Joint Effect of Modifiable Risk Factors on the Risk of Aneurysmal Subarachnoid Hemorrhage
A Cohort Study

Haakon Lindekleiv, MD, PhD; Marie S. Sandvei, MD, PhD; Pål R. Romundstad, PhD; Tom Wilsgaard, PhD; Inger Njolstad, MD, PhD; Tor Ingebrigtsen, MD, PhD; Anne Vik, MD, PhD*; Ellisiv B. Mathiesen, MD, PhD*

Background and Purpose—The joint effect of risk factors on the risk of aneurysmal SAH (aSAH) has been studied sparsely.

Methods—We examined the potential synergism between cigarette smoking, hypertension, and regular alcohol consumption and the risk of aSAH in a prospective, population-based cohort of participants from the Nord-Trøndelag Health Study and the Tromsø Study in Norway. Interaction was assessed on additive and multiplicative scales.

Results—we identified 122 cases of aSAH over 977 895 person-years of follow-up. Interaction was observed between current smoking and hypertension on the additive scale, (relative excess risk because of interaction, 6.40; 95% CI, 0.88–11.92, adjusted for sex and age). We found no significant interaction between hypertension and regular alcohol consumption or current cigarette smoking and regular alcohol consumption on the additive scale. No significant interaction was detected on the multiplicative scale.

Conclusions—The joint effect of current smoking and hypertension on the risk of aSAH was stronger than was the sum of the independent effects of each factor. Persons at risk of aSAH should be advised of a markedly stronger risk for aSAH with the combination of current smoking and hypertension. In addition, the finding suggests that combining smoking cessation and blood pressure lowering may have an extra risk reduction effect on preventing aSAH. (Stroke. 2012;43:1885-1889.)

Key Words: risk factors  ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH) is a frequent cause of mortality and morbidity in young and middle-aged adults.1,2 Although improvements in treatment and intensive care have resulted in more patients surviving aSAH,3,4 the case fatality of aSAH remains high.5 Knowledge about modifiable risk factors is important for primary disease prevention,6 and we have previously examined risk factors for aSAH in our prospective cohort.7–9 Studies suggest a joint effect of risk factors with respect to ischemic stroke, hemorrhagic stroke, and coronary heart disease.10–13 Previous studies have not found a joint effect of risk factors on the risk of aSAH.14–17

In the present study, we examined the joint effect of cigarette smoking, hypertension, and regular alcohol consumption on the risk of aSAH in a large, population-based, prospective cohort.

Methods

Study Population
The Nord-Trøndelag (HUNT) and Tromsø studies are 2 prospective, population-based cohort studies. The HUNT study is conducted in the county of Nord-Trøndelag, Norway, and the Tromsø Study is conducted in the municipality of Tromsø, Troms County, Norway. Nord-Trøndelag and Tromsø comprise a homogeneous, white population. The design of both studies includes repeated population health surveys.

The second survey of the HUNT Study was conducted between 1995 and 1997. All residents age ≥20 years were invited to participate. Of the eligible population, 65 625 persons participated (71.2%).14 In total, 102 persons were excluded because they were not officially registered as inhabitants of the county at the date of attendance (n=58), or had previous SAH (n=44) before entering the study; this left 65 526 participants for follow-up in the present study.

The fourth survey of the Tromsø Study was conducted in 1994 and 1995. All residents age ≥25 years were invited. Of the eligible population, 27 158 persons participated (77%).15 In total, 102 persons were excluded because they were not officially registered as inhabitants of the county at the date of attendance (n=58), or had previous SAH (n=44) before entering the study; this left 27 526 participants for follow-up in the present study.

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Participants were excluded because of lack of consent to medical research (n=201), because they were not officially registered as inhabitants of the municipality at the date of attendance (n=44), or because of previous SAH (n=31); this left 26,882 participants for follow-up in the present study.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee for Medical Research Ethics approved this study. All participants included in this analysis gave informed, written consent to research.

