Risk Factors for Aneurysmal Subarachnoid Hemorrhage in a Prospective Population Study
The HUNT Study in Norway

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Background and Purpose—The morbidity and mortality of subarachnoid hemorrhage (SAH) are high, and established risk factors are scarce. We prospectively assessed the association of blood pressure, smoking, and body mass with the risk of aneurysmal SAH.

Methods—All residents ≥20 years were invited to the Nord-Trøndelag Health (HUNT) Study (1984 to 1986) and 74 977 (88.1%) attended. The study included standardized measurements of blood pressure, body weight and height, and self-administered questionnaires. Participants who later had aneurysmal SAH (n=132) were identified, and hazard ratios (HRs), adjusted for age and sex, were estimated using Cox regression analysis.

Results—The crude annual incidence of aneurysmal SAH was 9.9 per 100 000 people; the incidence was almost twice as high in women as in men (12.9 versus 6.8, P<0.001). Systolic blood pressure was positively associated with risk (P for trend<0.001). Compared with the reference (<130 mm Hg), the adjusted HR in people with systolic blood pressure of 130 to 139 mm Hg was 2.3 (95% CI, 1.4 to 3.8) and for systolic blood pressure ≥170 mm Hg, the HR was 3.3 (95% CI, 1.7 to 6.3). Diastolic pressure showed similar positive associations. Compared with never smokers, former (HR, 2.7; 95% CI, 1.4 to 5.1) and current (HR, 6.1; 95% CI, 3.6 to 10.4) smokers had substantially higher risk. Compared with normal weight (body mass index, 18.5 to 24.9 kg/m²), overweight people were at lower risk (HR, 0.6; 95% CI, 0.4 to 1.0).

Conclusions—Systolic and diastolic blood pressure were strong predictors of aneurysmal SAH, and there was a substantially increased risk associated with smoking. However, high body mass was associated with reduced risk of aneurysmal SAH. (Stroke. 2009;40:1958-1962.)

Key Words: blood pressure • population study • risk factors • smoking • subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) accounts for approximately 1% to 7% of all cerebral strokes. The estimated incidence is approximately 9 per 100 000 people and appears to be relatively stable over time and between countries. Exceptions may be Finland and Japan, where the incidence is higher, and South and Central America, where it appears to be lower. Morbidity related to aneurysmal SAH remains severe, and case fatality has not substantially improved over time. Although SAH accounts for a small proportion of all strokes, the loss of productive life years that can be attributed to this condition is comparable to that of cerebral infarction (the most common stroke), because SAH typically occurs at a younger age and mortality is high.

Due to the low incidence of SAH, it has been difficult to identify risk factors in prospective studies. There is some evidence that certain lifestyle factors may be of importance, but most studies have collected the information on possible risk factors after the SAH event, and these studies are therefore prone to bias in selection and information. Previously, it has been shown that hypertension and smoking are likely to increase the risk of SAH. It has also been suggested that high alcohol consumption may increase risk, whereas high total serum cholesterol has been associated with reduced risk; however, findings have not been consistent. In another, but smaller, prospective study from Norway, it was suggested that excessive coffee consumption was associated with higher risk of SAH.

In a large prospective study of the general population, we have assessed the association of blood pressure, smoking, body mass index, and other common factors with the risk of developing aneurysmal SAH.

Materials and Methods

Study Population
Between 1984 and 1986, all residents aged ≥20 years in Nord-Trøndelag County, Norway, were invited to participate in the Nord-Trøndelag Health (HUNT) Study. Of the 85 100 eligible people, 74 977 (88.1%) accepted the invitation. The study has been...
described in detail elsewhere. Briefly, the participants filled in a questionnaire that was included with the invitation and attended a clinical examination conducted by trained nurses. Among other factors, the examination included measurements of blood pressure, body weight, and body height using standardized methods and the questionnaire contained a range of health-related items.

