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# Smoking status and unruptured intracranial aneurysm among brain health check-up examinees: a cross-sectional study in Japan

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## Abstract

**Objective:** Although it is well known that smoking is a risk factor for subarachnoid hemorrhage, the association between smoking and unruptured intracranial aneurysms remains unclear. The aim of the present study was to investigate whether smoking status was associated with unruptured intracranial aneurysms among Japanese brain health check-up examinees.
**Materials and Methods:** We conducted a cross-sectional study of 1,496 adults (aged 26–90 years) undergoing brain health check-ups at a single community medical support hospital in Akita, Japan between 2009 and 2013. In Japan, people can discretionarily undergo a brain health check-up for early detection of unruptured intracranial aneurysms or subarachnoid hemorrhages. Participants responded to a questionnaire on lifestyle, such as smoking status, and were classified into three groups: never, former, and current smoker. The evaluation of unruptured intracranial aneurysms detected by magnetic resonance angiography was performed by an expert physician. Multiple logistic regression models were used to estimate the odds ratio for unruptured intracranial aneurysms. We performed statistical analyses by age, sex, and family history of stroke.
**Results:** The number of participants with unruptured intracranial aneurysms was 43 (2.9%). The mean age (standard deviation) and proportion of males was 55.8 (9.5) years and 53.3%, respectively. The adjusted odds ratios (95% confidence intervals) for unruptured intracranial aneurysms of 1.21 (0.48–3.08) among former smokers and 2.88 (1.10–7.50) among current smokers were compared to those of never smokers (p-trend = 0.041). After stratifying by age, sex, and family history of stroke, no interactions were found.
**Conclusion:** This cross-sectional study conducted in Japan showed that smoking was positively associated with unruptured intracranial aneurysms among brain health check-up examinees.

**Key words:** smoking, intracranial aneurysm, health check-up, Japan

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## Introduction

Cerebrovascular diseases are the fourth leading cause of death in Japan with a mortality rate of 87.1 deaths per 100,000 in 2018[1]. Additionally, cerebrovascular diseases are the second leading cause of functional disability in Japan[2], causing decreased life expectancy. Thus, early detection is important to prevent cerebrovascular diseases. Japanese can discretionarily undergo a brain health check-up, called “Nou-Dock,” to detect unruptured intracranial aneurysms (UIAs)[3, 4]. It is well known that intracranial aneurysms can cause subarachnoid hemorrhages (SAH), leading to functional disability or death[5]. Thus, it is important that UIA is detected early, promoting secondary prevention of SAH.

Most studies have focused on the risk factors of SAH[6–10], whereas only two studies have investigated the risk factors of UIA in the general population[11, 12]. It is well known that cigarette smoking is the greatest risk factor for SAH since it can grow intracranial aneurysms[8–10]. The results of the two studies on UIA were inconsistent: one reported that smoking was associated with UIA incidence[11], but the other did not observe the association[12]. Therefore, it is unclear wheth-

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er smoking is a risk factor for UIA incidence. If smoking is a modifiable risk factor for UIA, promoting not only secondary prevention (i.e. undergoing a health check-up) but also primary prevention (i.e. smoking cessation) may contribute to decreased incidence of UIA and SAH.

The aim of the present cross-sectional study was to investigate whether smoking status was associated with UIA among Japanese brain health check-up examinees.

## Materials and Methods

### *Study design and participants*

This was a cross-sectional study[13]. The source population for this study comprised all examinees who underwent brain health check-ups, the Japanese "Nou-Dock," at a single community medical support hospital in Akita Prefecture, northeastern Japan between April 1, 2009 and August 30, 2013. This included 1,531 men and women, aged 26–90 years.

Participants underwent brain health check-ups by magnetic resonance angiography (MRA) and measurements of their weight (kg), height (m), and blood pressure (mmHg) were taken. We also obtained blood samples to measure high-density lipoprotein (HDL) cholesterol (mg/dL), triglyceride (TG) (mg/dL), and hemoglobin A1c (HbA1c) (%). Participants further responded to questions about smoking status, family history of stroke, frequency of drinking per week, and job type by a self-administered questionnaire.

Of the 1,531 individuals, we excluded 10 people who had no MRA data and 25 who did not enter responses for smoking status. Thus, 1,496 individuals were included for the study.

### *Ethical issues*

We obtained and used information from brain health check-ups and self-administered questionnaires after obtaining written consent from the participants. The Ethics Committee of Hiraka General Hospital (Akita, Japan) approved the protocol of this study (approval number: 108).

### *Measurements*

The main exposure was smoking status, determined by the self-administered questionnaire. We classified participants into three groups: never smoker, former smoker, and current smoker. Former smokers were defined as those who reported "I quit smoking", regardless of the timeframe.

