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Published in:
Neurology

DOI:
10.1212/WNL.0000000000012885
10.1212/WNL.0000000000012885

Publication date:
2021

Published Ahead of Print on October 20, 2021 as 10.1212/WNL.0000000000012885

Neurology®

The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

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Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000012885

Difference in Rupture Risk Between Familial and Sporadic Intracranial Aneurysms: An Individual Patient Data Meta-analysis

Author(s):
Charlotte CM Zuurbier, MD[1]; Liselore A Mensing, MD[1]; Marieke JH Wermer, prof MD[2]; Seppo Juvela, MD[3]; Antti E Lindgren, MD[4]; Timo Koivisto, MD[4]; Juha E Jääskeläinen, prof MD[4]; Tomosato Yamazaki, MD[5]; Rob Molenberg, BsC[6]; J Marc C van Dijk, MD[6]; Maarten Uyttenboogaart, MD[6]; Marlien Aalbers, MD[6]; Akio Morita, prof MD[7]; Shinjiro Tominari, MD[8]; Hajime Arai, MD[9]; Kazuhiko Nozaki, MD[10]; Yuichi Murayama, MD[11]; Toshihiro Ishibashi, MD[11]; Hiroyuki Takao, MD[11]; Gabriel JE Rinkel, prof MD[1]; Jacoba P Greving, PhD[12]; Ynte M Ruigrok, MD[1]

Corresponding Author:
Ynte M Ruigrok
ij.m.ruigrok@umcutrecht.nl

Affiliation Information for All Authors: 1. Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands; 2. Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands;3. Department of Clinical Neurosciences, University of Helsinki, Helsinki, Finland; 4.Neurosurgery of NeuroCenter, University of Eastern Finland, Kuopio, Finland;5. Department of Neurosurgery, National Hospital Organization, Mito Medical Center, Japan; 6. Departments of Neurosurgery, University Medical Center Groningen, Groningen, The Netherlands ;7. University of Tokyo-Nippon Medical School, Tokyo, Japan; 8. Department of Health Informatics, School of Public Health, Kyoto University, Japan;9. Department of Neurosurgery, Juntendo University- Medical School, Tokyo, Japan; 10. Department of Neurosurgery, Shiga University of Medical Science, Shiga, Japan;11. Department of Endovascular Neurosurgery, Tokyo Jikei University School of Medicine, Tokyo, Japan; 12. Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands

Contributions:

Charlotte CM Zuurbier: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Liselore A Mensing: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Marieke JH Wermer: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Seppo Juvela: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Antti E Lindgren: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Timo Koivisto: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Juha E Jääskeläinen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Tomosato Yamazaki: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Rob Molenberg: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

J Marc C van Dijk: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Maarten Uyttenboogaart: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Marlien Aalbers: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Akio Morita: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Shinjiro Tominari: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Hajime Arai: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Kazuhiko Nozaki: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Yuichi Murayama: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Toshihiro Ishibashi: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Hiroyuki Takao: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Gabriel JE Rinkel: Drafting/revision of the manuscript for content, including medical writing for content;

Study concept or design; Analysis or interpretation of data
Jacoba P Greving: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Ynte M Ruigrok: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Number of characters in title: 121

Abstract Word count: 343

Word count of main text: 3638

References: 31

Figures: 3

Tables: 3

Supplemental: Prisma 2009 Checklist, Supplemental tables and figures
https://datadryad.org/stash/share/Ctz9U1rWebLPT14bAL199ISES4NvAOqp3GfSA2acU4cpoint-by-point responses to reviewers

Search Terms: [2] All Cerebrovascular disease/Stroke, [8] Subarachnoid hemorrhage

Study Funding: We acknowledge the support from the Netherlands Cardiovascular Research Initiative: An initiative with support of the Dutch Heart Foundation, CVON2015-08 ERASE. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No. 852173).

Disclosures: The authors report no disclosures relevant to the manuscript

ABSTRACT

Objective: We combined individual patient data (IPD) from prospective cohorts of patients with unruptured intracranial aneurysms (UIA) to assess to what extent patients with familial UIA have a higher rupture risk than those with sporadic UIA.

Methods: For this IPD meta-analysis we performed an Embase and Pubmed search for studies published up to December 1, 2020. We included studies that 1) had a prospective study design; 2) included 50 or more patients with UIA; 3) studied the natural course of UIA and risk factors for aneurysm rupture including family history for aneurysmal subarachnoid haemorrhage and UIA; and 4) had aneurysm rupture as an outcome. Cohorts with available IPD were included. All studies included patients with newly diagnosed UIA visiting one of the study centers. The primary outcome was aneurysmal rupture. Patients with polycystic kidney disease and moyamoya disease were excluded. We compared rupture rates of familial versus sporadic UIA using a Cox proportional hazard regression model adjusted for the PHASES score and smoking. We performed two analyses: 1. only studies defining first-degree relatives as parents, children, and siblings and 2. all studies, including those in which first-degree relatives are defined as only parents and children, but not siblings.

