# Risk Factors of Intracerebral Hemorrhage: a Case-Control Study


## Abstract

**Background** Hypertension is a well-known risk factor for intracerebral hemorrhage (ICH). On many of the other potential risk factors, such as smoking, diabetes, and alcohol intake, results are conflicting. We assessed risk factors of ICH, taking also into account prior depression and fatigue.

**Methods** This is a population-based case-control study of 250 primary ICH patients, conducted in Helsinki University Hospital, Finland. The controls (n=750) were participants of the FINRISK study, a large Finnish population survey on risk factors of chronic non-communicable diseases, matched with cases by sex and age. Ages were matched in 5-year age bands. However, as the oldest FINRISK participants were 74-year-olds, controls for the age group 75-84 were selected from the age group of 70-74 years. Patients aged ≥85 years were excluded. Patients and controls were compared in univariate analyses. The age categories <70, and ≥70 years were also analyzed separately. Binary logistic regression analysis was performed for variables with $P < 0.1$ in univariate analysis.

**Results** Analyzing all cases and controls, the cases had more hypertension, history of heart attack, lipid-lowering medication, and reported more frequently fatigue prior to ICH. In persons aged <70 years, hypertension and fatigue were more common among cases. In persons aged ≥70 years, factors associated with risk of ICH were fatigue prior to ICH, use of lipid-lowering medication, and overweight.

**Conclusions** Hypertension was associated with risk of ICH among all patients and in the group of patients under 70 years. Fatigue prior to ICH was more common among all ICH cases.

## Introduction

Several studies have assessed risk factors of intracerebral hemorrhage (ICH), the second most common form of stroke.[1] Incidence of ICH increases with age.[2] A systematic review analyzing 14 case-control studies and 11 cohort studies showed age, male sex, hypertension, and high alcohol intake as risk factors for ICH.[3] In the INTERSTROKE study, a large international case-control study on risk factors of stroke with 3059 ICH cases, hypertension, regular physical activity, diet, waist-to-hip ratio, psychosocial factors, cardiac causes, and alcohol consumption were associated with ICH, whereas current smoking, diabetes, and apolipoproteins were not.[4] In a prospective cohort of 15 792 persons with over 263 489 person-years of follow-up age, African-American ethnicity (versus Whites), and hypertension were positively associated with incident ICH, and low-density lipoprotein cholesterol and triglycerides inversely related to ICH. Sex, smoking, alcohol intake, body mass index, waist-to-hip ratio, and diabetes were not related to ICH.[5]

Hypertension is a well-known risk factor for ICH, shown in several case-control studies.[3,4] Hypertension participates to the etiology of ICH via, e.g., hypertensive microangiopathy. On many of the other potential risk factors, such as smoking, diabetes,

and alcohol intake, the results have been conflicting.

In this study, we wanted to further assess risk factors in a population-based cohort of ICH patients, taking into consideration several novel factors such as feelings of depression and fatigue prior to the index ICH. We compared the risk factors of ICH patients with their age- and sex-matched controls.

## Materials and Methods

This case-control study is a part of an ongoing study on genetic and environmental risk factors of ICH, and the protocol has been described more detailed earlier.[6] We aimed to recruit all consecutive patients admitted to Helsinki University Hospital, Finland, between May 2014 and December 2016 with findings of primarily appearing ICH on admission imaging. Helsinki University Hospital is an academic teaching hospital, and the only hospital with a 24/7 emergency neurological service in the area, with a catchment area of 1.6 million inhabitants. Hemorrhages related to tumor, trauma, ischemic stroke, vascular malformations, and other structural abnormalities were excluded.

A signed informed consent was required for participation. The consent could be given by the patient, the patient's proxy, or if the patient was unable to write, orally in the presence of a witness not related to the study. Patients were asked to fill in a structured questionnaire including medical history, education, profession, feelings of depression,

smoking, and alcohol consumption before ICH. The questionnaire was given upon recruitment in hospital, i.e. in the acute/subacute phase, and if left unanswered, sent to the patient's home address. The questionnaire could be filled together with proxy. The return times of the questionnaires were not registered systematically. Additionally, medical records were used. The size of ICH in admission head CT was calculated using ABC/2 method, where A, B and C are the largest perpendicular measures of the hematoma on CT images. Outcome at 3 months after ICH was evaluated by a combination of revisiting the electronic medical charts, including therapists' evaluations, and telephone call (3 months +/- one week), using a structured questionnaire including mRS, Barthel Index, possible recurrent strokes, and working and living status (HS).