Blood pressure was measured twice. Thus, we used the average in regard to both the systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension was defined as an SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg or use of an antihypertensive medication[14, 15].

According to the definition of the Japan Diabetes Society (JDS), the HbA1c (%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS) (%) + 0.4%, considering the relational expression of HbA1c (JDS)(%) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP)[16]. We classified participants into two groups: lower (<6.5%) and higher (≥6.5%)[17, 18]. Consequently, diabetes mellitus was defined as HbA1c ≥6.5% or the use of diabetes medication.

Body mass index (BMI) was calculated from height and weight using the following formula: weight (kg)/height (m). We classified participants into four groups: <18.5, 18.5–25.0, ≥25.0 kg/m$^2$, and missing (no data).

Drinking status (frequency per week) was determined by the self-administered questionnaire and was classified into four groups: never/non-drinkers, less than 6 days, daily, and missing (no data).

Job type was determined by the self-administered questionnaire and was classified into five groups: primary industry (e.g. agriculture, fishing and forestry), employed by a company, civil service, medical, welfare or education personnel, and other (e.g. self-employed, freelance professional, housewife, or unemployed).

### *Outcome measurements: UIA*

MRA was used to detect UIAs. UIA evaluation by image interpretation was performed by an expert physician. Participants with one or more UIAs, regardless of size, were considered cases.

### *Statistical analysis*

We classified participants into three groups based on smoking status. Their baseline characteristics included age, sex, family history of stroke, prevalence of hypertension, HDL cholesterol, TG, diabetes mellitus, BMI, frequency of drinking per week, and job type.

To examine the association between smoking status and UIA, we used multiple logistic regression models and estimated the adjusted odds ratio (OR) with a 95% confidence interval (CI). In this analysis, we classified age, HDL cholesterol, and TG as continuous variables and sex, family history of stroke, hypertension, diabetes mellitus, BMI, frequency of drinking per week, and job type as categorical variables. Never smokers were a reference category. For cases where values for a covariate were missing, we created a separate category for missing responses and included this in the model. The following three models were used to analyze the association between smoking status and UIA. Model 1 was adjusted by age and sex. Model 2 was adjusted by model 1 plus BMI, frequency of drinking per week, and job type. Model 3 was adjusted by model 2 plus family history of stroke, hypertension, HDL cholesterol, TG, and diabetes mellitus. We also entered the categories of smoking status as ordinal numbers (never, former, or current smoker: 1, 2, or 3) in the corresponding multiple logistic regression models to test for linear trends.

We performed tests of interaction to assess whether the association between smoking status and UIA differed by age (<65 years or ≥65 years), sex (male or female), or family history of stroke (presence or absence) as unmodifiable factors. As post-hoc analyses, we also performed tests of interaction for BMI and frequency of drinking as modifiable factors. The P-value for interaction in the stratified analysis was computed by entering an interactive term (i.e. cross product) into the multiple logistic regression models, which was created by multiplying smoking status and age, sex, family history of stroke, BMI, and frequency of drinking. The exposure categories were treated as ordinal numbers (never, former, or current smoker: 1, 2, or 3).

All data were analyzed using IBM SPSS Statistics (version 25; IBM SPSS, Chicago, IL, USA). All statistical tests were 2-sided and differences at $P<0.05$ were accepted as significant.

## Results

For the 1,496 participants, 55.8 (9.5) years and 53.3% were the mean age (standard deviation) and proportion of males, respectively, and 43 (2.9%) had one or more UIAs. One participant had two UIAs. Among the 43 cases, 8 (18.6%) had an aneurysm sized ≥5 mm. The UIAs were found in the following locations: middle cerebral artery (N=17, 39.5%); anterior communicating artery (N=8, 18.6%); internal carotid-posterior communicating artery (N=13, 30.2%); and basilar tip, basilar-superior cerebellar artery, vertebral artery-posterior inferior cerebellar artery, or vertebrobasilar junction (N=6, 1.4%).

Baseline characteristics according to each smoking status group are shown in Table 1. The numbers of never, former, and current smokers were 846 (56.6%), 382 (25.5%), and 268 (17.9%), respectively. Current smokers were more likely to be younger, male, overweight or obese, daily drinkers, employed by a company or civil service, and have higher TG levels. Moreover, current smokers were less likely to have lower HDL cholesterol levels and to be medical, welfare, or education personnel.

