Independent Risk Factors for Intracranial Aneurysms and Their Joint Effect

A Case-Control Study

Monique H.M. Vlak, MD; Gabriel J.E. Rinkel, MD; Paut Greebe, RN, PhD; Ale Algra, MD

Background and Purpose—Three percent of the population has an unruptured intracranial aneurysm (UIA). We aimed to identify independent risk factors from lifestyle and medical history for the presence of UIAs and to investigate the combined effect of well-established risk factors.

Methods—We studied 206 patients with an UIA who never had a subarachnoid hemorrhage and 574 controls who were randomly retrieved from general practitioner files. All participants filled in a questionnaire on potential risk factors for UIAs. With logistic regression analysis, we identified independent risk factors for UIA and assessed their combined effect.

Results—Independent risk factors were current smoking (odds ratio [OR], 3.0; 95% confidence interval [CI], 2.0–4.5), hypertension (OR, 2.9; 95% CI, 1.9–4.6), family history of stroke other than subarachnoid hemorrhage (OR, 1.6; 95% CI, 1.0–2.5), hypercholesterolemia (OR, 0.5; 95% CI, 0.3–0.9), and regular physical exercise (OR, 0.6; 95% CI, 0.3–0.9). The joint risk of smoking and hypertension was higher (OR, 8.3; 95% CI, 4.5–15.2) than the sum of the risks independently.

Conclusions—Current smoking, hypertension, and family history of stroke increase the risk of UIA, with smoking and hypertension having an additive effect, whereas hypercholesterolemia and regular physical exercise decrease this risk. A healthy lifestyle probably reduces the risk of UIA and thereby possibly also that of aneurysmal subarachnoid hemorrhage. Whether smoking and hypertension increase the risk of aneurysmal subarachnoid hemorrhage only through an increased risk of aneurysm formation or also through an increased risk of rupture remains to be established. **(*Stroke*. 2013;44: 984-987.)**

Key Words: intracranial aneurysm ■ risk factors ■ stroke

Three percent of the general population harbors an unruptured intracranial aneurysm (UIA).[1] Reducing the risk of developing UIAs is an important method for reducing the incidence of aneurysmal subarachnoid hemorrhage (aSAH), which has remained relatively stable during the past decades.[2]

Female sex, a positive family history for aSAH or UIA, and polycystic kidney disease are nonmodifiable risk factors for UIAs.[1] Hypertension and smoking are well-established modifiable risk factors. Data on other modifiable risk factors, such as hypercholesterolemia, ischemic heart disease, diabetes mellitus, low body mass index, and excessive alcohol use as independent risk factors, are limited and sometimes conflicting.[3–5] Also, the joint effect of these risk factors is unknown.

The aim of the current study was to identify risk factors for UIAs from lifestyle and medical history data in a white population and to study the joint effect of well-established risk factors.

Methods

Study Population

Between September 2006 and September 2009, we included 206 patients who were known at the Utrecht Stroke Center of the University Medical Center Utrecht for having an UIA. Eligible were patients who had an UIA, who never had an aSAH, were 18 years or older, and spoke Dutch. The UIA had to be confirmed by computed tomography angiography, magnetic resonance angiography, or conventional angiography. The study protocol was approved by the medico-ethical review committee of our hospital. Between January 2009 and January 2010, 574 controls were recruited from 5 different general practices in the catchment area of the Utrecht stroke center.[6]

Data Collection

All patients and controls were asked to fill in a structured questionnaire. We collected data on demographics (age, sex), height, weight, smoking, use of alcohol, and physical exercise. For medical history, patients were asked whether they had been diagnosed with having

Received December 2, 2012; final revision received December 16, 2012; accepted December 31, 2012.

From the Department of Neurology and Neurosurgery, Utrecht Stroke Center, Rudolf Magnus Institute of Neuroscience, University Medical Center, Utrecht, the Netherlands (M.H.M.V., G.J.E.R., P.G., A.A.); Department of Neurology, Slotervaart Hospital, Louwesweg, Amsterdam, the Netherlands (M.H.M.V.); and Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands (A.A.).

