ONLINE SUPPLEMENT

Title: Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama Study

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Short Title: Late-life and midlife blood pressure and dementia

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EXPANDED MATERIALS AND METHODS

Follow-up survey

The subjects were followed up prospectively for 17 years, from December 1988 to November 2005. Details about the follow-up survey on dementia have been described elsewhere.[1,2] Briefly, we established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office.[3] Regular health checks were given annually to obtain information on any stroke or dementia missed by the monitoring network. Health status was also checked yearly by mail or telephone for any subject who did not undergo regular examinations or who had moved out of town. Additionally, comprehensive surveys of cognitive function including neuropsychological tests (Hasegawa's dementia scale [HDS],[4] its revised version [HDS-R],[5] and the Mini-Mental State Examination [MMSE][6]) were conducted in 1985, 1992, 1998, and 2005. All the participation rates of these surveys were more than 90% of the total population aged 65 years or more. The examination was performed in the public hall of Hisayama town or in their home. The study physicians also visited the hospital or health care facilities for examining hospitalized people.

Diagnosis of dementia

Because the neuropsychological tests were likely to cause the over-diagnosis of cognitive impairment by the several factors (e.g. low education, hearing loss, etc.)[7], we performed two-step procedures on the diagnosis of dementia.[1,2] First, the neuropsychological tests were performed by trained nurses or physicians. When the test scores were below the cut-off points (22/32.5 for HDS,[4] 21/30 for the HDS-R[5] and MMSE[6]) or new neurological symptoms including cognitive impairment were suspected, the subject was carefully evaluated by the study physician and psychiatrist, who conducted comprehensive investigations including interviews of the family or attending physician, physical and neurological examinations, and a review of the clinical records. Diagnoses of dementia and its subtypes were based on the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition,[8] the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,[9] and the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences[10] Every dementia case was adjudicated by expert neurologists and psychiatrists. Possible or probable dementia subtypes were diagnosed with clinical information including neuroimaging. Definite dementia subtypes were also determined on the basis of clinical and neuropathological information in deceased dementia subjects who underwent autopsy. The diagnostic procedure for autopsy cases has been reported previously.[11] A neuropathological diagnosis of AD was made following the National Institute on Aging–Reagan Institute criteria,[12] where the frequencies of senile plaques and neurofibrillary tangles were evaluated using the criteria of the Consortium to Establish a Registry for Alzheimer's Disease[13] and the Braak stage.[14] Definite VD cases were confirmed with causative stroke or cerebrovascular change.

Other risk factors

At the baseline examination, each participant completed a self-administered questionnaire covering educational status, medical history, anti-hypertensive treatment, smoking habits, and alcohol consumption. Educational status was categorized as ≤6 year, 7-9 years, and ≥10 years. Because only 45 subjects had an academic background of ≥12 years, of which 10 subjects attended university, these subjects were included in the category of ≥10 years. Smoking habits and alcohol consumption were classified as either current use or not. History of stroke was determined as preexisting a sudden onset of nonconvulsive and focal neurological deficit

persisting for >24 hours on the basis of all available clinical data including medical records, neurological examination, and brain imaging. Body height and weight were measured in light clothing without shoes, and body mass index (kg/m^2) was calculated. Diabetes was defined by fasting glucose concentrations ≥ 7.0 mmol/L), postprandial glucose concentrations ≥ 11.1 mmol/L, and/or medical history of diabetes in 1973-1974, and by the criteria of the American Diabetes Association[15] for subjects undergoing a 75-g oral glucose tolerance test or the foregoing definition for subjects not undergoing the tolerance test in 1988. Chronic kidney disease was defined as estimated glomerular filtration rate of <60 ml/min/1.73 m^2, which was calculated using the 3-variable equation, proposed by the Japanese Society of Nephrology.[16] Serum total cholesterol levels were measured by the Zurkowski method in 1973-1974 and by the enzymatic method in 1988. The data of serum homocysteine levels was only available in 1988, which were assayed the high-performance liquid chromatography method.

Statistical analysis

The software package SAS (version 9.2, SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. The linear trends in the mean values and the frequencies of risk factors across the blood pressure levels were tested using linear regression analysis and logistic regression analysis, respectively. The incidence rates of dementia were calculated by a person-year method and adjusted for the age and sex distribution of the overall study population using the direct method; the differences among blood pressure levels were tested using the Cox proportional hazards model including age and sex. The age- and sex-adjusted or multivariate-adjusted hazard ratios with 95% confidence intervals of blood pressure levels for the development of dementia were also estimated using the Cox proportional hazards model. The heterogeneity in the relationship between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model. The risk estimates per every 10 mmHg increment in systolic and diastolc blood presure were computed using the relavant Cox model including each variable taken as a continuous variable. Two-sided $p<0.05$ was considered statistically significant in all analyses.

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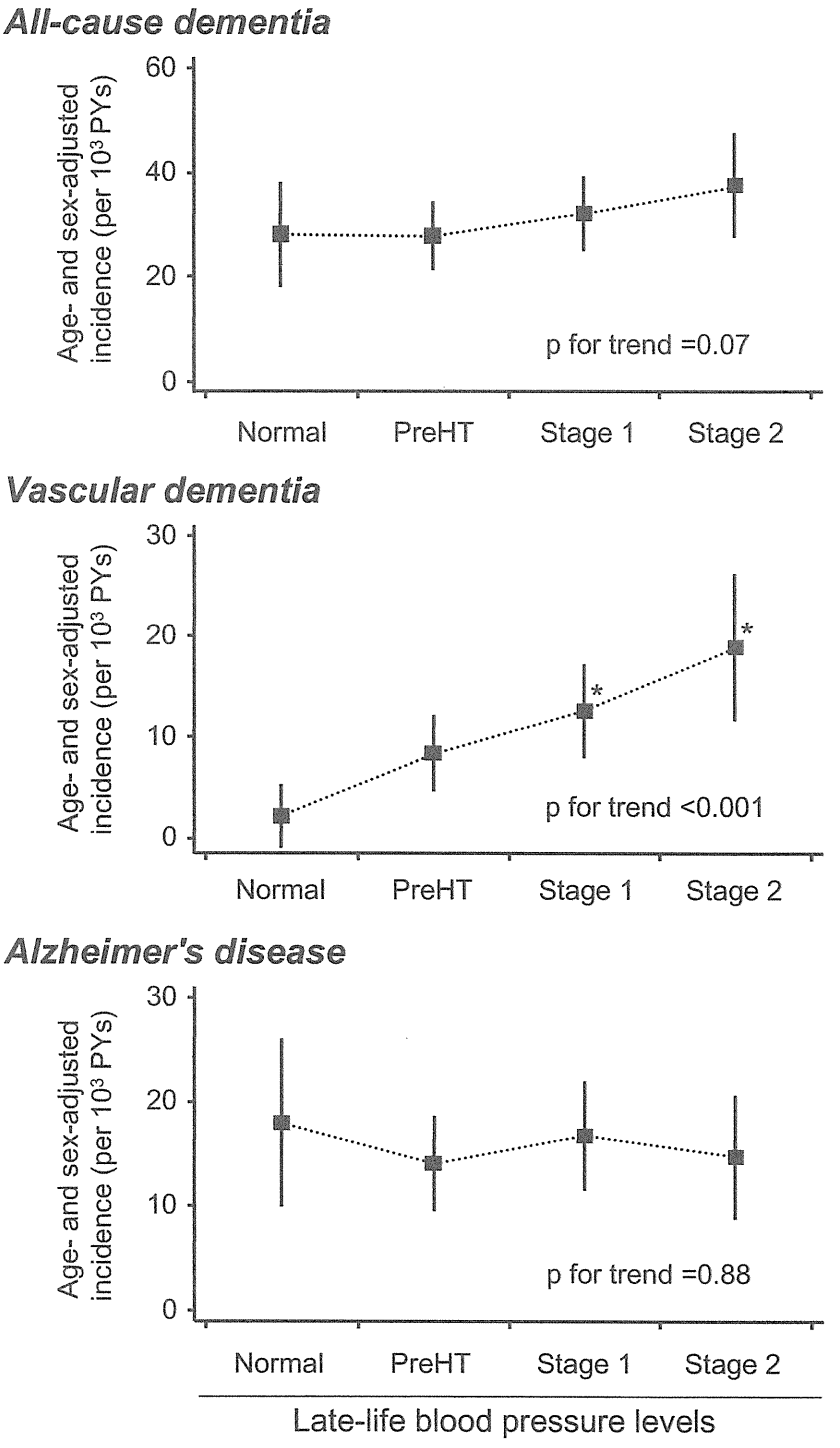

