Body Mass Index and Stroke Incidence in Japanese Community Residents.

日本人における Body Mass Index と脳卒中の罹患に関するコホート研究

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Contents

１．　本研究の背景

脳卒中は、日本における主な死因であり、後遺症の原因ともなっている。2015 年の厚生労働省人口動態調査によれば、約 112,000 人が死亡し、全死亡の 8.67%に及んでいる。日本人においては、脳梗塞の急性期死亡率は 10%を下回っているが、重い後遺症を残すことで、介護保険の支給が必要となる原因の一位となっており、保健医療福祉における大きな問題である。

Body mass index (BMI)は、体脂肪率との相関が高く、肥満や太り気味、あるいは痩せの指標として疫学研究で用いられている。欧米やアジアの研究では、高い BMI は脳卒中を含む循環器疾患の危険因子であると報告されている。

BMI と脳卒中の関連について、いくつかの欧米の研究では、高い BMI は脳卒中の危険因子であるとされているものの、交絡因子を調整することで、関連がみられなくなるものもある。日本人を対象とした 3 つの先行研究でも、BMI と脳卒中の罹患との関連に関する研究では、線形の関係を示さなかったり、統計学的に有意でなかったりと、様々な報告が有り、一定の結論を得ていない。日本人を対象とした BMI と脳卒中の罹患との関連についてはさらなる研究が必要である。

脳卒中の中でも、くも膜下出血は、2015 年の厚生労働省人口動態調査によれば、約 12,000 人が死亡している。その急性期死亡率（致命率）は 40～60%と高く、働き盛りの世代に多いのも特徴である。BMI とくも膜下出血の罹患との関連に関して先行研究では一定した結果が得られていない。日本人を

対象とした先行研究は2つ存在しているが、一方は低いBMIはくも膜下出血の危険因子であるとし、もう一方は、関連がみられないとしている。

このように、BMIと脳卒中との関連は、世界的に見ても、我が国でも、未だ一致した結論を得ていない。脳梗塞、脳出血では急性期死亡率が低いことから、その医療および福祉への影響を検討する上では死亡ではなく、罹患を帰結とした研究が必要である。また、くも膜下出血では、罹患者数が少ないことから、従来は症例対照研究での検討が多い。より高いエビデンスを求めるためにも、罹患を帰結とした前向きコホート研究が必要である。

そのため、本研究では、BMIと脳卒中の罹患についての研究を、地域住民を対象とした大規模コホート研究のデータを用いて行った。

本研究では、既存の研究で指摘されてきた危険因子の内容と臨床像の違いから、脳出血および脳梗塞を主体とする全脳卒中と、くも膜下出血に焦点を当てた、2つの研究を行った。

２．Body mass index and stroke incidence in Japanese community residents: The Jichi Medical School (JMS) Cohort Study

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Abstract

Background: High body mass index (BMI) has been reported as a risk factor for cardiovascular events in Western countries, while low BMI has been reported as a risk factor for cardiovascular death in Asian countries, including Japan. Although stroke is a major cause of death and disability in Japan, few cohort studies have examined the association between BMI and stroke incidence in Japan. This study aimed to examine the association between BMI and stroke incidence using prospective data from Japanese community residents.

Methods: Data were analyzed from 12,490 participants in the Jichi Medical School Cohort Study. Participants were categorized into five BMI groups: ≤18.5, 18.6-21.9, 22.0-24.9, 25.0-29.9, and ≥30.0 kg/m^2. Multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazard model. The group with a BMI of 22.0-24.9 kg/m^2 was used as the reference category.

Results: During mean follow-up of 10.8 years, 395 participants (207 men and 188 women) experienced stroke, including 249 cerebral infarctions and 92 cerebral hemorrhages. Men with a BMI ≤18.5 kg/m^2 (HR 2.11; 95% CI, 1.17-3.82) and women with a BMI ≥30.0 kg/m^2 (HR 2.25; 95% CI, 1.28-5.08) were at significantly higher risk for all-stroke. Men with a BMI ≤18.5 kg/m^2 were at significantly higher risk for cerebral infarction (HR 2.15; 95% CI, 1.07-4.33).

Conclusions: The association between BMI and stroke incidence observed in this population was different than those previously reported: low BMI was a risk factor for all-stroke and cerebral infarction in men, while high BMI was a risk factor for all-stroke in women.

Introduction

Stroke is a major cause of death and disability in Japan. In 2013, stroke was responsible for nearly 120,000 deaths, and stroke currently accounts for 9.3 percent of all-cause death in Japan.[1] Body mass index (BMI) is used as a measure of body fat metabolism and has been used to define obesity, overweight, and leanness in numerous epidemiological studies.[2] Epidemiologic studies[3-5] in Western and Asian countries have reported that high BMI is a significant risk factor for mortality due to cardiovascular disease (CVD), including stroke. However, several epidemiologic studies on the association between BMI and stroke mortality in Japan have reported non-linear relationships[6-11] and no significant association.[12] Considering the serious consequences of stroke, information regarding stroke incidence and mortality is important. Among the Japanese population, the acute case-fatality rate for cerebral infarction is less than 10 percent.[13,14] Nevertheless, non-fatal stroke is a major cause of lifelong disability and places a heavy burden on Japan's long-term care insurance system.[15]

European and North American studies[16-22] have reported that high BMI is significantly associated with an increased incidence of stroke. However, in some of those studies,[18,22] the significance of this association disappeared after adjusting for potential confounders. To the best of our knowledge, only a few cohort studies[23-25] have examined the association between BMI and stroke incidence in Japan. Additionally, the sex ratios, implementation periods, stroke types, BMI ranges, and adjusted factors differed among these studies; therefore, the association between BMI and stroke incidence in the Japanese population remains unclear.

In this study, we examined the association between BMI and stroke incidence in Japanese community residents using data from the Jichi Medical School Cohort Study.

Methods

Study population

We obtained baseline data from the Jichi Medical School Cohort Study, a population-based prospective study conducted in 12 rural Japanese communities between April 1992 and July 1995 that investigated risk factors for CVD.[26] In accordance with the Health and Medical Service Law for the Aged of 1982, mass screening examinations for CVD have been conducted since 1983. Study data were collected on the basis of these examination results. The participants for the mass screening examinations were residents aged 40-69 years in eight areas, and residents aged 19 years and older in another area. Participants from other age groups in the remaining three areas were also included.

