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Risk factors for all-cause death after diagnosis of unruptured intracranial aneurysms

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ABSTRACT

Objectives: We investigated all-cause mortality and risk factors of death of patients with unruptured intracranial aneurysms (UIAs) in a long-term follow-up study.

Methods: A total of 142 patients with 181 UIAs diagnosed between 1956 and 1978 when UIAs were not treated were included in this study. Patients were followed until death or until 2011 to 2012. Mortality rates and risk factors were studied with Kaplan-Meier survival analysis and the Cox proportional hazards regression models.

Results: During 3,530 person-years, 113 (80%) had died, giving an average annual mortality of 3.2%. Of them, 19 (17%) died of aneurysm rupture from the index UIA, 6 (5%) of other aneurysm-related causes, and 2 (2%) of unspecified subarachnoid hemorrhage. The remaining 86 died of causes unrelated to intracranial aneurysms. The cumulative death rate was 20% (95% confidence interval 14%–27%) at 10 years and 60% (52%–68%) at 30 years. Independent risk factors for subsequent death were patient age (adjusted hazard ratio 1.09 per year, 95% confidence interval 1.05–1.12, $p < 0.001$), male sex (2.81, 1.59–4.96, $p < 0.001$), heavy alcohol use (4.22, 2.22–8.02, $p < 0.001$), and cigarette smoking (1.72, 0.97–3.07, $p = 0.064$). History of hypertension, family history of subarachnoid hemorrhage, and diameter of UIA predicted death only in univariable analysis.

Conclusions: In patients of working age with a UIA, alcohol consumption and cigarette smoking are modifiable risk factors for untimely death through several causes and should be taken into account when treatment is considered. *Neurology*® 2015;84:456–463

GLOSSARY

BP = blood pressure; **CI** = confidence interval; **HR** = hazard ratio; **SAH** = subarachnoid hemorrhage; **UIA** = unruptured intracranial aneurysm.

Saccular intracranial aneurysms develop during the lifetime in 3% of the population.¹ Of these, approximately 25%, or nowadays even less, ever rupture.² Rupture of an aneurysm results in subarachnoid hemorrhage (SAH) with a high case fatality rate.^{3–5}

Those who survive 1 year after SAH seem to have almost 2-fold-higher mortality rate during subsequent decades as compared with the general population.^{5–7} This excess mortality is heterogeneous but is mostly attributable to vascular events including ischemic cerebrovascular stroke, poor outcome after SAH, sequelae of SAH, nonocclusion of ruptured aneurysms, or SAH from another aneurysm.^{5,7} Patients with untreated and even treated unruptured intracranial aneurysms (UIAs) seem also to have long-term excess mortality compared with the general population.^{8,9} This elevated mortality rate is likely attributable to both aneurysm ruptures and other cerebrovascular events.^{8,9}

This elevated mortality rate of aneurysm patients mainly because of cerebrovascular diseases and subsequent new SAH episodes may be explained by the risk factors smoking, hypertension, and excessive alcohol drinking.¹⁰ UIAs, most of which (65%–85%) are <7 mm in diameter, are now increasingly discovered.^{2,4} To estimate effectiveness of a preventive intervention, it is

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Supplemental data
at Neurology.org

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essential to know, in addition to the risk of aneurysm rupture, also the life expectancy and risk factors for the observed excess mortality.

Unruptured aneurysms were not operated on in Finland before 1979.² This long-term natural history study reports all-cause mortality and risk factors for death in patients of working age with UIAs covering almost the whole of their remaining life.

METHODS Patients. The series included 142 patients with UIAs diagnosed between 1956 and 1978 at the Department of Neurosurgery, Helsinki University Central Hospital, which was the only neurosurgical center in Finland until 1967 and remained responsible for neurosurgical services for 60% to 88% of the Finnish population between 1967 and 1978.² For the detailed baseline characteristics of the 142 patients, see our previous reports.^{2,11,12} Most patients ($n = 131$) were those with multiple aneurysms in whom only the ruptured one was clipped and occlusion was confirmed by postoperative angiography. Verification of the ruptured aneurysm was based on the signs of rupture in the surgical record.¹¹ Additional evidence for the identification of ruptured aneurysm in these patients was as follows¹¹: the greater size of the ruptured aneurysm in 10 patients; the size with a secondary sac in 69 patients; intracerebral hematoma caused by the ruptured aneurysm in 38 patients; and oculomotor palsy associated with a ruptured internal carotid artery aneurysm in 14 patients. Patients with SAH and 2 or more aneurysms of equal size but without other evidence indicating which aneurysm had bled were treated conservatively and excluded from this study. Angiographies in the remaining 11 patients discovered either incidental ($n = 5$; chronic headache, nausea, dizziness, visual disorders) or symptomatic ($n = 6$; cranial nerve deficits or cerebral infarction) UIAs.¹¹

