INTRACRANIAL ANEURYSMS

towards better screening and prediction of rupture

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UMC Utrecht Brain Center

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Intracraniële aneurysma's

op weg naar betere screening en voorspelling van ruptuur

(met een samenvatting in het Nederlands)

Proefschrift

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te Amsterdam

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Voor Annet

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CHAPTER 1

General Introduction

GENERAL INTRODUCTION

Unruptured intracranial aneurysms and subarachnoid haemorrhage

A saccular intracranial aneurysm is an acquired dilatation of the vessel wall of a cerebral artery. An aneurysm is most often located at a bifurcation of an artery of the circle of Willis, an anastomotic ring of arteries at the base of the brain that provides the blood supply to the brain.[1] The prevalence of intracranial aneurysms in the general adult population is around 3%.[2] Most intracranial aneurysms will remain asymptomatic, but some can rupture, which results in aneurysmal subarachnoid haemorrhage (aSAH). This is a subset of stroke that carries a high case fatality (around 30%)[3] and considerable morbidity including long-term disability and cognitive impairment.[4] aSAH is one of the few cardiovascular diseases that occurs more often in women than in men.[3] Lifetime risk of aSAH in the general population is estimated to be 0.7%.[5] Although aSAH constitutes only around 10% of all strokes,[6] the young age at onset (mean 50–55 years)[3] and severity lead to a loss of productive life years similar to the far more common ischaemic stroke.[7] Since brain damage from the initial haemorrhage is a major cause of the poor outcome after aSAH,[8] prevention of aSAH has high potential to reduce its burden.

Identification of persons at high risk of aneurysmal rupture

Non-invasive screening for unruptured intracranial aneurysms with Magnetic Resonance Angiography can prevent future aSAH by early detection and preventive treatment of identified aneurysms. The purpose of screening is to prevent life years in good quality being lost through aSAH. This purpose should be carefully weighed against the disadvantages of screening, of which complications of preventive aneurysm treatment and anxiety induced by the screening are considered the most important ones. Screening should therefore ideally be done in persons in whom a high lifetime risk of aSAH outweighs this risk of complications and potential negative effects of screening on quality of life. The lifetime aSAH risk is highest for persons with a positive family history for aSAH[5] and screening has been shown cost-effective for this group of persons. In persons with at least two affected first-degree relatives with aSAH, screening every five to seven years between the age of 20 and 70–80 years is most cost-effective.[9] The yield of screening in this group is 11% at first screening,[10] with a lifetime aSAH risk of up to 20% depending on the presence of other risk factors.[11] In persons with only one first-degree relative with aSAH, screening twice at the age of 40 and 55 years may be considered,[12] with unruptured intracranial aneurysms being identified in 4% at first screening[11] and a lifetime aSAH risk of around 3%.[13] Thus, the high lifetime risk of aSAH in persons with a positive family history for aSAH is caused by an increased risk of both intracranial aneurysm development and rupture.[10,11,13] For first-degree relatives of patients with unruptured intracranial aneurysms however, the yield of screening and rupture risk are unknown. Therefore, it is currently unknown whether screening may also be effective in persons with at least one first-degree relative with an unruptured intracranial aneurysm, but a negative family history for aSAH.

Besides the group of persons with a positive family history for aSAH, the group of persons aged 35 years or older with hypertension who smoke or have a history of smoking also have a high lifetime risk of aSAH of up to 7%.[5] Whether screening may be effective in this group as well is as yet unknown.

To determine the cost-effectiveness of screening, information on complication risk of preventive aneurysm treatment and effects of screening on quality of life is needed. The risk of procedural clinical complications within 30 days of preventive aneurysm treatment is around 5% for endovascular treatment and around 8% for neurosurgical treatment.[14] Next to potential complications of preventive aneurysm treatment, an additional disadvantage of screening may be a negative impact of screening for intracranial aneurysms on quality of life (QoL) as shown in a previous study.[15] However, in that study QoL was assessed retrospectively many years after the initial screening and thereby this study was subject to bias.[15] To improve counselling persons at high risk of aSAH on the advantages and disadvantages of screening for unruptured intracranial aneurysms, more information on the course and predictors of the effect of screening on QoL is needed.

Characteristics of familial intracranial aneurysms

If intracranial aneurysms are identified with screening, the appropriate management for these aneurysms needs to be decided upon, in which the risk of rupture needs to be weighed against the risk of complications of preventive treatment. Since the complication risks of preventive aneurysm treatment are not negligible,[14] the estimated risk of complications outweighs the risk of rupture for many intracranial aneurysms identified with screening. In such instances, follow-up imaging to determine potential aneurysmal growth, which is a risk factor for aneurysm rupture, is often advised.[16] When aneurysmal growth is detected with follow-up imaging, preventive aneurysm treatment should be reconsidered.[17] The PHASES score was developed to predict the 5-year risk of aneurysm rupture, taking into account several characteristics associated with an increased risk of rupture: Population, Hypertension, Age, Size of the aneurysm, Earlier aSAH from another aneurysm and Site of the aneurysm.[18] However, this score was developed for sporadic (i.e. non-familial) aneurysms. A previous study, indirectly comparing familial and sporadic intracranial aneurysms retrieved from two different cohorts, suggested a higher rupture rate for familial intracranial aneurysms.[19] Therefore, more information on the additional risk of rupture of familial intracranial aneurysms is needed to improve decision-making on the management of unruptured intracranial aneurysms. It is unknown what may cause this additional risk of rupture of familial aneurysms. Several aneurysm related characteristics have been identified that influence the risk of rupture of sporadic intracranial aneurysms.[20] Whether these characteristics may be more prevalent in familial intracranial aneurysms and thereby explain the higher risk of rupture of familial intracranial aneurysms needs to be investigated, in order to better identify those aneurysms with an increased risk of rupture. Also, the current screening strategy is not that efficient, as it only identifies

an intracranial aneurysm in about 10% of persons at the initial screening. The efficiency of the current screening strategy could be improved by better identifying persons at the highest risk of aSAH. Next to aneurysm related characteristics, there may also be patient related characteristics that could help to optimize this identification. Since siblings of aSAH patients have the highest risk of also suffering from aSAH as compared with parents or children, type of kinship between the relative and the index aSAH patient is associated with risk of aneurysm rupture.[21] Patients with familial intracranial aneurysms are younger at time of aneurysm rupture as compared to patients with sporadic intracranial aneurysms.[22] However, it is unknown if age at time of aSAH correlates among first-degree relatives, and thereby if age at time of aSAH of the affected relative could be used to identify family members with an increased risk of aneurysm rupture.

