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Trends in the Incidence, Mortality, and Survival Rate of Cardiovascular Disease in a Japanese Community

The Hisayama Study

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Background and Purpose—The slowdown of a steeply declining trend in cardiovascular mortality has been reported in Japan, but precise reasons for this trend are uncertain.

Methods—We established 3 study cohorts of Hisayama residents aged ≥40 years without a history of stroke or myocardial infarction in 1961 (1618 subjects, first cohort), 1974 (2038 subjects, second cohort), and 1988 (2637 subjects, third cohort). We followed up with each cohort for 12 years, comparing the incidence, mortality, and survival rate of cardiovascular disease.

Results—The age-adjusted incidence of cerebral infarction significantly declined by 37% for men and by 32% for women from the first to the second cohort. It continued to decline by 29% for men, but the decline decelerated for women in the third cohort. The incidence of cerebral hemorrhage steeply declined by 61% from the first to the second cohort in men only, while it was sustained for both sexes in the third cohort. Stroke mortality continuously declined as a result of these incidence changes and significant improvement of survival. In contrast, the incidence and mortality rate of coronary heart disease were unchanged except for the increasing incidence in the elderly. The prevalence of severe hypertension and current smoking significantly decreased, while that of glucose intolerance, hypercholesterolemia, and obesity greatly increased among the cohorts.

Conclusions—Our data suggest that the decline in stroke incidence is slowing down and that the incidence of coronary heart disease has been increasing in the elderly in recent years. Insufficient control of hypertension and the increase in metabolic disorders may contribute to these trends. (***Stroke.*** **2003;34:2349-2354.)**

Key Words: coronary heart disease ■ incidence ■ mortality ■ secular trend ■ stroke

According to world vital statistics in the 1950s and 1960s, the Japanese were characterized by the highest stroke mortality and by a lower coronary heart disease (CHD) mortality compared with Western populations.[1–4] In Japan, the stroke mortality rate started to decline steeply in the 1970s, but the slowdown of this decline has been reported in recent years.[1,2] However, vital statistics are not always accurate with regard to the cause of death listed on death certificates.[5] It is also difficult to know precise trends in mild cases of cardiovascular disease (CVD), and it is not possible to know whether these trends reflect a changing incidence or an improvement of case fatality rate. These facts imply that population-based studies collecting CVD incidence data are needed to elucidate secular trends.

Most previous epidemiological studies have examined CVD incidence trends by comparing prevalence rates of hospitalized cases among different time periods in registration studies[6–9] or by dividing a long-term follow-up period into several parts in cohort studies.[10,11] These methods, however, are potentially biased by the improvement of diagnostic techniques and by changes in the characteristics of the study subjects. The World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) Project is a well-performed epidemiological study that examined CVD incidence and mortality trends from 37 populations in 21 countries; however, it did not include Japan.[12] The Hisayama Study is a population-based study that has established 3 study cohorts at times corresponding to periods of remarkable lifestyle changes in Japan.[13–15] In this study, study team physicians performed physical examinations of those subjects who developed CVD and collected detailed clinical information about them. Furthermore, morphological examinations were performed in most of the CVD cases in each cohort.[16] These characteristics of the study design provide us with an opportunity to determine secular trends in cardiovascular incidence and mortality with a high degree of accuracy.

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Subjects and Methods

Study Population

Hisayama Town is a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town has been stable for many years (annual variation rate <5%)[14] and has been shown to be representative of Japan as a whole on the basis of data from the national census.[13,15] The study design and characteristics of the subject population have been described in detail elsewhere.[13–16] Briefly, we established 3 study cohorts from Hisayama residents aged ≥40 years in 1961, 1974, and 1988 after screening examinations. In 1961, a total of 1658 subjects in that age group consented to participate in the screening examination (participation rate, 90.1%). After the exclusion of 28 subjects with a history of CVD and 12 subjects who died or moved out of town during the examination, 1618 subjects were enrolled as the first cohort. In the same manner, we established the second cohort consisting of 2038 subjects from 2135 participants (participation rate, 81.2%) in 1974 and the third cohort of 2637 subjects from 2742 participants (participation rate, 80.9%) in 1988.

Follow-Up

The cohort populations have been undergoing longitudinal observations by repeated health examinations. Health status was checked every year by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. When the subjects died, autopsy examinations were performed at the Department of Pathology of Kyushu University. During the 12-year follow-up period of each cohort, autopsy examinations were performed on 327 subjects (81.6% of the deceased subjects) in the first cohort, 342 subjects (86.2%) in the second cohort, and 366 subjects (75.5%) in the third cohort. Only 2 subjects in the first cohort, 2 in the second cohort, and 1 in the third cohort were lost to follow-up.

Definition of Cardiovascular Events

The diagnosis of stroke was determined on the basis of clinical information and autopsy findings.[16] In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours and was classified as either cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type. Subjects who died within 24 hours after the onset of the symptoms and had evidence of stroke were also included as stroke cases.

The diagnosis of CHD included acute myocardial infarction (MI), silent MI, and sudden cardiac death within 1 hour after the onset of acute illness. The diagnosis of MI was made on the basis of clinical symptoms, ECG recordings, cardiac enzymes, and morphological changes.[17] Acute MI was diagnosed when the suspected subject met at least 2 of the following criteria: (1) typical symptoms including prolonged severe chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic ECG changes; and (4) morphological changes including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent MI was defined as myocardial scars without any information indicated in the history regarding clinical symptoms or abnormal cardiac enzyme changes. Cases experiencing MI during surgery or during a cardiac intervention procedure were excluded.

We gathered all available information about potential cardiovascular events and death among the study participants. All these materials were reviewed by a panel of physician members of the Hisayama Study to determine the occurrence of CVD and/or cause of death under the standard criteria throughout the study period.

Risk Factors

Recumbent blood pressures were measured at every examination, and hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. Blood pressures were also categorized as normal (<130/85 mm Hg), high-normal (<140/90 mm Hg), stage 1 (<160/100 mm Hg), stage 2 (<180/110 mm Hg), and stage 3 (≥180/110 mm Hg).[18] Glucose intolerance was defined by an oral glucose tolerance test in the subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988, in addition to medical history of diabetes. Serum cholesterol levels were measured by the modified Zak-Henly method in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1988.[16] Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/L. Obesity was defined as body mass index ≥25.0 kg/m^2. Information on antihypertensive treatment, alcohol intake, and smoking habits was obtained with the use of a standard questionnaire and was categorized as current habitual use or not. Subjects who reported smoking at least 1 cigarette per day were defined as current smokers, and subjects who reported consuming alcohol at least once a month were regarded as current drinkers.

Statistical Analysis

We counted only first-ever cardiovascular events in this study. The CVD incidence and mortality rates were calculated by the person-year method and adjusted for the age distribution of the world standard population by the direct method. The differences in the incidence and mortality among 3 cohorts were tested by sex with the use of the Cox proportional hazards model after adjustment for age. Subjects who developed cardiovascular events were also followed up for the subsequent 5 years or to the end of the follow-up in every cohort, and survival rates were estimated with the Cox proportional hazards model. The significance of risk factor trends was examined with the χ^2 test. All statistical analyses were performed with the SAS program package. $P<0.05$ was considered statistically significant in all analyses.

Results

Trends in CVD Risk Factors

We compared the prevalence of cardiovascular risk factors at the baseline examination among the 3 study cohorts by sex (Table 1). In both sexes, the prevalence of hypertension was not different among the cohorts, but the proportion of individuals using antihypertensive agents consistently increased with time. When we compared blood pressure levels among the cohorts, the proportion of subjects with stage 2 and 3 hypertension declined, while that of subjects with stage 1 hypertension increased in both sexes. The prevalence of glucose intolerance, hypercholesterolemia, and obesity increased progressively with time. The proportion of current smokers in both sexes and that of male drinkers declined linearly over the cohorts.

Trends in CVD incidence

The age-adjusted stroke incidence significantly declined by 48% for men ($P<0.01$) and tended to decline by 25% for women ($P=0.06$) from the first to the second cohort, but this declining trend was slowed in the third cohort (Table 2). The age-adjusted incidence of cerebral infarction for men significantly declined throughout the cohorts. For women, the incidence also declined from the first to the second cohort, but the decline decelerated in the third cohort. The age-adjusted incidence of cerebral hemorrhage for men significantly declined by 61% from the first to the second cohort but remained unchanged in the third cohort. The age-adjusted incidence of cerebral hemorrhage for women and that of subarachnoid hemorrhage for both sexes were constant among the cohorts.

The age-adjusted incidence of CHD did not significantly change throughout the cohorts for either sex. The age-adjusted incidence of acute MI, silent MI, and sudden death also did not significantly change among the cohorts.