Follow-up methods. Follow-up evaluation was performed mainly by means of repeated postal questionnaires and telephone interviews obtained from patients and close relatives every 10 years from the 1960s onward.^{2,11–15} During the previous follow-up evaluations, the patients were interviewed (S.J.) by means of a structured questionnaire eliciting data on patient characteristics, previous diseases and hospital visits, use of medicines, and health habits.^{11–13} For the recording of blood pressure (BP) values, see our previous reports.^{11,13} Those who were alive between 1996 and 1998 were also interviewed in the outpatient clinic and a follow-up CT angiogram was performed.¹² New questionnaires were filled in between 2011 and 2012 based on telephone interviews either with patients or with relatives on demand.¹³ Alcohol consumption was recorded at the beginning of the follow-up in grams of absolute ethanol consumed within 1 week (standard drink 12 g of alcohol). Cigarette smoking was categorized as follows: never a smoker, formerly a regular cigarette smoker (quit before or during the follow-up), and current cigarette smoker. A family history of aneurysms was defined as ≥ 2 verified ruptured aneurysm cases in first-degree relatives.^{2,13}

Information on all the patients was also obtained from the medical records of other hospitals and general practitioners to confirm the accuracy of the data concerning diseases, medicines, and BP readings.^{11,13} UIAs without any rupture were occluded in 3 patients between 1997 and 1999 after follow-ups of 24.4 to 25.9 years.² Of 34 UIAs that ruptured during the follow-up, 16 were occluded after a rupture. Of these patients, 15 were conscious and one was in deep coma.¹⁶ Autopsy reports and official

death certificates from the Causes of Death Register (Statistics Finland) were examined for all the deceased patients. In Finland, a statutory medicolegal autopsy is performed on all those who die due to trauma or unknown cause (Act on the Inquest into the Cause of Death, 459/1973, Finnish Law). The follow-up was complete.

Standard protocol approvals, registrations, and patient consents. All patients gave their written informed consent. The approval for the surveys and follow-up data collection has been obtained from the local ethics committee and in compliance with national legislation and the Declaration of Helsinki.

Statistical analysis. The data were analyzed with the IBM SPSS Statistics 22.0 for Windows (IBM Corp., Armonk, NY). Categorical variables were compared using Fisher exact 2-tailed test or the Pearson χ^2 test, while the continuous variables were compared between groups using the Mann–Whitney U test or t tests.

For the life-table analysis and the Cox proportional hazards regression model, each patient was followed up until death or the last contact between 2011 and 2012. The average annual mortality was calculated by dividing the number of deaths by the number of person-years in the follow-up. Cumulative rates of death were estimated using the Kaplan–Meier product-limit method, and the curves for the groups were compared using the log-rank test.

Cox proportional hazards regression with a backward stepwise procedure (removal if $p > 0.1$) and Wald statistics was used to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for several variables in predicting death. These variables, which were known at the beginning of the follow-up, were the following: age, sex, maximum aneurysm diameter, location of the largest UIA in each patient, presence of multiple UIAs, type of aneurysm (symptomatic or incidental vs those with prior SAH), cigarette-smoking status and current smoking, alcohol consumption, a family history of ruptured intracranial aneurysms, a history of hypertension (systolic BP >140 or diastolic BP >90 mm Hg or use of antihypertensive medication), and BP (systolic, diastolic, mean) values. Interactions between significant predictors of death were tested to see the extent to which they deviated from the additive effects of the main risk factors. The proportionality assumption was checked. The test of significance was based on changes in the log (partial) likelihood. A 2-tailed p value <0.05 was considered statistically significant.

RESULTS Patient characteristics. Association of subsequent deaths with the baseline characteristics of the patient population is shown in table 1. Patient age ($p < 0.05$), approximate amount of alcohol consumed within 1 week ($p < 0.05$), and particularly heavy alcohol consumption ($p < 0.01$) were associated with subsequent death, as were male sex ($p = 0.062$) and smoking status ($p = 0.086$) but without reaching significance. Those who were active smokers the entire follow-up time had a higher death rate compared with others ($p = 0.016$), but current smokers at the beginning of follow-up had not because quitters accumulated among those who were alive at the end of follow-up. Men smoked more frequently both at the beginning (74% vs 42%, $p < 0.001$) and at the end (60% vs 36%, $p = 0.01$) of follow-up, and they were also more frequently heavy alcohol drinkers (38% vs 4%, $p < 0.001$) than women.

