Risk Factors of Sudden Death From Subarachnoid Hemorrhage

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Background and Purpose—One in every 4 subarachnoid hemorrhage (SAH) patients dies suddenly outside hospital, but most SAH risk factor studies focus on hospitalized patients. We studied the differences in risk factors between hospitalized SAH and sudden-death SAH patients.

Methods—The population-based FINRISK study cohort of 65 521 individuals was followed up for 1.52 million person-years. The Cox proportional hazards model calculated hazard ratios (HRs), with all analyses adjusted for known SAH risk factors, marital status, and socioeconomic status. A competing risks model analyzed differences in risk factors between hospitalized SAHs and sudden-death SAHs.

Results—We identified 98 sudden-death SAHs and 445 hospitalized SAHs confirmed by autopsy or by standard SAH diagnostics. Increase by 5 cigarettes smoked per day elevated sudden-death SAH risk (HR, 1.28; 95% confidence interval [CI], 1.17–1.39) more than hospitalized SAH risk (HR, 1.19; 95% CI, 1.13–1.24; *P*=0.05 for difference). Per SD (21.4 mm Hg) increase, systolic blood pressure elevated risk of sudden-death SAH (HR, 1.34; 95% CI, 1.09–1.65) more than risk for hospitalized SAH (HR, 1.25; (95% CI, 1.12–1.38; *P*=0.05 for difference). Participants living without a partner were at elevated risk of sudden-death SAH (HR, 2.09; 95% CI, 1.33–3.28) but not of hospitalized SAH. No sudden-death SAHs occurred in normotensive never smokers aged <50 years.

Conclusions—Sudden-death SAH risk seems to be highest among those individuals with the most adverse risk factor profiles and among those who live without a partner, whereas it is rare among normotensive never smokers aged <50 years. **(*Stroke*. 2017;48:2399-2404. DOI: 10.1161/STROKEAHA.117.018118.)**

Key Words: cohort studies ■ death ■ epidemiology ■ risk factors ■ subarachnoid hemorrhage

According to a recent nationwide study, one fourth of those experiencing their first-ever subarachnoid hemorrhage (SAH) die suddenly before being admitted to a hospital ward.[1] These sudden deaths often occur in asymptomatic and working-age individuals with no previous history of intracranial aneurysms or cardiovascular diseases. If epidemiological SAH studies include only hospital-admitted patients, a significant percentage of those experiencing SAH are overlooked, meaning that such studies present considerable risk of selection bias.[2] In only a limited number of countries, ones like Finland, is a forensic autopsy legally mandatory for all sudden and unexpected deaths to confirm the diagnosis. Prospective, long-term, and population-based studies that include sudden deaths have reported that smoking, high blood pressure, increasing age, and possibly female sex are independent risk factors for SAH.[3–6] However, none of these studies have analyzed whether risk factor profiles differ between sudden-death and hospital-admitted SAH patients.

This population-based risk factor study, which includes outside-hospital sudden deaths from SAH, is based on a following hypothesis: overall risk factors for sudden deaths from SAH are the same as for hospital-admitted SAH patients, but sudden-death SAH patients have more adverse risk factor profile than hospitalized SAH patients. If true, such results indicate that people with most adverse SAH risk factor profiles are more likely to die suddenly outside hospitals from SAH.

Methods

Data Collection

Our earlier studies report the research protocol in detail.[3,7,8] In brief, the National FINRISK surveys have been conducted every 5 years since 1972, with independent population-based random samples from various geographical areas of Finland. Experienced research nurses perform clinical measurements including systolic blood pressure (SBP), height, and weight and acquire semi-fasting blood samples for cholesterol measurement after at least 4-hour fasting. Body mass index is calculated by dividing body weight in kilograms by square of body height. Participants are categorized as hypertensive or normotensive based on an SBP 140-mm Hg cutoff.

Smoking status, parents' stroke, socioeconomic status, and marital status were assessed by a standardized self-administered questionnaire.

