Intracranial aneurysms

Family history and risk of rupture

Charlotte Zuurbier

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Intracraniële aneurysmata

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(met een samenvatting in het Nederlands)

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te Wognum

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Contents

Chapter 1

General introduction and outline of this thesis

Introduction

Intracranial aneurysms are acquired abnormal focal dilations, which are most often located at bifurcations of the arteries of the circle of Willis.[1] The prevalence of intracranial aneurysms is approximately 3% in the adult population, which means that around 300,000 adults in the Netherlands have an aneurysm.[2] Intracranial aneurysms often remain undiagnosed until they rupture. Rupture results in aneurysmal subarachnoid haemorrhage (aSAH), a subtype of stroke with an incidence of around 6 per 100,000 person-years.[3] Although aSAH is relatively rare constituting only 5% of all strokes,[1] it has a major impact due to its high case fatality and morbidity and the relatively young age it occurs compared to other types of stroke.[4, 5] Early diagnosis of intracranial aneurysms can influence clinical management and prognosis, as timely intervention might prevent aSAH. Preventive treatment of intracranial aneurysms carries a 5% risk of treatment-related fatality and morbidity,[6] and should ideally be reserved for patients at high risk of aneurysmal rupture.

Familial predisposition of aSAH is the strongest risk factor for aSAH.[7] According to the number of affected relatives, the lifetime risk of aSAH can be as high as 25%.[8] In persons with two or more affected first-degree relatives preventive screening for intracranial aneurysms using Magnetic Resonance Angiography or Computed Tomography Angiography is cost-effective when this is repeated every five to seven years between 20 and 70-80 years of age.[9, 10] An intracranial aneurysm is found at first screening in 10% and during follow-up screening in 5%.[11, 12] Early risk stratification may help to identify persons at low or high risk of intracranial aneurysms and thereby improve the efficiency of screening. Not only a higher risk of developing intracranial aneurysms, also a higher risk of aneurysmal rupture has been suggested in patients with a positive family history compared to patients without such a history.[13, 14] However, it is not yet known to what extent patients with a positive family history have a higher rupture risk.

Both unruptured intracranial aneurysm and aSAH occur more often in women than in men.[5, 15] Overall, 65% of the patients with aSAH are women.[5] The reason for this female preponderance is thus far unknown. We do not yet know whether the higher risk of aSAH in women can be explained by the higher prevalence of unruptured intracranial aneurysm in women or also by a higher rupture rate of these aneurysms.

The present thesis aims to optimise the identification and screening of persons with a positive family history of aSAH and intracranial aneurysms, and to investigate the risk factors positive family history of aSAH and sex for aneurysmal rupture.

Outline of the thesis

Part I: Positive family history of aneurysmal subarachnoid haemorrhage

The first part of this thesis focuses on optimising the identification and screening of persons with a positive family history of aSAH and intracranial aneurysms. In **chapter 2,** we present a questionnaire for persons who have first-degree relatives with a stroke that could be used to identify whether this relative has experienced an aSAH or another subtype of stroke. In **chapter 3,** we describe a cohort study in which we investigated whether the type of kinship (parents, siblings, or children) of first-degree relatives of aSAH patients influences the risk for unruptured intracranial aneurysms and aSAH. In **chapter 4,** we present a prediction model for predicting the probability of an unruptured intracranial aneurysm at first screening in persons with a positive family history of aSAH. We developed a prediction model at first screening, and in **chapter 5** we also report a model for predicting the probability of an unruptured intracranial aneurysm at 5 and 10 years after initial screening.

Part II: Risk of aneurysmal rupture according to positive family history and female sex

The second part of this thesis focuses on family history of aSAH and sex as risk factors for aneurysmal rupture. In **chapter 6,** we studied in an individual patient data meta-analysis to what extent patients with familial unruptured intracranial aneurysms have a higher risk of rupture than those with sporadic unruptured intracranial aneurysms. In **chapter 7**, we describe an individual patient data meta-analyses on sex differences in rupture rate.

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Part I

Positive family history of aneurysmal subarachnoid haemorrhage

Chapter 2

Development and validation of a screening questionnaire to identify persons with a family history of aneurysmal subarachnoid haemorrhage

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Abstract

Background: Preventive screening for intracranial aneurysms is effective in persons with a positive family history of aneurysmal subarachnoid haemorrhage (aSAH), but for many relatives of aSAH patients it can be difficult to assess if their relative had an aSAH or another type of stroke. We aimed to develop a family history questionnaire for such relatives, and to assess its accuracy to identify relatives of aSAH patients.

Patients and methods: A questionnaire to distinguish between aSAH and other stroke types (ischaemic stroke and intracerebral haemorrhage) was developed by a team of clinicians and consumers. The level of agreement between the questionnaire outcome and medical diagnosis was pilot tested in 30 previously admitted aSAH patients. Next, the sensitivity, specificity, positive and negative predictive value of the questionnaire was assessed in 91 first-degree relatives (siblings/children) of previously admitted stroke patients.

Results: All 30 aSAH patients were identified by the questionnaire in the pilot study. 29 of 30 first-degree relatives of aSAH patients correctly were identified. The questionnaire had a sensitivity of 97% (95% CI: 83-100%), specificity of 93% (95% CI: 84-98%), positive predictive value of 88% (95% CI: 74-95%), and negative predictive value of 98% (95% CI: 89-100%) when tested in the first-degree relatives of stroke patients.

Discussion and conclusion: Our questionnaire can help persons to discriminate an aSAH from other types of stroke in their affected relative. This family history questionnaire is developed in the Netherlands, but could also be used in other countries after validation.

Introduction

A positive family history of aneurysmal subarachnoid haemorrhage (aSAH) is a strong risk factor for aSAH and the lifetime risk of aSAH for first-degree relatives of aSAH patient can be as high as 25%.[1] Screening for and preventive treatment of unruptured intracranial aneurysms (UIAs) in these relatives can prevent aSAH.[2, 3, 4]

Currently, the potential of screening is not optimally used. For persons who have first-degree relatives with stroke it can be difficult to distinguish between aSAH and other types of stroke. The relative with a stroke may have died, and the medical records may not always be available. A previous study showed that with a telephone interview with a next of kin of a patient who died of either aSAH, ischaemic stroke, or intracerebral haemorrhage the positive predictive value of the diagnosis of probable aSAH was 70%.[5] For persons who have first-degree relatives with stroke a family history questionnaire that they can fill out themselves online could be a useful tool in the identification of persons with a positive family history of aSAH. Subsequently, preventive screening can be advised to persons with a first-degree relative who has had an aSAH. However, currently no reliable, standardized family history questionnaire for aSAH is available.

Our aim was to develop a questionnaire for persons who have first-degree relatives with a stroke which they can use to identify whether their relative experienced an aSAH or another stroke type.

Patients and methods

Development of the questionnaire

The questionnaire was developed by a multidisciplinary team of clinicians and consumers. As input for its development we used questions from a family history interview in persons with a relative who died of stroke in order to distinguish death from aSAH form other types of stroke.[5] The clinicians were two vascular neurologists and a research nurse, all three specialized in the care of UIAs and aSAH patients, and the consumers were members of the Dutch brain aneurysm patient association.[6] The two vascular neurologists wrote a first version of the questionnaire, while the research nurse and the consumers provided feedback on this questionnaire. The questionnaire was designed to distinguish between

aSAH on the one hand and ischaemic stroke and intracerebral haemorrhage on the other hand. The questionnaire consisted of four questions on the symptoms (1), age at onset of the stroke (2), explanation of the stroke by the then treating physician (3) and treatment given for the stroke (4; Table 1). Multiple response options could be entered for questions 1, 3 and 4. These different response options were given different points, and the amount of points assigned to each option was based on the expert opinion of the multidisciplinary team. Answers that pointed in the direction of a diagnosis of aSAH were assigned positive points, while answers that pointed in the direction of ischaemic stroke or intracerebral haemorrhage were assigned negative points. Answers that did not distinguish between the three different types of diagnoses were assigned zero points. These nondiscriminatory answers were included to avoid confusion in persons with a first-degree relative with ischaemic stroke or intracerebral haemorrhage if an answer option is not included and to avoid that they then might choose a second best answer instead. The individual points added up to a total questionnaire score (min:-180, max: 447). We found responses to questions 3 and 4 the most important ones to assess whether a family member had experienced an aSAH and therefore the answers that pointed in the direction of an aSAH received the highest score of 60 points. Given the importance we gave to these specific answers the cut-off for a diagnosis of aSAH was set at a total score of >60 points. If multiple answers were given that pointed in the direction of an aSAH the points from these different answers were all included in the total score. The questionnaire was written in the lay Dutch language. For the purpose of this article it was translated into English using input for the translation from the patient information folder of the British Heart Foundation and this translation was checked by an English translator. The questionnaire in Dutch can be requested from the authors.

Table 1. Questions and answers of the family history questionnaire with the point value assigned to the various answer options.

Questions	Point value
1.* Which symptoms were caused by stroke in your family member?	
◯ Sudden (onset within 1 minute) severe headache	10
◯ Loss of consciousness	5
◯ Confusion	2
◯ Weakness of the limbs or face	0
◯ Speech problems (unable to speak or using the wrong words)	0
◯ Unknown	0
2. How old was your family member at the time of the stroke?	
◯ ≤60 years old	20
◯ >60 years old	0
◯ Unknown	0
3.* How was the stroke explained to your family member by the treating physician?	
◯ It occurred because a **blood clot** blocked a blood vessel in the brain.	-60
◯ It occurred because of a **weakness** in a blood vessel; the weakness can slowly develop into a balloon (bulge).	60
◯ This is caused by a **bulge** in the wall of a blood vessel. It can be compared to a damaged **bicycle tyre**: there is a weak spot in the outer tyre, causing the inner tyre to bulge out.	60
◯ The stroke is caused by part of the brain not receiving oxygen and nutrients.	-60
◯ It occurred because a blood vessel in the brain ruptured.	0
◯ The stroke is caused by blood accumulating in the **brain tissue.**	0
◯ The stroke is caused by bleeding into the space around the brain. This space is filled with cerebrospinal fluid and blood vessels. The space can be compared to the **crawl space** of a house (a space where pipes run under the floor of the house).	60
◯ The stroke is caused by bleeding into the subarachnoid space, the space between the brain membranes (the soft meninges and the spider web membrane).	60
◯ Other	0
4.* How was your family member treated?	
◯ Treatment of the vascular abnormality by brain surgery (clipping)	60
◯ Treatment of the vascular abnormality via the blood vessels in the groin (coiling/ stenting)	60

Table 1. Continued

Questions	Point value
◯ Removal of the clot through the blood vessels in the groin (endovascular thrombectomy)	-60
◯ A clot-busting medication (known as thrombolysis)	-60
◯ Other	0
◯ Unknown	0

* *multiple answer options may be given.*

Pilot study in patients with aSAH

We tested the level of agreement between the outcome of the family history questionnaire and the diagnosis based on the medical record in a consecutive series of aSAH patients previously admitted to the University Medical Centre Utrecht (UMCU), the Netherlands and visiting the outpatient clinic 6-8 weeks after admission between October 2017 and July 2018. Inclusion criteria were a modified Rankin scale of <3 at the time of discharge[7] and no symptoms of a- or dysphasia. Forty-two aSAH patients were approached, of whom 30 patients (71%) consented to participate and who completed the questionnaire. In advance, we had decided that the questionnaire should have an optimal performance in which all aSAH patients should have a total score of >60 points. If not, the questionnaire would have to be optimized and this testing step would have to be redone in a new group of aSAH patients.

Questionnaire in first-degree relatives of patients with stroke

Next, the family history questionnaire was tested in its ability to distinguish between aSAH on the one hand and ischaemic stroke and intracerebral haemorrhage on the other hand. Patients admitted with these three types of stroke in the UMCU between 2017 and 2019 were asked for permission to contact one of their children or siblings to complete a family history questionnaire on their case history. We excluded parents because the age of the stroke patients was often >60 years old, and therefore, their parents might have passed away. One hundred forty-three siblings or children were approached one to two years after the stroke of the index patient. Of these 143 first-degree relatives, 91 (response rate: 64%; 30 relatives of aSAH patients, 31 of ischaemic stroke, and 30 of intracerebral haemorrhage patients) completed the questionnaire. Demographic information collected included the first-degree relatives' age and type of kinship. The outcome of the questionnaires filled in by the relatives was

considered as positive for aSAH if it had a total score of >60, and this outcome was compared with the diagnosis of the index patient.

Statistical analysis

The sensitivity, specificity, positive predictive value, and negative predictive value of the questionnaire for the diagnosis aSAH in the index patient were calculated. In case of insufficient performance (as defined as a sensitivity <0.80 and a positive predictive value <0.20), the questionnaire would have to be adapted and re-evaluated. We also assessed the sensitivity, specificity, positive predictive value, and negative predictive value of the family history questionnaire in the subgroups of women and men and of siblings and children.

Ethics

Patients and first-degree relatives gave written informed consent before filling in the questionnaire. This study was approved by the Medical Ethics Committee of the UMCU the Netherlands.

Results

Pilot study in patients with aSAH

30 aSAH patients completed the questionnaire; mean age was 57 years (range 43 to 74 years), and the majority of participants were women (18 out of 30, 60%). In all patients, the total points in the questionnaire was >60 points (mean: 180 points, range 70-330; sensitivity 100% (95% CI: 88-100%)). The answers of all patients to the questionnaire are specified in Supplemental Table I.

Diagnostic accuracy study in first-degree relatives of stroke patients

91 first-degree relatives completed the family history questionnaire (30 relatives of aSAH patients, 31 of ischaemic stroke patients, and 30 of intracerebral haemorrhage patients). Characteristics are summarized in Table 2. The mean age of the relatives was 42 ± 14 years, 59 (65%) were women, 18 (20%) were siblings. One person with a first-degree relatives with an episode of aSAH had a total score of ≤60 points in the questionnaire (while the cut-off for a diagnosis of aSAH was set at a score >60 points), while four persons with a first-degree relatives with ischaemic stroke or intracerebral haemorrhage had a total score of >60 points in the questionnaire. The answers to the questionnaire of the five relatives with these deviating scores are specified in Supplemental Table

II. Based on these results, the sensitivity of this questionnaire was 97% (95% CI: 83-100%), its specificity 93% (95% CI: 84-98%), while its positive predictive value was 88% (95% CI: 74-95%), and its negative predictive value 98% (95% CI: 89-100%). Table 3 shows the sensitivity, specificity, positive predictive value, and negative predictive values overall and in the subgroups of men and women and of children, and siblings.

Table 2. Questionnaire answers given by first-degree relatives of stroke patients.

	aSAH n (%)	Ischaemic stroke n (%)	ICH n (%)
Number of first-degree relatives	30	31	30
Age of first-degree relative (mean, SD)	37 ± 14	44 ± 13	44 ± 15
Female first-degree relatives	19 (63)	21 (68)	20 (67)
What is your relationship with your relative?			
Brother	4 (13)	3 (10)	1 (3)
Sister	4 (13)	2 (7)	4 (13)
Son	7 (23)	7 (23)	9 (30)
Daughter	15 (50)	19 (61)	16 (53)
Which symptoms were caused by stroke in your family member?*			
Sudden (onset within 1 minute) severe headache	25 (83)	0	12 (40)
Loss of consciousness	12 (40)	5 (16)	10 (33)
Confusion	6 (20)	9 (29)	8 (27)
Weakness of the limbs or face	5 (17)	26 (84)	19 (63)
Speech problems (unable to speak or using the wrong words)	6 (20)	17 (55)	10 (33)
Unknown	1 (3)	4 (13)	3 (10)
How old was your family member at the time of the stroke?			
≤60 years old	16 (53)	9 (29)	7 (23)
>60 years old	14 (47)	22 (71)	23 (77)
Unknown	0	0	0
How was the stroke explained to your family member by the treating physician?*			
It occurred because a blood clot blocked a blood vessel in the brain.	0 (0)	26 (84)	1 (3)
It occurred because of a weakness in a blood vessel; the weakness can slowly develop into a balloon (bulge).	12 (40)	0	3 (10)
This is caused by a bulge in the wall of a blood vessel. It can be compared to a damaged bicycle tyre: there is a weak spot in the outer tyre, causing the inner tyre to bulge out.	15 (50)	0	1 (3)

Table 2. Continued

	aSAH n (%)	Ischaemic stroke n (%)	ICH n (%)
The stroke is caused by part of the brain not receiving oxygen and nutrients.	1 (3)	2 (7)	0
It occurred because a blood vessel in the brain ruptured.	2 (7)	0	11 (37)
The stroke is caused by blood accumulating in the brain tissue.	0	0	2 (7)
The stroke is caused by bleeding into the space around the brain. This space is filled with cerebrospinal fluid and blood vessels. The space can be compared to the crawl space of a house (a space where pipes run under the floor of the house).	2 (7)	0	2 (7)
The stroke is caused by bleeding into the subarachnoid space, the space between the brain membranes (the soft meninges and the spider web membrane).	12 (40)	0	1 (3)
Other	0	8 (26)	9 (30)
How was your family member treated?*			
Treatment of the vascular abnormality by brain surgery (clipping)	15 (50)	0	0
Treatment of the vascular abnormality via the blood vessels in the groin (coiling/stenting)	12 (40)	3 (10)	0
Removal of the clot through the blood vessels in the groin (endovascular thrombectomy)	1 (3)	15 (48)	0 (3)
A clot-busting medication (known as thrombolysis)	2 (7)	21 (68)	6 (20)
Other	3 (10)	1 (3)	15 (50)
Unknown	1 (3)	3 (10)	5 (17)

*aSAH: aneurysmal subarachnoid haemorrhage; ICH: intracerebral haemorrhage; SD: standard deviation. * Multiple answer options could be entered.*

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value of the family history questionnaire overall, and in the subgroups of men verses women and of siblings versus children.

	Performance of the questionnaire
Overall sensitivity	**97% (95% CI: 83-100%)**
In men only	100% (95% CI: 74-100%)
In women only	94% (95% CI: 73-100%)
In children only	100% (95% CI: 85-100%)
In siblings only	88% (95% CI: 47-100%)
Overall specificity	**93% (95% CI: 84-98%)**
In men only	95% (95% CI: 75-100%)
In women only	93% (95% CI: 80-98%)
In children only	94% (95% CI: 84-99%)
In siblings only	90% (95% CI: 56-100%)
Overall positive predictive value	**88% (95% CI: 74-95%)**
In men only	92% (95% CI: 64-99%)
In women only	85% (95% CI: 65-94%)
In children only	88% (95% CI: 71-96%)
In siblings only	88% (95% CI: 52-98%)
Overall negative predictive value	**98% (95% CI: 89-100%)**
In men only	100% (95% CI: 79-100%)
In women only	97% (95% CI: 85-100%)
In children only	100% (95% CI: 93-100%)
In siblings only	90% (95% CI: 59-98%)

Discussion

This study demonstrates that a questionnaire consisting of four multiple-choice questions can help first-degree relatives to discriminate an aSAH from other types of stroke in their affected relative. The questionnaire included questions on the symptoms, age at onset of the stroke, explanation of the stroke by the then treating physician and treatment given for the stroke. The questionnaire can be used by people of the general population, if necessary with help of their general practitioner, as a screening tool to evaluate if they have a positive family history of aSAH. Persons who appear to have a positive family history of aSAH can be referred for preventive screening for intracranial aneurysms. To identify stroke episodes from the questionnaire it can be filled in multiple times

depending on the number of family members who have had a stroke. In case of one first-degree relative with a stroke episode suggestive for an aSAH the advice will be screening twice during life around the age of 40 and 55[4] while in case of two or more first-degree relative the advice will be screening every 5 years during life.[2, 3]

We found one previous study on the predictive value of family history of aSAH provided by a relative.[5] This study assessed the family history in relatives of patients who died of either aSAH, ischaemic stroke, and intracerebral haemorrhage and reported a positive predictive value of a diagnosis of aSAH of only 70%.[5] In contrast to our study, the relative with stroke died and the time period between the episode of stroke and the assessment of the family history was between 3 and 5 years[5] which may explain the lower predictive value than the one found in our study in which the family history was assessed 1-2 years after the stroke episode. We found no previous studies on questionnaires testing for a positive family history of aSAH nor for stroke in general but did find studies assessing family history questionnaires that can identify relatives who died from coronary heart disease. Both these questionnaires had lower sensitivity values (89%[8] and 85%[9]) than the sensitivity established in our study which may be explained by the shorter time period between the episode of stroke and filling out the questionnaire by a relative in our study compared to the studies on coronary heart disease in which death of a relative occurred 10[8] or 20[9] years earlier.

Strengths of our study include that we developed the questionnaire with a multidisciplinary team of clinicians and consumers in a centre specialized in aSAH, and we performed a pilot study prior to the main study to test the performance of the questionnaire. Our study also has limitations that need to be considered. First, the response rate of first-degree relatives to fill in the questionnaire was 64% which can have resulted in sampling bias. The decision of a family member to participate in the study may be related to how involved a person was during their relative's stroke episode. As a result, these family members may better recall the stroke episode and complete the questionnaire better compared to non-responders. Consequently, the results in our study could be too optimistic. Second, performance of the family history questionnaire to identify persons with first-degree relatives who have had an aSAH was assessed with relatives who completed the family history questionnaire 1-2 years after a stroke episode. The performance of the questionnaire may decrease after a longer time period, because relatives recall of the episode may decrease. Third, we did not study the accuracy of this questionnaire in patients who died of aSAH,

ischaemic stroke, or intracerebral haemorrhage. As a result, we do not know the performance of the questionnaire in these relatives. Fourth, we did not ask parents to fill out the family history questionnaire because we expected that many parents might have already passed away. Consequently we do not know the performance of the questionnaire in parents. Finally, this questionnaire was developed in the Netherlands and before it can be used in other countries translated versions of the questionnaire should be validated first.

Conclusion

We have demonstrated the diagnostic accuracy of a short, simple family history questionnaire to help first-degree relatives to discriminate an aSAH from other types of stroke in their affected relative. This family history questionnaire is developed in the Netherlands. To enable wider implementation this questionnaire could be translated to other languages and after validation of these translated versions the questionnaire could be used in other countries as well.