Figure S1: Age- and sex-adjusted incidence rates of dementia and its subtypes according to blood pressure categories in late life

Vertical bars represented 95% confidence intervals of incidence rates.

PreHT, prehypertension; PYs, person-years*p<0.01 vs. normal

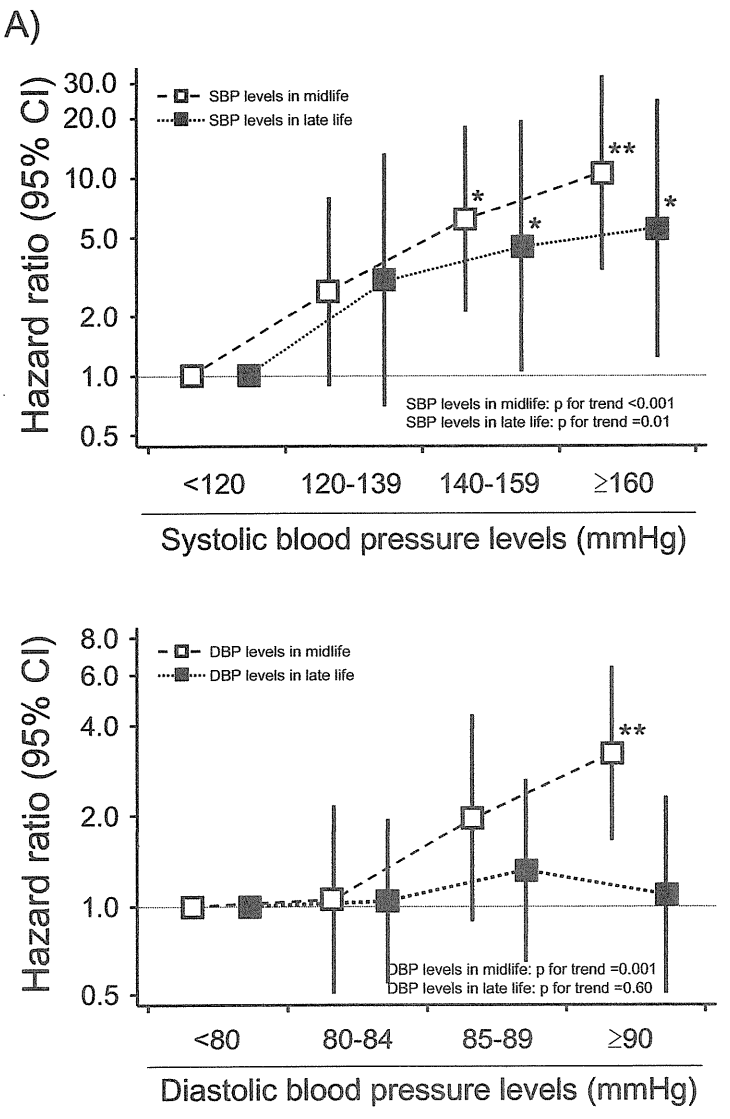

Figure S2: Multivariate-adjusted hazard ratios of vascular dementia according to systolic (A) and diastolic (B) blood pressure levels in midlife and late life
Vertical bars represented 95% confidence intervals of hazard ratios.

The risk estimates were adjusted for potential confounding covariates in midlife or late life : namely, age, sex, education level, use of anti-hypertensive agents, diabetes, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake. CI, confidence interval

*p<0.05, **p<0.01 vs. systolic blood pressure <120 mmHg or diastolic blood pressure <80 mmHg

Table S1: Multivariate-adjusted HRs of late-life and midlife blood pressure levels for late-life onset of dementia determined by autopsy

BP levels defined by JNC-7	Late-life BP				Midlife BP			
	No of events	HR (95% CI)	p	p for trend	No of events	HR (95% CI)	p	p for trend
All-cause dementia								
Normal	14	1.00 (reference)			19	1.00 (reference)		
Prehypertension	40	1.11 (0.58-2.10)	0.76	0.67	26	0.87 (0.48-1.60)	0.66	0.005
Stage1 hypertension	33	0.98 (0.50-1.93)	0.96		42	2.06 (1.15-3.70)	0.01	
Stage2 hypertension	29	1.26 (0.60-2.66)	0.54		16	1.86 (0.91-3.83)	0.09	
Vascular dementia								
Normal	1	1.00 (reference)			4	1.00 (reference)		
Prehypertension	14	4.12 (0.52-32.38)	0.18	0.03	7	1.11 (0.32-3.84)	0.87	<0.001
Stage1 hypertension	17	4.76 (0.61-37.44)	0.14		21	4.86 (1.59-14.85)	0.006	
Stage2 hypertension	19	7.68 (0.94-62.84)	0.06		13	7.05 (2.17-22.88)	0.001	
Alzheimer's disease								
Normal	7	1.00 (reference)			10	1.00 (reference)		
Prehypertension	20	1.36 (0.55-3.37)	0.51	0.92	16	1.03 (0.46-2.32)	0.94	0.87
Stage1 hypertension	13	1.01 (0.38-2.71)	0.98		14	1.37 (0.57-3.31)	0.48	
Stage2 hypertension	10	1.19 (0.39-3.65)	0.76		2	0.49 (0.10-2.38)	0.37	

BP, blood pressure; HR, hazard ratio; CI, confidence interval

The risk estimates were adjusted for potential confounding covariates in midlife or late life: namely, age, sex, education level, use of anti-hypertensive agents, diabetes, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

Endpoints were only definite dementia cases determined by autopsy.

