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Difference in Rupture Risk Between Familial and Sporadic Intracranial Aneurysms

An Individual Patient Data Meta-analysis

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Abstract

Background and Objectives
We combined individual patient data (IPD) from prospective cohorts of patients with unruptured intracranial aneurysms (UIAs) 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 aneurysm rupture. Patients with polycystic kidney disease and moyamoya disease were excluded. We compared rupture rates of familial vs sporadic UIA using a Cox proportional hazard regression model adjusted for PHASES score and smoking. We performed 2 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 8 cohorts with a low and moderate risk of bias. First-degree relatives were defined as parents, siblings, and children in 6 cohorts (29% Dutch, 55% Finnish, 15% Japanese), totaling 2,297 patients (17% familial, 399 patients) with 3,089 UIAs and 7,301 person-years follow-up. Rupture occurred in 10 familial cases (rupture rate: 0.89%/person-year; 95% confidence interval [CI] 0.45–1.59) and 41 sporadic cases (0.66%/person-year; 95% CI 0.48–0.89); adjusted hazard ratio (HR) for familial cases 2.56 (95% CI 1.18–5.56). After adding the 2 cohorts excluding siblings as first-degree relatives, resulting in 9,511 patients, the adjusted HR was 1.44 (95% CI 0.86–2.40).

Discussion
The risk of rupture of UIA is 2.5 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.

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Persons with a positive family history of aneurysmal subarachnoid hemorrhage (aSAH) or unruptured intracranial aneurysms (UIAs) have a 10% risk of having a UIA. 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 as they are based on 2 cases of aSAH in 113 patients with UIAs. 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 3 times higher risk.

The definition of a positive family history may also play a role in the level of risk of rupture of familial UIA. 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. 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 cohorts 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: doi.org/10.5061/dryad.3bkj99kjz). 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 UIAs; (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 (C.C.M.Z.) 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. 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 2 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 is 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines throughout our review. We assessed the quality of the observational studies using the Quality in Prognosis Studies (QUIPS) tool.

Statistical Approach

Information on the outcome measure and aneurysm characteristics was complete for all patients. In 4 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). 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.9 Forty-two patients were included in 2 Japanese cohorts10,11 and 11 patients were included in 2 Dutch cohorts3,8 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 of aSAH or UIA (familial UIAs) or not (sporadic UIAs). Categorical variables of baseline characteristics were compared using the χ² 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 UIAs were analyzed. Rupture rate was analyzed with a Cox proportional hazard regression model and adjusted for the PHASES score5 and smoking. A 2-stage approach was used with random effect for cohort, because beforehand we expected heterogeneity as studies were performed in different countries that used different treatment regimens, and a fixed effect for the PHASES score and smoking. In the 2-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 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 8 studies that fulfilled the inclusion criteria,3,7-11,13 and 7 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 unpublished 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, 8 studies met our inclusion criteria (Figure 1). In these studies, 68 patients with polycystic kidney disease and 2 patients with moyamoya disease were excluded. In 6 studies, first-degree relatives were defined as parents, siblings, or children,3,7-10,15 while in 2 studies, only parents and children were referred to as first-degree relatives.11,13 The 8 cohorts are listed in Table 1 and the baseline characteristics of patients in all separate cohorts in eTable 1 (available from Dryad: doi.org/10.5061/dryad.3bk3j9kjz). Quality assessment of included cohort studies by QUIPS tool is shown in eTable 2 (available from Dryad: doi.org/10.5061/dryad.3bk3j9kjz). The 6 cohorts that defined first-degree relatives as parents, siblings, and children totaled 2,297 patients with 3,089 UIA and 7,501 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, less often had hypertension, and more often were smokers than patients with sporadic aneurysms. Familial cases more often had small UIA and aneurysms were more often located at the middle cerebral artery compared to sporadic cases. 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) and in 37% of sporadic UIA (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: doi.org/10.5061/dryad.3bk3j9kjz).

In 53 patients, UIA rupture occurred. Of these 53 patients, 11 patients had multiple UIA, and in 1 of 53 patients (96%), the

### Table 1 Characteristics of Included Studies

| Country       | Recruitment period | Patients, n | UIA, n | First-degree relatives including siblings | Patients with positive family history | Age, y, mean (range) | Follow-up, y, median (range) | aSAHs during follow-up, n |
|---------------|--------------------|-------------|--------|-------------------------------------------|-------------------------------------|----------------------|-----------------------------|-----------------------------|
| Juvela et al.7| Finland            | 1956–1978   | 93     | 116                                       | Yes                                 | 9                    | 42 (15–61)                  | 27.2 (1–52)                 | 22                          |
| Lindgren et al.4| Finland          | 1977–2016   | 1,181  | 1,658                                     | Yes                                 | 248                  | 56 (16–85)                  | 0.5 (0–23)                  | 14                          |
| Mensing et al.5| The Netherlands  | 1994–2016   | 474    | 633                                       | Yes                                 | 62                   | 56 (22–81)                  | 0.8 (0–21)                  | 10                          |
| Morita et al.11| Japan              | 2001–2004   | 5,702  | 6,675                                     | No                                  | 327                  | 63 (23–98)                  | 1.0 (0–9)                   | 111                         |
| Murayama et al.13| Japan            | 2003–2012   | 1,561  | 1942                                     | No                                  | 184                  | 66 (25–100)                 | 3.2 (0–11)                  | 56                          |
| Wermer et al.6| 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                           |

Abbreviations: aSAH = aneurysmal subarachnoid hemorrhage; UIA = unruptured intracranial aneurysm.