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Supplemental Table I. Questionnaire answers given by aneurysmal subarachnoid haemorrhage patients in the pilot study.

	aSAH n (%)
Number of patients	30
Age (mean, SD)	57 ± 9
Which symptoms were caused by stroke?	
Sudden (onset within 1 minute) severe headache	21 (70)
Loss of consciousness	10 (33)
Confusion	6 (20)
Weakness of the limbs or face	3 (10)
Speech problems (unable to speak or using the wrong words)	2 (7)
Unknown	2 (7)
How old were you at the time of the stroke?	
≤60 years old	20 (67)
>60 years old	10 (33)
Unknown	0
How was the stroke explained to you by the treating physician?	
It occurred because a blood clot blocked a blood vessel in the brain.	0 (0)
It occurred because of a weakness in a blood vessel; the weakness can slowly develop into a balloon (bulge).	21 (70)
This is caused by a bulge in the wall of a blood vessel. It can be compared to a damaged bicycle tyre: there is a weak spot in the outer tyre, causing the inner tyre to bulge out.	5 (17)
The stroke is caused by part of the brain not receiving oxygen and nutrients.	0
It occurred because a blood vessel in the brain ruptured.	2 (7)
The stroke is caused by blood accumulating in the brain tissue.	0
The stroke is caused by bleeding into the space around the brain. This space is filled with cerebrospinal fluid and blood vessels. The space can be compared to the crawl space of a house (a space where pipes run under the floor of the house).	6 (20)
The stroke is caused by bleeding into the subarachnoid space, the space between the brain membranes (the soft meninges and the spider web membrane).	19 (63)
Other	1 (3)
How were you treated?	
Treatment of the vascular abnormality by brain surgery (clipping)	8 (27)
Treatment of the vascular abnormality via the blood vessels in the groin (coiling/stenting)	20 (67)

Supplemental Table I. Continued

	aSAH n (%)
Removal of the clot through the blood vessels in the groin (endovascular thrombectomy)	1 (3)
A clot-busting medication (known as thrombolysis)	0
Other	0
Unknown	2 (7)

aSAH: aneurysmal subarachnoid haemorrhage; SD: standard deviation.

Supplemental Table II. Answers (●) on the questionnaire of patients in whom the diagnosis based on the total score in the family history questionnaire (>60 points relative with aneurysmal subarachnoid haemorrhage (aSAH) and ≤60 points no relative with aSAH) did not match the diagnosis of the relative in the medical records.

	Relative 1	Relative 2	Relative 3	Relative 4	Relative 5
Diagnoses of relative	aSAH	ICH	ICH	ICH	ICH
Age of relative	54	48	52	64	26
Type of kinship	sister	daughter	son	sister	daughter
Total score in the questionnaire	35	77	67	65	92
Sudden (onset within 1 minute) severe headache	●	●			●
Loss of consciousness	●	●	●	●	
Confusion		●	●		●
Weakness of the limbs or face			●		●
Speech problems				●	●
≤60 years old	●				●
>60 years old		●	●	●	
It occurred because of a weakness in a blood vessel; the weakness can slowly develop into a balloon (bulge).			●		●
This is caused by a bulge in the wall of a blood vessel. It can be compared to a damaged bicycle tyre: there is a weak spot in the outer tyre, causing the inner tyre to bulge out.	●				
The stroke is caused by bleeding into the space around the brain. This space is filled with cerebrospinal fluid and blood vessels. The space can be compared to the crawl space of a house (a space where pipes run under the floor of the house).				●	
The stroke is caused by bleeding into the subarachnoid space, the space between the brain membranes (the soft meninges and the spider web membrane).		●			
Other		●			
Removal of the clot through the blood vessels in the groin (endovascular thrombectomy)	●				

Supplemental Table II. Continued

	Relative 1	Relative 2	Relative 3	Relative 4	Relative 5
A clot-busting medication (known as thrombolysis)	●				
Other		●	●		
Unknown				●	●

aSAH: aneurysmal subarachnoid haemorrhage; ICH: intracerebral haemorrhage.
●: answer given by first-degree relative.

Chapter 3

Higher risk of intracranial aneurysms and subarachnoid haemorrhage in siblings of families with intracranial aneurysms

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Abstract

Introduction: First-degree relatives of patients with familial aneurysmal subarachnoid hemorrhage (aSAH) have an increased risk of unruptured intracranial aneurysms (UIA) and aSAH. We assessed whether the type of kinship (parents, siblings, or children) of first-degree relatives of aSAH patients influences this risk.

Patients and methods: We used all available data from the prospectively collected database of families with familial aSAH consulting our outpatient clinic between 1994-2016. We constructed pedigrees for all families with ≥2 first-degree relatives with aSAH or UIA. The proband was defined as the first family member with aSAH who sought medical attention. We compared both the proportion of aSAH and UIA in proband's first-degree relatives by calculating risk ratios (RR) with children as the reference.

Results: We studied 154 families with 1,105 first-degree relatives of whom 146 had aSAH. UIAs were identified in 63 (19%) of the 326 screened relatives. Siblings had a higher risk of aSAH (RR: 1.62, 95% CI: 1.12-2.38) and parents a lower risk (RR: 0.44, 95% CI: 0.24-0.81) than children. Siblings also had a higher risk of UIA (RR: 2.28, 95% CI: 1.23-4.07, age adjusted RR: 2.04, 95% CI: 1.07-3.92) than children. Because of small numbers we were not able to calculate RR's for the risk of UIA in parents.

Discussion and conclusion: Siblings of patients with familial aSAH have a significant higher risk of both UIAs and aSAH and parents have a lower risk of aSAH than children. The type of kinship is a relevant factor to consider in the risk prediction and screening advice in families with familial aSAH.

Introduction

Intracranial aneurysms are present in approximately 3% of the adult population.[1] Rupture of an intracranial aneurysm results in aneurysmal subarachnoid hemorrhage (aSAH), which subtype of stroke carries a high morbidity and fatality.[2] A positive family history of aSAH is an important risk factor for aSAH. First-degree relatives of patients with aSAH have an increased risk of unruptured intracranial aneurysms (UIA) and aSAH.[3,4] In 25% of persons with two or more affected first-degree relatives with aSAH, UIA are detected during life.[5] Currently, a more tailored screening is not yet possible within relatives of patients with familial aSAH, as we are not able to further specify the risk of developing UIA. Consequently, we apply the same screenings program to all first-degree relatives.

The type of kinship may influence the risk of UIA and of aSAH, with siblings having the highest risk, but studies so far have conflicting results which might be caused by the small number of families with familial aSAH in these studies.[3, 6-12] Furthermore, none of the studies assessed the risk of both UIA and aSAH together.

The aim of this study was to assess in a large study population whether the type of kinship (parents, siblings, or children) of the first-degree relatives of aSAH patients influences the risk for UIA and aSAH.

Patients en methods

Study population

All individuals who are screened at the University Medical Center (UMC) Utrecht, the Netherlands for intracranial aneurysms because of familial aSAH are recorded in a prospectively collected database. A positive family history was defined as two or more first-degree relatives (parents, siblings, or children) with aSAH or UIA. All patients with aSAH who were admitted or individuals with an UIA who visited the outpatient clinic at the UMC Utrecht, were routinely asked for details about their family history. If aSAH occurred in their relatives, we suggested that they extend an invitation to their relatives to visit the outpatient clinic to be informed about screening for UIA. Individuals were also referred for screening by their general practitioner or neurologist. We retrieved all available information from the period April 1994 up to December 2016.

Data collection

Pedigrees were constructed based on the familial history of the probands or relatives who presented for screening in the UMC Utrecht. For the purpose of our study the proband was defined as the relative with aSAH who was first brought under medical attention. aSAH must have been identified in a hospital. We obtained information about age, sex, and familial and personal history of UIA or aSAH of all relatives from the database. All UIA in first-degree relatives were identified by CT, MRI or conventional angiogram in the UMC Utrecht. Screening was usually performed from the age of 18 years until the age of approximately 70 years, with the precise cut-off depending on their state of health. In case of a negative screen, people were advised to contact us after 5 years to repeat screening. Individuals were not actively invited for repeated screening. Performed screening reflects clinical practice and was not according to a study protocol. Consequently screening intervals shorter and longer than the advised 5 years could occur. Only relatives screened for UIA in the UMC Utrecht were included. We excluded patients with autosomal-dominant polycystic kidney disease. This study was approved by the institutional Research Ethics Board of the UMC Utrecht.

Statistical analysis

To assess the association between type of kinship of a probands' first-degree relative and risk of aSAH and UIA, we calculated proportions and relative risks (RR) with corresponding 95% confidence intervals (CI) with Poisson regression with children as the reference. For the analysis on the risk of UIA, we included only proband's relatives screened for UIA. This analysis was repeated with adjustment for age. Adjustment for age was not possible in our analysis to assess the association between type of kinship of a probands' first degree relative and risk of aSAH as data on age was missing in >70% of all first-degree relatives.

Results

We studied 154 families (Figure 1) with a total of 1,105 proband's first-degree relatives. The mean number of relatives per family was 7 (range 3-23). Of those 1,105 relatives, 146 had a aSAH and 326 relatives were screened for UIA, with UIA identified in 63 (19%) of them (Table 1). The mean duration of follow-up of screened relatives was 87 ± 80 months in siblings and 69 ± 76 months in children. The mean age at time of UIA diagnosis was 47 years in children and 52 years in siblings.

Figure 1. Flow chart of included patients.

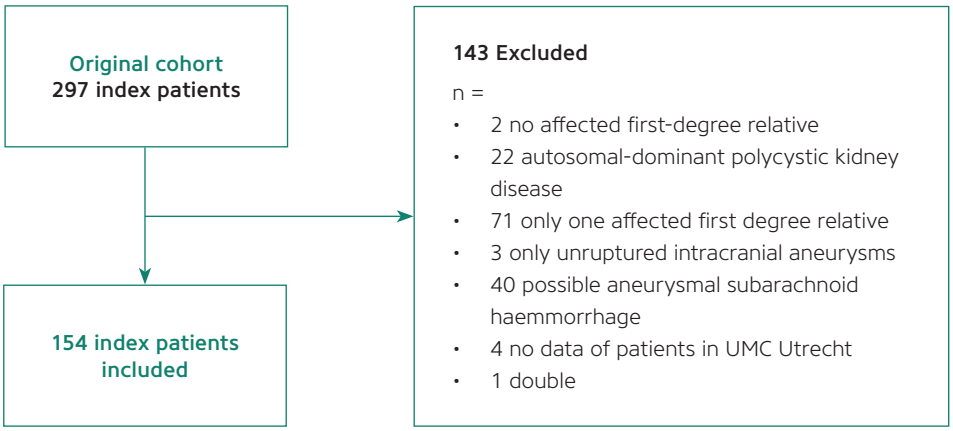

Table 1. Total number of first-degree relatives and number of screened relatives of 154 probands with definite aneurysmal subarachnoid hemorrhage.

	Total proband's relatives (n)	Screened family members (n, %)
Children	298	144 (48)
Siblings	499	181 (36)
Parents	308	1 (0)
Total	1105	326 (30)

Table 2. Number of aneurysmal subarachnoid hemorrhage (aSAH) in first-degree relatives of 154 index patients with aSAH.

	aSAH (n, %)	No aSAH (n, %)	Total proband's relatives	RR (95% CI)
Children	35 (12)	263 (78)	298	reference
Siblings	95 (19)	404 (81)	499	1.62 (1.12-2.38)
Parents	16 (5)	292 (95)	308	0.44 (0.24-0.81)
Total	146 (13)	959 (87)	1105	

aSAH: aneurysmal subarachnoid hemorrhage; RR: relative risks; CI: confidence interval.

Table 3. Number of unruptured intracranial aneurysms (UIA) in screened first-degree relatives of index patients with aneurysmal subarachnoid hemorrhage.

	UIA (n, %)	No UIA (n, %)	Screened family members (n, %)	RR (95% CI)	RR adjusted* (95% CI)
Children	16 (11)	128 (89)	144	reference	
Siblings	46 (25)	135 (75)	181	2.28 (1.23-4.07)	2.04 (1.07-3.92)
Parents	1 (100)	0	1	NR	
Total	63 (19)	263 (81)	326		

UIA; unruptured intracranial aneurysms; RR: relative risk; CI: confidence interval.
** adjusted for age.*

Siblings of aSAH patients had a 1.62 (95% CI: 1.12-2.38) times higher risk of aSAH than children. Parents had a 0.44 (95% CI: 0.24-0.81) times lower risk than children (Table 2).

Siblings of aSAH patients had a 2.28 (95% CI: 1.23-4.07) times higher risk of UIA than children. When adjusted for age the RR was 2.04 (95% CI: 1.07-3.92) (Table 3). The age at first screening was 40 years in children, 54 in parents and 55 in siblings. Because of the small numbers we were not able to compare the risk of UIA in parents.

Discussion

Siblings of patients with familial aSAH have a significant higher risk of both UIA and aSAH than children, and parents of patients with familial aSAH have a lower risk of aSAH compared to children. Analysis on the risk of UIA in parents compared to children was not possible because of the small number of parents screened for UIA.

Our results are in line with the findings of previous studies. In these studies the risk of UIA and aSAH in siblings was in general somewhat higher than in our study, but confidence intervals in these studies were wide. Our study is the largest study so far, and we found statistically significant results in contrast to some previous smaller studies. In a Dutch prospective screening study on UIA in 626 relatives of 160 aSAH patients, siblings had a four times higher risk of UIA than children.[3] Another Finnish screening study in 837 relatives of 91 families with two or more affected members also found that the most common

affected kinship were siblings.[6] Furthermore, a community-based study from the US on 608 first-degree relatives of 81 aSAH patients found a higher ratio of the total observed cases with aSAH to the total expected in siblings in comparison to children and parents.[7] One Swedish population-based case-control study on the risk of aSAH showed that type of kinship did not influence the risk on aSAH for individuals with one or more affected relatives. However, in this study a population-based registry was used, in which case verification was conducted less strict which may explain the differences in results.[12]

It is not clear why UIA and aSAH are more common in siblings as opposed to children and parents. UIA and aSAH are complex disorders which are caused by a complex interplay of multiple genetic and environmental risk factors.[13] A higher burden of UIA and aSAH in siblings may suggest that there is a greater sharing of environmental risk factors between siblings than between children and parents. For example, previous studies have already shown that shared environmental effects on cardiovascular risk factors, including hypertension which is an important risk factor for both UIA and aSAH,[14,15] are stronger for sibling pairs than for parent–offspring pairs.[16] Generally additive effects of multiple genetic risk factors contribute to a complex disorder which would lead to comparative risks independent of family relationship. As an alternative explanation for the higher risk in siblings, it may be suggested that non-additive genetic effects are also involved.

The strength of our study is the large number of families included and the standardized screening protocol in our center. There are also some limitations that need to be addressed. First of all, the children analyzed were overall younger than the parents and siblings consequently might not have developed an UIA or aSAH yet. However, we do not think this has influenced our results as when we adjusted for age in our analysis on UIA the established higher risk in siblings compared to children remained essentially the same. We were not able to correct for age in our analysis on aSAH, because these data were frequently missing. Yet, siblings had a an even higher risk on aSAH than parents, while parents were older and had more time to develop aSAH than siblings. Secondly, selection bias could have occurred. Probands or relatives of probands might not be well-informed about their own family history, which may result in missing relatives who have had aSAH. Additionally, not all relatives who qualified to participate in the familial screening program actually consented to undergo screening and some relatives performed screening in another hospital than the UMC Utrecht.

Conclusion

Our study shows that siblings have an increased risk of UIA and aSAH compared to children. The type of kinship is a relevant factor to consider in the risk prediction and screening advice in families with familial aSAH.

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Chapter 4

The NASH prediction score for intracranial aneurysms in persons with a family history of subarachnoid hemorrhage

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Stroke, in press

Abstract

Background and Purpose: Persons with a positive family history of aneurysmal subarachnoid hemorrhage (aSAH) are at increased risk of aSAH. Preventive screening for intracranial aneurysms (IAs) in these persons is cost-effective, but not very efficient. We aimed to develop and externally validate a model for predicting the probability of an IA at first screening in persons with a positive family history of aSAH.

Methods: For model development, we studied results from initial screening for IAs in 660 prospectively collected persons with ≥2 affected first-degree relatives screened at the University Medical Center Utrecht. For validation, we studied results from 258 prospectively collected persons screened in the University Hospital of Nantes. We assessed potential predictors of IA presence in multivariable logistic regression analysis. Predictive performance was assessed with the c-statistic and a calibration plot, and corrected for overfitting.

Results: IAs were present in 79 (12%) persons in the development cohort. Predictors were Number of affected relatives, Age, Smoking, and Hypertension (NASH). The NASH score had a c-statistic of 0.68 (95% CI 0.62-0.74) and showed good calibration in the development data. Predicted probabilities of an IA at first screening varied from 5% in persons aged 20-30 years with two affected relatives, without hypertension who never smoked, up to 36% in persons aged 60-70 years with ≥3 affected relatives, who have hypertension and smoke(d). In the external validation data IAs were present in 67 (26%) persons, the model had a c-statistic of 0.64 (95% CI 0.57-0.71) and slightly underestimated IAs risk.

Conclusions: For persons with ≥2 affected first-degree relatives the NASH score improves current predictions and provides risk estimates for an IA at first screening between 5 to 36% based on four easily retrievable predictors. With this information such persons can now make a better informed decision about whether or not to undergo preventive screening.

Introduction

Persons with a positive family history of aneurysmal subarachnoid hemorrhage (aSAH) have an increased risk of aSAH. According to the number of affected relatives, the lifetime risk of aSAH can be as high as 25%.[1] Early diagnosis of unruptured intracranial aneurysms (IAs) can influence clinical management and prognosis, as timely intervention might prevent aSAH. In persons with two or more affected first-degree relatives preventive screening for IAs is cost-effective when this is repeated every five to seven years between 20 and 70-80 years of age.[2, 3]

During screening in persons with a positive family history of aSAH an IA is found at initial screening in only 10%.[4, 5] Early risk stratification of persons with IAs may help to identify persons at high or low risk of IAs, and thereby improve efficiency of screening.

Several prognostic factors increase the likelihood of having an IA in the general population. These include older age, female sex, cigarette smoking, history of hypertension, history of aSAH, and positive family history of aSAH.[5-7] In persons with familial aSAH screened for IAs all these factors were also found to be associated with an increased risk of having an IA.[4, 8-11]

We aimed to develop and externally validate a prediction model for predicting the probability of an IA at first screening in persons with a positive family history of aSAH.

Methods

Study population

For the development of the model we used a prospectively collected cohort of 660 persons, with two or more first-degree relatives who had aSAH, or persons with one first-degree relative with aSAH and one or more first-degree relative with an unruptured IA, who were screened for IAs at the University Medical Center Utrecht (UMC Utrecht), the Netherlands. Screening for IAs at this center started in April, 1993 and we retrieved all available information from April 1993 up to April 2020. Persons who underwent screening for IA were referred for screening in different ways. First of all, all persons with aSAH who were admitted at the Neurology ward or persons with an IA who visited the outpatient clinic at the UMC Utrecht, were routinely asked for details about their family history.

If aSAH occurred in their relatives, we informed them that their relatives were welcome to visit the outpatient clinic to be informed about screening for IAs. Secondly, persons were also referred for screening by general practitioners or by neurologists or neurosurgeons from other hospitals. Thirdly, persons with aSAH and a positive family history of aSAH were advised to undergo screening for de novo IAs five years after having had their aSAH.

We included all persons with two or more first-degree relatives (parents, siblings, or children) who had had a definite or probable aSAH. We also included persons with one first-degree relative with aSAH and another first-degree relative with an unruptured IA proven by computed tomography angiography (CTA), magnetic resonance angiography (MRA), or conventional angiography. Definite aSAH was defined as an abrupt onset of severe headache or loss of consciousness with or without focal neurological signs, the presence of subarachnoid blood on head computed tomography (CT) compatible with a ruptured IA and an IA on CTA, MRA, or digital subtraction angiography (DSA). Probable aSAH was defined as an episode suspected to be aSAH in a person younger than 70 years, such as stroke with a second ictus within four weeks followed by death.[12] The standard screening modality was MRA, and in case of contraindications screening was performed by CTA instead. Screening was usually performed from the age of 18 years until the age of approximately 70 years, with the precise cut-off depending on the state of health of the screenees. Performed screening reflects clinical practice, and was not according to a study protocol. We excluded persons screened for IAs because of autosomal dominant polycystic kidney disease. The outcome of interest was the presence of an IA at first screening.

Model development

We obtained information about candidate predictors preselected based on the literature, which included age, sex, smoking, history of hypertension, history of previous aSAH, and number of affected family members with aSAH and/or IAs.[4-9] Smoking was defined as former or current smoking, and hypertension as a history of hypertension or use of antihypertensive drugs. The number of affected family members with aSAH or IAs was categorized into two affected relatives versus three or more affected relatives.

External validation

For external validation of the model we used the Understanding the Pathophysiology of Intracranial Aneurysm (ICAN) prospective familial IA cohort.

In this study the family history was taken in persons with an IA with at least one first-degree relative with an IA and additional family members identified were contacted for MRI screening.[13] From this cohort we selected those relatives with two or more first-degree relatives who had an aSAH or with one first-degree relative with aSAH and one or more first-degree relative(s) with an unruptured IA, who were screened for IAs at the University Hospital of Nantes, France between December 2012 and April 2019. In total, 265 persons were included for external validation.

Statistical analysis

The proportion of missing data within the development data was zero for most candidate predictors, except for smoking (33%) and hypertension (37%). Missing data were imputed with multiple imputation, creating 10 imputed datasets. In the validation cohort, data were missing on hypertension for seven cases (3%) and these seven cases were excluded from the analysis. Restricted cubic splines were used to assess whether continuous predictors (age) could be analyzed as linear term or needed transformation. Age showed a linear association with the outcome. We performed multivariable logistic regression analysis to study the association between candidate predictors and the presence of an IA at first screening. We studied this association in all ten imputed datasets. All potential predictors were considered for inclusion in the model regardless of their association in the univariable analysis, and the model was simplified by performing backward selection based on Akaike Information Criterion.[14] The interaction between age and number of affected family members was included in the model, as with older age more affected family members can expected to be found. Because prognostic models derived from multivariable regression analysis can be optimistic and thereby overestimate predictions when applied to a new cohort of persons,[15, 16] we internally validated the model with bootstrapping techniques. A shrinkage factor was estimated from the bootstrap procedure and regression coefficients were multiplied by this shrinkage factor to correct for overfitting. The regression coefficients in each imputation dataset were pooled with Rubin's rules.[17] We examined the performance of the final prediction model by determining its discrimination and calibration. Discrimination refers to what extent the model distinguishes between individuals with and without an IA and was assessed with the concordance (c) statistic, which was corrected for over optimism. We pooled the c statistics of each multiple imputed dataset with Rubin's rules. Calibration refers to the agreement between observed and predicted risk and was studied with a calibration plot. A sensitivity analysis including only persons with complete data for smoking and hypertension was performed.

