayama[d], Hirotsugu Ueshima[e]

[a] *Department of Epidemiology, Radiation Effects Research Foundation Hiroshima, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan*
[b] *Shimane University School of Medicine, Japan*
[c] *Murakami Memorial Hospital, Japan*
[d] *National Cardiovascular Center, Japan*
[e] *Shiga University of Medical Science, Japan*

Available online 9 May 2007

Abstract

In Japan, cohort studies on stroke have been mainly conducted in rural areas, with few studies comparing stroke mortality between urban and rural areas. We aimed to explore urban–rural difference in stroke mortality throughout Japan using a representative sample of the general Japanese population, the NIPPON DATA80. This study included 9309 subjects (4080 men and 5229 women) aged 30 years or older who were residents of 294 areas in 211 municipalities of Japan in 1980 and followed-up until 1999. Population size of the municipality in which the aforementioned areas were located was used to distinguish between urban and rural areas, because municipalities in Japan are classified as village, town or city principally by population size. We applied a multilevel logistic regression model to take into account the hierarchical data structure of individuals (subjects) (level 1) nested within areas (level 2), and then calculated odds ratios and 95% confidence intervals (CIs) of deaths from total stroke. Statistically significant variance between areas was not observed in men but was in women. Age-adjusted odds ratios of the areas in the medium (population≥30,000 and <300,000) and small municipalities (<30,000) compared with the areas in the large municipalities (≥300,000) were 1.31 and 1.40 in men, and 1.32 and 1.62 in women, respectively. Multivariate-adjusted odds ratios (adjusted for age, body mass index, total cholesterol, diabetes, hypertension, current smoking, and daily alcohol consumption) of the areas in the medium and small municipalities compared with the areas in the large municipalities were 1.29 and 1.36 in men, and 1.34 and 1.68 in women, respectively. In conclusion, stroke mortality tended to be higher in rural areas than in urban areas in Japan, especially among women.

Keywords: Japan; Stroke; Mortality; Urban population; Rural population; Multilevel analysis

Introduction

Socioeconomic differences in cardiovascular disease mortality have been reported in many countries (Kaplan & Keil, 1993; Mackenbach, Cavelaars, Kunst, Groenhof, & the EU Working Group on Socioeconomic Inequalities in Health, 2000). The

*Corresponding author. Tel.: +81 82 261 3131; fax: +81 82 262 9768.
E-mail addresses: nnishi@rerf.or.jp (N. Nishi), sugi@rerf.or.jp (H. Sugiyama), kasagi@rerf.or.jp (F. Kasagi), kodama@rerf.or.jp (K. Kodama), hayakawa@med.shimane-u.ac.jp (T. Hayakawa), 8kazu-ueda@jcom.home.ne.jp (K. Ueda), aokayama@hsp.ncvc.go.jp (A. Okayama), hueshima@belle.shiga-med.ac.jp (H. Ueshima).

0277-9536/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.socscimed.2007.04.013

findings are nearly consistent in that the lower the socioeconomic status, the higher the mortality, although the magnitude varies from study to study. In Japan, where mortality from heart disease is low and that from stroke high compared with other countries (WHO, 2002), several studies support such findings (Fukuda, Nakamura, & Takano, 2005).

In Japan, stroke was the leading cause of death from the 1950s to the 1970s (Health and Welfare Statistics and Information Department, 2005). Geographical variation in stroke mortality was first recognized in the 1950s, and standardized mortality ratios for cerebral hemorrhage and cerebral infarction were found to be high in the northeastern part of the country, especially the Tohoku region (Takahashi, Sasaki, Takeda, & Ito, 1957; Tamashiro et al., 1981; Ueshima, Ohsaka, & Asakura, 1986). This geographical variation in stroke mortality (cerebral hemorrhage) was related to average daily salt intake of farmers (Dahl, 1960). The finding prompted cohort studies mainly in rural areas throughout Japan, including the Tohoku region. Subsequently, stroke mortality started to decline in the 1970s as a result of community efforts, such as detection and control of hypertension and reduction of dietary sodium intake (Kodama, 1993; Kubo et al., 2003; Morikawa et al., 2000; Shimamoto et al., 1989). Thus, cohort studies on stroke have mainly focused on rural areas, with few studies comparing stroke mortality between urban and rural areas in Japan. Kitamura et al. (2001) conducted cohort studies in a rural town in the Tohoku region and in an urban community in western Japan from 1964 to 1995, and reported that stroke mortality in the rural town was consistently higher than in the urban community, especially among younger men aged 40–59 years. However, their comparison was based on data from two areas in vastly different regions, and did not reflect overall difference in stroke mortality between urban and rural areas in Japan. Moreover, as is the case with most cohort studies in Japan, their study involved intervention by health professionals.

Stroke mortality has decreased in parallel with the urbanization of rural areas in Japan. According to a special report regarding vital statistics in Japan (Statistics and Information Department, 1995 and 2000), the ratio of age-standardized mortality from stroke for those aged 20–64 years (per 100,000) among primary industry workers to tertiary industry workers was 2.3 (37.1/15.8) in 1995 and 2.8 (33.7/12.2) in 2000 for men, whereas for women, the ratio was 1.8 (13.2/7.5) and 2.4 (13.9/5.7) in the same years, respectively. Thus, recent vital statistics of Japan indicate that stroke mortality is higher for primary industry workers than for tertiary industry workers (respective figures were not available before 1995). These results are possibly related to urban–rural difference in stroke mortality, but they are limited to the Japanese working population.

NIPPON DATA80 is an observational cohort study on a representative sample of the general Japanese population aged 30 years or older, with a 19-year follow-up in the last two decades of the 20th century (Nippon Data 80 Research Group, 2003). This cohort is suitable for exploring urban–rural difference in stroke mortality for two reasons because of its hierarchical data structure. First, the study areas were randomly selected from throughout Japan, allowing any urban–rural difference to be distinguished from geographical variation between regions in Japan. Second, each study area was located in a municipality, and population information about the municipality was readily available. This municipality population size is thought to be an objective indicator of whether the area was urban or rural because population size is principally used to classify municipalities as village, town or city in Japan. The aim of this study was to explore urban–rural difference in stroke mortality throughout Japan using municipality population size in a representative sample of the general Japanese population.

Materials and methods

Study population

The present study is based on the National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged, which was conducted in 1980 (NIPPON DATA80), and the details of which have been reported elsewhere (Hayakawa et al., 2000; Nippon Data 80 Research Group, 2003; Okamura et al., 2004; Ueshima et al., 2004). Briefly, a total of 10,546 community residents (4640 men and 5906 women) aged 30 years or older from 300 randomly selected areas participated in the National Survey on Circulatory Disorders 1980. Each survey area was located in a public health center district, and the chief of the public health center was responsible for conduct of the survey. Public health centers have been founded by all 47 prefectures and designated cities (municipalities of large population) since 1937 and by special wards in the Tokyo Metropolitan Area since 1946 and have played a pivotal role in the administration of public health in Japan. Establishment of a public health center is closely related to municipality population size. A public health center founded by a prefecture might include several small municipalities such as villages, towns and (small) cities, whereas a designated city or special ward might include one or more public health centers. Thus, a public health center district is designated either by combining small municipalities or by dividing large municipalities, to ensure that each public health center covers approximately 100,000 people. A total of 855 public health centers and about 3250 municipalities existed in Japan in 1980. The 300 study areas in our study were located in 300 public health center districts in 211 municipalities.

Outcome surveys were conducted in 1994 and 1999. In 1994, 91.4% of the original participants' whereabouts were known. The present study is based on the outcome information obtained through November 1999, making the observation period a total of 19 years. Of the 10,546 participants, 1237 were excluded because of past history of coronary heart disease or stroke at baseline survey ($n = 280$), missing information at baseline survey ($n = 84$), or designation of "lost to follow-up" due to failed efforts to locate certain subjects ($n = 873$). This left 9309 participants (4080 men and 5229 women) from 294 areas in 211 municipalities.

Baseline examinations

Trained observers measured blood pressure with a standard mercury sphygmomanometer on the right arm of seated subjects after a 5-min rest. Hypertension was defined as systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, use of antihypertensive agents, or any combination of these. Height in stocking feet and body weight in light clothing were measured. Body mass index was calculated as weight (kilogram) divided by the square of height (meter). Public health nurses obtained information on smoking, drinking, and medical history.

Non-fasting blood samples were drawn and centrifuged within 60 min of collection. Serum total cholesterol was analyzed in an auto analyzer (SMA12/60; Technicon, Tarrytown, USA) at one specific laboratory (Center for Adult Diseases, Osaka). The laboratory has been certified since April 1975 by the CDC-NHLBI Lipid Standardization Program of the Centers for Disease Control and Prevention (CDC), Atlanta, regarding the precision and accuracy of its cholesterol measurements (Nakamura, Sato, & Shimamoto, 2003). Serum glucose was measured by cupric–neocuproine method with an auto-analyzer instrument (Bittner & McCleary, 1963). Diabetes was defined as serum glucose of 11.1 mmol/l or higher, history of diabetes, or both.