Results: We pooled IPD from eight cohorts with a low and moderate risk of bias. First-degree relatives were defined as parents, siblings and children in six cohorts (29% Dutch, 55% Finnish, 15% Japanese), totalling 2,297 patients (17% familial, 399 patients) with 3,089 UIA and 7,301 person-years follow-up. Rupture occurred in 10 familial patients (rupture rate: 0·89%/person-year; 95% CI:0·45-1·59) and 41 sporadic patients (0·66%/person-year; 95% CI:0·48-0·89); adjusted HR for familial patients 2·56 (95% CI: 1·18–5·56). After adding also the two cohorts excluding siblings as first-degree relatives resulting in 9,511 patients the adjusted HR was 1·44 (95% CI: 0·86–2·40).

Conclusion: The risk of rupture of UIA is two and a half times higher, with a range from a 1.2 to 5 times higher risk, in familial than in sporadic UIA. When assessing the risk of rupture in UIA, family history should be taken into account.

INTRODUCTION

Persons with a positive family history of aneurysmal subarachnoid hemorrhage (aSAH) or unruptured intracranial aneurysms (UIAs) have a 10% risk of having an UIA.[1] A higher rupture risk of UIA has been suggested in these patients compared to patients without such a history. The Familial Intracranial Aneurysm study reported a 17-times higher rupture rate for individuals with a family history of aSAH plus hypertension or smoking, or both compared to individuals with sporadic UIA. However, these data lack precision since it is based on two cases of aSAH in 113 patients with UIAs.[2] Another prospective, single center cohort with familial patients not selected for smoking or hypertension, and taking risk factors for rupture into account, found a not statistically significant three times higher risk.[3]

The definition of a positive family history may also play a role in the level of risk of rupture of familial UIA.[4] In most countries first-degree relatives are defined as parents, siblings, or children while in some other countries first-degree relatives are defined as only parents and children, but not siblings. We recently showed that within families, siblings have a higher risk of UIA and aSAH than parents and children.[4] Thus, to assess the risk of rupture of familial aneurysms, it is important to include siblings in the category of first-degree relatives.

We aimed to assess to what extent patients with familial UIA have a higher risk of rupture than those with sporadic UIA, when defining first-degree relatives as parents, siblings, or children. Secondly, we assessed this association in cohort both including and excluding siblings in the definition of first-degree relatives.

METHODS

Search strategy and selection criteria

We performed a systematic search in Embase and Pubmed to retrieve all studies on rupture risk of UIA published up to December 1, 2020. Our search strategy included the keywords "(intracranial aneurysm(s) OR cerebral aneurysm(s) AND (risk of rupture OR aneurysm rupture OR risk factors OR rupture OR unruptured OR subarachnoid hemorrhage) AND (follow-up OR natural history OR natural course)" (eFigure 1, available from Dryad: https://doi.org/10.5061/dryad.3bk3j9kjz). We searched the reference list of all relevant publications for additional studies. We included studies that 1) had a prospective study design; 2) included 50 or more patients with UIA; 3) studied the natural course of UIA and risk factors for aneurysm rupture including family history for aSAH and UIA; and 4) had aneurysm rupture as an outcome. There was no language restriction other than the requirement of an abstract in English. One author (CCMZ) performed the literature search, checked the titles and abstracts of search records, and assessed eligible articles to decide which met the predefined inclusion criteria.

Study design

For the eligible studies meeting the inclusion criteria, we approached the research groups that performed these studies asking if they could provide us with their individual patient data. Only cohorts with available individual patient-level data were included in our meta-analysis.

Data collection

Data requested for each patient at baseline of the different included studies were the following: age, sex, history of aSAH, smoking status, positive family history for aSAH or UIA, hypertension status, number of aneurysms, maximum diameter of aneurysms, and aneurysm location. For each patient we summarized the data on the different risk factors for rupture by calculating the PHASES score.[5] Data requested for each patient during follow-up were the following: occurrence of rupture, date of rupture, data of a surgical or endovascular

intervention, date of death, date of last follow-up assessment, and whether a patient was lost to follow-up. Individuals with a positive family history were defined as individuals with at least two affected first-degree relatives with aSAH whether or not in combination of first-degree relatives with UIA. A smoker was defined as a former or current smoker and a person with hypertension as a history of a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or use of antihypertensive drugs. The location of the aneurysm was classified into the categories internal carotid artery, posterior communicating artery, anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery), middle cerebral artery, or posterior circulation (including the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery). Patients with polycystic kidney disease and moyamoya disease were excluded as we are not sure whether the rupture risk of patients with familial UIA and these diseases are similar to the rupture risk of patients with sporadic UIA with these diseases or patients with familial UIA without these diseases.. The primary outcome was the rupture of an UIA. We followed PRISMA guidelines throughout our review. We assessed the quality of the observational studies using the Quality In Prognosis Studies" (QUIPS) tool.[6]

