subgroup analysis was difficult. But we found a significant reduction in cumulative incidence (log-rank test: p = 0.027) for the subjects with a BMI> 22.5. Thus the effects of the intervention for lean subjects might attenuate the impact on the incidence. Regarding this, it would be important to clarify an effective measure for the prevention of diabetes in subjects with a low BMI in future studies, since the Japanese IGT population includes a considerable number of such subjects.

In the DPP, weight reduction was found to be essential for the lifestyle intervention to be beneficial [5]. In an Indian Study [7], however, the benefits seemed independent of weight change. In a hospital-based lifestyle intervention, Kosaka concluded that the benefits of lifestyle intervention could not be solely ascribed to weight reduction [6]. The present study found that minimal weight reduction in the intervention group (less than 3% on average) lowered the relative risk to 53% over 3 years, similar to the risk reduction seen in the DPS and DPP (58%) where the subjects lost 5-7% of body weight on average. Thus it seems that the relationship between body weight and diabetes risk in Asians is not as straightforward as in Western people. Asians have lower BMI but higher body fat levels than do whites [25,26]. Japanese Americans are prone to develop visceral obesity and metabolic syndrome [27,28]. A reasonable explanation for the present findings might be a more profound reduction in specific fat depots, such as visceral fat and liver fat. It has been reported that lifestyle intervention with diet and physical activity is effective at reducing hepatic steatosis in patients with non-alcoholic fatty liver disease [29]. Although there was no difference in daily alcohol consumption between the groups, we found that serum GGT levels decreased in the intervention group, but increased in the control group. These findings are important, since it has been reported that the serum concentrations of GGT and ALT are a predictive marker of type 2 diabetes [30-33], even at concentrations still considered to be within the normal range [34]. Thus, the difference in the changes in GGT levels between the groups is likely to reflect changes in liver fat contents. Further examination including abdominal ultrasonography and computed tomography [35] will be needed.

Conclusions

In conclusion, the present study suggests that lifestyle intervention using existing healthcare resources in communities and workplaces is beneficial in preventing or delaying the development of diabetes in middle aged Japanese with IGT. General improvements in lifestyle including dietary and exercise habits might be meaningful even if the weight reductions achieved are only modest. The findings have important implications for primary healthcare-based diabetes prevention.

List of abbreviations used

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CPG: Casual plasma glucose; DPP: Diabetes Prevention Program; DPS: Diabetes Prevention Study; FFQ: Food frequency questionnaire; FPG: Fasting plasma glucose; GGT: Gamma-glutamyltransferase; HDL: High-density lipoprotein; HOMA: Homeostasis model assessment; IGT: Impaired glucose tolerance; LTPA: Leisure time physical activity; OGTT: Oral glucose tolerance test.

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Author details

[1]Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan. [2]Department of General Medicine, Nagoya University Hospital, Nagoya, Japan. [3]Comprehensive Health Science Center, Aichi Health Promotion Foundation, Aichi, Japan. [4]Diabetes Center, Tenri Yorozu-sodansho Hospital, Tenri, Japan. [5]Department of Clinical Laboratory Medicine, Jichi Medical School, Tochigi, Japan. [6]Division of Internal Medicine, Hananoki Hospital, Tochigi, Japan. [7]Department of Diabetes and Metabolism,Marunouchi Hospital, The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan. [8]Department of Health Science, Faculty of Psychological and Physical Science, Aichi Gakuin University, Aichi, Japan. [9]Division of Endocrinology, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan. [10]JPMA Pharmacoeconomics Program, Graduate School of Health Management, Keio University, Fujisawa, Japan. [11]Department of Diabetes and Metabolism, Kyoto City Hospital, Kyoto, Japan. [12]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyusyu University, Fukuoka, Japan. [13]Aino Hospital, Ibaraki, Japan. [14]National Hospital Organization Kyoto Medical Center, Kyoto, Japan. [15]Higashiyama Takeda Hospital, Kyoto, Japan.

