Risk Factors for Subarachnoid Hemorrhage
An Updated Systematic Review of Epidemiological Studies

Valery L. Feigin, MD, MSc, PhD; Gabriel J.E. Rinkel, FAHA; Carlene M.M. Lawes, MBChB, FAFPHM, PhD; Ale Algra, FAHA; Derrick A. Bennett, MSc, PhD, CStat; Jan van Gijn, MD, FRCP; Craig S. Anderson, PhD, FRACP

Background and Purpose—After a 1996 review from our group on risk factors for subarachnoid hemorrhage (SAH), much new information has become available. This article provides an updated overview of risk factors for SAH.

Methods—An overview of all longitudinal and case-control studies of risk factors for SAH published in English from 1966 through March 2005. We calculated pooled relative risks (RRs) for longitudinal studies and odds ratios (ORs) for case-control studies, both with corresponding 95% CIs.

Results—We included 14 longitudinal (5 new) and 23 (12 new) case-control studies. Overall, the studies included 3936 patients with SAH (892 cases in 14 longitudinal studies and 3044 cases in 23 case-control studies) for analysis. Statistically significant risk factors in longitudinal and case-control studies were current smoking (RR, 2.2 [1.3 to 3.6]; OR, 3.1 [2.7 to 3.5]), hypertension (RR, 2.5 [2.0 to 3.1]; OR, 2.6 [2.0 to 3.1]), and excessive alcohol intake (RR, 2.1 [1.5 to 2.8]; OR, 1.5 [1.3 to 1.8]). Nonwhite ethnicity was a less robust risk factor (RR, 1.8 [0.8 to 4.2]; OR, 3.4 [1.0 to 11.9]). Oral contraceptives did not affect the risk (RR, 5.4 [0.7 to 43.5]; OR, 0.8 [0.5 to 1.3]). Risk reductions were found for hormone replacement therapy (RR, 0.6 [0.2 to 1.5]; OR, 0.6 [0.4 to 0.8]), hypercholesterolemia (RR, 0.8 [0.6 to 1.2]; OR, 0.6 [0.4 to 0.9]), and diabetes (RR, 0.3 [0 to 2.2]; OR, 0.7 [0.5 to 0.8]). Data were inconsistent for lean body mass index (RR, 0.3 [0.2 to 0.4]; OR, 1.4 [1.0 to 2.0]) and rigorous exercise (RR, 0.5 [0.3 to 1.0]; OR, 1.2 [1.0 to 1.6]). In the studies included in the review, no other risk factors were available for the meta-analysis.

Conclusions—Smoking, hypertension, and excessive alcohol remain the most important risk factors for SAH. The seemingly protective effects of white ethnicity compared to nonwhite ethnicity, hormone replacement therapy, hypercholesterolemia, and diabetes in the etiology of SAH are uncertain. (Stroke. 2005;36:2773-2780.)

Key Words: meta-analysis ■ risk factors ■ subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) comprises 1% to 7% of all strokes.1 Despite its relative rarity, the loss of productive life years in the general population from SAH is comparable to that of cerebral infarction, the most common stroke subtype.2 The main reasons for the huge impact of SAH are the relatively young age of onset and poor outcome.1,3,4 Although familial preponderance suggests a genetic influence, most instances of SAH can be attributed to lifestyle exposures.5 Hence, identification of modifiable risk factors for SAH is pivotal to reducing its incidence, which appears to have remained relatively stable in many countries6 over recent decades.3,7,8

Many etiological studies of SAH were based on small numbers and variable diagnostic criteria, and evaluations of only a single risk factor, often in a particular subgroup of patients, such as those admitted to hospitals. In this context, a systematic review of all published data can provide more reliable information on the relative importance of particular exposures. Ten years ago, we performed such a review,9 but the subsequent additional published epidemiological studies of SAH, including some previously unaddressed risk factors, have necessitated us to update these analyses.