To facilitate practical application of the model, we used the regression coefficients of the predictors in the final model, to allocate points to each predictor to generate a risk score. We translated the regression model into a score chart by dividing all regression coefficients by the smallest coefficient and subsequently rounded them to the nearest integer. The score chart is accompanied by a figure and table displaying estimated IA risks at first screening.

For external validation, we applied the original regression equation to the validation data from the French cohort and calculated the predicted probability of finding IAs at first screening for each person. We assessed model performance with the c-statistic and calibration plots. Results are reported in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement.[18] The NASH study was approved by the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands.

Results

The baseline characteristics of the persons of the development and validation cohorts are presented in Table 1. Among 660 persons included in the development cohort, 79 (12%) had an IA at first screening. Of these persons, 26 (33%) persons had multiple IAs (for all IA characteristics, see Supplemental Table I). In the validation cohort an IA was found in 67 of 258 persons (26%) of whom 21 (31%) persons had multiple IAs. Persons in the validation cohort were slightly older (mean age 40 ± 14 years vs 48 ± 15 years), were more often current or past smokers (54% versus 68%), and more often had three or more affected family members than persons in the development cohort (48% versus 66%). The frequencies for the number of affected relatives per person is shown in Supplemental Table II.

The results of the multivariable logistic regression analysis are presented in Table 2. The following predictors were identified: number of affected family members ≥3, older age, smoking, hypertension, and the interaction between age and number of affected family members ≥3 (NASH, i.e., **N**umber of affected relatives, **A**ge, **S**moking, **H**ypertension).

Table 1. Baseline characteristics of persons of the development and external validation cohort.

	Development cohort n=660 (%)	Validation cohort n=258 (%)
Female sex	392 (59)	156 (61)
Age at first screening (± SD)	40 ± 14	48 ± 15
Number of affected relatives		
2	343 (52)	87 (34)
≥3	318 (48)	171 (66)
Smoking*	325 (51)	176 (68)
Hypertension*	119 (29)	61 (24)
Previous aSAH	67 (11)	32 (12)

*aSAH: aneurysmal subarachnoid haemorrhage; SD: standard deviation. * Data on smoking is missing in 220/660 persons and on hypertension in 243/660 persons in the development cohort.*

Table 2. Multivariable ratios for risk of intracranial aneurysm from the final model after shrinkage.

	OR (95% CI)*
Age (per 10 years) †	1.17 (0.87-1.56)
Hypertension	1.15 (0.64-2.05)
Smoking	1.77 (0.97-3.23)
≥3 affected relatives †	0.52 (0.09-3.08)
Interaction age x ≥3 affected relatives ‡	1.34 (0.92-1.95)

** Adjusted for optimism with bootstrapping techniques; † OR for ≥3 affected relatives is 2.01 (1.21-3.33) when interaction between age and ≥3 affected relatives is not included in the model; ‡ The variance inflation factor for interaction age x ≥3 affected relatives is 14.*

After shrinkage, the model had a c-statistic of 0.68 (95% CI 0.62-0.74). The calibration plot showed good correspondence between predicted and observed risk (Figure 1), with a Brier score of 0.10, Brier scaled of 0.06 and calibration slope of 1.12. The original regression equation is provided in Supplemental Table III. In a sensitivity analysis including only persons with complete data for smoking and hypertension, the results of the multivariable logistic regression analysis with its corresponding c-statistic remained essentially the same (c-statistic: 0.69 (0.62-0.76)).

Figure 1. Calibration plot in the development and validation cohort.

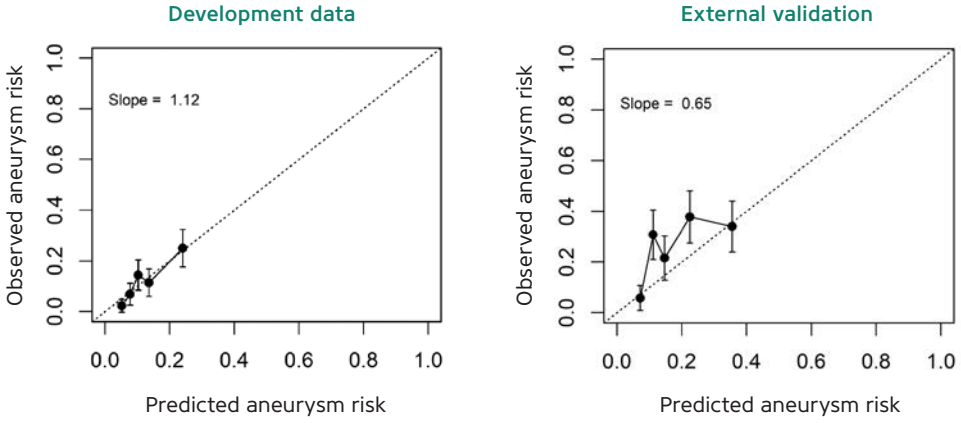

Table 3. Calculation of the NASH prediction score.

NASH score		
Age	**Two affected relatives**	**≥Three affected relatives**
20-29	0	0
30-39	1	3
40-49	2	6
50-59	3	9
60-69	4	12
Hypertension		
No	0	0
Yes	1	1
Smoking		
No	0	0
Yes*	4	4

** former or current smoker; An individual score is the sum of the points assigned to each of the predictors.*

Table 4. Predicted probability of an intracranial aneurysm at first screening based on the NASH prediction score.

Risk score	N	Predicted probability (95% CI)
0	98	5.0 (1.7-11.5)
1	39	5.8 (0.6-17.3)
2	35	6.6 (0.7-19.2)
3	58	8.1 (2.9-19)
4	88	8.8 (4.0-17.1)
5	40	9.8 (2.8-23.7)
6	65	11.7 (5.5-22.8)
7	78	13.4 (6.3-22.3)
8	31	14.7 (5.5-33.7)
9	27	17.0 (6.3-38.1)
10	38	19.6 (7.7-34)
11	16	23.4 (7.3-52.4)
12	10	25.5 (6.7-65.3)
13	20	28.8 (11.9-54.3)
≥14	18	36.3 (17.3-64.3)

Figure 2. Prediction chart with absolute probabilities (%) of an intracranial aneurysm at first screening.

* *former or current smoker.*

We translated regression coefficients into a score chart presented in Table 3. Our NASH score can be used in combination with Table 4 and the graphic display in Supplemental Figure I to obtain predicted probabilities for individual persons. Figure 2 shows a risk chart with estimated probabilities of finding an IA at first screening according to age, smoking status, hypertension status, and number of affected family members. The probability of finding an IA ranged from 5% in persons aged 20-30 years with two affected relatives, without hypertension who never smoked, up to 36% in persons aged 60-70 years with three or more affected relatives, who have hypertension, and smoke or have smoked in the past.

External validation

External validation of the NASH model showed a c-statistic of 0.64 (95% CI 0.57-0.71). The calibration plot shows that the likelihood of finding an IA increased along the range of predicted probabilities. The prediction score slightly underestimated the probability of finding an IA, in particular in the middle risk quintile. Overall, observed risks were within the range of expected risks with moderate calibration. The Brier score was 0.20, the Brier scaled -0.01 and the calibration slope 0.65.

Discussion

We developed the NASH score that predicts the risk of IAs at first screening in persons with a positive family history of aSAH. Based on the number of affected relatives, age, smoking, and hypertension, the risk of an IA can vary from 5% in persons aged 20-30 years with two affected relatives, who have no hypertension and never smoked, to 36% in persons aged 60-70 years with three or more affected relatives, who have hypertension, and smoke or have smoked in the past.

We found that sex and previous aSAH had no added value for the prediction of an IA at first screening when other risk factors were taken into account. The limited role of sex as a predictor of IAs in persons with a positive family history of aSAH may be caused by a less dominant role of sex in these persons compared to persons with a negative family history. IAs are more prevalent in woman than in men in the general population,[6] but in studies with familial patients the difference between women and men with IAs is less profound[19, 20] The lack of added value of a previous aSAH in the risk of finding an IA at screening may

be explained by the fact that aSAH patients with a positive family history of aSAH were advised repeated screening for de novo IAs five years after having their aSAH. Consequently, five years might have been too short to develop a de novo IA.

In our study we found an OR for hypertension of 1.15, with upper range of 2.05 of the 95% CI when other risk factors were taken into account. This was lower than expected as hypertension has been identified as a stronger risk factor for unruptured IAs with ORs ranging from 2.2 to 2.9 in previous studies.[21] Moreover, in a study on risk factors for unruptured IAs specifically in persons with a positive family history of aSAH a comparable OR for hypertension of 1.9 (95% CI 1.0-3.7) was found.[10] These studies used the same definition for hypertension which definition was also used in our current study. However, data on the precise risk of hypertension are inconsistent as in a more recent study on risk factors for unruptured IAs an association with hypertension could not be established.[22] More data on the role of hypertension in the development of IAs in both persons with and without a positive family history of aSAH are needed using a large prospective cohort and taking into account other risk factors associated with an increased risk of IA.

Although the observed and predicted IA risk corresponded accurate in the development data, the predicted IA risk was slightly underestimated in the external validation data. This is likely due to differences between the development and validation cohort in terms of included persons. In the validation cohort more persons had an IA (26%) than in the development cohort (12%). This may have resulted in an underestimated risk of finding an IA when the prediction model was applied in the validation cohort. In addition, selection of persons at high risk in the validation cohort may also have altered predictor-outcome associations. As a consequence, the ability of the model to distinguish between individuals with and without an IA may have decreased.

Strengths of our study include the prospectively collected data of the development and validation cohort. Moreover, the data used for development of the model encompassed the entire period that our center has offered screening to persons with a positive family history of aSAH and included a large sample size, which enabled us to study a broad range of prognostic factors. Another strength is the external validation using data from another center based in another country. Our study also has limitations that need to be considered. First, despite the prospective data collection, still some data on smoking and

hypertension were missing in our development cohort. However, multiple imputation was used to predict missing values with information from all potential predictors and outcome. Thus, we were able to include all persons in our model, which resulted in a prediction rule with high precision. Second, although the current model provides risk estimates for IAs development at first screening, we have no individualised data on risks of IAs at follow up screening as in this study we only included data at first screening and did not include data at follow-up screening. In general, the risk of finding a new aneurysm five years after a negative screen is around 5-7%,[4] but the influence of risk factors on this proportion is unknown. Thirdly, our study population may be selected. Hospitalized aSAH patients were routinely asked for details about their family history, and in case of positive family history they are informed that their relatives are eligible for screening for IAs. In patients who die soon after admission a positive family history may have been missed, and consequently less persons with relatives with a severe form of aSAH may have been included. Also, persons with a positive family history of aSAH who are from low socioeconomic status may not present for screening due to costs or because they do not fully understand the value of screening. These persons may have more risk factors for IA development and a higher risk of finding an IA at first screening. Fourth, the performance of the model to distinguishes between individuals with and without an IA was moderate. Moreover, the 95% CI's of the predicted probabilities of finding an IA at first screening on which the risk scores are based are relatively wide due to the relatively low number of persons included per different risk score. However, as our model was both internally and externally validated we do think these are reliable estimates that can be used in clinical practice. On top of that, this is the best data we currently have to predict the probability of an IA at first screening. Finally, we did not study persons screened with only one affected first-degree relative and therefore our results cannot be extrapolated to persons screened for IAs who have only one affected relative. For persons with only one affected relative as a group, screening twice, at age 40 and 55, is cost-effective,[23] but if and how risk factors affect this strategy is yet unknown.

Our risk prediction chart based on easily available patient characteristics predicts the probability of finding an IA at first screening in persons with two or more affected first-degree relatives. Based on the risk estimates from the prediction model, persons with a positive family history of aSAH can now make a better informed decision about whether or not to undergo preventive screening. Future studies should assess individualized risk prediction of

IAs during follow-up screening, and develop a decision model to define the optimal screening strategies in persons based on their individualized risk of IA development. Persons with a high risk of IAs can have intensified screening, while in persons with a lower risk screening may be reduced. Future studies should also assess individualized risk prediction of IAs for persons with only one affected first-degree relative. Further risk-prediction models on the risk of IAs may not only include patient-based and environmental factors, but also other type of factors including genetic factors. A genome-wide association studies meta-analysis recently identified several risk loci explaining over half of the heritability of IAs.[24]

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Supplemental Table I. Characteristics of intracranial aneurysms identified in the development and the validation cohort.

	Development cohort n=114 (%)	Validation cohort* n=99 (%)
Location		
Internal carotid artery	50 (44)	36 (36)
Middle cerebral artery	38 (33)	41 (41)
Anterior communicating artery	20 (18)	14 (14)
Posterior circulation	6 (5)	4 (4)
Size		
<2 mm	32 (28)	13 (13)
2-5 mm	60 (53)	65 (65)
>5mm	22 (19)	11 (11)

** data on location missing in 4 persons in validation cohort and data on size missing in 10 persons in validation cohort.*

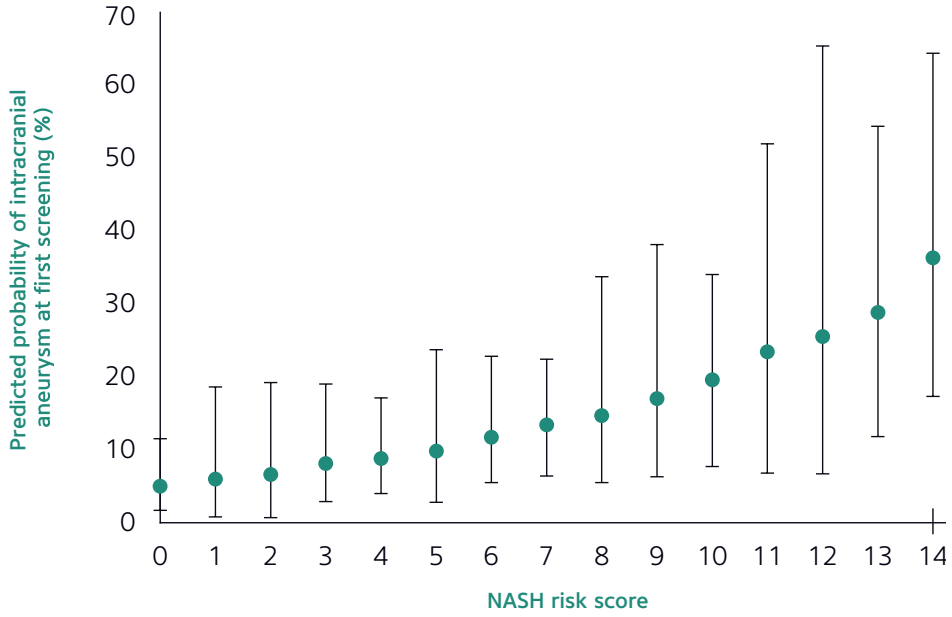
Supplemental Table II. Number of affected relatives in the development cohort and the validation cohort.

Number of affected relatives	Development cohort n=660 (%)	Validation cohort n=258 (%)
2	343 (52)	87 (34)
3	152 (23)	91 (35)
4	55 (8)	71 (28)
5	44 (7)	9 (4)
6	32 (5)	0
7	7 (1)	0
8	1 (0)	0
9	27 (4)	0

Supplemental Table III. Regression equations of multivariable models.

Regression equation model based on person characteristics
-3.324946 - 0.64194*≥3Affected relatives + 0.01532*Age + 0.13517*Hypertension + 0.56427* Smoking + 0.02924*Interaction Age and ≥3 Affected relatives

Supplemental Figure I. Predicted probability of an intracranial aneurysm at first screening based on the NASH prediction score*



* *graphic display of Table 4.*

Chapter 5

The SPA prediction score for presence of intracranial aneurysms during follow-up screening in persons with a positive family history of subarachnoid hemorrhage

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In preparation

Abstract

Background and purpose: First-degree family members of patients with aneurysmal subarachnoid hemorrhage (aSAH) are at increased risk of aSAH. The risk of an intracranial aneurysm (IA) at initial screening in these persons can be predicted, but knowledge on the risk at follow-up screening is lacking. We aimed to develop a model for predicting the probability of an IA during follow-up screening in persons with a positive family history of aSAH.

Methods: We studied results from follow-up screening for IAs in 499 prospectively collected persons with ≥2 affected first-degree relatives screened at the University Medical Center Utrecht and the University Hospital of Nantes. Cox regression analysis was performed to study the association between potential predictors and IA presence. A risk prediction model was derived, and predictive performance around 5 and 10 years after initial screening was assessed with the c-statistic and a calibration plot, corrected for overfitting.

Results: IAs were present in 52 persons during 5,050 person-years of follow-up. The mean observed 5-year risk of an IA after initial screening was 5.2% (95% confidence interval [CI]: 3.4-7.5) and the cumulative 10-year risk was 9.0% (95% CI: 6.7-11.9). Predictors were female Sex, Previous IA/aSAH, and older Age (SPA). The SPA score had a c-statistic at 5 years of 0.70 (95% CI: 0.61-0.78) and at 10 years of 0.71 (95% CI: 0.64-0.78), and showed good calibration. The 5-year risk after initial screening ranged from 2% to 12% and the 10-year risk from 4% to 28%, depending on the presence of the three predictors.

Conclusions: For persons with ≥2 affected first-degree relatives the SPA score provides risk estimates for IAs found around 5 and 10 years after initial screening based on three easily retrievable predictors.

Introduction

First-degree family members of patients with aneurysmal subarachnoid hemorrhage (aSAH) are at increased risk of aSAH with a lifetime risk which can be as high as 25%.[1] Preventive screening for unruptured intracranial aneurysms (IAs) may therefore be considered in these family members. In persons with two or more affected first-degree relatives preventive screening for IAs is cost-effective when repeated every five to seven years between 20 and 70-80 years of age.[2, 3] Timely intervention of IAs found during screening can prevent aSAH.

During screening in persons with a positive family history of aSAH an IA is found at initial screening in 10% and during follow-up screening in 5%.[4, 5] Prediction of the risk of an IA may help identify persons at high or low risk of IAs, thereby improving the efficiency of screening. Recently, the NASH prediction score (NASH, i.e., Number of affected relatives, Age, Smoking, Hypertension) was developed to predict the risk of an IA at initial screening in persons with a positive family history of aSAH.[6] In the development of this score candidate predictors increasing the likelihood of having an IA, being age, sex, smoking, history of hypertension, history of previous aSAH, and number of affected family members with aSAH and/or IAs were analyzed.[6] We do not yet know whether these same predictors can also be used to predict the probability of an IA during follow-up screening or whether (a combination of) other predictors play a role.

We aimed to develop a prediction model for predicting the probability of an IA during follow-up screening in persons with two or more affected first-degree relatives.

Methods

Study population

For the development of the model we used a cohort of persons with a positive family history of aSAH, defined as two or more first-degree relatives who had an aSAH or one first-degree relative with an aSAH and one or more first-degree relative(s) with an unruptured IA, who were screened for IAs in two hospitals: University Medical Center Utrecht (UMCU; Utrecht, The Netherlands) and Centre Hospitalier Universitaire de Nantes (Nantes, France). Both centers have a prospectively collected database with detailed information on consecutive screened patients between April 1993 and April 2018 (Dutch database)

and between December 2012 and April 2017 (French database). The standard screening modality was magnetic resonance angiography (MRA) and in the case of contraindications screening was performed by computed tomography angiography (CTA) instead. Screening was usually performed from the age of 18 years until the age of approximately 70 years, with the precise cut-off depending on the state of health of the screenees. Performed screening reflects clinical practice and was not according to a study protocol. In the Dutch center, persons who underwent screening for IAs were referred for screening in different ways. First of all, all persons with aSAH who were admitted at the Neurology ward or persons with an IA who visited the outpatient clinic at the UMCU, were routinely asked for details about their family history. If aSAH occurred in their relatives, the patients were informed that their relatives were welcome to visit the outpatient clinic to be informed about screening for IA. Secondly, persons were also referred for screening by general practitioners or by neurologists or neurosurgeons from other hospitals. Thirdly, persons with aSAH and a positive family history of aSAH were advised to undergo screening for de novo IAs five years after having had their aSAH. For the French screenees, data from the Understanding the Pathophysiology of Intracranial Aneurysm (ICAN) project were used.[7] In this study the family history was taken in persons with an IA with at least one first-degree relative with an IA and additional family members identified were contacted for MRI screening. From this cohort, those relatives fulfilling our criteria for a positive family history of aSAH and who were screened for IAs were selected. Our study was approved by the Medical Ethics Committee of the UMCU, the Netherlands. The ICAN project is an observational clinical research study approved by the Institutional Review Boards (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, Commission Nationale de l'Informatique et des Libertés) and Ethics Committees of Nantes (GNEDS).

Definitions

Affected first-degree relatives (parents, siblings, or children) could have had a definite or probable aSAH. Definite aSAH was defined as an abrupt onset of severe headache or loss of consciousness with or without focal neurological signs, the presence of subarachnoid blood on head computed tomography (CT) compatible with a ruptured IA and an IA on CTA, MRA, or digital subtraction angiography (DSA). Probable aSAH was defined as an episode suspected to be aSAH in a person younger than 70 years, such as stroke with a second ictus within four weeks followed by death.[8] In affected first-degree relative with an unruptured IA, the IA had to be proven by CTA, MRA, or conventional angiography. IAs that

were visible in retrospect on previous imaging were included at the time of this previous imaging. We included patients who had at least one follow-up screening performed minimal three years after the initial screening. We excluded persons screened for IAs because of autosomal dominant polycystic kidney disease. The outcome of interest was the presence of an IA during follow-up screening.

Model development

We selected candidate predictors preselected based on literature including age, sex, smoking (former or current smoking), history of hypertension (defined as history of hypertension or use of antihypertensive drugs), history of previous IA/aSAH, and number of affected family members with aSAH and/or IAs.[4, 5, 9-12] The number of affected family members with aSAH or IAs was categorized into two affected relatives versus three or more affected relatives. Information on candidate predictors was collected at baseline (i.e. during first screening) in each cohort. A history of a previous IA/aSAH was defined as a aSAH before initial screening or an IA found at initial screening.