Authors' contributions

HK, the project leader, is involved in all aspects of the study. JS, ST, MT, SK, YS, IK, KY, and SS designed the study, and prepared the protocol of intervention. TK contributed to study design and coordination. NS, KK, and KT performed the statistical analysis and prepared the manuscript. TU and YT helped to draft the manuscript participated in the critical revision of the manuscript and the trial management. All authors have read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

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

Koji Yonemoto[1], Yasufumi Doi[1,2], Jun Hata[1,2], Toshiharu Ninomiya[1,2], Masayo Fukuhara[1,2], Fumie Ikeda[1,2], Naoko Mukai[1,2], Mitsuo Iida[2] and Yutaka Kiyohara[1]

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

[1]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan and [2]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
Correspondence: Dr Y Kiyohara, Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail: kiyohara@envmed.med.kyushu-u.ac.jp
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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

Table 1 Age-adjusted baseline characteristics according to body mass index level by sex, the Hisayama Study, 1988

	Body mass index, kg m^{-2}				
	<21	*21–22.9*	*23–24.9*	*≥25*	*P for trend*
Men					
No at risk	283	255	247	252	—
Age (years)	60.5 (0.6)	56.8 (0.6)	56.2 (0.7)	54.4 (0.6)	<0.001
SBP (mm Hg)	127.1 (1.1)	132.2 (1.2)	135.5 (1.2)	141.2 (1.2)	<0.001
DBP (mm Hg)	75.5 (0.6)	79.3 (0.7)	82.0 (0.7)	86.3 (0.7)	<0.001
Hypertension (%)	32.6	37.4	46.9	58.7	<0.001
Antihypertensive drug (%)	9.0	10.8	15.1	23.6	<0.001
ECG abnormalities (%)[a]	20.6	20.9	19.3	18.7	0.28
Diabetes (%)	10.1	16.9	13.6	20.9	0.005
Total cholesterol (mmol l^{-1})	4.95 (0.06)	5.05 (0.07)	5.13 (0.07)	5.31 (0.07)	<0.001
HDL cholesterol (mmol l^{-1})	1.37 (0.02)	1.30 (0.02)	1.22 (0.02)	1.14 (0.02)	<0.001
Triglycerides (mmol l^{-1})	1.01 (0.94–1.07)	1.28 (1.20–1.37)	1.46 (1.36–1.56)	1.77 (1.65–1.90)	<0.001
Smoking (%)	68.7	47.0	44.5	36.6	<0.001
Drinking (%)	59.7	65.9	64.7	58.6	0.63
Regular exercise (%)[b]	12.8	11.1	11.0	10.9	0.34
Women					
No at risk	380	347	318	339	
Age (years)	59.1 (0.5)	57.0 (0.6)	57.0 (0.6)	57.6 (0.6)	0.052
SBP (mm Hg)	125.2 (1.0)	130.2 (1.0)	131.1 (1.1)	136.9 (1.0)	<0.001
DBP (mm Hg)	71.8 (0.5)	74.4 (0.6)	77.0 (0.6)	80.0 (0.6)	<0.001
Hypertension (%)	24.2	30.9	34.5	50.3	<0.001
Antihypertensive drug (%)	7.5	14.1	14.2	21.5	<0.001
ECG abnormalities (%)[a]	15.2	14.3	9.4	11.6	0.03
Diabetes (%)	7.5	6.8	8.8	16.6	<0.001
Total cholesterol (mmol l^{-1})	5.31 (0.05)	5.54 (0.06)	5.74 (0.06)	5.66 (0.06)	<0.001
HDL cholesterol (mmol l^{-1})	1.44 (0.01)	1.35 (0.02)	1.30 (0.02)	1.26 (0.02)	<0.001
Triglycerides (mmol l^{-1})	0.88 (0.84–0.92)	1.04 (0.99–1.09)	1.15 (1.10–1.21)	1.24 (1.18–1.30)	<0.001
Smoking (%)	8.1	3.5	6.6	8.1	0.72
Drinking (%)	9.5	10.3	5.1	10.7	0.79
Regular exercise (%)[b]	9.4	10.5	8.9	6.3	0.11

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.
Data are shown as the means (standard error) or a percentage. Geometric mean values and 95% confidence intervals of serum triglycerides are shown attributable to the skewed distribution. Mean age was not age-adjusted.
[a]Minnesota codes: 3–1, 4–1, 2, 3 or 8–3
[b]Engaging in sports or other forms of exertion regularly ≥three times a week during leisure time.

stroke (P=0.01), whereas the interactions between obesity and hypertension and between obesity and smoking habits were not significant.