Table 1 Baseline characteristics of patients at the beginning of follow-up, grouped by subsequent death during follow-up

Characteristic	Deceased (n = 113)	Alive (n = 29)	All patients (n = 142)
Women, n (%)	56 (50)	20 (69)	76 (54)
Age, mean $\pm$ SD, y	42.9 $\pm$ 9.9 ^a	37.6 $\pm$ 9.6	41.8 $\pm$ 10.1
Body mass index, mean $\pm$ SD, kg/m ²	25.8 $\pm$ 3.8	26.4 $\pm$ 4.2	25.9 $\pm$ 3.9
Blood pressure, mean $\pm$ SD, mm Hg	141 $\pm$ 19/85 $\pm$ 10	135 $\pm$ 15/85 $\pm$ 9	140 $\pm$ 19/85 $\pm$ 10
History of hypertension, n (%)	43 (38)	8 (28)	51 (36)
Smoking status (n = 123), n (%)			
No	27 (29)	10 (34)	37 (30)
Quit before follow-up	9 (10)	6 (21)	15 (12)
Quit during follow-up	8 (9)	5 (17)	13 (11)
Current	50 (53) ^a	8 (28)	58 (47)
Alcohol consumption (n = 95)			
Median (range), g/wk	70 (0–1,000) ^a	2 (0–350)	20 (0–1,000)
≥ 300 g/wk, n (%)	19/66 (29) ^b	1/29 (3)	20/95 (21)
Family history of aneurysms (n = 94), n (%)	8 (12)	1 (3)	9 (10)
Diameter of largest aneurysm, n (%)			
≤ 6 mm	92 (81)	24 (83)	116 (82)
≥ 7 mm	21 (19)	5 (17)	26 (18)
Location of largest aneurysm, n (%)			
Internal carotid artery	47 (42)	13 (45)	60 (42)
Anterior cerebral artery	5 (4)	1 (3)	6 (4)
Anterior communicating artery	6 (5)	2 (7)	8 (6)
Middle cerebral artery	52 (46)	12 (41)	64 (45)
Vertebrobasilar artery	3 (3)	1 (3)	4 (3)
Multiple unruptured aneurysms, n (%)	28 (25)	5 (17)	33 (23)

History of hypertension was defined as systolic pressure repeatedly >140 mm Hg or diastolic pressure >90 mm Hg, or as use of antihypertensive medication. Aneurysm size = largest diameter in millimeters. Family history of aneurysms was defined as ≥ 2 verified ruptured aneurysm cases in first-degree relatives.

^a $p < 0.05$ and ^b $p < 0.01$ for difference between groups.

At the beginning of follow-up, age by sex was similar (mean $\pm$ SD age for men 42.2 $\pm$ 9.2 years vs for women 43.0 $\pm$ 10.1 years). At the end of follow-up, patient age was 66.6 $\pm$ 13.4 years (for men 62.5 $\pm$ 12.4 years and for women 70.2 $\pm$ 13.2 years, $p < 0.001$). Mean $\pm$ SD age of 113 patients who had died was 64.0 $\pm$ 13.1 years (range 33.9–93.6 years; for men 60.2 $\pm$ 11.6 and for women 67.9 $\pm$ 13.6 years, $p < 0.01$) and that of those who were alive was 77.0 $\pm$ 8.6 years (for men 77.0 $\pm$ 5.7 years and for women 76.9 $\pm$ 9.8 years). Age at death was higher ($p < 0.001$) in those without SAH from UIA than in those with aneurysm rupture (66.6 $\pm$ 13.3 vs 56.5 $\pm$ 9.3 years). Those who had died of unrelated causes (65.9 $\pm$ 13.2 years; for men 61.0 $\pm$ 11.8 years and for women 71.5 $\pm$ 12.6 years, $p < 0.001$) outlived those who died of SAH from UIA (53.7 $\pm$ 6.7 years; for men 52.0 $\pm$ 5.0 years and for women 54.5 $\pm$ 7.4 years) by approximately 12 years ($p < 0.001$), even more in women (by 17 years).