Definition of urban and rural areas

The data were characterized as a three-level structure of individuals at level 1 nested within areas at level 2 nested within regions at level 3. Regions (level 3) were defined by dividing Japan's 47 prefectures into six: Hokkaido-Tohoku (seven prefectures), Kanto-Koshin (nine), Hokuriku-Tokai (eight), Kinki (six), Chugoku-Shikoku (nine) and Kyushu (eight). Areas (level 2) were classified as urban or rural based on population size of the municipality in which they were located. As mentioned above, each survey area was located in a public health center district, but population size of the municipality proved to be more reliable for defining whether a given area was urban or rural. This was because municipalities in Japan are designated by the government as *mura* (village), *machi* (town), or *shi* (city) according to their level of development (special wards in the Tokyo Metropolitan Area are called *ku*), and a key determinant of this classification is population size. In our study, 294 areas in the six regions were categorized into three groups according to population size of the municipalities: small municipality with less than 30,000 people, medium municipality with 30,000 or more and less than 300,000 people, and large municipality with 300,000 or more people. These categories were used because a population of 30,000 was required for a city designation, with a population of 300,000 required for a core city designation, in accordance with Japan's Local Autonomy Law.

Numbers and percentages of areas and subjects by municipality population size in the six regions are shown in Table 1. Numbers of municipalities with large, medium and small population size were 40, 104, and 67, respectively, while numbers of areas in municipalities with large, medium, and small population size were 114, 113, and 67, respectively.

Table 1
Numbers and percentages of areas (level 2) and subjects (level 1) in six regions (level 3) by municipality population size (Japanese men and women aged 30 years and older in 1980, NIPPON DATA80)

Region (level 3)	Areas (level 2) and subjects (level 1)	Municipality population size (n = 211)							
		Large (n = 40)		Medium (n = 104)		Small (n = 67)		Total	
		No.	%	No.	%	No.	%	No.	%
Hokkaido-Tohoku	Areas	4	11.4	18	51.4	13	37.1	35	100.0
	Subjects	79	5.8	596	43.9	682	50.3	1357	100.0
Kanto-Koshin	Areas	44	47.8	34	37.0	14	15.2	92	100.0
	Subjects	784	34.1	826	35.9	691	30.0	2301	100.0
Hokuriku-Tokai	Areas	15	30.0	23	46.0	12	24.0	50	100.0
	Subjects	480	22.9	930	44.3	689	32.8	2099	100.0
Kinki	Areas	27	51.9	20	38.5	5	9.6	52	100.0
	Subjects	549	41.5	564	42.6	210	15.9	1323	100.0
Chugoku-Shikoku	Areas	10	34.5	7	24.1	12	41.4	29	100.0
	Subjects	319	31.2	240	23.5	464	45.4	1023	100.0
Kyushu	Areas	14	38.9	11	30.6	11	30.6	36	100.0
	Subjects	330	27.4	406	33.7	470	39.0	1206	100.0
Total	Areas	114	38.8	113	38.4	67	22.8	294	100.0
	Subjects	2541	27.3	3562	38.3	3206	34.4	9309	100.0

Municipality population size: Large (⩾300,000); Medium (30,000–<300,000); Small (<30,000).

This information indicates that municipalities with large population size had one or more public health center in their municipalities. Percentages of municipalities with large, medium, and small population size differed significantly by region ($p<0.001$). The regions were listed from the northeastern (Hokkaido-Tohoku) to the southwestern (Kyushu) part of the Japanese archipelago, and the percentage of municipalities with large population size was lower in the Hokkaido-Tohoku region and higher in the Kanto-Koshin and Kinki regions.

End point determination

The procedure used for end point determination in our study has been reported elsewhere (Okamura et al., 2003, 2004; Ueshima et al., 2004). Briefly, the underlying causes of death for Japan's National Vital Statistics were coded according to the 9th International Classification of Disease (ICD-9) through the end of 1994 and the 10th International Classification of Disease (ICD-10) from the beginning of 1995. Codes 430–434 and 436–438 in ICD-9 and I60–I69 in ICD-10 were defined as death from total stroke, which included death from cerebral infarction (codes 433, 434, 437.7a, 7b in ICD-9 and I63 and I69.3 in ICD-10) and from cerebral hemorrhage (codes 431–432 in ICD-9 and I61 and I69.1 in ICD-10).

Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency of Japan's national government. Approval for this study was obtained from the Institutional Review Board of the Shiga University of Medical Science (No. 12–18, 2000).

Statistical analysis

To illustrate the model for a three-level structure of individuals at level 1 nested within areas at level 2 nested within regions at level 3, we used multilevel regression procedures (Goldstein, 1995). As the response consisted of a binary variable of deaths from total stroke, we used multilevel logistic regression on a logit-link function. Models were fitted using MLwiN software version 2.0 (Rasbash, Steele, Browne, & Prosser, 2004). Parameters were estimated using iterative generalized least squares and marginal quasi-likelihood first-order estimation procedures (Rasbash et al., 2004). The results were expressed as regression coefficients and standard error, and odds ratios and 95% confidence intervals (CIs). Significance of the regression coefficients was tested by Wald statistic. Intraclass correlation coefficient was estimated from the two-level null random intercept model as $r_0^2/(r_0^2+3.29)$, where r_0^2 was unexplained random variance at level 2 (Snijders & Bosker, 1999). The following variables were added successively to the null model (Model 1): age (Model 2), municipality population size (medium and small population sizes compared with large population size) (Model 3), and body mass index, serum total cholesterol, diabetes (serum glucose of 11.1 mmol/l or higher, history of diabetes, or both), hypertension (systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or antihypertensive drug use), current smoking, and daily alcohol consumption (Model 4). All probability values were two tailed with significance level of $p<0.05$.

Results

Table 2 shows the baseline characteristics of the subjects by municipality population size. The subjects in the small population size were significantly older, both for men and women ($p<0.001$). Percentages of hypertension were significantly higher among the subjects in the small population size, both for men ($p = 0.01$) and women ($p<0.001$). On the other hand, serum total cholesterol was significantly higher among the subjects in the large population size, both for men ($p<0.001$) and women ($p = 0.001$). As for obesity, a divergent pattern was observed between men and women, wherein body mass index was significantly higher in men ($p = 0.001$) but significantly lower in women ($p = 0.01$), among the subjects in the large population size. Percentages of current smokers and daily alcohol drinkers were significantly higher among the subjects in the large population size for women ($p<0.001$), whereas current smokers occupied a higher percentage among the subjects in the medium population size and daily alcohol drinkers exhibited no significant difference in percentage by municipality population size in men.

Table 3 shows the numbers of persons, person-years, and numbers of deaths and mortality rate from total stroke as well as the percentages of cerebral infarction and cerebral hemorrhage by municipality population size. Crude mortality rates were higher in municipalities with large population size both in men and women, but this tendency was not observed for age-adjusted mortality rate in men. Age-adjusted mortality rate from total stroke was highest in the large municipalities in men because

Table 2
Baseline characteristics of subjects by municipality population size (Japanese men and women aged 30 years and older in 1980, NIPPON DATA80)

	Municipality population size			
	Large	Medium	Small	p
Men				
Number of subjects	1082	1570	1428	
Age (years)	49.0 (12.6)	49.5 (12.9)	52.1 (13.6)	<0.001
Body mass index (kg/m^2)	22.8 (3.0)	22.5 (2.9)	22.3 (2.7)	0.001
Serum total cholesterol (mmol/l)	5.0 (0.8)	4.8 (0.9)	4.7 (0.8)	<0.001
Diabetes (%)	7.1	6.1	7.7	0.22
Hypertension (%)	47.0	49.2	52.9	0.01
Current smoker (%)	60.4	65.7	62.7	0.02
Daily alcohol drinker (%)	48.0	47.1	49.5	0.41
Women				
Number of subjects	1459	1992	1778	
Age (years)	48.8 (12.8)	50.2 (13.1)	53.0 (13.6)	<0.001
Body mass index (kg/m^2)	22.7 (3.3)	22.8 (3.5)	23.0 (3.3)	0.01
Serum total cholesterol (mmol/l)	5.0 (0.9)	4.9 (0.9)	4.9 (0.9)	0.001
Diabetes (%)	3.8	4.5	4.0	0.52
Hypertension (%)	37.6	40.8	44.7	<0.001
Current smoker (%)	11.7	9.4	5.7	<0.001
Daily alcohol drinker (%)	4.2	2.7	1.9	<0.001

Note. Numbers in parentheses indicate standard deviation. p values were calculated by ANOVA for continuous variables and by chi square test for categorical variables. Municipality population size: Large (⩾300,000); Medium (30,000–<300,000); Small (<30,000). Diabetes was defined as serum glucose of 11.1 mmol/l or higher, history of diabetes, or both. Hypertension was defined as systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or antihypertensive drug use.