**Data Collection**

In both studies, baseline information on cardiovascular risk factors and use of antihypertensive treatment was obtained by self-reported questionnaires and physical examinations. Based on questionnaires, the participants were classified as never, former, or current smokers. Alcohol consumption was classified as abstinent, or as drinking alcohol <1 time per month, 1 to 4 times per month, or ≥5 times per month. Regular alcohol consumption was defined as drinking alcohol ≥5 times per month. Blood pressure was measured by specially trained nurses using an automatic device (Dinamap, Contion). Cuff size was adjusted after measuring the arm circumference. After 2 minutes of seated resting, 3 recordings were made at 1-minute intervals. The mean value of the second and third measurements was used in the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or as current use of antihypertensive treatment.

**Inclusion Criteria**

We included patients as aSAH cases if the diagnosis had been verified by cerebral angiography or autopsy, or if the medical history was highly suggestive for fatal aSAH, but the patient had died before undergoing cerebral angiography and was not autopsied. A medical history highly suggestive for fatal aSAH was defined as: sudden headache or unconsciousness, death ≤4 weeks, and findings on noncontrast enhanced computed tomography scans that were typical for aSAH (massive basal SAH). All criteria had to be fulfilled. In HUNT, 2 neurosurgeons reviewed and consented on all cases. In the Tromsø Study, an independent end point committee of 1 neurologist and 2 experienced physicians validated the cases. Cases suggestive for fatal aSAH were in Tromsø validated by a neurologist and a neuroradiologist.

**Identification of SAH Cases**

The national identification number allowed linkage of baseline data to national and regional registers, and ensured complete follow-up for all-cause mortality. For the HUNT population, information about SAH was obtained by linkage to the diagnosis register at the 2 local hospitals and at St Olavs University Hospital, the only hospital with a neurological department that serves the HUNT population. We confirmed our search strategy by searching for patients treated for cerebral aneurysms with surgical clipping or endovascular embolization. We found 1 additional aSAH patient who had participated in the HUNT study. To determine the extent of aSAH misdiagnosed as intracranial hemorrhages, we identified patients that died ≤6 months after being diagnosed with intracranial hemorrhage on brain computed tomography at 1 of the 2 local hospitals between 2003 and 2007. Two neurosurgeons reviewed the computed tomography scans, but found no new aSAH cases. All patients who survive the acute phase of the SAH are treated at the department, and people who live in the area, but experience a nonfatal SAH outside the area, are usually transferred to the department after acute treatment elsewhere. An identical procedure was followed in the Tromsø Study, using information from the University Hospital of North Norway, which is the only local hospital serving the Tromsø population. Further, information from both studies was linked to the nationwide Causes of Death Registry at Statistics Norway, using codes for aSAH according to the International Classification of Diseases, Ninth Edition (code 430) and Tenth Edition (code I60). Hospital charts for the identified patients were reviewed. Individuals who had died or emigrated from Nord-Trøndelag or Tromsø were identified through the Population Register of Norway. Follow-up time was assigned from the date of examination in each of the studies (from 1994–1997) until the first aSAH occurred, until death from other causes, emigration, or to the end of follow-up (December 31, 2007), whichever occurred first.

We identified 122 cases of aSAH (103 cases verified by angiography or at autopsy and 19 cases with a medical history highly suggestive of fatal aSAH), 71 cases from HUNT and 51 cases from Tromsø. The cohort consisted of 92,408 persons, with 977,895 person-years of follow-up.

**Statistical Analyses**

A Cox proportional hazards model was used to estimate hazard ratios (HR) of aSAH with 95% CI. The relationship between hypertension, smoking, alcohol consumption, and aSAH were examined in a multivariate analysis adjusted for age and sex. Departure from the proportional hazards assumption was evaluated by Schönfeld’s residuals and by inspection of log-log plots. Interaction between the risk factors for aSAH was assessed on an additive and multiplicative scale. Interaction on the additive scale was assessed by calculating the relative excess risk caused by interaction (RERI), using the algorithm of Andersson et al.**18** RERI was calculated as HR11−HR10−HR01+1, where HR11 is the hazard ratio for both risk factors present, HR10 is the hazard ratio for the first risk factor present and the second risk factor absent, and HR01 is the hazard ratio for the first risk factor absent and the second risk factor present. RERI values ≠ 0 indicate statistically significant additive interaction. Interaction on the multiplicative scale was assessed by comparing multiplicative models with and without an interaction term using the log-likelihood ratio test.