Statistical analysis

Data were missing for smoking (33%) and hypertension (39%) in the Dutch cohort, while the proportion of missing data was zero for the remaining candidate predictors. There were no missing data in the French cohort. Missing data were imputed in the Dutch cohort with multiple imputation, creating ten imputed datasets. Restricted cubic splines were used to assess whether the continuous predictor age could be analyzed as linear term or needed transformation. Age showed a linear association with the outcome. Predictors for IAs during screening were studied with Cox regression analysis in all ten imputed datasets. The full model containing all potential predictors was simplified with backward selection based on Akaike Information Criterion.[13] The proportional hazards assumption was checked by visually inspecting the log minus log plot for each predictor. The model was internally validated with bootstrapping techniques because prognostic models derived from multivariable regression analysis can be too optimistic and overestimate predictions when applied to a new cohort. A shrinkage factor was estimated from the bootstrap procedure, and regression coefficients were shrunk to correct for overfitting. Discrimination of the model was examined with the concordance (c) statistic, which was corrected for overoptimism by bootstrapping. Discrimination refers to the ability of the model to distinguish between persons with and without an IA. The c statistics of each multiply imputed data set were pooled with Rubin's rules.[14] Calibration of the model, which refers to the correspondence between the observed and

the predicted risk, was visually inspected with 5-year and 10-year calibration plots. The regression coefficients in each imputation dataset were pooled with Rubin's rules.[14] To facilitate the practical application of the model we used the β coefficients of the predictors in the final model to allocate points to each predictor to generate a risk score. The score chart is accompanied by a figure that provides the 5-year absolute risk and the 10-year cumulative absolute risks of IA development.

Results

The baseline characteristics of the included persons are presented in Table 1. Among 499 included persons, an IA was found in 52 persons (10%) during 5,050 person-years of follow-up. The mean observed 5-year risk of an IA after initial screening was 5.2% (95% CI: 3.4-7.5) and the mean observed cumulative 10-year risk was 9.0% (95% CI: 6.7-11.9).

The results of the multivariable and univariable Cox regression analysis are presented in Table 2, and Supplemental Table I. The following predictors of an IA were identified: female sex, history of previous IA/aSAH, and older age (SPA, i.e., **S**ex, **P**revious IA/aSAH, **A**ge). We combined all identified predictors in one model. After shrinkage, the model had a c-statistic of 0.70 (95% CI 0.61-0.78) at 5 year after initial screening and a c-statistic of 0.71 (95% CI 0.64-0.78) at 10 year after initial screening. The calibration plot showed good correspondence between predicted and observed risk (Figure 1) with a Brier score of 0.05 and a calibration slope of 1.31 at 5 years after initial screening and a Brier score of 0.08 and a calibration slope of 1.13 at 10 years after initial screening. The original regression equation and baseline survival function are provided in Supplemental Table II.
We translated regression coefficients into a score chart presented in Table 3. Our SPA score chart can be used in combination with Supplemental Figure I to obtain predicted probabilities of finding an IA for individual persons around 5 and 10 years after initial screening. Figure 2 shows a risk chart with estimated probabilities of finding an IA around 5 and 10 years after initial screening according to sex, previous IA/aSAH, and age. The probability of finding an IA ranged from 2% in men aged 20-30 years without a previous IA/aSAH at 5 years after initial screening up to a cumulative risk of 28% in women aged 60-70 years with a previous IA/aSAH at 10 years after initial screening.

Table 1. Baseline characteristics of screened first-degree relatives.

	Screened first-degree relatives n=499 (%)
Population	
French	103 (21)
Dutch	396 (79)
Number of screenings after initial screening (median, range)	2 (1-8)
Female sex	312 (63)
Age at initial screening (± SD)	40 ± 13
Number of affected relatives	
2	225 (45)
≥3	274 (55)
Smoking*	
Current	129 (35)
Past	77 (21)
Hypertension*	99 (29)
Previous IA/aSAH	157 (32)

SD: standard deviation; IA: intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage.
** data on smoking is missing in 131/499 persons and on hypertension in 153/499 persons.*

Table 2. Multivariable hazard ratios for risk of intracranial aneurysm from the final model after shrinkage.

	Multivariable hazard ratio* (95% CI)
Female sex	1.77 (0.94-3.32)
Age (per 10 years)	1.32 (1.05-1.59)
Previous IA/aSAH	1.57 (0.87-2.82)

IA: intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage.
** adjusted for optimism with bootstrapping techniques.*

Figure 1. Calibration plot A) around 5 years after initial screening B) around 10 years after initial screening.

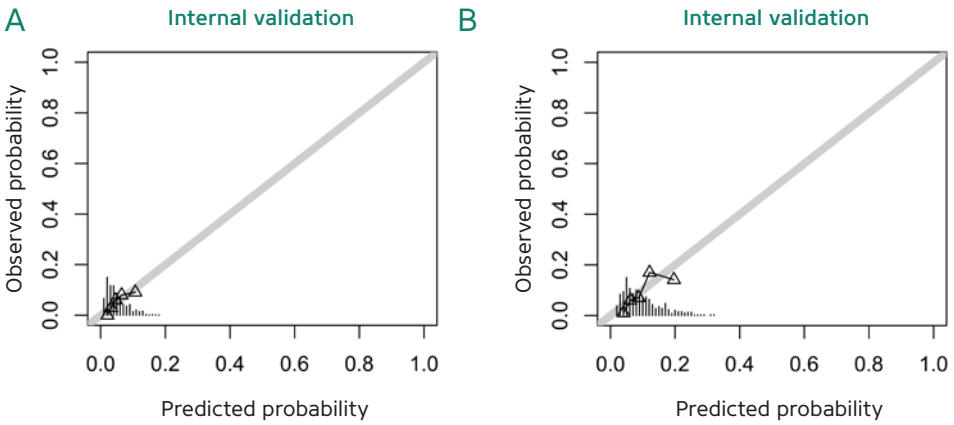

Figure 2. Prediction chart with absolute probabilities (%) of an intracranial aneurysm during follow-up screening. A) around 5 years after initial screening B) around 10 years after initial screening.

A

	Age	No previous aneurysm	Previous aneurysm
Men	20-29	2	3
	30-39	3	3
	40-49	3	5
	50-59	5	6
	60-69	6	9
Women	20-29	3	5
	30-39	5	6
	40-49	6	9
	50-59	9	12
	60-69	12	12

B

	Age	No previous aneurysm	Previous aneurysm
Men	20-29	4	6
	30-39	6	8
	40-49	8	11
	50-59	11	15
	60-69	15	20
Women	20-29	8	11
	30-39	11	15
	40-49	15	20
	50-59	20	28
	60-69	28	28

0%
28%

Table 3. SPA score for intracranial aneurysm during follow-up screening in persons with a positive family history derived from the multivariable Cox regression model.

SPA score	
Sex	
Women	0
Men	2
Previous IA/aSAH	
No	0
Yes	1
Age	
20-29	0
30-39	1
40-49	2
50-59	3
60-69	4

IA: intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage. An individual score is the sum of the points assigned to each of the predictors.

Discussion

We developed the SPA score that predicts the individualized risk of an IA at follow-up screening in persons with a positive family history of aSAH. Based on the predictors Sex, history of a Previous IA/aSAH and Age (SPA) the risk of finding an IA ranged from 2% in men aged 20-30 years without a previous IA/aSAH at 5 years after initial screening up to a cumulative risk of 28% in women aged 60-70 years with a previous IA/aSAH at 10 years after initial screening.

At initial screening the NASH prediction model can predict the individualized risk of an IA in persons with a positive family history of aSAH using the predictor's number of affected relatives, age, smoking, and hypertension.[6] We found that the predictors number of affected relatives, smoking and hypertension had no added value for the prediction of an IA at follow-up screening while the predictors previous IA/aSAH and sex were important predictors at follow-up screening instead. A possible explanation for sex being an important predictor of IAs during follow-up screening and not for IAs at initial screening might be that at follow-up persons are of older age compared to the moment when initial screening was performed. A previous meta-analysis with 68 studies showed that in study populations with a mean age of 50 years or younger the prevalence ratio of women vs men equals 1.1, while in persons older than 50 this sex difference becomes more prominent, with a prevalence ratio of women versus men of 2.2.[10] Factors explaining the sex difference in risk of IA development after the age of 50 may be female-specific hormonal and reproductive factors. A previous systematic literature review on female risk factors for a aSAH found an increased risk of aSAH for postmenopausal versus premenopausal women although the pathophysiology of this effect and its influence on the difference in incidence of aSAH between the sexes remains unclear.[15] In addition, female-specific genetic factors such as genetic factors of the X-chromosome or sex-specific effects of yet unknown clinical factors which occur more often or have a stronger effect in women than in men may explain the difference. At initial screening, a previous aSAH was not identified as a predictor, which might be caused by the fact that initial screening was advised five years after patients have had their aSAH which time period may be too short of developing a de novo IA. In the SPA prediction model, we included not only persons who had an aSAH before but also persons with an IA found at first screening (32%) and these persons had a longer follow-up period (10 years) during which a de novo IA could develop.

Our study found no added value of smoking and hypertension to predict an IA during follow-up when other risk factors were taken into account, while it was found as a predictor at initial screening. Hypertension and smoking have previously been identified as a strong risk factor for IAs with ORs for hypertension of 2.2 and smoking of 1.7.[16] In persons with a positive family history of aSAH an OR for smoking of 1.5 (95% CI 0.7-3.2) and hypertension of 1.9 (95% CI 1.0-3.7) have been described.[17] In our study we only had data of smoking and hypertension at baseline and not during follow-up. It could be that after initial screening persons become more aware about risk factors for IA development and more often quit smoking and have better blood pressure control. As a result, they have a lower risk of IAs during follow-up screening compared to initial screening. In a study with persons with a positive family history of aSAH an association with current smoking was found while not for former smoking.[18] More data on the risk factors smoking and hypertension during follow-up screening in persons with a positive family history of aSAH are needed.

An important strength of our study is the large sample size which enabled us to study a broad range of prognostic factors. Our study also has limitations that need to be considered. First, despite the prospective data collection still some data on smoking and hypertension were missing in the Dutch cohort. However, we used multiple imputation to predict missing values in this cohort with information from all potential predictors and outcomes. As a result, we were able to include all Dutch persons in our model, which resulted in a prediction rule with high precision. Secondly, we were not able to externally validate our model. We used data from two different centers from two different countries to develop the prediction model and the number of events were too low to develop the model in data from one center and externally validate this model in data from the other center. However, we did internally validate our data with bootstrapping techniques which showed good correspondence between observed and predicted risks. Thirdly, although calibration of our model was good at 5 years after initial screening, IA risk was slightly underestimated at 10 years, especially in the higher risk quintile. However, this is the best data we currently have to predict the probability of an IA at follow-up screening. Finally, we did not include persons screened with only one affected first-degree relative. Consequently, our results cannot be extrapolated to persons screened for IAs who have only one affected relative. In these persons, screening twice, at age 40 and 55, is cost-effective[19] but if and how risk factors affect this strategy is yet unknown.

Our study provides a prediction score designed to predict absolute probabilities of finding an IA during follow-up screening in persons with two or more affected first-degree relatives around 5 and 10 years after initial screening based on three easily available patient characteristics: female sex, history of previous IA/aSAH and age. This score gives insight into which persons with a positive family history of aSAH have a low or high risk of IAs during follow-up screening, which can help persons make a better-informed decision about whether or not to undergo follow-up screening. This score could also be used to study the most cost-effective time intervals for follow-up screening for persons with different SPA scores. Persons with a high risk of IAs could have intensified screening, while in persons with a lower risk screening may be reduced.

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Supplemental Table I. Original regression equation and baseline survival.

Linear predictor (LP)
0.03147*age + 0.56994*women + 0.45023*history of previous IA/aSAH
Baseline survival
t (5-year after initial screening): 0.9536993 t (10-year after initial screening): 0.8868476
Mean linear predictor
1.770503

IA: intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage.

The absolute risk of an IA during follow-up (%) is calculated as:
1-S(t) $^{\exp(\text{LP-mean LP})}$
The beta coefficients of the final Cox regression model are used to calculate the linear predictor (LP), as described in the table. The latter is corrected for the averages of the patients risk factors (mean LP). S(t) is the baseline at t=5, and t=10.

As an example how to use this formula: consider a 45-year-old women without a previous IA screened 5 years after initial screening.

In this instance the LP is:
*0.03147*45 (for age 45) + 0.56994 (for being women) + 0 (no previous IA) = 1.98609*
LP-mean LP = 1.98609 - 1.770503= 0.215616
1 – 0. 9536993exp(0.215587) = 0.05711803
She will have a risk of an IA at 5 years after initial screening of 6%.

Supplemental Table II. Univariable hazard ratios for risk of an intracranial aneurysm at follow-up screening.

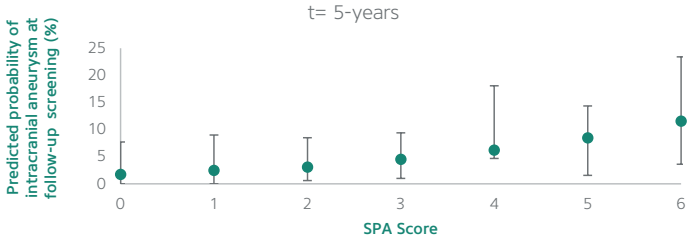
	Univariable hazard ratio (95% CI)
Female sex	2.09 (1.12-3.93)
Age (per 10 years)	1.48 (1.23-1.73)
≥3 affected first-degree relatives	1.53 (0.86-2.71)
Smoking	0.97 (0.54-1.72)
Hypertension	1.35 (0.70-2.61)
Previous IA/aSAH	2.49 (1.44-4.30)

IA: intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage.

Supplemental Figure I. Predicted probability of an intracranial aneurysm at follow-up screening based on the SPA prediction score A) around 5 years after initial screening B) around 10 years after initial screening.

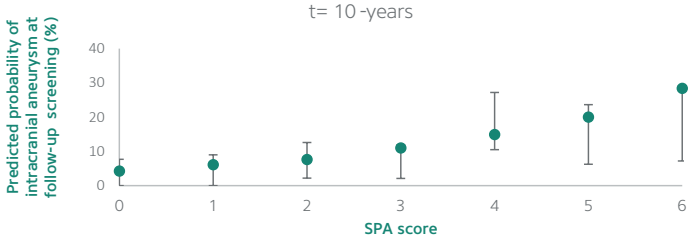
A

Risk score	N	Predicted probability (95% CI)
0	46	1.7 (0-7.7)
1	39	2.5 (0-9.0)
2	100	3.1 (0.6-8,5)
3	106	4.5 (1.0-9.4)
4	90	6.2 (4.7-18.1)
5	68	8.5 (1.6-14.4)
≥6	50	12.4 (4.5-24.3)



B

Risk score	N	Predicted probability (95% CI)
0	46	4.3 (0-7.7)
1	39	6.1 (0-9.0)
2	100	7.6 (2.2-12.6)
3	106	11.0 (2.1-11.9)
4	90	14.9 (10.5-27.2)
5	68	20.0 (6.2-23.6)
≥6	50	28,4 (7.2-29.1)



Part II

Risk of aneurysmal rupture according to positive family history and female sex

Chapter 6

Difference in rupture risk between familial and sporadic intracranial aneurysms: an individual patient data meta-analysis

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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 of aneurysmal subarachnoid hemorrhage 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, thus both including and excluding siblings as first-degree relatives.

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)" (Supplemental Figure I). 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 of 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 of 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 of 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 studies both including and excluding siblings in the definition of first-degree relatives. A sensitivity analysis was performed comparing cohorts from European and Japanese populations.

Results

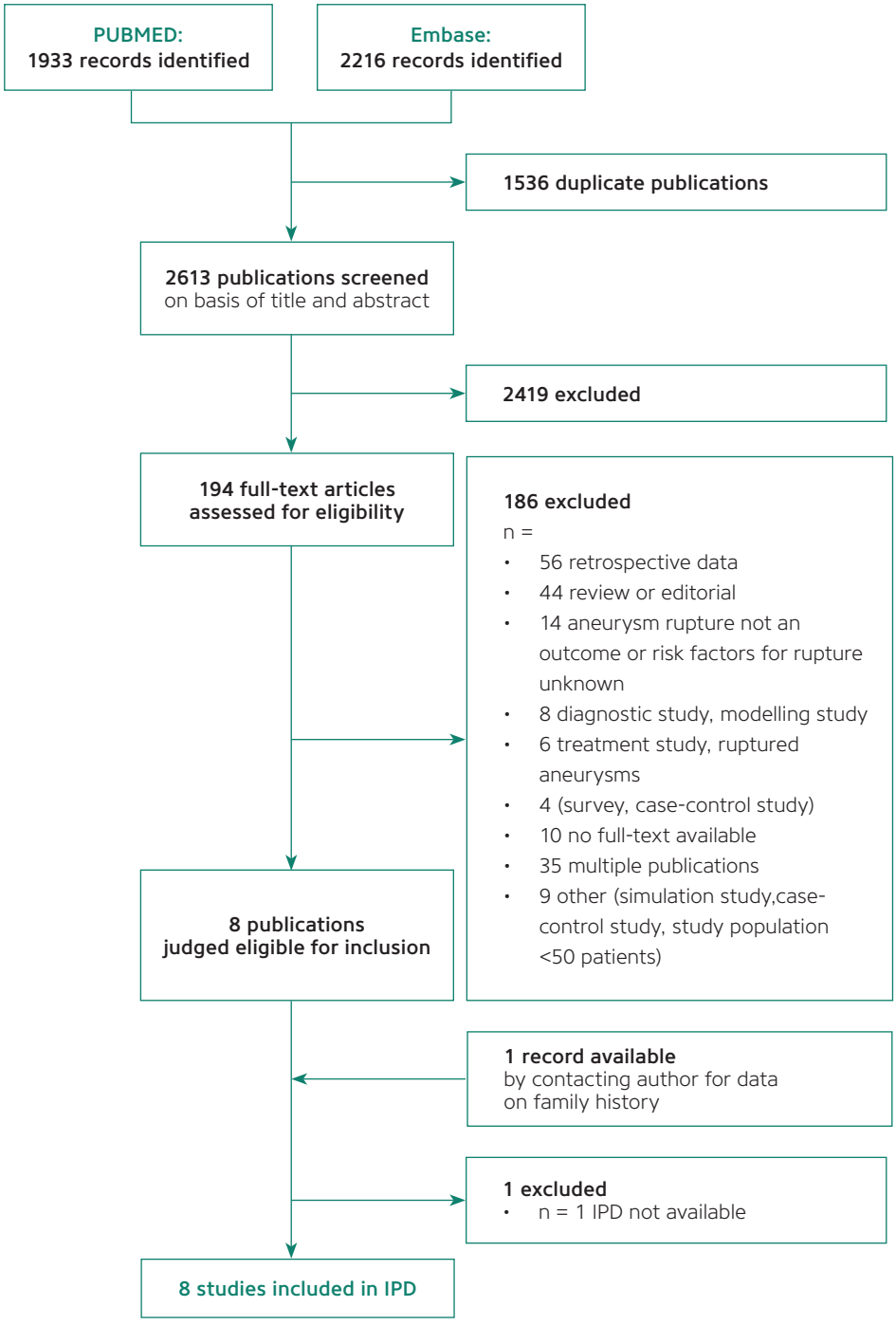
We found 8 studies that fulfilled the inclusion criteria[3, 7-11, 13, 14], and 7 research groups provided us with their individual patient data.[3, 7-11, 13] All studies included patients with newly diagnosed UIA visiting one of the study centers. We also found one additional cohort study on UIA, which did not report on family in the Pubmed search,[15] but authors of this study provided non-published data on family history of 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

Table 1. Characteristics of included studies.

	Lindgren et al*	Mensing et al[3]	Juvela et al[7]	Wermer et al[8]	Molenberg et al[9]	Sonobe et al[10]	Morita et al[11]	Murayama at al[13]
Country	FIN	NL	FIN	NL	NL	JPN	JPN	JPN
Recruitment period	1977-2016	1994-2016	1956-1978	2002-2004	1998-2017	2000-2004	2001-2004	2003-2012
Number of patients	1181	474	93	89	122	349	5702	1561
Number of UIA	1658	633	116	119	159	419	6675	1942
First-degree relatives including siblings	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Patients with positive family history	248	62	9	26	33	31	327	184
Mean age (range; years)	56 (16-85)	56 (22-81)	42 (15-61)	50 (20-69)	55 (33-77)	62 (23-89)	63 (23-98)	66 (25-100)
Median follow-up (range; years)	0.5 (0-23)	0.8 (0-21)	27.2 (1-52)	2.2 (1-15)	1 (0-2)	3.2 (0-7)	1.0 (0-9)	3.2 (0-11)
Number of aSAH during follow-up	14	10	22	1	0	6	111	56

*JPN: Japan; NL: the Netherlands; FIN: Finland; UIA: unruptured intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage. * unpublished data.*

Figure 1. Prisma flow diagram.



in all separate cohorts in Supplemental Table I. Quality assessment of included cohort studies by QUIPS tool is shown in Supplemental Table II.

The 6 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

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* (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)	1143 (50)	0.138
Previous aSAH*	34 (9)	242 (13)	276 (12)	0.018
Population*				
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*				
<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	83 (21)	413 (22)	496 (22)	0.065
Middle cerebral artery	189 (47)	783 (41)	972 (42)	
Anterior circulation & 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

SD: standard deviation; aSAH: aneurysmal subarachnoid hemorrhage.
∗ statistically significant difference.

years, 399 patients (17%) had a positive family history of 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

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*	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; SD: standard deviation.
** In case of multiple aneurysms, the largest aneurysm was used for analysis.*

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 cohorts both including and excluding siblings in the definition of first-degree relatives are provided in Supplemental Table III.

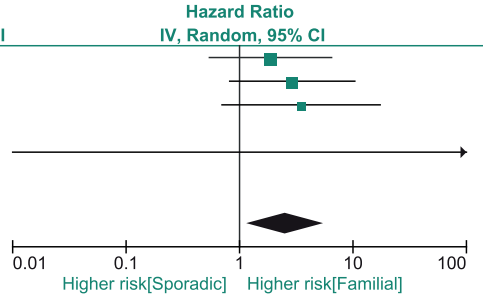
In 53 patients UIA rupture occurred. Of these 53 patients 11 patients had multiple UIA and in 51 of 53 patients (96%) the largest aneurysm ruptured. Rupture of the largest aneurysm occurred in 10 patients with familial UIA (rupture rate 0.89%/person-year; 95% CI: 0.45-1.59) and in 41 patients with sporadic 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 cohorts both including and excluding siblings in the definition of first-degree relatives are provided in Supplemental Table IV.

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 comparing European and Japanese populations resulted in similar results (Supplemental Figure II). The unadjusted HR of patients with familial aneurysms compared to those with sporadic aneurysms in cohorts both including and excluding siblings in the definition of first-degree relatives was 1.02 (95% CI: 0.62–1.67) and 1.44 (95% CI: 0.86–2.40, I^2=0%; Supplemental Figure III, IV and V) after adjustment for the PHASES score and smoking.

Figure 2. Hazard ratio 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.