Outline of thesis

The present thesis aims to improve screening and prediction of rupture by 1) studying the yield of screening for unruptured intracranial aneurysms and the effect of screening on QoL in high-risk groups, and by 2) studying the rupture risk of familial intracranial aneurysms, and patient and aneurysm related characteristics contributing to this risk.

Part I: Screening for unruptured intracranial aneurysms in high-risk groups

In **Chapter 2**, we present the results of a multicentre prospective cohort study to determine the yield and effects on QoL of screening for unruptured intracranial aneurysms in first-degree relatives of patients with unruptured intracranial aneurysms and present a model for predicting the probability of an intracranial aneurysm at screening. In **Chapter 3**, we study the yield of screening for unruptured intracranial aneurysms in persons aged 35 years or more with hypertension who smoke or have a history of smoking, and present a model for predicting the probability of an intracranial aneurysm at screening in this group. In **Chapter 4**, we describe a prospective cohort study on the effects on QoL of screening for familial intracranial aneurysms.

Part II: Characteristics of familial intracranial aneurysms

In **Chapter 5**, we assess the rupture rate of familial intracranial aneurysms compared with sporadic intracranial aneurysms retrieving patients from a prospectively collected cohort. In **Chapter 6**, this risk of rupture of familial intracranial aneurysms as compared to sporadic intracranial aneurysms is assessed further in an individual patient data meta-analysis using data from eight prospective cohorts. In **Chapter 7**, we present a multicentre cohort study to evaluate whether age at time of aSAH of first-degree relatives may be a factor to consider in determining the optimal screening strategy. In **Chapter 8**, we describe whether geometric and morphological risk factors for aneurysm rupture have a higher prevalence in patients with familial intracranial aneurysms compared with patients with sporadic intracranial aneurysms retrieved from a prospectively collected cohort.

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PART I

Screening for unruptured intracranial aneurysms in high-risk groups

CHAPTER 2

Aneurysm prevalence and quality of life during screening in relatives of unruptured intracranial aneurysm patients: a prospective study

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ABSTRACT

Background and objectives

Screening for unruptured intracranial aneurysms (UIAs) is effective for first-degree relatives (FDRs) of aneurysmal subarachnoid haemorrhage (aSAH) patients. Whether screening is also effective for FDRs of UIA patients is unknown. We determined the yield of screening in such FDRs, assessed rupture risk and treatment decisions of aneurysms that were found, identified potential high-risk subgroups and studied effects of screening on quality of life (QoL).

Methods

In this prospective cohort study we included FDRs, aged 20–70 years, of UIA patients without a family history of aSAH who visited the Neurology outpatient clinic in one of three participating tertiary referral centres in the Netherlands. FDRs were screened for UIA with magnetic resonance angiography (MRA) between 2017 and 2021. We determined UIA prevalence and developed a prediction model for UIA risk at screening using multivariable logistic regression. QoL was evaluated with questionnaires six times during the first year following screening and assessed with a linear mixed effects model.

Results

We detected 24 UIAs in 23 of 461 screened FDRs, resulting in a 5.0% prevalence (95% CI: 3.2 – 7.4%). Median aneurysm size was 3mm (IQR: 2 – 4mm) and median 5-year rupture risk assessed with the PHASES score was 0.7% (IQR: 0.4 – 0.9%). All UIAs received follow-up imaging, none were treated preventively. After a median follow-up of 24 months (IQR: 13 – 38 months) no UIA had changed. Predicted UIA risk at screening ranged between 2.3 – 14.7% with the highest risk in FDRs who smoke and have excessive alcohol consumption (c-statistic: 0.76; 95% CI: 0.65 – 0.88). At all survey moments health-related QoL (HRQoL) and emotional functioning were comparable with those in a reference group from the general population. One FDR with a positive screen expressed regret about screening.

Discussion

Based on the current data, we do not advise screening FDRs of UIA patients, since all identified UIAs had a low rupture risk. We observed no negative effect of screening on QoL. Longer follow-up should determine the risk of aneurysm growth requiring preventive treatment.

INTRODUCTION

Aneurysmal subarachnoid haemorrhage (aSAH) carries a high case-fatality rate of 30%,[1] and results in considerable morbidity including long-term disability and cognitive impairment.[2] Although aSAH constitutes only 5% of strokes, the young age at onset (mean 50 – 55 years),[2] and severity lead to a loss of productive life years similar to the far more common ischaemic stroke.[3] Non-invasive screening for unruptured intracranial aneurysms (UIAs) with Magnetic Resonance Angiography (MRA) can prevent future aSAH by early detection and preventive treatment of UIAs. Potential disadvantages of screening should also be considered. A previous study showed that screening for UIAs may have considerable negative effects on quality of life (QoL).[4] However, QoL was assessed retrospectively in this study, and therefore subject to bias. Also, the risks of complications of preventive aneurysm treatment are not negligible,[5] and thus for many UIAs identified at screening the risk of rupture does not outweigh the risk of complications.[6] Screening should therefore ideally only be done in persons with a high lifetime risk of aSAH.

The prevalence of UIA in the general population is around 3%.[7] The lifetime aSAH risk in the general population is highest for persons with a positive family history for aSAH[8] and screening is cost-effective in persons with ≥2 affected first-degree relatives (FDRs) with aSAH.[9] The yield of screening in this group is 11% at first screening,[10] with a lifetime aSAH risk of up to 20% depending on the presence of other risk factors.[5] Screening twice at the age of 40 and 55 years may also be considered in persons with only one FDR with aSAH,[5] with 4% UIAs being identified at first screening[11] and a lifetime aSAH risk of around 3%.[5] Thus, the high lifetime aSAH risk in FDRs of aSAH patients is caused by an increased risk of both UIA development and rupture.[5,8,10,11] For FDRs of UIA patients however, UIA prevalence and rupture risk are unknown. Therefore, it is currently unknown whether screening may also be effective in persons with ≥1 FDR with an UIA, but no FDR with aSAH.

We aimed to determine the yield of screening in persons with ≥1 FDR with an UIA, assess rupture risk, treatment decisions and short-term follow-up of the aneurysms found, and assess the effects of this screening on QoL. In addition, we aimed to develop a prediction model to identify potential high-risk groups among these persons who may benefit most from screening.