DISCUSSION

In this prospective study of a community-dwelling Japanese population, we demonstrated that higher BMI was a significant risk factor for the development of ischemic stroke in men. This association remained unchanged even after adjustment for other risk factors. In addition, the combinations of obesity plus diabetes or obesity plus a smoking habit synergistically increased the risk of ischemic stroke. However, there was no significant association between BMI levels and the risk of hemorrhagic stroke in either sex.

Some cohort studies have shown an increased risk of total stroke or ischemic stroke with elevating BMI,[8–14] which is in accord with the findings of the risk of ischemic stroke in our male subjects. On the other hand, other studies have found no association,[15–18] an inverse or a U-shaped association.[19–22] One possible explanation for this difference in findings may be that stroke was not evaluated by its subtype in all these studies, as the effect of obesity is different among stroke subtypes. Another explanation may be that most of these studies used mortality data as an endpoint. Our previous study showed that lower BMI was a significant risk factor for death after total stroke and ischemic stroke.[26] Epidemiological studies of body weight and mortality are affected by methodological problems, such as failure to control the harmful biological effects of smoking and subclinical diseases resulting in weight loss. Thus, the association of BMI with stroke mortality should be interpreted with caution.

In the literature, the associations between BMI levels and the risk of hemorrhagic stroke have been inconsistent, with some studies showing a positive association,[8,11,14] and others showing no, a negative or a U-shaped, association.[9,12,13,16,19,21,22] In the present study, we did not find a clear association between BMI levels and hemorrhagic stroke in men or women. The lack of a clear consensus on this association may be partly due to the low number of cases of hemorrhagic stroke in most of the studies, including our present work, or differences in ethnicities, study populations or study methods. Future studies will be needed to resolve this issue.

A number of studies have reported that the association between BMI and total or ischemic stroke was attenuated or eliminated after adjustment for potential mediators, such as hypertension, diabetes

and dyslipidemia.[9,10,12–14,19,22] In our study, however, the association between BMI and ischemic stroke was not attenuated even after adjusting for these risk factors. This finding indicates an independent effect of overweight and obesity on the development of ischemic stroke. A similar independent association has been observed in other studies of stroke.[10,12,14] These findings, together with our present results, suggest a link between overweight/obesity and ischemic stroke independent of established risk factors. Some investigators have proposed that the increase in prothrombotic factors[27–29] and inflammatory markers,[30–33] and the enhancement of insulin resistance and metabolic syndrome[34] observed among overweight and obese individuals may have a role in their increased risk of ischemic stroke.

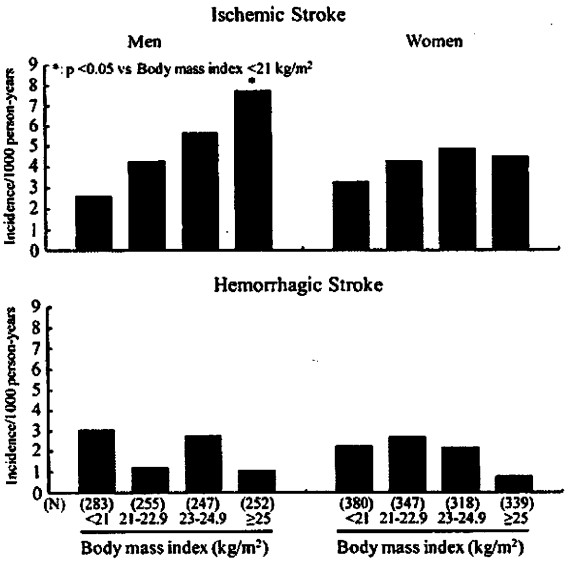

Figure 1 Age-adjusted incidence of stroke by body mass index levels during 12-year follow-up, the Hisayama Study, 1988–2000.