In each community, a local government office sent personal invitations to all participants by mail. Among the 12,490 individuals (4911 men and 7579 women) who participated in the mass screening examinations and underwent a basic medical checkup, the response rate was about 99%. Those who did not agree to be followed (n. 95), those without BMI data (n. 504), and/or those with a history of stroke (n. 113), myocardial infarction (n. 65), angina pectoris (n. 221) or cancer (n. 142) were excluded. Ultimately, overlapping data from 11,404 participants

(4444 men and 6960 women; age range, 19-90 years) were analyzed.

Baseline examinations

Health checkups were carried out in each community. Body height was measured without shoes, and body weight was recorded while fully clothed and then adjusted by subtracting 0.5 kg (in the summer) or 1 kg (in other seasons) to account for clothing. BMI was calculated as weight (kg) divided by the square of height (m). Systolic blood pressure (SBP) was measured using a fully automatic sphygmomanometer (BP203RV-II; Nippon Colin, Komaki, Japan). Serum lipids (total cholesterol [TC], high-density lipoprotein [HDL] cholesterol, and triglycerides [TG]) and blood glucose (BG) were also measured using standard methods, as previously reported.[26]

Information regarding medical history and sociodemographic characteristics was obtained by trained interviewers using standardized questionnaires. Smoking status was defined as current smoker, ex-smoker, or never smoker, and alcohol drinking status was categorized as current drinker, ex-drinker, or never drinker.

Follow-up

We obtained baseline data from the mass screening examinations and subsequently attempted to follow all of the participants annually. We asked the participants directly whether they had experienced stroke or myocardial infarction after the baseline study. If they had, we asked which hospital they had visited and when they did so in order to ascertain the incidence of disease. The participants who had not undergone screening examinations were contacted via mail or telephone or visited at home by a public health nurse. We also checked medical records to verify whether the participants had visited the hospital. If an incident case was suspected, we collected computed tomography or magnetic resonance imaging for evidence of stroke, or electrocardiograms for evidence of myocardial infarction. Death certificates were collected at public health centers with permission from the Agency of General Affairs and the Ministry of Health, Labour and Welfare. Based on data obtained annually from each municipal government, a total of 386 participants moved out of the study area during the follow-up period. We stopped following such participants on the day they left their respective areas. Follow-up was also discontinued for participants who died before the end of the study. Death resulting from CVD was included in the CVD incidence data. Follow-up of all participants was continued until the end of 2005.

Diagnostic criteria

CVD was defined as stroke, myocardial infarction, or sudden death, whichever occurred first. The diagnoses were determined independently by a diagnosis committee consisting of a radiologist, a neurologist, and two cardiologists. To establish diagnosis, stroke was defined as sudden onset of a focal, non-convulsive neurological deficit persisting longer than 24 h. Stroke subtypes were classified as cerebral infarction, hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), or undetermined according to the criteria of the National Institute of Neurological Disorders and Stroke.[27]

Myocardial infarction was diagnosed according to the criteria of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease Project.[28] Details of the design of this study have been described previously.[26]

Statistical analysis

All analyses were performed separately for men and women using SPSS for Windows (version 21.0; IBM Japan, Inc., Tokyo, Japan). First, BMI was categorized into the following five groups based partly on the Criteria for Obesity Disease by the Japan Society for the Study of Obesity: ≤18.5, 18.6-21.9, 22.0-24.9, 25.0-29.9, and ≥30.0 kg/m^2.[29] One-way analysis of variance and the chi-square test for variables were performed to clarify the associations between BMI and potential confounders. Finally, the Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for stroke incidence in relation to BMI, adjusting for age (HR1), as well as SBP, TC, HDL cholesterol, TG, diabetes mellitus (DM), smoking status and alcohol drinking status (HR2). All categorical variables, including BMI, were treated as dummy variables. The group with a BMI 22.0-24.9 was used as the reference category in all analyses. Age, SBP, TC, HDL cholesterol and TG were entered into the model as continuous variables. DM (fasting BG ≥126 mg/dL or casual BG ≥200mg/dL, or history of use of diabetic medication), smoking status (current, ex-, or never smoker), and alcohol drinking status (current, ex-, or never drinker) were entered as categorical variables.

All reported P values are two-tailed. P values < 0.05 were considered statistically significant.

Ethical considerations

This study was approved by the Institutional Review Board of Jichi Medical School (Epidemiology 03-01) and the Ethics Committee of Saitama Prefectural University (25518). Written informed consent was obtained from all participants.

Results

The baseline characteristics of participants by BMI group are shown in Table 1. In both sexes, BMI was positively correlated with SBP, TC, and TG, and inversely correlated with HDL cholesterol. The group with a BMI $\geq$30.0 kg/m^2 tended to have DM, and men in the higher BMI groups were less likely to be current and ex-smokers. During an average follow-up period of 10.8 years, 395 participants (207 men and 188women) experienced stroke. Regarding the type of stroke, 249 cerebral infarctions (149 men and 100 women), 92 cerebral hemorrhages (45 men and 47 women), and 54 subarachnoid hemorrhages (13 men and 41 women) were reported.

Incidence rates for stroke in each BMI group are shown in Tables 2 and 3 and in Fig. 1. In men, the group with a BMI $\leq$18.5 kg/ m^2 had the highest stroke incidence. Conversely, in women, the group with a BMI $\geq$30.0 kg/m^2 had the highest stroke incidence.

Adjusted HRs and 95% CIs are shown also in Tables 2 and 3. In men, the BMI 25.0-29.9 kg/m^2 group was combined with the BMI $\geq$30.0 kg/m^2 group because both groups only had one case of cerebral infarction, and only the BMI $\geq$30.0 kg/m^2 group had a case of hemorrhagic stroke. In women, the BMI $\leq$18.5 group was combined with the BMI

18.6-21.9 kg/m^2 group because no cases of hemorrhagic stroke were reported in the BMI ≤18.5 group.