The controls were frequency-matched to cases by sex and age, and randomly selected among the participants of the FINRISK study after all patients had been recruited. FINRISK is a large Finnish population survey on risk factors of chronic non-communicable diseases, conducted by National Institute for Health and Welfare of Finland, described elsewhere.[7,8] Control participants with a history of stroke or TIA were excluded. The ages were matched in 5-year age bands. However, the oldest participants in the FINRISK study were 74-year-olds, hence we needed to select the controls for the ICH patients aged 75 to 84 years from the age group of 70-74 years. Patients aged 85 years and older (N=27) were excluded from the analyses. For each case 3 controls were selected. The control participants filled in structured questionnaires including medical history, health-related lifestyle habits, and socio-economic status. Collections from years 2002 and 2007 were used.

The ICH cases were patients treated in the Helsinki University Hospital, and thus mostly residents of the Uusimaa province in southern Finland. The controls were also from other provinces/regions of Finland (five regions around Finland), in order to obtain the adequate number of controls. The majority of cases and controls were ethnic Finns.

Hypertension was defined as a self-reported premorbid history of hypertension; for the ICH cases medical records were used additionally on medical history. Use of alcohol during the past 12 months was questioned, and any alcohol including beer, wine, and spirits was taken into account. Amount of alcohol was estimated based on regularity and amount of alcohol used, estimating the value in grams/week. Comparable measurements for binge drinking were not available to compare cases and controls. Heavy exercise was defined as weight lifting, aerobics, brisk cycling, or any strenuous exercise. For cases, the regularity of fatigue as almost every day and 3-4 times a week was considered as "often" to be able to compare with the controls; the questionnaire for controls differentiated regularity as often, sometimes or not at all. The cases and controls were questioned if they had been feeling sad or depressed for at least two weeks during the past year (for cases the year prior to ICH).

The characteristics of the patients and controls were first compared in univariate analysis. In addition to all cases and controls, the age categories under 70, and 70 years or older were analyzed separately, in order to estimate the influence or the age difference between

cases and controls among the older group. Next, binary logistic regression analysis was performed for variables with $P < 0.1$ in univariate analysis.

We performed a sensitivity analysis for potential ICH risk factors, and compared the ICH cases with the controls from Uusimaa (Helsinki/Vantaa) region (n=198) in binary logistic regression analysis, adjusting the analysis for age and sex. A separate analysis was performed for each potential risk factor. Due to smaller sample sizes, different analyses for the two age groups were not done.

SPSS v.24 (IBM, Armonk, NY) was used for the statistical analyses. We express categorical variables as counts (%), and continuous variables with normal distribution as mean (SE), and continuous variables not normally distributed as median (IQR) values. The differences between the groups were calculated using the $\chi 2$ test, the t test, or the Mann-Whitney U test as appropriate.

This study has been approved by the local ethical committee and the institutional review board of the Helsinki University Hospital (11.12.2013 311/13103/01/2013 and 12.10.2016 HUS/1662/2016).

**Results**

Two-hundred and fifty patients fulfilled the study criteria, and 750 controls were selected. Approximately half of the participants (128 cases; 51.2 %) were under 70 years old.

Table 1 shows the demographic comparison of the cases and controls. Additional characteristics of the ICH patients are depicted in Table 2.

The cases in all age groups had more frequently history of hypertension, heart attack, and feelings of depression and fatigue, as well as higher education level. In the older age group, compared to their controls, there were less overweight and more underweight cases. More cases than controls were on lipid-lowering medication in the older age group. The patients with lobar ICH were older (median 74.0 years; IQR 62.0-78.5 years) than the patients with deep hemispheric (median 68.0 years; IQR 68.0-80.0 years) and infratentorial ICH (median 64.0 years; IQR 53.0-72.0 years). Mixed ICH was rare, and the values could not be calculated.

Table 3 outlines multivariable analysis for risk factors of ICH. When analyzing all age groups of cases and controls, the cases had more frequently history of hypertension, heart attack, and fatigue, as well as lipid-lowering medication, and higher education than their controls. Overweight was more common in the control group. In the cohort younger than 70 years – in which the cases were more precisely age -matched – hypertension, higher education, and fatigue were significantly more common among cases. In the cohort of 70 years and over, the ICH cases had higher education, and more fatigue prior to ICH, use of lipid-lowering medication, and overweight. We also tested the same potential risk factors including age as a continuous variable in the model for the older age group. Overweight was the only parameter, which did not significantly differ between patients and controls.