Table S2: Multivariate-adjusted HRs of systolic or diastolic blood pressure levels in late life and midlife for late-life onset of dementia

	Late-life BP						Midlife BP					
BP levels (mmHg)	Median of SBP or DBP (mmHg)	No of events	No of participants	HR (95% CI)	p	HR per 10 mmHg increment in SBP or DBP (95% CI)	Median of SBP or DBP (mmHg)	No of events	No of participants	HR (95% CI)	p	HR per 10 mmHg increment in SBP or DBP (95% CI)
All-cause dementia												
SBP <110	105	15	47	1.06 (0.53-2.12)	0.87		105	17	59	0.85 (0.45-1.62)	0.62	
SBP 110-119	114	18	60	1.00 (reference)			115	22	69	1.00 (reference)		
SBP 120-139	130	72	228	0.88 (0.52-1.49)	0.63	1.06 (1.00-1.13), p=0.06	129	60	193	0.91 (0.55-1.51)	0.72	1.09 (1.03-1.16), p=0.006
SBP 140-159	148	74	198	1.10 (0.64-1.89)	0.73		148	61	140	1.60 (0.96-2.66)	0.07	
SBP ≥160	173	53	135	1.16 (0.64-2.10)	0.62		173	33	73	1.87 (1.05-3.32)	0.03	
p for trend				0.28						<0.001		
DBP <70	63	64	182	0.88 (0.63-1.23)	0.44		64	30	94	0.88 (0.56-1.38)	0.57	
DBP 70-79	74	92	258	1.00 (reference)			74	62	183	1.00 (reference)		
DBP 80-84	82	35	108	0.85 (0.57-1.27)	0.44	1.02 (0.90-1.16), p=0.74	81	42	105	1.27 (0.85-1.91)	0.24	1.20 (1.05-1.36), p=0.008
DBP 85-89	87	17	53	0.83 (0.49-1.41)	0.50		87	18	62	1.12 (0.65-1.92)	0.68	
DBP ≥90	93	24	67	0.99 (0.62-1.59)	0.97		95	41	90	2.29 (1.50-3.51)	<0.001	
p for trend				0.94						<0.001		

Vascular dementia												
SBP <110	105	1	47	1.13 (0.07-18.11)	0.93		105	2	59	1.19 (0.17-8.48)	0.86	
SBP 110-119	114	1	60	1.00 (reference)			115	2	69	1.00 (reference)		
SBP 120-139	130	19	228	3.24 (0.43-24.71)	0.26	1.18 (1.07-1.31), p=0.002	129	17	193	2.94 (0.67-12.95)	0.15	1.24 (1.12-1.37), p<0.001
SBP 140-159	148	29	198	4.81 (0.64-36.34)	0.13		148	24	140	6.82 (1.57-29.58)	0.01	
SBP ≥160	173	26	135	6.00 (0.77-46.95)	0.09		173	18	73	11.68 (2.61-52.22)	0.001	
p for trend				0.01						<0.001		
DBP <70	63	12	182	0.45 (0.22-0.91)	0.03		64	7	94	0.67 (0.27-1.66)	0.39	
DBP 70-79	74	31	258	1.00 (reference)			74	18	183	1.00 (reference)		
DBP 80-84	82	14	108	0.78 (0.4-1.52)	0.46	1.21 (0.98-1.49), p=0.07	81	12	105	0.93 (0.43-2.01)	0.86	1.37 (1.09-1.72), p=0.007
DBP 85-89	87	10	53	0.98 (0.46-2.06)	0.95		87	9	62	1.74 (0.75-4.01)	0.2	
DBP ≥90	93	9	67	0.85 (0.39-1.86)	0.69		95	17	90	2.85 (1.38-5.90)	0.005	
p for trend				0.16						0.001		
Alzheimer's disease												
SBP <110	105	12	47	1.66 (0.71-3.88)	0.24		105	12	59	0.83 (0.39-1.80)	0.65	
SBP 110-119	114	10	60	1.00 (reference)		1.01 (0.92-1.1), p=0.83	115	15	69	1.00 (reference)		1.02 (0.93-1.12), p=0.72
SBP	130	39	228	0.93	0.84		129	34	193	0.72	0.31	

120-139				(0.46-1.89)						(0.39-1.35)		
SBP 140-159	148	39	198	1.22 (0.59-2.53)	0.58		148	29	140	1.13 (0.59-2.17)	0.72	
SBP ≥160	173	23	135	1.06 (0.47-2.40)	0.89		173	12	73	0.99 (0.44-2.23)	0.98	
p for trend				0.91						0.47		
DBP <70	63	40	182	1.06 (0.69-1.65)	0.78		64	18	94	0.91 (0.50-1.63)	0.74	
DBP 70-79	74	51	258	1.00 (reference)			74	36	183	1.00 (reference)		
DBP 80-84	82	15	108	0.70 (0.39-1.26)	0.24	0.88 (0.73-1.06), p=0.18	81	22	105	1.31 (0.76-2.26)	0.33	1.12 (0.93-1.34), p=0.25
DBP 85-89	87	8	53	0.89 (0.42-1.89)	0.76		87	9	62	1.01 (0.48-2.13)	0.98	
DBP ≥90	93	9	67	0.74 (0.35-1.55)	0.42		95	17	90	1.67 (0.90-3.10)	0.1	
p for trend				0.21						0.09		

BP, blood pressure; HR, hazard ratio; CI, confidence interval

The risk estimates were adjusted for potential confounding covariates in midlife or late life: namely, age, sex, education level, use of anti-hypertensive agents, diabetes, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

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Combined Effects of Smoking and Hypercholesterolemia on the Risk of Stroke and Coronary Heart Disease in Japanese: The Hisayama Study

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Key Words
Smoking · Hypercholesterolemia · Stroke · Coronary heart disease · Cohort study

Abstract
Background: Cigarette smoking is an established risk factor for stroke and coronary heart disease (CHD) in Western countries. However, it is uncertain whether or not smoking raises the risk of stroke in Japanese. We examined the influence of smoking on the development of stroke and CHD and the effects of interactions between smoking and hypercholesterolemia on these outcomes in a general Japanese population. ***Methods:*** A total of 2,421 community-dwelling Japanese individuals, aged 40–79 years, with no history of cardiovascular disease, were followed up for 14 years. ***Results:*** During the follow-up, 194 total stroke and 112 CHD events occurred. Compared with never smokers, the multivariate-adjusted hazard ratios for the occurrence of total stroke were 1.53 (95% confidence interval = 0.90–2.61) in former smokers, 1.90 (1.18–3.06) in current light smokers (<20 cigarettes/day) and 2.01 (1.11–3.65) in current heavy smokers (≥20 cigarettes/day). The multivariate-adjusted hazard ratios for the development of CHD were 1.10 (0.56–2.15), 1.88 (1.02–3.47) and 2.31 (1.17–4.57), respectively. In regard to stroke subtypes, current smoking was an independently significant risk factor for ischemic stroke and subarachnoid hemorrhage. Furthermore, the combination of smoking and hypercholesterolemia synergistically increased the risks of total stroke and CHD (all p for interaction <0.05). ***Conclusion:*** Our findings suggest that smoking raises the risks of ischemic stroke, subarachnoid hemorrhage and CHD occurrence in the Japanese population, and that this effect is strengthened by hypercholesterolemia.