METHODS

Study population

We performed an observational prospective cohort study including FDRs, aged 20 – 70 years, of a consecutive series of index patients with UIA who visited the Neurology outpatient clinic of the University Medical Centre Utrecht (UMCU), Leiden University Medical Centre or Amsterdam University Medical Centre in the Netherlands between April 2017 and October 2021. Index patients were defined as adults with an incidental finding of saccular UIA(s) on MRA, computed tomography angiography or conventional angiography and no family history of aSAH (defined as no FDR (parent, sibling or child) with aSAH), nor a medical history of aSAH, polycystic kidney disease (PCKD) or other disease known to predispose for aneurysm development. Eligible index patients gave written informed consent to contact their FDRs. Exclusion criteria for FDRs were 1) age <20 years or >70 years at time of screening, 2) a medical history of UIA, PCKD, Ehlers-Danlos or fibromuscular dysplasia, 3) previous UIA screening, 4) severe comorbidity resulting in a reduced life expectancy that would potentially interfere with decision-making about UIA treatment, 5) relative contraindications for MRA such as pregnancy, a pacemaker or claustrophobia, and 6) cognitive deficits or language barrier.

We assumed a 5% prevalence of UIAs in our screening cohort based on 1. the 3.2% UIA prevalence in the general population,[7] the 4% UIA prevalence established in a screening cohort of FDRs of families with only one aSAH patient performed more than 20 years ago[11] which percentage was slightly increased to 5% taking into account the increased sensitivity of MRA over the years,[12] and 2. combined with an at least 2-fold increased aSAH risk in families with one FDR with aSAH[13] which may be extrapolated to a 2-fold increased UIA prevalence in these groups as compared with the general population.[7] With an expected sensitivity of MRA of 95%,[12] the target enrollment was set at 500 subjects which is equivalent to the identification of 25 UIA. Since recruitment was slow, partly due to the COVID-19 pandemic,[14] we decided during the course of our study to stop inclusion when 25 UIAs were discovered instead of continuing until 500 FDRs had been scanned.

Standard protocol approvals, registrations, and patient consents

The Medical Ethical Review Committee of the UMCU approved the study protocol (approval number 16-777). Eligible FDRs were included in the study after obtaining written informed consent.

Data collection

Baseline characteristics were assessed through a structured questionnaire. Smoking was defined as current smoking or smoking stopped within the last 20 years, since the cardiovascular morbidity of former smokers who stopped <20 years ago remains increased compared with never smokers.[15] Definitions of other baseline characteristics are described in Supplementary Table 1.

Yield of screening

In all FDRs 3-Tesla TOF-MRA was performed at the UMCU and these scans were independently evaluated for the presence of intradural UIAs by one of two experienced neuroradiologists (BKV and ICvdS), both with >15 years of experience in neurovascular imaging. In case of uncertainty, a decision was reached by consensus. Aneurysm location and size were recorded. The PHASES score was calculated to estimate 5-year rupture risk of the UIAs identified.[6] In case an UIA was identified the appropriate management (preventive treatment versus follow-up imaging to determine potential aneurysm growth) was determined by a multidisciplinary team, consisting of vascular neurologists, neuro-interventional radiologists and vascular neurosurgeons, and discussed with the FDR. Follow-up data up to September 2022 were included.

QoL

Coping style was assessed as a baseline characteristic related to QoL with a subscale of the Utrecht Coping List (UCL-P).[16] QoL was assessed through structured E-questionnaires that were sent to FDRs six times during one year (Supplementary Figure 1). If FDRs did not have email, questionnaires were sent by post instead. The E-questionnaires consisted of three validated questionnaires: 1. the EuroQol 6 Dimensions (EQ-6D) was used to measure health-related QoL (HRQoL);[17] 2. the Hospital Anxiety and Depression Scale (HADS) was used to measure emotional functioning in terms of anxiety and depression;[18] and 3. the Utrecht Scale for Evaluation of Rehabilitation - Participation (USER-P) restriction subscale was used to measure social participation.[19] Other baseline characteristics related to QoL and further details of the questionnaires used are described in Supplementary Table 1.

Statistical analysis

We calculated UIA prevalence in our screening cohort by dividing the total number of FDRs with a positive screen by the total number of FDRs screened. We performed multivariable logistic regression analysis to study the association between candidate predictors and the presence of an UIA at screening. Candidate predictors were pre-specified based on literature: age at screening, female sex, type of kinship with index being siblings, smoking, excessive alcohol consumption, hypertension, hyperlipidemia, diabetes, hypertensive pregnancy complication, regular physical exercise, the interaction between female sex/smoking, and smoking/excessive alcohol consumption.[7,20-24] Number of affected relatives was not included as a candidate predictor since all FDRs only had one FDR with UIA(s) (the index patient) at time of inclusion.[22] All candidate predictors were included in the full model, regardless of their association in the univariate analysis. Backward selection was performed based on Akaike Information Criterion (AIC).[25] The resulting model was subsequently corrected for overfitting using Ridge regression. The tuning parameter used in Ridge estimation for amount of shrinkage was based on the full model with all candidate predictors to reflect the selection of predictors.

The 95% CIs for the risk ratios after shrinkage were estimated based on the 95% CIs before shrinkage. We examined the performance of the final prediction model by determining its discrimination expressed by the C-statistic and corrected this for optimism. The C-statistic indicates to what extent the model could distinguish FDRs with a positive and a negative screen. We displayed the discrimination graphically with a receiver operating characteristic (ROC) curve. Subsequently, we generated a risk score by dividing the regression coefficients of the predictors in the final model by the smallest regression coefficient, resulting in points for each predictor. This risk score was displayed as a score chart accompanied by a table showing the mean estimated risk of finding an UIA at screening for each score. The high-risk group was defined as an absolute probability of finding an UIA at screening ≥10%, based on the UIA prevalence of 11% at first screening in persons with ≥2 affected FDRs with aSAH in whom screening has been shown cost-effective.[10]