Cumulative rates and causes of death. Annual and cumulative death rates according to baseline characteristics are shown in table 2. Patient age, male sex, cigarette smoking, and heavy alcohol consumption ($p < 0.01$) as well as hypertension ($p = 0.052$) and family history of ruptured aneurysms ($p = 0.073$) increased cumulative mortality. Survival curves of those with later SAH from UIA and those without are shown in figure e-1 on the *Neurology*[®] Web site at Neurology.org. Curves did not differ significantly because not all patients with an aneurysm rupture die of SAH. However, mortality of those younger than 41 years was significantly higher if a UIA ruptured during the follow-up (figure e-2). Men, cigarette smokers, and heavy alcohol drinkers had higher mortality rates ($p < 0.01$) than others (figures e-3 to e-5). Prior SAH as well as the size, location, and multiplicity of UIAs did not predict subsequent death.

Table 2 Annual and cumulative death rates, grouped by factors known at the beginning of follow-up

Characteristic	No. of patients	Annual death rate, % (n)	Cumulative death rates, % (95% CI)		
			10 y	20 y	30 y
All patients	142	3.2 (113/3,530)	20 (14-27)	39 (31-47)	60 (52-68)
Prior SAH					
No	11	3.6 (8/225)	46 (16-75)	55 (25-84)	64 (35-92)
Yes	131	3.2 (105/3,305)	18 (12-25)	37 (29-46)	60 (51-68)
Sex^a					
Men	66	4.0 (57/1,408)	24 (14-35)	52 (39-64)	76 (65-86)
Women	76	2.6 (56/2,121)	17 (9-26)	28 (18-38)	46 (35-57)
Age, y^a					
≤30	25	2.5 (19/757)	12 (0-25)	24 (7-41)	52 (32-72)
31-40	40	2.3 (27/1,173)	10 (1-19)	25 (12-38)	48 (32-63)
41-50	46	3.5 (38/1,101)	20 (8-31)	39 (25-53)	61 (47-75)
51-60	31	5.8 (29/498)	42 (24-59)	68 (51-84)	81 (67-95)
History of hypertension					
No	91	2.9 (70/2,455)	19 (11-27)	31 (21-40)	52 (41-62)
Yes	51	4.0 (43/1,074)	24 (12-35)	53 (39-67)	75 (63-86)
Current cigarette smoking^a					
No	53	2.2 (37/1,672)	4 (0-9)	19 (8-29)	42 (28-55)
Yes	70	3.4 (57/1,672)	20 (11-29)	43 (31-54)	63 (52-74)
Alcohol consumption^a					
<300 g/wk	75	1.9 (47/2,469)	1 (0-4)	13 (6-21)	35 (24-45)
≥300 g/wk	20	5.4 (19/352)	35 (14-56)	70 (50-90)	85 (69-100)
Family history of aneurysms					
No	85	2.2 (57/2,578)	8 (2-14)	22 (13-31)	42 (32-53)
Yes	9	3.5 (8/229)	22 (0-49)	33 (3-64)	56 (23-88)
Diameter of unruptured aneurysm					
≤6 mm	116	3.1 (92/2,989)	18 (11-25)	35 (26-43)	58 (49-67)
≥7 mm	26	3.9 (21/540)	31 (13-49)	58 (39-77)	69 (51-87)
Multiple unruptured aneurysms					
No	109	3.1 (85/2,785)	20 (13-28)	38 (29-47)	58 (49-67)
Yes	33	3.8 (28/744)	21 (7-35)	42 (26-59)	67 (51-83)

Abbreviations: CI = confidence interval; SAH = subarachnoid hemorrhage.

Annual death rate is calculated by dividing the number of deceased patients by person-years of follow-up shown in parentheses.

^a*p* < 0.01 for difference of cumulative mortality between groups (log-rank test).

The mean follow-up time per patient was 24.9 years (median 24.2, range 0.8–52.3 years). Of the 142 patients, 113 (80%) had died during the follow-up of 3,530 person-years, yielding an average annual mortality of 3.2%. Of the 34 patients with SAH from previously diagnosed UIA, 18 patients died of either an aneurysm rupture or rerupture during a mean follow-up time of 11.4 years (range 1.4–24.2 years), and one of late rebleeding 2.9 years after aneurysm rupture with conservative treatment during a total follow-up of 20.1 years. Four patients died of SAH from a nonindex aneurysm (2 patients with

verified de novo aneurysms and 2 with aneurysms diagnosed with follow-up CT angiograms but without having previous vertebral angiographies) during a mean follow-up of 28.5 years (range 13.4–51.0 years). Two patients aged 42.7 and 49.6 years died of typical SAH but without angiograms or autopsy 12.7 and 13.6 years after controlled occlusions of ruptured aneurysms, which were previously diagnosed index UIAs. One patient died of expansion of an unruptured giant aneurysm but without rupture and another patient aged 58.4 years died of SAH caused by fracture of aneurysm clip 24.0 years after

