Risk Factors for Intracerebral Hemorrhage in the General Population
A Systematic Review

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Background and Purpose—Although data on some risk factors for intracerebral hemorrhage (ICH) already are beyond doubt, for other factors, the evidence is less clear. We performed a systematic overview of case-control and cohort studies on risk factors for ICH.

Methods—We searched MEDLINE, LILACS, EXTRAMED, and Pascal from 1966 to 2001 to identify studies. Studies were included if they met predefined methodological criteria. When possible, 2×2 tables were extracted and combined with the Mantel-Haenszel method. Summary odds ratios (ORs) were calculated for case-control studies, and summary relative risks (RRs) were found for cohort studies and for case-control and cohort studies combined.

Results—Fourteen case-control and 11 cohort studies were identified. We could not always combine the results of case-control and cohort studies. In cohort studies, the crude RR for age (every 10-year increase) was 1.97 (95% confidence interval [CI], 1.79 to 2.16). In case-control studies, the crude OR for high alcohol intake was 3.36 (95% CI, 2.21 to 5.12) and for hypertension was 3.68 (95% CI, 2.52 to 5.38). Two cohort studies showed an increasing risk of ICH with increasing degree of hypertension. In cohort and case-control studies combined, the crude RR for sex (male versus female) was 3.73 (95% CI, 3.28 to 4.25); for current smoking, 1.31 (95% CI, 1.09 to 1.58); and for diabetes, 1.30 (95% CI, 1.02 to 1.67).

Conclusions—Risk factors for ICH appeared to be age, male sex, hypertension, and high alcohol intake. High cholesterol tends to be associated with a lower risk of ICH. We could not assess whether these risk factors are independent. (Stroke. 2003;34:2060-2066.)

Key Words: intracerebral hemorrhage • meta-analysis • risk factors

Spontaneous intracerebral hemorrhage (ICH) is a serious disease despite progressing medical knowledge. ICH appears suddenly without warning, unlike ischemic strokes that are often preceded by a transient ischemic attack. Outcome is determined by the initial severity of the bleeding; mortality and morbidity of ICH are high. So far, treatment regimens are limited. Therefore, prevention of ICH is the most effective approach. Until now, limited attempts have been made to search systematically for risk factor profiles in these patients. Studies conducted to evaluate risk factors for stroke focused mainly on ischemic stroke or a combination of ICH and subarachnoid hemorrhage rather than on spontaneous ICH as a separate entity. The studies that focus on spontaneous ICH often address 1 risk factor in particular and do not give an overview of all important risk factors. Hence, we conducted a meta-analysis to evaluate risk factors for ICH in the general population.

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Methods

Literature Search

We searched MEDLINE from 1966 to 2001 and EMBASE from 1974 to 2001 for case-control and cohort studies on risk factors for ICH. We also searched LILACS, EXTRAMED, and Pascal to identify studies with non-English publications. The terms we used were "hemorrhage, cerebral"; "case control studies" or "cohort studies"; and "adult," combined with "risk factors" and with potential risk factors "cholesterol," "alcohol," "hypertension," "oral contraceptives," "body height," "body weight," and "race." OLDMEDLINE was not searched because it contains only studies published before 1966; at that time, brain imaging was not yet available for the diagnosis of ICH. Reference lists of all relevant publications were checked for additional relevant articles. Publications had to be in English, French, German, or Spanish.

Inclusion Criteria

Studies were included if they were conducted in the general population. ICH needed to be recognized and analyzed as a separate
stroke entity and not to be combined with subarachnoid hemorrhage. For case-control studies, the diagnosis of ICH needed to be confirmed in at least 70% of the cases by the presence of intracerebral blood on a CT or MR scan or by autopsy. Case and control subjects had to be comparable. For longitudinal studies, the diagnosis had to be based on a review of medical records and not only on International Classification of Diseases codes. The studies had to present crude data to allow calculations in our analyses. Studies in postoperative patients were excluded, as were studies on patients with ICH as result of a trauma.

Data Extraction
Studies were assessed independently by 2 researchers (M.J.A. and S.P.C.). We systematically extracted data by means of a predefined data extraction form. Any discrepancies in the data extracted by the 2 researchers were resolved through discussion.

Data Analysis
Studies were included only once if there were multiple publications, and there had to be at least 2 studies available on the same potential risk factor. We used Poisson regression (allowing multivariate adjustments) to combine the data of the cohort studies. If this was not possible because of a lack of crude data, we combined the maximal adjusted estimates (adjusted relative risk [RRadjusted]) with the general variance-based method.3 For case-control studies, we reconstructed 2×2 tables and combined them with the Mantel-Haenszel method. The boxes in the figures describe both the study size (the larger the box, the larger the study) and the value of the point estimate of the crude odds ratio (ORcrude). Overall estimates of the case-control and cohort studies were combined with the general variance-based method.