St Olavs University Hospital is the only hospital with a neurological department that serves the HUNT population. The catchment area of this department is approximately 660,000 inhabitants, and the HUNT population constitutes approximately 10% of the inhabitants. All patients who survive the acute phase of the SAH are treated at this department, and people, who live in the area but experience a nonfatal SAH outside of the area, are usually transferred to this department after acute treatment. Unfortunately, we do not have data on how many inhabitants moved out of the region and therefore could not be reached during the follow-up period.

We identified all patients admitted to the hospital who were diagnosed with SAH from 1984 until the end of 2005. In this search, we used 2 different strategies. First, a computerized search of the St Olavs University Hospital’s patient administrative database was used to identify patients diagnosed with SAH according to the International Classification of Diseases (8th and 9th revision code 430 and 10th revision code 160) yielding a total of 1214 patients. For the period 1984 to 1986, when the patient administrative database was not complete, we also searched operation protocols manually to identify patients who were operated with clipping of an aneurysm or patients who had received an external drain. This search resulted in 86 additional cases of SAH. In addition, we identified patients from the catchment area of the HUNT Study who died from SAH from 1984 to 2005 without being admitted to St Olavs University Hospital. This was done by information from the Cause of Death Registry in Norway, a search that resulted in 73 patients not detected by the other methods.

The 1373 patients who were identified through these procedures were individually linked to the database of the HUNT Study. Among all identified patients, 225 had participated in the HUNT Study. We reviewed the hospital charts at St Olavs University Hospital and the 2 local hospitals in the county to verify the diagnosis of aneurysmal SAH. Patients with conventional and CT angiographic evidence of an aneurysm or with an aneurysm found during operation (n=106) and patients identified with aneurysmal SAH at autopsy (n=5) were included as verified cases of aneurysmal SAH. In addition, we included patients whose clinical history and conventional CT scan findings (including hyperacute onset of severe headache, basal subarachnoid blood, and death shortly after ictus) were typical for fatal aneurysmal SAH (n=21) as independently reviewed and consented by 2 classified neurosurgeons (T.B.M. and A.V.). Among the 225 potential cases of aneurysmal SAH, 94 were excluded from further analyses due to the following reasons: 25 were nonaneurysmal SAH, because no aneurysm was found at angiography (n=24) or autopsy (n=1). Some patients had traumatic SAH (n=4), arteriovenous malformation (n=3), other types of cerebral bleeding (n=9), or SAH likely caused by antithrombotic or anticoagulation therapy (n=4). Twenty-two patients were erroneously coded in the hospital charts; the diagnostics were too sparse in 6 patients and therefore these patients could have been erroneously coded. For 15 patients, the hospital charts could not be found, and for these patients, erroneous coding in the Cause of Death Registry could have occurred. In addition, 5 patients had SAH before participating in the HUNT Study and were therefore excluded.

In the statistical analysis, we therefore included 132 patients with a verified diagnosis of SAH, and all these patients had developed their disease during the 22 years of follow-up subsequent to attending the HUNT Study in the mid-1980s. Specifically, the HUNT Study population was followed from 1984 until the end of 2005, irrespective of whether they had participated in the HUNT Study or not. A complete follow-up was achieved for 128 patients (97.7%). In 4 patients, the follow-up status could not be traced, and in 1 patient, the follow-up status was unknown.

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In the statistical analysis, we therefore included 132 patients with a verified diagnosis of SAH, and all these patients had developed their disease during the 22 years of follow-up subsequent to attending the HUNT Study in the mid-1980s. Specifically, the HUNT Study population was followed from enrollment (February 1984 to February 1986) until they experienced a SAH (n=132), until death from other causes (n=24,972), until emigration (n=298), or until the end of follow-up on December 31, 2005, whichever event occurred first. The HUNT Study is a collaboration among the Faculty of Medicine, the Norwegian University of Science and Technology, the Norwegian Institute of Public Health, and Nord-Trøndelag County Council. The Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee for Ethics in Medical Research approved this study.