In men, the HR2 for all-stroke was significantly higher in the BMI ≤18.5 kg/m^2 group (HR2 2.11; 95% CI, 1.17-3.82). In women, the BMI ≥30.0 kg/m2 group had significantly higher HR1 (HR1 3.61; 95% CI, 1.99-6.57) and HR2 (HR2 2.25; 95% CI, 1.28-5.08) for all stroke. HR2 for cerebral infarction was high with borderline significance (HR2 2.48; 95% CI, 0.94-6.56). HR2 for cerebral hemorrhage was also high, but not statistically significant (HR2 2.41; 95% CI, 0.54-10.72). In addition, HRs were calculated using BMI as a continuous value. HR1 for all-stroke in women and HR2 for cerebral hemorrhage in men were statistically significant.

Discussion

After adjusting for potential confounders, men with a BMI ≤18.5 kg/m^2 were at significantly higher risk for all-stroke and cerebral infarction, whereas women with a BMI ≥30.0 kg/m^2 were at increased risk for all-stroke.

To the best of our knowledge, the association between BMI and stroke incidence in Japan has only been evaluated in three previous cohort studies. Although our study was similar to those previous studies in terms of design, period of implementation, and age range of participants, our results were inconsistent with previous findings. The Hisayama study reported that high BMI was associated with a high incidence of cerebral infarction in men, but not in women.[25] The Japan Public Health Center-Based Prospective (JPHC) Study reported that higher BMI was associated with an increased risk of stroke in women, but not in men.[23] Females in the Hisayama study were more likely to be current smokers than those in our study. In addition, the JPHC study used a self-administered questionnaire to identify hypertension, DM, and dyslipidemia, and calculated BMI using self-reported information. These differences could explain the inconsistencies in the findings between our study and the previous studies. A meta-analysis performed by the Japan

Atherosclerosis Longitudinal Study group reported a significantly elevated incidence of cerebral infarction and hemorrhage in both sexes with a BMI ≥27.5 kg/m^2, although this significance disappeared after adjusting for SBP.[24] In our study, adjusting for SBP did not attenuate the significance of the association between high BMI and an elevated risk of stroke in women. Significant positive associations have been reported between high BMI and incidence of cerebral infarction in both sexes in North American and European studies.[16-22] However, some of those results were no longer statistically significant after adjusting for potential confounders, such as hypertension, DM, and dyslipidemia. [18,22] In addition, to date, no significant association between low BMI and an increased risk of stroke incidence has been reported. Therefore, our study may represent new epidemiologic findings.

Furthermore, in terms of studies in which the end point was mortality, only non-linear relationships, such as U-shaped,[7,10,11] Jshaped,[6] and inverted J-shaped relationships,[8] have been reported between BMI and stroke mortality. Our incidence study observed a similar relationship to that reported in the Miyako study (conducted in Japan), in which low BMI appeared to be associated with an increased risk of stroke mortality in men.[9]

Our results suggest that low BMI in men is associated with an increased risk of stroke. Even though BMI measurement is limited in that fat-related weight is not distinguished from muscle-related weight, it is widely used and well accepted in epidemiologic research and clinical practice. Although the association between physiological factors, such as obesity, leanness, and proneness to disease, remains unknown, low BMI may result in health risks, such as low muscle mass, which are associated with worsening nutritional status, poor physical fitness, inflammation, and altered hormonal milieu.[30] Further investigations are needed to achieve a better understanding of the risk of stroke in patients with low BMI.

The primary strength of our study was that it evaluated stroke incidence among both sexes based on a large Japanese cohort study. In addition, data were obtained in a standardized fashion. Only validated cases of stroke among annual health examination participants who had no history of CVD at baseline were included. The diagnosis of stroke was made by an independent committee using accepted diagnostic criteria, which minimized the possibility of information bias.

However, this study did have several limitations. First, although the study participants were selected from a population-based health examination, the selections were not randomized. Among the health examination participants, the proportions treated for hypertension, DM, and/or dyslipidemia were lower than those reported in a national health and nutrition examination survey.[31] Therefore, the participants in this study appeared to be somewhat healthier than the general population. Second, smoking status, alcohol drinking status, and history of medication were all self-reported, and the participants were weighed with their clothes on; therefore, some inaccuracies can be expected. Third, cases involving asymptomatic stroke were not included; therefore, stroke incidence may have been underestimated. Finally, the significant findings were based on 11 incident stroke cases involving lean men and 13 cases involving obese women. Even though these results were statistically significant after adjusting for age and other major potential CVD risk factors, these findings may have been a chance observation.

Conclusion

The results of this study suggest that men with a BMI ≤18.5 kg/m^2 and women with a BMI ≥30.0 kg/m^2 are at significantly higher risk for all-stroke, and men with a BMI ≤18.5 kg/m^2 are at significantly increased risk for cerebral infarction. These results could provide potentially useful information to stimulate further studies regarding the association between BMI and stroke incidence among Japanese community residents.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.je.2016.08.007.