Statistical approach

Information on the outcome measure and aneurysm characteristics was complete for all patients. In four studies no data on family history were available for a small subset of patients, and these patients were excluded from the pooled analysis (146 patients excluded).[7-10] Information on patient characteristics was also complete except for smoking which was available in 9,276/9,511 (97,5%) patients and for hypertension which was available in 9,424/9,511 (99,1%) patients. These missing data were imputed using multiple imputation. In one study smokers were defined as current smokers and no data on former smoking was availaible.[9] 42 patients were included in two Japanese cohorts[10 11], and 11 patients were included in two Dutch cohorts[3 8] and these patients were excluded in one of these cohorts in

the pooled analysis. For data analysis we categorized according to the presence of a family history for aSAH or UIA (familial UIAs) or not (sporadic UIAs). Categorical variables of baseline characteristics were compared using the $\chi 2$ test. Continuous variables of baseline characteristics were compared among groups using the Mann–Whitney U test or the Student t test. A p-value ≤ 0.05 was considered statistically significant. We analyzed rupture rates per patient in all cohorts. In case of multiple aneurysms, the largest aneurysm was used for analysis. In addition, we performed an aneurysm-based analysis, where all UIA were analyzed. Rupture rate was analyzed with a Cox proportional hazard regression model and adjusted for the PHASES score[5] and smoking. A two-stage approach was used with random effect for cohort, because beforehand we expected heterogeneity since studies were performed in different countries which used different treatment regimes, and a fixed effect for the PHASES score and smoking. In the two-stage IPD meta-analysis individual patient data from each study were analyzed separately in order to obtain hazard ratios in each study, Next, these were combined by a random effect meta-analysis model. Proportional hazard assumptions were checked using diagnostics based on the scaled Schoenfeld residuals.[12] Follow-up data for patients started at time of UIA diagnosis and were censored at the time of an aneurysm rupture, death, last follow-up assessment, or at the time of surgical or endovascular aneurysm occlusion. Regarding the definition of first-degree relatives, we performed our primary analysis on studies including parents, siblings, or children as affected first-degree relatives and our secondary analysis on all studies including those in which first-degree relatives are defined as only parents and children, but not siblings. A sensitivity analysis was performed with cohorts from European and Japanese populations.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. All authors

had full access to all the data in the study, the corresponding author had final responsibility for the decision to submit for publication.

Data availability

All study data are available on request.

RESULTS

We found eight studies that fulfilled the inclusion criteria[3, 7-11, 13, 14], and seven research groups provided us with their individual patient data.[3, 7-11, 13] All studies included patients with newly diagnosed UIA visiting one of the study centers. We also found one additional cohort study on UIA, which did not report on family in the Pubmed search,[15] but authors of this study provided non-published data on family history for aSAH, and therefore we could include this cohort as well. This prospective cohort study consisted of data on patients with UIA collected between 1980 and 2017 from the IA database of Neurosurgery of Kuopio University Hospital. This database included 1,181 patients with 1,653 UIA, of whom 248 had a positive family history. In total eight studies met our inclusion criteria (Figure 1). In these studies 68 patients with polycystic kidney disease and two patients with moyamoya disease were excluded. In six studies first-degree relatives were defined as parents, siblings, or children,[3, 7-10, 15] while in two studies, only parents and children were referred to as first-degree relatives.[11, 13] The eight cohorts are listed in Table 1 and the baseline characteristics of patients in all separate cohorts in eTable 1 (available from Dryad: https://doi.org/10.5061/dryad.3bk3j9kjz). Quality assessment of included cohort studies by QUIPS tool is shown in eTable 2 (available from Dryad: https://doi.org/10.5061/dryad.3bk3j9kjz).

The six cohorts that defined first-degree relatives as parents, siblings and children totalled 2,297 patients with 3,089 UIA and 7,301 person-years of follow-up. Baseline characteristics are shown in Table 2. The mean age was 56 ± 12 years, 399 patients (17%) had a positive family history for aSAH and UIA and patients came from Dutch (29%), Finnish (55%) and Japanese (15%) populations. Patients with familial UIA were younger, had less often hypertension, and were more often smokers than patients with sporadic aneurysms. Familial patients more often had small sized UIA and aneurysms were more often located at the