TABLE 1. Prevalence by Sex of Cardiovascular Risk Factors at Baseline Among 3 Cohorts in 1961, 1974, and 1988 (the Hisayama Study)

Variables	Men				Women			
	1st Cohort (n=705)	2nd Cohort (n=855)	3rd Cohort (n=1110)	*P* for Trend	1st Cohort (n=913)	2nd Cohort (n=1183)	3rd Cohort (n=1527)	*P* for Trend
Age, y	55±11	56±11	57±12	<0.001	57±12	58±12	59±12	0.002
Hypertension, %	38.6	40.4	41.5	0.22	37.4	44.0	38.4	0.98
Antihypertensive agents, %	2.1	8.5	14.3	0.001	2.2	8.3	15.5	0.001
Blood pressure category, %				0.052				0.001
Normal	48.4	44.7	43.7		48.5	41.6	51.2	
High-normal	13.3	16.6	19.6		14.4	15.2	14.3	
Stage 1	19.2	22.7	25.5		19.3	23.7	22.6	
Stage 2	10.6	9.7	8.6		11.0	12.3	8.6	
Stage 3	8.5	6.3	2.6		6.9	7.3	3.4	
Glucose intolerance, %	12.1	13.8	31.9	0.001	4.8	8.1	27.2	0.001
Hypercholesterolemia, %	1.7	5.3	14.9	0.001	3.2	9.6	25.9	0.001
Obesity, %	7.4	11.6	23.2	0.001	12.9	20.8	23.4	0.001
Current smoker, %	76.3	73.0	49.9	0.001	16.8	10.7	6.9	0.001
Current drinker, %	69.4	64.0	60.2	0.001	8.3	5.6	8.7	0.41

Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or a current use of antihypertensive agents. Hypercholesterolemia was defined as total cholesterol level ≥240 mg/dL. Obesity was defined as body mass index ≥25.0 kg/m^2.

Trends in Age-Specific CVD Incidence

The age-specific incidence rates of CVD for men and women combined among the 3 cohorts are shown in Figure 1. The incidence of cerebral infarction consistently decreased mainly in the aged subjects. The incidence of cerebral hemorrhage in the subjects aged <80 years greatly decreased from the first to the second cohort, but it showed no further change in the third cohort. In contrast, the incidence of cerebral hemorrhage in the subjects aged ≥80 years continuously increased. The incidence of CHD showed no significant trend among subjects aged <80 years, while it tended to increase in the oldest age group.

Trends in CVD Survival

Age- and sex-adjusted 5-year survival curves after CVD events are shown in Figure 2. The 5-year survival after cerebral infarction significantly improved from the first (40%) to the third cohort (61%). The 5-year survival after cerebral hemorrhage greatly increased from 3% to 55%, mainly as a result of the improvement of the 1-month survival. A pattern similar to that of cerebral hemorrhage was observed for subarachnoid hemorrhage, but the differences were not significant. The 5-year survival after acute MI significantly improved from the first to the second cohort (18% to 52%, respectively) but remained constant in the third cohort (63%).

Trends in CVD Mortality

The age-adjusted stroke mortality significantly declined from the first to the third cohort for both sexes (Table 3). The age-adjusted mortality as a result of cerebral infarction for both sexes and that of cerebral hemorrhage for men linearly

TABLE 2. Age-Standardized Incidence Rate (per 100 000 Person-Years) of Cardiovascular Disease Among 3 Cohorts of the Hisayama Study by Sex, With a 12-Year Follow-Up in Each Cohort

	Men						Women					
	1st Cohort (1961–73)		2nd Cohort (1974–86)		3rd Cohort (1988–2000)		1st Cohort (1961–73)		2nd Cohort (1974–86)		3rd Cohort (1988–2000)	
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
Stroke	97	1210 (953, 1466)	73	631* (481, 781)	86	529* (411, 647)	78	598 (465, 731)	93	447 (356, 539)	111	388* (309, 467)
Cerebral infarction	63	801 (588, 1015)	59	506* (372, 640)	60	357*† (264, 451)	59	450 (335, 566)	65	304* (230, 379)	77	260* (195, 325)
Cerebral hemorrhage	27	321 (196, 446)	14	125* (57, 192)	20	130* (68, 192)	8	63 (19, 107)	14	73 (34, 111)	21	70 (38, 101)
Subarachnoid hemorrhage	5	59 (5, 112)	0	0 (0, 0)	6	42 (4, 79)	9	70 (24, 116)	14	70 (33, 107)	13	58 (25, 90)
Undetermined	2	28 (0, 69)	0	0 (0, 0)	0	0 (0, 0)	2	14 (0, 34)	0	0 (0, 0)	0	0 (0, 0)
Coronary heart disease	25	340 (178, 501)	32	392 (179, 605)	56	348 (227, 469)	15	113 (55, 170)	30	133 (85, 181)	43	181 (79, 284)
Acute myocardial infarction	15	219 (79, 359)	15	243 (43, 443)	26	154 (92, 216)	9	66 (23, 109)	20	89 (50, 128)	26	87 (47, 126)
Silent myocardial infarction	8	100 (25, 175)	12	108 (43, 173)	16	84 (43, 125)	5	38 (4, 71)	7	32 (8, 56)	11	26 (10, 41)
Sudden death	2	20 (0, 47)	5	40 (5, 76)	14	76 (36, 116)	1	9 (0, 26)	3	12 (0, 26)	6	19 (3, 35)

*P<0.05 vs 1st cohort; †P<0.05 vs 2nd cohort. 95% confidence intervals are shown in parentheses.

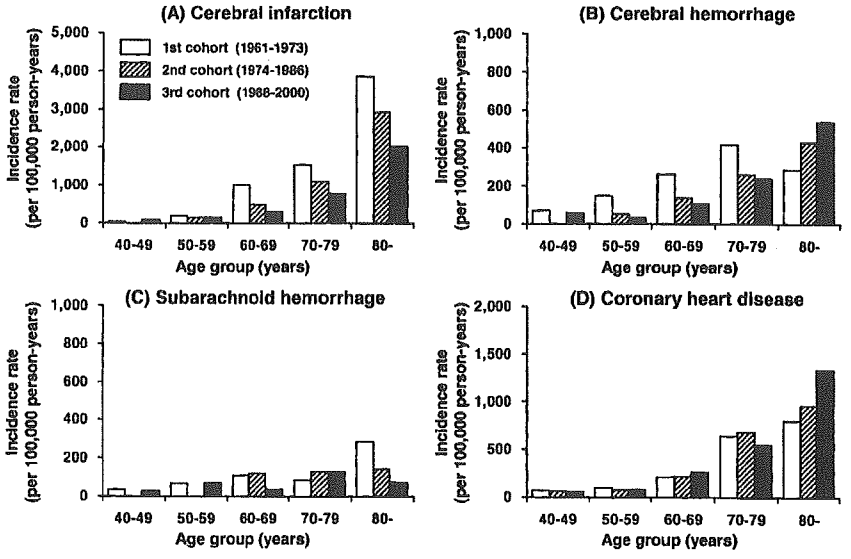

Figure 1. Age-specific incidence of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and coronary heart disease of men and women combined among 3 cohorts of the Hisayama Study, with a 12-year follow-up in each cohort.

declined throughout the study period. The age-adjusted mortality from subarachnoid hemorrhage and that from CHD did not significantly change among the cohorts for either sex.

Discussion

By comparing the incidence, mortality, and survival rates of CVD among 3 cohorts established at different times in a Japanese community, we demonstrated that stroke incidence significantly declined from the first to the second cohort but that a slowdown of this declining trend was observed in the third cohort. In contrast, CHD incidence and mortality remained low and showed no apparent secular trend. Changes in risk factors, namely, the improvement of hypertension control and the increase in metabolic disorders, may have affected these trends. Another striking finding is that the incidence of cerebral hemorrhage and CHD, contrary to that of cerebral infarction, increased with time in very old subjects.

Hypertension is a strong risk factor for cerebral infarction.[16,18] During the study period, the prevalence of hypertension remained stable, but the blood pressure level significantly decreased as a result of the 7-fold increment in the use of antihypertensive medication. This apparently resulted in a reduction in the incidence of cerebral infarction.[19] However, despite continuing improvement in hypertension management, the decline in the incidence of cerebral infarction slowed down in the third cohort. One of the probable reasons is the steep increase in obesity, hyperlipidemia, and diabetes, which significantly increase the risk of cerebral infarction.[15,16] Another reason may be that two thirds of the hypertensives have not yet received antihypertensive medication, and one fourth of the hypertensives still have stage 2 or 3 hypertension.

The incidence of cerebral hemorrhage was unchanged except for the steeply declining incidence from the first to the second cohort in men. Our previous report showed that heavy alcohol consumption led to a great increase in the risk of

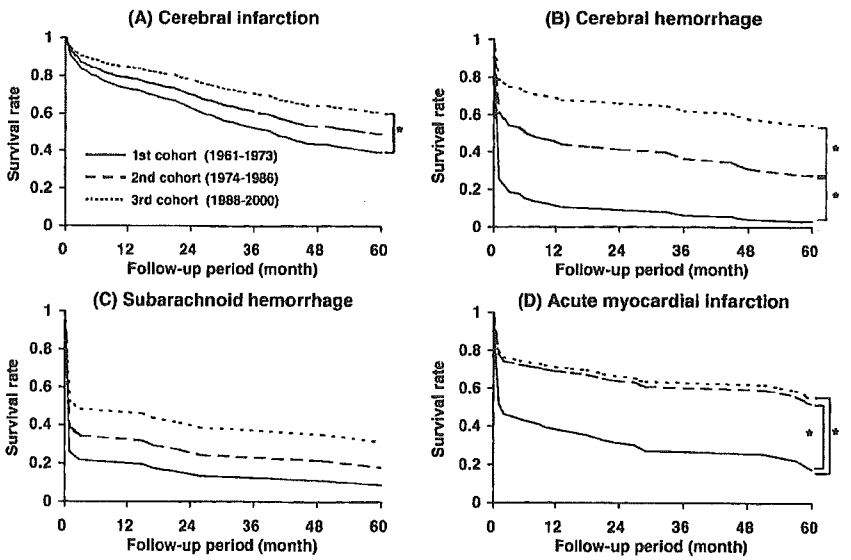

Figure 2. Age- and sex-adjusted 5-year survival rates after cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and acute myocardial infarction among 3 cohorts of the Hisayama Study. *$P<0.01$.