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.000329/-/DC1.

Correspondence to Ale Algra, MD, Julius Center Health Sciences and Primary Care, University Medical Center, Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands. E-mail a.algra@umcutrecht.nl

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.111.000329**

diabetes mellitus, heart disease, hypertension, hypercholesterolemia, or migraine. We also collected data on family history of stroke (aSAH or other).[6] Obesity was defined as a body mass index ≥30 according to the World Health Organization classification.[7] Smoking was defined as smoking at the time of diagnosis of the UIA (patients) or at the time of interview (controls). Excessive alcohol use was defined as ≥18 U (ie, ≥150 g) per week.[8] Regular physical activity was defined as vigorous physical exercise (metabolic equivalent >6) >3 times a week.[9] For history of heart disease, we included those persons who had a myocardial infarction, angina pectoris, coronary artery bypass grafting, and percutaneous transluminal coronary arterioplasty. In UIA patients, diagnoses of diabetes mellitus, hypertension, heart disease, and hypercholesterolemia were checked against medical records to confirm that the diagnosis had been made before discovery of the UIA. For these diagnoses, it was adequate if they were listed in the medical record as past medical history. We did not check blood pressure values, blood glucose levels, or blood cholesterol levels assessed in hospital because these diagnoses are usually made by the general practitioner who also installs treatment.

Family history was based on the information from the questionnaire. In patients with an UIA, we collected data on the indication for imaging from their medical records and predefined 5 categories as follows: (1) atherosclerotic disease (including transient ischemic attack and stroke, but not aSAH), (2) positive family history for UIA or aSAH, (3) headache, (4) screening without obvious medical indication, and (5) other.

Statistical Analysis

All variables listed in Table 1 were assessed as possible risk factors. The controls we used for the current study had also served as controls in a previous case-control study for which they had been matched for sex and age with a cohort of patients with aSAH.[10] Because the age and sex distribution of patients with aSAH and patients with UIAs did not differ to a large extent, the controls were approximately matched for sex and age with the group of UIA patients as well. For this reason, we were unable to study age and sex as risk factors for UIAs.

Table 1. Characteristics of the 206 Patients With an UIA and 574 Population-based Controls

Characteristics	Patients With UIA (n=206)	Controls (n=574)
Men, n (%)	68 (33.0)	177 (30.8)
Mean age, y	54.6	54.8
Alcohol use, n (%)	173 (84.0)*	475 (83.2)*
Alcohol ≥18 U/week, n (%)	26 (12.6)*	67 (11.7)*
Smoking, n (%)	96 (46.8)*	138 (24.1)*
Body mass index ≥30, n (%)	32 (15.8)*	72 (12.9)*
Vigorous exercise ≥3 times/wk, n (%)	35 (17.2)*	147 (25.7)*
Medical history, n (%)		
Hypertension	77 (38.1)	104 (19.0)*
Hypercholesterolemia	26 (14.4)†	76 (14.9)†
Diabetes mellitus	9 (4.4)*	26 (4.6)*
Atrial fibrillation	5 (2.6)*	10 (1.8)*
Heart disease	12 (6.0)*	37(6.7)*
Migraine	14 (7.0)*	62 (11.1)*
Family history, n (%)		
Stroke‡	62 (32.5)	127 (22.7)*
Myocardial infarction	22 (11.4)§	40 (7.2)*

UIA indicates unruptured intracranial aneurysm.

*<5% missing data; §5% to 10% missing data; †10% to 15% missing data; ‡including ischemic and hemorrhagic stroke, but excluding subarachnoid hemorrhage.

Because a family history of aSAH or UIA or a history of (transient) cerebral ischemia was often the reason for detecting the aneurysm, we also decided not to study these factors because of the high likelihood of selection bias.