We calculated mean sum-scores with standard deviation (SD) for the EQ-5D, EQ-VAS, HADS and USER-P at all survey moments, and expressed changes as mean differences with 95% confidence intervals (CI). QoL outcomes were compared between all screened FDRs and a reference group from the general Dutch population,[26,27] except for USER-P as no data on reference groups are available for this score. Linear mixed effect models (LMEs) with random intercept, random slope and fixed time effects were used to assess the course of QoL during the first year following screening and variables associated with QoL outcome. Time was included as a categorical variable based on survey moments; all other variables were included as fixed effects. LMEs were performed for all screened FDRs and stratified by screening result. Only variables available pre-screening were included in the model. During the conduct of the study, we decided to compare E-questionnaires on QoL completed before the start of the COVID-19 pandemic in the Netherlands (March 2020) to those completed after its start to assess if the pandemic had influenced QoL. Statistical analyses were performed using R software (version 3.6.2 R Foundation).[28]

RESULTS

Study population

79% of eligible FDRs (461/587) of 252 index patients were screened (Supplementary Figure 2). Most common reasons of FDRs to decline participation and thereby screening were ‘not wanting to know’, ‘afraid not being able to cope with the presence of an UIA’ or ‘too time-consuming’. 50% of FDRs that declined participation were women with a mean age of 51 years (SD 13 years), 46% were siblings and 54% children of the index patients. Of all included FDRs, 1% were parents, 36% siblings, and 63% children of the index patients. At time of inclusion all FDRs had one affected relative, namely the index

patient. Mean age at time of screening was 47 years (SD 13 years) and 55% were women. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics

	Positive screen (n, %)	Negative screen (n, %)
Number of patients	23 (5)	438 (95)
Women	15 (65)	239 (55)
Age at screening in years, mean (SD)	53 (10)	47 (13)
Ethnicity		
North-American/European	22 (96)	411 (94)
Other (Chinese, Indonesian, Surinamese, Turkish)	1 (4)	27 (6)
Type of kinship with index patient		
Parents	0 (0)	5 (1)
Siblings	12 (52)	156 (36)
Children	11 (48)	277 (63)
Affected FDRs with UIA after screening		
1	19 (83)	416 (95)
2	4 (17)	15 (3)
3	0 (0)	7 (2)
Smoking		
Current	9 (39)	92 (21)
Former[#]	8 (35)	85 (19)
Excessive alcohol consumption (≥18U/week)	4 (17)	15 (3)
Drugs		
Current	0 (0)	28 (6)
Former	5 (22)	44 (10)
Medical history		
Hypertension	7 (30)	84 (19)
Hyperlipidaemia	8 (35)	66 (15)
Diabetes	2 (9)	14 (3)
Migraine	3 (13)	41 (9)
Coronary artery disease	0 (0)	11 (3)
Hypertensive pregnancy complications*	3 (13)	46 (11)
Psychiatric history (ever)		
Depression	4 (17)	29 (7)
Anxiety	3 (13)	11 (3)
Other	1 (4)	17 (4)

Table 1. Baseline characteristics *(continued)*

	Positive screen (n, %)	Negative screen (n, %)
Medication (ever)		
Oral contraceptive	14 (61)	212 (49)
Hormone replacement therapy	0 (0)	9 (2)
Perceived stress previous year		
Always	4 (17)	21 (5)
Often	6 (26)	87 (20)
Sometimes	9 (39)	237 (54)
Never	4 (17)	93 (21)
Perceived stress lifelong		
Always	2 (9)	8 (2)
Often	8 (35)	71 (16)
Sometimes	12 (52)	283 (65)
Never	1 (4)	76 (17)
Physical complaints influencing mood	6 (26)	49 (11)
Educational level		
Primary school	2 (9)	6 (1)
All types of secondary education[$]	14 (61)	253 (58)
Higher vocational education and university	7 (30)	178 (41)
Married/living with partner	17 (74)	332 (76)[a]
Paid work	11 (48)	342 (78)
Regular physical exercise	4 (17)	128 (29)
Passive coping style, median UCL-P (IQR)	12 (9–15)	9 (8–11)
Physical examination at time of MRA		
Systolic blood pressure in mmHg, mean (SD)	135 (19)	137 (19)[b]
Diastolic blood pressure in mmHg, mean (SD)	83 (10)	83 (10)[b]
BMI in kg/m^2, mean (SD)	26 (4)	26 (4)[a]

[#] = stopped smoking <20 years ago; [*] = gestational hypertension and/or pre-eclampsia and/or HELLP syndrome; [$] = lower secondary education, higher secondary education, pre-university secondary education, secondary vocational education; [a] = ≤ 0.5% missing; [b] = ≤ 2.5% missing; BMI = Body Mass Index; IQR = interquartile range; n = number; SD = standard deviation; U= unit; UCL-P = Utrecht Coping List Passive

Yield of screening

According to our sample size calculation, inclusion was stopped after 25 UIAs were detected. However, during follow-up one of these UIA was assessed as being extradural instead and removed from the group of detected UIAs. Thus, we identified 24 UIAs in 23 FDRs from the total group of 461 FDRs, resulting in an UIA prevalence of 5.0% (95% CI, 3.2 – 7.4%). The UIAs identified had a median size of 3mm (IQR 2 – 4mm) and a median 5-year risk of rupture according to the PHASES score of 0.7% (IQR 0.4 – 0.9%) (Table 2).[6] Follow-up imaging was advised for all identified UIA, and none were advised to undergo preventive treatment. For 96% (22/23) of FDRs with a positive screening at least one radiological follow-up was available, one FDR declined follow-up. After a median follow-up period of 24 months (IQR 13 – 38 months), no aneurysm growth was detected (Table 2). Incidental findings diagnosed on the brain sequences of the MRA are described in Supplementary Table 2.

Table 2. Results of screening in first-degree relatives of patients with unruptured intracranial aneurysms

	461 screened persons (n, %)
FDRs with positive screen	23 (5)
FDRs with multiple UIA	1 (0)
UIA identified with screening	24 (5)
Aneurysm size in mm, median (IQR)	3 (2–4)
Aneurysm location	
Internal carotid artery	3 (13)
Ophthalmic artery	1 (4)
Anterior choroid artery	1 (4)
Anterior communicating artery	5 (21)
Middle cerebral artery	10 (42)
Posterior communicating artery	4 (17)
PHASES, median % 5-year rupture risk (IQR)	0.7 (0.4–0.9)
Treatment UIA	
Follow-up imaging	24 (100)
Preventive treatment	0 (0)
Duration of follow-up in months, median (IQR)	24 (14–38)
Detection of growth (≥1mm) during follow-up[29]	0 (0)

FDRs = first-degree relatives; IQR = interquartile range, MRA = magnetic resonance angiography; n = number; SD = standard deviation; UIA = unruptured intracranial aneurysm

High-risk groups

We had no missing data for the candidate predictors. The full model had a C-statistic of 0.80 (95% CI, 0.72 – 0.89), univariate and multivariate ratios for risk of UIA at screening for all candidate predictors are shown in Supplementary Table 3. Multivariable logistic regression identified three predictors for finding an UIA at screening: higher age at time of screening, smoking and excessive alcohol consumption (Table 3). After shrinkage, the selected model had a C-statistic of 0.76 (95% CI, 0.65 – 0.88) (Figure 1). The regression equation is provided in the legend of Table 3.