			Familial UIA	Sporadic UIA		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI
Juvela	0.628	0.633	9	84	39.2%	1.87 [0.54, 6.48]
Lindgren	1.07	0.648	248	933	37.4%	2.92 [0.82, 10.38]
Mensing	1.249	0.819	62	412	23.4%	3.49 [0.70, 17.36]
Molenberg	0	0	33	89		Not estimable
SUAVE	-13.035	930.459	31	318	0.0%	0.00 [0.00, Not estimable]
Wermer	0	0	16	62		Not estimable
Total (95% CI)			**399**	**1898**	**100.0%**	**2.56 [1.18, 5.56]**

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 3 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)

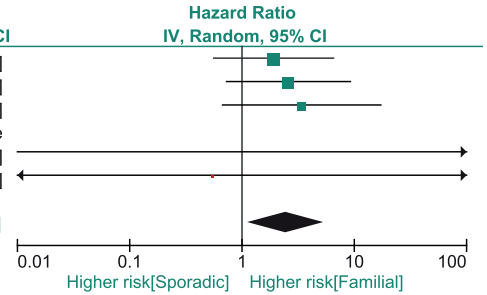


In the study from Wermer et al 1 aneurysm ruptured, in a patient with multiple aneurysms. The ruptured aneurysm was the smallest aneurysm and consequently this rupture was not included in the analysis per patient.

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.

			Familial UIA	Sporadic UIA		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI
Juvela	0.648	0.627	10	106	39.8%	1.91 [0.56, 6.53]
Lindgren	0.953	0.648	381	1277	37.3%	2.59 [0.73, 9.24]
Mensing	1.224	0.828	91	542	22.8%	3.40 [0.67, 17.23]
Molenberg	0	0	38	121		Not estimable
SUAVE	-13.082	904.819	41	378	0.0%	0.00 [0.00, Not estimable]
Wermer	-0.61	11.662	20	84	0.1%	0.54 [0.00, 4589789446.32]
Total (95% CI)			**581**	**2508**	**100.0%**	**2.44 [1.12, 5.30]**

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)



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 in cohorts both including and excluding siblings in the definition of first-degree relatives. 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 of 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. Fifthly, 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. In cohorts both including and excluding siblings in the definition of first-degree relatives 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.

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Supplemental Table I. Baseline characteristics of all separate cohorts.

	Mensing et al[3]		Juvela et al[7]		Lindgren et al*		Wermer et al[8]	
	Familial	Sporadic	Familial	Sporadic	Familial	Sporadic	Familial	Sporadic
Number of patients	62	412	9	84	248	933	26	63
Women	44 (71)	276 (67)	3 (33)	49 (58)	161 (65)	532 (57)	21 (81)	46 (73)
Age (mean, SD)	49 ± 10	57 ± 11	42 ± 7	40 ± 10	51 ± 11	57 ± 12	45 ± 12	53 ± 9
Hypertension	12 (19)	185 (45)	0	27 (32)	93 (38)	395 (42)	13 (50)	33 (52)
Smoking	32 (52)	171 (41)	7 (78)	56 (67)	127 (51)	456 (49)	24 (92)	58 (92)
Previous aSAH	0	0	9 (100)	78 (93)	7 (3)	37 (4)	10 (38)	63 (100)
Multiple aneurysms	19 (31)	90 (22)	1 (11)	18 (21)	84 (34)	312 (33)	7 (27)	15 (24)
Size								
<7.0 mm	49 (79)	172 (42)	9 (100)	70 (83)	189 (76)	627 (67)	26 (100)	63 (100)
7.0-9.9mm	8 (13)	124 (30)	0	10 (12)	31 (13)	154 (17)	0	0
10.0-19.9mm	4 (6)	96 (23)	0	3 (4)	24 (10)	117 (13)	0	0
>20.0 mm	0	19 (5)	0	1 (1)	4 (2)	35 (4)	0	0
Aneurysm location								
ICA	16 (26)	57 (14)	1 (11)	37 (44)	44 (18)	162 (17)	6 (23)	7 (11)
MCA	20 (32)	154 (37)	7 (78)	35 (42)	129 (52)	422 (45)	13 (50)	24 (38)
ACA & P	26 (42)	201 (49)	1 (11)	12 (14)	75 (30)	349 (37)	7 (27)	32 (51)
Phases (median, range)	4.0 (0-8)	5.0 (5-15)	8.0 (6-10)	8.0 (5-15)	8.0 (5-19)	9.0 (5-21)	3.0 (0-5)	5.0 (1-6)
Phases (mean, SD)	3.2 ± 2.1	6.0 ± 3.3	8.0 ± 1.0	8.3 ± 2.3	8.8 ± 2.8	9.6 ± 3.2	3.0 ± 1.5	4.3 ± 1.6
Ruptured aneurysms	3	7	3	18	4	10	0	0
Person-years of follow-up	228	948	191	2221	520	1541	60	247
Follow up years (median)	2.0 (0-15)	0.8 (0-21)	24.1 (7-35)	28.2 (1-52)	0.5 (0-23)	0.5 (0-18)	1.8 (1-9)	2.2 (1-15)
Rupture rate	1.32 (0.33-3.58)	0.74 (0.32-1.46)	1.57 (0.40-4.28)	0.81 (0.50-1.26)	0.77 (0.24-1.86)	0.65 (0.33-1.16)	-	-

aSAH: aneurysmal subarachnoid haemorrhage; SD: standard deviation; ICA: internal carotid artery; MCA: middle cerebral artery; ACA: anterior cerebral arteries; P: posterior circulation.
** unpublished data.*

	Molenberg et al[9]		Sonobe et al[10]		Morita et al[11]		Murayama et al[13]	
	Familial	Sporadic	Familial	Sporadic	Familial	Sporadic	Familial	Sporadic
	33	89	31	318	327	5375	184	1377
	22 (67)	63 (71)	21 (68)	204 (64)	220 (67)	3580 (67)	134 (73)	905 (66)
	51 ± 11	57 ± 10	61 ± 10	62 ± 10	58 ± 10	63 ± 10	63 ± 12	66 ± 12
	13 (39)	41 (46)	13 (42)	142 (45)	120 (37)	2351 (44)	77 (42)	665 (48)
	20 (61)	41 (46)	14 (45)	151 (47)	66 (20)	891 (17)	51 (28)	456 (33)
	10 (30)	63 (71)	3 (10)	30 (9)	16 (5)	170 (3)	3 (2)	40 (3)
	6 (18)	23 (26)	9 (29)	53 (17)	59 (18)	730 (14)	70 (38)	438 (32)
	28 (85)	72 (81)	31 (100)	318 (100)	250 (76)	3822 (71)	181 (98)	1308 (95)
	5 (15)	12 (13)	0	0	51 (16)	906 (17)	0	34 (2)
	0	4 (4)	0	0	25 (8)	565 (11)	3 (2)	27 (2)
	0	1 (1)	0		1 (0)	82 (2)	0	8 (1)
	5 (15)	21 (24)	13 (42)	118 (37)	63 (19)	1008 (19)	57 (31)	379 (28)
	14 (42)	32 (36)	11 (35)	117 (37)	120 (37)	1907 (35)	58 (32)	351 (25)
	14 (42)	36 (40)	7 (23)	83 (26)	144 (44)	2460 (46)	69 (38)	647 (47)
	4.0 (0-6)	4.0 (0-13)	5.0 (3-9)	6.0 (3-10)	7.0 (3-17)	7.0 (3-19)	6.0 (3-15)	7.0 (3-19)
	3.7 ± 1.7	4.1 ± 2.4	5.3 ± 1.9	5.6 ± 1.7	7.0 ± 2.6	7.6 ± 3	6.0 ± 2.3	6.6 ± 2.4
	0	0	0	6	4	102	5	50
	35	94	111	1126	468	9137	734	5025
	1.0 (0-2)	1.0 (0-2)	3.4 (1-6)	3.2 (0-7)	0.3 (0-8)	1.0 (0-9)	3.6 (0-11)	3.1 (0-11)
	-	-	-	0.53 (0.22-1.11)	0.86 (0.27-2.06)	1.12 (0.91-1.35)	0.68 (0.25-1.51)	1.0 (0.75-1.30)

Supplemental Table II. Quality assessment of prognosis cohort studies by QUIPS tool.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting
Juvela et al[7]	moderate	low	moderate	moderate	moderate	low
Mensing et al[3]	low	high	moderate	moderate	moderate	low
Morita et al[11]	low	moderate	low	moderate	moderate	low
Murayama et al[13]	low	low	moderate	low	moderate	low
Wermer et al[8]	low	low	moderate	moderate	low	low
Molenberg et al[9]	low	high	moderate	low	low	low
Sonobe et al[10]	low	moderate	low	low	low	low

Supplemental Table III. Baseline characteristics in cohorts both including and excluding siblings in the definition of first-degree relatives.

Pooled data	Familial (n,%)	Sporadic (n,%)	Total	P-value
Number of patients	903	8608	9511	
Women	612 (68)	5628 (65)	6240 (66)	0.15
Mean age* (range)	56 (20-89)	62 (15-100)	61 (15-100)	<0.01
Hypertension*	333 (37)	3809 (44)	4142 (44)	<0.01
Ever smoker*	326 (36)	2260 (26)	2586 (27)	<0.01
Previous aSAH	53 (6)	451 (5)	504 (5)	0.421
Population*				
Finnish	257 (28)	1017 (12)	1274 (13)	<0.01
Dutch	111 (12)	563 (7)	674 (7)	
Japanese	535 (59)	7028 (82)	7563 (80)	
Multiple aneurysms*	250 (28)	1669 (19)	1919 (21)	<0.01
Aneurysm size*				
<7.0 mm	746 (83)	6408 (74)	7154 (75)	<0.01
7.0-9.9 mm	94 (10)	1242 (14)	1336 (14)	
10.0-19.9 mm	58 (6)	812 (9)	870 (9)	
>20.0 mm	5 (1)	146 (2)	151 (2)	

Supplemental Table III. Continued

Pooled data	Familial (n,%)	Sporadic (n,%)	Total	P-value
Aneurysm location*				
Internal carotid artery	200 (22)	1782 (21)	1982 (21)	<0.01
Middle cerebral artery	364 (40)	3023 (35)	3387 (36)	
Anterior circulation & Posterior circulation	339 (38)	3803 (44)	4142 (44)	
Aneurysm treatment during follow-up*	382 (42)	3200 (37)	3582 (38)	<0.01
PHASES score* (median, range; mean, SD)	7.0 (0-19) 6.8 ± 2.9	7.0 (0-21) 7.3 ± 3.0	7.0 (0-21) 7.3 ± 3.0	<0.01

*aSAH: aneurysmal subarachnoid hemorrhage; SD: standard deviation. * statistically significant difference.*

Supplemental Table IV. Characteristics of ruptured intracranial aneurysms in cohorts both including and excluding siblings in the definition of first-degree relatives.

Pooled data	Familial (n,%)	Sporadic (n,%)	Total
Number of patients	19	200	219
Women	13 (68)	145 (73)	158 (72)
Mean age (SD)	60 ± 14	65 ± 15	65 ± 15
Hypertension	7 (37)	104 (52)	111 (51)
Ever smoker	5 (26)	46 (23)	51 (23)
Previous aSAH	3 (16)	29 (15)	32 (15)
Population			
Finnish	7 (37)	29 (15)	36 (16)
Dutch	3 (16)	8 (4)	11 (5)
Japanese	9 (47)	163 (81)	172 (79)
Multiple aneurysms	3 (16)	59 (30)	62 (28)
Aneurysm size			
<7.0 mm	11 (58)	93 (47)	104 (48)
7.0-9.9 mm	3 (16)	37 (19)	40 (18)
10.0-19.9 mm	5 (26)	49 (25)	54 (25)
>20.0 mm	0 (1)	21 (2)	21 (2)

Supplemental Table V. Continued

Pooled data	Familial (n,%)	Sporadic (n,%)	Total
Aneurysm location			
Internal carotid artery	2 (11)	21 (11)	23 (11)
Middle cerebral artery	11 (58)	50 (25)	61 (28)
Anterior circulation & Posterior circulation	6 (32)	129 (65)	135 (62)
PHASES score (median, range)	8.0 (2-16)	9.0 (2-20)	9.0 (2-20)

aSAH: aneurysmal subarachnoid hemorrhage; SD: standard deviation.

Supplemental Figure I. Search strings.

Pubmed search string

#1:
"intracranial aneurysm"[Title/Abstract] OR "intracranial saccular aneurysm"[Title/Abstract] OR "cerebral aneurysm"[Title/Abstract] OR "intracranial aneurysms"[Title/Abstract] OR "intracranial saccular aneurysms"[Title/Abstract] OR "cerebral aneurysms"[Title/Abstract]

#2:
"risk of rupture"[Title/Abstract] OR "aneurysm rupture"[Title/Abstract] OR "risk factors"[Title/Abstract] OR "rupture"[Title/Abstract] OR "unruptured"[Title/Abstract] OR "subarachnoid hemorrhage"[Title/Abstract]

#3:
"follow-up"[Title/Abstract] OR "follow up"[Title/Abstract] OR "natural history"[Title/Abstract] OR "naturalcourse"[Title/Abstract]

#1 AND **#2** AND **#3**

Embase search string

#1:
'intracranial aneurysm':ti:ab OR 'intracranial saccular aneurysm':ti:ab OR 'cerebral aneurysm':ti:ab OR 'intracranial aneurysms':ti:ab OR 'intracranial saccular aneurysms':ti:ab OR 'cerebral aneurysms':ti:ab

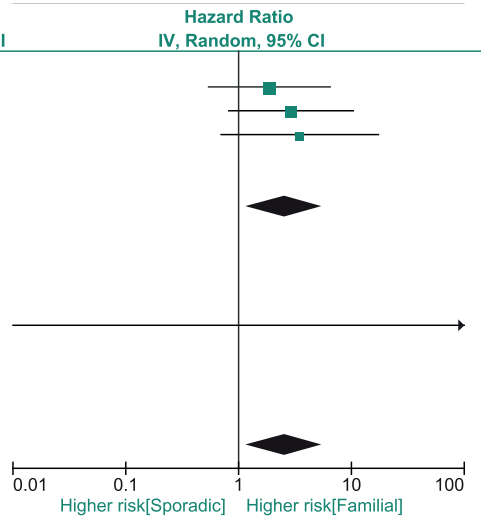
#2:
'risk of rupture':ti:ab OR 'aneurysm rupture':ti:ab OR 'risk factors':ti:ab OR 'rupture':ti:ab OR 'unruptured':ti:ab OR 'subarachnoid hemorrhage':ti:ab

#3:
'follow-up':ti:ab OR 'follow up':ti:ab OR 'natural history':ti:ab OR 'natural course':ti:ab

#1 AND **#2** AND **#3**

Supplemental Figure II. Hazard ratio 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 and stratified for European and Japanese populations.

Study or Subgroup	log[Hazard Ratio]	SE	Familial UIA Total	Sporadic UIA Total	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 European population						
Juvela	0.628	0.633	9	84	39.2%	1.87 [0.54, 6.48]
Lindgren	1.07	0.648	248	933	37.4%	2.92 [0.82, 10.38]
Mensing	1.249	0.819	62	412	23.4%	3.49 [0.70, 17.36]
Molenberg	0	0	33	89		Not estimable
Wermer	0	0	16	62		Not estimable
Subtotal (95% CI)			**368**	**1580**	**100.0%**	**2.56 [1.18, 5.56]**
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.37 (P = 0.02)						
1.1.2 Japanese population						
SUAVE	-13.035	930.459	31	318	0.0%	0.00 [0.00, Not estimable]
Subtotal (95% CI)			**31**	**318**	**0.0%**	**0.00 [0.00, Not estimable]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)			**399**	**1898**	**100.0%**	**2.56 [1.18, 5.56]**
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 3 (P = 0.93); I² = 0%						
Test for overall effect: Z = 2.37 (P = 0.02)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						

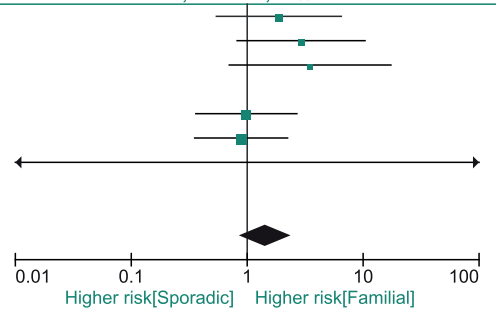


In the study from Wermer et al 1 aneurysm ruptured, in a patient with multiple aneurysms. The ruptured aneurysm was the smallest aneurysm and consequently this rupture was not included in the analysis per patient.

Supplemental Figure III. Hazard ratio of the rupture rate in patients with familial aneurysms compared to sporadic aneurysms adjusted for the PHASES score and smoking in cohorts both including end excluding siblings in the definition of first-degree relatives, analyzing the data per patient.

Study or Subgroup	log[Hazard Ratio]	SE	Familial UIA Total	Sporadic UIA Total	Weight	Hazard Ratio IV, Random, 95% CI
Juvela	0.628	0.633	9	84	17.0%	1.87 [0.54, 6.48]
Lindgren	1.07	0.648	248	933	16.2%	2.92 [0.82, 10.38]
Mensing	1.249	0.819	62	412	10.1%	3.49 [0.70, 17.36]
Molenberg	0	0	33	89		Not estimable
Morita	-0.017	0.512	327	5375	26.0%	0.98 [0.36, 2.68]
Murayama	-0.121	0.471	184	1377	30.7%	0.89 [0.35, 2.23]
SUAVE	-13.027	324.132	24	276	0.0%	0.00 [0.00, 1.754E270]
Wermer	0	0	16	62		Not estimable
Total (95% CI)			**903**	**8608**	**100.0%**	**1.44 [0.86, 2.40]**

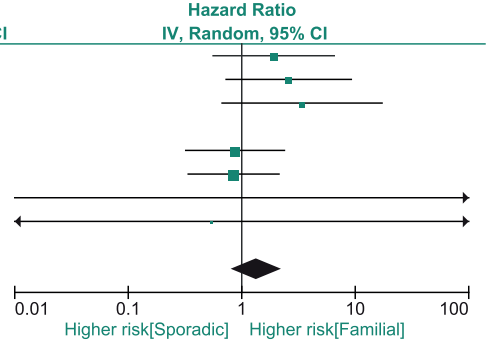
Heterogeneity: Tau² = 0.00; Chi² = 4.14, df = 5 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)



Supplemental Figure IV. Hazard ratio of the rupture rate adjusted for the PHASES score and smoking for familial aneurysms compared to sporadic aneurysms in cohorts both including and excluding siblings in the definition of first-degree relatives, analyzing the data per aneurysm.

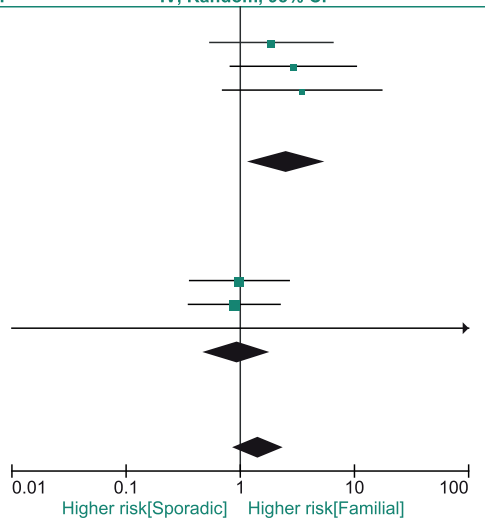
Study or Subgroup	log[Hazard Ratio]	SE	Familial UIA Total	Sporadic UIA Total	Weight	Hazard Ratio IV, Random, 95% CI
Juvela	0.648	0.627	10	106	17.2%	1.91 [0.56, 6.53]
Lindgren	0.953	0.648	381	1277	16.1%	2.59 [0.73, 9.24]
Mensing	1.224	0.828	91	542	9.9%	3.40 [0.67, 17.23]
Molenberg	0	0	38	121		Not estimable
Morita	-0.135	0.511	401	6274	26.0%	0.87 [0.32, 2.38]
Murayama	-0.165	0.47	229	1713	30.7%	0.85 [0.34, 2.13]
SUAVE	-13.078	990.496	33	327	0.0%	0.00 [0.00, Not estimable]
Wermer	-0.61	11.662	20	84	0.0%	0.54 [0.00, 4589789446.32]
Total (95% CI)			**1203**	**10444**	**100.0%**	**1.35 [0.81, 2.25]**

Heterogeneity: Tau² = 0.00; Chi² = 4.28, df = 6 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.15 (P = 0.25)



Supplemental Figure V. Hazard ratio of the rupture rate in patients with familial aneurysms compared to sporadic aneurysms adjusted for the PHASES score and smoking in cohorts both including and excluding siblings in the definition of first-degree relatives, analyzing the data per patient and stratified for European populations and Japanese populations.

Study or Subgroup	log[Hazard Ratio]	SE	Familial UIA Total	Sporadic UIA Total	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 European population						
Juvela	0.628	0.633	9	84	17.0%	1.87 [0.54, 6.48]
Lindgren	1.07	0.648	248	933	16.2%	2.92 [0.82, 10.38]
Mensing	1.249	0.819	62	412	10.1%	3.49 [0.70, 17.36]
Molenberg	0	0	33	89		Not estimable
Wermer	0	0	16	62		Not estimable
Subtotal (95% CI)			**368**	**1580**	**43.3%**	**2.56 [1.18, 5.56]**
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.37 (P = 0.02)						
1.1.2 Japanese population						
Morita	-0.017	0.512	327	5375	26.0%	0.98 [0.36, 2.68]
Murayama	-0.121	0.471	184	1377	30.7%	0.89 [0.35, 2.23]
SUAVE	-13.022	1,041,762	24	276	0.0%	0.00 [0.00, Not estimable]
Subtotal (95% CI)			**535**	**7028**	**56.7%**	**0.93 [0.47, 1.83]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Total (95% CI)			**903**	**8608**	**100.0%**	**1.44 [0.86, 2.40]**
Heterogeneity: Tau² = 0.00; Chi² = 4.14, df = 5 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 3.69, df = 1 (P = 0.05), I² = 72.9%						



In the study from Morita et al and Murayama et al siblings were excluded in the definition of first-degree relatives.

Chapter 7

Sex difference and rupture rate of intracranial aneurysms: an individual patient data meta-analysis

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Stroke, in revision

Abstract

Background and purpose: In previous studies women had a higher risk of rupture of intracranial aneurysms than men, but female sex was not an independent risk factor. This may be explained by a higher prevalence of patient- or aneurysm-related risk factors for rupture in women than in men or by insufficient power of previous studies. We assessed sex differences in rupture rate taking into account other patient- and aneurysm-related risk factors for aneurysmal rupture.