If there was statistically significant heterogeneity (P<0.10) among the results of the included studies, we used random-effects models as opposed to fixed-effect models because they include both within-study sampling error (variance) and between-study variation in the assessment of the uncertainty (confidence interval [CI]) of the results of a meta-analysis.3

We found data on age, sex, alcohol, cholesterol, smoking, diabetes, physical activity, and hypertension. To allow comparison of data from different studies, we recategorized some factors. Alcohol was recalculated in grams per day. Because not all studies distinguished between never and former smokers, we performed separate analyses for current smokers versus previous and nonsmokers and for ever smokers versus never smokers. Physical activity was recategorized as active versus inactive. For hypertension, hypercholesterolemic and diabetic subjects were dichotomized according to the criteria used in the separate studies. There was no information available on duration of hypercholesterolemia, diabetes, and hypertension; diabetes could not be divided into type I or II.

Results
Of the 497 abstracts identified in the different searches with both the general term “risk factors” and the separate risk factors themselves, 118 were considered possibly relevant after a quick screen of title and abstracts. Of these 118, 62 were considered potentially relevant after careful reading of the abstract. These 62 articles were reviewed in detail, and data were extracted. Finally, we included in the analysis 33 articles that met the inclusion criteria. These 33 articles contained data on 14 different case-control studies and 11 different cohort studies; some studies had multiple publications. Details on the studies are given in the Table.

In the following sections, we report on the results of case-control studies (Mantel-Haenszel method) and cohort studies (age and sex, univariate Poisson regression; other factors, general variance-based method). Because of the use of different cutoff points or the lack of crude data, it was not always possible to combine the data.

Age and Sex
The investigators of 5 cohort studies reported on age and risk of ICH; the crude RR (RRcrude) was 1.06. After recalculation into 10-year increase, we found an RRcrude of 1.97 (95% CI, 1.79 to 2.16).4–9 Almost all case-control studies matched their cases and controls on age; the 2 studies that did not match did not show crude data, so it was not possible to evaluate this association in the case-control studies.

The RRcrude for men compared with women was 4.64 (95% CI, 4.02 to 5.40).4–7,9,10 From the 2 case-control studies without matching for sex, we recalculated an overall ORcrude of 1.35 (95% CI, 0.99 to 1.86).11–13 Combining the cohort and case-control studies resulted in an overall RRcrude of 3.73 (95% CI, 3.28 to 4.25).

Alcohol
The investigators of 8 case-control studies reported on alcohol intake and risk of ICH.12,14–20 Because the definitions of high alcohol intake differed in the studies from >36 g/d to >100 g/d, we arranged the studies according to cutoff point from low to high. The overall OR should be interpreted at an approximate mean cutoff of 56 g/d, the weighted mean. The ORcrude at this cutoff was 3.36 (95% CI, 2.21 to 5.12) (Figure 1). Figure 1 also indicates a possible trend of higher risks of ICH with higher alcohol intake (ORcrude, 2.12 with the lowest cutoff and 4.86 with the highest cutoff; value for heterogeneity, P=0.014). To further evaluate a possible dose-response effect, we dichotomized the studies into moderate intake (≤56 g/d alcohol) and high intake (>56 g/d). We found an overall ORcrude of 2.05 (95% CI, 1.35 to 3.11) for moderate intake and 4.11 (95% CI, 2.54 to 6.65) for high intake.

The investigators of 3 cohort studies4,9,21 reported on a average alcohol intake of 36 g/d (compared with nondrinkers) and found an overall RRadjusted of 1.12 (95% CI, 0.89 to 1.41). Hirvonen et al22 compared the risk of ICH in subjects who drank ≥1 glasses of wine a week with subjects who drank less than that and found an RRadjusted of 1.01 (95% CI, 0.50 to 2.03).

Hypercholesterolemia
The investigators of 4 case-control studies reported on hypercholesterolemia and the risk of ICH.16,17,20,23 The overall ORcrude for high cholesterol was 1.22 (95% CI, 0.56 to 2.67) (Figure 2).