Fatigue was not associated with heavy exercise in cases or controls in any of the age groups. There was no association between fatigue and ICH location.

When the controls were compared by region, education level was significantly higher among controls from Uusimaa province than from other regions. The other variables with significant difference between cases and controls (history of hypertension, heart attack, lipid-lowering medication, overweight, underweight, feelings of depression, and fatigue) did not differ between regions, as did not chronic heart failure, COPD/asthma, current smoking, and heavy exercise. Controls from Uusimaa had more frequently history of smoking ($p = 0.0034$) and had used more commonly alcohol within previous 12 months ($p < 0.001$).

In the sensitivity analysis of the potential risk factors for ICH (Supplementary Table 1), comparing ICH cases, and controls from Uusimaa region, the variables with a statistically significant difference between cases and controls were the same as for the whole cohort, apart from alcohol use within previous 12 months, and history of heart attack. Alcohol use was more common among controls. However, the amount of alcohol as grams per week did not differ between the groups. History of heart attack was almost significantly ($p = 0.0679$) more common among cases, and presumable the reason for this is the smaller sample size.

## Discussion

This study compared ICH patients and their stroke-free controls. To our knowledge, this study is the first to assess the association of prior feelings of depression and fatigue with the risk of ICH; the INTERSTROKE study used a combined measure of psychosocial factors combining stress, depression and life events.[4]

As earlier studies imply, hypertension is a significant risk factor for ICH.[4,5,9,10] However, in our cohort of 70 years and older, in the multivariable analysis there was no difference regarding history of hypertension between cases and controls – the reason for which remained unclear. This is in line with an earlier study, which demonstrated a difference in risk factors in several age groups. In that study, hypertension was a risk factor for ICH only in patients under 70 years old.[11] A possible explanation would be other causes than hypertensive angiopathy having a larger role in the pathological mechanisms of ICH among the eldest, such as amyloid angiopathy, which becomes more prevalent among aging.[12]

A recent meta-analysis of 27 studies showed that light and moderate (up to 2 drinks/day) alcohol intake/drinking was associated with a reduced risk of ischemic stroke, but was not associated with risk of ICH. Heavy alcohol consumption was associated with an increased risk of all stroke subtypes.[13] In a case-control study of 2660 cases and controls, rare and moderate alcohol consumption decreased risk of ICH. Heavy alcohol consumption was associated with a significant increase in nonlobar ICH risk in black and

Hispanic participants, however, a similar association was not found in white participants.[14] We did not find any association with alcohol consumption, defined as alcohol use within the previous 12 months or estimated amount of alcohol per week. In the sensitivity analysis comparing the ICH cases and controls, alcohol use within previous 12 months was more common among the controls from Uusimaa region than among the ICH cases. However, the proportion of users is rather large in both groups (cases 80.2 %; controls 88.8 %), as it includes even rare alcohol consumption, and on the other hand abstinent prior alcoholics are categorized as non-users. Estimated amount of alcohol as grams per week did not differ between groups in the sensitivity analysis. It is noteworthy that the vast majority of our study population are ethnic Finns, i.e. white Caucasians.

In our study, current smoking or history of smoking was not associated with risk of ICH, as has been the case in many earlier studies.[4,5,15,16] Some of the studies have reported smoking to be associated with ICH risk,[17] some of them in the dose-dependent manner.[18]

History of heart attack was associated with elevated risk for ICH in our whole cohort, but not in the two age groups analyzed separately, possibly due to smaller sample sizes. The association between history of heart attack and ICH would be expected to be due to the common vascular risk factors between the two diseases. Lipid-lowering medication was more frequently used among the older ICH patients than their controls, but not in the younger age group. Several studies have reported a protective association between

hypercholesterolemia and ICH,[4,5,17,19] and low cholesterol levels to correlate to increased risk of ICH.[20] In a meta-analysis including 31 case-control studies there was no significant association of statin use and risk of ICH.[21] As statin use is commonly used in primary and secondary prevention for subjects with risk factors for cardiovascular diseases, it cannot be excluded that higher use of lipid-lowering medication among the older ICH patients reflects their higher cardiovascular risk factors.