Methods: We searched Embase and Pubmed for articles published until December 1, 2020. Cohorts with available individual patient data were included in our meta-analysis. We compared rupture rates of women versus men using a Cox proportional hazard regression model adjusted for the PHASES (Population, Hypertension, Age, Size of aneurysm, Earlier subarachnoid hemorrhage from another aneurysm, Site of aneurysm) score, smoking and a positive family history of aneurysmal subarachnoid hemorrhage (aSAH).

Results: We pooled individual patient data from nine cohorts totaling 9,940 patients (6,555 women, 66%) with 12,193 unruptured intracranial aneurysms and 24,357 person-years follow-up. Rupture occurred in 163 women (rupture rate 1.04%/person-years; 95% CI: 0.89-1.21) and 63 men (rupture rate 0.74%/person-years; 95% CI: 0.58-0.94). Women were older (61.9 vs 59.5 years), were less often smokers (20% vs 44%), more often had hypertension (44% vs 42%), internal carotid artery aneurysms (24% vs 17%), and larger sized aneurysms (≥7 mm, 24% vs 23%) than men. The crude women/men ratio of rupture was 1.43 (95% CI: 1.07-1.93) and the adjusted women/men ratio was 1.39 (95% CI 1.02-1.90).

Conclusion: Women have a higher risk of aneurysmal rupture than men and this sex difference is not explained by differences in patient- and aneurysm-related risk factors for aneurysmal rupture. Future studies should focus on the factors explaining the higher risk of aneurysmal rupture in women.

Introduction

Approximately 3% of the general population has an unruptured intracranial aneurysm (UIA).[1] Rupture of an intracranial aneurysm results in aneurysmal subarachnoid hemorrhage (aSAH), a subtype of stroke which carries a high morbidity and case fatality.[2] UIA and aSAH occur more often in women than in men with overall 65% of the patients being women.[1, 3]

In the decision whether to treat UIA with neurosurgical or endovascular treatment to prevent future aSAH, the risk of rupture and the risk of complications of preventive treatment have to be balanced.[4] The five-year risk of rupture of UIA can be assessed using the PHASES (Population, Hypertension, Age, Size of aneurysm, Earlier SAH from another aneurysm, Site of aneurysm) score which takes into account several patient- and aneurysm-related factors associated with rupture including geographic location, hypertension, age, history of aSAH, aneurysm size and location.[5] The PHASES score is based on a pooled analysis of individual patient data from prospective cohort studies on rupture rates of UIAs and risk factors for rupture. In this pooled analysis, women had a higher risk of rupture, but in multivariable analysis female sex was not an independent risk factor. Another meta-analysis including both retrospective and prospective studies reported a statistically significantly higher rupture risk in women compared to men, but whether female sex was an independent risk factor could not be investigated because multivariable analysis was not possible due to lack of individual patient data.[6] The higher risk of UIA rupture in women may therefore be explained by a higher prevalence of patient or aneurysm-related risk factors for UIA rupture in women.

We performed a pooled analysis of individual patient data from prospective cohort studies to assess if sex is a risk factor for intracranial aneurysm rupture independent from other risk factors for rupture including the PHASES score, smoking, and a positive family history of aSAH.

Material and methods

Search strategy and selection criteria

We performed a systematic search of the Pubmed and Embase database to retrieve all studies on rupture risk published up to December 1, 2020. We used 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)" (Supplemental Figure I). In addition, we checked the reference list of all relevant publications for further eligible studies. We performed our systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[7, 8] We included studies that 1) used a prospective study design; 2) included at least 50 patients with UIA; and 3) studied the rupture rate of UIA and risk factors for aneurysm rupture. There was no language restriction other than the requirement of an abstract in English. When multiple publications reported on the same study population, the most recent publication was used. One author (CCMZ) performed the literature search, checked the titles and abstracts for studies meeting the inclusion criteria. Next, full-text copies of eligible studies were reviewed.

In total, 2,613 articles were screened (Figure 1). 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. We found twelve studies that fulfilled the inclusion criteria,[9-19] and nine research groups provided us with their individual patient data.[12-19] One of these population based cohort studies on UIA, did not report on family history,[20] but its authors could provide data including data on family history of aSAH for a selection of cases. These were data on patients with UIA collected between 1980 and 2017 from the IA database of Neurosurgery of Kuopio University Hospital and included 1,181 patients with 1,653 UIA, of whom 693 were women. The nine cohorts are listed in Table 1, and the baseline characteristics of patients in all separate cohorts in Supplemental Table I. Quality assessment of included cohort studies by QUIPS tool is shown in Supplemental Table II.

Figure 1. Prisma flow diagram.

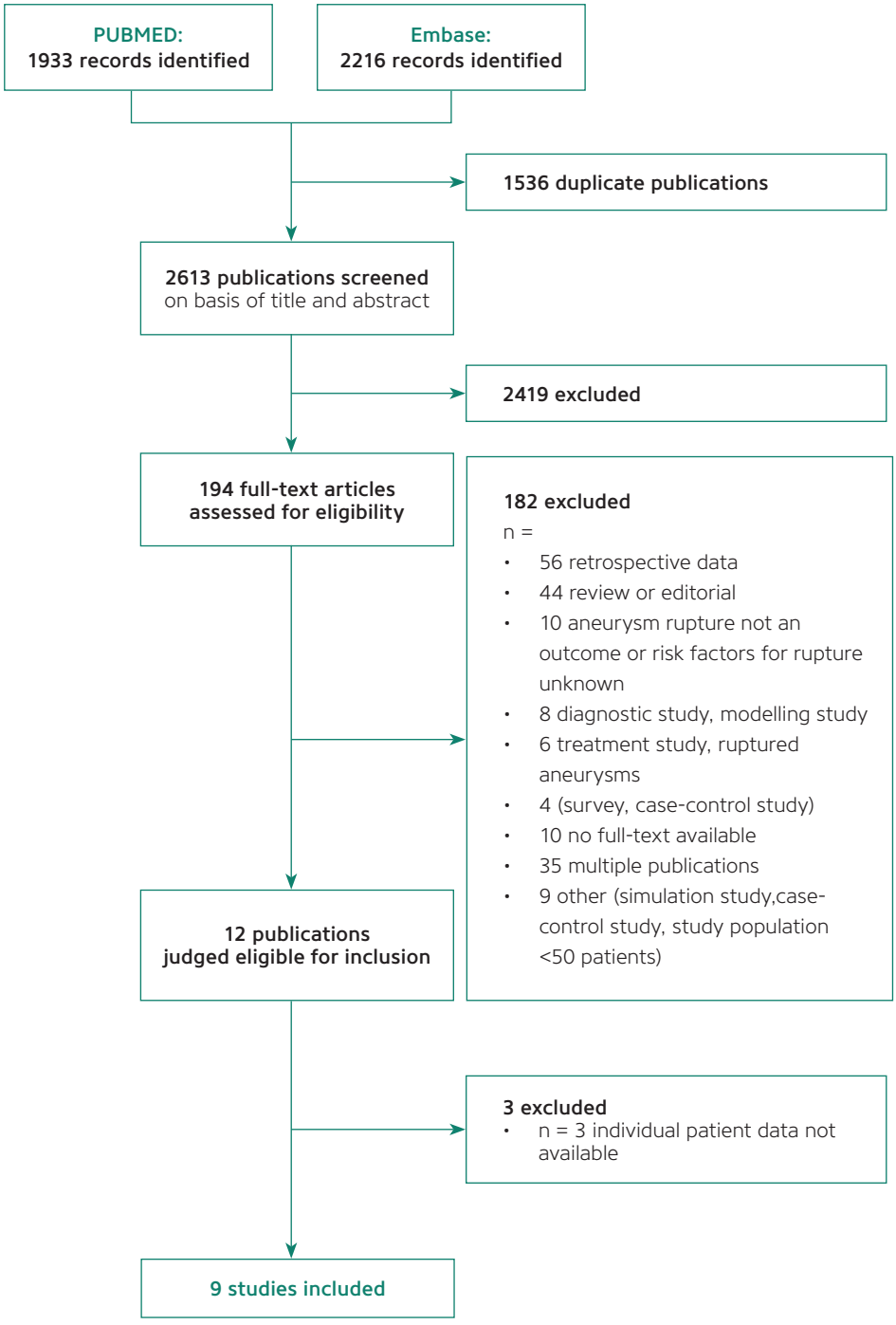


Table 1. Baseline characteristics of included studies.

	Juvela et al[12]	Mensing at al[13]	Morita et al[14]	Muray-ama et al[15]	Wermer et al [16]	Molen-berg et al[17]	Sonobe et al[18]	Gondar et al[19]	Lindgren et al[20]
Country	FIN	NL	JPN	JPN	NL	NL	JPN	CH	FIN
Recruitment period	1956-1978	1994-2016	2001-2004	2003-2012	2002-2004	1998-2017	2000-2004	2006-2014	1977-2016
Number of patients	140	474	5702	1561	93	198	368	291	1181
Number of UIA	179	633	6675	1942	125	257	441	367	1658
Women (%)	75 (54)	320 (68)	3779 (66)	1039 (67)	70 (75)	145 (73)	236 (64)	225 (86)	693 (59)
Mean age in years (range)	42 (15-61)	56 (22-81)	63 (23-98)	66 (25-100)	51 (20-69)	56 (28-79)	62 (23-89)	55 (20-91)	56 (16-85)
Median follow-up in years (range)	21.0 (0-52)	0.8 (0-21)	1.0 (0-9)	3.2 (0-11)	2.2 (1-15)	1 (0.3-2)	3.2 (0-7)	2.5 (0-13)	0.5 (0-23)
Number of UIA rupture during follow-up	33	10	111	56	1	1	6	3	14

FIN: Finland; NL: the Netherlands; JPN: Japan; CH: Switzerland; UIA: unruptured intracranial aneurysm; aSAH: aneurysmal subarachnoid hemorrhage.

Data extraction

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 of aSAH, hypertension status, number of aneurysms, maximum diameter of aneurysms, aneurysm location. These data were recorded individually and also summarized in the PHASES score which includes data on the risk factors geographic location, hypertension, age, history of aSAH, aneurysm size and location.[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. A smoker was defined as a former or current smoker, and person with hypertension as a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or use of antihypertensive drugs. 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. The location of the aneurysm was classified as the 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. We predefined the primary endpoint as the rupture of UIA.

Statistical approach

Missing data were imputed using multiple imputation. In one study only data on current smoking was available but no data on former smoking, and therefore in our analysis data on current smoking was considered as current or former smoking.[17] Fifty-seven patients were included in two Japanese cohorts,[14, 15] and 11 patients were included in two Dutch cohorts[13, 16] and these patients were excluded in one of these cohorts in the pooled analysis. 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 pooled the individual patient data of the included studies and estimated sex-specific rupture rates for each cohort separately. In case of multiple UIAs, the largest UIA was used to categorize the patient regarding site and size of the aneurysm. In addition, we performed an aneurysm-based analysis where all UIAs were analyzed. Rupture rate was analyzed with a Cox proportional hazard regression model, adjusted for the PHASES score,[5] smoking and positive family history of aSAH. A two-stage approach was used with random effect for cohort, because we expected heterogeneity since studies were performed in different countries which used different treatment regimes, and a fixed effect for the PHASES score, smoking and positive family history of aSAH. Proportional hazard assumptions were checked. Follow-up data for patients started at time of UIA diagnosis and patients were followed up until aneurysmal rupture occurred. Patients were censored at the time of death, last follow-up assessment, or at the time of surgical or endovascular aneurysm treatment without preceding rupture. When patients underwent a surgical or endovascular aneurysm treatment, data from the period up to the time of the intervention were included in the analysis, while data from the period after the intervention were not included.

Results

We pooled individual patient data from 9,940 patients with 12,193 UIAs and 24,357 person-years follow-up using data from nine prospective cohort studies.[12-20] Studies were at low and moderate risk of bias. Baseline characteristics of patients are shown in Table 2. Data on patient characteristics was almost

Table 2. Baseline characteristics of included patients.

Pooled data	Women (n,%)	Men (n,%)	Total (n,%)	p-value
Number of patients	6555	3385	9940	
Mean age (range)	61.9 (15-100)	59.5 (16-94)	61.1 (15-100)	<0.001
Hypertension	2913 (44)	1431 (42)	4344 (44)	0.039
Ever smoker	1330 (20)	1500 (44)	2830 (29)	<0.001
Previous aSAH	405 (6)	188 (6)	593 (6)	0.213
Positive family history of aSAH	676 (10)	316 (9)	992 (10)	0.123
Population				<0.001
Finnish	768 (12)	553 (16)	1321 (13)	
Japanese	5035 (77)	2539 (75)	7574 (76)	
Dutch	527 (8)	227 (7)	754 (8)	
Swiss	225 (4)	66 (2)	291 (3)	
Multiple aneurysms	1466 (22)	552 (16)	2018 (20)	<0.001
Aneurysm size				0.07
<7.0 mm	4951 (76)	2589 (77)	7540 (76)	
7.0-9.9 mm	887 (14)	475 (14)	1326 (14)	
10.0-19.9 mm	618 (9)	266 (8)	884 (9)	
>20.0 mm	99 (2)	55 (2)	154 (2)	
Aneurysm location				<0.001
Internal carotid artery	1551 (24)	584 (17)	2135 (22)	
Middle cerebral artery	2305 (35)	1242 (37)	3547 (36)	
Anterior circulation or posterior circulation	2699 (41)	1559 (46)	4258 (43)	
Phases score (median, range, mean, standard deviation)	7.0 (0-21) 7.2 ± 3.2	7.0 (0-20) 7.4 ± 3.0	7.0 (0-21) 7.2 ± 3.1	<0.001

aSAH; aneurysmal subarachnoid hemorrhage.

complete except for smoking which was available in 9,705/9,940 (98%), for hypertension which was available in 9,853/9,940 (99%) and for family history of aSAH which was available in 9,794/9,940 (99%). Information on outcome measure was complete for all patients. The mean age was 61 ± 12 years, 6,555 patients (66%) were women, and patients came from Dutch (8%), Finnish (12%), Japanese (77%) and Swiss (4%) populations. Women were older (61.9 vs 59.5 years), less often smokers (20% vs 44%) and more often had hypertension (44% vs 42%), internal carotid artery aneurysms (24% vs 17%), and larger aneurysms (≥7 mm, 24% vs 23%) than men. There was also a difference in sex in the different populations which was attributable to more women being from a Japanese (67% vs 33%), Dutch (70% vs 30%) and Switch population (77% vs 23%) and less often from a Finnish population (58% vs 42%) than men. The median PHASES score was the same in women (7.0 (range 0-21)) and men (7.0 (range 0-20)) and the mean PHASES score was 7.2 ± 3.2 in women and 7.4 ± 3.0 in men. The mean follow-up time for women was 2.4 ± 3.5 years (median: 1.5 (0-52) year) and 2.5 ± 3.7 years (median: 1.5 (0-50) year) for men. Preventive neurosurgical or endovascular treatment during follow-up occurred in 36% of women (median: 60 days) patients and in 37% of men (median: 61 days). When assessing these characteristics per UIA, similar differences in characteristics were found (data not shown).

In 234 patients UIA rupture occurred. Of these 234 patients, 67 patients had multiple UIA and in 226 of 234 patients (97%) the only aneurysm (n=167) or the largest aneurysm in case of multiple aneurysms (n=59) ruptured. In 8 of the 67 patients with multiple aneurysms another than the largest aneurysm ruptured. Of the 226 patients in whom the single or largest UIA ruptured, 163 were women (rupture rate 1.04%/person-years; 95% confidence interval (CI): 0.89-1.21) and 63 men (0.74%/person-years; 95% CI: 0.58-0.94). Characteristics of ruptured aneurysms are shown in Table 3.

The unadjusted women-to-men hazard ratio (HR) was 1.43 (95% CI: 1.07-1.93). After adjustment for the PHASES score, smoking, and positive family history of aSAH the women-to-men HR was slightly lower (1.39, 95% CI: 1.02-1.90; Figure 2). In the aneurysm-based analysis where all UIAs were analyzed the results were essentially the same (Figure 3).

Table 3. Characteristics of ruptured intracranial aneurysms per aneurysm.

Pooled data	Women (n,%)	Men (n,%)	Total (n,%)	p-value
Number of ruptured IA	169	65	234	
Largest IA ruptured*	163	63	226	
Not largest IA ruptured	6	2	8	
Mean age (range)	64.2 (23-93)	61.2 (28-87)	63.4 (23-93)	0.19
Hypertension	89 (53)	31 (48)	120 (52)	0.50
Ever smoker	28 (17)	33 (51)	61 (26)	<0.001
Previous aSAH	28 (17)	12 (19)	40 (17)	0.73
Positive family history of aSAH	18 (11)	8 (12)	26 (11)	0.72
Population				0.20
Finnish	30 (18)	17 (26)	47 (20)	
Japanese	129 (76)	43 (66)	172 (74)	
Dutch	9 (5)	3 (5)	12 (5)	
Swiss	1 (1)	2 (3)	3 (1)	
Multiple aneurysms	51 (30)	16 (25)	67 (29)	0.40
Aneurysm size				0.33
<7.0 mm	79 (47)	34 (52)	113 (48)	
7.0-9.9 mm	35 (21)	7 (11)	42 (18)	
10.0-19.9 mm	40 (24)	16 (25)	56 (24)	
>20.0 mm	15 (9)	8 (12)	23 (10)	
Aneurysm location				0.15
Internal carotid artery	26 (15)	4 (6)	30 (13)	
Middle cerebral artery	45 (27)	21 (32)	66 (28)	
Anterior circulation or posterior circulation	98 (58)	40 (62)	138 (59)	
Phases score (median, range, mean, standard deviation)	9.0 (2-19) 10.1 ± 4.0	9.0 (4-20) 10.4 ± 3.9	9.0 (2-20) 10.3 ± 4.0	0.60

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

Figure 2. Hazard ratio of the rupture rate in women compared to men adjusted for the PHASES score, smoking and positive family history of aneurysmal subarachnoid hemorrhage, analyzing the data per patient.

Study or Subgroup	log[Hazard Ratio]	SE	Women Total	Men Total	Weight	Hazard Ratio IV, Random, 95% CI
Gondar et al. 2016	-1.582	1.237	225	66	1.6%	0.21 [0.02, 2.32]
Juvela et al. 2013	0.843	0.421	75	65	14.2%	2.32 [1.02, 5.30]
Lindgren et al. 2016	-0.156	0.572	693	488	7.7%	0.86 [0.28, 2.63]
Mensing et al. 2019	0.865	0.83	320	154	3.7%	2.38 [0.47, 12.08]
Molenberg et al. 2019	0	2.276	145	53	0.5%	1.00 [0.01, 86.56]
Morita et al. 2012	0.339	0.231	3799	1903	47.1%	1.40 [0.89, 2.21]
Murayama et al. 2016	0.189	0.328	1039	522	23.4%	1.21 [0.64, 2.30]
Sonobe et al. 2010	0.819	1.174	197	114	1.8%	2.27 [0.23, 22.65]
Wermer et al. 2006	0	0	62	20		Not estimable
Total (95% CI)			**6555**	**3385**	**100.0%**	**1.39 [1.02, 1.90]**

Heterogeneity: Tau² = 0.00; Chi² = 5.39, df = 7 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)

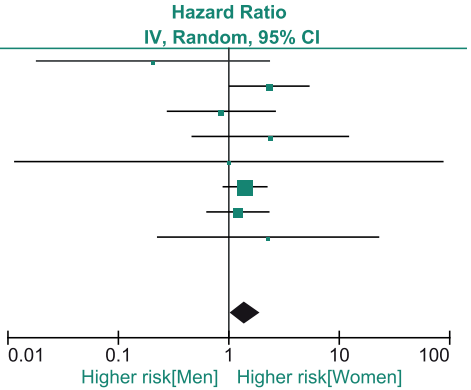
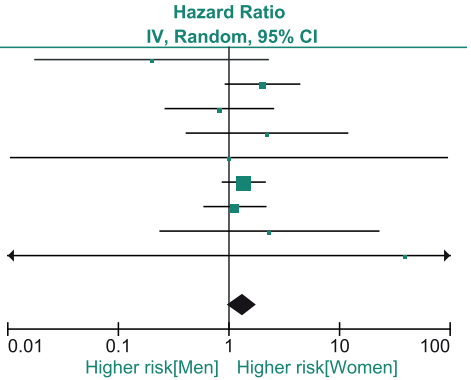


Figure 3. Hazard ratio of the rupture rate in women compared to men adjusted for the PHASES score, smoking and positive family history of aneurysmal subarachnoid hemorrhage, analyzing the data per aneurysm.

Study or Subgroup	log[Hazard Ratio]	SE	Women Total	Men Total	Weight	Hazard Ratio IV, Random, 95% CI
Gondar et al. 2016	-1.612	1.238	284	83	1.6%	0.20 [0.02, 2.26]
Juvela et al. 2013	0.698	0.394	97	82	15.6%	2.01 [0.93, 4.35]
Lindgren et al. 2016	-0.2	0.574	994	664	7.3%	0.82 [0.27, 2.52]
Mensing et al. 2019	0.791	0.856	451	182	3.3%	2.21 [0.41, 11.81]
Molenberg et al. 2019	0	2.319	192	65	0.4%	1.00 [0.01, 94.18]
Morita et al. 2012	0.308	0.226	4526	2149	47.3%	1.36 [0.87, 2.12]
Murayama et al. 2016	0.124	0.327	1323	619	22.6%	1.13 [0.60, 2.15]
Sonobe et al. 2010	0.843	1.161	237	135	1.8%	2.32 [0.24, 22.61]
Wermer et al. 2006	3.658	10.874	85	25	0.0%	38.78 [0.00, 6.992E10]
Total (95% CI)			**8189**	**4004**	**100.0%**	**1.33 [0.98, 1.80]**

Heterogeneity: Tau² = 0.00; Chi² = 5.11, df = 8 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)



Discussion

in our pooled analysis of individual patient data from prospective cohort studies we found that women have a higher risk of aneurysmal rupture, and this increased rupture risk for women is not explained by differences in patient- and aneurysm-related risk factors for aneurysmal rupture, being risk factors of the PHASES score, smoking, and a positive family history of aSAH.

Some of the risk factors for rupture were more often present in women, but others in men. As the patient- and aneurysm-related risk factors for which we corrected in our analysis, do not explain the increased rupture risk in women, additional factors contributing to the increased risk remain to be detected. We had no data on the shape of the aneurysm in our data set. Since aspect ratio and irregular aneurysm shape are also known factors for UIA rupture,[21, 22] a higher prevalence of irregular aneurysms in women than in men may contribute to the sex difference in rupture, but it is unlikely that such a difference would explain the sex difference in rupture completely. Since we could not find data in the literature on sex differences regarding shape of the aneurysms, it is currently unknown if or to what extent differences in shape of aneurysms between women and men play a role in the higher rupture risk in women.