The investigators of the following cohort studies reported on hypercholesterolemia and ICH; all studied total serum cholesterol levels. Leppäla et al17 found an RRadjusted of 0.20 (95% CI, 0.10 to 0.42) for ≥7.0 mmol/L (compared with ≤4.9 mmol/L). Iribarren et al4 found for each 1-SD increase in serum cholesterol (1.45 mmol/L in men and 1.24 mmol/L in women) an RRadjusted of 0.84 (95% CI, 0.69 to 1.02) in men and 0.92 (95% CI, 0.79 to 1.08) in women. Suh et al24 found for >4.31 mmol/L an RRadjusted of 1.22 (95% CI, 0.88 to 1.69) compared with ≤5.69 mmol/L. Yano et al25 found an RRadjusted of 0.64 (95% CI, 0.46 to 0.91) for >4.80 mmol/L compared with ≤4.80 mmol/L.
Smoking

In some case-control studies, the investigators did not specify in detail whether smokers were current smokers, former smokers, or both. We took these studies into account in the analyses of both current and ever smoking.

The investigators of 10 case-control studies reported on current smoking and ICH (Figure 3).11,15,17,18,20,25–29 The overall OR crude for current smoking was 1.25 (95% CI, 0.94 to 1.66). The investigators of 3 cohort studies reported on current smoking for an overall RR adjusted of 1.36 (95% CI, 1.07 to 1.73).4,9,31 Combining the case-control and cohort studies resulted in an overall RR of 1.31 (95% CI, 1.09 to 1.58).

The investigators of 9 case-control studies reported on ever smoking and ICH. The overall OR crude was 1.01 (95% CI, 0.71 to 1.44).15,17,18,20,25–29 The investigators of 3 cohort studies reported on ever smoking for an overall RR adjusted of 1.07 (95% CI, 0.88 to 1.31).4,9,31 Combining the case-control and cohort studies resulted in an overall RR of 1.06 (95% CI, 0.89 to 1.26).

Diabetes Mellitus

The investigators of 8 case-control studies reported on diabetes mellitus.13,16,17,20,23,26,28,30 The overall OR crude was 1.27 (95% CI, 0.98 to 1.65) (Figure 4). Leppäälä et al7 reported on diabetes and risk of ICH; the RR adjusted was 1.64 (95% CI, 0.77 to 3.51). Combining the case-control studies and the finding of Leppäälä resulted in an overall RR of 1.30 (95% CI, 1.02 to 1.67).

Physical Activity

The investigators of 2 cohort studies reported on physical activity and ICH; overall RR crude was 0.76 (95% CI, 0.48 to 1.20) (active versus inactive).32,33

## Study Details

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Cohort studies

Yano et al24, Abbott et al33 | 1989/1994 | 77/92 | 7850/7530 | – | ‡ | – | – | – | – | – | – | – | – |

Klatsky et al21 | 1989 | 28 | 107137 | – | – | – | – | – | – | – | – | – | – |

Kawachi et al31 | 1993 | 53 | 117006 | – | – | + | + | + | + | + | + | + | – |

Iribarren et al4 | 1996 | 386 | 61756 | + | + | + | + | + | + | + | + | + | – |

Gueroshi et al9 | 1997 | 33 | 3852 | + | – | – | – | – | – | – | – | – | – |

Nakayama et al10 | 1997 | 27 | 2302 | – | – | – | – | – | – | – | – | – | – |

Leppäälä et al7 | 1999 | 112 | 28519 | + | + | – | – | + | + | + | + | + | – |

Hirvonen et al22 | 2000 | 95 | 26593 | – | – | – | – | – | – | – | – | – | – |

Hu et al23 | 2000 | 42 | 72488 | – | ‡ | – | – | – | – | – | – | – | – |

Ito et al6,6 | 1999–2001 | 74 | 85764 | + | + | – | – | – | – | – | – | – | – |

Su et al3 | 2001 | 372 | 114793 | + | + | + | + | + | + | + | + | + | – |

P indicates population based; H, hospital based.

‡Study was conducted in men or women alone.

§These studies evaluated recent heavy drinking and risk of ICH and were therefore not included in the analyses of alcohol intake and risk of ICH.
Hypertension

The investigators of 11 case-control studies reported on hypertension and risk of ICH. All studies showed a positive association between hypertension and ICH. The overall OR crude was 3.68 (95% CI, 2.52 to 5.38) (Figure 5).

Three cohort studies evaluated this association. Suh et al found an RR adjusted of 2.2 (95% CI, 1.5 to 3.2) for high-normal, 10.4 (95% CI, 7.1 to 15.3) for stage 2 hypertension, and 33 (95% CI, 23 to 49) for stage 3 hypertension. Iribarren et al found for each 1-SD increase (18 mm Hg in men; 19 mm Hg in women) an RR adjusted of 1.14 (95% CI, 0.96 to 1.36) in men and 1.17 (95% CI, 0.98 to 1.39) in women. Leppä et al found an RR adjusted of 2.20 (95% CI, 1.34 to 3.61) for 140 to 159 mm Hg and 3.78 (95% CI, 2.28 to 6.25) for ≥160 mm Hg compared with ≤139 mm Hg.