middle cerebral artery compared to sporadic patients. These described characteristics are all included in the PHASES score except smoking.[6] Patients with familial UIA had a similar median PHASES score of 7·0 (range 0-19) as patients with sporadic UIA 7·0 (range 0-21), but the mean PHASES score was lower in patients with familial UIA (7.1, SD 3.5) compared to sporadic UIA (7.7, SD 3.6). The mean follow-up time for patients with familial UIA was 2·8 ± 4·5 years (median: 1.0 (0-35) year) and for patients with sporadic UIA 3·3 ± 6·2 years (median: 1.1 (0-52) year). Preventive neurosurgical or endovascular treatment during follow-up occurred in 47% of familial UIA (median: 107 days) patients and in 37% of sporadic UIA patients (median: 121 days). When assessing the baseline aneurysm characteristics on aneurysm level instead of patient level, results were similar (data not shown). Baseline characteristics of 9,511 patients with 11,647 UIA included in all cohorts including those in which first-degree relatives are defined as only parents and children, but not siblings are provided in eTable 3 (available from Dryad: https://doi.org/10.5061/dryad.3bk3j9kjz).

In 53 patients UIA rupture occurred. Of these 53 patients 11 patients had multiple UIA and in 51 of 53 patients (96%) the largest aneurysm ruptured. Rupture of the largest aneurysm occurred in 10 patients with familial UIA (rupture rate 0·89%/person-year; 95% CI: 0·45-1·59) and in 41 patients with sporadic UIA (0·66%/person-year; 95% CI:0·48-0·89). Characteristics of ruptured aneurysms are shown in Table 3. Characteristics of ruptured aneurysms in all cohorts including those in which first-degree relatives are defined as only parents and children, but not siblings are provided in eTable 4 (available from Dryad: https://doi.org/10.5061/dryad.3bk3j9kjz).

The unadjusted hazard rate (HR) of patients with familial compared to those with sporadic aneurysms was 1·49 (95% CI: 0·73–3·07) in cohorts defining first-degree relatives as parents, children, and siblings. After adjustment for the PHASES score and smoking the adjusted HR was 2·56 (95% CI: 1·18–5·56, I^2=0%; Figure 2). In the aneurysm-based analysis the results were essentially the same (Figure 3). A sensitivity analysis with European and

Japanese population resulted in similar results (eFigure 2, available from Dryad: https://doi.org/10.5061/dryad.3bk3j9kjz). The unadjusted HR of patients with familial aneurysms compared to those with sporadic aneurysms in all cohorts including those in which first-degree relatives are defined as only parents and children, but not siblings was 1·02 (95% CI: 0·62–1·67) and 1·44 (95% CI: 0·86–2·40, I^2=0%; eFigure 3, 4 and 5, available from Dryad: https://doi.org/10.5061/dryad.3bk3j9kjz) after adjustment for the PHASES score and smoking.

DISCUSSION

In this individual patient data meta-analysis we found a higher risk of rupture for familial compared to sporadic UIA, with a point estimate of a two and a half times higher risk, and a range from a 1.2 to 5 times higher risk when restricting our analysis to cohorts referring to affected first-degree relatives as parents, siblings and children in defining a positive family history. We found a slightly but not statistically significantly increased risk of aneurysm rupture for familial compared to sporadic UIA when we analyzed all cohorts including those in which first-degree relatives are defined as only parents and children, but not siblings s. When assessing the risk of rupture in UIA the family history which includes affected siblings as first-degree relatives should be taken into account.

Our study showed a less strongly increased risk of rupture rate in persons with a positive family history for aSAH/UIA than reported in the previous Familial Intracranial Aneurysm study.[2] In this study individuals diagnosed with an UIA were compared with historic controls[14] and all patients had a positive family history together with a positive history of smoking and/or hypertension. The higher risk in this highly selective population can be explained because this population already had a higher risk of UIA rupture due to the presence of the additional risk factors smoking and hypertension.[2] Our findings are consistent with a previous cohort study on the natural course of UIA in patients with and without a positive family history.[3] In our study we found a statistically significant higher risk of UIA rupture for familial compared to sporadic patients, while in the previous cohort study a statistically non-significant effect was found which can be explained by the smaller number of patients included. However, both our and the previous cohort study[3] found an increased risk for rupture in familial patients which is much lower than the 17 times higher risk found in the Familial Intracranial Aneurysm study.[2]

Relatives of patients with familial aSAH have a higher incidence of aSAH than relatives without such a family history.[16] The higher incidence of aSAH in relatives of patients with

familial aSAH is in part explained by a higher prevalence of UIA in these relatives.[17] Our study shows that a higher rupture risk of familial UIA also contributes to the higher incidence of aSAH in relatives with a family history of aSAH. This higher incidence of familial aSAH is likely due to shared genes and/or common environmental risk factors as smoking, and hypertension.[1] A prospective cohort study showed that smoking and hypertension were independent additional risk factors for the presence of IAs in persons with a positive family history of aSAH. [18] A population-based heritability study assessed the contribution of genetic factors to aSAH cohorts and reported a 41% heritability,[19] which is comparable with heritability estimates of other complex diseases.[20] In a genome-wide association study meta-analysis of intracranial aneurysms half of this heritability could already be explained. [21]