Table 3. Multivariable ratios for risk of unruptured intracranial aneurysms at screening from the final model before and after shrinkage

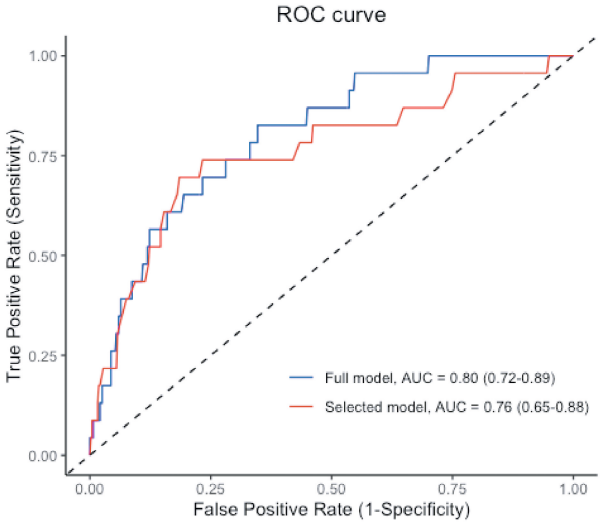
	Multivariate OR (95% CI) before shrinkage	Multivariate OR (95% CI) after shrinkage*
Age per year	1.05 (1.01–1.09)	1.02 (0.98–1.06)
Smoking#	4.63 (1.83–13.38)	1.82 (0.67–4.93)
Excessive alcohol use	4.50 (1.15–14.67)	3.04 (0.85–10.85)

*# = current smoker or stopped <20 years ago; * = adjusted for optimism using Ridge regression; CI = confidence interval; OR = Odds Ratio.*

*Regression equation: -4.19333657 + 0.60054111 * Smoking + 0.01819373 * Age at time of screening + 1.11170844 * Excessive alcohol consumption*

Regression coefficients were subsequently translated into a score chart (Supplementary Table 4) with mean predicted probabilities per score shown in Supplementary Table 5. The mean absolute UIA risk at screening ranged from 2.3% in persons aged 20 – 29 years who did not smoke and/or did not consume excessive alcohol to 14.7% in persons who smoke and consume excessive alcohol regardless of their age (Figure 2).

Figure 1. Receiver operating characteristic (ROC) curve for predicted probability of finding an unruptured intracranial aneurysm at screening



AUC = area under the curve; ROC = receiver operating characteristic

Figure 2. Risk chart with absolute probabilities (%) of finding an unruptured intracranial aneurysm at screening

	No smoking#	Smoking#	Age
No excessive alcohol consumption	2.3	4.0	20-29y
	2.8	4.8	30-39y
	3.3	5.9	40-49y
	4.0	6.9	50-59y
	4.8	8.0	60-69y
Excessive alcohol consumption	6.9	14.7	20-29y
	8.0	14.7	30-39y
	14.7	14.7	40-49y
	14.7	14.7	50-59y
	14.7	14.7	60-69y

<5%
5-10%
>10%

 # = current smoker or stopped <20 years ago; y = year

QoL

89% (2460/2766) of all E-questionnaires were returned. Return rates were not related to screening result. The proportion of major life events reported during the study period (which may influence QoL) was comparable between screen-positives (6/19 (32%)) and screen-negatives (124/374 (33%)). Of all FDRs who returned the E-questionnaire one year after screening and answered the question how they felt about their decision to be screened for UIA (n=129), one FDR with a positive screen expressed regret about screening (1/129 (0.8%)).

Analysis of the complete screening cohort showed similar unadjusted HRQoL and emotional functioning compared with the general population (Supplementary Figure 3).[26,27] One year after screening, HRQoL improved slightly compared with pre-screening (mean adjusted EQ-5D sum-score improvement 1.38; 95% CI 0.36 – 2.40), levels of anxiety remained the same, levels of depression slightly increased but remained lower than the general population (mean adjusted HADS depression sum-score increase 0.24; 95% CI 0.03 – 0.45), while social participation slightly decreased (mean adjusted USER-P sum-score change -1.21; 95% CI -1.96 – -0.47)(Supplementary Table 6). Factors that negatively influenced all QoL outcomes were a psychiatric history, passive coping style, experienced stress throughout life rated as always or often, and the presence of physical complaints that subjectively affect mood (Supplementary Table 6). FDRs with a positive screen for UIA already reported a lower HRQoL before the screening (positive screen mean EQ-5D 80.3 (95% CI 72.3 – 88.3) compared with negative screen mean EQ-5D 91.6 (95% CI 90.2 – 93.0)) (Table 4 and Supplementary Figure 3).

Table 4. Quality of life outcomes for first-degree relatives with a positive and negative screening for unruptured intracranial aneurysms in unadjusted mean sum-scores with standard deviation