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Those participants reporting no smoking at all or <100 cigarettes in their lifetime were considered never smokers. Former smokers were those who had quit >6 months before completing the questionnaire. Current smokers reported how many cigarettes they smoked per day (CPD) on average; these were categorized as light and moderate (1–20 CPD) or heavy (>20 CPD) smokers. The validity of smoking data using cotinine as a biomarker was assessed to be good in a 1992 survey.[9] Socioeconomic status is measured as years of education and divided into tertiles of education (low, intermediate, and high). Marital status is divided into 4 categories: (1) married or cohabiting, (2) single, (3) divorced, (4) widowed or into 2 categories: (1) married or cohabiting and (2) without a partner (single, divorced, or widowed).

Follow-Up

Follow-up started at enrolment and ended at first-ever SAH, emigration, death, or by end of follow-up on December 31, 2014, whichever came first. The nationwide Hospital Discharge Register and Causes of Death Register recorded fatal (including out-of-hospital, in-ambulance, and emergency-room SAH deaths) and nonfatal SAHs with high accuracy.[10] The study cohort comprised 65 521 men and women who experienced 445 first-ever hospitalized SAHs and 98 sudden-death SAHs during the 1.52 million person-years of follow-up. Sudden deaths from SAH were defined as those occurring away from hospital, in an ambulance, or in an emergency room. One sudden-death SAH individual had inhalation of gastric content as an immediate cause of death and SAH as a main (underlying) cause of death, whereas all the others had SAH as both the immediate and main cause of death. Sudden-death SAHs were confirmed by extensive (including brain) forensic autopsy and, when necessary, a specialized nosologist checked and corrected the underlying cause of death reported. Of all sudden-death SAH diagnoses, 80% were based on autopsy, whereas the remainders were based on clinical examinations (computer tomography of head and spinal tap). Sudden-death SAHs occurring soon after arrival at an emergency department were not recorded in the hospital discharge register, and, therefore, the clinical examination includes these cases. Thus, hospitalized SAHs were defined as SAH patients admitted to hospital, whereas sudden-death SAHs had SAH as their cause of death but were not included in hospital discharge register. Regarding deaths and hospitalizations, the follow-up was complete when hospitalized patients continued to live in Finland; emigration during the follow-up was rare.[8] The STROBE statement (Strengthening the Reporting of Observational studies in Epidemiology)[11] guided the reporting.

Statistical Analyses

t test provided *P* values for normally distributed variables, Wilcox-rank test for skewed variables, and χ^2 test for categorical variables. Because we had <2% of missing data per variable (except for alcohol use and parents' stroke), we used complete case analyses. We used a covariate-adjusted competing risks model based on the Cox proportional hazard model[12] to calculate HRs and the 95% confidence interval (CI) and to compare the differences in risk factors between hospitalized and sudden-death SAHs. On the basis of earlier prospective and population-based studies,[3–5] our final adjusted models included age, smoking, SBP, cholesterol, and sex as SAH risk factors. We also included body mass index, study year, and study area as possible confounders and marital status and socioeconomic status as predictors of access to acute treatment. The preliminary models examined also the role of alcohol consumption and parents' stroke. Age, SBP, body mass index, smoking, and cholesterol served as continuous variables and smoking, socioeconomic status, marital status, study area, and study year as categorical variables in the final adjusted model. According to Schoenfeld residuals and log–log inspection, separate models of sudden-death SAHs and hospitalized SAHs met the proportional assumption criteria of the Cox model. The likelihood ratio test served to evaluate the evidence of multiplicative interactions. All statistical analyses used Stata Corp version 12.1 (College Station, TX) with R 3.3.0.

Ethics Statement

Ethical approval came from the corresponding ethics committee according to the commonly required research procedures and Finnish legislation for each survey, and the study was conducted according to the World Medical Association's Declaration of Helsinki on ethical principles for medical research. From 2002 onward, written informed consent has been provided by each participant.[7]

Results

Cohort

During the follow-up, we identified 98 sudden-death SAH and 445 hospitalized SAH patients (Table 1).

Unadjusted Analyses

Sudden-death SAH women were older when compared with hospitalized SAH women (*P*=0.01). Sudden-death SAH men lived more often alone when compared with hospitalized SAHs (*P*=0.03). In addition, pack-years, CPD, and average alcohol consumption seemed higher and education lower in male SAH patients (Table 1).