The patients with familial UIA analyzed in this study had a lower PHASES score, thus indicating a lower risk of rupture than patients with sporadic UIA. A lower PHASES score in familial than in sporadic UIA was also found in a previous study analyzing patients with familial and sporadic UIA.[3] Numerous studies comparing the characteristics of familial UIA with those of sporadic UIA have found that familial UIA are more often located at the middle cerebral artery, and rupture at a younger age.[22] These findings may explain the lower PHASES score in these patients. Alternatively, selection bias may have occurred since the proportion of patients undergoing preventive treatment was higher in patients with familial than in patients with sporadic UIA. As a result, in the group of familial patients the UIA with high PHASES scores may have been preventively treated more often. Despite the lower PHASES score and the shorter period of follow up, both factors implying a lower risk of rupture, and the higher proportion of familial aneurysms undergoing preventive treatment, familial aneurysms still had a higher risk of rupture. If proportions of patients undergoing preventive treatment would have been similar for familial and sporadic UIA the rupture risk of familial UIA might have even been higher than we found.

A strength of our study is that we evaluated the association between a positive family history and the rupture risk of UIA using individual patient data from eight prospective cohort studies of which six cohorts defined first-degree relatives as parents, children, and siblings, and by that were able to include a large sample size with a large number of outcomes and person-years of follow-up. This allowed us to estimate the risk with high precision. Additionally, in cohorts defining first-degree relatives as parents, children, and siblings the subgroup of familial patients was 17% of the total group of UIA patients and included 399 patients with familial UIA. All studies had a prospective design, and the quality was assessed with the QUIPS tool.

A limitation of this study is that selection bias may have occurred due to informative censoring (loss to follow-up) within each cohort study. For example, in cohorts some patients were treated more aggressively and many patients received treatment during follow-up. In treated patients growth of the UIA may have occurred, which is associated with a higher risk of rupture[23] and consequently may have led to selection bias. Secondly, we performed patient-level analysis and in patients with multiple aneurysms we have made the assumption that the largest aneurysms ruptured. In previous studies a greater likelihood of multiple UIAs in patients with a positive family history is described.[24] In our study, familial patients did not have multiple IAs more often than sporadic patients when rupture occurred. Performing an additional analysis per aneurysm resulted in similar results so this assumption did not influence our analysis. Thirdly, data on aspect ratio and irregular aneurysm shape were not available for neither of the cohort studies included. Aspect ratio and irregular aneurysm shape are also known factors for UIA rupture,[25, 26] and a higher prevalence of irregular aneurysms in familial patients may contribute to the difference in rupture. However, according to a previous study, the prevalence of these risk factors for aneurysm rupture was not higher in patients with aSAH compared to patients with sporadic aSAH.[27] Fourthly, in our primary analysis patients from Finnish populations were overrepresented (55%) compared to Dutch

(29%) and Japanese (15%) populations. Across all populations a higher risk of rupture for familial compared to sporadic UIA was found, with the highest HR in the non-Finnish and non-Japanese cohort, so we think that our results are generalizable to all populations. Fiftly, the subgroup of familial patients was 17% of the total group of UIA patients ranging from 9% up to 29%. In previous studies the proportion of familial patients is around the 10%.[1] A possible explanation for this higher proportion in studies included in our meta-analysis could be that many included patients were treated in tertiary referral centers and that patients with a positive family history were referred to such centers more often. Regardless of the proportion of familial patients for all the different cohorts a higher rupture risk of familial aneurysms was found suggesting that despite of differences in proportion of familial patients our results are generalizable. Sixthly, we had no data on confirmed consanguinity for the different cohorts. Finally, the difference in definition for a positive family history in all available studies resulted in systematic differences in the rupture risk. In six studies siblings were included in the definition of first-degree relatives,[3, 7-10] compared to two studies in which first-degree were defined as parents or children.[11, 13] Consequently, the increased rupture risk in familial patients may have been diluted in these two studies because less patients are categorized as patients with familial UIA and because siblings with a positive family history are included in the group of patients with sporadic UIA. This effect cannot be counteracted by including both first-degree relatives and second-degree relatives in this family group. In this way, siblings are included in the familial group but also grandchildren and grandparents and these family relatives are likely to dilute the rupture risk in the familial group as they are known to have a risk of aSAH comparable to the general population.[23] Alternatively, in our data we were also not able to re-analyze the six cohorts excluding siblings in their definition as first-degree relatives. Future studies should assess the extent to which the siblings influence the higher risk of rupture in familial patients.