Table 3
Numbers of persons and person-years, numbers of deaths and crude and age-adjusted mortality rates from total stroke, and percentages of cerebral infarction and cerebral hemorrhage for total stroke by municipality population size in 19-year follow-up of Japanese men and women aged 30 years and older in 1980 (NIPPON DATA80)

Municipality population size	No. of persons	No. of person-years	No. of deaths from total stroke	Mortality rate from total stroke (per 1000)		Stroke type (%)		
				Crude	Age-adjusted	Total stroke	Cerebral infarction	Cerebral hemorrhage
Men								
Large	1082	18,719	30	1.6	2.4	100	70	13
Medium	1570	26,869	59	2.2	1.4	100	58	24
Small	1428	23,502	73	3.1	1.7	100	60	27
Women								
Large	1459	26,086	25	1.0	0.9	100	44	24
Medium	1992	35,196	52	1.5	1.1	100	58	19
Small	1778	30,464	73	2.4	1.3	100	53	16

Note. Municipality population size: Large (⩾300,000); Medium (30,000–<300,000); Small (<30,000). Age-adjusted mortality rate was standardized in accordance with the world population.

the age-specific mortality rate in the oldest age group comprised of those 85 years and older contributed to a marked rise in the overall age-adjusted mortality rate (only one person belonged to the oldest age group, and he died of a stroke after a relatively short time). Among deaths from total stroke, the percentage of deaths from cerebral infarction was consistently higher than deaths from cerebral hemorrhage by municipality population size, both in men and women.

In the three-level model where six regions of Japan were entered at level 3, no variance was observed at level 3, and the parameters at level 2 (areas) and level 1 (individuals) differed only slightly from the two-level model (individuals at level 1 nested within areas at level 2). The results of the two-level multilevel analyses are therefore shown in Table 4. In Model 1 (null model), statistically significant variance between areas was not observed in men ($p = 0.12$) but was in women ($p = 0.04$). Intraclass correlation coefficients were 7.3% for men and 10.6% for women. In Model 2, age had statistically significant effects ($p<0.001$), and variance between areas was no longer statistically significant. In the age-adjusted model (Model 3) and the multivariate-adjusted model (Model 4), women had higher regression coefficients for municipality population sizes. Odds ratios and 95% CIs were calculated in Models 3 and 4, and significantly elevated odds ratio for the small population size compared with the large population size was observed for women in Model 4. In multivariate analyses, we used a dichotomous variable for hypertension. We then analyzed the data using instead a continuous variable for systolic and diastolic blood pressure, but similar results were obtained.

The results of two-level multilevel analyses for cerebral infarction, which was a dominant stroke type in our cohort as indicated in Table 3, are shown in Table 5. In Model 1 (null model), statistically significant variance between areas was not observed in men ($p = 0.41$) but was in women ($p = 0.04$). Intraclass correlation coefficients were 5.6% for men and 18.6% for women. In Model 2, age had statistically significant effects ($p<0.001$), and variance between areas was no longer statistically significant. In the age-adjusted model (Model 3) and the multivariate-adjusted model (Model 4), odds ratios and 95% CIs were calculated. Significantly elevated odds ratios for the small population size compared with the large population size were not observed for men or women, but odds ratios were higher for women than for men both in Models 3 and 4. In multivariate analyses, we used a dichotomous variable for hypertension. We then analyzed the data using instead a continuous variable for systolic and diastolic blood pressure, but similar results were obtained.

Discussion

In our study, we discovered a tendency for stroke mortality to be higher in rural areas than in urban areas, especially in women, using municipality population size as an indicator of urban and rural.

Table 4
Regression coefficients and odds ratios of deaths from total stroke for municipality population size by two-level multilevel logistic regression analysis in 19-year follow-up of Japanese men and women aged 30 years and older in 1980 (NIPPON DATA80)

	Regression coefficients (SE)				Odds ratios (95%CI)	
	Model 1	Model 2	Model 3	Model 4	Model 3	Model 4
Men						
Fixed parameters						
Constant	−3.21 (0.09)	−9.16 (0.48)	−9.35 (0.51)	−9.81 (1.10)		
Individual level						
Age		0.10 (0.01)	0.10 (0.01)	0.10 (0.01)	1.11 (1.09–1.12)	1.11 (1.09–1.12)
Area level						
Municipality population size						
Medium			0.27 (0.25)	0.26 (0.25)	1.31 (0.81–2.13)	1.29 (0.80–2.10)
Small			0.33 (0.24)	0.30 (0.24)	1.40 (0.87–2.24)	1.36 (0.84–2.18)
Random parameters						
Between areas	0.26 (0.17)	0.16 (0.15)	0.15 (0.15)	0.12 (0.15)		
Women						
Fixed parameters						
Constant	−3.55 (0.09)	−10.05 (0.52)	−10.25 (0.54)	−11.28 (0.95)		
Individual level						
Age		0.11 (0.01)	0.11 (0.01)	0.10 (0.01)	1.11 (1.10–1.13)	1.11 (1.09–1.12)
Area level						
Municipality population size						
Medium			0.28 (0.26)	0.29 (0.26)	1.32 (0.79–2.20)	1.34 (0.80–2.23)
Small			0.48 (0.25)	0.52 (0.25)	1.62 (0.99–2.65)	1.68 (1.02–2.77)
Random parameters						
Between areas	0.39 (0.19)	0.12 (0.15)	0.09 (0.15)	0.10 (0.15)		

Note. Model 1, null model; Model 2, age-adjusted; Model 3, adjusted for age and municipality population size; Model 4, adjusted for age, municipality population size, body mass index, serum total cholesterol, diabetes, hypertension, current smoking, and daily alcohol drinking. Municipality population size: Large (⩾300,000); Medium (30,000–<300,000); Small (<30,000).

As our study areas were randomly selected from throughout Japan, the results are considered to reflect a general urban–rural difference in stroke mortality in Japan. As no variance was found between regions (level 3) in the three-level model, the geographical variation in stroke mortality reported a few decades ago in several ecological studies (Takahashi et al., 1957; Tamashiro et al., 1981; Ueshima et al., 1986) might have been partly a reflection of unbalanced distribution of urban and rural areas by region. This is a plausible explanation because distributions of municipalities by population size were significantly different (Table 1), and the northeastern part of Japan in particular was characterized as the region with a higher proportion of municipalities with small population size, that is, rural areas.

The urban–rural difference was more pronounced in women than in men for total stroke. To examine these results in further detail, we also showed the results for cerebral infarction, which is a dominant stroke type in our cohort. Although statistically significant variance in the two-level null model was observed only for women, the odds ratios of deaths from cerebral infarction for the medium and small municipality population sizes compared with the large population size were higher than unity only for women. This contrast between men and women in urban–rural difference of cerebral infarction deaths seems to have contributed to the gender difference in urban–rural gradient.

Gender difference was also observed in the change of odds ratios from age-adjusted model to multivariate-adjusted model for total stroke. Multivariate analyses revealed that the urban–rural difference in stroke mortality remained after adjustment for such risk factors as hypertension and cigarette smoking. However, the odds ratios of the multivariate-adjusted model by municipality population size were slightly lower in men and slightly higher in women. This result may have been because the baseline characteristics were differently associated with municipality population size between men and women. In the multivariate-adjusted

Table 5
Regression coefficients and odds ratios of deaths from cerebral infarction for municipality population size by two-level multilevel logistic regression analysis in 19-year follow-up of Japanese men and women aged 30 years and older in 1980 (NIPPON DATA80)

	Regression coefficients (SE)				Odds ratios (95%CI)	
	Model 1	Model 2	Model 3	Model 4	Model 3	Model 4
Men						
Fixed parameters						
Constant	−3.71 (0.11)	−10.56 (0.66)	−10.59 (0.68)	−10.93 (1.43)		
Individual level						
Age		0.12 (0.01)	0.11 (0.01)	0.12 (0.01)	1.12 (1.10–1.14)	1.12 (1.10–1.15)
Area level						
Municipality population size						
Medium			0.05 (0.30)	0.03 (0.30)	1.05 (0.58–1.89)	1.03 (0.57–1.86)
Small			0.10 (0.29)	0.07 (0.29)	1.10 (0.62–1.96)	1.07 (0.60–1.91)
Random parameters						
Between areas	0.20 (0.24)	0.18 (0.23)	0.18 (0.23)	0.13 (0.22)		
Women						
Fixed parameters						
Constant	−4.19 (0.13)	−12.22 (0.80)	−12.54 (0.83)	−13.96 (1.37)		
Individual level						
Age		0.13 (0.01)	0.13 (0.01)	0.13 (0.01)	1.14 (1.11–1.16)	1.13 (1.11–1.16)
Area level						
Municipality population size						
Medium			0.52 (0.37)	0.54 (0.37)	1.68 (0.81–3.47)	1.71 (0.83–3.53)
Small			0.56 (0.36)	0.56 (0.36)	1.75 (0.86–3.57)	1.76 (0.86–3.58)
Random parameters						
Between areas	0.75 (0.36)	0.23 (0.27)	0.18 (0.26)	0.10 (0.25)		

Note. Model 1, null model; Model 2, age-adjusted; Model 3, adjusted for age and municipality population size; Model 4, adjusted for age, municipality population size, body mass index, serum total cholesterol, diabetes, hypertension, current smoking, and daily alcohol drinking. Municipality population size: Large (⩾300,000); Medium (30,000–<300,000); Small (<30,000).

model, statistically significant risk factors other than age were hypertension and current smoking for men and hypertension for women. For hypertension, the larger the municipality population size was, the lower the percentage of hypertension both in men and women. On the other hand, for current smoking in women, though it was not significant in the multivariate-adjusted model, the larger the municipality population size was, the higher the percentage of current smokers in women. For current smoking in men, no consistent trend with municipality population size was found.