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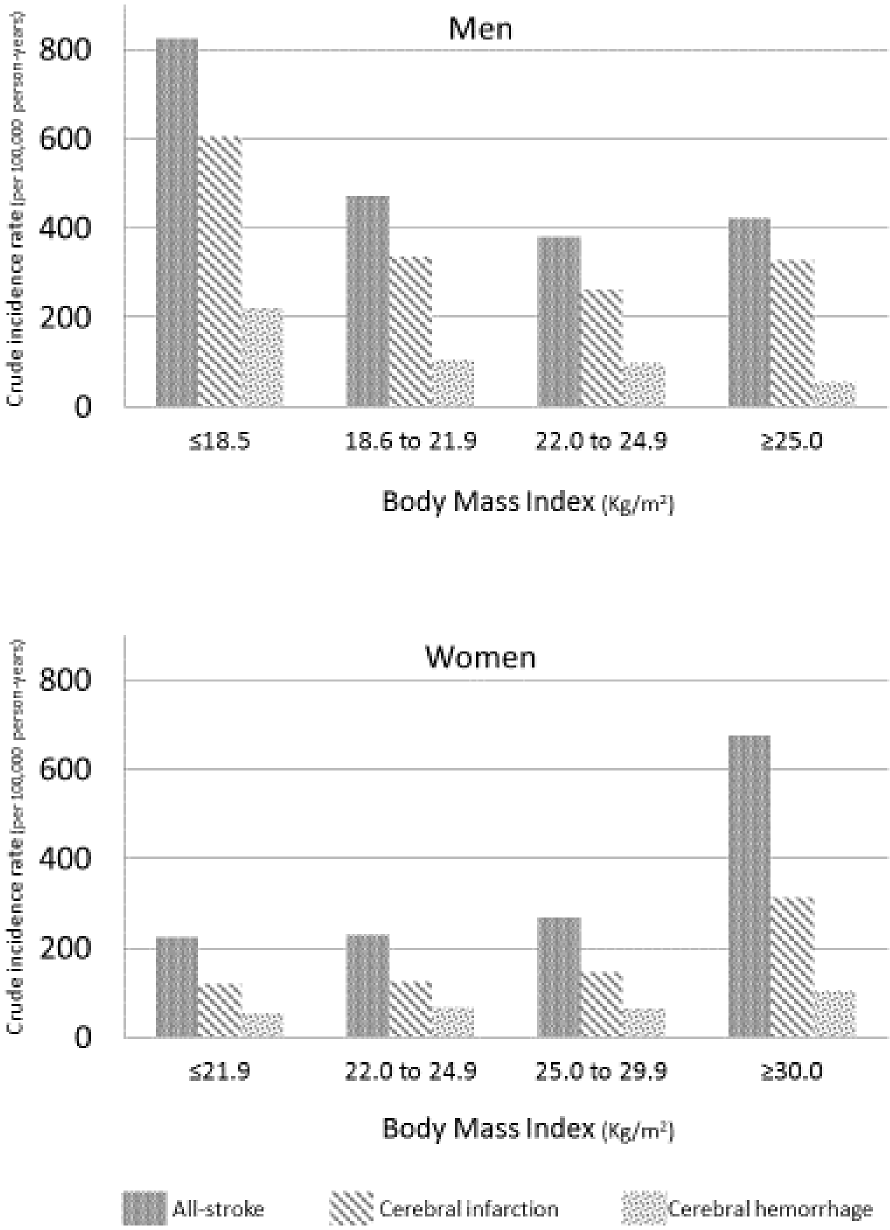

Figure 1. Crude incidence rate based on body mass index

Table 1. Baseline relationships between body mass index and potential confounders

	Body mass index, kg/m^2					P-value [a]	Body mass index, kg/m^2					P-value [a]
	≤18.5	18.6 to 21.9	22.0 to 24.9	25.0 to 29.9	≥30.0		≤18.5	18.6 to 21.9	22.0 to 24.9	25.0 to 29.9	≥30.0	
	Men						Women					
No. of subjects	190	1,533	1,725	932	64		365	2,272	2,567	1,569	187	
Age, years	59.6	55.3	54.9	53.3	53.3	<0.01	55.2	53.3	55.8	56.8	55.4	<0.01
	(13.4)	(12.5)	(11.5)	(11.0)	(11.5)		(14.6)	(12.2)	(10.2)	(9.6)	(9.1)	
Systolic blood pressure, mmHg	123.6	126.6	132.1	138.2	145	<0.01	118.3	122.4	129.3	135.3	140.6	<0.01
	(20.7)	(19.8)	(19.9)	(19.9)	(20.1)		(20.5)	(19.9)	(20.1)	(20.5)	(21.5)	
Serum cholesterol concentration												
Total cholesterol, mg/dL	171.6	178.3	187.2	193.7	202.2	<0.01	186.4	191.5	197.9	204.5	206.1	<0.01
	(30.8)	(33.2)	(33.0)	(34.8)	(36.9)		(35.5)	(34.5)	(34.2)	(34.3)	(34.4)	
High-density lipoprotein cholesterol, mg/dL	55.3	52.4	48	43.8	40.9	<0.01	58.6	55.6	51.8	48.9	47.2	<0.01
	(15.5)	(13.3)	(13.0)	(11.5)	(11.6)		(13.3)	(12.4)	(12.2)	(11.3)	(10.9)	
Triglycerides, mg/dL	88.5	103.5	130.8	167.1	221.5	<0.01	83.0	91.6	111.8	135.7	150.5	<0.01
	(58.4)	(72.7)	(80.1)	(101.3)	(150.5)		(43.8)	(48.4)	(63.7)	(85.5)	(89.2)	
Diabetes mellitus [b], %	4.2	4.2	4.4	5.1	7.8	0.57	1.7	1.4	1.6	2.1	9.6	<0.01
Current smoker, %	62.2	57.4	47.2	44.8	45.8	<0.01	8.5	6.9	4.2	4.9	8.1	<0.01
Current alcohol drinker, %	65.2	76.4	76.9	74.9	56.6	<0.01	32.4	33.2	34.9	33.5	30.7	0.61

Data are expressed as mean (standard deviation) or percentage of participants.

a) P values were calculated using one-way analysis of variance or the chi-square test for variables.

b) Fasting blood glucose level ≥126mg/dL or casual blood glucose level ≥200mg/dL, or history of diabetic medication.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) based on body mass index and adjusted for potential confounders in men

	Body mass index, kg/m^2			
	≤18.5	18.6 to 21.9	22.0 to 24.9	≥25.0
Person-years	1,820	16,092	18,613	10,676
All-stroke				
No. of cases	15	76	71	45
Incidence rate*	824	472	381	421
HR1 (95%CI)	1.52 (0.87 - 2.66)	1.16 (0.84 - 1.61)	1.00	1.31 (0.90 - 1.90)
HR2 (95%CI)	2.11 (1.17 - 3.82)	1.35 (0.95 - 1.91)	1.00	0.97 (0.64 - 1.48)
Cerebral infarction				
No. of cases	11	54	49	35
Incidence rate*	604	336	263	327
HR1 (95%CI)	1.59 (0.82 - 3.07)	1.19 (0.81 - 1.76)	1.00	1.51 (0.98 - 2.32)
HR2 (95%CI)	2.15 (1.07 - 4.33)	1.42 (0.94 - 2.15)	1.00	1.13 (0.69 - 1.83)
Cerebral hemorrhage				
No. of cases	4	17	18	6
Incidence rate*	220	106	97	56
HR1 (95%CI)	1.70 (0.57 - 5.07)	1.04 (0.54 - 2.02)	1.00	0.66 (0.26 - 1.65)
HR2 (95%CI)	2.78 (0.86 - 9.01)	1.11 (0.53 - 2.33)	1.00	0.43 (0.14 - 1.31)

HR1: Hazard ratios adjusted for age.