CONCLUSION

We found a higher risk of rupture for familial compared to sporadic UIA, with a point

estimate of a two and a half times higher risk, and a range from a 1.2 to 5 times higher risk when using a definition for a positive family history which includes affected parents, siblings, and children. On analyzing all cohorts including those in which first-degree relatives are defined as only parents and children, but not siblings a slightly but not statistically significantly increased risk of aneurysm rupture for familial compared to sporadic UIA was found. When assessing the risk of rupture of UIAs in familial patients defined as individuals with at least two affected first-degree relatives including parents, children, and siblings, this higher risk should be taken into account and a more aggressive treatment approach in these patients as compared to sporadic patients is justified. To assess whether this increased rupture risk should influence the current screening strategy of families of patients with familial UIA an updated cost-effectiveness analysis with this increased rupture risk is needed.[28-30] Further studies are also needed on frequency of follow up imaging in familial UIA. Growth of UIA is associated with a higher risk of rupture.[31] Thus, a higher frequency of follow up imaging may detect growth before rupture, and provide the opportunity of targeted aggressive preventive treatment in familial UIA.

Appendix 1. Authors

Name	Location	Contribution
Charlotte C.M. Zuurbier, MD	University Medical Center Utrecht, Utrecht, The Netherlands	Literature search, statistical analysis, writing of the manuscript
Liselore A. Mensing, MD	University Medical Center Utrecht, Utrecht, The Netherlands	Data collection, review of manuscript
Prof Marieke J.H. Wermer, MD	Leiden University Medical Center, Leiden, The Netherlands	Data collection, review of manuscript
Prof Seppo Juvela, MD	University of Helsinki, Helsinki, Finland	Data collection, review of manuscript
Antti E. Lindgren, MD	University of Eastern Finland, Kuopio, Finland	Data collection, review of manuscript
Timo Koivisto, MD	University of Eastern Finland, Kuopio, Finland	Data collection, review of manuscript
Prof Juha E. Jääskeläinen, MD	University of Eastern Finland, Kuopio, Finland	Data collection, review of manuscript
Tomosato Yamazaki,	Department of Neurosurgery, National Hospital Organization, Mito Medical	Data collection, review of manuscript

	Center, Japan	
Rob Molenberg BsC	Departments of Neurosurgery, University Medical Center Groningen, Groningen, The Netherlands	Data collection, review of manuscript
J. Marc C. van Dijk, MD	Departments of Neurosurgery, University Medical Center Groningen, Groningen, The Netherlands	Data collection, review of manuscript
Maarten Uyttenboogaart MD	Departments of Neurology and Medical Imaging Center, University Medical Center Groningen, Groningen, The Netherlands	Data collection, review of manuscript
Marlien W Aalbers	Departments of Neurosurgery, University Medical Center Groningen, Groningen, The Netherlands	Data collection, review of manuscript
Prof Akio Morita, MD	University of Tokyo- Nippon Medical School, Tokyo, Japan	Data collection, review of manuscript
Shinjiro Tominari MD	Department of Health Informatics, School of Public Health, Kyoto University, Japan	Data collection, review of manuscript

Hajime Arai, MD	Juntendo University- Medical School, Tokyo, Japan	Data collection, review of manuscript
Kazuhiko Nozaki, MD	Shiga University of Medical Science, Shiga, Japan	Data collection, review of manuscript
Yuichi Murayama, MD	Tokyo Jikei University School of Medicine, Tokyo, Japan	Data collection, review of manuscript
Toshihiro Ishibashi, MD	Tokyo Jikei University School of Medicine, Tokyo, Japan	Data collection, review of manuscript
Hiroyuki Takao, MD	Tokyo Jikei University School of Medicine, Tokyo, Japan	Data collection, review of manuscript
Prof Gabriel J.E. Rinkel, MD	University Medical Center Utrecht, Utrecht, The Netherlands	Statistical analysis, review of manuscript
Jacoba P. Greving, PhD	University Medical Center Utrecht, Utrecht, The Netherlands	Statistical analysis, review of manuscript
Ynte M. Ruigrok, MD	University Medical Center Utrecht, Utrecht, The Netherlands	Outline of study, statistical analysis review of manuscript

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TABLES

Table 1. Characteristics of included studies.

	Country	Recruitment period	Number of patients	Number of UIA	First-degree relatives including siblings	Patients with positive family history	Mean age(range; years)	Median follow-up (range; years)	Number of aSAH during follow-up
Juvela et al[7]	Finland	1956-1978	93	116	Yes	9	42 (15-61)	27.2 (1-52)	22
Lindgren et al[a]	Finland	1977-2016	1181	1658	Yes	248	56 (16-85)	0.5 (0-23)	14
Mensing et al[3]	the Netherlands	1994-2016	474	633	Yes	62	56 (22-81)	0.8 (0-21)	10
Morita et al[11]	Japan	2001-2004	5702	6675	No	327	63 (23-98)	1.0 (0-9)	111
Murayama at al[13]	Japan	2003-2012	1561	1942	No	184	66 (25-100)	3.2 (0-11)	56

Wermer et al[8]	the Netherlands	2002-2004	89	119	Yes	26	50 (20-69)	2.2 (1-15)	1
Molenberg et al[9]	the Netherlands	1998-2017	122	159	Yes	33	55 (33-77)	1 (0-2)	0
Sonobe et al[10]	Japan	2000-2004	349	419	Yes	31	62 (23-89)	3.2 (0-7)	6

UIA: unruptured intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage. [a] unpublished data

Table 2. Baseline characteristics of patients in cohorts defining first-degree relatives as parents, children, and siblings.