Introduction

In Western countries, cigarette smoking is an established major risk factor for cardiovascular diseases (CVD) such as stroke [1] and coronary heart disease (CHD) [2]. Therefore, smoking cessation is currently recognized as a key target of prevention strategies for CVD [3]. While most cohort studies in Japan confirmed the harmful effect of smoking on the risk of CHD [4, 5], there is no con-

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sensus on whether or not smoking increases the risk of stroke in Japanese [4–8]. Furthermore, some studies have evaluated the interaction between smoking and hypercholesterolemia, which is also an important risk factor for CVD, but their conclusions have not been consistent [4, 9–13]. The purposes of the present study were to assess the effect of smoking on the development of stroke and CHD, and to clarify the interactions between smoking and hypercholesterolemia as well as other risk factors in a population-based cohort study in Japan.

Methods

Study Subjects

In 1988, a screening examination for the present study was performed in the town of Hisayama, a suburban community in the Fukuoka metropolitan area on Kyushu Island, Japan. A detailed description of this examination was published previously [14, 15]. Briefly, a total of 2,587 residents aged 40–79 years (80.2% of the total population in this age range) participated in the examination. After the exclusion of 88 subjects with a history of stroke or CHD, 77 who did not complete a 75-gram oral glucose tolerance test, and 1 who died before the initiation of follow-up, the remaining 2,421 (1,037 men and 1,384 women) were enrolled in the present study. This study was conducted with the approval of the ethics committee of the Faculty of Medicine, Kyushu University, and written informed consent was obtained from the subjects.

Risk Factors

At the baseline examination, each subject completed a self-administered questionnaire covering medical history, treatment for hypertension and diabetes, smoking status, alcohol intake and leisure time activity. The smoking status was classified into 4 categories: never smokers, former smokers, current light smokers (<20 cigarettes per day) and current heavy smokers (≥20 cigarettes per day). Alcohol intake was defined as customary drinking of an alcoholic beverage at least once a month. Subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group.

The sitting blood pressure was measured 3 times using a standard mercury sphygmomanometer after rest for at least 5 min. The mean of the 3 measurements was used for the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg or current use of antihypertensive agents. Obesity was defined as body mass index ≥25. Electrocardiogram abnormalities were defined as left ventricular hypertrophy (Minnesota Code, 3–1), ST depression (4–1, 2 or 3) or atrial fibrillation (8–3).

We performed the 75-gram glucose tolerance test after at least a 12-hour overnight fast. The plasma glucose levels were determined by the glucose-oxidase method. Diabetes mellitus was defined as any of the following: fasting plasma glucose ≥7.0 mmol/l, 2-hour postload glucose ≥11.1 mmol/l, or current use of oral hypoglycemic agents or insulin. The total cholesterol levels were determined enzymatically. Hypercholesterolemia was defined as total cholesterol ≥5.69 mmol/l.

Follow-Up Survey

The subjects were followed up prospectively for 14 years from December 1988 to November 2002 by repeated health examinations. Their health status was checked yearly by mail or telephone for any subjects who did not undergo a regular examination or who had moved out of town. We also established a daily monitoring system among the study team and local physicians or members of the town's health and welfare office. Using this system, we gathered information on new events of stroke and CHD, including suspected cases. When a new CVD event occurred or was suspected, physicians in the study team examined the subject and evaluated his or her detailed clinical information, including medical history and physical, neurological, laboratory and radiological examinations, to determine whether or not this event met the definition of an outcome. In addition, when a subject died, an autopsy was usually performed at the Department of Pathology of Kyushu University. During the follow-up period, 1 subject was lost to follow-up and 418 died, of whom 312 (74.6%) underwent autopsy.

Study Outcomes

Study outcomes were the development of CVD consisting of stroke and CHD. Stroke was defined in principle as a sudden onset of nonconvulsive and focal neurological deficit persisting for ≥24 h and was classified into 3 subtypes: ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage. All stroke events were morphologically examined by computed tomography, magnetic resonance imaging or autopsy findings. CHD included acute and silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, and coronary artery disease treated by coronary artery bypass surgery or angioplasty. Acute myocardial infarction was diagnosed when a subject met at least 2 of 4 criteria: (1) typical symptoms including prolonged severe anterior chest pain; (2) evolving diagnostic electrocardiographic changes; (3) cardiac enzyme levels more than twice the upper limit of the normal range; (4) morphological changes (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 myocardial infarction was defined as a morphological change of the myocardium without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. During the follow-up period, 281 subjects developed CVD for the first time. These included 194 cases of all forms of stroke (132 ischemic stroke, 43 intracerebral hemorrhage and 19 subarachnoid hemorrhage) and 112 cases of CHD.

Statistical Analysis

SAS software version 9.2 was used to perform all statistical analyses. The frequency of each risk factor at baseline across the smoking status was adjusted for age and sex by a direct method and compared by logistic regression analysis. The age- and sex-adjusted mean of each risk factor at baseline was estimated and compared by the analysis of covariance. The age- and sex-adjusted and multivariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. The interaction between smoking and each of the other risk factors was tested by adding an interaction term to the relevant Cox model. $p < 0.05$ was considered statistically significant.

