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Excess Mortality and Cardiovascular Events in Patients Surviving Subarachnoid Hemorrhage

A Nationwide Study in Sweden

Dennis J. Nieuwkamp, MD; Ale Algra, MD; Paul Blomqvist, MD, PhD; Johanna Adami, MD, MPH, PhD; Erik Buskens, MD; Hendrik Koffijberg, PhD; Gabriël J.E. Rinkel, MD

Background and Purpose—Survivors of aneurysmal subarachnoid hemorrhage (SAH) may have an increased risk of cardiovascular events because of shared risk factors. We compared incidences of vascular diseases, vascular death, and all-cause death after SAH with those in the general population.

Methods—From the Swedish Hospital Discharge and Cause of Death registries, we identified patients with SAH between January 1987 and January 2003. Conditional on survival of 3 months after SAH, we calculated standardized mortality and incidence ratios with corresponding 95% CIs for vascular death, all-cause death, and fatal or nonfatal vascular diseases. Cumulative risks were estimated with survival analysis.

Results—Of 17 705 patients with SAH (mean age, 59.7 years; 59.5% women), 11 374 survived at least 3 months after SAH. During follow-up (mean, 6.8 years), 2152 (18.9%) died. The risk of death was 12.9% within 5 years, 23.6% within 10 years, and 35.4% within 15 years after SAH. The overall standardized mortality ratio was 1.57 (95% CI, 1.44 to 1.70) for vascular death and 1.61 (95% CI, 1.52 to 1.70) for all-cause death. The standardized mortality ratios were particularly high in younger individuals, ranging from 2.1 to 3.7 for vascular death and from 2.1 to 2.6 for all-cause death for patients between 50 and 65 years of age. The standardized incidence ratio for fatal or nonfatal vascular diseases was 1.51 (95% CI, 1.45 to 1.56).

Conclusions—Mortality and risk of vascular diseases are increased in survivors of SAH. Prevention of new vascular diseases after SAH by management of risk factors seems important. (*Stroke*. 2011;42:902-907.)

Key Words: cardiovascular disease ■ cerebrovascular disease ■ epidemiology ■ mortality
■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (SAH) used to be considered a once-in-a-lifetime event, but patients who survive an SAH have an increased risk of developing new intracranial aneurysms and new episodes of SAH.^{1,2} Because hypertension and smoking are important risk factors for SAH,³ people who survive SAH may also carry an increased risk for other vascular diseases. Indeed, in a Finnish prospective cohort study⁴ and in the International Subarachnoid Aneurysm Trial,⁵ survivors of SAH had an increased mortality compared with that of the general population. In those 2 studies, cerebrovascular diseases other than recurrent SAH and cardiovascular diseases were important causes of death, which suggests that the increased mortality after SAH is caused by other vascular diseases. In another prospective cohort study, mortality was also increased after surviving SAH, but in that study, the risk of vascular events after SAH was lower than in a sex- and age-matched cohort of patients

with a transient ischemic attack or minor stroke.⁶ The included numbers of patients in those studies, however, were not very large, and they concerned only patients in whom the aneurysm was treated. Detailed and accurate information on age- and sex-specific risks, vascular disease subtypes, and nonfatal vascular diseases requires large numbers of patients with long-term follow-up. Because individual hospitals and even multicenter studies include too few patients with SAH for accurate estimates, large patient registers with reliable follow-up are needed. In Sweden, discharge and cause-of-death registers cover all inpatient care and causes of death for all Swedish citizens. These registers are a reliable and valid source of data.⁷⁻¹⁰

For this report, we determined the long-term risks of vascular death, all-cause death, and first vascular events in Swedish SAH survivors and compared these risks with those in the general Swedish population.

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From the Department of Neurology (D.J.N., A.A., G.J.E.R.), Rudolf Magnus Institute of Neuroscience, and Julius Center for Health Sciences and Primary Care (A.A., H.K.), University Medical Center Utrecht, Utrecht, The Netherlands; Department of Medicine at Karolinska University Hospital Solna, and Clinical Epidemiology Unit, Karolinska Institute (P.B., J.A.), Stockholm, Sweden; and Department of Epidemiology (E.B.), University Medical Center Groningen, Groningen, The Netherlands.