**Measurements**

Blood pressure was measured using a calibrated mercury manometer with a standard cuff size (12×14 cm) after a minimum of 2 minutes’ rest. The first pulse sound (Phase 1) was recorded as systolic pressure, and the level when the pulse disappeared (Phase 5) was recorded as diastolic blood pressure. Both pressures were registered with an accuracy of 2 mm Hg, and the measurements were repeated 2 minutes after the first recording. In the analyses, we used the average value of the 2 measurements of systolic and diastolic blood pressure; and in the few cases with only one measurement, this was used instead of the average. We categorized systolic and diastolic blood pressure into 7 clinical categories (<130, 130 to 139, 140 to 149, 150 to 159, 160 to 169, and ≥170 mm Hg for systolic blood pressure and <75, 75 to 79, 80 to 84, 85 to 89, 90 to 94, 95 to 99, and ≥100 mm Hg for diastolic blood pressure). In the analyses, we used the lowest category as the reference (ie, <130 mm Hg for systolic and <75 mm Hg for diastolic blood pressure).

Participants were classified as never smokers, former smokers, or current smokers, and in the analysis of smoking, risk of SAH in never smokers was used as the reference.

Body mass index (BMI) was calculated as weight (in kilograms) divided by the squared value of height (in meters). BMI was divided into groups according to the World Health Organization’s classification: <18.5 as underweight, 18.5 to 24.9 as normal weight, 25 to 29.9 as overweight, and ≥30 kg/m² as obese. In the analyses, we used the normal weight group as the reference.

In addition to the basic questionnaire that was included with the invitation, the participants received a second questionnaire at attendance. They were asked to fill in the second questionnaire at home and return it by mail. The second questionnaire included frequency of alcohol consumption during the last 14 days, which we classified according to response as abstinent, no consumption during the last 14 days but not totally abstinent (reference), 1 to 4 times, or ≥5 times or too much. A large proportion of the participants failed to return the second questionnaire, and information on alcohol consumption was therefore missing for 13,404 participants.

In the second questionnaire, frequency of physical activity also was classified as never (reference category), less than once a week, once a week, 2 to 3 times a week, and usually everyday. Information on physical activity was missing for 13,323 participants.

**Statistical Analysis**

We used the Cox proportional hazards model to estimate hazard ratios (HRs) of SAH with 95% CIs. Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals and by inspection of the log-log plots. Each study factor (eg, blood pressure, smoking, BMI) was categorized, and the risk of aneurysmal SAH was estimated for each category and compared with a defined reference category. In the analyses, we adjusted for age and sex. In subsequent analyses, we also adjusted for other potentially confounding factors. We also assessed whether the estimated associations differed between men and women.

All analyses were performed using the statistical software Stata for Windows (Version 10.0, Stata Corp, College Station, Texas).

**Results**

**Characteristics of Patients and Cohort Members**

During 22 years of follow-up (more than 1.3 million person-years), the crude annual incidence of aneurysmal SAH was 9.9 per 100,000 people. The incidence in women (12.9 per 100,000 women) was nearly twice as high as in men (6.8 per 100,000 men, P=0.001).
Mean age at diagnosis was 60.5 (SD, 13 years; range, 28 to 90 years) with no difference between men and women (59.9 versus 60.7 years). On average, SAH was diagnosed 132 months (SD, 70; range, 0 to 262 months) after baseline measurements. More detailed information of the cohort is given in Table 1.

Risk Factors for Subarachnoid Hemorrhage

There was a positive association of systolic and diastolic blood pressure with the risk of SAH ($P$ for trend $<0.001$). Compared with the reference level (<130 mm Hg for systolic pressure), risk increased gradually with increasing pressure; the age- and sex-adjusted HR was 2.3 (95% CI, 1.4 to 3.8) associated with systolic pressure of 130 to 139 mm Hg, and for systolic pressure 170 mm Hg and higher, the adjusted HR was 3.3 (95% CI, 1.7 to 6.3). For diastolic pressure, the results showed similarly strong positive associations (Table 2).