Additional factors explaining the sex difference in risk of UIA rupture may be female-specific hormonal and reproductive factors. A previous systematic literature review on female risk factors for a SAH found an increased risk of aSAH for postmenopausal versus premenopausal women although the pathophysiology of this effect and its influence on the difference in incidence of SAH between the sexes remains unclear.[23] Alternatively, female-specific genetic factors such as genetic factors of the X-chromosome, sex-specific effects of environmental risk factors such as smoking[24] or other yet unknown clinical factors which occur more often or having stronger effect in women than in men may explain the difference.

Our study has several strengths. It includes a large data set with individual patient data from several cohorts including risk factors for aneurysmal rupture. Also, almost all study cohorts included in this meta-analysis showed a higher rupture rate in women compared to men. This means that our data are consistent, and generalizable for both Asian and European countries.

A first limitation of this study is that selection bias may have occurred due to informative censoring (loss to follow-up) within each cohort study. If men were treated more aggressively during follow-up than women for example upon growth of the UIA, which is associated with a higher risk of rupture,[25] this may have led to selection bias. However, we found no difference in preventive neurosurgical or endovascular treatment during follow-up between men and women as it was done in 36% of women (median: 60 days) and in 37% of men (median: 61 days). Therefore, it is unlikely that differences in preventive treatment have influenced our results considerably. Second, in most studies we only had data on smoking at the time of UIA detection but not for smoking status during follow-up. As a previous study showed that continuation of smoking is a significant risk factor for UIA rupture, no conclusions can be drawn about the effect of a change in smoking status after aneurysm detection during follow-up on our outcomes.[26] Cessation of smoking might have occurred more often in men during follow-up compared to women. Similarly, in most studies we only had data on hypertension at time of UIA detection and not during follow-up. Better control of blood pressure might have been achieved in men during follow-up compared to women. Third, although nine research groups[12-20] provided us with their individual patient data, three research groups[9-11] were not able to do so, which could possibly lead to a bias. However, the population characteristics between the three cohorts not included (Matsumoto[9]: 63% female, Güresir[10]: 78% female, and International Study of Unruptured Intracranial Aneurysms Investigators (ISUIA)[11]: 75% female) and rupture risk (Matsumoto[9]: 6/111 patients, all female; Güresir[10]: 3/263 patients, all female; and ISUIA[11]: 51/1692, sex unknown) differed not much from those of the nine cohorts analyzed (66% (range 54-86) female), and therefore do not think that such a potential bias influences our conclusions. Fourth, in our analysis patients from Japanese populations were overrepresented (77%) compared to Dutch (8%), Finnish (12%) and Swiss (4%) populations. Except for a small study in the Swiss population, in all populations a higher risk of rupture for women compared to men was found, so we think our results are generalizable to all populations. Finally, in our study we performed patient-level analysis, and in patients with multiple UIAs we analyzed data of the largest UIA, which is not always the UIA that actually ruptures.[27] However, in our analysis for rupture rate on aneurysm-level we found comparable results.

Conclusion

Our results show that UIAs in women have a higher rupture risk than UIAs in men, which is not explained by differences in patient- and aneurysm-related risk factors for aneurysmal rupture, being risk factors of the PHASES score, smoking, and a positive family history of aSAH. When assessing the risk of rupture of UIAs in women, this higher risk should be taken into account and a more aggressive treatment approach in women as compared to men is justified. Future studies should focus on the identification of the factors explaining the higher rupture risk of UIA in women such as different approach during follow-up, female-specific hormonal and reproductive factors, or female-specific genetic and environmental risk factors.

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Supplemental Figure I. Search strings.

Pubmed search string

#1:
"intracranial aneurysm"[Title/Abstract] OR "intracranial saccular aneurysm"[Title/Abstract] OR "cerebral aneurysm"[Title/Abstract] OR "intracranial aneurysms"[Title/Abstract] OR "intracranial saccular aneurysms"[Title/Abstract] OR "cerebral aneurysms"[Title/Abstract]

#2:
"risk of rupture"[Title/Abstract] OR "aneurysm rupture"[Title/Abstract] OR "risk factors"[Title/Abstract] OR "rupture"[Title/Abstract] OR "unruptured"[Title/Abstract] OR "subarachnoid hemorrhage"[Title/Abstract]

#3:
"follow-up"[Title/Abstract] OR "follow up"[Title/Abstract] OR "natural history"[Title/Abstract] OR "naturalcourse"[Title/Abstract]

#1 AND **#2** AND **#3**

Embase search string

#1:
'intracranial aneurysm':ti:ab OR 'intracranial saccular aneurysm':ti:ab OR 'cerebral aneurysm':ti:ab OR 'intracranial aneurysms':ti:ab OR 'intracranial saccular aneurysms':ti:ab OR 'cerebral aneurysms':ti:ab

#2:
'risk of rupture':ti:ab OR 'aneurysm rupture':ti:ab OR 'risk factors':ti:ab OR 'rupture':ti:ab OR 'unruptured':ti:ab OR 'subarachnoid hemorrhage':ti:ab

#3:
'follow-up':ti:ab OR 'follow up':ti:ab OR 'natural history':ti:ab OR 'natural course':ti:ab

#1 AND **#2** AND **#3**

Supplemental Table I. Baseline characteristics of all separate cohorts.

	Wermer et al[6]		Juvela et al[12]		Mensing et al[13]		Morita et al[14]	
	Women	Men	Women	Men	Women	Men	Women	Men
Number of patients	70	23	75	65	320	154	3799	1903
Age (mean, SD)	51 ± 10	51 ± 11	42 ± 11	41 ± 10	55 ± 11	57 ± 11	63 ± 10	61 ± 10
Hypertension	38 (54)	11 (48)	24 (32)	26 (40)	130 (41)	67 (44)	1682 (44)	789 (41)
Smoking	62 (89)	22 (96)	39 (52)	60 (92)	146 (46)	61 (40)	340 (9)	617 (32)
Previous aSAH	59 (84)	18 (78)	67 (89)	62 (95)	0	0	138 (4)	48 (3)
Positive family history	23 (33)	6 (26)	12 (16)	15 (23)	44 (14)	18 (12)	220 (6)	107 (6)
Multiple aneurysms	19 (27)	5 (22)	19 (25)	14 (22)	86 (27)	23 (15)	587 (15)	201 (11)
Size								
<7.0 mm	70 (100)	23 (100)	61 (81)	54 (83)	154 (48)	67 (44)	2670 (70)	1402(74)
7.0-9.9 mm	0	0	8 (11)	8 (12)	85 (27)	47 (31)	651 (17)	306 (16)
10.0-19.9 mm	0	0	4 (5)	2 (3)	69 (22)	32 (21)	418 (11)	172 (9)
>20.0 mm	0	0	2 (3)	1 (2)	11 (3)	8 (5)	60 (2)	23 (1)
Aneurysm location								
ICA	11 (16)	2 (9)	37 (49)	23 (35)	63 (20)	10 (7)	789 (21)	282 (15)
MCA	29 (41)	10 (44)	30 (40)	32 (49)	106 (33)	68 (44)	1333 (35)	694 (36)
ACA & P	30 (43)	11 (48)	8 (11)	10 (15)	151 (47)	76 (49)	1677 (44)	927 (49)
Phases (median, range)	4 (1-6)	5 (1-6)	8 (5-15)	8 (5-14)	5 (0-15)	5 (0-15)	7 (3-19)	7 (3-19)
Phases (mean, SD)	4.0 ± 1.6	4.2 ± 1.7	8.3 ± 2.4	8.6 ± 2.2	5.5 ± 3.3	6.1 ± 3.4	7.6 ± 3.1	7.5 ± 2.8
Ruptured aneurysms	0	0	22	10	8	2	79	27
Person-years of follow-up	234.1	82.4	1764.4	1259.2	799.5	377.08	6329.77	3271.89
Follow-up years (median)	2.2 (1-15)	2.3 (1-10)	23.5 (1-52)	15.4 (1-50)	0.7 (0-21)	1 (0-18)	1.0 (0-8)	1.0 (0-9)
Rupture rate	-	-	1.25 (0.8-1.9)	0.79 (4.0-14.2)	1.0 (0.46-1.9)	0.53 (0.09-1.75)	1.25 (0.99-1.55)	0.83 (0.55-1.18)

aSAH: aneurysmal subarachnoid hemorrhage, SD: standard deviation, ICA: internal carotid artery, MCA: middle cerebral artery, ACA: anterior cerebral arteries, P: posterior circulation.

Murayama et al[15]		Molenberg et al[17]		Sonobe et al[18]		Gondar et al[19]		Lindgren et al[20]	
Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
1039	522	145	53	236	132	225	66	693	488
66 ± 12	64 ± 11	56 ± 11	57 ± 11	63 ± 10	60 ± 10	56 ± 15	53 ± 15	57 ± 13	54 ± 11
479 (46)	253 (49)	70 (48)	19 (36)	107 (45)	53 (40)	101 (45)	38 (58)	302 (44)	186 (38)
220 (21)	287 (55)	76 (52)	29 (55)	89 (38)	85 (64)	112 (50)	41 (62)	273 (39)	310 (64)
28 (3)	15 (3)	68 (47)	13 (25)	25 (11)	9 (7)	3 (1)	0	21 (3)	23 (5)
134 (13)	50 (10)	42 (29)	18 (34)	24 (10)	12 (9)	27 (12)	10 (15)	161 (23)	87 (18)
387 (37)	121 (23)	7 (5)	8 (15)	42 (18)	23 (17)	47 (21)	9 (14)	247 (36)	150 (31)
984 (95)	505 (97)	127 (88)	37 (70)	236 (100)	132 (100)	212 (94)	59 (89)	484 (70)	332 (68)
24 (2)	10 (2)	14 (10)	10 (19)	0	0	8 (4)	5 (8)	97 (14)	88 (18)
25 (2)	5 (1)	4 (3)	4 (8)	0	0	5 (2)	2 (3)	92 (13)	49 (10)
6 (1)	2 (0)	0	2 (4)	0	0	0	0	20 (3)	19 (4)
311 (30)	125 (24)	29 (20)	9 (17)	92 (39)	50 (38)	90 (40)	20 (30)	140 (20)	66 (14)
281 (27)	128 (25)	62 (43)	23 (43)	82 (35)	49 (37)	80 (36)	18 (27)	321 (46)	230 (47)
447 (43)	269 (52)	54 (37)	21 (40)	62 (26)	33 (25)	54 (24)	28 (42)	232 (34)	192 (39)
7 (3-19)	7 (3-17)	4 (0-11)	4 (0-16)	6 (3-10)	5 (3-9)	2 (0-12)	4 (0-10)	9 (5-21)	9 (5-20)
6.5 ± 2.5	6.5 ± 2.2	3.9 ± 2.0	4.6 ± 3.0	5.6 ± 1.8	5.4 ± 1.6	2.5 ± 2.1	3.4 ± 2.3	9.4 ± 3.2	9.6 ± 3.1
41	14	0	1	5	1	1	2	8	6
3858.28	1901.12	150.7	56.6	814.1	485.9	706.58	227.3	1163.6	898.09
3.2 (0-11)	3.1 (0-11)	1 (0-2)	1 (0-2)	3.2 (0-7)	3.3 (0-7)	2.5 (0-13)	2.7 (0-10)	0.5 (0-18)	0.5 (0-23)
1.06 (0.77-1.43)	0.74 (0.42-1.21)	-	1.77 (0.09-8.71)	0.61 (0.23-1.36)	0.21 (0.01-1.02)	0.14 (0.01-0.70)	0.88 (0.15-2.91)	0.69 (0.32-1.31)	0.69 (0.27-1.39)

Supplemental Table II. Risk of bias assessment tool (QUIPS).

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting
Juvela et al[12]	moderate	low	low	moderate	moderate	low
Mensing et al[13]	low	high	low	moderate	moderate	low
Morita et al[14]	low	moderate	low	moderate	moderate	low
Murayama at al[15]	low	low	low	low	moderate	low
Wermer et al[16]	low	low	low	moderate	low	low
Molenberg et al[17]	low	high	low	low	low	low
Sonobe et al[18]	low	moderate	low	low	low	low
Gondar et al[19]	low	low	low	moderate	low	low
Lindgren et al[20]	low	moderate	low	moderate	moderate	low

Supplemental Table III. Baseline characteristics of patients with and without aneurysm rupture.

Pooled data	No aneurysm rupture (n,%)	Aneurysm rupture (n,%)	Total (n,%)	p-value
Number of patients	9714	226	9940	
Women	6392 (66)	163 (72)	6555 (66)	0.047
Mean age (range)	61.0 (15-100)	63.7 (23-93)	61.1 (15-100)	0.001
Hypertension	4230 (44)	114 (50)	4344 (44)	0.039
Ever smoker	2772 (29)	58 (26)	2830 (29)	0.34
Previous aSAH	556 (6)	37 (16)	593 (6)	<0.001
Positive family history of aSAH	969 (10)	23 (10)	992 (10)	0.92
Population				**0.004**
Finnish	1275 (13)	46 (20)	1321 (13)	
Japanese	7408 (76)	166 (74)	7574 (76)	
Dutch	743 (8)	11 (5)	754 (8)	
Swiss	228 (3)	3 (1)	291 (3)	
Multiple aneurysms	1960 (20)	58 (26)	2018 (20)	<0.001
Aneurysm size				**<0.001**
<7.0 mm	7435 (77)	105 (47)	7540 (76)	
7.0-9.9 mm	1320 (14)	42 (19)	1326 (14)	
10.0-19.9 mm	828 (9)	56 (25)	884 (9)	
>20.0 mm	131 (1)	23 (10)	154 (2)	
Aneurysm location				**<0.001**
Internal carotid artery	2107 (22)	28 (12)	2135 (22)	
Middle cerebral artery	3483 (36)	64 (28)	3547 (36)	
Anterior circulation or posterior circulation	4124 (43)	134 (59)	4258 (43)	
Phases score (median, range, mean, standard deviation)	7.0 (0-21) 7.2 ± 3.1	9.0 (2-20) 9.8 ± 4.0	7.0 (0-21) 7.2 ± 3.1	<0.001

aSAH; aneurysmal subarachnoid hemorrhage.

Chapter 8

General discussion

The studies described in this thesis were carried out to optimise the identification and screening of persons with a positive family history of aneurysmal subarachnoid haemorrhage (aSAH) and intracranial aneurysms, and to investigate risk factors for aneurysmal rupture. In this chapter, the main results of this thesis are put into perspective and implications for future directions are presented.

Part I: Positive family history of aneurysmal subarachnoid haemorrhage

There are several options to improve the screening of persons with a positive family history of aSAH and eventually decrease the risk of aSAH. First, the awareness in the general population that aSAH can have a hereditary basis can be improved by providing tools for people to find out themselves whether aSAH occurs in their family and whether or not screening may be beneficial. Increasing awareness in the general population about the fact that one may have an increased risk of aSAH may also cause distress among relatives. A screening tool can then provide reassurance if it turns out that they do not have an increased risk, while for persons with a first-degree relatives who have had aSAH preventive screening for intracranial aneurysms can be considered. This screening is known to be cost-effective for persons with two or more first-degree relatives when repeated every five to seven years between 20 and 70-80 years of age.[1, 2] For persons with only one affected first-degree relative screening twice during life at the age of 40 and 55 seems cost-effective.[3] For persons who have a first-degree relatives with stroke, it may be difficult to distinguish between aSAH and other types of stroke. Therefore, in **chapter 2** of this thesis, we aimed to develop a questionnaire for these persons with a first-degree relative who had a stroke that could be used to identify whether this relative has experienced an aSAH or another type of stroke. We found that with our questionnaire consisting of four multiple-choice questions on the symptoms, age at onset of the stroke, explanation of the stroke by the then treating physician and treatment given for the stroke, we can help first-degree relatives to discriminate an aSAH from other types of stroke in their affected relative. The positive predictive value of the questionnaire was 88% and the negative predictive value 98%. With the family history questionnaire, people in the general population can find out themselves whether aSAH occurs in their family and whether or not screening may be beneficial. To further optimise early identification of persons with a positive family history of aSAH who are eligible for screening, a study with a longer time period between the questionnaire and the stroke episode can be performed. The performance of the questionnaire may decrease after a longer time period because relatives' recall of the episode may decrease. Also, patients who died of aSAH, ischaemic stroke, or intracerebral haemorrhage could be included as currently we do not know the performance of our questionnaire in these relatives.

Second, more knowledge on risk factors for developing intracranial aneurysms in persons with a positive family history of aSAH enables a better selection of persons for screening and more tailored screening. The type of kinship may influence the risk of intracranial aneurysms and in **chapter 3** we found that in persons with ≥2 affected first-degree relatives, siblings have a higher risk of intracranial aneurysms than children. When preventive screening for intracranial aneurysms is offered to siblings this higher risk can be discussed with them when making a decision whether or not to undergo preventive screening.

Third, with known risk factors for the development of intracranial aneurysms, a model for predicting the probability of an intracranial aneurysm at first and follow-up screening in persons with a positive family history of aSAH can be developed for early risk stratification of persons at low or high risk of intracranial aneurysms. In **chapter 4** we therefore developed a risk score for intracranial aneurysms at first screening in persons with ≥2 affected first-degree relatives. This NASH score provides risk estimates for an intracranial aneurysm identified at first screening based on four characteristics (NASH, i.e., **N**umber of affected relatives, **A**ge, **S**moking, **H**ypertension). The risk of an intracranial aneurysm at first screening can now be individualized to a risk of 5% in persons aged 20-30 years with two affected relatives, without hypertension who never smoked, up to 36% in persons aged 60-70 years with ≥3 affected relatives, who have hypertension and smoke(d).

With the NASH score we were not able to predict the risk of an aneurysm during follow-up screening, and in **chapter 5** we developed a prediction score that predicts the risk of intracranial aneurysms during follow-up screening in persons with ≥2 affected first-degree relatives. Based on three characteristics (SPA, i.e., female **S**ex, **P**revious intracranial aneurysm/aSAH, **A**ge) the risk of an intracranial aneurysm during screening can now be individualized into a probability of finding an intracranial aneurysm from 2% in men aged 20-30 years without a previous intracranial aneurysm/aSAH at 5 years after initial screening up to a cumulative risk of 28% in women aged 60-70 years with a previous intracranial aneurysm/aSAH at 10 years after initial screening.

With the family history questionnaire, people in the general population can find out themselves whether aSAH occurs in their family and whether or not screening may be beneficial. For persons with ≥2 affected first-degree relatives individualized risk predictions of intracranial aneurysms at first and at follow-up screening may inform them about the risks and help to decide whether they

will undergo preventive screening. This gives the opportunity to use screening in a more targeted way. An advantage of identifying persons at low and high risk of developing intracranial aneurysms is that persons at high-risk can be given absolute risks of developing an aneurysm and are more informed about the importance of screening. Another advantage is that in persons with a low-risk, screening can be reduced which will reduce unnecessary radiological screening and inherent stress and anxiety. However, a disadvantage could be that persons with a low individualized risk decide not to perform screening, but present later with aSAH.

Future directions

The benefits of screening in persons with a positive family history of aSAH have been studied before with decision models.[1-3] However, individualized risks of intracranial aneurysm development in screening were not included in these models as these were not available at that time. In order to meaningfully inform decisions on screening in clinical practice we should therefore define the optimal screening strategy for each risk group. Using a Markov decision-analytic model with Monte Carlo simulation overall benefits of screening by analysing the health outcomes and costs of screening for intracranial aneurysms in persons with a low and high risk of intracranial aneurysms can be compared to no screening. The optimal screening strategy regarding age ranges and screening intervals in persons with a positive family history of aSAH can vary and the impact in costs and quality-adjusted life-years can be assessed. Persons with a high risk of intracranial aneurysms may turn out to benefit from intensified screening, while in persons with a lower risk screening may be reduced.

Work described in the first part of this thesis has mainly focussed on improving screening in persons with two affected first-degree with ruptured intracranial aneurysms. Evidence suggests that for persons with only one affected relative with aSAH, screening twice, at age 40 and 55, is also cost-effective.[3] In a prospective cohort with screened persons with only one affected relative with aSAH individualized risk of intracranial aneurysm development should be assessed and a decision model to define the optimal screening strategies in persons with only one affected relative with aSAH should be developed. Furthermore, it is thus far unknown whether screening is also cost-effective in persons with one or more first-degree relatives with an unruptured intracranial aneurysm. An observational screening cohort study is underway to determine the prevalence of intracranial aneurysms in persons with a positive family history with one or more first-degree relatives with unruptured intracranial aneurysms. A

promising feature is risk-prediction models on the risk of intracranial aneurysm not only with patient-based and environmental factors, but also including genetic and imaging risk factors. A genome-wide association studies meta-analysis recently identified several risk loci explaining over half of the heritability of intracranial aneurysms,[4] and sharper bifurcation angles of the arteries of the circle of Willes have been identified as predictive imaging markers for aneurysm development.[5, 6] With these genetic factors a polygenic risk score can be constructed and subdivisions into high and low polygenic risk scores can be made. These risk scores can be integrated into the risk predictions models to assess whether the risk prediction can be optimised. Imaging markers may to help to improve the risk prediction of finding an aneurysm during follow-up screening. Currently, these analyses are performed in our research group.

Part II: Risk of aneurysmal rupture according to positive family history and female sex

This second part of this thesis (**chapter 6 and 7**) was based on the results of meta-analyses of individual patient data from prospective cohort studies. In intervention research, the use of individual patient data is the 'gold standard' when performing a meta-analysis.[7] Also in prognostic research it is an increasingly popular tool as an alternative to meta-analyses based on aggregated data. A meta-analysis of individual patient data for prognostic research has clinical and statistical advantages: 1) individual patient data of multiple studies increase the sample size, and a larger sample size reduces the possibility of chance findings and increases the precision of the result;[8] 2) individual patient data allows for the use of standardised definitions, inclusion, and exclusion criteria;[8] 3) individual participant data facilitates standardisation of analyses and adjusted analyses with a consistent set of adjustment factors in each study and gives the possibility to check model assumptions;[9] 4) individual patient data meta-analysis allows for a more informative analysis of time-dependent data derived from the whole period of follow-up.[7]

In our individual patient data meta-analysis, we focused on family history of aSAH and sex as risk factors for aneurysmal rupture. To assess the risk of aneurysmal rupture on an individual basis, prediction models such as the PHASES score can be used. The PHASES score includes six predictors for rupture: **P**opulation, **H**ypertension, **A**ge, **S**ize, **E**arlier subarachnoid haemorrhage, and

Site.[10] A limitation of the PHASES study is that family history of aSAH was not taken into account to predict the risk of aneurysmal rupture because data on family history were not consistently available for all cohorts included. A higher rupture risk of intracranial aneurysms had been suggested in patients with a positive family history of aSAH compared to patients without such a history.[11] The definition of a positive family history may also play a role in the level of risk of rupture of familial intracranial aneurysms. In **chapter 3** we found that within families, siblings have a higher risk of intracranial aneurysms and aSAH than parents and children. In most countries, first-degree relatives are defined as parents, siblings, or children, while in some other countries, including Japan, first-degree relatives are defined as only parents and children, but not siblings. When defining first-degree relatives as parents, siblings, or children, the risk of aneurysmal rupture was two and a half times higher in familial than in sporadic patients (**chapter 6**). In cohorts both in- and excluding siblings in the definition of first-degree relatives, the risk of aneurysmal rupture decreased to a one and a half times higher risk in familial compared to sporadic intracranial aneurysms.