Analyses were performed using Stata (version 12.0, Stata Corp) and Microsoft Excel (version 2003, Microsoft Corp).

**Results**

We identified 122 aSAH cases over 977,895 person-years of follow-up. Baseline characteristics are provided in Table 1.

The HRs of current smoking, hypertension, and regular alcohol consumption, adjusted for age and sex, are shown in Table 2.

We observed interaction between current smoking and hypertension on the additive scale (RERI, 6.5; 95% CI, 1.0–12.9, adjusted for sex and age), suggesting that the joint effect of current smoking and hypertension is stronger than is the sum of the independent effects of each factor. The joint effect of current smoking and hypertension on the risk of aSAH is shown in Table 3 and is visualized in the Figure.

No clear evidence of interaction was observed on the additive scale with respect to hypertension and regular alcohol consumption (RERI, 1.3; 95% CI, −0.9 to 3.8, adjusted for sex, age, and current cigarette smoking), or current cigarette smoking and regular alcohol consumption (RERI, 1.0; 95% CI, −3.2 to 5.2, adjusted for sex, age, and hypertension). No substantial interaction was observed on the multiplicative scale for hypertension and current cigarette smoking (P=0.81, log-likelihood ratio test), hypertension and regular alcohol consumption (P=0.31, log-likelihood ratio test), or current cigarette smoking and regular alcohol consumption (P=0.91, log-likelihood ratio test).

**Discussion**

The present cohort study found that the joint effect of current smoking and hypertension on the risk of aSAH was stronger...
than was the sum of the independent effects of each factor. This finding may be of benefit in the management of persons at risk for aSAH. Persons at risk of aSAH should be advised of a markedly increased risk for aSAH with the combination of current smoking and hypertension. Further, the finding suggests that combining smoking cessation and blood pressure lowering may have an extra risk reduction effect on preventing aSAH.

Interaction in epidemiology refers to the extent to which the joint effect of 2 risk factors on disease differs from the independent effects of each of the factors. Interaction can be measured on an additive or a multiplicative scale. Interaction on the additive scale concerns whether the observed risk for disease in those with both risk factors is greater (synergism) or lower (antagonism) than is adding the individual risk ratios of each risk factor separately. Interaction on the multiplicative scale concerns whether the risk for disease in those with both risk factors was greater or lower than was the multiplied risk ratios of each risk factor alone. Interaction can be present on 1 scale or both scales. Although there is no consensus on whether the additive or multiplicative scale is the most appropriate, additive interaction may be of more relevance from the viewpoint of translating epidemiological findings into prevention of disease events, as it is readily translated into impact of intervention in terms of absolute number of preventable outcomes. The implications of finding interaction on the additive scale between current smoking, hypertension, and the risk of aSAH may suggest that these risk factors share a common pathway in the pathogenesis of aSAH, and that combining smoking cessation and blood pressure lowering may have an extra risk reduction effect in preventing aSAH.

Our findings disagree with previous studies examining the joint effect of risk factors for aSAH. These studies

Table 1. Baseline Characteristics of aSAH Cases and Entire Cohort: The HUNT and Tromsø Studies

<table>
<thead>
<tr>
<th>Variable*</th>
<th>aSAH Cases</th>
<th>Entire Cohort*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n</td>
<td>122</td>
<td>922 408</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>81 (66%)</td>
<td>48 996 (53%)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>46.8 (13.7)</td>
<td>43.1 (15.2)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>144.0 (22.3)</td>
<td>137.0 (21.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85.0 (13.7)</td>
<td>79.7 (12.3)</td>
</tr>
<tr>
<td>Hypertension†, n (%)</td>
<td>74 (61%)</td>
<td>38 325 (42%)</td>
</tr>
<tr>
<td>Cigarette smoking habits, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>21 (17%)</td>
<td>38 930 (43%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>18 (15%)</td>
<td>23 918 (26%)</td>
</tr>
<tr>
<td>Current daily smoker</td>
<td>83 (68%)</td>
<td>28 746 (31%)</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent</td>
<td>13 (11%)</td>
<td>11 528 (13%)</td>
</tr>
<tr>
<td>&lt;1 time per month</td>
<td>32 (26%)</td>
<td>24 905 (27%)</td>
</tr>
<tr>
<td>1–4 times per month</td>
<td>57 (47%)</td>
<td>42 461 (47%)</td>
</tr>
<tr>
<td>≥5 times per month</td>
<td>19 (16%)</td>
<td>12 399 (14%)</td>
</tr>
</tbody>
</table>

aSAH indicates aneurysmal subarachnoid hemorrhage.
*Missing data on blood pressure, 922; hypertension, 841; cigarette smoking habits, 814; and alcohol consumption, 1115.
†Defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive treatment.