Table 3 Causes of subsequent death in 113 patients by sex, current cigarette smoking, and heavy alcohol drinking

Characteristic	Current cigarette smoking		Heavy alcohol drinking		Sex	
	No	Yes	No	Yes	Men	Women
No. of patients	37 (44)	57 (50)	47	19	57	56
Mean ± SD age at the beginning of follow-up, y	45.5 ± 10.4 (45.2 ± 10.2)	39.7 ± 9.2 ^a (39.2 ± 9.2) ^b	42.3 ± 9.3	39.8 ± 11.6	42.1 ± 9.8	43.7 ± 10.1
Mean ± SD age at the end of follow-up, y	73.5 ± 11.3 (73.6 ± 10.5)	60.2 ± 12.2 ^a (58.2 ± 11.6) ^a	71.4 ± 12.2	56.3 ± 12.3 ^a	60.2 ± 11.6 ^a	67.9 ± 13.6
Cause of death						
Cardiovascular	9 (10)	15 (14)	12	6	21 ^b	10
Cerebrovascular	7 (8)	8 (7)	8	2	7	12
Malignant neoplasm	7 (10)	12 (9)	13	2	9	12
Other diseases	7 (9)	7 (5)	9	2	8	7
Trauma or suicide	1 (1)	4 (4)	—	3 ^b	3	2
SAH from index aneurysm	3 (3)	10 (10)	2	3	6	12
Nonindex/de novo aneurysm rupture	3 (3)	1 (1)	3	1	3	1

Abbreviation: SAH = subarachnoid hemorrhage.

Current cigarette smoking indicates smoking at the beginning of follow-up (smoking at the end of follow-up is shown in parentheses). Heavy alcohol drinker consumes approximately ≥ 300 g/wk of alcohol. Lifetime for noncurrent smoker and nonheavy drinkers was 77.5 ± 8.3 years and for current smoking heavy drinkers was 55.2 ± 12.5 years. Cause of death was pulmonary cancer in 2 nonsmokers and 8 smokers. ^a $p < 0.01$ and ^b $p < 0.05$ for difference between groups.

treatment of a ruptured aneurysm. The remaining 86 died of unrelated causes (31 of cardiovascular diseases, 14 of cerebrovascular diseases, 21 of malignant neoplasms, and 20 of other diseases or traumas).

Causes of death of 113 patients according to sex, cigarette smoking, and heavy alcohol consumption are shown in table 3. Men died of cardiovascular causes more frequently than women ($p = 0.024$) and heavy alcohol drinkers more frequently of trauma or suicide than others ($p = 0.042$). Furthermore, women died nonsignificantly more likely of SAH, cerebrovascular diseases, and malignancies, smokers of SAH, and heavy drinkers of SAH and liver cirrhosis but less likely of malignancies, probably because they were relatively young at the time of death.

Other causes of untimely deaths were primary intracerebral hemorrhage (mean age 57.1, range 50.6–64.2 years), trauma or suicide (46.1, 33.9–71.3 years), and hepatic cirrhosis (48.2, 40.7–55.6 years). However, those who died of SAH caused by de novo aneurysm or aneurysm verified during the follow-up were older (mean 70.5, range 63.4–80.2 years).

Risk factors for death. Univariable and multivariable HRs for the risk factors known at the beginning of the follow-up are shown in table 4. In univariable analysis, patient age (particularly older than 50 years), male sex, cigarette smoking, and heavy alcohol consumption were risk factors for death ($p < 0.01$). History of hypertension, family history of ruptured aneurysms, and diameter of UIA as a continuous variable did not reach significance. In multivariable analysis, age and male sex were independent risk factors for death. Current cigarette smoking at the beginning of follow-up also increased the risk for death (table 4; model I). When heavy alcohol consumption was included in the multivariable model, age, male sex, and heavy drinking were independent significant predictors of subsequent death (table 4; model II). Current cigarette smoking was not an independent predictor ($p = 0.12$) because it was closely correlated with the alcohol consumption ($p < 0.001$). There were no significant interactions between the independent risk factors for death.