Correspondence to D.J. Nieuwkamp, MD, Department of Neurology, C03.236, University Medical Center Utrecht, PO Box 85500, 3584 CX Utrecht, The Netherlands. E-mail d.nieuwkamp@umcutrecht.nl

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Table 1. Number and Subtype of Vascular Disease From 3 Months After SAH Onward and Corresponding ICD Codes

Diagnosis	Patients		ICD-9 Codes	ICD-10 Codes
	No.	%		
Hypertensive heart or renal disease*	23	0.2%	402–404	I11–I13
Myocardial infarction	524	4.6%	410	I21
Ischemic heart disease*	877	7.7%	410–414	I20–I25
Pulmonary heart disease and diseases of the pulmonary circulation*	71	0.6%	415–417	I26–I28
Other forms of heart disease*	609	5.4%	420–429	I30–I52
Ischemic stroke	632	5.6%	434, 436	I63
Intracerebral hemorrhage	276	2.4%	431	I61
Cerebrovascular disease, limited*†	1385	12.2%	431–434, 436, 437	I61–I68
Cerebrovascular disease, all‡	2224	19.6%	430–434, 436–438	I60–I69
Aortic aneurysm	87	0.8%	441	I71
Diseases of arteries, arterioles, and capillaries*	297	2.6%	440–448	I70–I74, I77–I79
Retinal vascular occlusion*	4	0.0%	362.3	H34
Sudden death, cause unknown*	0	0.0%	798	R96
Renal failure*	64	0.6%	584–586	N17–N19

*Vascular death is defined as death from the composite of these vascular diseases.

†Cerebrovascular diseases other than SAH, transient ischemic attack, and sequelae of cerebrovascular disease.

‡Cerebrovascular diseases after including SAH and sequelae of cerebrovascular disease.

Methods

SAH Patients

The Swedish Hospital Discharge Register covers all inpatient care in Sweden from 1987 onward. The registry holds prospectively collected data on main diagnosis (the principal cause of hospital stay), secondary diagnoses indicating comorbidity, sex and age of the patients, and dates of admission and discharge. All Swedish citizens have a unique identification number. Until 1996, the Swedish version of the 9th revision of the World Health Organization's International Classification of Diseases (ICD-9) was used; ICD-10 was introduced in 1997.

We searched all records for the diagnosis of SAH on the basis of ICD codes 430 (ICD-9) and I60 (ICD-10). To limit selection bias, only patients discharged with SAH as a main diagnosis were selected. In total, 15 782 patients with SAH who were ≥ 18 years old at the time of the hemorrhage were identified from the period January 1987 to January 2003.

The Swedish Cause of Death Register holds records of the underlying and contributing causes of death for all Swedish citizens. Data from 5233 patients with SAH as the cause of death between January 1987 and January 2003 who were ≥ 18 years old at the time of death were retrieved. Of these, 3310 patients were also registered in the Hospital Discharge Register. After combining data from the 2 registers, we identified 17 705 patients with SAH as the main discharge diagnosis or with SAH as the cause of death.

Reference Population

We used the entire Swedish population as the reference population. Data were extracted from the Web site of the National Board of Health and Welfare (<http://www.socialstyrelsen.se>) and from the Web site of Statistics Sweden (<http://www.scb.se>). Data on hospital admissions were available for the years 1998 to 2002; data on cause of death were available for the years 1997 to 2002. The Swedish population increased from 8 897 619 in 1997 to 8 954 175 persons in 2002.

Outcome Events

The ICD codes that we used to retrieve outcome events are listed in Table 1. The main outcome events were vascular death and all-cause death. The vascular diseases included in the definition of vascular death

are given in Table 1. All-cause death was defined as death from any cause. Additional outcome events were the composite of fatal and nonfatal vascular diseases (defined as in vascular death).