TABLE 3. Age-Standardized Mortality Rate (per 100 000 Person-Years) of Cardiovascular Disease Among 3 Cohorts of the Hisayama Study by Sex, With a 12-Year Follow-Up in Each Cohort

	Men						Women					
	1st Cohort (1961–73)		2nd Cohort (1974–86)		3rd Cohort (1988–2000)		1st Cohort (1961–73)		2nd Cohort (1974–86)		3rd Cohort (1988–2000)	
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
Stroke	53	634 (454, 814)	25	232* (135, 329)	24	138* (79, 196)	38	286 (195, 378)	36	162* (108, 215)	34	102*† (66, 138)
Cerebral infarction	21	268 (145, 390)	15	147* (68, 227)	12	68*† (29, 107)	21	159 (90, 227)	20	84* (47, 121)	16	45*† (21, 68)
Cerebral hemorrhage	25	283 (169, 398)	9	77* (25, 130)	6	30* (6, 55)	8	61 (18, 103)	7	32 (8, 57)	10	29 (10, 47)
Subarachnoid hemorrhage	5	56 (5, 108)	0	0 (0, 0)	6	40 (4, 76)	6	44 (9, 80)	9	45 (15, 75)	7	27 (6, 47)
Undetermined	2	27 (0, 67)	1	7 (0, 21)	0	0 (0, 0)	3	23 (0, 49)	0	0 (0, 0)	1	2 (0, 6)
Coronary heart disease	8	87 (25, 149)	12	92 (40, 145)	21	111 (63, 158)	9	66 (23, 110)	12	51 (22, 80)	15	39 (18, 59)

*$P<0.05$ vs 1st cohort; †$P<0.05$ vs 2nd cohort. 95% confidence intervals are shown in parentheses.

cerebral hemorrhage in hypertensive men in the first cohort.[20] Control of hypertension diminished this synergic effect and resulted in this steeply declining trend in men. Despite the improvement of hypertension management, the incidence of cerebral hemorrhage remained stable in the third cohort. The precise reasons for this trend are unknown, but the aforementioned insufficient control of hypertension and the increasing incidence in the elderly subjects may contribute to this trend.

In contrast to the dynamic changes in stroke incidence, CHD incidence remained low and showed no apparent secular change. It is well known that hypertension, smoking, and hyperlipidemia are important risk factors for CHD[18,21]; however, the prevalence of hyperlipidemia was low,[17] and its impact on CHD was much weaker in Japanese than in Western populations.[22] Moreover, the increase in metabolic disorders may negate the beneficial effects of secular improvement of hypertension control and the decreasing prevalence of smoking habits.

In our population, the incidence of CHD and cerebral hemorrhage in very old subjects increased with time. The decreased incidence and mortality of cerebral infarction, the most common type of CVD in Japanese, may contribute to the longevity of persons with atherosclerosis. It is reasonable to think that these elderly subjects with relatively severe atherosclerosis had a higher risk of other atherosclerotic disease, such as CHD and cerebral hemorrhage.

There are several points to remember when the results of our study are interpreted. First, the method for diagnosing CVD was changed remarkably by the improvement of diagnostic techniques, and this may affect the incidence rate.[9,10,23] In our study, however, methods for case ascertainment and diagnostic criteria of CVD were consistent throughout the study period. Moreover, the presence and type of CVD were confirmed by morphological examinations in most of the deceased subjects throughout the study period. Second, we established 3 cohorts independently in the same manner, but the subjects in later cohorts included many survivors of the former cohorts. This may affect the development of CVD; however, we enrolled most of the unselected residents in every cohort (participation rate >80%), and the prevalence rate of cardiovascular risk factors in the third cohort was similar to those of the national survey on circulatory disorders[24] and the national dietary survey[25] of Japan conducted during the same time period (data not shown). Third, the criteria for glucose intolerance were different among cohorts, suggesting an underestimation of its prevalence in the former cohorts. Fourth, there were a small number of CVD cases in each cohort, indicating a larger chance of bias in its trends. Nonetheless, we believe that the findings of our study represent precise secular trends, since we performed this study using a highly accurate method for determining all cardiovascular events.

In conclusion, in a Japanese population, stroke incidence and mortality declined markedly between the 1960s and 1970s, mainly as a result of the improvement of hypertension management. However, the increase in metabolic disorders and insufficient control of hypertension slowed this declining trend in the late 1980s and 1990s. These changes in risk factors also contributed to the lowered and sustained low incidence and mortality of CHD. In addition to strict hypertension management, urgent care for metabolic disorders is needed for further prevention of CVD in Japan.

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Original Article

Dietary Factors and Development of Impaired Glucose Tolerance and Diabetes in a General Japanese Population: The Hisayama Study

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BACKGROUND: There have been few prospective studies on diet and glucose abnormalities as determined by oral glucose tolerance test.

METHODS: To investigate the impact of dietary factors on the development of glucose intolerance including diabetes and impaired glucose tolerance, we performed a follow-up survey of 1,075 subjects aged 40-74 years of normal glucose tolerance from 1988 through 1993/1994 by repeated 75 g oral glucose tolerance test and dietary survey. Information on habitual food consumption was obtained using a semiquantitative food frequency method.

RESULTS: Of the total subjects studied, 119 (11.1 %) developed impaired glucose tolerance and 24 (2.2 %) developed diabetes during the follow-up. At baseline, the age-adjusted amount of alcohol intake was significantly higher in males who developed glucose intolerance than in those who did not (26.7 g vs. 15.7 g, $p<0.05$), while the polyunsaturated/saturated fatty acids (P/S) ratio was significantly higher in females with future glucose intolerance (1.42 vs. 1.31, $p<0.05$). Among the female subjects who developed glucose intolerance, the intake of animal fat less decreased during the follow-up period compared with normal subjects, resulting in a significant decrease in the P/S ratio (-0.09 vs. 0.05, $p<0.05$). In a multiple logistic regression analysis, alcohol intake at baseline for males and decreased P/S ratio during the follow-up for females remained a significant risk factor for glucose intolerance independent of other dietary and non-dietary factors as well.

CONCLUSIONS: These results suggest that a high intake of alcohol and a decreased P/S ratio contribute to the risk of glucose intolerance in contemporary Japanese.

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Key words: alcohol drinking, fatty acids, food habits, glucose intolerance, prospective studies.

Diabetes mellitus appears to confer an excess risk of cardiovascular disease and premature death. In Japan, the prevalence of diabetes has increased over the past several decades.[1,2] Although Japanese are thought to be predisposed to diabetes,[3,4,5] it is conceivable that the recent increase in diabetes in Japan is due largely to westernization of the Japanese life-style.[2] Among the life-style factors that might influence the development of diabetes, dietary intake is one of the most important. In the literature, a number of studies have presented cross-sectional associations of dietary intake with glucose levels[6,7,8,9] and hyperinsulinemia,[6,10,11,12] but there have been very few studies of Japanese. Moreover, only a few prospective studies on diet and glucose abnormalities have been reported,[13,14,15] and those using an oral glucose tolerance test (OGTT) have been fewer still even in western countries.[16,17]

In 1988, we performed a prevalence study of diabetes and impaired glucose tolerance (IGT) using OGTT in a defined general Japanese population, Hisayama.[18] The present follow-up study used OGTT and nutritional surveys to investigate the longitudinal association between dietary factors and the development of diabetes and IGT among subjects having normal glucose tolerance at

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baseline.

METHODS

Study population

The town of Hisayama is a suburban community adjoining the city of Fukuoka, a metropolitan area on Kyushu Island in Japan. The population of the town is approximately 7,500 and has scarcely changed over the last 40 years. According to the census information for this period, the population of the town, in terms of age, sex, and occupational distribution, reflects the population of Japan as a whole.[18,19] Full community surveys of the residents aged 40+ years were repeated since 1961.

The diabetes prevalence study was performed by simultaneously using a 75 g OGTT and a nutritional survey in a screening examination from June 29th through November 14th in 1988. A detailed description of this survey was published previously.[18] Briefly, among the total of 3,227 Hisayama residents aged 40 to 79 years, 2,587 (80.2%) took part in the examination. After excluding 82 non-fasting subjects, 10 subjects under insulin therapy, and 15 subjects who could not complete the OGTT due to complaints of nausea or general fatigue during ingestion of a glucose solution, 2,480 remaining subjects (1,073 males and 1,407 females) completed the OGTT and the nutritional survey. In accordance with the 1998 World Health Organization criteria,[20] these participants were classified into three groups: a normal glucose tolerance, an IGT, and a diabetes mellitus group. The criteria are as follows: for diabetes, fasting plasma glucose 7.0+ mmol/L or 2 hr plasma glucose 11.1+ mmol/L in the OGTT; for IGT, fasting plasma glucose <7.0 and 2 hr plasma glucose 7.8-11.0 mmol/L; for normal glucose tolerance, fasting glucose <7.0 mmol/L and 2 hr glucose <7.8 mmol/L.