Price et al found obesity to correlate with the risk of ischemic stroke but not with ICH.[22] The INTERSTROKE study found an association between larger BMI and ICH.[4] In another large prospective cohort of 15 792 persons, BMI was not associated with risk for ICH.[5] In our study, there was no significant difference in overweight in age-adjusted analysis.

Lower socio-economic status has been shown to increase ICH incidence and mortality in the Finnish population.[23] A nationwide cohort study in England observed an association with higher incidence in hospitalization for first-ever intracerebral hemorrhage and lower socioeconomic status[24] In deprived areas, the patients were also more likely to be less independent before stroke[24] In our study, high education was more common among ICH cases, which could partly be explained by higher education level in Uusimaa province,[25] and controls coming also from other provinces of Finland. The controls from Uusimaa had higher education than controls from other regions; the other variables differing between cases and controls did not differ between regions. However, also in the sensitivity analysis comparing the ICH cases with controls from

Uusimaa, higher education was more common among the cases than the controls. Among subarachnoid hemorrhage (SAH) patients, there is a trend (P=0.06) for lower education among sudden-death SAHs i.e. patients dying suddenly before being admitted to hospital ward.[26] Around 30 % of ICH patients die before transfer to hospital in Uusimaa (21-36 % during years 2000-2014).[27] As the cohort includes proportionally less patients with larger ICH, and the majority of patients are independent before ICH, these factors might cause bias in education differences between cases and controls.

We compared cases and controls reporting heavy exercise at least 3 hours per week, and no difference was found. Unfortunately, no comparable data was available for any specific type of exercise or exercising at all compared to no exercise. Earlier studies have reported leisure time activity to associate with lower overall stroke risk among women[28] and men.[29] Vigorous exercise was not associated with stroke risk (hemorrhagic or ischemic), and in the women's cohort, leisure time activity did not lower the risk for hemorrhagic stroke.[28]

Psychosocial stressors have been reported to increase risk for myocardial infarction.[30,31] Psychosocial factors were associated with risk of ICH in the INTERSTROKE study.[4] In our study, the ICH cases in all age groups reported significantly more often fatigue prior to ICH than their controls. Premorbid feelings of depression were more common among the cases than controls, however the difference was no longer significant in multivariable analysis. In an earlier study, longer sleep duration was associated with risk of ICH.[32] The possible mechanisms would include a

combination of underlying factors causing fatigue (such as sleep apnea, other underlying diseases, and overall poor health), need for longer resting and different psychosocial factors. Likely, the studies so far have failed in taking into account all possible risk factors, including the psychosocial factors.

The strengths of our study include questioning psychosocial factors in addition to diseases and lifestyle habits such as smoking. As ethnicity influences the risk factors of ICH,[5,14,33] the majority of cases and controls are ethnic Finns.

Limitations of our study include a large amount of missing data on cases regarding questions on premorbid habits, fatigue, and feelings of depression, which is due to the nature of the illness – many patients being unable to answer the questions due to their neurological deficits such as aphasia. For the same reason, among the participants, milder strokes are overrepresented. As the eldest controls are 74 years old, the cases are significantly older than controls. Also, as patients' premorbid feelings of fatigue and depression are evaluated after ICH, it is possible that the current situation may affect the results. The regularity of fatigue was questioned using different terms for cases and controls, and had to be re-classified, which might affect the results. As the control group was significantly younger, the cases and controls were compared in several age groups: all, under 70-year-olds, and 70 years and older. Thus, in the younger age group, the ages of cases and controls were similar. To get an adequate number of controls, we were not able to limit the control population to the Uusimaa region, where the majority of the cases came from.

## Summary & Conclusion

In conclusion, hypertension was associated with risk of ICH among all patients and in the group of patients under 70 years of age. Lipid-lowering medication was associated with the risk among the older patients. Fatigue prior to ICH was more common among all ICH cases, which might be linked to a combination of underlying factors causing fatigue (such as sleep apnea), need for longer resting and different psychosocial factors, which could be interesting topic for future studies.

**Declarations of interests:**

HS and DS report no conflicts of interests. VS has participated in a conference trip sponsored by Novo Nordisk and received a honorarium for participating in an advisory board meeting. He also has ongoing research collaboration with Bayer Ltd. (All unrelated to the present study)

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