*Unpublished data.
largest aneurysm ruptured. Rupture of the largest aneurysm occurred in 10 patients with familial UIA (rupture rate 0.89%/person-year; 95% confidence interval [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: 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 populations provided similar results (eFigure 2, available from Dryad: 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, $I^2 = 0\%$; eFigures 3–5, available from Dryad: doi.org/10.5061/dryad.3bk3j9kjz) after adjustment for the PHASES score and smoking.

## Table 2 Baseline Characteristics of Patients in Cohorts Defining First-Degree Relatives as Parents, Children, and Siblings

| Pooled data               | Familial | Sporadic | Total   | $p$ Value |
|---------------------------|----------|----------|---------|------------|
| Patients                  | 399      | 1,898    | 2,297   |            |
| Women                     | 265 (66) | 1,169 (62)| 1,434 (62)| 0.07       |
| Age,* y, mean (range)     | 51 (20–80)| 57 (15–89)| 56 (15–89)| <0.01      |
| Hypertension*             | 139 (35) | 818 (43) | 957 (42) | <0.01      |
| Ever smoker               | 212 (53) | 931 (49) | 1,143 (50)| 0.138      |
| Previous aSAH*            | 34 (9)   | 242 (13) | 276 (12) | 0.018      |
| Population*               |          |          |         |            |
| Finnish                   | 257 (64) | 1,018 (54)| 1,274 (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, mm*        |          |          |         |            |
| <7.0                      | 322 (81) | 1,321 (70)| 1,643 (72)| <0.01      |
| 7.0–9.9                   | 43 (11)  | 301 (16) | 344 (15) |            |
| 10.0–19.9                 | 30 (8)   | 220 (12) | 250 (11) |            |
| >20.0                     | 4 (1)    | 56 (3)   | 60 (3)   |            |
| Aneurysm location         |          |          |         |            |
| Internal carotid artery   | 83 (21)  | 413 (22) | 496 (22) | 0.065      |
| Middle cerebral artery    | 189 (47) | 783 (41) | 972 (42) |            |
| Anterior and posterior circulation | 127 (32) | 702 (37) | 829 (36) |            |
| Aneurysm treatment during follow-up* | 186 (47) | 702 (37) | 888 (38) | <0.01      |
| PHASES score,* 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 |

Abbreviation: aSAH = aneurysmal subarachnoid hemorrhage. Values are n (%) unless otherwise specified. * Statistically significant difference.

**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 2.5 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,
In this study, individuals diagnosed with an UIA were compared with historic controls and all patients had a positive family history together with a positive history of smoking 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 nonsignificant effect was found, which can be explained by the smaller number of patients included. However, both our and the previous cohort study 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 UIA is likely due to shared genes and/or common environmental risk factors such 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

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. When assessing the risk of rupture in UIA, the family history that 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
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 8 prospective cohort studies, of which 6 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. In cohorts defining first-degree relatives as parents, children, and siblings the subgroup of familial patients was 17% of the total group of patients with UIA 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, and consequently may have led to selection bias. Secondly, we performed patient-level analysis and in patients with multiple aneurysms we 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. In our study, familial cases did not have multiple IA's more often than sporadic cases 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 either of the cohort studies included. Aspect ratio and irregular aneurysm shape are also known factors for UIA rupture, and a higher prevalence of irregular aneurysms in familial cases 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. Fourth, 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 our results are generalizable to all populations. Fifth, the
A subgroup of familial patients was 17% of the total group of patients with UIA, ranging from 9% up to 29%. In previous studies, the proportion of familial cases is around 10%. 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 differences in proportion of familial cases, our results are generalizable. Sixth, 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 6 studies, siblings were included in the definition of first-degree relatives, compared to 2 studies in which first-degree were defined as parents or children. Consequently, the increased rupture risk in familial cases may have been diluted in these 2 studies because fewer 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. Alternatively, in our data we were also not able to re-analyze the 6 cohorts excluding siblings in their definition as first-degree relatives. Future studies should assess the extent to which siblings influence the higher risk of rupture in familial cases.

We found a higher risk of rupture for familial compared to sporadic UIA, with a point estimate of a 2.5 times higher risk, and a range from a 1.2 to 5 times higher risk when using a definition for a positive family history that 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 2 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 cases 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. 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. Thus, a higher frequency of follow-up imaging may detect growth before rupture, and provide the opportunity for targeted aggressive preventive treatment in familial UIA.

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| Liselore A. Mensing, MD     | University Medical Center Utrecht, the Netherlands | Data collection, review of manuscript   |
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Difference in Rupture Risk Between Familial and Sporadic Intracranial Aneurysms: An Individual Patient Data Meta-analysis
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