All those with missing data for either cigarette smoking or alcohol consumption were dead at the end of follow-up. If all patients with missing smoking status ($n = 19$) are considered nonsmokers, current cigarette smokers at the beginning of follow-up still had almost significant increased risk of death after adjustment for age and sex (adjusted HR 1.45, 95% CI 0.97–2.16, $p = 0.068$). If those with missing alcohol status ($n = 47$) are considered also to be nondrinkers, heavy drinking was still a risk factor for death after adjustment for sex, age, cigarette

Table 4 Risk factors for all-cause death

Characteristic	No. of patients	Univariable HR (95% CI)	Multivariable HR (95% CI)	
			Model I	Model II
Sex				
Women	76	1.00	1.00	1.00
Men	66	1.74 (1.19–2.53) ^a	2.32 (1.30–4.17) ^a	3.00 (1.41–6.40) ^a
Age, y				
<31	25	1.00		
31–40	40	0.98 (0.54–1.79)		
41–50	46	1.71 (0.96–3.03)		
>50	31	3.50 (1.89–6.47) ^a		
Continuous, per year	142	1.05 (1.03–1.07) ^a	1.07 (1.03–1.10) ^a	1.10 (1.06–1.15) ^a
History of hypertension				
No	91	1.00		1.00
Yes	51	1.46 (1.00–2.15) ^b	1.00 (0.55–1.82)	0.90 (0.44–1.85)
Current smoking				
No	53	1.00	1.00	1.00
Yes	70	1.88 (1.23–2.88) ^a	1.89 (1.09–3.28) ^c	1.67 (0.88–3.19)
Alcohol consumption				
<300 g/wk	75	1.00		1.00
≥300 g/wk	20	4.31 (2.48–7.51) ^a		3.98 (1.68–9.43) ^a
Alcohol consumption, per 100 g/wk	95	1.38 (1.23–1.55) ^a		
Family history of aneurysms				
No	85	1.00	1.00	1.00
Yes	9	1.96 (0.93–4.16) ^d	1.12 (0.48–2.57)	1.42 (0.56–3.63)
Diameter of unruptured aneurysm				
≤6 mm	116	1.00		
≥7 mm	26	1.36 (0.85–2.19)		
Continuous, per mm	142	1.06 (0.99–1.12) ^d	0.99 (0.87–1.12)	0.84 (0.70–1.02)

Abbreviations: CI = confidence interval; HR = hazard ratio.

In multivariable analyses, the HRs were adjusted for the other variables listed in the table.

^a $p < 0.01$.

^b $p = 0.053$.

^c $p < 0.05$.

^d $p = 0.08$.

smoking, hypertension, and aneurysm diameter (2.09, 1.22–3.58, $p = 0.008$).

DISCUSSION The patient's age, male sex, heavy alcohol consumption, and cigarette smoking seem, from the present results, to be independent risk factors for death among patients of working age with UIAs. Nonsmokers and nondrinkers outlived current smokers and heavy drinkers by approximately 10 to 20 years. History of hypertension or family history of ruptured aneurysms and size of aneurysm had only trend in univariable analysis for increased mortality.

Survivors 1 year after SAH as well as those with both untreated and possibly also treated UIAs seem

to have higher mortality during subsequent decades as compared with the general population.^{5–9} This excess mortality is attributable to both aneurysm-related and -unrelated causes. Our study demonstrated that the ruptures from untreated UIAs accounted for 17% of all deaths and intracranial aneurysms including also ruptures from nonindex aneurysms (e.g., de novo aneurysms) and their sequelae for 24%. Distribution of aneurysm-unrelated causes of death was similar to general Western populations. Mortality caused by a rupture of a diagnosed untreated UIA seems to be important because SAH causes only 0.6% of all deaths in Finland (approximately 300 SAH deaths/50,000 all annual deaths;

Statistics Finland). This is also supported by our previous observation of the lifelong rupture risk of 30% irrespective of aneurysm size among patients younger than 50 years.^{2,17}

Apart from being indisputable modifiable risk factors for SAH,¹⁰ cigarette smoking and heavy alcohol drinking seem to be main risk factors for all-cause mortality of patients with UIA, even much more important than aneurysm-associated factors. After inclusion of deceased patients with missing values for alcohol and smoking variables as nonsmokers and nondrinkers in models, smoking and heavy drinking were still important risk factors for death. These habits were also clearly more common in men than in women. However, this only partly explained the higher mortality rate in men because adjustment by these factors did not abolish the significant difference of mortality rates between men and women. Cardiovascular deaths seemed to account for the excess mortality among men. Although hypertension is the main risk factor for cardiovascular diseases, it unexpectedly did not predict independently the risk for subsequent mortality likely because of several reasons: (1) BP values correlated with age, (2) BP values were recorded at the beginning of follow-up and likely varied during the very long-lasting follow-up, (3) the patient population was relatively young and hypertension may be more important in older patients, and (4) all patients already had aneurysms, which are known to be associated with increased prevalence of hypertension.