**Table 1** Characteristics of study participants by smoking status groups (N=1,496)

| | Number (%) | | |
|---|---|---|---|
| | Never smoker (N=846) | Former smoker (N=382) | Current smoker (N=268) |
| Age, mean ± standard deviation | 56.6 ± 9.8 | 56.4 ± 8.8 | 52.1 ± 8.1 |
| Sex | | | |
| Male | 436 (51.5) | 214 (56.0) | 147 (54.9) |
| Family history of stroke | 328 (38.8) | 139 (36.4) | 92 (34.3) |
| Hypertension | 396 (46.8) | 218 (57.1) | 127 (47.4) |
| High-density lipoprotein cholesterol (mg/dL), median (interquartile range) | 69.2 (58.8–82.3) | 63.7 (52.3–75.2) | 54.6 (47.2–68.2) |
| Triglyceride (mg/dL), median (interquartile range) | 109.0 (78.0–161.0) | 138.5 (93.0–210.0) | 163 (109.0–255.8) |
| Diabetes mellitus | 80 (9.5) | 49 (12.8) | 33 (12.3) |
| Body mass index (kg/m$^2$) | | | |
| <18.5 | 41 (4.8) | 8 (2.1) | 14 (5.2) |
| 18.5-25.0 | 566 (66.9) | 230 (60.2) | 161 (60.1) |
| ≥25.0 | 239 (28.3) | 144 (37.7) | 92 (34.3) |
| Missing | 0 (0.0) | 0 (0.0) | 1 (0.4) |
| Frequency of drinking per week | | | |
| Never/non-drinkers | 462 (54.6) | 58 (15.2) | 57 (21.3) |
| Less than 6 days | 239 (28.3) | 133 (34.8) | 63 (23.5) |
| Daily | 139 (16.4) | 186 (48.7) | 144 (53.7) |
| Missing | 6 (0.7) | 5 (1.3) | 4 (1.5) |
| Type of job | | | |
| Primary industry | 89 (10.5) | 40 (10.5) | 26 (9.7) |
| Employed by company | 162 (19.1) | 103 (27.0) | 67 (25.0) |
| Civil service | 152 (18.0) | 116 (30.4) | 106 (39.6) |
| Medical, welfare or education personnel | 138 (16.3) | 46 (12.0) | 23 (8.6) |
| Other | 305 (36.1) | 77 (20.2) | 46 (17.2) |

The association between smoking status and UIA is shown in Table 2. In model 1, which adjusted for age and sex, the adjusted ORs (95% CIs) for UIA were 0.75 (0.33–1.68) among former smokers and 1.74 (0.80–3.79) among current smokers, which were not significant (p-trend=0.335). After adjusting for all confounders, a positive association was found in model 3. In the model 3, the adjusted ORs (95% CIs) for UIA were 1.21 (0.48–3.08) among former smokers and 2.88 (1.10–7.50) for current smokers, in comparison with never smokers (p-trend=0.041).

Table 3 shows the results of the stratified analysis on the association of smoking status with UIA. The adjusted OR increased among current smokers even after being stratified by age (<65 or ≥65 years) and family history of stroke (presence or absence) and showed no interaction: age (p-interaction=0.844) and family history of stroke (p-interaction=0.470). In the stratified analysis by sex, although the adjusted OR among males was more likely to be higher than among females, there was no interaction (p-interaction=0.599). Additionally, there was no interaction for BMI (p-interaction=0.612) and frequency of drinking (p-interaction=0.760) (data not shown).

**Table 2** Association between smoking status and intracranial aneurysm (N=1,496)

| | Smoking status | | | p-trend |
|---|---|---|---|---|
| | Never smoker | Former smoker | Current smoker | |
| Number of participants | 846 | 382 | 268 | |
| Number of participants with aneurysm | 25 | 8 | 10 | |
| OR (95% CI) in Model 1 | 1.00 (reference) | 0.75 (0.33–1.68) | 1.74 (0.80–3.79) | 0.335 |
| OR (95% CI) in Model 2 | 1.00 (reference) | 1.24 (0.50–3.10) | 2.94 (1.21–7.16) | 0.024 |
| OR (95% CI) in Model 3 | 1.00 (reference) | 1.21 (0.48–3.08) | 2.88 (1.10–7.50) | 0.041 |

CI: confidence interval; OR: odds ratio. Model 1: Adjusted for age and sex. Model 2: Adjusted for model 1 + body mass index (<18.5, 18.5–25.0, ≥25.0, missing), frequency of drinking per week (never/non-drinkers, less than 6 days, daily, missing) and job type [primary industry, employed by company, civil service, (medical, welfare or education personnel), other]. Model 3: Adjusted for model 2 + family history of stroke, hypertension, high-density lipoprotein cholesterol, triglycerides, and diabetes mellitus.