Table 1. Age- and sex-adjusted mean values or frequencies of cardiovascular risk factors by smoking status at baseline

	Never smoker (n = 1,477)	Former smoker (n = 332)	Current smoker	
			<20 cigarettes/day (n = 348)	≥20 cigarettes/day (n = 264)
Age, years (sex-adjusted)	57 ± 12	61 ± 12*	59 ± 11	55 ± 12*
Men, % (age-adjusted)	14.3	92.6*	77.0*	94.8*
Systolic blood pressure, mm Hg	133 ± 23	133 ± 22	130 ± 21	129 ± 22
Diastolic blood pressure, mm Hg	79 ± 13	79 ± 12	75 ± 12*	75 ± 12*
Hypertension, %	38.6	43.0	35.2	21.1*
Fasting plasma glucose, mmol/l	5.8 ± 1.5	6.0 ± 1.5	5.8 ± 1.4	5.7 ± 1.4
Two-hour postload glucose, mmol/l	7.5 ± 4.3	7.9 ± 4.1	7.5 ± 3.8	7.4 ± 4.0
Diabetes, %	10.3	12.1	12.5	11.0
Total cholesterol, mmol/l	5.37 ± 1.27	5.44 ± 1.21	5.20 ± 1.14	5.40 ± 1.19
Hypercholesterolemia, %	35.3	38.0	37.1	22.5
Body mass index	23.1 ± 3.7	23.3 ± 3.5	22.3 ± 3.3*	22.5 ± 3.4*
Obesity, %	25.1	27.1	19.8*	23.9
Electrocardiogram abnormalities, %	17.4	16.1	16.3	13.4
Current alcohol intake, %	26.6	56.0*	46.3*	51.9*
Regular exercise, %	10.0	10.9	9.9	3.5

Values presented are means ± SD or percentages. * $p < 0.05$ compared with never smokers.

Results

The baseline characteristics of the study subjects are summarized in table 1. Compared with never smokers, the mean age was higher in former smokers but lower in current heavy smokers. The proportions of men and alcohol drinkers were higher in former and current smokers. Current heavy smokers had a lower prevalence of hypertension. Current light and heavy smokers had a lower body mass index.

In men, the risk for the development of CVD was significantly higher in current smokers than in never smokers (age-adjusted HR = 1.65; 95% CI = 1.04–2.63), and the risk of CVD was almost the same in women as in men (age-adjusted HR = 1.68; 95% CI = 0.94–2.98). Because there was no evidence of interaction between sex and current smoking (p for interaction = 0.97), we analyzed both sexes together in the following evaluations.

Table 2 shows the effects of smoking on the development of CVD, total stroke and CHD. The age- and sex-adjusted HRs for CVD and total stroke were significantly higher in current light and heavy smokers, and that for CHD was significantly higher in current heavy smokers than in never smokers. Former smoking was not a significant risk factor for each outcome. After adjusting for risk factors (age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise), both current light and heavy smokers had a significantly higher risk of each outcome than never smokers. Table 3 shows the effects of smoking on the risks of stroke subtypes. Current light and heavy smokers were combined here because of the limited number of events. Current smoking was an independently significant risk factor for ischemic stroke and subarachnoid hemorrhage, but not for intracerebral hemorrhage, after adjustment for confounding factors.

As shown in table 4, we assessed the combined and separate effects of smoking and each of the other established risk factors on the development of CVD. Compared with nonsmokers (never or former smokers) without hypercholesterolemia, current smokers with hypercholesterolemia had significantly higher multivariate-adjusted HRs for CVD. However, no significant elevations in HRs were observed in nonsmokers with hypercholesterolemia or in current smokers without hypercholesterolemia. A significant interaction between smoking and hypercholesterolemia was revealed in the risk of CVD, while we failed to detect any significant interaction between current smoking and hypertension, diabetes, obesity, alcohol intake or regular exercise. Table 5 shows the interaction analyses between current smoking and hypercholesterolemia on the development of stroke and CHD. The combination of current smoking and hyper-

Table 2. Risks for the development of cardiovascular disease, total stroke and coronary heart disease according to smoking status

	Events/ population	Age- and sex-adjusted			Multivariate-adjusted		
		HR	95% CI	p	HR	95% CI	p
Cardiovascular disease							
Never smoker	137/1,477	1.00			1.00		
Former smoker	50/332	1.26	0.83–1.91	0.29	1.25	0.80–1.93	0.32
Current smoker (<20 cigarettes/day)	54/348	1.60	1.09–2.34	0.02	1.80	1.21–2.66	0.004
Current smoker (≥20 cigarettes/day)	40/264	1.88	1.20–2.95	0.006	2.04	1.29–3.24	0.003
Total stroke							
Never smoker	104/1,477	1.00			1.00		
Former smoker	34/332	1.52	0.91–2.52	0.11	1.53	0.90–2.61	0.12
Current smoker (<20 cigarettes/day)	34/348	1.70	1.07–2.71	0.02	1.90	1.18–3.06	0.009
Current smoker (≥20 cigarettes/day)	22/264	1.87	1.05–3.32	0.03	2.01	1.11–3.65	0.02
Coronary heart disease							
Never smoker	43/1,477	1.00			1.00		
Former smoker	23/332	1.19	0.63–2.26	0.60	1.10	0.56–2.15	0.78
Current smoker (<20 cigarettes/day)	25/348	1.61	0.88–2.93	0.12	1.88	1.02–3.47	0.04
Current smoker (≥20 cigarettes/day)	21/264	2.07	1.07–4.01	0.03	2.31	1.17–4.57	0.02

Multivariate-adjusted: adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise.

Table 3. Risks for the development of stroke subtypes according to smoking status

	Events/ population	Age- and sex-adjusted			Multivariate-adjusted		
		HR	95% CI	p	HR	95% CI	p
Ischemic stroke							
Never smoker	69/1,477	1.00			1.00		
Former smoker	26/332	1.72	0.95–3.12	0.08	1.70	0.90–3.20	0.10
Current smoker	37/612	1.78	1.05–3.01	0.03	2.03	1.18–3.49	0.01
Intracerebral hemorrhage							
Never smoker	24/1,477	1.00			1.00		
Former smoker	7/332	1.00	0.34–2.91	>0.99	1.11	0.37–3.33	0.85
Current smoker	12/612	1.20	0.48–3.00	0.70	1.21	0.47–3.15	0.70
Subarachnoid hemorrhage							
Never smoker	11/1,477	1.00			1.00		
Former smoker	1/332	0.86	0.09–8.32	0.89	0.92	0.09–9.08	0.95
Current smoker	7/612	3.39	1.00–11.54	0.051	3.85	1.05–14.13	0.04

Multivariate-adjusted: adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise.

cholesterolemia significantly increased the risks of total stroke and CHD, and their interactions were statistically significant. In regard to stroke subtypes, similar findings were observed in the risks of ischemic stroke and subarachnoid hemorrhage, although interaction was significant only for subarachnoid hemorrhage.