HR2: Hazard ratios adjusted for age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides, diabetes mellitus, smoking, and alcohol consumption.

*: per 100,000 person-years.

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) based on body mass index and adjusted for potential confounders in women

	Body mass index, kg/m^2			
	≤21.9	22.0 to 24.9	25.0 to 29.9	≥30.0
Person-years	28,442	28,285	17,135	1,924
All-stroke				
No. of cases	64	65	46	13
Incidence rate*	225	230	268	676
HR1 (95%CI)	1.03 (0.73 - 1.45)	1.00	1.15 (0.79 - 1.67)	3.61 (1.99 - 6.57)
HR2 (95%CI)	1.12 (0.78 - 1.60)	1.00	0.94 (0.62 - 1.41)	2.25 (1.28 - 5.08)
Cerebral infarction				
No. of cases	34	35	25	6
Incidence rate*	120	124	146	312
HR1 (95%CI)	1.24 (0.86 - 1.80)	1.00	1.52 (0.98 - 2.36)	1.36 (0.32 - 5.57)
HR2 (95%CI)	1.03 (0.63 - 1.70)	1.00	0.90 (0.51 - 1.59)	2.48 (0.94 - 6.56)
Cerebral hemorrhage				
No. of cases	15	19	11	2
Incidence rate*	53	67	64	103
HR1 (95%CI)	0.82 (0.41 - 1.61)	1.00	0.94 (0.45 - 1.97)	1.95 (0.45 - 8.43)
HR2 (95%CI)	0.94 (0.46 - 1.94)	1.00	0.88 (0.40 - 1.94)	2.41 (0.54 - 10.72)

HR1: Hazard ratios adjusted for age.

HR2: Hazard ratios adjusted for age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides, diabetes mellitus, smoking, and alcohol consumption.

*: per 100,000 person-years.

３． Body Mass Index and Incidence of Subarachnoid Hemorrhage in Japanese Community Residents: The Jichi Medical School Cohort Study

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Abstract

Background: Whereas high body mass index (BMI) is reportedly a risk factor for cardiovascular events in Western countries, low BMI has been reported as a risk factor for cardiovascular death in Asia, including Japan. Although subarachnoid hemorrhage (SAH) is a highly fatal disease and common cause of disability, few cohort studies have examined the associations between BMI and SAH in Japan. This study investigated the associations between BMI and incidence of SAH using prospective data from Japanese community residents.

Methods: Data were analyzed from 12,490 participants in the Jichi Medical School Cohort Study. Participants were categorized into 5 BMI groups: ≤18.5, 18.6-21.9, 22.0-24.9, 25.0-29.9, and ≥30.0 kg/m^2. Multivariate-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazard model with BMI of 22.0-24.9 kg/m^2 as the reference category.

Results: During the mean follow-up period of 10.8 years, 55 participants (13 men, 42 women) experienced SAH. BMI ≥30.0 kg/m^2 was associated with significantly higher risk for SAH (HR, 5.98; 95% CI, 2.25-15.87). BMI ≤18.5 kg/m^2 showed a nonsignificant tendency toward high risk of SAH (HR, 2.51; 95% CI, .81-7.79).

Conclusions: High BMI was a significant risk factor for SAH.

Lower BMI showed a nonsignificant tendency toward higher risk of SAH. Our results suggest a J-shaped association between BMI and risk of SAH incidence.
Key Words: Body mass index, subarachnoid hemorrhage, community-based cohort study, Japanese population.

Introduction

Subarachnoid hemorrhage (SAH) was responsible for the deaths of almost 12,476 people in 2015 in Japan,[1] and the estimated annual number of patients was 36,000 in 2011.[2] The rate of acute case fatality for SAH is very high (40%-60%),[3,4] particularly among the young.

Body mass index (BMI) is used as a measure of body fat metabolism and has been used to define obesity, overweight, and leanness in many epidemiologic studies. This index has been recognized as an important risk factor for the development of cardiovascular diseases (CVD). Nevertheless, limited information is available regarding the association between BMI and SAH in community based cohort studies. Some European cohort studies have shown that subjects with high BMI had a low risk of SAH,[5,6] but the results were not statistically significant. A meta-analysis of 26 Asian-Pacific cohorts suggested BMI had no significant association with SAH.[7]

To the best of our knowledge, only 2 cohort studies have reported on the association between BMI and SAH in Japan. The Japan Collaborative Cohort (JACC) study showed low BMI as a risk factor for SAH mortality.[8] However, another study reported a nonsignificant trend toward an association between BMI and incidence of SAH.[9]

The significance of BMI as a risk factor for SAH incidence thus remains controversial.

This study examined the association between BMI and spontaneous SAH incidence in Japanese community residents using data from the Jichi Medical School Cohort Study.

Methods

Study Population

We used data from the Jichi Medical School Cohort Study, a population-based prospective study. The baseline survey administered in 12 Japanese municipalities between April 1992 and July 1995 collected data on sociodemographic characteristics, anthropometric measurements, and potential risk factors for CVD.[10] This survey was conducted in accordance with the Health and Medical Service Law for the Aged of 1982.

Study data were collected on the basis of these examination results. Participants for the baseline examinations were residents between 40 and 69 years old in 8 areas, and residents ≥19 years old in one other area. Participants from other age groups in the remaining 3 areas were also included.

In each community, a local government office mailed invitations to all residents who were eligible for the health mass screening based on the law, and 62.7% of them participated. Finally, 99% of the participants (12,490 participants; 4911 men and 7579 women) consented to be subjects of this study. Figure 1 shows the geographic location of the 12 municipalities and the number of participants.

Individuals who did not agree to be followed (n = 95), those without BMI data (n = 504), and those with a history of stroke (n = 113), myocardial infarction (n = 65), angina pectoris (n = 221), or malignant neoplasm (n = 142) were excluded. Finally, data from 11,404 participants (4444 men and 6960 women; age range, 19-90 years) were available for analysis.