Table 2. Adjusted* hazard ratios of aSAH for hypertension, smoking, and alcohol consumption: The HUNT and Tromsø Studies

<table>
<thead>
<tr>
<th>Variable†</th>
<th>aSAH</th>
<th>Participants</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension‡</td>
<td>74</td>
<td>38 325</td>
<td>2.1</td>
<td>1.4–3.2</td>
</tr>
<tr>
<td>Current smoking</td>
<td>83</td>
<td>28 746</td>
<td>5.2</td>
<td>3.6–7.7</td>
</tr>
<tr>
<td>Regular alcohol consumption§</td>
<td>19</td>
<td>12 399</td>
<td>1.4</td>
<td>0.8–2.3</td>
</tr>
</tbody>
</table>

aSAH indicates aneurysmal subarachnoid hemorrhage.
*Adjusted for age and sex.
†Missing data on hypertension, 841; cigarette smoking, 814; alcohol consumption, 1115.
‡Defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive treatment.
§Defined as drinking alcohol ≥5 times per month.

Figure. Joint and individual effects of current smoking and hypertension on the risk of aSAH: The HUNT and Tromsø Studies.
concluded that there was no joint effect of smoking and hypertension on the risk of aSAH.\textsuperscript{14–17} However, interaction in these studies was examined on a multiplicative scale only. We examined interaction of risk factors on both an additive and a multiplicative scale and found interaction between smoking and hypertension present on the additive, but not the multiplicative, scale. Our findings of an additive joint effect of smoking and hypertension on the risk of aSAH is supported by a previous case-control study that found the odds ratio of combined smoking and hypertension almost 15-fold (OR, 14.7; 95% CI, 9–24) compared with those who neither smoked nor had a history of hypertension.\textsuperscript{22} This study did not statistically examine interaction, as additive interaction can only be examined in prospective cohort studies because incidence rates are required for the calculations.

Our findings are similar to those reported from studies suggesting a joint effect of risk factors with respect to ischemic stroke, hemorrhagic stroke, and coronary heart disease.\textsuperscript{10–13} The pathophysiological explanation for a synergistic effect of current smoking and hypertension is unknown. One might speculate that the vascular damage from hypertension enhances the endothelial injury caused by tobacco combustion products entering the circulation, and vice versa.

Our findings add to the evidence of the importance of smoking cessation in primary prevention of aSAH. Previous studies have found that current cigarette smoking is a strong risk factor for aSAH. In a meta-analysis of 5 prospective cohort studies on smoking and the risk of aSAH, current smoking was associated with a relative risk of 2.2 (95% CI, 1.3–3.6) for aSAH.\textsuperscript{23} A relationship between former smoking and the risk of aSAH has not been established.\textsuperscript{23–26} Sex differences in the risk of aSAH have been reported, with female smokers at increased risk of aSAH compared with male smokers.\textsuperscript{7} Further, a gene-environment interaction with smoking has been suggested. In a study of 339 aSAH cases and 1016 matched controls, an additive interaction between smoking, family history of aSAH, and the risk of aSAH was found. The odds ratio for aSAH for current smokers with a family history of aSAH was 6.4 (95% CI, 3.1–13.2), compared with current nonsmokers with no first-degree relatives with aSAH.\textsuperscript{27}