Vascular events were included only when these concerned main discharge diagnoses, because this increases the proportion of patients accurately classified.^{8,11,12} Because the hospital discharge register does not discriminate between first and recurrent events, only data from the first mention of specific ICD codes were extracted. Additionally, only vascular events or deaths that occurred later than 3 months after SAH were considered an outcome event to avoid including complications from the initial SAH, such as delayed cerebral ischemia.

Data Analysis

For SAH patients, person-time at risk was calculated as the time between the SAH and censoring, vascular disease, or death. The demographic large-scale method for calculating person-time within dynamic populations was used to calculate person-time at risk in the reference population. It was calculated as the sum of the mean size of the reference population in the subsequent calendar years.

We calculated standardized mortality ratios (SMRs) with corresponding 95% CIs for vascular death and for all-cause death that occurred from 1997 until the end of 2002. For this purpose, we compared vascular-specific mortality and all-cause mortality for the cohort of patients with SAH with those in the general Swedish population from the age of 20 onward in sex-specific age categories of 5 years. Similarly, we calculated standardized incidence ratios for the composite of fatal and nonfatal vascular diseases.

Cumulative risks with corresponding 95% CIs were estimated with survival analysis. Patients who died of a nonvascular cause were censored at the time of death in the analysis of vascular events. By means of Cox regression analysis, we calculated age-adjusted hazard ratios with 95% CIs of sex for the risk of vascular death and all-cause death. In addition, we calculated age-stratified risk differences in vascular and all-cause mortality rates between patients with SAH and the reference population.

To enable a comparison of the proportions of SAH patients who died of a vascular cause with data reported in the literature, we calculated the proportion of patients who died of vascular events,

Table 2. Age- and Sex-Specific Number of Outcome Events From 3 Months After SAH Onward

SAH Age Category, years	Sex	Total No. of Patients	Patients					
			Vascular Death		All-Cause Death		Composite Fatal and Nonfatal Vascular Disease	
			No.	%	No.	%	No.	%
18–29	Women	228	1	0.4	4	1.8	17	7.5
	Men	239	0	0.0	7	2.9	19	7.9
30–39	Women	556	2	0.4	16	2.9	60	10.8
	Men	450	5	1.1	20	4.4	50	11.1
40–49	Women	1350	9	0.7	64	4.7	195	14.4
	Men	1021	32	3.1	99	9.7	192	18.8
50–59	Women	1668	41	2.5	155	9.3	300	18.0
	Men	1301	69	5.3	172	13.2	286	22.0
60–69	Women	1422	121	8.5	321	22.6	391	27.5
	Men	965	116	12.0	273	28.3	327	33.9
70–79	Women	1016	195	19.2	402	39.6	387	38.1
	Men	548	132	24.1	265	48.4	230	42.0
≥80	Women	417	134	32.1	233	55.9	181	43.4
	Men	193	57	29.5	121	62.7	78	40.4
Total	Women	6657	503	7.6	1195	18.0	1531	23.0
	Men	4717	411	8.7	957	20.3	1182	25.1

after including SAH and late effects of cerebrovascular disease as a cause of death in the analysis.

Results

Of the 17 705 SAH patients for whom we retrieved data (mean age, 59.7 years; 59.5% women), 5620 (31.7%) had died within 28 days and 6146 (34.7%), within 3 months. One hundred eighty-five patients had survived the SAH but had a follow-up period of <3 months in the registry. The cohort of 11 374 SAH patients who were alive after the initial 3 months yielded a total follow-up of 77 217 patient-years. The mean follow-up time was 6.8 years (SD=4.4).

Table 2 shows age- and sex-specific numbers of outcome events. Overall, 2152 patients (18.9%) had died during follow-up (mortality rate of 27.8 per 1000 patient-years). In 914 of the 2152 patients (42.5%) who had died during follow-up, the cause of death was vascular other than SAH or late effects of cerebrovascular disease. Table 3 shows age- and sex-specific SMRs for vascular death and all-cause death compared with those of the general population. The SMRs for both sexes were particularly high in younger individuals, with SMRs ranging from 2.1 to 3.7 for vascular death and from 2.1 to 2.6 for all-cause death for patients between 50 and 65 years of age. Figure 1 shows cumulative risks of vascular death and all-cause death. The risk of death was 12.9% within 5 years, 23.6% within 10 years, and 35.4% within 15 years after SAH. Figure 2 shows yearly SMRs for all-cause death during follow-up. The increased mortality risk decreased slightly during the first years after SAH but then seemed to stabilize during the remaining follow-up years. In age-adjusted multivariable Cox regression analyses, male sex was an independent predictor of vascular death (hazard

ratio=1.55; 95% CI, 1.36 to 1.76) and all-cause death (hazard ratio=1.42; 95% CI, 1.30 to 1.54).