We used population size of a municipality to define whether a given area was urban or rural. The questionnaire of the 1980 survey asked subjects whether the type of location of their residence was "urban" or "rural," with the latter defined as farming and fishing villages. According to this survey, percentages of subjects indicating that the location of their residence was rural were 79%, 29%, and 14% for municipalities with small, medium, and large population sizes, respectively. This is further evidence that municipality population size is a valid indicator of the definition.

The reasons for the geographical variation of stroke mortality investigated in several ecological studies (Takahashi et al., 1957; Tamashiro et al., 1981; Ueshima et al., 1986) could be associated with urban–rural difference by area. These research groups observed that excess intake of sodium and insufficient intake of animal protein were related to high stroke mortality. Ueshima et al. (1986) examined the relationship between alcohol consumption and stroke mortality in an ecological study with prefectures as units of analysis, and found that stroke mortality was higher in the areas with high alcohol consumption. Our analyses have included several risk factors, such as hypertension and daily consumption of alcohol in multivariate models, but there remained an urban–rural gradient even after adjustment for these factors. Therefore, the gradient we observed could be related to dietary factors, such as animal protein intake. This possibility is partly explained in a pooled data analysis by

Okayama et al. (1995), which revealed that changes in serum cholesterol levels among middle-aged Japanese were consistent with the increase in meat consumption per day per capita from 23.9 to 66.2 g in rural populations and from 51.2 to 77.6 g in urban populations, based on Japan's National Nutrition Surveys conducted in 1966 and 1990.

Differences in medical resources might also have affected the urban–rural difference in stroke mortality in the study. For many years rural areas faced a lack of medical resources, and to remedy this shortage, many medical schools were founded throughout Japan in the 1980s. However, Kobayashi and Takaki (1992) revealed that a doubling of the number of physicians due to the increased number of medical schools failed to improve the disproportionate urban–rural distribution of physicians. It is no wonder that areas with fewer medical resources are disadvantaged with respect to the early detection and treatment of stroke.

Stroke incidence and mortality have been compared between urban and rural areas in several countries (Correia et al., 2004; Hong et al., 1994; Powles, Kirov, Feschieva, Stanoev, & Atanasova, 2002; Walker et al., 2000; Yiannakoulias et al., 2004). Some studies have reported higher rates in rural areas (Correia et al., 2004; Hong et al., 1994; Powles et al., 2002). Others have reported similar rates in the two areas (Yiannakoulias et al., 2004), or even lower rates in rural areas (Walker et al., 2000). Correia et al. (2004) reported higher stroke incidence among a rural population compared with an urban population in northern Portugal. In China, incidence among rural men and mortality rate among rural men and women aged 65–74 years were higher than those of their urban counterparts from 1984 to 1991 in Shanghai (Hong et al., 1994). As our data only involved stroke mortality, it is necessary to further investigate difference in stroke incidence and case fatality between urban and rural areas.

There were some limitations in our study. First, individual socioeconomic factors were not taken into account because data for income and level of education were not available and data for occupation were limited to working subjects. Second, use of Japan's National Vital Statistics for stroke deaths where stroke subtypes may generally be misclassified on death certificates is considered to be one possible shortcoming. However, most stroke cases in Japan are referred to hospitals. Moreover, computerized tomography scanning was performed in over 85% of stroke patients in the 1980s, even in rural areas throughout Japan (Kita et al., 1999). Finally, we used a multilevel logistic regression model that did not take observation period into consideration. When we applied a frailty model of Cox regression (Therneau & Grambsch, 2000), hazard ratios for the medium and small population sizes compared with the large population size were slightly higher than the respective odds ratios from the present study, but the results did not change materially.

In conclusion, in a cohort established in 1980 and followed-up until 1999, mortality from stroke was higher in rural areas than in urban areas, especially in women. This gradient remained even after adjustment for traditional risk factors. Therefore, we next need to investigate difference in stroke incidence and case fatality between urban and rural areas.

Acknowledgements

This study was supported by the grant-in-aid of the Ministry of Health and Welfare under the auspices of Japanese Association for Cerebro-cardiovascular Disease Control, the Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, 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). The NIPPON DATA80 research group is listed as Appendix A.

Appendix A

The NIPPON DATA80 Research group NIPPON DATA80: "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) Research Member: Akira Okayama (Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka), Kazunori

Kodama, Fumiyoshi Kasagi (Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga), Takehito Hayakawa, Shinichi Tanihara (Department of Public Health, School of Medicine, Shimane University, Izumo, Shimane), Shigeyuki Saitoh (Second Department of Internal Medicine School of Medicine,Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate), Yosikazu Nakamura (Department of Health Science Division of Epidemiology and Community Health, Jichi Medical School, Minami Kawachi, Tochigi), Fumihiko Kakuno (Hikone Public Health Center, Hikone, Shiga) Research Associate Member: Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano, Takahisa Kawamoto and members of 300 Public Health Centers in Japan, Masumi Minowa (Faculty of Humanities, Seitoku University, Matsudo, Chiba), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako, Saitama), Sohel R. Choudhury, (National Heart Foundation Hospital & Research Institute, Dhaka, Bangladesh), Yutaka Kiyohara (Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Fukuoka), Minoru Iida (Kansai University of Welfare Sciences, Kashihara, Kashiwara Osaka), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama).

References

Bittner, D. L., & McCleary, M. L. (1963). The cupric-phenanthroline chelate in the determination of monosaccharides in whole blood. *American Journal of Clinical Pathology*, *40*, 423.

Correia, M., Silva, M. R., Matos, I., Magalhaes, R., Lopes, J. C., Ferro, J. M., et al. (2004). Prospective community-based study of stroke in Northern Portugal: Incidence and case fatality in rural and urban populations. *Stroke*, *35*, 2048–2053.

Dahl, L. K. (1960). Possible role of salt intake in the development of essential hypertension. In P. Cottier, & K. D. Bock (Eds.), *Essential hypertension—An International Symposium* (pp. 53–65). Berlin: Springer.

Fukuda, Y., Nakamura, K., & Takano, T. (2005). Cause-specific mortality differences across socioeconomic position of municipalities in Japan, 1973–1977 and 1993–1998: Increased importance of injury and suicide in inequality for ages under 75. *International Journal of Epideiology*, *34*, 100–109.

Goldstein, H. (1995). *Multilevel statistical models*. London, United Kingdom: Edward Arnold.

Hayakawa, T., Okayama, A., Ueshima, H., Kita, Y., Choudhury, S. R., & Tamaki, J. (2000). Prevalence of impaired activities of daily living and the impact of stroke and lower limb fracture in elderly persons in Japan. *CVD Prevention*, *3*, 187–194.

Health and Welfare Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour, and Welfare (2005). Health and Welfare Statistics Association (in Japanese).

Hong, Y., Bots, M. L., Pan, X., Hofman, A., Grobbee, D. E., & Chen, H. (1994). Stroke incidence and mortality in rural and urban Shanghai from 1984 through 1991: Findings from a community-based registry. *Stroke*, *25*, 1165–1169.

Kaplan, G. A., & Keil, J. E. (1993). Socioeconomic factors and cardiovascular disease: A review of the literature. *Circulation*, *88*, 1973–1998.

Kita, Y., Okayama, A., Ueshima, H., Wada, M., Nozaki, A., Choudhury, S. R., et al. (1999). Stroke incidence and case fatality in Shiga, Japan 1989–1993. *International Journal of Epidemiology*, *28*, 1059–1065.

Kitamura, A., Sato, S., Naito, Y., Nakagawa, Y., Imano, H., Ohira, T., et al. (2001). Trends in the incidence of cardiovascular diseases and risk factors among urban and rural Japanese males. *Japanese Journal of Public Health*, *48*, 378–394.

Kobayashi, Y., & Takaki, H. (1992). Geographic distribution of physicians in Japan. *Lancet*, *340*, 1391–1393.

Kodama, K. (1993). Stroke trends in Japan. *Annals of Epidemiology*, *3*, 524–528.

Kubo, M., Kiyohara, Y., Kato, I., Tanizaki, Y., Arima, H., Tanaka, K., et al. (2003). Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: The Hisayama Study. *Stroke*, *34*, 2349–2354.

Mackenbach, J. P., Cavelaars, A. E. J. M., Kunst, A. E., Groenhof, F. & the EU Working Group on Socioeconomic Inequalities in Health. (2000). Socioeconomic inequalities in cardiovascular disease mortality: An international study. *European Heart Journal*, *21*, 1141–1151.

Morikawa, Y., Nakagawa, H., Naruse, Y., Nishijo, M., Miura, K., Tabata, M., et al. (2000). Trends in stroke incidence and acute case fatality in a Japanese rural area: The Oyabe Study. *Stroke*, *31*, 1583–1587.

Nakamura, M., Sato, S., & Shimamoto, T. (2003). Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US cholesterol reference method laboratory network. *Journal of Atherosclerosis Thrombosis*, *10*, 145–153.

Nippon Data 80 Research Group. (2003). 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. *Journal of Human Hypertension*, *17*, 851–857.

Okamura, T., Hayakawa, T., Kadowaki, T., Kita, Y., Okayama, A., Elliott, P., et al. (2004). Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. *American Heart Journal, 147*, 1024–1032.