Univariable analyses were performed to calculate crude odds ratios (OR) with 95% confidence intervals (CI). Subsequently, we performed a multivariable backward stepwise logistic regression analysis to identify independent risk factors. Risk factors with P value <0.05 were considered statistically significant.

Because many patients with an UIA had imaging because of atherosclerotic disease, we did 2 sensitivity analyses to investigate the role of selection bias. First, we did an analysis excluding UIA patients who were investigated for atherosclerotic disease. Second, we did an analysis excluding all UIA patients and controls with a history of stroke. Because a considerable proportion of patients with an UIA were screened because of a positive family history, we also performed a sensitivity analysis to investigate the role of a family history of aSAH.

In an additional logistic regression analysis, we assessed the joint effect of smoking and hypertension, which are the most established risk factors of UIAs.

Results

Study Population

The baseline demographic data and risk factor data of cases and controls are summarized in Table 1. Reasons for imaging in UIA patients were atherosclerotic disease (23%), positive family history for UIA or aSAH (18%), headache (8%), screening without obvious medical indication (3%), and other (46%).

Risk Factors for UIAs

Current smoking, hypertension, and family history of stroke—all 3 independently increased the risk of UIAs; hypercholesterolemia and regular physical exercise independently decreased the risk of UIAs (Table 2).

Current smoking and history of hypertension were the strongest independent risk factors (Table 2). In the sensitivity analysis excluding UIA patients who were investigated for atherosclerotic disease and in the sensitivity analysis excluding all UIA patients and controls with a history of stroke, we found that point estimates for smoking, a history of hypertension, or hypercholesterolemia remained essentially the same, although the OR for hypercholesterolemia was no longer statistically significant because of wider CIs attributable to the smaller sample size (Table I in the online-only Data Supplement).

In the sensitivity analysis excluding patients with a family history of aSAH, point estimates remained essentially the same, although the OR for hypercholesterolemia and a family history of stroke were no longer statistically significant (Table I in the online-only Data Supplement).

The joint risk of smoking and hypertension (OR, 8.3; 95% CI, 4.5–15.2) was higher than the sum of the individual risks for smoking (OR, 3.0; 95% CI, 2.0–4.4) and hypertension (OR, 2.9; 95% CI, 1.9–4.6) (Table 3).

Discussion

Current smoking, hypertension, and family history of stroke other than aSAH increase the risk of UIA, whereas hypercholesterolemia and regular physical exercise decrease this risk. Smoking and hypertension combined yielded a higher risk increase than expected on basis of the individual components.

Table 2. Risk Factors for Unruptured Intracranial Aneurysms

	Univariable Analysis (n=780) OR (95% CI)	Multivariable Analysis (n=615) OR (95% CI)
Alcohol ≥18 U/week, n (%)	1.1 (0.7–1.8)	…
Smoking	2.8 (2.0–3.9)	3.0 (2.0–4.5)
Body mass index ≥30	1.3 (0.8–2.0)	…
Vigorous exercise ≥3 times/week	0.6 (0.4–0.9)	0.6 (0.3–0.9)
Medical history		
Hypertension	2.6 (1.8–3.7)	2.9 (1.9–4.6)
Hypercholesterolemia	1.0 (0.6–1.6)	0.5 (0.3–0.9)
Diabetes mellitus	0.9 (0.4–2.1)	…
Atrial fibrillation	1.4 (0.5–4.2)	…
Heart disease	0.9 (0.5–1.7)	…
Migraine	0.6 (0.3–1.1)	…
Family history		
Stroke*	1.6 (1.1–2.4)	1.6 (1.0–2.5)
Myocardial infarction	1.7 (1.0–2.9)	…

CI indicates confidence interval; and OR, odds ratio.

*Including ischemic and hemorrhagic stroke, but excluding subarachnoid hemorrhage; ... indicates not statistically significant in multivariate analysis.