Methods

Methods of literature search, inclusion criteria for studies, and diagnostic criteria for SAH were the same as that in the previous overview.9 In brief, the following key words or subject headings were used for the MEDLINE search from 1966 through March 2005: subarachnoid h(a)emorrhage, h(a)emorrhagic stroke(s), case-control, longitudinal, cohort, prospective, and risk factors. Bibliographies of retrieved articles were examined for further relevant publications.
This method of cross-checking was continued until no further publications were found. Only studies published in English that reported crude data on risk factors for SAH were included in the meta-analysis. Crude data referred to the actual numbers of exposed and nonexposed subjects reported in the publication that allowed recalculation of the risk associated with the exposure. Studies confined to a particular subgroup of patients (eg, young subjects [except for studies of oral contraceptives] and familial ruptured aneurysms) were not included in the meta-analysis. Hospital-based and population-based case-control studies were analyzed separately and combined. For the longitudinal studies, the diagnosis had to be based on a review of the medical records and not only on International Classification of Diseases codes. For the case-control studies, SAH had to be confirmed in >70% of the cases by characteristic computed tomography, angiography, or autopsy findings. To assess eligibility of the studies and extract data for the meta-analysis, 3 authors (V.L.F., C.M.M.L., and G.J.E.R.) independently assessed the studies and cross-checked the data extracted. In case of disagreement, this was resolved by discussion between the reviewers. In case of multiple publications from 1 center, relevant data from most recent publication were extracted and included in the analysis. We also recorded whether the investigators had adjusted for major confounders in the original publication.

To allow comparison of data from different studies, risk factors were standardized across studies whenever possible. Alcohol consumption was categorized in 3 groups: (1) no alcohol consumption; (2) consumption of <150 g per week; and (3) consumption of ≥150 g per week. We assumed that 1 standard drink contains 12 g of ethanol. No alcohol consumption was taken as reference in the comparison with the other 2 categories. For smoking, case and control subjects were divided into never smokers, former smokers, current smokers, former/never smokers, and ever smokers (current and former smokers combined) depending on availability of the data. In addition to the list of risk factors analyzed in the previous overview, for this study, we also included data on body mass index (BMI), diabetes mellitus, and ethnicity. Lean BMI was defined as

| Study (in ascending chronological order), Country, and Year of Publication | No. of SAH Cases | Person-Years of Follow-Up | Baseline Age or Mean Age, y | Follow-Up Period | Diagnostic Criteria | M/F | Alcohol | Smoking | HT | OC | HRT | High TC | Physical Activity | Diabetes | BMI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abbott (Japan 1994) | 37 | 165,660 | 45–68 | 1965–1990 | † | M | – | – | – | – | – | + | – | – | – |
| Donahue (USA 1986) | 32 | 96,072 | 45–69 | 1965–1977 | † | M | + | – | – | – | – | – | – | – | – |
| Yano (USA 1989) | 39 | 144,148 | 45–68 | 1965–1985 | § | M | – | – | + | – | – | + | – | – | – |
| Knekt (Finland 1991) | 187 | 503,485 | 20–69 | 1966–1988 | ICD | M/F | – | + | – | – | – | – | – | + | – |
| Vessey (UK 1989) | 8 | 271,268 | 25–39 | 1968–1987 | #88% | F | – | – | + | – | – | – | – | – | – |
| Iso (USA 1989) | 55 | 2,169,972 | 35–57 | 1973–1981 | ‡ | M | – | – | + | – | – | + | – | – | – |
| Sankai (Japan 2000) | 71 | 116,297 | 40–69 | 1975–1993 | #83% | M/F | + | – | – | – | – | – | – | – | – |
| Stampfer (USA 1991) | 36 | 337,854 | 30–63 | 1976–1984 | ‡ | F | – | – | – | + | – | – | – | – | – |
| Stampfer (USA 1988) | 28 | 334,382 | 34–59 | 1976–1984 | ‡ | F | – | – | – | – | – | – | – | – | – |
| Kawachi (USA 1993) | 108 | 1,404,072 | 30–55 | 1976–1988 | ‡ | F | – | – | – | – | – | – | – | – | – |
| Klatsky (USA 2002) | 133 | 2,320,812 | mean 47.5 | 1978–1996 | † | M-F | + | – | – | – | – | – | – | – | – |
| Kurth (USA 2003) | 31 | 385,419 | 45+ | 1982–2002 | ‡ | M | – | – | – | – | – | – | – | – | – |
| Suh (Korea 2001) | 98 | 619,463 | 35–59 | 1993–1998 | #89% | M | + | – | – | – | – | – | – | – | + |
| Kurth (USA 2003) | 29 | 354,899 | 45+ | 1993–2003 | ‡ | F | – | – | – | – | – | – | – | – | – |

*Studies listed in the ascending order of year of data collection and are additional to those in the previous overview.
†Diagnosis based on medical records, mostly on clinical grounds; †criteria of National Survey of Stroke (probable or definite); #percentage of SAH cases diagnosed by computed tomography, angiography, or autopsy; §63% SAH diagnosed by computed tomography, angiography, or autopsy.
M/F indicates separate data for men and women; M-F, data for men and women together; HT, hypertension; OC, oral contraceptive use; TC, total cholesterol.
TABLE 2. Characteristics of Case-Control Studies Included in the Analysis*