Okamura, T., Kadowaki, T., Hayakawa, T., Kita, Y., Okayama, A., & Ueshima, H. (2003). What cause of mortality can we predict by cholesterol screening in the Japanese general population? *Journal of Internal Medicine, 253*, 169–180.

Okayama, A., Ueshima, H., Marmot, M. G., Elliott, P., Yamakawa, M., & Kita, Y. (1995). Different trends in serum cholesterol levels among rural and urban populations aged 40–59 in Japan from 1960 to 1990. *Journal of Clinical Epidemiology, 48*, 329–337.

Powles, J., Kirov, P., Feschieva, N., Stanoev, M., & Atanasova, V. (2002). Stroke in urban and rural populations in north-east Bulgaria: Incidence and case fatality findings from a 'hot pursuit' study. *BMC Public Health, 2*, 24–32.

Rasbash, J., Steele, F., Browne, W., & Prosser, B. (2004). *A user's guide to MlwiN*, version 2.0. London, United Kingdom: Institute of Education, University of London.

Shimamoto, T., Komachi, Y., Inada, H., Doi, M., Iso, H., Sato, S., et al. (1989). Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation, 79*, 503–515.

Snijders, T. A. B., & Bosker, R. J. (1999). *Multilevel analysis: An introduction to basic and advanced multilevel modelling.* London, United Kingdom: Sage.

Statistics and Information Department, Minister's Secretariat (1995 and 2000). Special Report of Vital Statistics in FY 2000: Occupational and Industrial Aspects: Ministry of Health, Labour, and Welfare (in Japanese).

Takahashi, E., Sasaki, N., Takeda, J., & Ito, H. (1957). The geographic distribution of cerebral hemorrhage and hypertension in Japan. *Human Biology, 29*, 139–166.

Tamashiro, H., Enomoto, N., Minowa, M., Shibata, S., Ashizawa, M., Shigematsu, I., et al. (1981). Geographical distributions of cerebrocardiovascular diseases in Japan: 1969–1974. *Social Science and Medicine, 15D*, 173–186.

Therneau, T. M., & Grambsch, P. M. (2000). Frailty models. In T. M. Therneau, & P. M. Grambsch (Eds.), *Modeling survival data: Extending the Cox model* (pp. 231–260). New York: Springer.

Ueshima, H., Choudhury, S. R., Okayama, A., Hayakawa, T., Kita, Y., Kadowaki, T., et al. (2004). Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke, 35*, 1836–1841.

Ueshima, H., Ohsaka, T., & Asakura, S. (1986). Regional differences in stroke mortality and alcohol consumption in Japan. *Stroke, 17*, 19–24.

Walker, R. W., McLarty, D. G., Kitange, H. M., Whiting, D., Masuki, G., Mtasiwa, D. M., et al. (2000). Stroke mortality in urban and rural Tanzania. *Lancet, 355*, 1684–1687.

World Health Organization (2002). WHO Statistical Information System Mortality Database.

Yiannakoulias, N., Svenson, L. W., Hill, M. D., Schopflocher, D. P., Rowe, B. H., James, R. C., et al. (2004). Incident cerebrovascular disease in rural and urban Alberta. *Cerebrovascular Diseases, 17*, 72–78.

Original Article

The Proportion of Individuals with Alcohol-Induced Hypertension among Total Hypertensives in a General Japanese Population: NIPPON DATA90

Koshi NAKAMURA[1)], Tomonori OKAMURA[1)], Takehito HAYAKAWA[2)], Atsushi HOZAWA[1)], Takashi KADOWAKI[1)], Yoshitaka MURAKAMI[1)], Yoshikuni KITA[1)], Akira OKAYAMA[3)], and Hirotsugu UESHIMA[1)], for the NIPPON DATA90 Research Group*

Japanese men consume more alcoholic beverages than men in many other developed countries. The high consumption rate of alcoholic beverages among Japanese men may contribute to the high prevalence of hypertension in Japan. In the present study, we calculated the odds ratio for hypertension in alcohol drinkers based on recent criteria using data from a nationwide survey conducted in Japan in 1990, and estimated, among total hypertensives in a general Japanese population, the percentage of hypertensives whose condition was due to alcohol consumption. Of 3,454 male participants, 64.8% were drinkers (1 *gou*/day, 28.9%; 2 *gou*/day, 20.1%; 3 *gou*/day or more, 8.7%; ex-drinkers, 7.0%) and 49.8% were hypertensive, whereas 7.6% of 4,808 female participants were drinkers (1 *gou*/day, 5.2%; 2 *gou*/day or more, 1.3%; ex-drinkers, 1.1%) and 43.1% were hypertensive (1 *gou*=23.0 g of alcohol). In both sexes, drinkers had a higher odds ratio for hypertension than never drinkers, and there was a significant dose-response relationship between the amount of alcohol consumed and the odds ratio for hypertension. Among all hypertensives, the percentage whose hypertension was due to alcohol consumption was 34.5% (95% confidence interval, 10.9%–51.9%) for men and 2.6% (0.8%–5.8%) for women. The corresponding proportion based on daily alcohol intake was 12.7% for 1 *gou*/day, 11.1% for 2 *gou*/day, 5.8% for 3 *gou*/day or more, and 4.8% for ex-drinkers in men, and 1.8% for 1 *gou*/day, 0.7% for 2 *gou*/day or more, and −0.1% for ex-drinkers in women. In conclusion, we found that a large percentage of the hypertensives in a general Japanese male population had alcohol-induced hypertension. (*Hypertens Res* 2007; 30: 663–668)

Key Words: alcohol drinking, hypertension, Japan

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; and [3)]The First Institute of Health Service, Japan Anti-Tuberculosis Association, Tokyo, Japan.
*Members of the Research Group are listed in the Appendix.
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).
Address for Reprints: Koshi Nakamura, M.D., Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu 520–2192, Japan. E-mail: ksnkmr@belle.shiga-med.ac.jp
Received September 14, 2006; Accepted in revised form March 15, 2007.

Introduction

Alcohol consumption has been associated with the development of hypertension (*1–10*), and Japanese men consume more alcoholic beverages than men in many other developed countries, including the United States and the United Kingdom (*11–15*). These facts suggest that the high consumption of alcoholic beverages among Japanese men may contribute to the high prevalence of hypertension in Japan (*12, 16*). Thus, it is important to clarify the proportion of hypertensives in the general Japanese population whose hypertension was induced by alcohol. Although this percentage has been determined in previous studies (*17*), it has not been estimated since the recent establishment of new criteria for hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg).

In the present study, we attempted to estimate the proportion of individuals with alcohol-induced hypertension among total hypertensives in a randomly selected Japanese population using the recently established criteria for hypertension.

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. In the present study, we analyzed baseline data from NIPPON DATA90 (data from the Fourth National Survey on Circulatory Disorders, Japan in 1990); the details of this cohort study have been reported previously (*18–21*).

A total of 8,384 community residents (3,504 men and 4,880 women; ≥30 years old) from 300 randomly selected districts participated. The overall population aged 30 and over in all districts was 10,956 and the participation rate in this survey was 76.5%. Of the 8,384 participants, 122 were excluded because of 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 the present study 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

Public health nurses asked the participants about their alcohol consumption habits and classified them into the following five groups: never drinker, current daily drinker of 1 *gou*/day, 2 *gou*/day, or 3 *gou*/day or more, or ex-drinker. The *gou* is a traditional Japanese alcohol drinking unit, and 1 *gou* is equivalent to 180 mL of sake (Japanese rice wine), which contains 23.0 g of alcohol. Its alcohol content is roughly equivalent to 663 mL (1 bottle) of beer, 70 mL (two single shots) of whisky, or 110 mL (a half glass) of "shochu" (spirits made from barley, sweet potato, rice or any combination of these). In order to estimate the proportion of individuals with alcohol-induced hypertension among total hypertensives in the study population, male and female participants were classified into two categories, never drinkers and drinkers, with the latter category consisting of current drinkers and ex-drinkers. We included ex-drinkers in the drinker category because drinkers diagnosed with hypertension might have been advised to quit drinking alcohol. In addition to the above analysis, we estimated the proportion of individuals with alcohol-induced hypertension among total hypertensives by taking the quantity of alcohol consumed into consideration. In this analysis, male participants were classified into the following five categories: never drinker, 1 *gou*/day, 2 *gou*/day, 3 *gou*/day or more, and ex-drinker. Furthermore, female participants were classified into the following four categories: never drinker, 1 *gou*/day, 2 *gou*/day or more, and ex-drinker. A category of 3 *gou*/day or more was not used in women, because only 1.3% of the female participants were heavy drinkers (2 *gou*/day, $n=36$; 3 *gou*/day or more, $n=27$).

Baseline blood pressures were measured once by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a sufficient period of rest. Information on the use of antihypertensive agents was also obtained by public health nurses. Referring to the Seventh Report of the Joint National Committee (*17*), 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. Body mass index was calculated as weight (kg) divided by the square of height (m).