	HRQoL EQ-5D		EQ-VAS		Emotional functioning HADS		Restrictions daily activities USER-P	
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
Positive screen								
Pre-MRA	21	80.3 (18.8)	21	78.1 (14.4)	21	10.1 (7.8)	21	94.9 (11.3)
Post-MRA, before result	22	85.5 (18.6)	22	75.7 (17.2)	22	10.5 (8.0)	20	95.4 (9.5)
2 weeks post-MRA result	20	86.8 (12.5)	20	75.6 (14.8)	20	9.7 (7.3)	20	94.1 (10.2)
4 weeks post-MRA result	20	86.7 (11.4)	20	73.2 (20.5)	20	9.9 (7.3)	20	93.1 (12.7)
6 months post-MRA result	20	86.8 (14.4)	20	73.3 (17.6)	20	10.6 (8.2)	19	89.9 (17.3)
1 year post-MRA result	18	85.8 (20.0)	18	81.2 (9.3)	18	8.3 (8.3)	18	89.6 (18.7)
Negative screen								
Pre-MRA	434	91.6 (14.4)	432	84.3 (10.9)	434	6.7 (5.4)	419	98.0 (7.3)
Post-MRA, before result	430	92.0 (13.5)	428	84.4 (11.0)	428	6.5 (5.7)	420	98.0 (7.7)
2 weeks post-MRA result	347	93.3 (12.9)	346	84.5 (10.9)	347	6.1 (6.0)	336	98.3 (5.8)
4 weeks post-MRA result	392	93.9 (12.3)	391	84.7 (11.3)	389	6.0 (6.0)	383	97.6 (9.4)
6 months post-MRA result	394	92.7 (14.2)	391	83.6 (11.2)	392	6.2 (6.1)	386	98.1 (6.2)
1 year post-MRA result	365	93.0 (13.5)	363	83.8 (12.1)	363	6.7 (6.4)	354	97.0 (10.3)

EQ-5D = EuroQol 5 Dimensions; EQ-VAS = EuroQoL Visual-Analog Scale; HADS = Hospital Anxiety and Depression Scale; HRQoL = Health Related Quality of Life; MRA = magnetic resonance angiography; n = number; SD = standard deviation; USER-P = Utrecht Scale for Evaluation of Rehabilitation - Participation

FDRs with a positive screen reported a higher level of depression six months after screening, a lower HRQoL (EQ-5D) four weeks after receiving the screening result and rated their health lower on the EQ-VAS two weeks, four weeks and six months after the screening result (Supplementary Figure 3) as compared to FDRs with a negative screen. One year after screening, FDRs with a positive screen reported a lower social participation (mean adjusted USER-P sum-score change -5.90; 95% CI, -9.94 – -1.86) as compared to pre-screening (Supplementary Table 7 and Supplementary Figure 5). Comparison of E-questionnaires on QoL completed before and after the start of the COVID-19 pandemic, did not show worse reported QoL after the start of the pandemic.

DISCUSSION

In this observational prospective cohort study, we found a 5% UIA prevalence in FDRs of patients with UIA and a negative family history for aSAH. Predictors for finding UIA at screening were higher age at time of screening, smoking and excessive alcohol consumption with predicted UIA risk ranging between 2.3 – 14.7% depending on the presence of these predictors. All UIAs identified at screening were small with a low rupture risk requiring no preventive treatment, and follow-up imaging in the initial years after screening showed no growth of the UIAs detected. No clinically relevant negative effect of screening on QoL was found one year after screening.

The 5% (95% CI 3 – 7%) UIA prevalence in our study is in the same range as the previously reported UIA prevalence of 4% (95% CI 3 – 6%) established in a screening cohort study of persons with one FDR with aSAH performed >20 years ago.[11] However, we identified smaller UIAs (mean size 3mm [range 1 – 7mm]) compared with this previous study (mean size 4.5mm [range 2 – 11mm]).[11] Small aneurysms may have been missed in that previous study as the sensitivity of MRA has increased over the years,[12] thus the previously reported UIA prevalence of 4% in persons with one FDR with aSAH could be an underestimation. We found lower predicted probabilities of identifying an UIA at screening (mean 5%, range 2 – 15%) compared with screening persons with ≥2 FDRs with aSAH (mean 12%, range 5 – 36%).[22] This is probably explained by the number of affected FDRs and the aneurysm being unruptured or ruptured in these FDRs (in the present study most persons only had one FDR with UIA versus ≥2 FDRs with aSAH in the previous study). Predictors of a positive screen for UIA in persons with ≥2 FDRs with aSAH were age, smoking, hypertension and number of affected FDRs.[22] We also identified age and smoking as predictors of a positive screen, but not hypertension and number of affected relatives. The latter is because all our included FDRs had one affected FDR at time of screening. Results of previous studies on hypertension as an additional risk factor for UIA development in familial UIA patients are conflicting. A previous retrospective analysis of a prospectively collected database in the Netherlands identified hypertension as an additional risk factor for UIA development in 236 persons

screened because of familial aSAH (≥2 FDRs with aSAH),[30] while another retrospective analysis of a prospectively collected database in Finland showed that hypertension was no additional risk factor for UIA development in 1,520 persons with a positive family history (≥2 affected FDRs).[31] We also identified excessive alcohol consumption to be a predictor of a positive UIA screen, independently of and even to a greater extent than smoking, whereas previous studies showed excessive alcohol consumption to be a risk factor for aSAH but not for UIA.[20,24,32] This might be caused by methodological differences with our study in data collection and the decision to analyze alcohol consumption as a continuous or dichotomous variable.

Previously, the effect of screening for UIA on QoL has only been studied retrospectively in persons screened because of familial aSAH.[4] In that study, QoL was assessed by a structured telephone interview after a mean period of eight years after first screening, and a lower HRQoL was found in persons with a positive screen for UIA compared to both persons with a negative screen and a reference population.[4] Our study did not find such a negative effect, which suggests that the negative finding in the previous study can be explained by bias from its retrospective design. We only observed a slight increase in depression levels and decrease in social participation one year after screening, but the depression levels were still lower than those from the general population.[27] As the decrease in social participation was small and was not accompanied by a decrease of additional QoL outcome measures, we do not think this decrease is clinically meaningful. In our study, factors negatively influencing QoL after screening were a psychiatric history, passive coping style, perceived stress throughout life rated as always or often, and the presence of physical complaints that subjectively affect mood. These factors are consistent with previous studies.[33,34] Interestingly, we found reported HRQoL pre-screening to be lower for FDRs who later had a positive screen for UIA compared with FDRs who later had a negative screen. What causes this difference is unknown and requires further study. Hypothetically there could be an overlap in risk factors for lower HRQoL and UIA development since anxiety disorders and perceived stress have been associated with UIA and aSAH.[34]

Strengths of this study include the prospective design and the standardized investigation using TOF-MRA in a relatively large cohort of patients. Also, the high proportion (82%) of eligible FDRs agreeing to participate in our study leads to generalizable results. Moreover, obtaining prospective QoL data at multiple moments enabled us to compare QoL outcomes before and after screening and also study the course of QoL. Our study also has limitations that need to be addressed. First, the small number of UIAs found in our cohort, permits a selection of relatively few predictors in our multivariate models. Second, we were not able to externally validate our model predicting UIA risk at first screening since, to the best of our knowledge, there are no comparable prospective cohorts available.