Cigarette smoking and excess alcohol consumption increase premature death rate through several causes, e.g., cardiovascular and cerebrovascular events, some malignant neoplasms, liver cirrhosis, and trauma.^{18–20} Alcohol consumption is an important contributor to mortality and potential years of life lost, particularly in Europe. The average life expectancy of heavy alcohol drinkers is clearly lower than that of cigarette smokers because mortality caused by alcohol consumption occurs primarily among people of working age (approximately 5% of all deaths in people younger than 60 years).^{18–20} Compared with other risk factors (cigarette smoking, cholesterol, or hypertension), the alcohol-attributable disease burden is more important in younger people.¹⁹ The life expectancy is considerably shorter for men than for women. Much of the difference can be explained by cigarette smoking and harmful alcohol drinking.²¹

The strength of our cohort study is its unique nature with enrollment of patients of working age during the time when UIAs were not treated and the long-term follow-up covered the remainder of the patient's life in the majority of cases (80%).^{2,22} There were also only few surgical withdrawals after a long-term follow-up (>24 years), and the follow-up of our patients was complete.

A limitation of our study was that the patients were younger than in the other studies with UIA patients and mostly had multiple aneurysms, with the ruptured aneurysm clipped at the start of the follow-up. However, patients with either a history of SAH or multiple UIAs have not been shown to have a higher risk of aneurysm rupture than others when confounding factors are considered.^{2,22–24} Finnish people have also been considered to be subject to a higher risk of aneurysm rupture.²² However, there were 32 Finns enrolled in the International Study of Unruptured Intracranial Aneurysms during the 1990s,^{22,23} but none of them had an aneurysm rupture within more than 200 follow-up years. This suggests that risk factors themselves are much more important than nationality considering aneurysm rupture risk. In the present study, missing values for alcohol consumption and cigarette smoking did not change the results after considering these in additional analyses.

When assessing treatment for UIAs, not only should aneurysm-related risk factors (aneurysm size and location) be considered but also life expectancy and the risk factors that shorten the lifespan. The younger the patient and the larger the aneurysm, the higher the indications for treatment become.^{2,4} However, the indication and benefit for treatment of UIAs in heavy drinkers may be quite questionable when the risks associated with heavy drinking are compared with those of the UIA. However, the indication for UIA treatment seems to be relatively high in smoking women because they also have a higher lifelong UIA rupture risk.¹⁷ While smoking shortens life expectancy, it increases risk of UIA rupture, and women outlive men. Irrespective of treatment indications, cessation of smoking and excess alcohol drinking and treatment of hypertension are, however, important for all aneurysm patients.

AUTHOR CONTRIBUTIONS

S.J. was responsible for the study design and data interpretation. S.J. was responsible for data analysis. S.J. and H.L. collected the data. S.J. drafted the report, and both authors critically revised the manuscript.

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DISCLOSURE

S. Juvela serves as an associate editor for the *European Journal of Neurology* and on the editorial board of *Stroke*. H. Lehto reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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REFERENCES