**Table 3** Stratified analyses: Association between smoking status and intracranial aneurysm. (N=1,496)

| | Smoking status | | | p-trend |
|---|---|---|---|---|
| | Never smoker | Former smoker | Current smoker | |
| Age | | | | |
| <65 years | | | | |
| Number of aneurysm / participants | 15/664 | 4/312 | 9/252 | |
| Multivariate OR (95% CI) | 1.00 (reference) | 0.78 (0.22–2.69) | 2.65 (0.92–7.60) | 0.088 |
| ≥65years | | | | |
| Number of aneurysm / participants | 10/182 | 4/70 | 1/16 | |
| Multivariate OR (95% CI) | 1.00 (reference) | 2.73 (0.51–14.55) | 2.28 (0.17–29.84) | 0.323 |
| Sex | | | | |
| Male | | | | |
| Number of aneurysm / participants | 7/436 | 2/214 | 5/147 | |
| Multivariate OR (95% CI) | 1.00 (reference) | 1.56 (0.24–9.97) | 5.41 (1.03–28.61) | 0.050 |
| Female | | | | |
| Number of aneurysm / participants | 18/410 | 6/168 | 5/121 | |
| Multivariate OR (95% CI) | 1.00 (reference) | 1.27 (0.40–3.96) | 1.97 (0.54–7.25) | 0.320 |
| Family history of stroke | | | | |
| Presence | | | | |
| Number of aneurysm / participants | 15/328 | 4/139 | 7/92 | |
| Multivariate OR (95% CI) | 1.00 (reference) | 1.12 (0.29–4.28) | 3.38 (0.95–12.00) | 0.070 |
| Absence | | | | |
| Number of aneurysm / participants | 10/518 | 4/243 | 3/176 | |
| Multivariate OR (95% CI) | 1.00 (reference) | 1.73 (0.41–7.40) | 2.53 (0.50–12.83) | 0.249 |

CI: confidence interval; OR: odds ratio.

## Discussion

We investigated the positive association between smoking status and UIA among Japanese brain health check-up examinees in a cross-sectional study. Even when we stratified this association by age, sex, and family history of stroke, we observed unchanged trends and no interactions.

Several studies have reported the association between cigarette smoking and SAH[8–10], whereas few and inconsistent reports are available on UIA. A Korean prospective cohort study did not observe a significant association between smoking and the incidence of intracranial aneurysm or SAH[12]. In this study, authors referred to the cohort characteristics, which included healthcare screening program participants who were more concerned about their health and, thus, might have avoided smoking. On the other hand, in a Norwegian prospective study, current smoking was positively associated with the incidence of both intracranial aneurysm and SAH[11]. Our finding is consistent with this study.

In this study, smoking status displayed a dose-response trend even after adjusting for confounding factors such as age, sex, and family history of stroke. Previous studies have reported that smoking was associated with the growth and rupture of intracranial aneurysms[5, 19]. Brinjikji *et al.* reported that intracranial aneurysms among current smokers had high growth rates[19]. These findings implicate smoking in contributing to both the incidence and growth of intracranial aneurysms.

Although all participants of this study were health check-up examinees, there was a significant association between smoking status and UIA. The proportion of current smokers was lower (17.9%) than that of the Japanese national survey (19.3–23.4% between 2009 and 2013) [20]. Therefore, the study participants might be more concerned about their health. Additionally, since this brain health check-up was costly (~40,000 JPY= 404 USD in 2013), the participants might have been middle or upper class. Even in people concerned about their health and in the middle-upper class, smoking has an adverse effect on health. In fact, the present results imply the importance of not only secondary prevention (i.e. undergoing a health check-up) but also primary prevention (i.e. smoking prevention or cessation). On the other hand, lower class people who are unable to undergo the health check-up may have lost the opportunity for UIA detection, possibly causing SAH and subsequent death[21, 22]. In fact, this may cause health inequalities. In addition to encouraging primary prevention, further studies must pursue a prospective study in a large general population to reveal the risk of UIA stratified by social classes.

Our study had some methodological strengths. This study investigated factors related to UIA only. Most previous studies reported factors for intracranial aneurysm growth and SAH. Second, we revealed a notable result that smoking was positively associated with UIA among health check-up examinees who more concerned for their health and were middle-upper class. Third, we considered many confounding factors such as laboratory data, lifestyle, and socioeconomic status.

This study also had some limitations. First, this study was cross-sectional in design at a single hospital in Japan and all study participants were health check-up examinees; thus, the association of smoking and UIA remain unknown in the general population. Second, we did not consider all potential confounders, such as medical history, physical activity, and psychological distress, and may have overestimated the result. Third, we lacked information about the number of visits for “Nou-Dock”, which may have caused a misclassification. For example, examinees classified as current smokers in the first visit may have quit smoking by the second visit. Fourth, we were unable to consider smoking duration and intensity and past smokers were self-reported. Thus, there is an unclear association of UIA with smoking duration, intensity, and cessation in this study.

## Conclusion

This cross-sectional study conducted in Japan showed that smoking was positively associated with UIA among the brain health check-up examinees. Thus, further studies should prospectively explore the impact of smoking duration, intensity, and cessation on UIA incidence in the general population.

**Conflict of interest:** The authors declare that there are no conflicts of interest.

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