Other studies also found smoking and hypertension to be strong and independent risk factors for UIAs.[3–5,11,12] The novel finding that smoking and hypertension have an additive effect suggests a synergism between these 2 prominent risk factors in the development of UIAs.

A family history of aSAH or UIA was the primary reason for imaging in one fifth of the UIA patients. Therefore, we could not study this factor. Although we found that a family history of stroke other than aSAH also increases the risk for UIAs, these data should be interpreted with caution. Family members are known to have difficulty differentiating between ischemic stroke, intracerebral hemorrhage, and SAH. Therefore, the association with family history of stroke might be attributable to misclassification.[13] We could not compare our findings on family history of stroke with other studies because we did not find reports on this issue.

Our data on hypercholesterolemia are somewhat in contrast to previous data. Japanese investigators reported that hypercholesterolemia increases the risk of UIAs, whereas a Chinese study found no effect.[3,4] Our data show that hypercholesterolemia decreases the risk of UIAs, which is more plausible because it also decreases the risk of aSAH, at least in our European population.[8,10] The differences in findings between our study and previous studies may be explained by the difference in populations (whites versus Asians), the difference in controls (randomly retrieved from the general population in our study versus hospital-based controls in others), and the different methods used for data acquisition (questionnaire combined with medical records in our study versus review of medical records only in others). Our results on hypercholesterolemia may also be explained by the use of statins because a recent animal study has shown an association between statins and reduction of UIA formation.[14] However, a recent study in humans found no significant beneficial effect on UIA development.[5] Because of the small number of cases and controls using statins, we were unable to study the role of statins in our population.

Table 3. Interaction Between Smoking and Hypertension for the Risk of UIA

	Patients With UIA (n=206)	Controls (n=574)	OR (95% CI)
No smoking, no hypertension	65	353	Ref
Smoking, no hypertension	64	117	3.0 (2.0–4.4)
Hypertension, no smoking	45	83	2.9 (1.9–4.6)
Smoking and hypertension	32	21	8.3 (4.5–15.2)

CI indicates confidence interval; OR, odds ratio; and UIA, unruptured intracranial aneurysm.

Physical exercise decreased the risk of UIAs in our study. We could not find other studies reporting on physical exercise as an independent risk factor for UIAs. Previous research on risk factors for aSAH has shown a trend toward a decrease in risk with regular exercise,[8,10] but 2 case-crossover studies have also shown that, in the acute phase, physical exercise can trigger the rupture of an intracranial aneurysm.[6,15] However, the population attributable risk of physical exercise as a trigger factor is small and exercise also has a beneficial effect on other cardiovascular diseases. Therefore, we still advise patients at risk for UIAs and aSAH to engage in regular physical exercise.[6,15,16]

Selection bias is a potential limitation of our study, which may have influenced our results. First, we were unable to study family history of a SAH or a history of stroke as risk factors because this was the reason for imaging in many patients with UIAs and therefore influenced by selection bias. However, we have shown in a sensitivity analysis that point estimates remained virtually the same after the exclusion of patients with a positive family history. Second, in our multivariable analysis, only hypertension and smoking were statistically significant risk factors associated with an increased risk of UIA development. Because smoking and hypertension are risk factors for atherosclerosis, and many patients with an UIA had cerebral imaging because of atherosclerotic disease, we considered the possibility that the results on smoking and hypertension had been influenced by selection bias. In multivariable analysis, only hypertension and smoking were statistically significant atherosclerotic risk factors associated with an increased risk. To study the possible effect of selection bias on our results for smoking and hypercholesterolemia, we did 2 sensitivity analyses excluding patients screened for atherosclerotic disease or with a history of stroke, and found that point estimates for smoking and hypercholesterolemia remained virtually the same. Third, the risk of smoking could be somewhat underestimated because former smokers were classified as nonsmokers.