Third, to assess the rupture risk of identified UIA we used the PHASES score, but this score did not incorporate the known additional rupture risk for familial UIA.[6] Fourth, we included relatively few persons with multiple FDRs with UIA making it unable to draw definite conclusions on number of affected FDRs as a potential predictor of UIA risk. Last, two potential predictors of QoL were measured using non-validated questionnaires, e.g. perceived stress and the presence of physical complaints affecting mood.

Since all UIAs identified in our study were small with a low rupture risk and none were treated preventively, we currently do not advise screening in FDRs of patients with UIA and a negative family history for aSAH, even though we found no evidence that QoL is negatively influenced by screening. As UIAs may grow over a longer period of time and growth is a known risk factor for UIA rupture, preventive treatment of the UIAs identified in our study may be indicated in the future if growth is detected with follow-up imaging.[35] If during an extended follow-up UIA growth (or even UIA rupture) does occur, then our advice not to screen FDRs of UIA patients should be reconsidered. This would require a separate study to carefully weigh the risks and benefits of screening, for example in a decision model with various estimates of risks of growth and rupture. Final proof should come from long-term follow-up data of FDRs of UIA patients with a negative and a positive screen. At present, such FDRs should be informed on the negative effect of smoking and excessive alcohol consumption on their risk of developing an UIA.

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SUPPLEMENTARY CONTENT

Supplementary Table 1. Definitions of baseline characteristics and questionnaires on quality of life

Baseline characteristic	Definition
A medical history of a disease	A diagnosis of a specific disease by a physician and/or the use of the medication for the disease as reported by the FDR
Medication use	Specifically for hormone replacement therapy and oral contraceptives
Excessive alcohol consumption	≥18 units per week[1]
Hypertension	As diagnosed by a physician and/or the use of antihypertensive medication
Hypertensive pregnancy complication	Gestational hypertension and/or pre-eclampsia and/or HELLP syndrome
Physical exercise	As indicated by the FDR and converted to MET[2]
Regular physical exercise	≥3 times a week vigorous exercise with a MET >6[1]
Body Mass Index	Calculated from length and height as indicated by the FDR at time of screening
Psychiatric history	A psychiatric disease for which they were treated by a psychiatrist and/or with medication as reported by the FDR
Perceived stress	The subjective presence of psychological symptoms such as feeling tense, anxious or having sleeping difficulties[3]
Physical symptoms affecting mood	As indicated by the FDR

Supplementary Table 1. Definitions of baseline characteristics and questionnaires on quality of life *(continued)*

Questionnaire	Definition
UCL-P	The UCL-P consists of seven items that can be scored on a 4-point scale ranging from 1 (seldom) to 4 (very often), resulting in a sum score between 7 (low level) and 28 (high level of passive coping).[4]
EQ6D	The EQ-6D evaluates on a 3-point scale whether no, moderate or severe problems exist for six domains: mobility, self-care, daily activities, pain/discomfort, mood, and cognition. The EQ-6D is an extended version of the EQ-5D additionally evaluating the cognitive domain, we analyzed the EQ-5D and cognitive domain separately. The EQ-5D produces a five-digit health profile from which a health index score can be computed. This index score serves as a measure of HRQoL, ranging between 0 (worst) and 100 (best HRQoL). The cognitive domain of the EQ-6D was scored from 1 to 3 points, with higher scores indicating worse cognitive functioning. Subjects were asked to rate their health on a visual-analog scale (EQ-VAS), ranging from 0 (worst) to 100 (best imaginable health) as well.[5]
HADS	The HADS is a questionnaire consisting of 14 items, 7 items evaluating anxiety and 7 items evaluating depression. Each item can be scored from 0 to 3, with higher scores indicating higher levels of anxiety and/or depression. Usually, a sum score of 8/21 is used as a cut-off point for either anxiety or depression.[6]
USER-P	The USER-P assesses participation in eleven activities such as vocational, leisure or social activities. Each item can be scored as '0' (not possible), '1' (with help), '2' (with difficulty), '3' (without difficulty) or as 'not applicable'. Sum scores can be converted to an overall score ranging from 0 (unfavorable) to 100 (favorable participation) based on the items that are applicable. We defined the presence of restrictions in participation as scores ≤1 per activity.[7]

EQ6D = EuroQol 6 Dimensions; FDR = first-degree relative; HADS = Hospital Anxiety and Depression Scale; HELLP = Hemolysis Elevated Liver enzymes and Low Platelets; MET = Metabolic Equivalent Task units; MRA = magnetic resonance angiography; UCL-P = Utrecht Coping List Passive; USER-P = Utrecht Scale for Evaluation of Rehabilitation - Participation

Supplementary Table 2. Incidental findings on screening magnetic resonance angiography

	461 screened FDRs (n, %)
Total number of secondary findings	107 (23)
Clinical consequence*	10 (2)
Arachnoid cyst	5 (1)
Arteriovenous malformation	1 (0)
Atrophy	10 (2)
Carotid artery stenosis	1 (0)
Cavernoma	1 (0)
Empty sella	1 (0)
Extradural carotid aneurysm	13 (3)
Intracranial arterial stenosis	1 (0)
Ischaemic lesion	5 (1)
Mega cisterna magna	3 (1)
MVNT	1 (0)
Pineal cyst	1 (0)
Pituitary enlargement	2 (0)
White matter lesions	62 (13)

** = radiological follow-up or blood tests to test pituitary function because of pituitary enlargement on magnetic resonance angiography; FDR = first-degree relative; n = number; MVNT = multinodular vacuolating neuronal tumour*

Supplementary Table 3. Univariate and multivariate ratios for risk of unruptured intracranial aneurysms at screening from the full model