Statistical Analysis

The data were analyzed separately for men and women, because alcohol consumption habits are quite different between the sexes in Japan (*7, 11, 16, 22*). Initially, one way analysis of variance or a χ^2 test was used to compare risk characteristics at baseline among the different alcohol-intake categories. Next, we calculated the prevalence of hypertension in each of two alcohol drinking habit categories (never drinkers and drinkers [including ex-drinkers]). A logistic regression model was used to calculate the odds ratio for hypertension in drinkers with never drinkers serving as a reference. Age and body mass index were included in the regression models as potential confounding variables. We estimated the percentage of individuals having alcohol-induced hypertension among total hypertensives—*i.e.*, the population attributable fraction—using the following equation: [prevalence of drinkers among hypertensives × (odds ratio − 1)]/odds ratio (*23*). The 95% confidence interval for the corresponding proportion was calculated using the formula pro-

Table 1. Baseline Risk Characteristics in 1990 of 8,262 Japanese Participants Based on Sex and Alcohol Drinking Habit: NIPPON DATA90

	Alcohol drinking habit				
	Never drinker	1 *gou*/day	2 *gou*/day (or more for women)	3 *gou*/day or more	Ex-drinker
Men					
Number of participants (n (%))	1,217 (35.2)	998 (28.9)	694 (20.1)	302 (8.7)	243 (7.0)
Age (years)*,‡	54.3±14.7	52.9±13.5	51.1±11.8	49.4±10.9	61.3±14.1
Body mass index (kg/m²)*,‡	22.8±3.1	22.9±2.9	23.2±2.9	23.5±3.1	22.7±3.3
Systolic blood pressure (mmHg)*,‡	134.8±20.0	138.4±19.9	139.0±19.0	141.0±20.1	141.8±21.1
Diastolic blood pressure (mmHg)*,‡	81.2±10.9	84.0±11.2	85.6±11.9	86.3±12.1	84.0±12.8
Use of antihypertensive agents (%)†,‡	9.9	14.1	13.5	9.6	24.3
Women					
Number of participants (n (%))	4,442 (92.4)	251 (5.2)	63 (1.3)		52 (1.1)
Age (years)*,‡	53.1±14.2	47.1±11.4	47.7±10.5		51.5±13.7
Body mass index (kg/m²)*	22.9±3.3	22.5±3.1	22.8±3.5		22.5±3.4
Systolic blood pressure (mmHg)*,‡	133.9±20.8	131.1±20.8	132.7±19.3		128.2±22.2
Diastolic blood pressure (mmHg)*	79.4±11.7	81.0±13.0	81.6±10.4		77.7±13.2
Use of antihypertensive agents (%)†	15.9	10.8	20.6		19.2

Values indicate the mean±SD or the % of participants in that category. One *gou* contains 23.0 g of alcohol. *Mean values were compared among the categories by one way analysis of variance. †Proportions were compared among the categories by a χ^2 test. ‡The difference among the alcohol drinking habit categories was statistically significant ($p<0.05$).

posed by Greenland (*24*). Finally, in order to investigate the corresponding proportion of individuals with alcohol-induced hypertension by daily intake of alcohol, we analyzed the data using the above equation after classifying the male and female participants into five and four categories, respectively, based on their habits of alcohol consumption.

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

The mean values or proportions of risk characteristics for male and female participants grouped according to their alcohol consumption habits are summarized in Table 1. Of the 3,454 male participants (mean age, 53.3 years old), 64.8% had a current or past alcohol consumption habit and 49.8% were hypertensive, whereas only 7.6% of the 4,808 female participants (mean age, 52.7 years old) had a drinking habit and 43.1% were hypertensive. For both sexes, the mean age was higher in never drinkers and ex-drinkers than in daily drinkers. For men, the mean body mass index was lower in never drinkers and ex-drinkers than in daily drinkers of 2 *gou*/day or more.

Male drinkers had a higher prevalence of hypertension compared to never drinkers (54.2% for drinkers *vs.* 41.7% for never drinkers), and we confirmed a significantly higher odds ratio for hypertension in drinkers after adjustment for age and body mass index (1.96; 95% confidence interval, 1.67–2.29). Although female drinkers had a somewhat lower prevalence of hypertension (41.3% for drinkers *vs.* 43.3% for never drinkers), we confirmed a significantly higher odds ratio for hypertension in drinkers after adjustment for the same confounding factors (1.54; 95% confidence interval, 1.20–1.98). The proportion of individuals with alcohol-induced hypertension among total hypertensives was estimated to be 34.5% (95% confidence interval, 10.9%–51.9%) in men and 2.6% (95% confidence interval, 0.8%–5.8%) in women (the results described above are not shown in Table 1).

There was a dose-response relationship between daily alcohol intake and the odds ratio for hypertension in both sexes (Table 2). Even the odds ratio for hypertension in daily drinkers who consumed 1 *gou*/day was significantly higher in both sexes. Table 2 shows the percentage of individuals with alcohol-induced hypertension among total hypertensives in each daily-intake category. The proportion of individuals with alcohol-induced hypertension was highest in daily drinkers of 1 *gou*/day in both sexes.

Discussion

In the present study, we found a large proportion of individuals with alcohol-induced hypertension among all hypertensive participants in a representative Japanese male population. Approximately one-third of male hypertensives—but only a few percent of female hypertensives—had hypertension due to alcohol consumption. There are prominent regional differences in alcohol consumption in Japan (*11*, *22*, *25*), which may affect the proportion of individuals with alcohol-induced

Table 2. Prevalence of Hypertension, Odds Ratio for Hypertension in Alcohol Drinkers, and Proportion of Individuals with Alcohol-Induced Hypertension among Total Hypertensives in 1990 Grouped by Sex and Alcohol Drinking Habit among 8,262 Participants: NIPPON DATA90

Alcohol drinking habit	Number of participants (*n* (%))	Hypertension			Alcohol-induced hypertension among total hypertensives (%)
		Cases	Prevalence (%)	Adjusted odds ratio* (95% confidence interval)	
Men					
Never drinkers	1,217 (35.2)	508	41.7	1.00	
1 *gou*/day	998 (28.9)	514	51.5	1.74 (1.45–2.10)	12.7
2 *gou*/day	694 (20.1)	371	53.5	2.06 (1.67–2.53)	11.1
3 *gou*/day or more	302 (8.7)	168	55.6	2.46 (1.86–3.25)	5.8
Ex-drinkers	243 (7.0)	160	65.8	2.05 (1.49–2.81)	4.8
Women					
Never drinkers	4,442 (92.4)	1,923	43.3	1.00	
1 *gou*/day	251 (5.2)	101	40.2	1.58 (1.17–2.14)	1.8
2 *gou*/day or more	63 (1.3)	30	47.6	2.09 (1.17–3.72)	0.7
Ex-drinkers	52 (1.1)	20	38.5	0.94 (0.49–1.79)	−0.1

One *gou* contains 23.0 g of alcohol. 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 and body mass index.

hypertension among all hypertensives (*22*). Therefore, only data from a nationwide random sampling survey such as ours will generate a reliable estimate of the proportion of individuals with alcohol-induced hypertension among all hypertensives in the general Japanese population.

Previously, Ueshima *et al.* (*16*) reported that hypertension in 32% of Japanese hypertensive men (based on previous criteria of systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥95 mmHg, the use of antihypertensive agents, or any combination of these) aged 30–69 could be attributed to alcohol drinking using data from the nationwide survey in 1980. In 1990, using more recent criteria for hypertension (*17*) (*i.e.*, different from the above criteria), we calculated the odds ratio for the prevalence of hypertension in drinkers, and estimated the percentage of Japanese hypertensives whose condition could be attributed to alcohol. It is difficult to compare our results directly with the corresponding proportion in other countries due to the lack of available data. However, Japanese men consume more alcoholic beverages than men in many other developed countries (*11–15*). Klag *et al.* (*12*) previously reported that, in the 1970s, the prevalences of daily drinkers in a male population aged 35–59 working for an office in Japan or the United States were 48% (heavy drinkers, 6%) and 40% (heavy drinkers, 0%), respectively, and then estimated that hypertension in 29% of Japanese and 21% of American hypertensives (based on the same previous criteria) could be attributed to daily alcohol consumption (*12*). The prevalence of daily drinkers in Japanese male office workers is almost the same as the results from the nationwide survey in 1980 (*16*), although we do not have any information on the prevalence of daily drinkers in the whole male population in the United States at that time. In addition, Zhou *et al.* (*13*) recently reported that in the 1990s, the mean alcohol intake per day in a male population aged 40–59 was 186.8 kcal for Japan, 70.4 kcal for the United States and 116.1 kcal for the United Kingdom (7 kcal = 1.0 g of alcohol). Judging from these observations, the proportion of individuals with alcohol-induced hypertension among all hypertensives might be much higher in the Japanese male population than in the male population in other developed countries such as the United States and the United Kingdom.

We demonstrated that even a low-to-moderate alcohol intake of 1 *gou*/day contributes to the high prevalence of hypertension in Japan. Approximately 37% of all men and 75% of all women with alcohol-induced hypertension had a low-to-moderate alcohol intake. This is because the number of low-to-moderate drinkers was much greater than the number of heavy drinkers of 2 *gou*/day or more; approximately 50% of male current drinkers and 80% of female current drinkers were in the category of low-to-moderate alcohol intake. These results suggest that moderation of alcohol intake is not enough to reduce the prevalence of hypertension in the Japanese population. From the viewpoint of preventing hypertension, quitting habitual alcohol intake or never drinking in the first place may be required rather than reducing alcohol intake. However, a J-shaped association between alcohol intake and arterial stiffness quantified by pulse wave velocity has been suggested (*26*), even among normotensive individuals (*27*). A J-shaped association between alcohol intake and coronary heart disease (*28, 29*) or ischemic stroke (*30*) has also been suggested. Therefore, the protective effect of light-to-moderate alcohol intake on atherosclerotic cardiovascular risk should also be included in the overall consideration of the influence of alcohol drinking on human health.