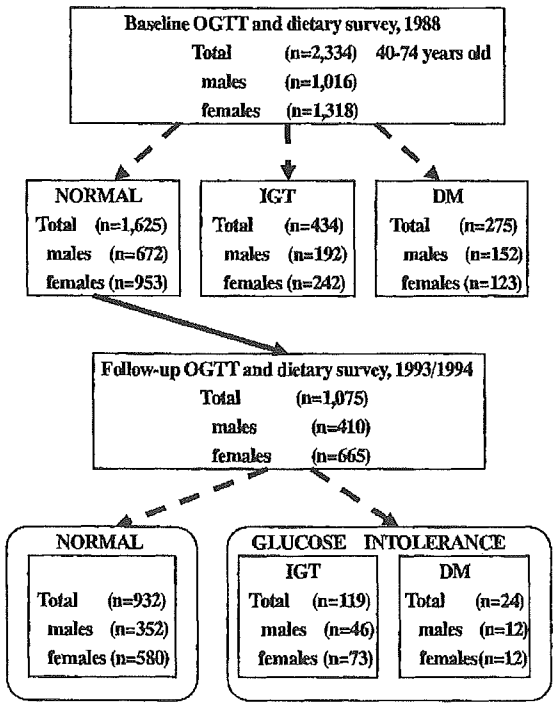

Figure. Flow diagram of the study.
OGTT: oral glucose tolerance test
IGT: impaired glucose tolerance
DM: diabetes mellitus

Follow-up examination

Among the 1,625 persons (672 males, 953 females) aged 40 to 74 years found to have normal glucose tolerance in 1988, 1,075 (66.2 %; 410 males, 665 females) also participated in the follow-up examination performed in 1993/1994, in which we repeated the OGTT and nutritional survey in the same manner as in the initial screening (Figure). Among these subjects, 119 (11.1 %) developed IGT and 24 (2.2 %) developed diabetes during this follow-up period, while the remaining 932 subjects remained normal. In the present study, we compared dietary factors at entry and their subsequent changes between the subjects who had developed glucose intolerance (GI, which means diabetes or IGT) by the time of the 1993/1994 survey and those who had not.

Nutritional survey

The dietary survey was conducted using a semiquantitative food frequency method,[21] and the nutritional elements were adjusted for energy intake using the method of Willet and Stampfer.[22] A self-administered questionnaire concerning food intake over the previous year, which consisted of 70 food items, was completed prior to the start of the study by each participant and was checked by experienced dieticians and nutritionists by showing food models of actual size in the survey. The average food intake per day was estimated based on detailed descriptions of the frequency of eating and the quantity of each food. Nutritional intake was calculated using the fourth revision of the Standard Tables of Food Composition in Japan[23] and its follow-up version for fatty acids, cholesterol, and vitamin E.[24] In regard to foods which were not included in these Tables, we estimated the amounts of nutritional elements by using the similar foods included in the Tables.

Laboratory testing and risk factor measurement

Blood samples were collected from an antecubital vein after an overnight fast for the determination of the serum insulin, serum lipid, and plasma glucose levels. After the fasting blood specimen was taken, each subject ingested a 75 g glucose-equivalent carbohydrate load (Trelan G, Shimizu Pharmaceutical, Shimizu, Japan) from 8:00 a.m. through 10:30 a.m. At 120 min after glucose loading, second blood sample was obtained to determine the postloading plasma glucose. Subjects receiving oral hypoglycemic agents were requested to avoid taking their medication until completion of the OGTT. The blood specimens were transferred immediately in ice-cooled containers to the central study laboratory (Japan Medical Laboratory Inc., Fukuoka, Japan) and were analyzed

within 24 hours. The plasma glucose level was measured by the glucose-oxydase method using a glucose autoanalyser (Glucoroder-MK2; A & T Inc., Tokyo, Japan). The serum insulin level was determined by a commercial double-antibody solid-phase radioimmunoassay (Phadeseph Insulin; Pharmacia Diagnostics AB, Uppsala, Sweden). The total cholesterol, HDL-cholesterol, and triglycerides were all measured enzymatically using an autoanalyser (TBA-80S; Toshiba Inc., Tokyo, Japan).

Body height and weight were measured with subjects wearing light clothing without shoes, and the body mass index (kg/m^2) was calculated. A questionnaire concerning physical activity during leisure time and smoking habits were also administered for all subjects. Those subjects engaging in sports at least once a week during their leisure time made up physically active group. Finally, subjects were classified into two groups according to their smoking habits: a habitual use and a non-habitual use group.

Statistical analysis

The SAS® statistical software package was used for data analysis. Because of the skewed distribution of serum triglycerides and insulin, these variables were log-transformed for statistical analysis. Mean values were compared using the least significant difference analysis after adjustment for age by the covariance method. The age-adjusted frequencies were calculated using the direct method and were compared by the Mantel-Haenzel chi-square test. We estimated the multivariate odds ratio and 95% confidence interval of each risk factor, including that of dietary nutrients, using beta coefficients from the stepwise multiple logistic regression model, with $p<0.1$ being required for entry into the model and for remaining there.

This study was conducted with approval of the ethical committee of Kyushu University.

RESULTS

Characteristics of the subjects

Table 1 shows age-adjusted mean values or frequencies of baseline non-dietary factors in the subjects who did and did not develop GI by sex. The female subjects who developed GI were significantly older than those with normal glucose tolerance (58 vs. 54 years, $p<0.01$), but were not for the male subjects. The GI subjects had a higher body mass index and systolic and diastolic blood pressures compared with normal subjects in both sexes; the differences in these factors, with the exception of female diastolic blood pressure, were statistically significant ($p<0.05$). Both male and female GI subjects had significantly higher fasting plasma glucose levels than their corresponding normal subjects ($p<0.01$), and serum fasting insulin levels were significantly higher in male GI than normal subjects ($p<0.01$). The mean values of triglycerides were also significantly higher in the GI group than in the normal group for males ($p<0.01$), while no significant difference was found among the groups for total and HDL cholesterols in both sexes. No significant difference in leisure-time physical activity was found between GI and normal subjects of either sex. Male smokers were more frequent than female ones; however, there was no difference between the glucose tolerance groups in either sex.

Table 1. Age-adjusted baseline characteristics of study subjects by sex and glucose tolerance status.

Variable	Males		Females	
	Normal n=352	Glucose Intolerance n=58	Normal n=580	Glucose Intolerance n=85
Age(years)	55 ± 0.5	56 ± 0.9	54 ± 0.3	58 ± 0.9**
Height(cm)	162 ± 0.3	162 ± 0.7	150 ± 0.2	150 ± 0.5
Weight(kg)	59 ± 0.4	62 ± 1.0*	51 ± 0.3	53 ± 0.7
Body mass index(kg/m^2)	22.5 ± 0.1	23.6 ± 0.3**	22.8 ± 0.1	23.5 ± 0.3*
Systolic blood pressure(mmHg)	128 ± 0.9	136 ± 2.2**	124 ± 0.7	133 ± 1.8**
Diatolic blood pressure(mmHg)	78 ± 0.5	83 ± 1.3**	74 ± 0.4	76 ± 1.1
Fasting glucose(mmol/l)	5.4 ± 0.02	5.8 ± 0.06**	5.3 ± 0.02	5.6 ± 0.05**
Fasting insulin(pmol/l)	30 ± 0.9	40 ± 2.0**	35 ± 0.7	40 ± 1.9
Triglycerides(mmol/l)	1.36 ± 0.05	1.90 ± 0.14**	1.09 ± 0.03	1.24 ± 0.08
Total cholesterol(mmol/l)	5.10 ± 0.05	4.90 ± 0.13	5.50 ± 0.04	5.50 ± 0.11
HDL cholesterol(mmol/l)	1.25 ± 0.02	1.20 ± 0.04	1.35 ± 0.01	1.35 ± 0.03
Physically active on leisure time(%)	25	16	14	19
Smoking(%)	47	52	4	6

Means±SEM or frequencies

Glucose Intolerance: impaired glucose tolerance and diabetes by the 1998 World Health Organization criteria

**: $p<0.01$, *: $p<0.05$ vs Normal

Effect of dietary factors on glucose intolerance

The age-adjusted mean values of baseline energy ratios of major nutrients and energy-adjusted nutrition intake in relation to sex and glucose tolerance status at the end of the follow-up period are depicted in Table 2. In males, subjects with future GI had slightly higher total energy intake and lower energy ratio of carbohydrates than did normal subjects. The amount of complex carbohydrate intake was slightly lower, but that of dietary cholesterol and ethanol intake was higher in the GI male subjects than in normal subjects; the difference in the amount of ethanol intake was statistically significant (26.7 vs. 15.7 g, $p<0.05$). The GI females had slightly but significantly higher mean values of the polyunsaturated/saturated fatty acids (P/S) ratio (1.42 vs. 1.31, $p<0.05$). The average amounts of other nutrients were not significantly different between GI and normal subjects of either sex.

Table 3 compares the age-adjusted mean values of changes in the energy ratio of major nutrients and energy-adjusted nutrition intake from 1988 to 1993/1994 between the groups. There was no difference in changes in the total energy intake and the energy ratios of major nutrients in either sex. The amount of protein intake increased more in the male subjects who developed GI than in those who did not (albeit to marginally significant, $p<0.1$). For females, the amount of animal fat less decreased in the GI group than in the normal group (-0.1 g vs. -1.7g), resulting in a significantly decreased P/S ratio in the GI subjects compared with normal subjects (-0.09 vs. 0.05, $p<0.05$). None of the other nutrients, i.e., carbohydrates, dietary fibers, cholesterol, or ethanol, showed any significant changes.