Our study has several strong points. First, because both patients with UIAs and controls came from the same catchment area, we were able to study risk factors for aneurysmal rupture in a rather defined population. Second, we only selected UIA patients without a history of aSAH. Third, we had access to individual patient data that allowed multivariable analysis, including a large number of potential risk factors and allowed us to study the interaction between the 2 most well-established risk factors.

Current smoking and hypertension increase the risk of UIA and have combined a higher risk than the sum of the separate risks. Smoking and hypertension are also important risk factors for aSAH. Whether the increased risk for aSAH from smoking and hypertension is only caused by an increased risk for UIA or also by an increased risk of rupture of an already existing UIA should be investigated in future studies. Improving lifestyle by not smoking, treating hypertension, and regular exercise, probably reduces the risk of UIA and maybe also that of aSAH. Why hypercholesterolemia, on one hand, is associated with increased risk of atherosclerotic diseases and, on the contrary, with a decreased risk of UIA should be further investigated. If the risk decreasing effect of hypercholesterolemia is mediated by statin use, statins might be an additional treatment option for decreasing the prevalence of UIAs and thereby the incidence of aSAH.

Sources of Funding

This study was funded by the Julius Center for Health Sciences and Primary Care and the Department of Neurology of the University Medical Center Utrecht.

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had the final responsibility for the decision to submit for publication.

Disclosures

None.

References

1. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol*. 2011;10:626–636.
2. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatr*. 2007;78:1365–1372.
3. Gu YX, Chen XC, Song DL, Leng B, Zhao F. Risk factors for intracranial aneurysm in a Chinese ethnic population. *Chin Med J*. 2006;119:1359–1364.
4. Inagawa T. Risk factors for the formation and rupture of intracranial saccular aneurysms in Shimane, Japan. *World Neurosurg*. 2010;73:155–164; discussion e23.
5. Marbacher S, Schläppi JA, Fung C, Hüsler J, Beck J, Raabe A. Do statins reduce the risk of aneurysm development? A case-control study. *J Neurosurg*. 2012;116:638–642.
6. Vlak MH, Rinkel GJ, Greebe P, van der Bom JG, Algra A. Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study. *Stroke*. 2011;10:626–636.
7. WHO Media Center. Obesity and overweight. http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed October 10, 2011.
8. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*. 2005;36:2773–2780.
9. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med*. 1993;329:1677–1683.
10. Vlak MH, Rinkel GJ, Greebe P, Greving JP, Algra A. Lifetime risks for aneurysmal subarachnoid haemorrhage: multivariable risk stratification. *J Neurol Neurosurg Psychiatry*. January 25, 2013. doi:10.1136/jnnp-2012-303783. http://jnnp.bmj.com/content/early/2013/01/24/jnnp-2012-303783.full. Accessed January 31, 2013.
11. Rasing I, Nieuwkamp DJ, Algra A, Rinkel GJ. Additional risk of hypertension and smoking for aneurysms in people with a family history of subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatr*. 2012;83:541–542.
12. Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. *Stroke*. 2001;32:485–491.
13. Bromberg JE, Rinkel GJ, Algra A, Greebe P, Beldman T, van Gijn J. Validation of family history in subarachnoid hemorrhage. *Stroke*. 1996;27:630–632.
14. Aoki T, Kataoka H, Ishibashi R, Nakagami H, Nozaki K, Morishita R, et al. Pitavastatin suppresses formation and progression of cerebral aneurysms through inhibition of the nuclear factor kappaB pathway. *Neurosurgery*. 2009;64:357–365; discussion 365.
15. Anderson C, Ni Mhurchu C, Scott D, Bennett D, Jamrozik K, Hankey G; Australasian Cooperative Research on Subarachnoid Hemorrhage Study Group. Triggers of subarachnoid hemorrhage: role of physical exertion, smoking, and alcohol in the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). *Stroke*. 2003;34:1771–1776.
16. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol*. 1990;132:612–628.