1. Vlak MHM, Algra A, Brandenburg R, Rinkel GJE. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, co-morbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol* 2011;10:626–636.
2. Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *Stroke* 2013;44:2414–2421.
3. Nieuwkamp DJ, Setz LE, Algra A, Linn FHH, de Rooij NK, Rinkel GJE. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol* 2009;8:635–642.
4. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European Stroke Organisation guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis* 2013;35:93–112.
5. Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Kaprio J. Cause-specific mortality of 1-year survivors of subarachnoid hemorrhage. *Neurology* 2013;80:481–486.
6. Wermer MJ, Greebe P, Algra A, Rinkel GJ. Long-term mortality and vascular event risk after aneurysmal subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 2009;80:1399–1401.
7. Huttunen T, von und Zu Fraunberg M, Koivisto T, et al. Long-term excess mortality of 244 familial and 1502 sporadic one-year survivors of aneurysmal subarachnoid hemorrhage compared with a matched Eastern Finnish catchment population. *Neurosurgery* 2011;68:20–27.
8. Britz GW, Salem L, Newell DW, Eskridge J, Flum DR. Impact of surgical clipping on survival in unruptured and ruptured cerebral aneurysms: a population-based study. *Stroke* 2004;35:1399–1403.
9. Pyysalo L, Luostarinen T, Keski-Nisula L, Öhman J. Long-term excess mortality of patients with treated and untreated unruptured intracranial aneurysms. *J Neurol Neurosurg Psychiatry* 2013;84:888–892.
10. Feigin VL, Rinkel GJ, Lawes CM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke* 2005;36:2773–2780.
11. Juvela S, Porras M, Heiskanen O. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *J Neurosurg* 1993;79:174–182.
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. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. *J Neurosurg* 2000;93:379–387.
14. Heiskanen O, Marttila I. Risk of rupture of second aneurysm in patients with multiple aneurysms. *J Neurosurg* 1970;32:295–299.
15. Heiskanen O. Risk of bleeding from unruptured aneurysm in cases with multiple intracranial aneurysms. *J Neurosurg* 1981;55:524–526.
16. Juvela S. Prehemorrhage risk factors for fatal intracranial aneurysm rupture. *Stroke* 2003;34:1852–1857.
17. Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish cohort study. *Stroke* 2014;45:1958–1963.
18. Rossow I, Amundsen A. Alcohol abuse and mortality: a 40-year prospective study of Norwegian conscripts. *Soc Sci Med* 1997;44:261–267.
19. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009;373:2223–2233.
20. Shield KD, Taylor B, Kehoe T, Patra J, Rehm J. Mortality and potential years of life lost attributable to alcohol consumption in Canada in 2005. *BMC Public Health* 2012;12:91.
21. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997;349:1436–1442.
22. Greving JP, Wermer MJH, Brown RD Jr, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014;13:59–66.
23. Wiebers DO, Whisnant JP, Huston J III, et al; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003;362:103–110.
24. Morita A, Kirino T, Hashi K, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med* 2012;366:2474–2482.

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SUPPLEMENTAL DATA

NEUROLOGY 2014/590349: Risk Factors for All-cause Death after Diagnosis of Unruptured Intracranial Aneurysms

Seppo Juvela and Hanna Lehto

Supplemental figure e-1: Cumulative survival curves of those with and without a later subarachnoid hemorrhage from diagnosed unruptured aneurysm.

Supplemental figure e-2: Cumulative survival curves of those with and without a later subarachnoid hemorrhage from diagnosed unruptured aneurysm according to age groups (<41 years vs. vs. $\geq$ 41 years).

Supplemental figure e-3: Cumulative mortality in relation to sex.

Supplemental figure e-4: Cumulative survival in relation to cigarette smoking.

Supplemental figure e-5: Cumulative survival in relation to heavy alcohol consumption.

Figure e-1. Cumulative survival curves of those with and without a later subarachnoid hemorrhage from diagnosed unruptured aneurysm.

Those who had an aneurysm rupture (red line) had nonsignificantly shorter survival time than others (black line) (difference of median survival times of 8.3 years, 18.4 vs. 26.7 years, $p=0.154$). The markers of the curves indicate censored events. SAH= subarachnoid hemorrhage.

Figure e-2. Cumulative survival curves of those with and without a later subarachnoid hemorrhage from diagnosed unruptured aneurysm according to age groups (<41 years vs. vs. ≥ 41 years).

Those aged <41 years who had an aneurysm rupture (red line) had significantly shorter survival time than others aged <41 years (black line) (difference of median survival times of 16.3 years, 20.8 vs. 37.1 years, $p=0.008$) while among those aged ≥ 41 years (green line for those without SAH and blue one for those with SAH), the difference was not significant (difference of median survival times of 12.8 years, 8.8 vs. 21.5 years, $p=0.77$). The markers of the curves indicate censored events. SAH= subarachnoid hemorrhage.

Figure e-3. Cumulative mortality in relation to sex.

Kaplan-Meier curves showing cumulative mortality in relation to sex. Men (red line) had a shorter survival rate than women (black line)(difference of median survival times of 11.1 years, 19.8 vs. 30.9 years, $p=0.004$). The markers of the curves indicate censored events.

Figure e-4. Cumulative survival in relation to cigarette smoking.

Kaplan-Meier curves showing cumulative mortality in relation to current cigarette smoking at the beginning of follow-up. Smokers (red line) had a shorter survival rate than nonsmokers (black line) (difference of median survival times of 12.0 years; 22.8 vs. 34.8 years, $p=0.003$). The markers of the curves indicate censored events.

Figure e-5. Cumulative survival in relation to heavy alcohol consumption.

Kaplan-Meier curves showing cumulative mortality in relation to heavy alcohol consumption at the beginning of follow-up. Heavy drinkers (red line) had a shorter survival rate than others (black line) (difference of median survival times of 23.0 years; 13.9 vs. 36.9 years, $p < 0.001$). The markers of the curves indicate censored events.