Discussion

In the present study of a population-based cohort in Japan, current smoking was an independently significant risk factor for the development of stroke and CHD. In regard to stroke subtypes, current smoking was clear-

Table 4. Combined and separate effects of smoking and each risk factor on the development of cardiovascular disease

	Events/ population	Multivariate-adjusted		
		HR	95% CI	p
Hypercholesterolemia				
Current smoking (–)/hypercholesterolemia (–)	108/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	79/710	1.08	0.80–1.47	0.60
Current smoking (+)/hypercholesterolemia (–)	57/435	1.36	0.96–1.93	0.08
Current smoking (+)/hypercholesterolemia (+)	37/177	2.68	1.81–3.95	<0.001
p for interaction				0.001
Hypertension				
Current smoking (–)/hypertension (–)	67/1,103	1.00		
Current smoking (–)/hypertension (+)	120/706	1.87	1.36–2.57	<0.001
Current smoking (+)/hypertension (–)	44/388	1.83	1.22–2.76	0.003
Current smoking (+)/hypertension (+)	50/224	2.97	1.98–4.45	<0.001
p for interaction				0.22
Diabetes				
Current smoking (–)/diabetes (–)	142/1,602	1.00		
Current smoking (–)/diabetes (+)	45/207	1.74	1.23–2.46	0.002
Current smoking (+)/diabetes (–)	73/524	1.70	1.24–2.34	0.001
Current smoking (+)/diabetes (+)	21/88	2.83	1.73–4.63	<0.001
p for interaction				0.82
Obesity				
Current smoking (–)/obesity (–)	139/1,348	1.00		
Current smoking (–)/obesity (+)	48/461	0.93	0.66–1.30	0.66
Current smoking (+)/obesity (–)	68/480	1.49	1.07–2.07	0.02
Current smoking (+)/obesity (+)	26/132	2.10	1.34–3.28	0.001
p for interaction				0.07
Alcohol intake				
Current smoking (–)/alcohol intake(–)	138/1,402	1.00		
Current smoking (–)/alcohol intake (+)	49/407	0.81	0.55–1.19	0.29
Current smoking (+)/alcohol intake (–)	39/250	1.19	0.79–1.80	0.40
Current smoking (+)/alcohol intake (+)	55/362	1.15	0.75–1.75	0.52
p for interaction				0.58
Regular exercise				
Current smoking (–)/regular exercise (–)	166/1,622	1.00		
Current smoking (–)/regular exercise (+)	20/185	0.81	0.51–1.29	0.38
Current smoking (+)/regular exercise (–)	89/556	1.83	1.36–2.48	<0.001
Current smoking (+)/regular exercise (+)	5/56	0.57	0.23–1.42	0.23
p for interaction				0.08

Current smoking (–) includes both never and former smoking. Multivariate-adjusted: adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise. The variable relevant to the subgroup was excluded from each model.

ly associated with the development of ischemic stroke and subarachnoid hemorrhage, but not with intracerebral hemorrhage. These findings are concordant with previously reported meta-analyses based mainly on Caucasian populations [1, 2]. In addition, we demonstrated that hypercholesterolemia strengthened the harmful effects of smoking on these outcomes, but such effects were not observed for other risk factors: hypertension, diabetes, obesity, alcohol intake and regular exercise.

Several injurious effects of cigarette smoking on arteries have been demonstrated. Smoking causes direct injury to endothelial cells [16], oxidation of low-density lipoprotein [17], and acceleration of thrombus formation through increased plasma fibrinogen [18], increased platelet aggregability [19] and decreased fibrinolytic ac-

Table 5. Combined and separate effects of smoking and hypercholesterolemia on the development of stroke and coronary heart disease

	Events/ population	Multivariate-adjusted		
		HR	95% CI	p
Total stroke				
Current smoking (–)/hypercholesterolemia (–)	83/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	55/710	0.92	0.65–1.31	0.64
Current smoking (+)/hypercholesterolemia (–)	36/435	1.34	0.87–2.06	0.19
Current smoking (+)/hypercholesterolemia (+)	20/177	2.08	1.25–3.45	0.005
p for interaction				0.048
Ischemic stroke				
Current smoking (–)/hypercholesterolemia (–)	54/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	41/710	1.14	0.74–1.74	0.55
Current smoking (+)/hypercholesterolemia (–)	23/435	1.37	0.80–2.33	0.25
Current smoking (+)/hypercholesterolemia (+)	14/177	2.24	1.21–4.14	0.01
p for interaction				0.15
Intracerebral hemorrhage				
Current smoking (–)/hypercholesterolemia (–)	19/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	12/710	0.87	0.41–1.85	0.72
Current smoking (+)/hypercholesterolemia (–)	10/435	1.29	0.55–3.03	0.56
Current smoking (+)/hypercholesterolemia (+)	2/177	0.86	0.19–3.80	0.84
p for interaction				0.83
Subarachnoid hemorrhage				
Current smoking (–)/hypercholesterolemia (–)	10/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	2/710	0.25	0.05–1.15	0.08
Current smoking (+)/hypercholesterolemia (–)	3/435	1.54	0.35–6.72	0.57
Current smoking (+)/hypercholesterolemia (+)	4/177	5.31	1.52–18.54	0.009
p for interaction				0.005
Coronary heart disease				
Current smoking (–)/hypercholesterolemia (–)	34/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	32/710	1.59	0.96–2.65	0.07
Current smoking (+)/hypercholesterolemia (–)	26/435	1.63	0.95–2.81	0.08
Current smoking (+)/hypercholesterolemia (+)	20/177	3.72	2.09–6.63	<0.001
p for interaction				0.01

Current smoking (–) includes both never and former smoking. Multivariate-adjusted: adjusted for age, sex, systolic blood pressure, diabetes, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise.

tivity [20], all of which are associated with the development of atherosclerotic diseases such as ischemic stroke and CHD. Smoking is also considered to cause the formation, growth and rupture of intracranial aneurysms [21, 22], probably due to an elastase/α_2-antitrypsin imbalance in the artery wall [23], leading to an elevated risk of subarachnoid hemorrhage [21, 22, 24].

While smoking is an established risk factor for CHD [4, 5], there is no consensus on whether or not smoking raises the risk of ischemic stroke in Japanese [4–8]. Using the first cohort of the Hisayama study, established in 1961, we previously reported that smoking was not a risk factor for ischemic stroke [4]. Similarly, no obvious relationship between smoking and ischemic stroke was observed in some old cohort studies in Japan that started their follow-up in the 1960s [6, 7]. On the other hand, some other recent cohort studies in Japan [5, 8], as well as our present study, showed statistical associations between smoking and the risk of ischemic stroke. We consider that these different conclusions can be explained in 2 possible ways. One is a secular change in the prevalence of hypercholesterolemia. According to our cross-sectional surveys in Hisayama, the prevalence of hypercholesterolemia was very low in 1961 (2.8% in men, 6.6% in women) but increased greatly in the following 4 decades (to 25.8% in men and 41.6% in women in 2002) [25]. Therefore, the harmful effect of smoking on the development of ischemic stroke might be obscured in studies in which the

population prevalence of hypercholesterolemia was low. The other possible reason is a change in the distribution of ischemic stroke subtypes. In Hisayama, while the proportion of lacunar infarctions among all ischemic stroke events has decreased during the past 4 decades, the proportions of atherothrombotic and cardioembolic stroke have increased [25]. These changes might affect the influence of smoking on the development of ischemic stroke.