Adjusted Analyses

The model including both men and women showed no association between hospitalized SAH and body mass index or cholesterol. One SD increase (21.4 mm Hg) in SBP elevated risk of hospitalization and sudden death with HRs 1.25 (95% CI, 1.12–1.38) and 1.34 (95% CI, 1.09–1.65), respectively. The model also provided moderate evidence that each increase of one SBP SD elevated sudden-death SAH risk more than hospitalized SAH risk (*P*=0.05). In the model including all SAHs, SBP violated Cox proportionality assumption, but the change in HR during follow-up was minor, and the results remained essentially the same after time-varying covariate was introduced.

Smoking elevated both risks (hospitalization and sudden death) at all CPD levels. Risk of hospitalization (HR, 2.93; 95% CI, 1.92–4.47) and sudden death (HR, 5.04; 95% CI, 2.22–11.44) was highest among those smoking more than one pack per day. Smoking elevated the risk of sudden-death SAHs more than risk for hospitalized SAHs with moderate evidence when our model included CPDs as a continuous variable (*P*=0.05). The associations remained essentially the same when the model included socioeconomic status or marital status or both.

Single, divorced, and widowed participants had elevated sudden-death SAH risk in the fully adjusted model when compared with those married and cohabiting. When those single, divorced, and widowed were combined into a group called without a partner, that group had an elevated risk of sudden death from SAH (HR, 2.09; 95% CI, 1.33–3.28), and this risk was similar in both men and women. The risk was only elevated for sudden-death SAH but not for hospitalized SAH (*P*=0.006; Table 2). Regarding other variables mentioned above, no evidence of differences by SAH type emerged.

Cumulative Incidence of SAH

The Figure presents the difference in cumulative incidence by main risk factor groups from competing risks model for

Table 1. Baseline Characteristics and Unadjusted Analysis of Differences in Baseline Risk Factors Between Hospitalized and Sudden-Death SAH Individuals

	Total Cohort	Hospitalized SAHs	Sudden-Death SAHs	*P* for Difference
Men	31 716	205	46	
Age*	67.3 (12.4)	59.9(12.7)	59.3 (9.1)	0.76
Alcohol, g/wk†	82 (123)	94 (131)	133 (177)	0.36
BMI, kg/m^2	26.5 (3.8)	26.1 (3.4)	26.2 (3.5)	0.81
Cholesterol, mmol/L	6.0 (1.3)	6.3 (1.4)	6.7 (1.3)	0.10
SBP, mm Hg	143 (20)	146 (20)	149 (21)	0.40
Smoking				
Never smokers, %	10 879 (35.1)	49 (24)	10 (23)	0.56‡
Ex-smokers, %	8228 (26.5)	52 (26)	8 (19)	…
Smokers, %	11 910 (38.4)	100 (50)	25 (58)	…
CPD	17.3 (9.6)	18.5 (8.7)	21.3 (10.7)	0.44
Pack-years	19.0 (16.0)	21.0 (15.8)	29.0 (21.9)	0.33
Marital status				
Married or cohabit, %	24 317 (77)	161 (79)	29 (63)	0.03‡
No partner, %	7324 (23)	44 (21)	17 (37)	…
Stroke in either parent				
No	26 679 (89)	166 (83)	38 (84)	0.82‡
Yes	3248 (11)	34 (17)	7 (16)	…
Education				
Low	8269 (27)	72 (34)	14 (31)	0.06‡
Intermediate	10 915 (35)	66 (32)	22 (49)	…
High	11 826 (38)	72 (34)	9 (20)	…
Women	33805	240	52	
Age at SAH	69.1 (13.5)	61.9 (12.7)	66.9 (14.1)	0.01
Alcohol, g/wk†	27 (50)	38 (82)	40 (60)	0.92
BMI, kg/m^2	26.2 (4.9)	26.1 (4.8)	25.9 (4.8)	0.76
Cholesterol, mmol/L	5.9 (1.3)	6.3 (1.4)	6.3 (1.4)	0.97
SBP, mm Hg	139 (23)	146 (27)	151 (22)	0.35
Smoking				
Never smokers, %	24 084 (72)	148 (63)	28 (56)	0.83‡
Ex-smokers, %	3623 (11)	16 (7)	4 (8)	…
Smokers, %	5681 (17)	72 (31)	18 (36)	…
CPD	12.0 (7.1)	13.4 (6.7)	13.8 (7.0)	0.95
Pack-years	10.7 (10.8)	11.9 (10.5)	10.0 (5.4)	0.85
Marital status				
Married or cohabit, %	24 692 (73.2)	166 (70)	30 (58)	0.09‡
No partner, %	9040 (26.8)	72 (30)	22 (42)	…
Stroke in either parent				
No stroke in either parent	28 051 (88)	195 (85)	42 (88)	0.63‡
Stroke in either parent	3848 (12)	35 (15)	6 (12)	…
Education				
Low	10 034 (30)	78 (33)	14 (28)	0.44‡
Intermediate	11 181 (34)	90 (38)	16 (33)	…
High	11 849 (36)	70 (29)	19 (39)	…