After including SAH and late effects of cerebrovascular diseases as vascular causes of death in the analysis, 1229 of the 2152 patients (57.1%) who died during follow-up had a vascular cause of death. The overall SMR for both sexes for vascular death now was 1.94 (95% CI, 1.80 to 2.09). Table 4 shows vascular and all-cause mortality rates per 1000 patient-years and the excess of vascular and all-cause deaths for SAH patients in comparison with the general population.

Throughout the follow-up period, 2713 patients (23.9%) had a fatal or nonfatal first vascular event (Table 2). The subtypes of vascular diseases are shown in Table 1. The age-specific ratios were increased for men with SAH in the age groups up to 85 years and for women up to 80 years of age (Table 3). The most prevalent vascular diseases were ischemic stroke (632 patients) and acute myocardial infarction (524 patients). The SMR for ischemic stroke was 3.4 (95% CI, 1.7 to 6.7) and for acute myocardial infarction, it was 1.4 (95% CI, 1.1 to 1.8).

Discussion

Patients who survive the initial 3 months after SAH have increased risks for vascular death, all-cause death, and fatal and nonfatal vascular diseases. Absolute risk increases, conditional on survival at 3 months after SAH, were most pronounced in the older age groups, with the exception of the oldest old (≥85 years). Thus, our study based on follow-up data on >11 000 patients with SAH and 77 000 patient-years with inherently accurate point estimates for risks and ratios

Table 3. Age- and Sex-Specific Ratios for Vascular Death, All-Cause Death, and the Composite of Fatal and Nonfatal Vascular Disease Compared With Those of the General Swedish Population

Age Category, years	Vascular Death				All-Cause Death				Composite of Fatal and Nonfatal Vascular Disease			
	Women		Men		Women		Men		Women		Men	
	Ratio	95% CI	Ratio	95% CI	Ratio	95% CI	Ratio	95% CI	Ratio	95% CI	Ratio	95% CI
20–24	0	...	0	...	0	...	0	...	17.6	2.5–125	0	...
25–29	0	...	0	...	0	...	4.0	0.6–28.4	18.5	6.9–49.4	5.0	1.3–20.1
30–34	0	...	0	...	5.2	0.7–36.7	0	...	12.5	5.6–27.9	7.6	3.4–1.9
35–39	18.2	2.5–130	0	...	5.2	1.7–16.1	2.2	0.6–8.8	8.5	4.7–15.4	2.6	1.1–6.2
40–44	5.8	0.8–41.6	15.7	7.0–35.0	4.3	2.0–8.9	6.6	3.8–11.3	8.9	6.3–12.5	5.8	4.1–8.2
45–49	0	...	5.1	2.3–11.4	1.9	0.9–3.8	3.5	2.1–5.7	4.8	3.6–6.5	3.3	2.5–4.3
50–54	4.5	2.0–10.0	3.9	2.2–6.7	2.3	1.6–3.5	3.0	2.1–4.2	3.4	2.7–4.2	2.1	1.7–2.6
55–59	2.6	1.2–5.5	2.8	1.7–4.4	2.7	2.0–3.6	2.1	1.6–2.9	2.9	2.4–3.4	1.7	1.5–2.0
60–64	2.5	1.4–4.5	2.2	1.4–3.2	2.3	1.8–3.1	2.1	1.6–2.7	2.4	2.0–2.8	1.7	1.5–2.0
65–69	2.4	1.6–3.6	2.0	1.4–2.8	1.9	1.5–2.5	1.8	1.4–2.2	1.8	1.5–2.1	1.5	1.3–1.7
70–74	2.0	1.5–2.8	1.4	1.0–2.0	1.8	1.5–2.2	1.8	1.5–2.2	1.7	1.5–1.9	1.2	1.1–1.4
75–79	1.9	1.5–2.4	1.4	1.0–1.8	1.9	1.6–2.3	1.3	1.0–1.6	1.5	1.4–1.7	1.3	1.1–1.5
80–84	1.5	1.2–1.9	1.7	1.3–2.3	1.5	1.3–1.8	1.6	1.3–2.0	1.0	0.9–1.2	1.5	1.3–1.8
≥85	1.2	1.0–1.5	1.0	0.7–1.4	1.1	1.0–1.3	1.1	0.9–1.4	0.9	0.7–1.0	1.1	0.9–1.3
All ages	1.62	1.45–1.82	1.64	1.46–1.86	1.66	1.54–1.79	1.66	1.54–1.80	1.62	1.54–1.71	1.51	1.43–1.60
All ages*	1.57	1.44–1.70	1.61	1.52–1.70	1.51	1.45–1.56
All ages†	2.10	1.91–2.32	1.92	1.72–2.15