The present study has several limitations. First, in the interview used to assess alcohol intake habits, each participant chose the category most applicable to his or her habit among the five categories on the basis of his or her own judgement. It is possible that some participants who occasionally consume alcoholic beverages choose "never drinker," and this might have underestimated the true proportion of individuals with alcohol-induced hypertension among total hypertensives, because even such drinkers are likely to be at risk for hypertension (*10*). Second, we did not take the type of alcoholic beverages consumed into consideration in our analysis, because this information was not available. However, Okamura *et al.* (*31*) reported that the effect of alcohol consumption on blood pressure does not depend on the type of alcoholic beverages consumed. Thus, information on the type of alcoholic beverages consumed may have little effect on the results of the present study. Third, blood pressure–related social factors (*e.g.*, stress, irregular lifestyle) and dietary factors (*e.g.*, sodium intake, potassium intake) were not adjusted in the analysis, because these data were also not available. However, Choudhury *et al.* (*32*) reported that there was little difference in sodium and potassium intake between Japanese male drinkers and never drinkers. Finally, our results are based on data from the survey conducted in 1990. The latest nationwide survey (the Fifth National Survey on Circulatory Disorders, Japan in 2000) (*33*) shows that the prevalences of alcohol drinkers (including ex-drinkers) and hypertensives are 62.4% (daily drinkers, 53.6%; ex-drinkers, 8.8%) and 57.1% for men, and 10.7% (daily drinkers, 9.3%; ex-drinkers, 1.5%) and 45.3% for women, respectively. We still observed a high prevalence of alcohol drinkers and hypertensives in men in 2000. Therefore, we believe that the proportion of individuals with alcohol-induced hypertension among total hypertensives remains quite high in the general Japanese male population.

In conclusion, alcohol consumption plays an important role in the high prevalence of hypertension in the Japanese male population. Thus, in any public health approach to combating hypertension, attention should be paid to alcohol consumption. This is also applicable to other countries where the prevalence of alcohol consumption remains high or is increasing.

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.

Appendix

List of the NIPPON DATA90 Research Group

NIPPON DATA90: National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged.

Chairman: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).
Consultants: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido), Teruo Omae (Health C&C Center, Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi).
Participating Researchers: Akira Okayama (The First Institute of Health Service, Japan Anti-Tuberculosis Association, Chiyoda-ku, Tokyo), Kazunori Kodama, Fumiyoshi Kasagi (Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Heath 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. Marmot MG, Elliott P, Shipley MJ, *et al*: Alcohol and blood pressure: the INTERSALT study. *BMJ* 1994; **308**: 1263–1267.
2. Puddey IB, Beilin LJ, Vandongen R, Rouse IL, Rogers P: Evidence for a direct effect of alcohol consumption on blood pressure in normotensive men. A randomized controlled trial. *Hypertension* 1985; **7**: 707–713.
3. Puddey IB, Beilin LJ, Vandongen R: Regular alcohol use raises blood pressure in treated hypertensive subjects. A randomised controlled trial. *Lancet* 1987; **1**: 647–651.
4. Ueshima H, Ogihara T, Baba S, *et al*: The effect of reduced alcohol consumption on blood pressure: a randomised, controlled, single blind study. *J Hum Hypertens* 1987; **1**: 113–119.
5. Ueshima H, Mikawa K, Baba S, *et al*: Effect of reduced alcohol consumption on blood pressure in untreated hyper-

tensive men. *Hypertension* 1993; **21**: 248–252.
6. Tsuruta M, Adachi H, Hirai Y, Fujiura Y, Imaizumi T: Association between alcohol intake and development of hypertension in Japanese normotensive men: 12-year follow-up study. *Am J Hypertens* 2000; **13**: 482–487.
7. Ohmori S, Kiyohara Y, Kato I, *et al*: Alcohol intake and future incidence of hypertension in a general Japanese population: the Hisayama study. *Alcohol Clin Exp Res* 2002; **26**: 1010–1016.
8. Nakanishi N, Yoshida H, Nakamura K, Suzuki K, Tatara K: Alcohol consumption and risk for hypertension in middle-aged Japanese men. *J Hypertens* 2001; **19**: 851–855.
9. Yoshita K, Miura K, Morikawa Y, *et al*: Relationship of alcohol consumption to 7-year blood pressure change in Japanese men. *J Hypertens* 2005; **23**: 1485–1490.
10. Nakanishi N, Makino K, Nishina K, Suzuki K, Tatara K: Relationship of light to moderate alcohol consumption and risk of hypertension in Japanese male office workers. *Alcohol Clin Exp Res* 2002; **26**: 988–994.
11. Hashimoto T, Fujita Y, Ueshima H, *et al*: Urinary sodium and potassium excretion, body mass index, alcohol intake and blood pressure in three Japanese populations. *J Hum Hypertens* 1989; **3**: 315-321.
12. 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**: 1407–1414.
13. Zhou BF, Stamler J, Dennis B, *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**: 623–630.
14. Sekikawa A, Ueshima H, Zaky WR, *et al*: Much lower prevalence of coronary calcium detected by electron-beam computed tomography among men aged 40–49 in Japan than in the US, despite a less favorable profile of major risk factors. *Int J Epidemiol* 2005; **34**: 173–179.
15. Geleijnse JM, Kok FJ, Grobbee DE: Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. *Eur J Public Health* 2004; **14**: 235–239.
16. Ueshima H, Ozawa H, Baba S, *et al*: Alcohol drinking and high blood pressure: data from a 1980 national cardiovascular survey of Japan. *J Clin Epidemiol* 1992; **45**: 667–673.
17. 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 (errata: *JAMA* 2003; **290**: 197).
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**: 143–150.
19. Nakamura K, Okamura T, Hayakawa T, *et al*, NIPPON DATA90 Research Group: Electrocardiogram screening for left high R-wave predicts cardiovascular death in a Japanese community-based population. *Hypertens Res* 2006; **29**: 353–360 (errata: *Hypertens Res* 2006; **29**: 833).
20. Nakamura K, Okamura T, Hayakawa T, *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**: 954–959.
21. Hozawa A, Okamura T, Kadowaki T, *et al*, The NIPPON DATA90 Research Group: Gamma-glutamyltransferase predicts cardiovascular death among Japanese women. *Atherosclerosis* (in press, Epub).
22. Ueshima H, Shimamoto T, Iida M, *et al*: Alcohol intake and hypertension among urban and rural Japanese populations. *J Chronic Dis* 1984; **37**: 585–592.
23. Rockhill B, Newman B, Weinberg C: Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88**: 15–19.
24. Greenland S: Re: "Confidence limits made easy: interval estimation using a substitution method." *Am J Epidemiol* 1999; **149**: 884–886.
25. Ueshima H, Ohsaka T, Asakura S: Regional differences in stroke mortality and alcohol consumption in Japan. *Stroke* 1986; **17**: 19–24.
26. Wakabayashi I, Kobaba-Wakabayashi R, Masuda H: Relation of drinking alcohol to atherosclerotic risk in type 2 diabetes. *Diabetes Care* 2002; **25**: 1223–1228.
27. Kurihara T, Tomiyama H, Hashimoto H, Yamamoto Y, Yano E, Yamashina A: Excessive alcohol intake increases the risk of arterial stiffening in men with normal blood pressure. *Hypertens Res* 2004; **27**: 669–673.
28 Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K: Alcohol and coronary heart disease: a meta-analysis. *Addiction* 2000; **95**: 1505–1523.
29. Okamura T, Kadowaki T, Sekikawa A, *et al*: Alcohol consumption and coronary artery calcium in middle-aged Japanese men. *Am J Cardiol* 2006; **98**: 141–144.
30. Elkind MS, Sciacca R, Boden-Albala B, Rundek T, Paik MC, Sacco RL: Moderate alcohol consumption reduces risk of ischemic stroke: the Northern Manhattan Study. *Stroke* 2006; **37**: 13–19.
31. Okamura T, Tanaka T, Yoshita K, *et al*, HIPOP-OHP Research Group: Specific alcoholic beverage and blood pressure in a middle-aged Japanese population: the High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) Study. *J Hum Hypertens* 2004; **18**: 9–16.
32. Choudhury SR, Okayama A, Kita Y, *et al*: The associations between alcohol drinking and dietary habits and blood pressure in Japanese men. *J Hypertens* 1995; **13**: 587–593.
33. Japan Heart Foundation: The Fifth National Survey on Circulatory Disorders. Tokyo, Chuohoki Publishers, 2003, pp 111–190 (in Japanese).

Circ J 2007; **71:** 814–819

Mortality Risk Attributable to Atrial Fibrillation in Middle-Aged and Elderly People in the Japanese General Population

— Nineteen-Year Follow-up in NIPPON DATA80 —

Masaki Ohsawa, MD; Akira Okayama, MD*; Tomonori Okamura, MD**; Kazuyoshi Itai, PhD; Motoyuki Nakamura, MD†; Kozo Tanno, MD; Karen Kato, MD; Yumi Yaegashi, MA; Toshiyuki Onoda, MD; Kiyomi Sakata, MD; Hirotsugu Ueshima, MD** for the NIPPON DATA80 Research Group

Background The extent to which atrial fibrillation (AF) contributes to mortality in the Japanese general population has not been clarified.