Baseline Examinations

Body height was measured without shoes, and body weight was recorded while fully clothed and then adjusted by subtracting 0.5 kg (in the summer) or 1 kg (in other seasons) to account for clothing. BMI was calculated as weight (in kilograms) divided by the square of height (in meters). Systolic blood pressure (SBP) was measured with a fully automatic sphygmomanometer (BP203RV-II; Nippon Colin, Komaki, Japan). Serum lipids (total cholesterol [TC], high-density lipoprotein [HDL] cholesterol, and triglycerides [TG]) and blood glucose (BG) were also measured using standard methods, as reported previously. Trained interviewers using standardized questionnaires obtained information regarding medical history and sociodemographic characteristics. Smoking status was defined as current smoker, ex-smoker, or never smoker, and alcohol drinking status was classified as current drinker, ex-drinker, or never drinker.

Follow-Up

We attempted annual follow-ups with all participants. Participants were asked directly whether they had experienced stroke or myocardial infarction after the baseline study. Participants who had not undergone annual screening examinations were contacted by mail or telephone, or received home visits by public health nurses. If an incident case was suspected, we reviewed the medical records to document symptoms and signs, images from computed tomography or magnetic resonance imaging as evidence of stroke, or electrocardiograms for evidence of myocardial infarction. Death certificates were collected at public health centers with permission from the Agency of General Affairs and the Ministry of Health, Labour and Welfare.

Based on data obtained annually from each municipal government, a total of 386 participants moved out of the study area during follow-up. Thus, follow-up of these participants were ceased on the day they moved out from their respective area. Follow-up was also discontinued for participants who died before the end of the study. Death caused by CVD was included in the CVD incidence data. Follow-up of all participants was continued until December 31, 2005.

Diagnostic Criteria

CVD was defined as stroke, myocardial infarction, or sudden death, whichever occurred first. Diagnoses were determined independently by a diagnosis committee comprising a radiologist, a neurologist, and 2 cardiologists. To establish diagnosis, stroke was defined as sudden onset of a focal, nonconvulsive neurologic deficit persisting longer than 24 hours. Stroke subtypes were classified as cerebral infarction, cerebral hemorrhage, SAH, or undetermined according to the criteria of the National Institute of Neurological Disorders and Stroke.[11] Spontaneous SAH was diagnosed with cranial computed tomography performed to confirm the hyperdense appearance of extravasated blood in the subarachnoid space or basal cisterns. SAH due to traumatic brain injury was excluded by reviewing medical records. Myocardial infarction was diagnosed according to the criteria of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease Project.[12] Details of the design of this study have been described previously.[10]

Statistical Analysis

All analyses were performed using the SPSS for Windows version 22.0 (IBM Japan, Tokyo, Japan). BMI was categorized into the following 5 groups based partly on the Criteria for Obesity Disease by the Japan Society for the

Study of Obesity: ≤18.5, 18.6-21.9, 22.0-24.9, 25.0-29.9, and ≥30.0 kg/m^2.[13] One-way analysis of variance and the chi-square test for variables were used to clarify the associations between BMI and potential confounders. Finally, Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of SAH in relation to BMI, adjusting for age and sex (HR1), SBP, TC, HDL, TG, diabetes mellitus (DM), smoking status, and alcohol drinking status (HR2). The group with BMI 22.0-24.9 was used as the reference category in all analyses. Age, SBP, TC, HDL, and TG were entered into the model as continuous variables. DM ([fasting BG ≥126 mg/dL or casual BG ≥200 mg/dL, or history of diabetic medication]), smoking status (current, ex-smoker, or never smoker), and alcohol drinking status (current, ex-smoker, or never drinker) were entered as categorical variables.

All reported P values are two-tailed. Values of $P < 0.05$ were considered statistically significant.

Ethical Considerations

This study was approved by the institutional review board of Jichi Medical School (Epidemiology 03-01) and he ethics committee of Saitama Prefectural University (27511). Written informed consent was obtained from all participants prior to enrollment. All municipal councils of the 12 communities approved this study design.

Results

The baseline characteristics of the participants categorized by BMI group are shown in Table 1. In both sexes, BMI correlated positively with SBP, TC, and TG, and inversely with HDL cholesterol. Men in the higher BMI groups were more likely to be younger, nonsmokers, nonalcohol drinkers, and diabetics. Women in the low and high BMI groups were more likely to be current smokers.

During the mean follow-up period of 10.8 years, 396 participants (207 men, 188 women) experienced stroke. The type of stroke was SAH in 55 patients (13 men, 42 women), cerebral infarction in 249 (149 men, 100 women), and cerebral hemorrhage in 92 (45 men, 47 women).

Incidence rates and adjusted HRs with 95% CI for stroke in each BMI group are shown in Table 2. The group with BMI 22.0-24.9 kg/m^2 was used as the reference group. The BMI ≥30.0 kg/m^2 group showed significantly higher HR1 (HR1, 6.99; 95% CI, 2.70-18.10) and HR2 (HR2, 5.98; 95% CI, 2.25-15.87). The BMI ≤18.5 kg/m^2 group showed a nonsignificant trend toward higher HR (HR1, 1.90; 95% CI, .63-5.74; HR2, 2.51; 95% CI, .81-7.79).

Discussion

We analyzed data from a community-based cohort study with a mean follow-up period of 10.8 years. After adjusting for age, sex, and potential confounders, HRs for SAH were significantly high in the group with BMI ≥30.0 kg/m^2. The group with BMI ≤18.5 kg/m^2 tended to show high HRs for SAH. Our results seem to show a J-shaped association between BMI and risk of SAH incidence.