Former or current use of antihypertensive medication at baseline was associated with a higher subsequent risk of SAH compared with the risk of those who had never used antihypertensive medication (HR, 1.7; 95% CI, 1.1 to 2.7). Current or former smoking at baseline was associated with higher subsequent risk of SAH compared with the risk of

<table>
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<td>&gt;170</td>
<td>18</td>
<td>8 070</td>
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$P$ for trend $<0.001$

| Diastolic blood pressure, mm Hg |                     |     |           |
| <75      | 9                | 14 308 | 1 | Reference |
| 75–79    | 17               | 10 615 | 2.5 | 1.1–5.6 |
| 80–84    | 24               | 13 951 | 2.7 | 1.3–5.9 |
| 85–89    | 20               | 11 771 | 2.7 | 1.2–6.0 |
| 90–94    | 18               | 9 906 | 3.0 | 1.3–6.9 |
| 95–99    | 17               | 6 376 | 4.5 | 1.9–10.3 |
| >100     | 27               | 7 825 | 6.4 | 2.9–14.2 |

$P$ for trend $<0.001$

<table>
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<td>Current</td>
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<td>20 654</td>
<td>6.1</td>
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</tbody>
</table>

| BMI, kg/m² |                     |     |           |
| Underweight (<18.5) | 3 | 1030 | 1.8 | 0.6–5.6 |
| Normal weight (18.5–24.9) | 79 | 38 877 | 1 | Reference |
| Overweight (25–29.9) | 37 | 26 317 | 0.6 | 0.4–1.0 |
| Obese (≥30) | 13 | 7 928 | 0.7 | 0.4–1.2 |

$P$ for trend $0.06$

| Alcohol |                  |     |           |
| Abstinent | 4 | 7 518 | 0.3 | 0.1–0.7 |
| Not last 14 days | 56 | 27 956 | 1 | Reference |
| 1–4 times | 38 | 22 299 | 1.1 | 0.7–1.6 |
| ≥5 times or too much | 8 | 3 598 | 1.4 | 0.6–2.9 |

$P$ for trend $0.03$

| Frequency of physical activity |                     |     |           |
| Never | 16 | 8 778 | 1 | Reference |
| <1 per week | 34 | 16 468 | 1.0 | 0.5–1.8 |
| Once a week | 25 | 14 826 | 0.7 | 0.4–1.4 |
| 2–3 times per week | 19 | 13 317 | 0.6 | 0.3–1.2 |
| Usually everyday | 14 | 8 157 | 0.8 | 0.4–1.7 |

$P$ for trend $0.2$

*Missing data on systolic blood pressure, n=91; diastolic blood pressure, n=93; smoking, n=12 403; BMI, n=693; alcohol, n=13 498; physical activity, n=13 323.
†Adjusted for sex and age in 10-year categories (<30, 30–39, . . . , 60–69, >70 years).
never smokers. Thus, the HR adjusted for age and sex was 2.7 (95% CI, 1.4 to 5.1) among former and 6.1 (95% CI, 3.6 to 10.4) among current smokers.

On the other hand, overweight was associated with a lower risk of SAH. Compared with normal weight people (BMI, 18.5 to 24.9 kg/m²), the HR adjusted for age and sex in the overweight people (BMI, 25 to 29.9 kg/m²) was 0.6 (95% CI, 0.4 to 1.0). In relation to alcohol consumption, people who reported total abstinence were at reduced risk (HR, 0.3; 95% CI, 0.1 to 0.7) compared with the reference group (no alcohol during the last 14 days but not totally abstinent). The analyses of physical activity showed no clear association with the risk of SAH.

In subsequent analyses, we included all potentially confounding factors (age, sex, systolic blood pressure, smoking, alcohol, BMI, physical activity, marital status, and education) in a multivariate model. However, these adjustments did not substantially influence the estimates.

We assessed whether the estimated associations differed between men and women by fitting appropriate interaction terms but found no evidence for heterogeneity (all probability values >0.20).