In previous studies, the relationship between smoking and the risk of intracerebral hemorrhage has been reported to be inconsistent. A few cohort studies [26, 27] showed that current smoking increased the risk of intracerebral hemorrhage, while other studies [5–8, 12, 28], including a meta-analysis [1] and ours, found no discernible association between the two. The reasons for these inconsistent conclusions are unknown. However, because smoking increases hypercoagulability rather than bleeding tendency [18–20], the effect of smoking on the risk of intracerebral hemorrhage seems to be weak, if any.

Because smoking oxidizes low-density lipoprotein [17], it is reasonable to think that the combination of smoking and hypercholesterolemia may accelerate the progression of atherosclerosis and the development of ischemic stroke and CHD. Some studies have evaluated the interaction between smoking and hypercholesterolemia in relation to CVD outcomes. However, the conclusions have not been consistent [4, 9–13]. In the present study, the synergistic effect of smoking and hypercholesterolemia on the development of CHD was significant, and a similar tendency was observed for ischemic stroke. Another Japanese cohort study [9] also demonstrated positive interactions between smoking and cholesterol for ischemic stroke and CHD mortality. On the other hand, the first cohort of the Hisayama study, established in 1961 [4], as well as the Asia Pacific Cohort Studies Collaboration [10], confirmed a positive interaction for CHD but not for ischemic stroke. Two Korean cohort studies [11, 12] and a meta-analysis of mainly Caucasian studies [13] did not find any interactions for CVD outcomes. These inconsistent conclusions may be explained in part by ethnicity and differences in average cholesterol levels. The effects of smoking and cholesterol on CVD outcomes may differ between Asians and Caucasians. Among Asian studies, the average cholesterol levels were lower in the first cohort of Hisayama [4], Pacific Cohort Studies Collaboration [10] and 2 Korean studies [11, 12] compared with the present study. We have no clear explanation of the synergistic effect of smoking and hypercholesterolemia on the risk of subarachnoid hemorrhage. In any case, we cannot draw any conclusion from the present results because of the small number of subarachnoid hemorrhages in our study. Our finding should be confirmed in larger cohort studies.

The advantages of the present analyses include accurate measurement of risk factors at baseline, the longitudinal population-based study design, the long duration of follow-up, perfect follow-up of study subjects and accurate diagnoses of CVD. However, a possible limitation should be discussed. Because we did not consider changes in smoking habits and other risk factors or treatments that occurred during the follow-up, our results may underestimate the effects of smoking and other risk factors on the risk of CVD.

In conclusion, we demonstrated that current smoking increases the risk of ischemic stroke, subarachnoid hemorrhage and CHD, especially in individuals with hypercholesterolemia. Although the smoking rates in Japanese men and women have been decreasing in the past 4 decades [25], Japanese men still have a higher smoking rate than people in Western countries [3]. Our findings highlight the importance of smoking cessation to reduce the burden of CVD in Japan, where the prevalence of hypercholesterolemia is escalating rapidly [25].

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ORIGINAL ARTICLE

Body mass index and stroke incidence in a Japanese community: the Hisayama study

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Although obesity is one of the major risk factors for coronary heart disease, its role in the development of stroke remains controversial. A total of 2421 residents, aged 40–79 years of a Japanese community were followed up prospectively for 12 years. The subjects were divided into four groups according to body mass index (BMI) levels (<21.0, 21.0–22.9, 23.0–24.9 and ⩾25.0 kg m^{-2}). During the follow-up, 107 ischemic and 51 hemorrhagic strokes occurred. The age-adjusted incidence of ischemic stroke for men significantly increased with increasing BMI levels (P for trend=0.005). This association remained substantially unchanged even after adjustment for other risk factors: namely, systolic blood pressure, electrocardiogram abnormalities, diabetes, total cholesterol, high-density lipoprotein-cholesterol, triglycerides, smoking habits, alcohol intake and regular exercise (P for trend<0.001). Compared with that of the BMI levels of <21.0 kg m^{-2}, the multivariate-adjusted risk of ischemic stroke was significant even in the BMI levels of 23.0–24.9 kg m^{-2} (multivariate-adjusted hazard ratio (HR)=3.12; 95% confidence interval (CI), 1.24–7.87; P=0.02) as well as in the BMI levels of ⩾25 kg m^{-2} (multivariate-adjusted HR=5.59; 95% CI, 2.09–14.91; P<0.001). In stratified analyses, the risk of ischemic stroke for men synergistically increased in subjects having both obesity and diabetes or a smoking habit. We found no significant associations between BMI levels and ischemic stroke in women and between BMI levels and hemorrhagic stroke in either sex. In conclusion, our findings suggest that overweight and obesity are independent risk factors for ischemic stroke in Japanese men.
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Keywords: body mass index; incidence; obesity; prospective study; stroke

INTRODUCTION

Stroke is a leading cause of death[1] and permanent disability in middle-aged and elderly people in Japan[2–4] as well as in other developed countries.[5] In Japan, the prevalence of obesity has increased rapidly along with the westernization of lifestyle,[6] although it remains considerably lower than that in Western populations.[7] Increased body mass index (BMI) is tightly related to an increased risk of coronary heart disease,[8] but its association with stroke is less well recognized because of conflicting results reported in the literature. Some cohort studies have found a positive association between BMI and the risk of stroke,[8–14] whereas others have shown no apparent association[15–18] or have even reported an inverse or a U-shaped association.[19–22] In Japan, no prospective study has provided incidence data on this issue nor observed a positive association between BMI and the risk of stroke until now.[21,22] Based on its pathogenesis, stroke is divided into several clinical subtypes, and the effects of BMI on stroke are considered to be different among these subtypes.[8,19] In addition, obesity is an important risk factor for hypertension, diabetes mellitus and dyslipidemia, which are known as major risk factors for stroke,[23,24] and therefore, whether obesity itself independently increases the risk of stroke remains controversial.

In the present article, we investigated the association between BMI and the occurrence of stroke by its subtype based on records of a prospective study of a general Japanese population, taking other known risk factors into account.

METHODS

Study population

In 1988, a screening survey for the present study was performed in the town of Hisayama, a suburb of the Fukuoka metropolitan area in southern Japan. Of a total of 3227 residents aged 40–79 years on the town registry, 2587 consented to participate in the examination (participation rate, 80.2%) and underwent a comprehensive assessment. After excluding 82 subjects who had already had breakfast, 10 who were on insulin therapy and 15 due to complaints of nausea or general fatigue during the ingestion of glucose, a total of 2480 subjects completed a 75-g oral glucose tolerance test. From a total of 2490 subjects including 10 on insulin therapy, 68 who had a history of stroke or coronary heart disease based on questionnaires and medical records, and one who died

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before follow-up was started were excluded. The remaining 2421 (1037 men and 1384 women) were enrolled in this study.