Methods and Results A randomly sampled general population from all over Japan (4,154 men, 5,329 women; age ≥30 years) was enrolled. Single electrocardiogram recordings were taken in the baseline survey. Stroke death, cardiovascular deaths and all-cause deaths during the subsequent 19 years were analyzed by the presence of AF at baseline. Cox's regression analysis was carried out to estimate the hazard ratios (HRs) of each cause of death attributable to AF after adjusting for other risk factors. Prevalence of AF was 0.64% in the study. The observed person-years were 162,980 among persons without AF and 699 among persons with AF. There were 1,919 deaths. Multivariate adjusted HRs for stroke death, cardiovascular death and all-cause death were 2.69, 2.76 and 1.88, respectively ($p<0.05$). These HRs were 14.7, 9.63 and 4.00 among persons aged 64 years or younger ($p<0.05$).

Conclusion AF affects stroke mortality, cardiovascular mortality and all-cause mortality in the Japanese general population. Careful attention should be paid to persons with AF in order to prevent future cardiovascular events. (*Circ J* 2007; **71:** 814–819)

Key Words: Atrial fibrillation; Japanese; Mortality; Stroke

Atrial fibrillation (AF) is a strong risk factor for death, especially from stroke[1] and ischemic stroke associated with AF frequently results in a serious outcome[2] Thus, AF contributes not only to an increase in mortality risk but also to the burden of disability, which combined with the medical costs associated with AF has become a critical issue[3]

The prevalence of AF among patients with ischemic stroke has been reported to be approximately 15%[4] and has been increasing over the past 2 decades[5] because of the aging population[6] and the age-specific prevalence of AF has been increasing in Western countries, especially among men[7,8]

(Received September 21, 2006; revised manuscript received February 2, 2007; accepted March 12, 2007)

Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Morioka, *Department of Preventive Cardiology, National Cardiovascular Center, Suita, **Department of Health Science, Shiga University of Medical Science, Otsu and †Department of Internal Medicine II, School of Medicine, Iwate Medical University, Morioka, Japan

Members of the NIPPON DATA80 Research Group are listed in Appendix 1.

Mailing address: Masaki Ohsawa, MD, Department of Hygiene and Preventive Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan. E-mail: masakio@iwate-med.ac.jp

Stroke incidence and mortality rates are higher than for coronary artery disease in Japanese people compared with Westerners[9–12] AF is an independent risk factor for stroke, resulting in an approximately 3- to 5-fold excess risk in the Japanese general population[13] and Japan has the most rapidly aging population in the world. The estimated number of Japanese adults with AF was 391,000 in 1980 and 729,000 in 2000, and in 2030 it is predicted to be 1,081,000[14] Consequently, there are expected increases in mortality, morbidity and the burden of disability associated with AF.

Therefore, determining the relative risk for mortality attributable to AF in Japan is an urgent task, but the extent to which AF contributes to mortality in the Japanese general population has not been clarified. In this study, we investigated the relative risks for stroke death, cardiovascular death and all-cause death attributable to AF in a representative Japanese population.

Methods

Subjects

The National Survey on Circulatory Disorders 1980 investigated household members aged 30 years or older (n=13,771) in 300 districts from all over Japan using the stratified random sampling method based on the national

Table 1 Baseline Characteristics of Participants With/Without AF in NIPPON DATA80

	Men		*Women*	
	Non-AF	*AF*	*Non-AF*	*AF*
n	4,127	27	5,296	33
Age (years)	50.6 (13.2)	63.4 (15.5)**	50.3 (13.1)	68.8 (10.3)**
BMI (kg/m²)	22.5 (2.9)	23.0 (2.9)	22.9 (3.4)	23.4 (4.0)
SBP (mmHg)	138.4 (20.8)	141.3 (21.9)	133.9 (21.4)	145.2 (21.5)*
DBP (mmHg)	83.5 (12.3)	83.5 (10.7)	79.5 (11.8)	85.7 (16.5)
TC (mg/dl)	186.1 (32.8)	181.0 (36.8)	190.9 (34.1)	198.6 (32.6)
PG (mg/dl)	130.8 (38.1)	145.3 (49.2)	29.2 (33.7)	142.9 (38.5)
HT	2,066 (50.1%)	17 (63.0%)	2,193 (41.4%)	23 (69.7%)†
DM	285 (6.9%)	5 (18.5%)	216 (4.1%)	4 (12.1%)†
VHD	20 (0.5%)	3 (11.1%)‡	31 (0.6%)	6 (18.2%)‡
LVH	621 (15.0%)	4 (14.8%)	253 (4.8%)	5 (15.2%)
Smoker	2,612 (63.3%)	10 (37.0%)†	469 (8.9%)	0 (0.0%)
Drinker	1,978 (47.9%)	12 (44.4%)	150 (2.8%)	1 (3.0%)

Data are means (standard deviations) or numbers of persons (percentages).
P values were obtained by Student's t-test, chi-square test.
**$p<0.05$, **$p<0.01$ by Student's t-test; †$p<0.05$, ‡$p<0.01$ by chi-square test.*
AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; PG, plasma glucose; HT, hypertension; DM, diabetes mellitus; VHD, valvular heart disease; LVH, left ventricular hypertrophy; Smoker, current smoker; Drinker, regular drinker.

census in 1975. A total of 10,897 persons (response rate: 79.4%) participated in the survey.[15]

A study group was formed in 1994 to conduct a follow-up study of 10,546 participants in the Survey under the auspices of the Ministry of Health and Welfare (The National Integrated Project for Prospective Observation of Non-communicable Diseases and Its Trends in the Aged: NIPPON DATA80).[16,17]

Initial Investigation

The initial investigations in the National Survey on Circulatory Disorders 1980 were conducted by public health centers and consisted of a questionnaire, measurements of blood pressure and anthropometric data, blood and urine tests, and a resting electrocardiogram (ECG). Public health nurses confirmed information on smoking and drinking habits, and present and past histories of myocardial infarction, stroke, valvular heart disease, hypertension (HT) and diabetes mellitus (DM) using questionnaires. Participants were asked to record whether they were current smokers, ex-smokers or non-smokers. Smokers were asked to note the number of cigarettes smoked per day. All participants were asked to record whether they were non-drinkers, ex-drinkers or current drinkers. Regular drinking was defined as a current drinker consuming alcohol every day or occasionally.

Participants were asked to avoid eating or exercise for 30 min before the measurements. Body weight was measured while the participants wore light clothing and no shoes, and the body mass index (BMI) was calculated. Single blood pressures and pulse rates were measured by a trained public health nurse in each public health center using a standard sphygmomanometer on the right arm of the seated subject after a 5-min rest.

Non-fasting blood samples were drawn and then centrifuged within 60 min of collection and stored at –70°C until analyses. Serum total cholesterol (TC) levels were analyzed in a sequential autoanalyzer (SMA12; Technicon, Tarrytown, USA) by the Liebermann-Burchard direct method at a laboratory (Osaka Medical Center for Health Science and Promotion). Casual blood glucose levels were determined in the same laboratory using the neocaprotine-copper method. Therefore, determined glucose levels in this survey tended to be 20–30 mg/dl higher than those measured by the deoxidized method. The laboratory belonged to the Cholesterol Reference Method Laboratory Network (CRMLN), and the measurement precision and accuracy for serum cholesterol were certified in the lipid Standardization Program administered by the Centers for Disease Control and Prevention in the United States. Details have been published elsewhere.[16,17]

HT was defined as systolic blood pressure (SBP) ≥140, diastolic blood pressure (DBP) ≥90 mmHg, use of anti-hypertensive agents or a combination of these. DM was defined as serum glucose level ≥200 mg/dl, a past history of diabetes, or both.

The ECG findings were independently evaluated by 2 trained doctors in each of 12 institutes (Department of Health Science, Jichi Medical School; Department of Public Health Science, Dokkyo Medical University; Fourth Department of Internal Medicine, Tokyo University; Tokyo Metropolitan Institute of Gerontology; National Institute of Public Health; Chiba University School of Nursing; Saku Central Hospital; Nagoya University Faculty of Medicine; Aichi Medical University; Department of Epidemiology, National Cardiovascular Center; Department of Preventive Cardiology, National Cardiovascular Center) according to the Minnesota Code. In cases of inconsistent judgments, the final judgments were made by the Approval Committee on Coding. AF was defined as 8-3 and left ventricular hypertrophy (LVH) was defined as 3-1 according to the Minnesota Code.[15]

Follow-up Surveys and Determination of Causes of Death

Follow-up surveys were performed in 1994 and 1999 to ascertain the status of each of the participants: 9,638 (91.4%) of the 10,546 original respondents were available. For longitudinal analyses, we excluded an additional 155 persons because they had a history of stroke (110 persons) or myocardial infarction (45 persons). Finally, the data from 9,483 subjects (4,154 men, 5,329 women) were used for the analyses.

National Vital Statistics were used to clarify the underlying causes of death. In accordance with Japan's Family