*All ages, women and men combined.

†Including SAH and late effects of cerebrovascular diseases as causes of death.

shows that the previously suggested increased mortality rates for SAH patients are real and demonstrate for the first time that this increased mortality rate is at least in part caused by an increased risk of vascular diseases. Ischemic stroke and acute myocardial infarction contributed importantly to these vascular diseases. We found that this increased risk of vascular diseases applied not only to older but also to younger

patients. The decrease of SMR with increasing age is probably explained by the increased background risk of vascular diseases in the general population with increasing age. Our analysis with yearly SMRs shows that the increased risk is stable over time and is not clustered in the first years after the SAH. We performed separate analyses with and without SAH and late effects of cerebrovascular diseases in the definition

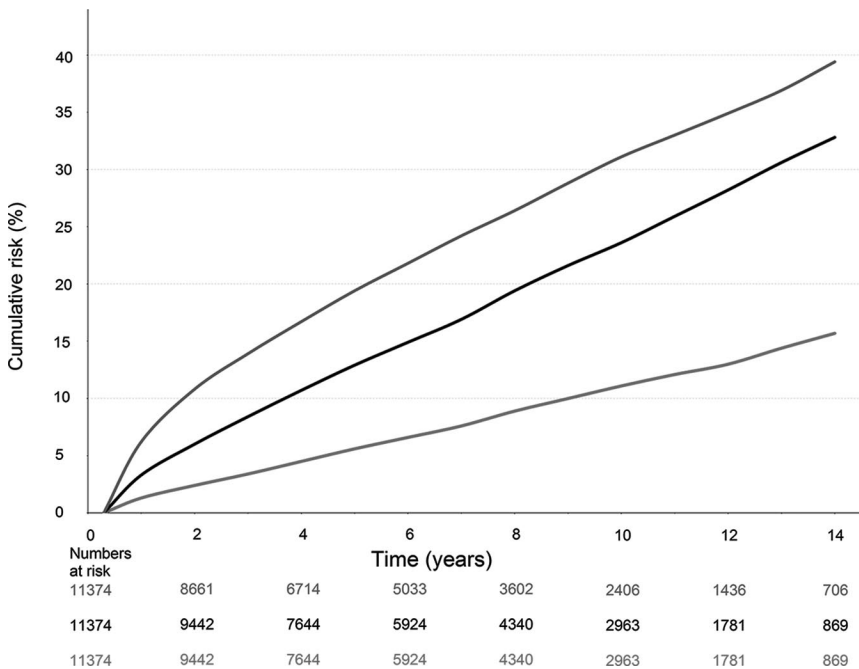


Figure 1. Time to vascular death (light grey line), all-cause death (black line), and composite fatal and nonfatal vascular disease (dark grey line) from 3 months after SAH onward.