The strengths of the present study include its population-based, prospective cohort design, rigorous case validation, and high attendance rate, which minimizes selection bias. The study has some limitations. The external validity refers to a white population and may not be generalizable to other ethnic groups. In 19 cases with a medical history of fatal aSAH, aneurysms were not verified by angiography or autopsy. However, exclusion of these cases from the analyses did not change the results. Information on family history of aSAH was not available. Bias may have been introduced because of risk factor levels that may have changed after baseline measurements. The alcohol variable in the present study was modeled on the frequency of consuming an unknown quantity of alcohol. To assess the sensitivity of this variable, we compared it with data on number of glasses of alcohol consumed during the last 14 days, available from self-reported questionnaires for the participants of the Tromsø Study. The HR of aSAH for ≥10 glasses of alcohol per fortnight (HR, 0.9; 95% CI, 0.4–1.9) was similar to the HR for drinking an unknown quantity of alcohol ≥5 times per month (HR, 0.9; 95% CI, 0.4–2.0), adjusted for age, sex, hypertension, and smoking habits. This indicates that the alcohol frequency variable used in the present study reflects the participants’ alcohol consumption. Further, the consumption of alcohol in the present cohort was sparse.

In conclusion, the main finding of the present cohort study is a stronger joint effect of current smoking and hypertension on the risk of aSAH than is the sum of the independent effects of each factor. Persons at risk of aSAH should be advised of a markedly increased risk for aSAH with the combination of current smoking and hypertension. In addition, the finding suggests that combining smoking cessation and blood pressure lowering may have an extra risk reduction effect in preventing aSAH.

Acknowledgments

H.L.: study idea, study design or concept, statistical analyses, drafting the manuscript, acquisition of data, analysis or interpretation of data. M.S.S.: study design or concept, acquisition of data, analysis or interpretation of data. T.I.: acquisition of data, analysis or interpretation of data. A.V. and E.B.M.: study concept or design, analysis and interpretation of data. A.V. and E.B.M.: study concept or design, analysis or interpretation of data. All co-authors revised the manuscript for content.

Disclosures

None.

References


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*Stroke*. 2012;43:1885-1889; originally published online April 19, 2012; doi: 10.1161/STROKEAHA.112.651315

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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動脈瘤性くも膜下出血のリスクに対する修正可能な危険因子の相乗作用 コホート研究

Joint Effect of Modifiable Risk Factors on the Risk of Aneurysmal Subarachnoid Hemorrhage
A Cohort Study

Haakon Lindekleiv, MD, PhD1,2; Marie S. Sandvei, MD, PhD3; Pål R. Romundstad, PhD3;
Tom Wilsgaard, PhD1; Inger Njølstad, MD, PhD1; Tor Ingebrigtsen, MD, Ph1,2;
Anne Vik, MD, PhD4,5; Ellisiv B. Mathiesen, MD, PhD1,2

1 Departments of Clinical and Community Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway; 2 Divisions of Neurosurgery and Neurology, University Hospital of North Norway, Tromsø, Norway; 3 Departments of Public Health and Community Medicine and 4 Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway; 5 Department of Neurosurgery, St Olavs University Hospital, Trondheim, Norway.

Abstract

背景および目的：動脈瘤性くも膜下出血（aSAH）のリスクに対する危険因子の相乗作用については、ほとんど研究されていない。

方法：ノルウェーの Nord-Troms Health (HUNT) Studyおよび Tromsø Study の登録者を対象に、aSAH のリスクに対する喫煙、血管圧、習慣的なアルコール摂取との相関

相乗作用の可能性について、集団ベースの前向きコホート研究を行った。相関作用の評価は加算法および乗算法を用いて行った。

結果：977,895 人・年の追跡調査で 122 例の aSAH が確認された。加算法で現在の喫煙と血管圧の間に相関が認められた（相関作用による適利相対リスク、6.40: 95% CL 0.88 ～ 11.92。性別および年齢について補正。）算

法では血管圧と習慣的なアルコール摂取または現在の喫煙と習慣的なアルコール摂取の間に有意な相関は認めなかった。乗算法でも有意な相関作用は認めなかった。

結論：aSAH のリスクに対する現在の喫煙と血管圧の相

相乗作用は、各因子単独の作用が合計よりも大きかった。

aSAH の高リスク者には、現在の喫煙と血管圧により aSAH のリスクが著しく高くなることを示唆するがある。さらに、この所見から、摂取とともに高血圧を避ける

ことにより、aSAH の予防に付加的なリスク軽減効果をもたらす可能性が示唆される。

Stroke 2012; 43: 1885-1889