(*Continued*)

Table 1. Continued

Mean and standard deviation or number and percentages are presented. *t* test provided *P* value for normally distributed variables, Wilcox-rank test for skewed variables, and χ^2 test for categorical variables. CPD and pack-years for current smokers only. BMI indicates body mass index; CPD, cigarettes per day; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

*Age at the end of follow-up for non-SAH patients and age at SAH for SAH patients.

†Data on alcohol consumption partly missing. Some percentages add up 101 because of rounding.

‡*P* for difference between all categories of the group (smoking status, parents' stroke, education, or marital status).

sudden-death SAHs and hospitalized SAHs. We observed no sudden-death SAHs among normotensive never smokers aged <50 years. Only 6% of all SAHs among normotensive never smokers aged <50 years experienced sudden-death SAHs.

Interactions

Female sex elevated risk for SAH (HR, 1.31; 95% CI, 1.07–1.61) and risk for hospitalized SAH (HR, 1.31; 95% CI, 1.05–1.63; Table 2). However, when interaction between smoking and sex was controlled for, female sex was not an independent risk factor in any of the models, as we have previously reported.[6]

Discussion

To our knowledge, this is the first study identifying risk factors for sudden-death SAHs. As expected, smoking and high SBP elevated risk of sudden-death SAHs, as they elevate SAH risk in hospital-based cohorts. However, we observed that smoking and high SBP potentially elevate the risk of sudden-death SAH more than of hospitalized SAHs. These findings are in line with those from studies on myocardial infarction reporting stronger associations between sudden-death myocardial infarctions and cardiovascular risk factors.[13,14] Interestingly, those who live without a partner were at elevated risk of sudden-death SAHs when compared with the risk affecting married or cohabiting participants. This association was similar in men and women and was absent in analysis regarding hospitalized SAHs. Sudden-death SAHs were rare among normotensive never smokers aged <50 years, and normotensive never smokers aged >50 years were at low risk of sudden-death SAH. Because incidence of SAH in Finland is similar to that in other countries, which also include sudden