Also a higher rupture risk in women compared to men has been reported in a previous meta-analysis including both retrospective and prospective studies, but whether female sex was an independent risk factor could not be investigated because a multivariable analysis was not possible due to lack of individual patient data.[12] In **chapter 7** we found in our pooled cohort from nine prospective cohort studies with individual patient data that women had a higher risk of aneurysmal rupture than men and this sex difference is not explained by differences in patient- and aneurysm-related risk factors for aneurysmal rupture, being risk factors of the PHASES score, smoking, and a positive family history of aSAH. Based on these chapters, a more aggressive treatment approach is justified in familial patients defined as individuals with at least two affected first-degree relatives including parents, children, and siblings and in women.

In our study, we were not able to collect individual patient data from all eligible cohorts despite many efforts to obtain the data. A recent systematic review has shown that in only 25% of published individual patient data meta-analyses access to all individual patient data from all eligible cohorts was available.[13] Individual patient data meta-analysis are resource-intensive because substantial time is required to contact study authors, obtain individual patient data, and generate a consistent data format across studies. Another challenge of our study was that, even though we had individual patient data, the level of detail about which relatives were affected with aSAH was insufficient to redefine a

positive family history with two affected parents, siblings, or children in all studies. A possible way to overcome this is to prospectively plan individual patient data meta-analyses in collaboration with other research groups or by developing guidelines on a comprehensive set of common data elements, definitions and case report forms. These approaches allow for consistency in definitions, criteria, and outcome assessment across studies. It is then essential to be inclusive to prevent bias when studies within the collaboration do not reflect the entire set of existing studies. Currently, in intracranial aneurysm research, collaborations have been set up to perform this type of study and guidelines for Common Data Elements for intracranial aneurysm and aSAH research have been published.[14, 15]

Future directions

In the future, a new prediction model for aneurysmal rupture in a large pooled meta-analysis of patients with intracranial aneurysms should include the candidate predictors positive family history of aSAH and sex. Additionally, candidate predictors aspect ratio and irregular aneurysm shape, which are imaging factors also known to be associated with aneurysmal rupture,[16, 17] should be taken into account as well. With this model, individual risk prediction with absolute risks for aneurysmal rupture can be calculated taking all known factors for aneurysmal rupture into account and the prediction for aneurysmal rupture can be improved. To prevent differences in definitions of family history of aSAH researchers should ideally prospectively plan individual patient data meta-analysis in collaboration with other research groups. Data collected should include which relatives (parents, siblings or children) are affected to be able to study the extent to which siblings influence the higher risk of rupture in familial patients. Study populations should be evenly represented from several populations to prevent overrepresentation from populations with a higher rupture risk such as Japanese and Finnish populations,[10, 12] and to improve generalizability of the results. Furthermore, data on female-specific hormonal and reproductive factors,[18] and female-specific genetic factors should be collected to identify factors contributing to the increased risk of rupture in women as we still do not understand why women are at increased risk compared to men. A final method to achieve an even more tailored decision to whether or not preventively treat intracranial aneurysms is to take individual procedural complication risk into account as well. In a prospective cohort with data on procedural complications and treatment risk factors, independent risk factors for procedural complications can be assessed, and a prognostic model to provide individual risk estimates of procedural complications can be developed. These individual

predictions of procedural complication risks can then be weighed against individual predictions of risk of aneurysmal rupture and will help physicians to balance benefits and risks of treatment for each individual patient to guide treatment decisions.

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Chapter 9

Summary
Nederlandse samenvatting
(Summary in Dutch)

Summary

Intracranial aneurysms may rupture, causing aneurysmal subarachnoid haemorrhage (aSAH). Screening for intracranial aneurysms is important to prevent aSAH in persons at increased risk of aSAH due to a positive family history of aSAH. For optimal use of preventive screening, it is essential to identify these persons with a positive family history. For persons with a positive family history of aSAH who present for screening, individualised screening based on their risk profile can improve screening efficiency. In persons with a positive family history in whom an intracranial aneurysm is found during screening, more information about the risk of rupture of this aneurysm will allow a better decision to be made about whether or not to perform preventive treatment. In women intracranial aneurysms and aSAH occur more often than in men, but the reason for this female preponderance is thus far unknown. We do not yet know whether the higher risk of aSAH in women can be explained by the higher prevalence of unruptured intracranial aneurysms in women or also by a higher rupture rate of these aneurysms. In this thesis, we optimised the identification and screening of persons with a positive family history of aSAH, and investigated risk factors for aneurysmal rupture.

Part I: Positive family history of aneurysmal subarachnoid haemorrhage

Chapter 2 provides a family history questionnaire for persons who have first-degree relatives with a stroke. They can use this questionnaire to identify whether their relative experienced an aSAH or another stroke type. We also report the questionnaires accuracy to identify relatives of aSAH patients. With four multiple-choice questions on the symptoms, age at onset of the stroke, explanation of the stroke by the then treating physician and treatment given for the stroke, 29 of 30 first-degree relatives of aSAH patients were correctly identified. The questionnaire had a sensitivity of 97%, specificity of 93%, positive predictive value of 88%, and negative predictive value of 98% for the diagnosis aSAH, when tested in first-degree relatives of stroke patients.

In **chapter 3**, we report a cohort study to describe the influence of the type of kinship (parents, siblings, or children) of first-degree relatives of aSAH patients on the risk for unruptured intracranial aneurysms and aSAH. We included 154 families with 1.105 first-degree relatives. Of those 1.105 relatives, 146 had a aSAH and 326 relatives were screened for intracranial aneurysms, with intracranial aneurysms identified in 19% of them. Siblings of patients with familial aSAH had a statistically significant higher risk of both intracranial aneurysms (age-adjusted relative risk (RR): 2.04) and aSAH (RR: 1.62) than children. Parents of patients with familial aSAH have a lower risk of aSAH (RR: 0.44) compared to children.

Chapter 4 describes the development and external validation of a prediction score, which aims to predict the presence of an intracranial aneurysm at first screening in persons with ≥2 affected first-degree relatives. In a prospective cohort of 660 persons with ≥2 affected first-degree relatives screened in the University Medical Center Utrecht, 79 (12%) persons had an intracranial aneurysm. Independent predictors for an intracranial aneurysm were combined in the NASH score: **N**umber of affected relatives, **A**ge, **S**moking, and **H**ypertension. The model showed good performance in the development cohort (c-statistic: 0.68; 95% CI: 0.62-0.74) and moderate performance (c-statistic: 0.64; 95% CI: 0.57-0.71, calibration plot: slightly underestimated aneurysm risk) in an external validation cohort of 258 prospectively collected persons with ≥2 affected first-degree relatives screened in the University Hospital of Nantes (67 intracranial aneurysms; 26%). Predicted probabilities varied from 5% in persons aged

20-30 years with two affected relatives, who have no hypertension and never smoked, to 36% in persons aged 60-70 years with three or more affected relatives, who have hypertension, and smoke or have smoked in the past.

In **chapter 5** a prediction model for intracranial aneurysms during follow-up screening in persons with ≥2 affected first-degree relatives is presented. This model was derived from a prospective cohort of 499 persons with ≥2 affected first-degree relatives screened in the University Medical Center Utrecht and the University Hospital of Nantes. Independent predictors were female **S**ex, **P**revious intracranial aneurysm/aSAH, and older **A**ge (SPA). The SPA score showed good performance at five years (c-statistic: 0.70; 95% CI: 0.61-0.78) and ten years (c-statistic: 0.71; 95% CI: 0.64-0.78). The probability of finding an intracranial aneurysm ranged from 2% in men aged 20-30 years without a previous intracranial aneurysm/aSAH at five years after initial screening up to a cumulative risk of 28% in women aged 60-70 years with a previous intracranial aneurysm/aSAH at ten years after initial screening. The NASH score and SPA score give insight into which persons have a low or high risk of an intracranial aneurysm at first and during follow-up screening, which can help persons make a better-informed decision about whether or not to undergo screening.

Part II: Risk of aneurysmal rupture according to positive family history and female sex

Chapter 6 shows the results of an individual patient data meta-analysis in which we examined to what extent patients with familial unruptured intracranial aneurysms have a higher risk of rupture than those with sporadic unruptured intracranial aneurysms. We pooled individual patient data from eight prospective cohort studies, including 9,511 patients. In chapter 3 we found that within families, siblings have a higher risk of 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. In some countries, siblings are not included in the definition of first-degree relatives which may result in a lower risk of rupture in studies from these countries. In six cohorts, totalling 2,297 patients (17% familial) with 7,301 person-years of follow-up first-degree relatives were defined as parents, siblings, and children. After adjustment for the PHASES score (a score which combines the risk factors Population, Hypertension, Age, Size, Earlier subarachnoid haemorrhage, and Site) and smoking the adjusted

hazard rate of patients with familial compared to those with sporadic aneurysms was 2.56 (95% CI: 1.18–5.56). The adjusted hazard rate of patients with familial aneurysms compared to those with sporadic aneurysms in all studies, including those in which first-degree relatives are defined as only parents and children, but not siblings, was lower and no longer statistically significant: 1.44 (95% CI: 0.86–2.40). This systematic review confirms a higher risk of rupture for familial compared to sporadic intracranial aneurysms when defining first-degree relatives as parents, children, and siblings.

In **chapter 7** an individual patient data meta-analysis on the sex differences in rupture rate is described. We pooled individual patient data from nine cohorts totaling 9,940 patients (6,555 women, 66%) with 12,193 unruptured intracranial aneurysms and 24,357 person-years follow-up. The women/men ratio was 1.39 (95% CI: 1.02-1.90) when adjusting for the PHASES score, smoking, and a positive family history of aSAH. When assessing the risk of rupture of intracranial aneurysms in women, this higher risk should be taken into account and a more aggressive preventive treatment approach of unruptured intracranial aneurysms in women as compared to men may be justified.

In conclusion, this thesis provides a family history questionnaire to identify persons with a positive family history of aSAH. It offers a risk score for risk estimates for finding intracranial aneurysm at first and follow-up screening for persons with ≥2 affected first-degree relatives. It confirms the higher rupture risk of intracranial aneurysms in persons with a positive family history of aSAH. Finally, it also shows the higher rupture risk of intracranial aneurysms in women compared to men.

Nederlandse samenvatting

Intracraniële aneurysmata zijn verworven uitstulpingen in de slagaders van de hersenen. Ongeveer 3% van de bevolking heeft een intracraniële aneurysma. Wanneer een intracranieel aneurysma knapt (dit wordt ook wel ruptuur genoemd) leidt dit tot een aneurysmatische subarachnoïdale bloeding (aSAB), een vorm van beroerte. Jaarlijks worden ongeveer duizend mensen getroffen door een aSAB en ongeveer een derde van de mensen overlijdt aan de gevolgen ervan. De belangrijkste groep personen met een sterk verhoogd risico op een aSAB zijn degenen die familieleden hebben die al eerder een aSAB hebben gehad (ook wel personen met een positieve familie-anamnese voor aSAB genoemd). Bij personen met een positieve familie-anamnese voor aSAB komen intracraniële aneurysmata vaker voor, namelijk bij ongeveer 10%. Afhankelijk van het aantal aangedane eerstegraads familieleden (ouders, broers en zussen, of kinderen) met een doorgemaakte aSAB kan het risico om ook zo een bloeding te krijgen in de loop van het leven oplopen tot 25%.

Voor mensen met een positieve familie-anamnese kan een aSAB worden voorkomen door beeldvorming van de hersenslagaders (MR- en CT-angiografie), waarbij gezocht wordt naar intracraniële aneurysmata. Intracraniële aneurysma die op deze manier op tijd worden ontdekt, kunnen dan behandeld worden voordat een bloeding optreedt. De behandeltechnieken zijn niet zonder risico op complicaties. Het risico op complicaties moet worden afgewogen tegen het risico op een ruptuur. Bij personen met een positieve familie-anamnese voor aSAB is het risico op een ruptuur mogelijk hoger dan bij personen zonder een positieve familie-anamnese. Omdat intracraniële aneurysmata in de loop van het leven ontstaan moet deze screening gedurende het leven herhaald worden.

Intracraniële aneurysmata en aSAB komen vaker voor bij vrouwen dan bij mannen. Het is nog niet bekend of het hogere risico op een aSAB bij vrouwen kan worden verklaard door het vaker voorkomen van intracraniële aneurysmata bij vrouwen, door een hoger risico op een ruptuur van intracraniële aneurysmata bij vrouwen of door beide oorzaken.

Het doel van de studies beschreven in dit proefschrift was ten eerste om de herkenning en screening van personen met een positieve familie-anamnese voor aSAB te verbeteren en ten tweede om het effect van de risicofactoren positieve familie-anamnese voor aSAB en daarnaast ook van geslacht op het ruptuur risico van aneurysmata te onderzoeken.

Deel I: Positieve familie-anamnese voor aneurysmatische subarachnoïdale bloedingen

Hoofstuk 2 beschrijft een familie-anamnese vragenlijst voor personen met eerstegraads familieleden die een beroerte hebben gehad. De familie-anamnese vragenlijst kan gebruikt worden om vast te stellen of een familielid een aSAB of een ander type beroerte heeft doorgemaakt. Daarnaast wordt beschreven hoe betrouwbaar deze vragenlijst is om vast te stellen of een familielid een aSAB of een ander type beroerte heeft doorgemaakt. Door middel van vier meerkeuzevragen over de symptomen, leeftijd tijdens de beroerte, uitleg van de beroerte door de toenmalige behandelend arts en de behandeling die voor de beroerte werd gegeven, kunnen personen na het invullen vaststellen of hun familielid een aSAB heeft gehad. De voorspellende waarde om vast te stellen of een familielid een aSAB heeft doorgemaakt was hoog (positief voorspellende waarde van 88% en negatief voorspellende waarde van 98%).

Hoofdstuk 3 beschrijft de invloed van het type verwantschap van eerstegraads familieleden van aSAB patiënten op het risico voor intracraniële aneurysmata en aSAB. We bekeken in 154 families het risico op intracraniële aneurysmata en een aSAB. Broers en zussen hebben een statistisch significant hoger risico op zowel intracraniële aneurysmata als aSAB dan kinderen. Ouders hebben een lager risico op aSAB in vergelijking met kinderen.

Een predictiemodel kan worden gebruikt om de kans op een intracranieel aneurysma te voorspellen voor een persoon met een positieve familie-anamnese voor aSAB die zich presenteert voor screening op de aanwezigheid van aneurysmata. Ten eerste ontwikkelden wij in **hoofdstuk 4** een predictiemodel op basis van gegevens van 660 personen met een positieve familie-anamnese voor aSAB die voor het eerst gescreend werden. Factoren die het risico op een aneurysma bij het eerste screeningsmoment verhoogden waren onder andere: aantal aangedane familieleden, hogere leeftijd, roken en hypertensie. We combineerden de voorspellers in een risicoscore: de NASH score (**N**umber of affected relatives, **A**ge, **S**moking, and **H**ypertension). Daarna onderzochten we de voorspellende waarde van de NASH score in een Franse populatie. We zagen dat de risicoscore robuust was en generaliseerbaar naar een groep personen buiten de groep waarin het predictiemodel onderzocht was. Het risico op een aneurysma bij de eerste screening varieert van een kans van 5% bij jonge personen met twee aangedane familieleden, zonder hypertensie en die nooit

gerookt hebben, tot 36% bij personen ouder dan zestig jaar met drie of meer aangedane familieleden, met hypertensie en die roken of gerookt hebben.

Daarna ontwikkelden wij in **hoofdstuk 5** een predictiemodel voor personen met een positieve familie-anamnese die vervolg screening kregen. Factoren die het risico op een aneurysma bij vervolg screening verhogen waren: vrouwelijk geslacht, een eerder aneurysma/aSAB en een hogere leeftijd. Ook deze voorspellers zijn gecombineerd in een risicoscore: de SPA score (female **S**ex, **P**revious intracranial aneurysm/aSAH, and older **A**ge). Het risico op een aneurysma bij personen met twee of meer aangedane familieleden varieert van 2% tot 28%. Het risico was 2% bij jonge mannen zonder een eerder aneurysma/aSAB, vijf jaar na de eerste screening. Het risico was 28% bij oudere vrouwen met een eerder aneurysma/aSAB, tien jaar na de eerste screening. De NASH-score en SPA-score geven inzicht in welke personen met een positieve familie-anamnese een laag of hoog risico op een intracranieel aneurysma hebben bij de eerste screening en tijdens de vervolgscreening. Dit kan personen helpen om een betere beslissing te kunnen nemen om wel of geen screening met beeldvorming te laten verrichten.

Deel II: Ruptuur risico van intracraniële aneurysma bij een positieve familieanamnese of vrouwelijk geslacht

In het tweede gedeelte van dit proefschrift hebben we ons op het ruptuur risico van intracraniële aneurysmata gericht. **Hoofdstuk 6** beschrijft een meta-analyse (een onderzoek waarin resultaten van een aantal studies worden gebundeld en herberekend) op basis van individuele patiëntgegevens van acht verschillende studies met in totaal 9.511 patiënten. Hierin onderzochten we in hoeverre patiënten met een positieve familie-anamnese voor aSAB een hoger risico op een ruptuur hebben dan patiënten die dit niet hadden. In hoofdstuk 3 hadden wij al geconcludeerd dat binnen families broers en zussen een hoger risico op aSAB hebben dan ouders en kinderen. Het is dan ook belangrijk om broers en zussen op te nemen in de definitie van eerstegraads familieleden. In Japanse studies worden broers en zussen echter niet in deze definitie opgenomen. Indien wij eerstegraads familieleden definieerden als ouders, broers en zussen, of kinderen konden wij gegevens uit zes studies met 2.297 patiënten met 3.089 intracraniële aneurysmata en 7.301 persoonsjaren van follow-up onderzoeken. Het risico op een ruptuur was tweeënhalf keer hoger bij patiënten

met een positieve familie-anamnese voor aSAB dan bij patiënten die dit niet hadden. In de analyses waarbij alle studies werden meegenomen, inclusief de studies waarin eerstegraads familieleden werden gedefinieerd als alleen ouders en kinderen en niet broers of zussen, was het risico lager niet meer statistisch significant: een anderhalf maal hoger risico bij patiënten met een positieve familie-anamnese.

Hoofdstuk 7 beschrijft een meta-analyse op basis van individuele patiëntgegevens van negen studies met in totaal 9.940 patiënten met 12.193 intracraniële aneurysmata en 24.357 persoonsjaren van follow-up. Hierin onderzochten we of vrouwen met intracraniële aneurysmata een hoger risico op een ruptuur hebben dan mannen met intracraniële aneurysmata. Vrouwen hadden een 1.4 keer groter risico op een ruptuur, als we rekening hielden met bekende risicofactoren op een ruptuur. Bij de beoordeling van het risico op een ruptuur van intracraniële aneurysmata moet dus rekening worden gehouden met een positieve familie-anamnese voor aSAB en vrouwelijk geslacht. Een agressievere behandelingsaanpak bij personen met een positieve familie-anamnese en bij vrouwen in vergelijking met mannen kan dus gerechtvaardigd zijn.

Appendices

Dankwoord

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Publications by the author

About the author

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Dit proefschrift is tot stand gekomen dankzij de hulp, het enthousiasme en de steun van veel mensen. Hieronder wil ik een aantal van hen in het bijzonder bedanken.

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This thesis

- **Zuurbier CCM**, Mensing LA, Wermer MJH, Juvela S, Lindgren AE, Jääskeläinen JE, Koivisto T, Yamazaki T, Molenberg R, Uyttenboogaart M, van Dijk JMC, Aalbers MW, Morita A, Tominari S, Arai H, Nozaki K, Murayama Y, Ishibashi T, Takao H, Rinkel GJE, Greving JP, Ruigrok YM. Difference in rupture risk between familial and sporadic intracranial aneurysms: an individual patient data meta-analysis. *Neurology 2021; 97:1-9*

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About the author

Charlotte Catharina Maria Zuurbier was born on June 19th, 1991, in Wognum, the Netherlands. In 2009 she finished secondary school at the Oscar Romero in Hoorn (Gymnasium) and started medical school at the Academic Medical Center, University of Amsterdam.

As part of her medical training, she went abroad for a research internship at the British Columbia Children's Hospital in Vancouver in 2012. After obtaining her master's degree in 2015, she started working as a neurology resident at Spaarne Gasthuis in Haarlem. Here, she worked on research on traumatic brain injury. Her interest grew in scientific research and specifically in cerebrovascular diseases. In 2017 she started as a PhD candidate at the Department of Neurology at the University Medical Center Utrecht. During her PhD program, she obtained a master's degree in Epidemiology. In 2019, she worked for six months as a researcher at the University Hospital of Nantes, resulting in two chapters of this thesis. Charlotte received a Young Investigator Award from the European Stroke Organisation for her research in Chapter 6 of this thesis. In July 2021, she started working as a neurology resident at St. Antonius Hospital and she aims to pursue a career in Neurology.

Intracranial aneurysms are acquired dilations of the arteries in the brain. Approximately 3% of the adult population has an intracranial aneurysm. When an intracranial aneurysm bursts (this is also called rupture) this results in aneurysmal subarachnoid haemorrhage (aSAH), a subtype of stroke. Around 1000 people are affected by aSAH each year, and about one-third of those die from its effects. The most important group of persons at increased risk for aSAH are those who have family members who have had an aSAH (also called those with a positive family history for aSAH). In persons with a positive family history, aSAH can be prevented by imaging the brain's arteries looking for intracranial aneurysms. Intracranial aneurysms detected in this way can then be treated before aSAH occurs.

This thesis presents ways to optimise the identification and screening of persons with a positive family history of aSAH, and describes the rupture risk of intracranial aneurysms in women and in persons with a positive family history of aSAH.