Independent risk factors for glucose intolerance

In order to examine the net effect of risk factors on the development of GI, we performed multiple logistic regression analyses (Table 4) using the marginally significant and significant nutrition intake and non-dietary risk factors such as age, fasting serum insulin, physical activity, body mass index, and smoking habits in each sex. Ethanol intake remained a significant independent risk factor for the development of GI in males (odds ratio for an increase of 10 g, 1.19; 95% confidence interval, 1.08-1.33), while the decreased P/S ratio during the follow-up period was an independent risk factor in females (odds ratio for an increase of 0.1, 0.94; 95% confidence interval, 0.90-0.99). Among non-dietary factors, fasting serum insulin was found to be an independent risk factor for GI in both sexes, and age was an additional risk factor in females.

Table 2. Age-adjusted mean values (95% confidence intervals) of baseline energy ratio of major nutrients and nutritional elements by sex and glucose tolerance status.

Nutrient	Males				Females			
	Normal n=352		Glucose Intolerance n=58		Normal n=580		Glucose Intolerance n=85	
Energy (kcal)	1947	(1903, 1990)	2048	(1941, 2155) †	1598	(1574, 1621)	1581	(1519, 1644)
Protein (% energy)	12.7	(12.5, 13.0)	12.4	(11.9, 13.0)	13.5	(13.4, 13.7)	13.7	(13.3, 14.1)
Total fat (% energy)	24.2	(23.6, 24.7)	23.2	(21.8, 24.5)	27.9	(27.5, 28.4)	28.3	(27.2, 29.4)
Carbohydrates (% energy)	54.9	(54.1, 55.7)	52.9	(50.9, 54.9) †	55.6	(55.1, 56.1)	55.4	(54.0, 56.7)
Protein (g)	54.9	(53.7, 56.1)	52.8	(49.8, 55.8)	58.6	(57.9, 59.3)	59.4	(57.7, 61.2)
Animal protein (g)	21.2	(20.2, 22.2)	22.0	(19.5, 24.5)	21.6	(21.1-22.2)	21.2	(19.8, 22.6)
Total fat (g)	46.7	(45.5, 48.0)	44.8	(41.8, 47.9)	52.9	(52.1, 53.7)	53.5	(51.4, 55.6)
Animal fat (g)	16.4	(15.5, 17.2)	15.3	(13.2, 17.4)	17.8	(17.2, 18.4)	16.4	(14.7, 18.0)
Polyunsaturated fatty acids (g)	15.2	(14.6, 15.8)	14.4	(12.9, 15.8)	17.7	(17.3, 18.1)	18.5	(17.5, 19.5)
Monounsaturated fatty acids (g)	18.7	(18.2, 19.1)	18.5	(17.4, 19.5)	20.7	(20.3, 21.0)	20.9	(20.1, 21.7)
Saturated fatty acids (g)	12.4	(12.0, 12.8)	11.6	(10.6, 12.6)	14.0	(13.7, 14.3)	13.6	(12.8, 14.3)
P/S ratio	1.31	(1.26, 1.36)	1.36	(1.24, 1.48)	1.31	(1.27, 1.35)	1.42	(1.32, 1.51)**
Carbohydrates (g)	239.6	(235.4, 243.8)	231.0	(220.6, 241.3)	237.0	(234.8, 239.2)	236.0	(229.7, 241.3)
Simple (g)	34.7	(32.2, 37.1)	35.8	(29.8, 41.8)	38.0	(36.5, 39.5)	38.8	(34.8, 42.7)
Complex (g)	204.9	(200.7, 209.2)	195.2	(184.7, 205.6) †	199.0	(196.7, 201.3)	196.8	(190.8, 202.8)
Dietary fiber (g)	3.8	(3.7, 3.9)	3.5	(3.2, 3.9)	4.5	(4.4, 4.6)	4.7	(4.4, 5.0)
Dietary cholesterol (mg)	237.4	(226.1, 248.7)	263.9	(236.0, 291.8) †	254.8	(247.9, 261.7)	251.6	(233.5, 269.7)
Ethanol (g)	15.7	(13.2, 18.2)	26.7	(20.4, 33.0)*	5.4	(4.7, 6.2)	5.1	(3.1, 7.1)

Nutritional elements were adjusted for energy intake using the method of Willet and Stampfer.[22]

Glucose Intolerance: impaired glucose tolerance and diabetes by the 1998 World Health Organization criteria

**: $p<0.01$, *: $p<0.05$, †: $p<0.1$ vs Normal

Table 3. Age-adjusted mean values (95% confidence intervals) of changes in energy ratio of major nutrients and amount of nutritional elements from 1988 through 1993/1994 by sex and glucose tolerance status.

Nutrient	Males				Females			
	Normal n=352		Glucose Intolerance n=58		Normal n=580		Glucose Intolerance n=85	
Energy (kcal)	-120	(-160, -79)	-129	(-229, -28)	-54	(-79, -29)	-74	(-141, -8)
Protein (% energy)	0.2	(-0.02, 0.5)	0.7	(0.03, 1.3)	0.4	(0.2, 0.5)	0.5	(0.05, 0.9)
Total fat (% energy)	0.1	(-0.5, 0.6)	0.2	(-1.2, 1.6)	-0.04	(-0.5, 0.4)	-0.03	(-1.2, 1.1)
Carbohydrates (% energy)	-0.5	(-1.2, 0.2)	-0.6	(-2.4, 1.2)	-0.4	(-0.9, 0.1)	-0.5	(-1.8, 0.9)
Protein (g)	0.7	(-1.1, 2.5)	5.2	(0.7, 9.6) †	-2.4	(-3.6, -1.3)	-2.9	(-5.8, 0.01)
Animal protein (g)	1.2	(-0.2, 2.5)	2.0	(-1.2 ,5.2)	0.1	(-0.5, 0.7)	0.3	(-1.4, 1.9)
Total fat (g)	-0.1	(-1.6, 1.4)	1.6	(-2.1, 5.2)	-3.4	(-4.5, -2.3)	-4.1	(-7.0, -1.2)
Animal fat (g)	-0.4	(-1.3, 0.5)	-1.4	(-3.6, 0.9)	-1.7	(-2.4, 1.1)	-0.1	(-1.8, 1.5) †
Polyunsaturated fatty acids (g)	0.02	(-0.7, 0.8)	1.4	(-0.5 ,3.2)	-1.1	(-1.6, -0.6)	-1.7	(-2.4, -1.1)
Monounsaturated fatty acids (g)	-0.04	(-0.6, 0.5)	0.01	(-1.3, 1.3)	-1.2	(-1.6, -0.8)	-2.0	(-3.0, -0.9)
Saturated fatty acids (g)	-0.2	(-0.6, 0.3)	0.2	(-0.9, 1.3)	1.1	(-1.5, 0.8)	-0.4	(-1.3, 0.5)
P/S ratio	0.01	(-0.05, 0.07)	0.05	(-0.1, 0.2)	0.05	(0.01, 0.09)	-0.09	(-0.2, 0.01)*
Carbohydrates (g)	-5.3	(-11.4, 0.8)	-1.7	(-16.7, 13.4)	-17.2	(-20.5, -13.9)	-21.6	(-30.3, 12.9)
Simple (g)	-1.7	(-3.9, 0.6)	-6.3	(-11.9, -0.8)	-2.7	(-4.4, -1.1)	-4.3	(-8.7, 0.06)
Complex (g)	-3.6	(-9.4, 2.2)	4.7	(-9.6, 18.9)	-14.5	(-17.6, -11.4)	-17.3	(-25.4, -9.1)
Dietary fiber (g)	-0.5	(-0.6, -0.3)	-0.07	(-0.5, 0.3)	-0.7	(-0.8, -0.6)	-0.8	(-1.1, -0.5)
Dietary cholesterol (mg)	1.5	(-11.5, 14.5)	-25.7	(-57.8, 6.4)	-16.5	(-24.9, -8.2)	-22.8	(-44.8, -0.9)
Ethanol (g)	0.1	(-1.8, 2.0)	-2.1	(-6.8, 2.6)	-0.5	(-0.8, -0.1)	-0.8	(-1.7, 0.2)

Nutritional elements were adjusted for energy intake using the method of Willet and Stampfer.[22]
Glucose Intolerance: impaired glucose tolerance and diabetes by the 1998 World Health Organization criteria
*: $p<0.05$, †: $p<0.1$ vs Normal

Table 4. Stepwise multiple logistic regression analysis of dietary and non-dietary risk factors for development of glucose intolerance by sex.