Pooled data	**Familial (n,%)**	**Sporadic (n,%)**	**Total**	**P-value**
Number of patients	399	1898	2297	
Women	265 (66)	1169 (62)	1434 (62)	0.07
Mean age[a] (range)	51 (20-80)	57 (15-89)	56 (15-89)	<0.01
Hypertension[a]	139 (35)	818 (43)	957 (42)	<0.01
Ever smoker	212 (53)	931 (49)	1143 (50)	0.138
Previous aSAH[a]	34 (9)	242 (13)	276 (12)	0.018
Population[a]				
Finnish	257 (64)	1018 (54)	1274 (55)	<0.01
Dutch	111 (28)	563 (30)	674 (29)	
Japanese	31 (8)	318 (17)	349 (15)	
Multiple aneurysms	122 (31)	511 (27)	633 (28)	0.227
Aneurysm size[a]				
< 7.0 mm	322 (81)	1321 (70)	1643 (72)	<0.01
7.0-9.9 mm	43 (11)	301 (16)	344 (15)	
10.0-19.9 mm	30 (8)	220 (12)	250 (11)	

> 20.0 mm	4 (1)	56 (3)	60 (3)	
Aneurysm location Internal carotid artery Middle cerebral artery Anterior circulation & Posterior circulation	 83 (21) 189 (47) 127 (32)	 413 (22) 783 (41) 702 (37)	 496 (22) 972 (42) 829 (36)	 0.065
Aneurysm treatment during follow-up[a]	186 (47)	702 (37)	888 (38)	<0.01
PHASES score[a] (median, range; mean, SD)	7.0 (0-19) 7.1 ± 3.5	7.0 (0-21) 7.7 ± 3.6	7.0 (0-21) 7.6 ± 3.6	<0.01

aSAH: aneurysmal subarachnoid hemorrhage [a] statistically significant difference

Table 3. Characteristics of ruptured intracranial aneurysms in cohorts defining first-degree relatives as parents, children, and siblings per aneurysm.

	Familial (n,%)	**Sporadic (n,%)**	**Total**
Number of ruptured IA	10	43	53
Largest IA ruptured[a]	10	41	41
Not largest IA ruptured	0	2	2
Women	6 (60)	28 (65)	34 (64)
Mean age (range)	58 (33-74)	52 (23-80)	53 (23-80)
Hypertension	1 (10)	23 (54)	24 (45)
Ever smoker	3 (30)	24 (56)	27 (51)
Previous aSAH	3 (30)	20 (47)	23 (43)
Population			
Finnish	7 (70)	29 (70)	36 (70)
Netherlands	3 (30)	8 (18)	11 (20)
Japanese	0	6 (13)	6 (10)
Multiple aneurysms	0	11 (28)	11 (21)
Aneurysm size at time of detection			
< 7.0 mm	6 (60)	23 (54)	29 (55)
7.0-9.9 mm	1 (10)	10 (23)	11 (21)

10.0-19.9 mm	3 (30)	9 (21)	12 (23)
> 20.0 mm	0	1 (2)	1 (2)
Aneurysm location			
Internal carotid artery	1 (10)	11 (26)	12 (23)
Middle cerebral artery	5 (50)	15 (35)	20 (38)
Anterior circulation & Posterior circulation	4 (40)	17 (40)	21 (42)
PHASES score (median, range; mean, SD)	8.0 (2-16) 8.8 ± 4.7	9.0 (2-20) 9.5 ± 4.1	8.0 (2-20) 9.4 ± 4.2

IA: intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage [a] In case of multiple aneurysms, the largest aneurysm was used for analysis

Figure 1. Prisma flow diagram.