<table>
<thead>
<tr>
<th>Study, Country and Year**</th>
<th>Population-Based Design</th>
<th>No. of SAH Cases</th>
<th>Selection Period</th>
<th>% CT</th>
<th>% Ang</th>
<th>% Aut</th>
<th>M/F</th>
<th>Alcohol</th>
<th>Smoking</th>
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<td>Pettiti (USA 1978)</td>
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<td>Inman (UK 1979)</td>
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<td>134</td>
<td>1976</td>
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<td>Gill (UK 1991)</td>
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<td>Juve (Finland 1993)</td>
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<td>WHO (Africa/Asia/Europe/Latin America 1996)</td>
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<td>Ohkuma (Japan 2003)*</td>
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<td>Ni Mhurchu (ANZ 2001)*</td>
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*Studies listed in the ascending order of year of data collection and are additional to those in the previous overview.
†100% CT or angiography; ‡100% angiography or autopsy; §99% CT, but unknown how many had SAH on CT.
** Study by the first author (in descending chronological order of data collection), country, and year of publication.
% CT, % Ang, and % Aut indicate percentage of SAH cases documented by computed tomography, angiography, or autopsy, respectively; M/F, separate data for men and women; M-F, data for men and women together; HT, hypertension; OC, oral contraceptive use; HRT, hormone replacement therapy; TC, total cholesterol.
BMI <22 (BMI of ≥22 was used as the reference category). Ethnicity was dichotomized into white and nonwhite, and for hypertension (present versus absent), physical activity level (regular rigorous exercise versus no regular rigorous exercise), serum cholesterol level (hypercholesterolemia versus normal), and diabetes (present versus absent). For hormone replacement therapy and oral contraceptives, current users were compared with never and former users combined (if only ever users were reported in the original publication, they were compared with never users). For all risk factor categories, we accepted criteria from original publications. No individual data from the parent articles were available for analyses of data according to predefined criteria.

For longitudinal studies, pooled relative risk (RR) estimates were calculated by means of the inverse-variance weighting method. For case-control studies, odds ratio (OR) estimates were combined with the Mantel–Haenszel method into pooled estimates. For studies reporting risk factors separately for men and women, overall and gender-specific estimates were calculated, and additional stratified analyses by sex were performed whenever possible. If no evidence for statistical heterogeneity was observed for the Cochrane Q statistic (P<0.10), fixed-effect models were used; otherwise, we used random-effect models.

**Results**

Based on the selection criteria, 5 longitudinal and 12 case-control studies published after the previous overview met our inclusion criteria (Figure 1). These were included in the meta-analysis in addition to the 9 longitudinal and 11 case-control studies included in the previous review (Tables 1 and 2). Most longitudinal studies were initiated in the 1970s and were restricted to the US, Japanese, UK, Korean, and Finnish populations. Of the 23 case-control studies, 10 (63% of SAH cases) were population based and 13 hospital based, covering a variety of populations: American (United States), Latin American (Chile, Colombia, Mexico, Brazil, and Jamaica), European (Norway, Germany, Hungary, Portugal, Denmark, Yugoslavia, Slovenia, Finland, and the United Kingdom), African (Kenya, Zambia, and Zimbabwe), and Australasian (China, Indonesia, Thailand, Australia, New Zealand, and Japan). Overall, 3936 cases of SAH (892 cases in longitudinal studies [9 223 763 person-years of follow-up] and 3044 cases in case-control studies) were available for the analysis, thus allowing 1984 more cases of SAH to be analyzed than in the previous overview.

An overview of the RRs of the studied factors according to study design and gender is presented in Figure 2 and Table 3. In the table, current and ever smoking are compared separately with never smoking. The risk of former smoking (not listed in the table) was twice the risk of never smoking in longitudinal studies (RR, 1.9; 95% CI, 1.5 to 2.3) and in case-control studies (OR, 2.3; 95% CI, 2.2 to 2.4). Ever smoking was associated with a 2.2- to 3.1-fold increase when
compared with never smoking, and current smoking had a 2.2- to 3.1-fold increased risk when compared with never and former smoking combined, with the most pronounced associations in case-control studies. In longitudinal studies, the risks of smoking for women were twice those for men, whereas in case-control studies, the risks were greater in men.