To the best of our knowledge, this represents the first cohort study to demonstrate a significant association between high BMI and increased risk of spontaneous SAH incidence in Japan. Only 2 previous cohort studies have evaluated the association between BMI and spontaneous SAH among Japanese community residents. A multisite community-based cohort study[9] indicated that BMI level was not associated with the incidence of spontaneous SAH. That study was similar to our own in terms of design and the age range of participants. On the other hand, implementation time in that study was 10 years earlier than in our study. At that point, images from computed tomography were not available for diagnosis in 17% of cases. In addition, hypertension was used as a category in multivariate analyses. The JACC study[8] reported low BMI (<18.5 kg/m^2) as a significant risk factor for spontaneous AH death in men, but not in women, although the significance of the results was attenuated in additional sex-stratified analyses. Implementation time, follow-up period, and some baseline characteristics of the JACC study were similar to those in our study. Sex ratios (men:women) for SAH cases in both previous studies were approximately 1:2, compared with 1:3 in our study. Case certification of SAH in the JACC study was inferred from the death registration under the Family Registration Law. These differences between previous studies from Japan and our own could explain inconsistencies in the results. In Europe and Asia, several population-based cohort studies have examined BMI and SAH risk. A cohort study in Finland showed BMI was inversely associated with risk of SAH.5 The HUNT study in Norway reported a U-shaped relationship, with the group with BMI 25-29.9 showing the lowest risk.[14] Two large-scale prospective studies using a nationwide database of medical record for about 1 million individuals were conducted in British women[6] and Korean men.[15] The former showed decreased SAH risk with increased BMI. In contrast, the latter reported a nonsignificant association between BMI and SAH risk. A pooled analysis of 26 cohorts from eastern Asia and Oceanian countries failed to identify BMI as a significant risk for SAH.[16] In a nested case-control study in Norway,[17] the odds ratios of SAH did not differ significantly among

BMI groups. Two case-control studies in the United States[18,19] reported the inverse relationship between BMI and SAH risk, whereas no significant association was revealed in an Australian study.[20] These studies varied in study design, implementation period, and case identification procedure. Furthermore, age, sex ratio, BMI, SAH incidence, and ethnicity of subjects all differed with our own. The group with the lowest BMI was categorized as <18.5 kg/m^2 in Asian studies, compared with about 23 kg/m^2 in European and North American studies. BMI ≥ 30 kg/m^2 accounted for over 10% of subjects in the HUNT study, whereas 2.1% of the subjects were in the group with BMI ≥ 30 kg/m^2 in our study. A meta-analysis suggested the risk of hemorrhagic stroke decreased with increasing BMI level in Western studies, but increased in Asian studies. Ethnicity could partly explain the differences in the results between Western studies and Asian studies, including our study.

Epidemiologic studies in Japan and Western countries have reported the risk factors for SAH such as female, hypertension,[7-9,14,16,21-23] smoking,[24] heavy alcohol drinking, high coffee consumption,[25] high mental stress, high salt intake, family history of stroke, history of blood transfusion, and low temperature and high atmospheric pressure in winter.[8,9,21-23,25,26] On the other hand, hypercholesterolemia decreased the risk of SAH.[21] After adjusting for some of these factors, our results remained statistically significant. Our study could identify new epidemiologic findings.

The strength of our study was that SAH incidence was evaluated based on a large Japanese cohort study that included both sexes. Data were obtained in a standardized manner. Validated cases of CVD among annual health examination participants who had no history of CVD at baseline examinations were included. The diagnosis of SAH was made by an independent committee using accepted diagnostic criteria, minimizing the possibility of information bias.

Several limitations to this study must be considered. Although study participants were selected from a population-based health examination, selections were not random. Selection bias is problematic if response rate is low. In this study, the response rate for the target population (62.7%) would be considered rather high.[10] However, the selection bias could exist to some extent. Among health examination participants, the proportions treated for hypertension, DM, or dyslipidemia were lower than those reported in a national health and nutrition examination survey.[27] Participants in this study thus appeared somewhat healthier than the general population.

Smoking status, alcohol drinking status, and history of medication were all self-reported, and BMI was calculated based on body weight of the fully clothed subject; therefore, some inaccuracies can be expected. Compared with the Western studies, the small number of participants with BMI ≥30.0 kg/m^2 reduced our statistical power to evaluate risk among obese subjects. The number of male incident cases (13) was small so that risk estimation for men was limited. Finally, a high prehospital mortality rate could make SAH diagnosis difficult. During follow-up, we documented 41 cases of sudden death, defined as death within 24 hours after symptom onset. However, all cases of sudden death were reviewed carefully by the diagnostic committee to rule out SAH.

Conclusion

In this community-based cohort study, the group with BMI ≥30.0 kg/m^2 was at significantly higher risk of SAH. Our results suggest a J-shaped association between BMI and risk of SAH incidence. This result could provide potentially useful information to stimulate further studies regarding associations between BMI and SAH incidence among community residents.

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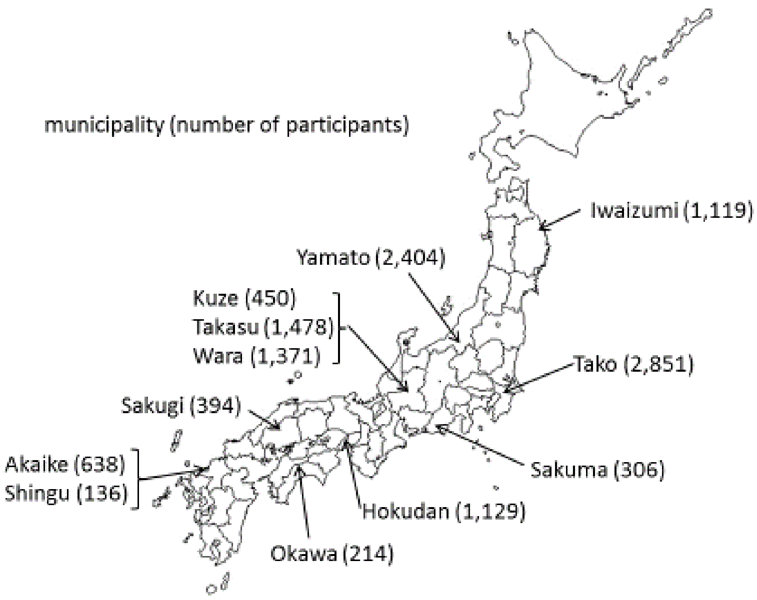

Figure 1. The twelve municipalities participating in the Jichi Medical School Cohort Study and the number of participants

Table 1. Baseline relationships between body mass index and potential confounders