Table 2. HRs and 95% CIs for All SAHs and by SAH Type

	All SAHs	Sudden Death HR (95% CI)	Cases (n)	Hospitalized HR (95% CI)	Cases (n)	*P* for Difference
BMI (per SD of 4.4 kg/m^2)	0.90 (0.81–0.99)	0.86 (0.68–1.09)	95	0.91 (0.81–1.01)	434	0.70
Cholesterol (per SD 1.3 mmol/L)	1.04 (0.95–1.15)	1.10 (0.88–1.37)	95	1.04 (0.94–1.16)	434	0.25
SBP (per SD 21.4 mm Hg)	1.27 (1.15–1.39)	1.34 (1.09–1.65)	95	1.25 (1.12–1.38)	435	0.05
Sex						
Male	1	1	46	1	205	
Female	1.31 (1.07–1.61)	1.45 (0.90–2.35)	52	1.31 (1.05–1.63)	240	0.68
Smoking						
Never	1	1	38	1	197	
Ex-smokers	1.37 (1.04–1.83)	1.35 (0.65–2.80)	12	1.37 (1.01–1.86)	68	0.91
1–20 CPD	2.50 (2.00–3.12)	3.41 (2.01–5.79)	34	2.34 (1.84–2.98)	142	0.18
>20 CPD	3.31 (2.28–4.81)	5.04 (2.22–11.44)	9	2.93 (1.92–4.47)	29	0.10
Per 5 cigarettes	1.21 (1.16–1.26)	1.28 (1.17–1.39)	81	1.19 (1.13–1.24)	367	0.05
Marital status						
Married or cohabiting	1	1	59	1	327	
Single	1.09 (0.84–1.42)	1.85 (1.07–3.19)	18	0.99 (0.74–1.33)	58	0.04
Divorced	1.56 (1.13–2.17)	2.83 (1.48–5.41)	12	1.33 (0.92–1.93)	32	0.05
Widowed	1.34 (0.91–1.97)	2.15 (1.02–4.56)	9	1.24 (0.81–1.90)	26	0.17
Living status						
Married or cohabiting	1	1	59	1	327	
No partner	1.25 (1.03–1.53)	2.09 (1.33–3.28)	39	1.01 (0.79–1.28)	116	0.006

HRs from model adjusted for age, sex, marital status, smoking, SBP, BMI, cholesterol, study year, and study area. Smoking was included in the model as continuous or as categorical variable, other HRs remained essentially the same in both models. Only current smokers were included in CPD groups. Model included 4 or 2 categories of marital status. No partner category was formed by combining single, divorced, and widowed groups. Data augmentation method provided *P* values for between-group differences. BMI indicates body mass index; CI, confidence interval; CPD, cigarettes per day; HR, hazard ratio; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

deaths in their incidence estimates,[2] these results are perhaps generalizable.

If sudden-death SAHs are excluded from epidemiological SAH studies, identification and evaluation of SAH risk factors may be limited. On the basis of data presented here, those with more adverse risk factor profiles are at higher risk of sudden-death SAH outside hospitals. Thus, in SAH risk factor studies, exclusion of sudden-death SAHs compromises the reliability of hospital-based studies, at least for less strong SAH risk factors. Ideally, all epidemiological SAH studies should include autopsy-confirmed sudden-death SAHs, but unfortunately, this is in many countries impossible. Although we did not study risk factors for rupture of an unruptured intracranial aneurysm (UIA), it is perhaps not a far-fetched conclusion that, for example, normotensive never smokers aged <50 years who have UIAs are at low risk not only for UIA rupture[3] but also for sudden death from SAH. Moreover, in line with our results, follow-up studies from a time when UIAs went untreated report that normotensive never smokers aged >50 years are at low risk for UIA rupture.[15,16] In addition, these studies report that smoking and possibly hypertension elevate UIA rupture rate,[15,16] further supporting our results.

Another novel finding was that those who live without a partner are at higher sudden-death SAH risk than are those who are married or cohabiting. To support this, studies on sudden cardiac death report that 80% of the incidents occur at home and that ≈60% of them are witnessed.[14] Because severe presentation with sudden loss of consciousness prevents those affected from calling for help, our results seem plausible. This finding is also in line with findings on ischemic heart disease of a more adverse outcome among those who live alone.[13,14,17] In clinical settings, it is perhaps conceivable that individuals who live alone with diagnosed UIAs and adverse risk factor profiles may benefit from different treatment or follow-up approaches than offered to married and cohabiting individuals with UIAs. Studies on the outcome advantages of such approaches are, however, evidently difficult or even impractical to design and conduct. A small fraction of those who did not have a partner may be living with a relative, so the actual risk associated with living alone may be higher than we estimated.