Our stratified analysis showed an extremely increased risk of ischemic stroke in men who have both obesity and diabetes or smoking habits. Although the mechanisms underlying this phenomenon are not clearly understood, a possible explanation can be proposed. Because diabetes and smoking are strong risk factors for the progression of systemic arteriosclerosis, it is reasonable to consider that subjects with these risk factors already have vascular injuries to some extent. Obesity-related disorders, such as inflammation, insulin resistance and metabolic syndrome, may accelerate the progression of preexisting vascular injuries, resulting in an increased risk of ischemic stroke. However, in the present study we did not find that obesity enhanced the effect of hypertension on stroke risk. Although the precise reason for this is not known, the popularization of antihypertensive treatment in our study population might have weakened the synergistic effects of these factors.

In our female subjects, we did not observe a significant association between BMI and the risk of ischemic stroke. Several cohort studies have also examined the effects of BMI on the risk of ischemic stroke in women,[9,13–15,21,22] but the findings were inconsistent, with some studies showing a positive association,[9,13,14] and others showing no association[15,21] like our study. Further studies will be needed to clarify the true association between BMI and stroke in women.

Table 2 Adjusted hazard ratio for stroke incidence according to body mass index level by sex, the Hisayama Study, 1988–2000

Body mass index, kg m^{-2}	*Person year*	*No. of events*	*Age-adjusted HR*	*95% CI*	*Multivariate-adjusted HR*[a]	*95% CI*
Men						
Ischemic stroke						
<21.0	2907	9	1.00	Referent	1.00	Referent
21.0–22.9	2736	10	1.70	0.69–4.20	2.34	0.91–6.00
23.0–24.9	2692	12	2.09	0.88–5.00	3.12	1.24–7.87
25.0≥	2790	16	3.32	1.43–7.73	5.59	2.09–14.91
P for trend			0.005		<0.001	
Hemorrhagic stroke						
<21.0	2907	9	1.00	Referent	1.00	Referent
21.0–22.9	2736	3	0.44	0.12–1.63	0.38	0.10–1.50
23.0–24.9	2692	6	0.89	0.31–2.55	0.90	0.28–2.87
25.0≥	2790	3	0.47	0.12–1.80	0.36	0.08–1.57
P for trend			0.41		0.31	
Women						
Ischemic stroke						
<21.0	4214	15	1.00	Referent	1.00	Referent
21.0–22.9	3935	15	1.41	0.69–2.90	1.37	0.65–2.88
23.0–24.9	3652	15	1.51	0.73–3.10	1.56	0.71–3.43
25.0≥	3794	15	1.41	0.69–2.91	1.27	0.58–2.80
P for trend			0.32		0.55	
Hemorrhagic stroke						
<21.0	4214	10	1.00	Referent	1.00	Referent
21.0–22.9	3935	10	1.26	0.52–3.04	1.32	0.52–3.35
23.0–24.9	3652	7	0.94	0.36–2.49	1.13	0.39–3.25
25.0≥	3794	3	0.38	0.10–1.39	0.35	0.09–1.35
P for trend			0.16		0.16	

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, total and high-density lipoprotein-cholesterols, triglycerides, smoking, drinking and regular exercise.

Table 3 Multivariate-adjusted[a] hazard ratios for the development of ischemic stroke according to the presence or absence of obesity and each established risk factor in men, the Hisayama Study, 1988–2000

		Population at risk	*No. of events*	*HR*	*95% CI*	*P value*
Obesity[b]	*Hypertension*					
No	No	477	14	1.00	Referent	
No	Yes	308	17	1.59	0.76–3.34	0.22
Yes	No	111	7	3.79	1.44–10.00	0.007
Yes	Yes	141	9	2.95	1.19–7.30	0.02
Obesity[b]	*Diabetes*					
No	No	678	25	1.00	Referent	
No	Yes	107	6	1.60	0.65–3.97	0.31
Yes	No	200	8	1.83	0.77–4.38	0.17
Yes	Yes	52	8	7.91	3.08–20.28	<0.001
Obesity[b]	*Smoking*					
No	No	369	17	1.00	Referent	
No	Yes	416	14	1.18	0.56–2.48	0.67
Yes	No	148	8	2.13	0.83–5.46	0.11
Yes	Yes	104	8	3.62	1.39–9.43	0.008

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, total and high-density lipoprotein-cholesterols, triglycerides, smoking, drinking and regular exercise, but the factor which was used for each grouping was excluded from the confounding factors.
[b]Obesity is defined as a body mass index $\geq 25\,kg\,m^{-2}$.