Hypertension increased the risk of SAH by $\approx 2.5 \times$ in longitudinal and case-control studies and was 30% more hazardous in women. Excessive (>150 g per week) alcohol consumption was associated with a 2-fold increased risk of SAH in longitudinal and case-control studies, with a more hazardous effect in women.

Use of oral contraceptives did not significantly affect the risk of SAH in 1 small longitudinal study or in 7 case-control studies. Hormone replacement therapy was associated with nonsignificantly reduced risk of SAH in 1 longitudinal study and with 40% significantly reduced risk of SAH in 2 population-based case-control studies.

Hypercholesterolemia was associated with reduced risk of SAH but to a statistically significant level only in case-control studies (40% risk reduction), with no clear gender differences in the strength of the associations. One longitudinal study demonstrated a marginally nonsignificant protective effect of regular vigorous physical activity in men, whereas 2 case-control studies showed a slightly hazardous albeit nonsignificant effect of regular vigorous physical activity on the risk of SAH.

Lean BMI was associated with a 70% decreased risk of SAH in men in 1 longitudinal study, but it was associated with an increased risk, although not statistically significant, in 2 case-control studies. Nonwhite ethnicity was associated with 3.4-fold increased risk of SAH in 2 case-control studies and with $\approx 2$-fold but not statistically significant risk of SAH in 1 longitudinal study. Diabetes was associated with reduced risk of SAH but to a statistically significant level in case-control studies only (30% risk reduction).
Discussion

This review was based on almost twice as many studies as in the previous review,9 and we have confirmed and extended the previous analyses. Smoking, hypertension, and excessive alcohol intake have statistically significant and consistent associations with an increased risk of SAH in case-control and longitudinal studies; because of the increase in the number of studies in this analysis, the estimates of association obtained are more precise. In addition to the previous overview, we found that the risk of SAH in former smokers is almost twice that of never smokers. Our previous research also showed that cardiovascular risk factors have the highest population-attributable risk associated with SAH.5 New information included in the current review has suggested that nonwhite ethnicity is associated with higher risk of SAH. In contrast, hormone replacement therapy and probably hypercholesterolemia appear to be risk-reducing factors. Use of oral contraceptives did not affect the risk of SAH, whereas data were inconsistent for lean BMI and regular rigorous physical activity.

Our findings concerning the nonsignificant effect of oral contraceptives on the risk of SAH do not confirm the increased risk found in another meta-analysis devoted to only oral contraceptives and SAH.35 The reason for the discrepancy might be the less stringent study selection criteria (especially for diagnosis of SAH) in the other review. The relatively high risk of SAH associated with nonwhite ethnicity found in this study was based only on 2 case-control studies and is probably linked with substantial differences in cardiovascular risk factor profiles (especially smoking and hypertension) between white and nonwhite populations.36,37 However, the extent and relative contribution of cardiovascular risk factors remain unclear because in our meta-analysis, we were not able to adjust the effect estimates for these confounders.

An unexpected and new finding in this review was that diabetes mellitus was associated with substantial reduction of the risk of SAH. This reduction was statistically significant in case-control studies but not in 1 longitudinal study available for the analysis. It is possible that patients with diabetes have a high risk of dying from other causes, and therefore the chances of developing SAH are smaller than in controls. A recent case-control study of SAH in Japan (not included in the present analysis because additional criteria [history of head trauma] were used for selection of controls) also demonstrated that diabetes mellitus was inversely associated with the risk of SAH.38 It has been suggested that lower or equivalent prevalence of diabetes mellitus in SAH patients than in the general population may be attributed to better medical treatment or altering lifestyle factors (eg, better dietary control) in the diabetic patients.39 However, the biological basis for inverse associations between diabetes mellitus and the risk of SAH is not well understood. Nevertheless, the size and consistency of the associations warrant further study.

Although the reduced risk of hypercholesterolemia for SAH was not statistically significant in longitudinal studies, it was in case-control studies. This reduced risk for SAH in patients with hypercholesterolemia is in line with findings for intracerebral hemorrhage.40 The predictive values of lean BMI were nonstatistically significant and were discordant between case-control and longitudinal studies. Despite known gender differences in the risk of SAH, only few epidemiological studies explored gender differences in risk factors for SAH. Our finding that most risk factors tend to be more hazardous in women than in men, although this difference is statistically nonsignificant, suggests that this may contribute to the higher incidence of SAH observed in women.
Although inferences from an overview without individual patient data are subject to limitations, our findings first reinforce the importance of smoking cessation, blood pressure control, and avoidance of excess in alcohol intake for SAH prevention, and second, they provide directions for further research into the pathogenesis of aneurysm formation and rupture.

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References


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