Risk Factor	Males		Females	
	Odds ratio	95%CI	Odds ratio	95%CI
Ethanol intake (10 g)	1.19	1.08 - 1.33**		
Dietary cholesterol (10 mg)	1.02	0.99 - 1.04 †		
Total energy (1kcal)	NS			
Complex carbohydrates (1g)	NS			
P/S ratio (0.1)			NS	
Change in P/S ratio (0.1)			0.94	0.90 - 0.99*
Change in animal fat (1g)			NS	
Change in protein (1g)	NS			
Age (10 years)	NS		1.68	1.28 - 2.20**
Fasting insulin (1 logarithm)	2.51	1.24 - 4.70**	1.88	1.07 - 3.28*
Physically active on leisure time (yes)	0.50	0.22 - 1.12 †	NS	
Body mass index (1kg/m²)	NS		NS	
Smoking (yes)	NS		NS	

Odds ratios represent risk for a difference indicated in parentheses
Blank column: not used in the analysis
CI: confidence interval
NS: not stayed in the final model due to $p \geq 1.0$
**: $p<0.01$, *: $p<0.05$, †: $p<0.1$

DISCUSSION

Importance of dietary factors

The present study revealed that, among dietary factors, baseline ethanol intake was significantly associated with the development of GI in males, while the decreased P/S ratio during the follow-up was a significant risk factor for GI in females. These associations remained significant even after controlling for other dietary and non-dietary factors such as age, body mass index, serum insulin, smoking and physical activity. Since most of our GI cases consisted of subjects with IGT, these nutrients were considered to be risk factors for the initiation of glucose abnormalities.

The males and females who developed GI had hallmarks of the metabolic syndrome such as concomitant increases in body mass index, blood pressures, triglycerides, serum insulin, and fasting glucose (Table 1). Insulin resistance was a central feature of the metabolic syndrome, and our previous study has identified insulin resistance as the major cause of GI in this population,[25] which may reflect a genetic predisposition to GI. In our subjects, however, dietary factors such as alcohol consumption and decreased P/S ratio were significant risk factors for the development of GI independent of metabolic syndrome. These findings support the concept that GI develops on the basis of an interaction between hereditary and environmental factors, and offer evidence that dietary intake, one of the most important environment factors, plays a crucial role in the development of GI in contemporary Japanese.

Dietary lipid and glucose intolerance

In the female subjects in the present study, the intake of animal fat less decreased in the GI group compared with the group of normal subjects, leading to a significant decrease in the P/S ratio in the former group. Several cross-sectional studies have indicated close associations of an increased intake of animal fat and saturated fatty acids with insulin resistance and hyperinsulinemia,[6,11] which play a fundamental role in the development of GI. Our data are consistent with these findings and suggest that an increased consumption of animal fat has a major causative effect on the development of GI in Japanese.

Among the females in the present study, the baseline P/S ratio was significantly higher in the GI subjects than in the normal subjects, suggesting that the former might initially have a more healthy diet than did the latter. In addition, none of the dietary factors, with the exception of baseline alcohol consumption, were risk factors for the development of GI in the male subjects. We did not give the participants systematic advice on diet, and the majority of the subjects with later developed GI who were all normal at baseline were considered to not be aware of their own decreased glucose tolerance status until the follow-up OGTT. Since the GI subjects included more persons with obesity, hypertension and hyperlipidemia (Table 1), they may have been more inclined to maintain a healthy diet at baseline and during the follow-up period. In females, however, the dietary pattern was reversed between the two groups during the follow-up period. Although the reason for this sex difference is not evident, one possibility is that females, because they are more likely to prefer to confectionery enriched with animal fat such as dairy product, might be difficult to maintain a healthy diet for a long time.

Westernization of dietary habits and glucose intolerance

There have been several reports suggesting that the Japanese may have an inherent risk of diabetes,[4,5] and also that the westernization- associated changes in environmental factors, especially dietary, may increase this risk. In a study comparing Japanese migrants and their offspring in Hawaii and Japanese living in Hiroshima, Kawate et al.[4] have indicated that the prevalence of diabetes among Japanese-Americans is 1.8 times higher than that among native Japanese. In this study, no difference in total energy intake was observed between the two groups, but the consumption of animal fat and simple carbohydrates was at least twice as high among Japanese-Americans. In contrast, Japanese in Hiroshima consumed about twice the amount of complex carbohydrates as Japanese in Hawaii. These observations support the hypothesis that a high-fat, high-simple carbohydrate, and low-complex carbohydrate diet increases the risk of diabetes, especially in Japanese. These findings are in accord with the recent trends in dietary style[26] and the increasing prevalence of diabetes in our country,[2,18,27] implying that the risk of diabetes may increase still further in the future: if the westernization of the Japanese lifestyle, including dietary intake, also continues to advance.

Alcohol and glucose intolerance

Among the males in the present study, baseline alcohol consumption was identified as a risk factor for future GI. However, this association could not be found in females, since the majority of female subjects did not consume alcoholic beverages or consumed only small amounts of alcohol. Recently, several cross-sectional epidemiologic studies have indicated the possibility that a small amount of alcohol intake reduces hyperinsulinemia, and thus that low doses of alcohol have a protective effect against insulin resistance and subsequent diabetes.[28,29] On the other hand, a dose-response relationship between an alcohol intake of eight drinks per day and postloading blood glucose level has been shown in a cross-sectional survey of a large Kaiser-Permanente cohort in the United State.[30] Our previous prevalence study also showed a significant association of alcohol intake with diabetes.[25] Yki-Jävinen et al.[31] have demonstrated in a clinical study using the euglycemic insulin clamp technique that moderate to high alcohol intake increases insulin resistance and reduces glucose metabolism. It has also been reported that alcohol intake increases the levels of diols in blood, an intermediate of alcohol metabolism, which powerfully suppresses the insulin action on fat tissue.[32] These previous and our present findings provide evidence that alcohol intake is closely related to the development of GI.

Limitation

First, it is probable that some heavy drinkers among our subjects underreported their alcohol intake. However, the findings of our study do not seem to be results of this under-reporting, since all subjects were of normal glucose tolerance at baseline, and under-reporting is considered to have occurred randomly in both groups irrespective of future glucose tolerance status. Second, the information regarding nutrient intake was derived from a semi-quantitative food frequency questionnaire that asked about average intake over the previous year. The limitations of this method are well known,[33] and random measurement error is likely to have contributed a bias toward a finding of no effect. Therefore, the estimates of effect that we have found are probably conservative. Third, our results might be biased by exclusion of subjects who did not return for the follow-up examination. At baseline, male subjects with missing values for follow-up were younger than those who were followed up (53.8 vs. 55.3 years, p=0.001, in males; 54.9 vs. 54.6 years, p=0.74, in females). In females, subjects without follow-up examination had a lower mean value of baseline body mass index (22.4 vs. 22.9 kg/m^2, p=0.02) and a higher mean value of systolic blood pressure (128 vs. 126 mmHg, p=0.04) than others, but such differences were not observed in males. In regard to dietary factors, baseline energy intake was lower in subjects without follow-up examination than in those with follow-up examination for both sexes (1880 vs. 1965 kcal, p=0.01, in males; 1523 vs. 1595 kcal, p=0.007, in females). Males without follow-up examination had lower intake of carbohydrates compared with those with follow-up examination (228.5 vs. 236.4 g, p=0.01), while females without follow-up examination had lower intake of protein (56.2 vs. 58.0 g, p=0.02). However, these facts make it unlikely that this selection bias invalidates the findings of the present study.

Conclusion

The results show that, in addition to fasting insulin, nutritional factors also predict the development of GI. A decreased P/S ratio is an independent risk factor for GI in females, as is alcohol intake in males. For the primary prevention of diabetes, of which the occurrence has increased steeply in Japan, it is important to restrict the westernization of dietary habits in addition to decreasing the incidence of both a sedentary lifestyle and obesity.

ACKNOWLEDGEMENTS

The authors thank the residents of Hisayama for their participation in the survey and the staff of the division of Health and Welfare of Hisayama for their cooperation in this study.

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Ten-Year Prognosis of Stroke and Risk Factors for Death in a Japanese Community

The Hisayama Study

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Background and Purpose—There have been very few population-based cohort studies of long-term prognosis and risk factors for death after stroke. We examined the 10-year prognosis, causes, and risk factors of death after stroke in a Japanese cohort.

Methods—During a 26-year follow-up of a cohort of 1621 subjects ≥40 years of age, 333 subjects developed first-ever stroke and were prospectively followed up for 10 years after onset. During these 10-year follow-up periods, 268 of the 333 stroke patients died. Of those, 239 (89.2%) underwent autopsy.

Results—The risk of death was greatest in the first year after first-stroke onset in both sexes (men, 40.3%; women, 43.7%). Thereafter, the survival curves decreased gradually, and risk of death reached 80.7% for men and 80.2% for women by the end of the 10-year follow-up. The 30-day case fatality rate was substantially greater in patients with cerebral hemorrhage (63.3%) or subarachnoid hemorrhage (58.6%) than in patients with cerebral infarction (9.0%). The risk of dying after the first stroke was twice the risk for stroke-free subjects. The most common cause of death was the index stroke in the first year. Thereafter, the impact of the first stroke gradually decreased, while that of recurrent stroke increased. Multivariate analysis revealed that age, lower body mass index, and hemorrhagic stroke were significant risk factors for death after stroke.