The strengths of our study include its longitudinal population-based design, the direct collection of height, weight and biological markers from all participants, long duration of follow-up, perfect follow-up of subjects and accuracy of diagnosis of stroke. One limitation of our study is that our findings are based on a one-time measurement of BMI, as was the case in most other epidemiological studies. During the follow-up, BMI and other risk factor levels were changed due to modifications in lifestyle or medication, and misclassification of BMI categories was possible. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown here.

In conclusion, our data suggest that overweight and obesity are significant risk factors for the development of ischemic stroke in contemporary Japanese men. In Japan, BMI levels have increased steadily over the last several decades. For prevention of stroke, it is important to correct obesity while controlling other risk factors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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

Jun Hata[a, b] Yasufumi Doi[a, b] Toshiharu Ninomiya[a, b] Masayo Fukuhara[a, b] Fumie Ikeda[a, b] Naoko Mukai[a, b] Yoichiro Hirakawa[a, b] Takanari Kitazono[b] Yutaka Kiyohara[a]

Departments of [a]Environmental Medicine and [b]Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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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Jun Hata
Department of Environmental Medicine, Graduate School of Medical Sciences
Kyushu University, 3-1-1 Maidashi, Higashi-ku
Fukuoka 812-8582 (Japan)
Tel. +81 92 652 3080, E-Mail junhata@envmed.med.kyushu-u.ac.jp

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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分担研究報告書

5年後の糖尿病発症リスクを指標とした耐糖能の評価基準の検討- 舟形研究(Funagata study)-

分担研究者　大門　真　山形大学医学部第三内科 准教授

研究要旨

メタボリックシンドロームの１要素である空腹時血糖値(FPG)の基準値(110 mg/dl)の妥当性に付いて、糖尿病発症リスクという観点から調べた。舟形糖尿病検診参加者の内、ベースライン時に非糖尿病で５年後の追跡調査にも参加した者を累計して対象とし(1631 人 3,516 (男/女：1,496/2,020；年齢：58.2±10.4)、糖尿病発症をエンドポイントとした。層別化解析：ベースライン時の FPG(≦79, 5 mg/dl 毎, 120-125 mg/dl)にて層別化し、各群の５年後の糖尿病累積発症率の違いを、年齢、性別補正多重ロジステイック回帰分析で解析。血糖値の上昇に伴いリスクは上昇し、FPG100-104 mg/dl の群(OR 12.7(1.7-95.1), p=0.013) 以上で、対照群（最低値群）に比して有意に発症率が高くなった。連続する群間での解析では、95-99 と 100-104 mg/dl の群間で初めて有意差がつき(2.1(1.1-3.8), 0.018)、最大 OR は 100-104 と 105-110 群間で(2.4(1.4-4.3), 0.002)であった。５年後の糖尿病発症を予測する最適な FPG を ROC 解析にて求めると、100 mg/dl となった。５年後の糖尿病発症リスクを指標とした場合の日本人での耐糖異常の FPG 基準値は、100 mg/dl が良い事が示唆された。

A. 研究目的

メタボリックシンドローム(MetS)は，内蔵肥満を背景として、耐糖能異常、脂質異常及び高血圧が重積した病態の総称である。本邦の MetS の診断基準は、内蔵脂肪の蓄積（ウエスト周囲径(Wc)を基準）が必須項目であり、その他の集積が問題となる（非必須項目）メタボリック因子として、血圧、脂質異常（中性脂肪、あるいは、HDLc)、及び、空腹時血糖値(FPG)が含まれる。今回、私達は、その１要素である FPG の基準値(110 mg/dl)の妥当性に付いて、糖尿病発症リスクという観点から調べた。