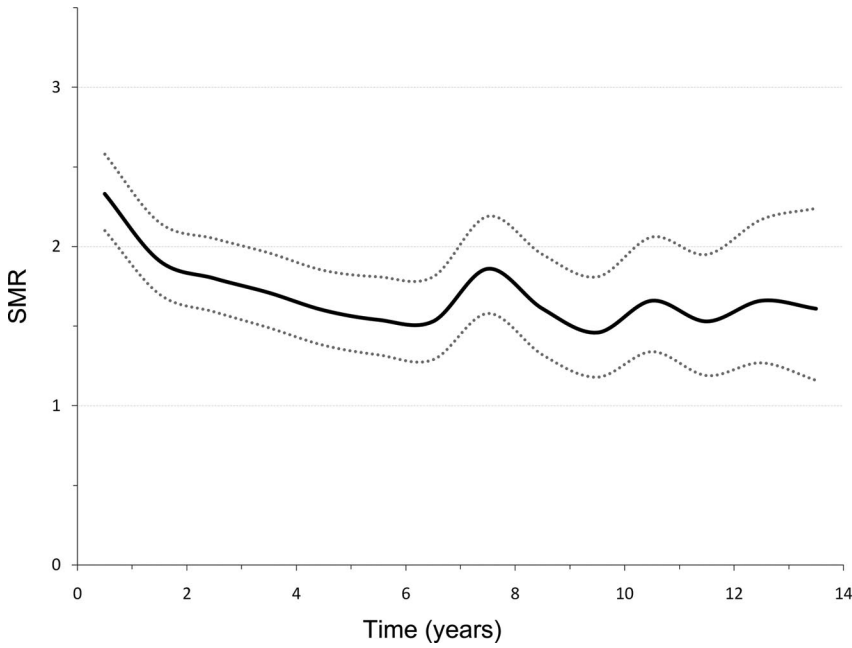


Figure 2. SMR per year, with corresponding 95% CIs for all-cause death from 3 months after SAH onward.

of vascular diseases because we aimed to assess the excess of cerebro- and cardiovascular diseases not related to SAH.

In general, there are some limitations regarding the accuracy of data from hospital discharge and death registers, but we believe that in our study, the results are unaffected by such limitations. Patient registers may contain errors in coding, but we have no reason to believe that these differ between the cohort of SAH survivors and the reference population. Consequently, the ratios that we calculated between the group of patients with SAH and the reference population will be valid. To increase the accuracy of coding, we chose to limit the identifying ICD code to the main diagnosis.^{8,11,12} This

would probably have led to an underestimation of the absolute risks that we found. Another reason for an underestimation of absolute risks of vascular diseases is that nonfatal outpatient vascular events have been missed; this probably concerns conditions such as angina pectoris or transient ischemic attacks in particular.¹³ We did not investigate nonfatal recurrent SAH or other recurrent vascular diseases because the use of the hospital discharge register precluded accurate discrimination between first and recurrent events. To avoid including complications from the initial SAH, we registered only vascular events or deaths that occurred >3 months after the SAH, although this time period is arbitrary.

Table 4. Vascular and All-Cause Mortality With Risk Differences per 1000 Patient-Years