Baseline data collection

At baseline, body height and weight were measured in light clothing without shoes, and BMI ($kg\,m^{-2}$) was calculated as an indicator of obesity. Information on antihypertensive treatment, smoking habits, alcohol intake and regular exercise were obtained with the use of a standard questionnaire. Subjects who reported smoking at least one cigarette per day were defined as current smokers, and subjects who reported consuming alcohol at least once a month were regarded as current drinkers. Subjects engaging in sports at least three times a week during their leisure time made up a regular exercise group. Sitting systolic and diastolic blood pressures were measured three times after a rest of at least 5 min by a standard mercury sphygmomanometer with a standard cuff. The average of three measurements was used for data analysis. Hypertension was defined as a systolic blood pressure $\geqslant$140 mm Hg, a diastolic blood pressure $\geqslant$90 mm Hg or current use of antihypertensive agents. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code 3–1), ST depression (4–1, 2 and 3) and/or atrial fibrillation (8–3). Blood samples were drawn after an overnight fast of at least 12 h. Fasting and 2-h post-load plasma glucose levels were determined by the glucose-oxidase method. Diabetes mellitus was defined as fasting plasma glucose $\geqslant$7.0 $mmol\,l^{-1}$, 2-hour post-load plasma glucose $\geqslant$11.1 $mmol\,l^{-1}$, or current use of insulin or oral medication for diabetes. Total cholesterol, high-density lipoprotein-cholesterol and triglyceride levels were all determined enzymatically.

Follow-up survey

The subjects were followed up prospectively for 12 years from December 1988 to November 2000 by repeated health examinations and by a daily monitoring system established by the study team and local physicians or members of the Health and Welfare Office of the town. Health status was checked once yearly by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. Study-team physicians performed physical and neurological examinations on all subjects who developed stroke and collected the relevant clinical information, including that on the disease course. During the follow-up period, only one subject was lost to follow-up, and 339 subjects died; among those who died, autopsy was performed on 253 (74.6%).

Stroke, defined as sudden onset of a non-convulsive and focal neurological deficit persisting for >24 h, was classified as ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage or undetermined type.[25] The clinical diagnosis of stroke and its subtypes was determined on the basis of a detailed history, neurological examination and ancillary laboratory examinations. In this paper, we focused on ischemic and hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage). During the follow-up period, we identified 107 cases of first-ever ischemic stroke (47 men and 60 women) and 51 cases of first-ever hemorrhagic stroke (21 men and 30 women), consisting of 34 cases of cerebral hemorrhage and 17 cases of subarachnoid hemorrhage. All of the stroke cases were examined by computed tomography and/or magnetic resonance imaging.

Statistical analysis

All statistical analyses were performed with the SAS program package Ver 9.2 (SAS Institute Inc, Cary, NC, USA). All tests were two-sided, and values of $P<0.05$ were considered statistically significant in all analyses. The subjects were divided into four groups according to BMI levels (<21.0, 21.0–22.9, 23.0–24.9 and $\geqslant$25.0 $kg\,m^{-2}$). Because of the skewed distribution of serum triglycerides, this value was log-transformed for statistical analysis. The age-adjusted mean values of risk factors were calculated by the analysis of covariance method, and their trends across BMI levels were tested by multiple regression analysis. Frequencies of risk factors were adjusted for age by the direct method and were examined for trends by the Cochran–Mantel–Haenszel test. The incidence of stroke was calculated by the person-year method and was adjusted for the age distribution of the study population by the direct method. Differences in the incidence of stroke among BMI levels were tested by the Cox proportional hazards model. The age- and multivariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were also calculated using the Cox proportional hazards model. The multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, total cholesterol, high-density lipoprotein-cholesterol, triglycerides, smoking habits, drinking status and regular exercise. To assess whether synergistic effect was observed between obesity and each of other risk factors, we added a multiplicative interaction term to the relevant Cox model.

Ethical considerations

The study protocol was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences, and a written informed consent was obtained from the study participants.

RESULTS

Characteristics of the subjects

The age-adjusted mean values or frequencies of risk factors by BMI levels at baseline are shown by sex (Table 1). Mean age significantly decreased with rising BMI levels for men, but such an association was not observed for women. In both sexes, the mean values of systolic and diastolic blood pressures, total cholesterol and triglycerides, and the frequencies of hypertension, antihypertensive drug use and diabetes increased significantly, whereas the mean high-density lipoprotein-cholesterol levels decreased significantly with increasing BMI levels. The frequency of smoking habits for men and that of ECG abnormalities for women decreased significantly with increasing BMI levels. No dose-response relationships were observed between BMI levels and the frequencies of alcohol intake or regular exercise for both sexes.

Impact of BMI on stroke

As shown in Figure 1, the age-adjusted incidence of ischemic stroke for men increased with increasing BMI levels: the difference was significant between the BMI level of <21.0 $kg\,m^{-2}$ and that of $\geqslant$25.0 $kg\,m^{-2}$ (age-adjusted HR=3.32; 95% CI, 1.43–7.72; P=0.005; Table 2). This association remained substantially unchanged even after adjustment for other risk factors (Table 2). The multivariate-adjusted risk of ischemic stroke was significant even in the subjects with BMI levels of 23.0–24.9 $kg\,m^{-2}$ (multivariate-adjusted HR=3.12; 95% CI, 1.24–7.87; P=0.02) as well as in those with BMI levels of $\geqslant$25 $kg\,m^{-2}$ (multivariate-adjusted HR=5.59; 95% CI, 2.09–14.91; $P<0.001$). We found no significant associations between BMI levels and the incidence of ischemic stroke in women and between BMI levels and the incidence of hemorrhagic stroke in either sex (Figure1 and Table 2).

Combined effects of obesity and other risk factors

Because hypertension, diabetes and smoking habits are major risk factors for ischemic stroke and are concurrently associated with obesity, we examined the combined effects of obesity and these risk factors on the development of ischemic stroke for men after adjustment for the above-mentioned confounding factors, except for the factor which was used for the grouping. As shown in Table 3, multivariate-adjusted HRs of ischemic stroke were significantly higher in the group of obese subjects irrespective of the presence or absence of hypertension. On the other hand, the risk of ischemic stroke synergistically increased in obese subjects with diabetes compared with non-obese subjects without diabetes (multivariate-adjusted HR=7.91; 95% CI, 3.08–20.28; $P<0.001$), whereas such an increased risk was not observed in non-obese subjects with diabetes or in obese subjects without diabetes. A similar synergistic pattern was observed for the coexistence of obesity and smoking habits (multivariate-adjusted HR=3.62; 95% CI, 1.39–9.43; P=0.008). A significant interaction between obesity and diabetes was revealed in the risk of ischemic