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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 $\geqslant 25.0\,kg\,m^{-2}$). 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 $\geqslant 25\,kg\,m^{-2}$ (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

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.

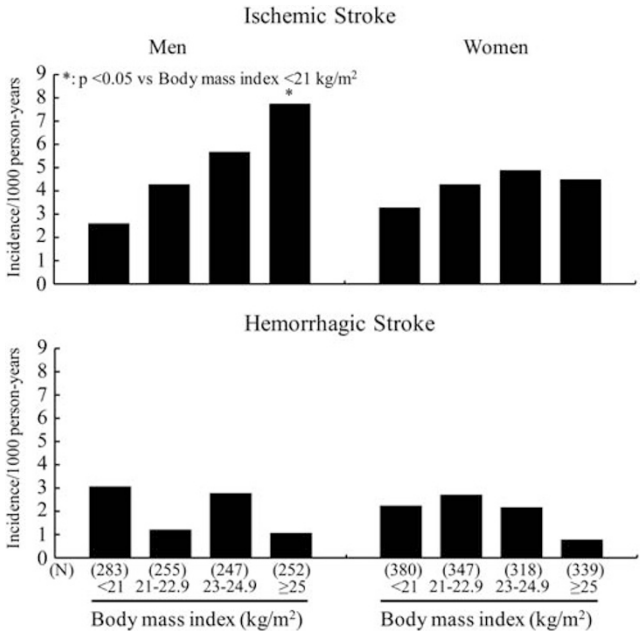

Figure 1 Age-adjusted incidence of stroke by body mass index levels during 12-year follow-up, the Hisayama Study, 1988–2000.

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 $\geqslant 25\,kg\,m^{-2}$.

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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