	Body mass index, kg/m^2					P [a)]	Body mass index, kg/m^2					P [a)]
	≤18.5	18.6 - 21.9	22.0 - 24.9	25.0 - 29.9	≥30.0		≤18.5	18.6 - 21.9	22.0 - 24.9	25.0 - 29.9	≥30.0	
	Men						Women					
No. of subjects	190	1,533	1,725	932	64		365	2,272	2,567	1,569	187	
Age, years	59.6	55.3	54.9	53.3	53.3	<0.01	55.2	53.3	55.8	56.8	55.4	<0.01
	(13.4)	(12.5)	(11.5)	(11.0)	(11.5)		(14.6)	(12.2)	(10.2)	(9.6)	(9.1)	
Systolic blood pressure, mmHg	123.6	126.6	132.1	138.2	145.0	<0.01	118.3	122.4	129.3	135.3	140.6	<0.01
	(20.7)	(19.8)	(19.9)	(19.9)	(20.1)		(20.5)	(19.9)	(20.1)	(20.5)	(21.5)	
Serum cholesterol concentration												
Total cholesterol, mg/dL	171.6	178.3	187.2	193.7	202.2	<0.01	186.4	191.5	197.9	204.5	206.1	<0.01
	(30.8)	(33.2)	(33.0)	(34.8)	(36.9)		(35.5)	(34.5)	(34.2)	(34.3)	(34.4)	
High-density lipoprotein cholesterol, mg/dL	55.3	52.4	48.0	43.8	40.9	<0.01	58.6	55.6	51.8	48.9	47.2	<0.01
	(15.5)	(13.3)	(13.0)	(11.5)	(11.6)		(13.3)	(12.4)	(12.2)	(11.3)	(10.9)	
Triglycerides, mg/dL	88.5	103.5	130.8	167.1	221.5	<0.01	83.0	91.6	111.8	135.7	150.5	<0.01
	(58.4)	(72.7)	(80.1)	(101.3)	(150.5)		(43.8)	(48.4)	(63.7)	(85.5)	(89.2)	
Diabetes mellitus [b)], %	4.2	4.2	4.4	5.1	7.8	0.57	1.7	1.4	1.6	2.1	9.6	<0.01
Current smoker, %	62.2	57.4	47.2	44.8	45.8	<0.01	8.5	6.9	4.2	4.9	8.1	<0.01
Current alcohol drinker, %	65.2	76.4	76.9	74.9	56.6	<0.01	32.4	33.2	34.9	33.5	30.7	0.61

Data are expressed as mean (standard deviation) or percentage of participants.

a) P values were calculated using one-way analysis of variance or the chi-square test for variables.

b) Fasting blood glucose level ≥126 mg/dL or casual blood glucose level ≥200 mg/dL, or history of diabetic medication.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for subarachnoid hemorrhage based on body mass index and adjusted for potential confounders

	Body mass index, kg/m^2				
	≤18.5	18.6 - 21.9	22.0 - 24.9	25.0 - 29.9	≥30
Person-years	5,650	40,704	46,898	27,164	2,572
No. of cases	4	17	15	13	6
Men	0	5	4	3	1
Women	4	12	11	10	5
Incidence rate*	71	42	32	48	233
HR1 (95%CI)	1.90 (0.63 - 5.74)	1.37 (0.68 - 2.74)	1.00	1.47 (0.70 - 3.10)	6.99 (2.70 - 18.10)
HR2 (95%CI)	2.51 (0.81 - 7.79)	1.58 (0.78 - 3.20)	1.00	1.22 (0.56 - 2.63)	5.98 (2.25 - 15.87)

HR1: Hazard ratios adjusted for age and sex.

HR2: Hazard ratios adjusted for age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides, diabetes mellitus , smoking, and alcohol consumption.

* per 100,000 person-years.

４．本研究のまとめ

平均追跡期間は 10.8 年であった。その間、395 名（男性 207 名、女性 188 名）が脳卒中を発症した。内訳は、脳梗塞が 249 名（男性 149 名、女性 100 名）、脳出血が 92 名（男性 45 名、女性 47 名）、くも膜下出血が 54 名（男性 13 名、女性 41 名）であった。

脳卒中のタイプ別 HR および 95％CI の算出にあたっては、脳梗塞、脳卒中においては、男性では BMI30 kg/m^2 以上での脳梗塞発症者が１名しかおらず、25 kg/m^2 以上のグループと合わせて解析することとした。また、女性では、18.5 kg/m^2 以下のグループで脳出血の発症者がおらず、18.6 kg/m^2 以上 21.9 kg/m^2 以下のグループと合わせることとした。

HR2 では、全脳卒中で男性の 18.5 kg/m^2 以下のグループが HR2=2.11（95％CI：1.17-3.82）、女性の 30 kg/m^2 以上グループで HR1=3.61(1.99-6.57)、HR2=2.25（1.28-5.08）と有意な結果となり、脳梗塞では、男性の 18.5 kg/m^2 以下のグループで HR2=2.15（1.07-4.33）となり、女子では 30 kg/m^2 以上のグループで HR2=2.48(0.94-6.56)と有意ではないがボーダーライン上にあった。脳出血では、男性の低い BMI グループと女性の高い BMI グループで高い HR を示したが有意ではなかった。くも膜下出血では前述の通り男女合わせての解析を行っているが、30 kg/m^2 以上のグループで HR1=6.99（2.70-18.10）、HR2＝5.98（2.25-15.87）と有意に高く、18.5 kg/m^2 以下のグループでも有意ではないものの

HR1=1.90(0.63-5.74)、HR2=2.51(0.81-7.79)と高くなる傾向にあった。

以上の結果を要約すると、年齢や血圧、耐糖能、脂質、喫煙などの伝統的な危険因子で調整しても、男性の全脳卒中、脳梗塞では低い BMI で、女性の全脳卒中では高い BMI で、それぞれ高い HR を示した。くも膜下出血では、高い BMI において HR が有意に高く、低い BMI においても統計的有意水準に達しなかったが HR が上昇する傾向がみられ、全体では J 字型の傾向となった。

以上より、欧米の従来の研究とは異なり、本研究対象者では高い BMI のみならず、低い BMI でも脳卒中の罹患が上昇することを示し、脳卒中予防における至適な BMI 値が示唆された。本文中で述べた本研究のいくつかの限界はあるが、我が国の脳卒中予防に寄与する新たな疫学的知見をえた。

今後の研究として、本対象者では該当者が少数のため検討が不可能であったが、今後の日本人集団において増加するであろう、高い BMI(30 kg/m^2 以上)の男性における脳卒中罹患の危険性についての検討が必要である。

また疾患予防や健康増進の視点からは、脳卒中を予防するに適切な BMI を維持するための食生活や身体活動、及びそれらの達成を支援する社会的資源についての研究も必要である。