Conclusions—Our findings suggest that the risk of death after first-ever stroke is high, in part because of the larger proportion of hemorrhagic stroke in Japanese relative to stroke victims in Western countries. (***Stroke.*** **2003;34:2343-2348.)**

Key Words: cause of death ■ cohort studies ■ risk factors ■ stroke ■ survival

In Japan, stroke is the third-leading cause of death.[1] Stroke is also a major cause of disability[2] and cognitive dysfunction in the elderly.[3,4] Because the elderly population in Japan has been increasing rapidly, stroke-related problems in Japanese health care have become important in recent years. Information on the risk of death after stroke and on stroke predictors would be helpful in coping with these problems. Although the literature concerning fatal prognosis after stroke is extensive, most studies are based on selected series of patients referred to a hospital.[5–9] Such patients are often not representative of all stroke cases, because patients with the most severe stroke die quickly, before reaching the hospital, and patients with mild stroke may not go to the hospital at all. A prospective study of a defined population can clearly assess this problem, but very few population-based cohort studies have been able to define accurately the pathological type of stroke and evaluate its long-term prognosis.[10–12]

Since 1961, we have been carrying out a prospective cohort study of cardiovascular disease in the town of Hisayama, Japan.[13,14] The most outstanding features of this study are that causes of death were verified by autopsy and that brain lesions of most stroke patients were examined morphologically during autopsy or by brain imaging such as CT and MRI. The purposes of this study are to determine the 10-year survival rate after first-ever stroke in the community of Hisayama; to compare the observed risks of death after first-ever stroke with those of age- and sex-matched stroke-free subjects selected from the same community; to determine the major causes of death during different time periods up to 10 years after a stroke; and to determine risk factors for death during this period.

See Editorial Comment, page 2347

Subjects and Methods

Follow-Up Survey

Hisayama is a suburb of Fukuoka on Kyushu Island in southern Japan. In 1961, a total of 1621 men and women ≥40 years of age

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who had never suffered a stroke were recruited from the residents (88.1% of the total population of this age range) as a cohort. These subjects were then followed up for 26 years, until 1987. A detailed description of the study methods was published previously.[12–14] Briefly, we collected information about new cardiovascular events through a daily monitoring system established by the study team, local practitioners, and the town government. When we suspected new neurological symptoms, the study physicians carefully evaluated the subject and tried to obtain information by further diagnostic examination, including lumbar puncture, cerebral angiography, or recent brain CT or MRI. During the 26-year study period, only 2 subjects were lost to follow-up, and 852 subjects died. Of those who died, 704 (82.6%) underwent autopsy examination.

Stroke Cases and Controls

Stroke, defined as a sudden onset of a nonconvulsive and focal neurological deficit persisting for >24 hours, was classified as cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type.[14,15] The diagnosis of stroke and determination of its pathological type were based on clinical history, neurological examination, all available clinical data (including brain CT or MRI), and autopsy findings. During follow-up, we identified 340 new stroke events and divided them into 244 cases of cerebral infarction (120 men, 124 women), 60 cases of cerebral hemorrhage (40 men, 20 women), 29 cases of subarachnoid hemorrhage (6 men, 23 women), and 7 cases of undetermined type (3 men, 4 women). After exclusion of the 7 cases of undetermined type, 333 were enrolled in the study (166 men, 167 women; mean age, 73±10 years; range, 46 to 97 years). As a reference group, we randomly selected individuals free from stroke at baseline among residents of Hisayama who participated in health checkups in 1973 or 1974, which was the middle of the study period. Each stroke case had 2 sex- and age-matched (±2 years) controls. The reference group consisted of 666 individuals (332 men, 334 women; mean age, 72±8 years; range, 46 to 97 years).

Follow-Up

We followed up the stroke patients from the onset of the stroke until death or 1997 and the reference group for 10 years from 1973 or 1974 to 1983 or 1985. No cases or controls were lost to follow-up.

During the 10-year follow-up, 268 of the 333 stroke patients died; of them, 239 (89.2%) underwent autopsy examination. We reviewed all the available clinical information and interviewed the attending physicians and the families of the deceased subjects. For each individual, the underlying disease was chosen as the cause of death. Diseases linked to the underlying cause of death were classified into the following 4 categories established in the Oxfordshire Community Stroke Project.[7] First-stroke deaths were due to the direct effects of a brain lesion or to complications of immobility resulting from the first stroke. These included deaths from bronchopneumonia even years after the stroke if stroke-related impairments were thought to be in some way responsible and there was no other, more likely, cause of death. Recurrent stroke deaths were attributed directly to brain lesions or complications of immobility after a recurrent stroke (ie, with symptoms that led to early death and were associated with an increase in disability). If a death from stroke-related impairments occurred after a recurrent stroke, it was attributed to the recurrent stroke rather than the first stroke. Cardiovascular deaths were due to definite or probable cardiac causes, ruptured aortic aneurysms, or peripheral vascular disease. Sudden deaths were regarded as cardiovascular unless an alternative explanation was found at autopsy. Nonvascular deaths were those unrelated to any stroke disability and clearly were due to a nonvascular cause, eg, cancer, bronchopneumonia, accidents, or suicide.

Risk Factors for Death

To elucidate the risk factors for death in stroke cases, we collected the following data from the regular health checks performed within 2 years before the onset of stroke: age at onset; sex; alcohol consumption; smoking habits; glucose intolerance; average of 3 systolic and diastolic blood pressures; hypertension (≥140/90 mm Hg or use of antihypertensive agents); body mass index; abnormal ECG findings, including left ventricular hypertrophy (Minnesota code 3-1) and/or ST depression (Minnesota code 4-1, 4-2, 4-3); atrial fibrillation (Minnesota code 8- 3); and serum total cholesterol. The categories used in the definition of glucose intolerance were described in a previous report.[16]

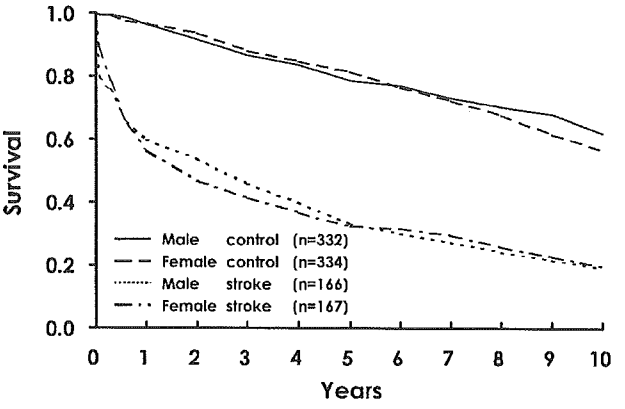

Figure 1. Kaplan-Meier survival curves by sex showing probability of survival after first-ever stroke vs a reference group free from stroke at baseline.

Statistical Analysis

SAS software (version 6.12) was used for the statistical analysis. Survival curves within the 10 years were calculated with the Kaplan-Meier product limit technique. The odds ratio and 95% confidence intervals (CIs) for stroke cases compared with reference subjects were calculated by the χ^2 test. We estimated the age-adjusted and multivariate relative risk (RR) of each potential risk factor for death by using the β coefficients available in the Cox proportional-hazards analysis.

Results

Absolute Risks for All Patients

Figure 1 shows Kaplan-Meier survival curves by sex for all 333 stroke patients. To similar degrees in both sexes, the risk of death was greatest in the first year (men: 40.3%; 95% CI, 32.9 to 47.8; women: 43.7%; 95% CI, 36.1 to 51.2) and particularly during the first 30 days after stroke (men: 24.7%; 95% CI, 18.1 to 31.3; women: 21.6%; 95% CI, 15.3 to 27.8%). Beyond the first year, the survival curves for the patients decreased similarly to those for reference subjects in both sexes. The risk of death reached 66.9% (95% CI, 59.7 to 74.0) for men and 67.7% (95% CI, 60.6 to 74.8) for women up to 5 years and 80.7% (95% CI, 14.9 to 27.2) and 80.2% (95% CI, 74.2 to 86.3) up to 10 years, respectively.

Absolute Risks for Subgroups

Stratification by age showed that patients <65 years of age had a worse prognosis during the early period after stroke than did older patients (Figure 2). Among other age groups, the risk of death increased the older the patient was, regardless of the poststroke period. The survival curves comparing prognoses among the different pathological types of stroke are shown in Figure 3. The fatality rate during the early period was substantially greater for patients with hemorrhagic stroke (cerebral hemorrhage: 63.3%; 95% CI, 51.1 to 75.5; subarachnoid hemorrhage: 58.6%; 95% CI, 40.7 to 76.5) than

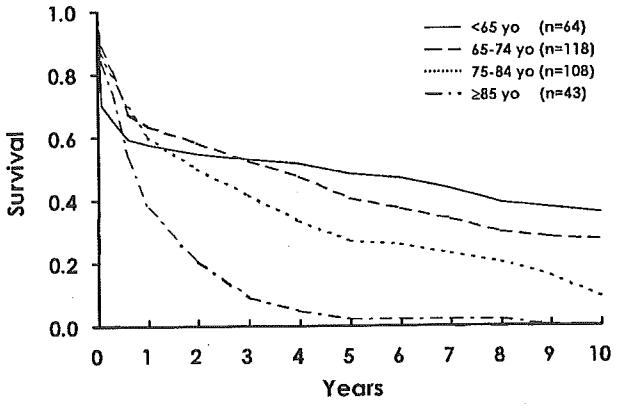

Figure 2. Kaplan-Meier survival curves stratified by age at onset showing probability of survival during 10 years of follow-up in patients with first-ever stroke.

for patients with cerebral infarction (9.0%; 95% CI, 5.4 to 12.6).

RR Compared With Controls

The risk of dying after first stroke was twice that of reference subjects (Table 1). In the first year after stroke, patients had a 12-fold RR of death, which declined to 2- or 3-fold over the subsequent years up to 5 years and to 1.6-fold in the next 5 years. Patients who survived at least 30 days had a 1.9-fold higher risk of dying over the next 10 years than reference subjects.