Discussion

In our systematic review, we identified 4 risk factors for ICH: male sex, age, hypertension, and alcohol intake. Suh et al and Leppä et al found an increasing risk of ICH with increasing blood pressure. Current smoking and diabetes mellitus are weak risk factors, if at all. Data are inconclusive for physical activity. Ever smoking was no risk factor. Data for hypercholesterolemia were conflicting. Thrift et al found a negative association; Giroud et al found no association; and Zodpey et al and Kubota et al found a positive association for hypercholesterolemia. The difference might be explained by the use of different definitions of hypercholesterolemia. The cohort studies, however, show a clear association: a decreasing risk with an increasing serum cholesterol level. Therefore, we interpret that the cumulative data on cholesterol may be summarized as follows: There tends to be a lower risk of ICH with higher cholesterol levels.

One of the strengths of this meta-analysis is that the literature was collected systematically from several different databases. Publication bias is less of a problem in our meta-analysis than in meta-analyses of randomized clinical trials because it is just as interesting whether there is no association between a potential risk factor and the risk of ICH.

Figure 1. Alcohol. Note that studies were sorted by increasing alcohol intake level. Value for heterogeneity was P=0.014. Alcohol cutoff used per study was as follows: (a) >36, (b) >43, (c) >57, (d) >60, (e) >70, (f) >80, (g) >80, and (h) >100 g/d.

Figure 2. Hypercholesterolemia. Value for heterogeneity was P=0.001. Definition of hypercholesterolemia per study was as follows: (a) history of hyperlipidemia (>5.18 mmol/L), (b) history of hyperlipidemia, (c) serum total cholesterol ≥5.72 mmol/L, and (d) history of high cholesterol.

Figure 3. Current smoking. Value for heterogeneity was P=0.006. Definition of current smoking per study was as follows: (a, e through j) current smoking versus ex-smoking and nonsmoking, (b, c) smoking yes versus no, and (d) current smoking yes versus no.

Figure 4. Diabetes mellitus. Value for heterogeneity was P=0.368. Definition of diabetes mellitus per study was as follows: (a) previous diagnosis or previous or intercurrent treatment, (b, c, d, g) past medical history, (e) glycemia ≥1.20 g/L, (f) previous clinical diagnosis, (h) hospital records, and (i) diagnosis by medical practitioner.
as when there is an association. With regard to the statistical analyses, we attempted to integrate as much of the available information as possible.

Because this study is a meta-analysis, we were able to study only risk factors on which much research was already done; therefore, the risk factors that we have identified probably do not represent all risk factors. Because we included only articles in English, German, French, or Spanish, whites are probably over represented in our results, so our results may be invalid for people of other races.

Another limitation of this meta-analysis is that we were not able to study the risk factors identified in this study simultaneously. Poisson regression that would have allowed adjustment for other potentially confounding ICH risk factors appeared not feasible because often crude data were not reported. Such an analysis could, for example, have shed more light on the different propensity for ICH between men and women: Is it truly a sex difference, or do other ICH risk factors such as a high alcohol intake contribute to this difference. This problem of confounding could also be solved in a project in which raw nondichotomized individual patient data are brought together for a pooled analysis. Within the constraints of the present study, this was not feasible.

Compared with a previous review of the epidemiology of ICH, ours is more extensive because it includes studies published until 2001 and uses an explicit and very elaborate search strategy. Additionally, our data analysis strategies were more extensive because we combined case-control studies separately, cohort studies separately, and these 2 types of studies together.

With regard to alcohol and ICH, a stronger association was found in the case-control studies than in the cohort studies. An explanation for the difference in strength of the association might be that the alcohol intake in the cohort studies was lower (~36 g/d) than in the case-control studies (average, ~56 g/d). We were unable to study binge drinking as a risk factor of ICH because of limited studies.

When we compare the risk factors identified for ICH with those for ischemic stroke, we see that current smoking and diabetes mellitus are risk factors for ischemic stroke but not obvious risk factors for ICH. Furthermore, hypercholesterolemia seems to lower the risk of ICH but clearly increases the risk of ischemic stroke. These differences in risk factors suggest different underlying mechanisms. If smoking, diabetest mellitus, and hypercholesterolemia are not risk factors for ICH, apparently atherosclerosis is not the prevailing pathophysiological mechanism in ICH. Because hypertension is a risk factor for ICH, increased fragility seems a plausible explanation. This fragility may be caused by microaneurysms, amyloid, vascular malformations, or other as-yet-unknown factors.