The strengths of our study include the following: a long follow-up of 40 years,[7] a substantial number of sudden-death SAHs, a prospective set-up reducing the risk for information bias and reverse causality, a population-based cohort, detailed risk factor data (including socioeconomic and marital status) that allows reliable subgroup analyses, accurate SAH diagnosis,[10,18] exceptionally high autopsy rate (80%) for sudden

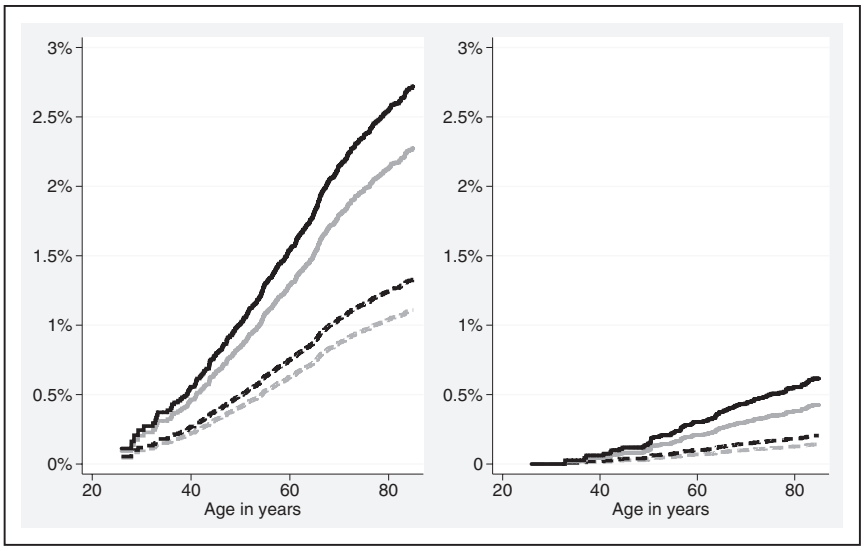

Figure. Cumulative incidence of hospitalized subarachnoid hemorrhage (SAHs; **left**) and cumulative mortality of sudden-death SAHs (**right**). Black line describes smokers with systolic blood pressure (SBP) ≥140 mm Hg. Gray line describes smokers with SBP <140 mm Hg, black dash line describes never smokers with SBP ≥140 mm Hg, and gray dash line describes never smokers with SBP <140 mm Hg.

deaths, and high overall (100%) diagnostic confirmation of sudden-death SAHs.

However, our study also has limitations. First, because of the study design, we do not know how the participants' risk factor profiles evolved during follow-up. Our risk factor estimates are, therefore, likely to be underestimated, because during long follow-up, adults are unlikely to initiate smoking, and about half of all smokers will quit.[19] In addition, marital status may change over time, and baseline hypertensive individuals may receive antihypertensive medication. However, we detected that only SBP violated proportionality assumption of Cox proportional hazards only when all SAHs were included, and this effect on results was minor. Second, we could not include alcohol consumption in our final adjusted model because of the small number of never smokers with high alcohol consumption, as we have previously reported.[3] Nevertheless, the associations remained essentially the same whether or not alcohol consumption was included in the adjusted model. Moreover, because SES is related to alcohol consumption, to access to special healthcare, and to other cardiovascular disease risk factors,[20,21] as well as to SAHs,[22] we also included in our analysis SES as years of education. This adjustment, however, did not change the associations or interactions significantly, so we excluded it from the final model. Third, we did not have specific information about participants' treatment delay, which could bias our results if treatment delays are associated with smoking or high SBP. Fourth, our data set may have included a small number of traumatic SAHs because of indexing errors, which could have weakened the observed associations. However, the data provided by nationwide Hospital Discharge Register and the nationwide Causes of Death Register are reliable with sensitivity of 93% and positive predictive value of 87% for aneurysmal SAHs.[10] Fifth, although SAH is mainly attributable to environmental risk factors,[23] we did not have information about familial SAHs. However, after including parents' stroke into our multivariate analysis, the results remained essentially the same.

Conclusions

More severe risk factor profile and living without a partner elevate sudden-death SAH risk more than they elevate hospitalized SAH risk. Exclusion of sudden-death SAHs from risk factor studies may lead to underestimation of associations between risk factors and SAH. Those who are aged <50 years, are normotensive, and are never-smokers are at low risk of sudden-death SAH.

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Disclosures

Dr Kaprio has consulted for Pfizer, Inc, on nicotine dependence. The other authors report no conflicts.

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