Age Category, years	Vascular Death*		All-Cause Death		Absolute Excess	
	Patients	General Population	Patients	General Population	Excess Vascular Death (95% CI)	Excess All-Cause Death (95% CI)
20–24	0.0	0.0	0.0	0.5	0.0 (0.0 to 0.0)	–0.5 (–0.5 to –0.5)
25–29	0.0	0.0	1.5	0.5	0.0 (0.0 to 0.0)	1.0 (–1.9 to 3.9)
30–34	0.0	0.0	0.9	0.6	0.0 (–0.1 to 0.0)	0.4 (–1.5 to 2.2)
35–39	0.5	0.1	2.7	0.8	0.4 (–0.6 to 1.5)	1.9 (–0.5 to 4.2)
40–44	3.5	0.2	6.9	1.3	3.2 (1.1 to 5.4)	5.6 (2.6 to 8.6)
45–49	3.0	0.5	5.6	2.1	2.6 (0.9 to 4.2)	3.5 (1.2 to 5.7)
50–54	4.4	0.9	9.0	3.5	3.6 (1.9 to 5.2)	5.6 (3.2 to 7.9)
55–59	5.3	1.5	11.9	5.2	3.8 (2.1 to 5.5)	6.7 (4.2 to 9.3)
60–64	8.2	2.8	18.0	8.5	5.4 (3.1 to 7.7)	9.4 (6.1 to 12.8)
65–69	14.0	5.5	26.1	14.6	8.5 (5.3 to 11.7)	11.4 (7.0 to 15.8)
70–74	21.5	10.4	42.8	24.7	11.1 (6.9 to 15.4)	18.1 (12.1 to 24.1)
75–79	39.7	19.9	65.8	42.3	19.8 (13.3 to 26.4)	23.6 (15.2 to 31.9)
80–84	63.5	37.4	108.4	72.2	26.1 (14.8 to 37.3)	36.2 (21.5 to 50.8)
≥85	115.4	93.9	189.5	171.8	21.5 (2.2 to 40.8)	17.6 (–7.1 to 42.4)
Unstandardized	15.2	6.5	27.8	13.8	8.7 (7.6 to 9.9)	14.0 (12.5 to 15.5)
Standardized	15.2	7.8	27.8	17.3	7.4 (6.0 to 8.8)	10.5 (8.6 to 12.4)

*Including SAH and late effects of cerebrovascular disease as causes of death.

Several studies have shown that the Swedish registries are a reliable and valid source of data.^{7–10} In a study in which several patient identification strategies were investigated in 2 prospective cohorts of patients, the strategy of combining the National Hospital Discharge Register and the National Cause of Death Register gathered 98% of probable cases of myocardial infarction and stroke.¹⁰ Another study in which the validity of the diagnosis of heart failure was assessed demonstrated a sensitivity of 95%.⁸ Other studies with the Swedish registries reported high sensitivities and positive predictive values for acute myocardial infarction and stroke.^{7,9} Further data underlining the accuracy of the data of our study are that the incidence of SAH found in the Swedish patient registers is in line with the incidence found in Swedish population-based studies.^{14,15} Also, the 1-month case-fatality rate derived from the registries is identical to the case-fatality rate from Swedish population-based studies (32%).¹⁶

Long-term follow-up data on patients surviving SAH are sparse. Our study is by far the largest on this topic. A Finnish prospective cohort study with 1537 SAH patients in whom the ruptured aneurysm was treated yielded excess long-term mortality after a median follow-up time of 7.5 years.⁴ Systemic cardiovascular disease appeared to be the most important cause of death, responsible for 60% of cases. This is comparable to the 57% that we found. We could not compare our data with those on nonfatal vascular events or subtypes of vascular disease because that information was lacking in the Finnish study. The estimated survival rate of 15 years after SAH was 65.6% in the Finnish study, which is also similar to the 64.6% that we found in our study. Recently published long-term follow-up data from the International Subarachnoid Aneurysm Trial concerning 2004 patients with a mean follow-up time of 9 years also showed increased death rates compared with those in the general population in the United Kingdom.⁵ In the International Subarachnoid Aneurysm Trial, 12.3% of the patients had died after 5 years of follow-up, which is in line with the 12.9% found in our study. Again, data on nonfatal vascular events were missing in that study, as well as age- and cause-specific SMRs. A third study demonstrated excess long-term mortality (mean follow-up of 8.1 years) in 752 patients with SAH.⁶ The risk of vascular events after SAH was lower than that after minor stroke but seemed to be higher in an indirect comparison with the general population. In this study, only patients who were clipped and who recovered to a functional independent state were included.

A possible explanation for the high risk of developing new vascular diseases after SAH is that smoking and hypertension are common risk factors for both SAH and ischemic cardiovascular disease and other stroke subtypes.^{3,17} The increased risk of vascular diseases and the inherent increased mortality ratio of patients who have survived an episode of SAH indicates that it is important to insist on cessation of smoking and stringent management of hypertension and other risk factors. Whether these patients would benefit from antiplatelet agents, antihypertensive drugs, and statins should be assessed in a future clinical trial.

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Disclosures

None.

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