Cause of Death

A histogram of causes of death during different time intervals from the onset of first-ever stroke is shown in Figure 4. During the first 30 days after first stroke, 83.1% of deaths were due to the direct neurological effects of the index stroke, and another 6.5% and 2.6% were due to recurrent stroke and other cardiovascular diseases, respectively. Thereafter, the frequency of first stroke gradually decreased, whereas that of recurrent stroke increased. Over the 10-year follow-up, 41.0% of deaths were due to first stroke and 21.6% to recurrent stroke. Only 5.6% of deaths were due to other cardiovascular causes.

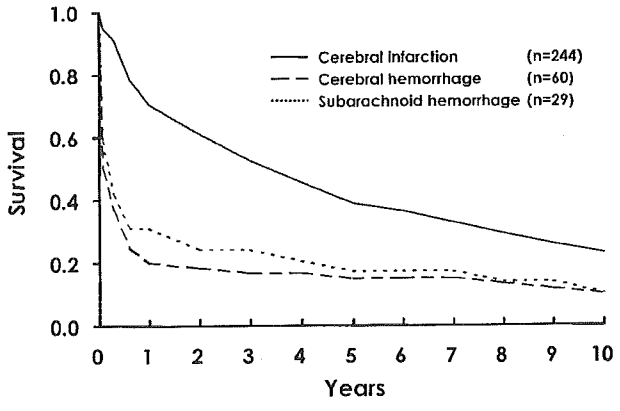

Figure 3. Kaplan-Meier survival curves stratified by pathological type of stroke showing probability of survival during 10 years of follow-up in patients with first-ever stroke.

TABLE 1. Odds Ratios of Death After a First-Ever Stroke During Different Time Intervals From Stroke Onset Compared With Controls

	CVA Cases, n		Controls, n			
Interval	At Risk	Deaths	At Risk	Deaths	Odds Ratio	95% CI
0–1 y	333	140	666	23	12.17	7.99–18.55
1–2 y	193	26	643	26	3.33	1.98–5.60
2–3 y	167	27	617	35	2.32	1.40–3.85
3–4 y	145	18	582	21	3.44	1.88–6.29
4–5 y	127	18	561	28	2.84	1.62–4.97
5–10 y	109	44	533	138	1.56	1.19–2.04
30 d–10 y	256	191	662	267	1.85	1.65–2.08
All intervals	333	268	666	271	1.98	1.78–2.20

CVA indicates cerebrovascular accident.

Risk Factors for Death Over 10 Years

Table 2 shows the multivariate prediction model for death 10 years after first-ever stroke among the 333 patients and the 244 patients diagnosed with cerebral infarction using baseline risk factors that appeared to be significant in the univariate analysis. The significant prognostic factors for death among stroke patients were age (RR for a 10-year increment, 1.55; 95% CI, 1.34 to 1.79), body mass index (RR, 0.95; 95% CI, 0.91 to 0.98), and hemorrhagic stroke, including cerebral hemorrhage and subarachnoid hemorrhage (RR, 2.84; 95% CI, 2.17 to 3.72). Among patients with cerebral infarction, significant predictors of death were age (RR, 2.03; 95% CI, 1.87 to 2.45), body mass index (RR, 0.91; 95% CI, 0.85 to 0.95), hypertension (RR, 1.57; 95% CI, 1.14 to 2.17), and atrial fibrillation (RR, 1.62; 95% CI, 1.11 to 2.36).

Discussion

The strengths of our study are that it is community based and includes almost all stroke cases developed in a cohort, thus eliminating the bias of case selection encountered in clinical series of hospital cases; a large proportion of the stroke patients underwent CT or MRI examination or autopsy to determine the pathological type; an autopsy was performed in almost 90% of deceased patients; and RRs and absolute risks of death were estimated up to 10 years after first-ever stroke.

Long-Term Prognosis

In our study, the 5-year risk of death after first stroke was 67% for men and 68% for women, exceeding the 40% to 54% rates reported in previous community-based studies.[6–8,10] The higher fatality rates of our stroke patients are attributed to the older age of our subjects and the larger proportion (26%) of hemorrhagic stroke. These findings were similar to those of a previous study performed in another part of Japan.[11] In particular, our patients with subarachnoid hemorrhage showed a higher fatality rate (59%) in the early period compared with other studies in which the risks were 37% to 46%.[6–8,10] This can be explained partly by the fact that we identified almost all instantaneous or sudden deaths by subarachnoid hemorrhage, even in cases lacking a correct diagnosis before death, because autopsies were performed in 83% of the deaths among our inception cohort.

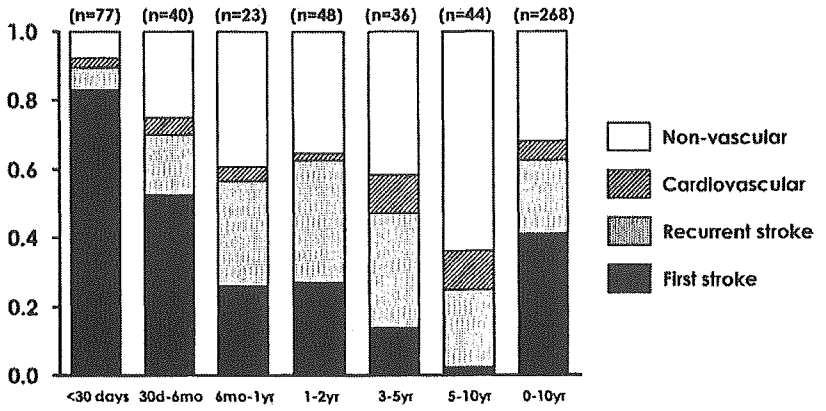

Figure 4. Histogram showing the proportion of patients dying from different causes during different time intervals from onset of index stroke.

Cause of Death

Our data confirm that the RR of death in the year after first-ever stroke for which the index stroke is mainly responsible is very high (odds ratio, 12.2; 95% CI, 7.99 to 18.55), and patients continue to die with a 2- to 3-fold excess risk in subsequent years up to 10 years. These late deaths are not due mainly to the index stroke but to recurrent stroke. Compared with Western populations,[7,8] our subjects are characterized by a relatively small proportion of other cardiovascular events among causes of death during the late period after stroke. This probably reflects the lower risk of atherosclerotic diseases such as coronary heart and peripheral vascular diseases in Japanese.

Risk Factor for Death

As in previous studies,[7,8,11] we found that advanced age was associated with a greater risk of death in the long-term period after stroke. This suggests that older patients may have more advanced underlying diseases. Meanwhile, in our subjects, the risk of death during the early period was worse in younger patients (<65 years of age) than in older patients. This phenomenon was attributed to a larger proportion of hemorrhagic stroke in this younger age group than among older patients.

In our study, the survival curves of hemorrhagic stroke dropped rapidly during the course of the first year after index stroke, particularly during the early period, and almost reached a plateau during the period after 1 year, whereas during the 10 years overall, the risk of dying from hemorrhagic stroke was 2.8-fold higher than the risk of dying from cerebral infarction. These findings imply that the risk of death from hemorrhagic stroke was determined in the acute period but that its adverse effect on fatal prognosis remained for the full 10-year follow-up period.

TABLE 2. Final Multivariate Analysis of Risk Factors at Baseline for Death After First-Ever Stroke During the 10-Year Follow-Up Period

	All Stroke		Cerebral Infarction	
Variable	RR	95% CI	RR	95% CI
Age (10 y)	1.55*	1.34–1.79	2.03*	1.87–2.45
Body mass index (1 kg/m^2)	0.95*	0.91–0.98	0.91*	0.86–0.95
Hemorrhagic stroke	2.84*	2.17–3.72	NI	
Hypertension	NI		1.57*	1.14–2.17
Atrial fibrillation	NI		1.62†	1.11–2.36

NI indicates not included in the model.
*P<0.01; †P<0.05.

There are conflicting reports of the impact of hypertension on survival after stroke.[8–11,17,18] In most of those reports,[8,9,17] blood pressure was taken after the stroke; thus, the measurements may have been influenced by the acute event and thereby may be difficult to evaluate accurately. As in our study, prospective cohort studies in Framingham (Mass)[10] and Manitoba (Canada)[18] demonstrated a significant association between hypertension before stroke and increased risk of subsequent death.

Among our subjects, lower body mass index was a significant risk factor for death among patients with cerebral infarction and among total stroke patients. Our previous study showed that low body mass index was a risk factor for death from pneumonia in the elderly.[19] Thus, being lean may reflect insufficient nourishment and decreased resistance to bacterial infection. Several previous reports have indicated excess mortality rates from cardiovascular disease among lean hypertensive subjects.[20–22] Lean hypertensive individuals tend to have more severe end-organ damage[20] and may suffer from higher peripheral vascular resistance than those who are obese[21] and may well carry stronger genetic determinants of cardiovascular disease than obese hypertensive subjects.[22]

Arial fibrillation was another independent risk factor for death among our patients with cerebral infarction, as in other population-based studies.[17,23] Atrial fibrillation often induces congestive heart failure and cerebral embolism, leading to early death.

Study Limitations

There are several potential limitations to the findings in our study. First, we collected stroke cases that developed among an inception cohort during 26 years of follow-up. Thus, their prognoses may have changed during the long-term observation period. Secular trends in the prognosis of stroke patients should be taken into account, and we will do so in another study. Second, the severity of the index stroke was not taken into account in the evaluation of risk factors for fatality. Thus, our estimates of the effects of risk factors are probably conservative. Finally, we could not provide information on