なお、FPG 110 mg/dl 以上は、糖尿病発症の高リスク群と位置づけられている糖尿病予備群と一致する。糖尿病予備群は FPG では 110-125mg/dl 、糖負荷後２時間血糖値(2hrPPG)では 140-199 mg/dl がそれに当たるとして WHO、日本糖尿病学会，等にて定義されている。一方、アメリカ糖尿病学会では、FPG 100-125 mg/dl が、それに当たるとしており、国際的には一定していない。今回、私達は、私達のコホートの追跡調査より、5 年後の糖尿病発症リスクを指標として、この血糖値の基準値の妥当性について検討した。

B. 研究方法

1979年より山形県舟形町の３５歳以上の住民を対象に行っている舟形研究では、1990 年から参加者全員に糖負荷試験を行い、確実な耐

糖能の評価を行いコホートとして追跡調査を行っている。本検診参加者の内、ベースライン時に非糖尿病で５年後の追跡調査にも参加した者を累計して対象とした(1631 人 3,516（男/女：1,496/2,020；年齢：58.2±10.4)。糖尿病発症の評価は、糖尿病治療の開始の有無（アンケート）及び追跡調査時の糖負荷試験（1999 年の WHO 基準）を用いて行った。

解析：1.層別化解析：ベースライン時の空腹時血糖値(FPG；≦79, 80-84, 85-89, 90-94, 95-99, 100-104, 105-109, 110-114, 115-119, 120-125 mg/dl)、及び、糖負荷後２時間血糖値(2hrPPG；≦99, 100-109, 110-119, 120-129, 130-139, 140-149, 150-159, 160-179, 180-199 mg/dl)にて層別化して、各群の５年後の糖尿病累積発症率(1000 人年当たりの発症数)の違いを層別化群の最低値群（基準解析)、及び、連続する２群間の低値群を対照（群間解析）として、年齢、及び、性別で補正した多重ロジステイック回帰分析で解析した。

解析 2. ５年後の糖尿病発症を予測する最適な FPG 及び、2hrPPG を Receiver Operator Characteristic (ROC) 解析にて求めた。

C. 研究結果

解析１(層別化解析)：a.基準解析：血糖値の上昇に伴いリスクは上昇し、FPG では 100-104 mg/dl の群 (OR 12.7(1.7-95.1), p=0.013) 以上で、2hrPPG では 130-140 mg/dl の群 (2.8(1.3-6.2), 0.011) 以上で、対照群に比して有意に発症率が高くなった。b.群間解析：FPG では、95-99 と 100-104 mg/dl の群間で初めて有意差がつき(2.1(1.1-3.8), 0.018)、低値群に対する高値群の OR は 100-104 と 105-110 群間で (2.4(1.4-4.3), 0.002)最大であった。2hrPPG では 130-139 と 140-149 mg/dl の群間で初めて有意差がつき(p=0.007)、OR もこの群間が、群間解析中最大であった(3.0(1.4-6.6))。

解析 2(ROC 解析)：５年後までの糖尿病発症を予測する、最適（感度、及び、特異度を最大とする）な血糖値のカットオフ値は、FPG は 100 mg/dl (感度：66.4%；特異度：81.5%)、2hrPPG は 135 mg/dl (62.0%; 85.9%)であった。

D. 考察

5 年後の糖尿病発症リスクを指標とした場合の日本人での耐糖能異常の基準値は、2hrPPG は現在の 140 ≧mg/dl が妥当と思われたが、一方、FPG は、現在の 110 ではなく、100 mg/dl が妥当と思われた。

MetS の診断基準は、血管障害の発症リスクの増加をエンドポイントとして検討しなければならない。本解析は、糖尿病発症をエンドポイントとしたもので、この結果は、MetS の診断基準の FPG 値の変更が望ましい事を直接示したものではないが、その可能性を示唆するものと思われた。

E. 結論

耐糖能異常の FPG 基準値、すなわち空腹時過血糖(IFG)の基準値は 100 mg/dl が妥当と思われた。

G. 研究発表

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H. 知的財産権の出願・登録状況

無し

別紙４

雑誌

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