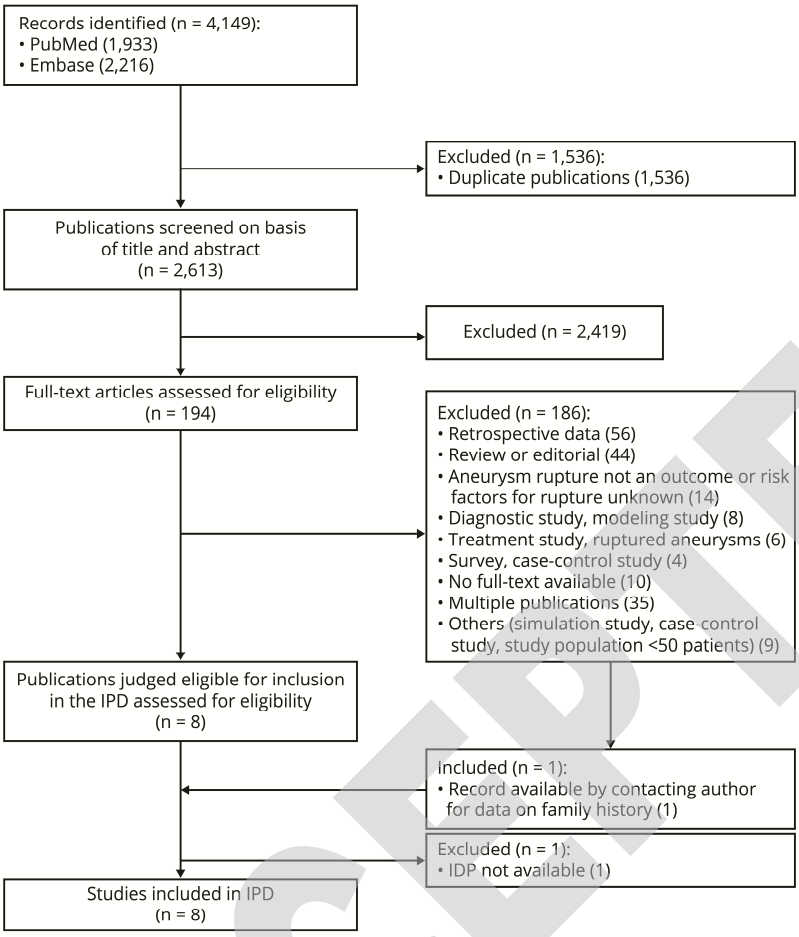


Figure 2. Hazard ratio (HR) of the rupture rate in patients with familial aneurysms compared to sporadic aneurysms adjusted for the PHASES score and smoking in cohorts defining first-degree relatives as parents, children, and siblings, analyzing the data per patient.

In the study from Wermer et al 1 aneurysm ruptured, in a patient with multiple aneurysms. The ruptured aneurysm was the smallest aneurysm and consequently this rupture was not included in the analysis per patient

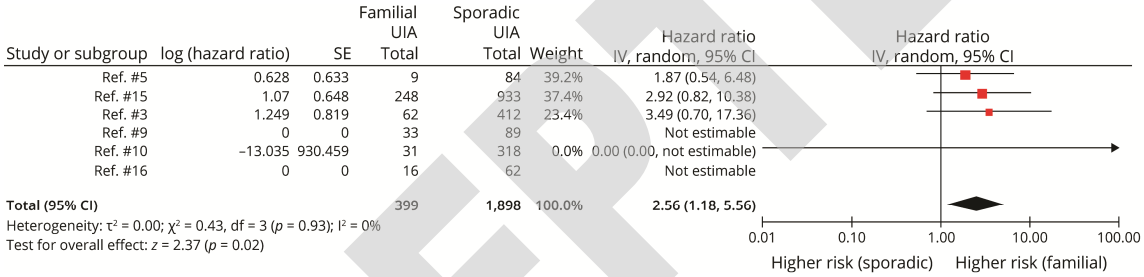
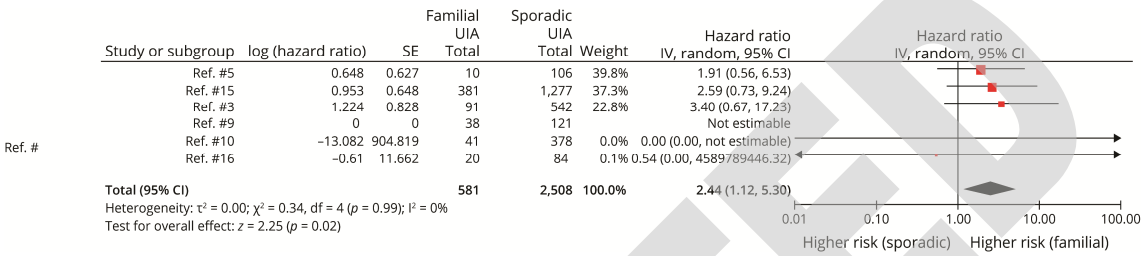


Figure 3. Hazard ratio of the rupture rate adjusted for the PHASES score and smoking for familial aneurysms compared to sporadic aneurysms in cohorts defining first-degree relatives as parents, children, and siblings, analyzing the data per aneurysm.



Difference in Rupture Risk Between Familial and Sporadic Intracranial Aneurysms: An Individual Patient Data Meta-analysis

Charlotte CM Zuurbier, Liselore A Mensing, Marieke JH Wermer, et al.

Neurology published online October 20, 2021
DOI 10.1212/WNL.0000000000012885