We also performed sensitivity analyses in which we compared the results of using cases with confirmed aneurysmal SAH and including cases in which the diagnosis was not confirmed, but the history and conventional CT scan were highly typical for the disease. The results were essentially identical.

Similarly, we performed sensitivity analysis comparing people with full information and people with missing data for systolic blood pressure, BMI, smoking, alcohol consumption, physical activity, marital status, and education and found that these groups of people did not differ in their risk of aneurysmal SAH (HR, 0.97; P=0.9).

Discussion

In this prospective population study, the incidence of aneurysmal SAH was twice as high in women as in men, and there were strong positive associations of blood pressure as well as current and former smoking with the risk of aneurysmal SAH. These findings confirm those of some previous studies.2,9,11–13 Maybe more surprising, we also found that overweight and obese people tended to have lower risk of SAH compared with normal weight people.

The prospective design and population base of this study make bias an unlikely explanation for the results. The cohort consists of the majority of adults in a stable20 homogenous population in Norway. Furthermore, the diagnosis of SAH was carefully verified in all patients. However, to be absolutely certain that aneurysmal SAH is correctly diagnosed, either angiography detection is required or the aneurysm needs to be detected during an operation or at necropsy. In this study, we also included 21 patients as cases whose clinical history and conventional CT scan were highly typical for fatal aneurysmal SAH even if supplementary diagnostic procedures were not performed to ascertain the diagnosis. We considered that including these patients from the analysis would be better than the potential error of excluding them. Also, the sensitivity analyses comparing results with and without these patients showed that the results were essentially identical. In addition, the observed incidence corresponds well to the incidence reported from other studies,2,3 suggesting that the identification of cases, although done retrospectively, may be accurate.

In our data, there was no clear association of physical activity with the risk of SAH. Information on physical activity was based on responses to a questionnaire that allows for subjective interpretation of the question and individual perception of the activity and misclassification of physical activity can be influenced by many factors such as age, social context, and seasonal variations.21 Therefore, the lack of any association with physical activity should be confirmed by other studies.

We found that people who reported total abstinence from alcohol were at lower risk of aneurysmal SAH compared with people who were not abstainers. However, this result should be interpreted with some caution because it was based on a rather small number of persons at risk and the result did not seem to increase with increasing alcohol consumption.

Although previous studies have reported strong positive associations of blood pressure and smoking with the risk of aneurysmal SAH, most of these studies were rather small or collected the information of possible risk factors after the patient experienced the SAH. Also, few studies have a population-based design, and the case ascertainment procedure in some of these studies may not be optimal. However, the consistency of findings across different study types and populations suggests that cigarette smoking and hypertension could be causally related to SAH.11

In our study, overweight people were at reduced risk of aneurysmal SAH, and previously, some case–control studies reported lower BMI among cases than control subjects,18,22 but most other studies have failed to show any association of BMI with the risk of SAH.2,12 Some studies have reported a negative association of total serum cholesterol with SAH16,17,19,21,22; unfortunately, we did not have information on serum lipids in our data. However, being overweight is positively correlated with cholesterol,23 and the negative association of BMI that we found with SAH could be mediated through serum lipids.

The higher incidence of SAH in women is well known from previous studies. However, the underlying cause of the sex difference is not clear. Established risk factors such as hypertension and smoking are more common in men and cannot explain the difference. Also, our estimated associations did not differ between men and women. Hormonal factors, including the use of hormone therapy after menopause, have been suggested,18,24 but in our study, the use of hormone therapy was modest and therefore not likely to explain the sex difference.

Summary

In this large prospective population study, we found strong positive associations of blood pressure (systolic and diastolic) and smoking (former and current) with the risk of aneurysmal SAH, whereas being overweight or obese was associated with reduced risk. Smoking and hypertension have been linked to SAH in other studies, but the lower risk associated with adiposity should be confirmed by others.
Acknowledgments
We thank Dr Sverre Torp at St Olavs Hospital, Trondheim for providing autopsy information.

Disclosures
None.

References
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