Because this study shows that age is a risk factor for ICH, one might expect an increasing incidence of ICH as our society ages. Therefore, prevention of ICH is highly important. More attention should be given to modifiable risk factors such as alcohol intake and hypertension to reduce the risk of ICH in the elderly. In further research, it might be interesting to pool individual patient data to evaluate whether these risk factors are independent.

Acknowledgments

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References

Prevention of intracerebral hemorrhage (ICH) is still the most effective method for reducing the impact of this devastating disease. To facilitate better development of prevention programs, we need precise estimates of risk and elucidation of minor risk factors.

In the past, there have been some major difficulties surrounding the identification of risk factors for ICH. The first is that ICH is a relatively uncommon disease, making up between 10% and 15% of all strokes in Western countries. Consequently, to ensure adequate cases of ICH, cohort studies must be very large, and patients must be accrued over many years. Alternatively, case-control methodology could be used and, if carefully conducted to reduce bias, may provide accurate results. Moreover, it is only since the CT era that ICH could be studied as a separate entity with diagnostic accuracy. Inclusion of cases with other types of stroke that have differing etiologies would result in a weakening of any associations identified.

To address some of the limitations of small data sets and diversity of risk factors studied, Ariesen and colleagues have conducted a meta-analysis of previous work in this area. This is a timely analysis, given the number of publications in recent years. Apart from age and sex, they have confirmed that the most important risk factor for ICH is hypertension. Despite different definitions of hypertension in these studies, the relationship between hypertension and ICH is clear. They have also confirmed an association between heavy alcohol consumption and ICH. Further support for alcohol consumption as a risk factor is provided by their summary showing increasing odds ratios with increasing level of alcohol consumption. The summary odds ratios are substantial, with an approximate doubling in the odds ratio of ICH with each decade of life, whereas among men, heavy drinkers, and hypertensive people, the risk of ICH approximately triples.

Although the associations between these 4 factors and ICH are impressive, the summary odds ratios for the case-control...
studies are subject to some imprecision for 2 main reasons. First, as acknowledged by the authors, only univariate odds ratios were summarized. The use of multivariate analyses would have enabled the isolation of the exposure (eg, hypertension) from the effects of any imbalance in the distribution of potentially confounding factors between cases and controls and would show whether the association is truly independent. Without this adjustment, the odds ratio can be altered in either direction; ie, it can be overestimated or underestimated. Second, some of the studies included in the meta-analyses were based on matched samples. Matching eliminates substantial imbalance and therefore controls for confounding on the matched variables. Because the matching was not retained in the analyses of these matched studies, there is a tendency for the odds ratio to be biased toward unity. Alternative analytic techniques incorporating the use of odds ratios and standard errors (or confidence intervals) would enable the production of summary odds ratios based on both adjusted and, when appropriate, matched analyses, as well as enabling inclusion of studies without published raw data.

Because of the likely imprecision in the odds ratios, particular caution must be taken in interpreting the results of the lesser potential risk factors, ie, smoking, hypercholesterolemia, and diabetes. Because the reported odds ratios are small (in the order of 1.2 to 1.3) and because there has been no adjustment for potentially confounding factors, these findings may be spurious.

In support of their findings, Ariesen et al also summarized relative risks from cohort studies (some were adjusted and others were not). These results were both in agreement with those of the case-control summary odds ratios (hypertension, smoking, and diabetes) and in disagreement with them (alcohol consumption and hypercholesterolemia). The disparate findings for alcohol consumption can be explained by the fact that alcohol consumption was not subcategorized according to level of consumption for the cohort studies. The findings for hypercholesterolemia were not in agreement between the cohort and case-control studies, making interpretation difficult.

In summary, Ariesen and colleagues have made an important contribution to our understanding of risk factors for ICH. Hypertension and heavy alcohol consumption are important and preventable risk factors for ICH. Treatment and management of hypertension remain the most effective prevention strategy for ICH, given both the relatively high prevalence of hypertension within the community and the strong association between hypertension and ICH. In regard to the other potential risk factors (hypercholesterolemia, smoking, and diabetes), the most important message is that if these factors increase the risk of ICH, this risk is modest. At present, there still remains insufficient evidence that these factors are important contributors to the development of ICH.

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References
Risk Factors for Intracerebral Hemorrhage in the General Population: A Systematic Review

M.J. Ariesen, S.P. Claus, G.J.E. Rinkel and A. Algra

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