Predictor	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age at screening, per year	1.04 (1.01–1.08)	1.05 (0.99–1.11)
Female sex	1.56 (0.65–3.76)	5.33 (0.75–113.60)
Siblings#	1.97 (0.85–4.57)	0.84 (0.22–3.08)
Smoking*	4.18 (1.62–10.80)	14.90 (2.05–336.38)
Excessive alcohol use	5.94 (1.80–19.61)	15.42 (0.65–190.46)
Hypertension	1.84 (0.74–4.62)	0.73 (0.19–2.39)
Hyperlipidaemia	3.01 (1.23–7.37)	1.75 (0.48–6.36)
Diabetes	2.88 (0.62–13.52)	3.18 (0.40–17.63)
Hypertensive pregnancy complication	1.28 (0.37–4.47)	0.77 (0.15–2.86)
Regular physical exercise	0.51 (0.17–1.53)	0.70 (0.19–2.07)
Female sex*smoking	2.57 (1.09–6.03)	0.26 (0.01–2.50)
Smoking*Excessive alcohol	6.42 (1.64–25.16)	0.24 (0.01–7.50)

*# = versus other (children/parents); * = current smoker or stopped <20 years ago; CI = confidence interval; OR = Odds Ratio.*

Supplementary Table 4. Score chart

	No smoking[#]	Smoking[#]	Age
No excessive alcohol consumption	0	3	**20-29y**
	1	4	**30-39y**
	2	5	**40-49y**
	3	6	**50-59y**
	4	7	**60-69y**
Excessive alcohol consumption	6	9	**20-29y**
	7	10	**30-39y**
	8	11	**40-49y**
	9	12	**50-59y**
	10	13	**60-69y**

[#] = current smoker or stopped <20 years ago; y = year

Supplementary Table 5. Predicted probability (%) of finding an unruptured intracranial aneurysm at screening based on the prediction score

Risk score	n	Mean predicted probability (%)
0	22	2.3
1	52	2.8
2	65	3.3
3	83	4.0
4	112	4.8
5	44	5.9
6	27	6.9
7	37	8.0
≥8	19	14.7

n = number of patients

Supplementary Table 6. Results from linear mixed model analysis of quality of life over time (A) and according to predictors (B) for the complete cohort

	HRQoL (EQ-5D)	Anxiety (HADS)	Depression (HADS)	Restrictions (USER-P)
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
A. Changes over time				
Pre-MRA	Ref	Ref	Ref	Ref
Post-MRA, before result	0.34 (-0.63–1.30)	-0.12 (-0.32–0.09)	-0.03 (-0.23–0.17)	-0.03 (-0.73–0.68)
2 weeks post-MRA result	1.29 (0.25–2.32)	-0.27 (-0.49– -0.05)	-0.00 (-0.22–0.21)	-0.16 (-0.91–0.60)
4 weeks post-MRA result	1.74 (0.75–2.74)	-0.40 (-0.61– -0.19)	0.02 (-0.19–0.22)	-0.96 (-1.68– -0.24)
6 months post-MRA result	0.90 (-0.10–1.89)	-0.31 (-0.53– -0.10)	0.06 (-0.14–0.27)	-0.62 (-1.34–0.11)
1 year post-MRA result	1.38 (0.36–2.40)	-0.14 (-0.35–0.08)	0.24 (0.03–0.45)	-1.21 (-1.96– -0.47)
B. Predictors[§]				
Age at screening (continuous)	-0.01 (-0.09–0.07)	-0.02 (-0.03–0.00)	-0.00 (-0.02–0.01)	-0.04 (-0.09–0.01)
Female sex	-1.39 (-3.30–0.52)	0.33 (-0.10–0.76)	-0.64 (-1.06– -0.22)	-0.06 (-1.23–1.12)
Psychiatric history	-3.36 (-6.41– 0.31)	1.02 (0.34–1.71)	1.06 (0.39–1.73)	-2.17 (-4.03– -0.31)
Anxiety history	-9.62 (-15.24– -4.01)	0.04 (-1.22–1.30)	-0.69 (-1.93–0.54)	-2.71 (-6.30–0.88)
Passive coping style[#]	-1.54 (-1.92– -1.15)	0.54 (0.46–0.63)	0.44 (0.35–0.52)	-0.46 (-0.70– -0.23)
Perceived stress previous year				
Never or sometimes	Ref	Ref	Ref	Ref
Always or often	1.07 (-1.47–3.61)	1.11 (0.54–1.68)	0.42 (-0.14–0.98)	0.34 (-1.24–1.91)
Perceived stress lifelong				
Never or sometimes	Ref	Ref	Ref	Ref
Always or often	-4.53 (-7.28– -1.77)	0.86 (0.24–1.48)	0.96 (0.35–1.56)	-2.69 (-4.41– -0.97)

Supplementary Table 6. Results from linear mixed model analysis of quality of life over time (A) and according to predictors (B) for the complete cohort *(continued)*

	HRQoL (EQ-5D)	Anxiety (HADS)	Depression (HADS)	Restrictions (USER-P)
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Physical complaints affecting mood	-6.50 (-9.45– -3.55)	1.01 (0.35–1.67)	0.87 (0.22–1.52)	-3.70 (-5.57– -1.83)
Regular physical exercise	0.40 (-1.65–2.45)	0.05 (-0.41–0.51)	-0.25 (-0.70–0.20)	1.08 (-0.18–2.33)
Educational level				
Other	Ref	Ref	Ref	Ref
Primary school or lower secondary	-2.82 (-5.11– -0.52)	0.78 (0.27–1.30)	0.90 (0.40–1.41)	-0.66 (-2.08–0.76)
Recent smoking	1.82 (-0.12–3.76)	-0.59 (-1.03– -0.16)	-0.46 (-0.89– -0.04)	0.05 (-1.14–1.24)
Excessive alcohol consumption	-1.95 (-6.67–2.77)	-0.26 (-1.32–0.79)	-0.19 (-1.23–0.85)	0.19 (-2.86–3.23)
Hypertension	-3.49 (-5.91– -1.06)	0.02 (-0.52–0.57)	0.34 (-0.19–0.88)	-1.83 (-3.32– -0.35)

[§] = to estimate for example the HRQoL outcome for persons with a psychiatric history at one year follow-up, you first add 1.38 to the reference value (the change in HRQoL over time) and subsequently subtract 3.36 (the influence of psychiatric history). [#] = per point increase UCL-P; CI = confidence interval; EQ-5D = EuroQol 5 Dimensions; HADS = Hospital Anxiety and Depression Scale; Ref = reference group; MRA = magnetic resonance angiography; USER-P = Utrecht Scale for Evaluation of Rehabilitation - Participation.

Supplementary Table 7. Results from linear mixed model analysis of quality of life over time (A) and according to predictors (B) for screen-positives vs. screen-negatives (I)

	Anxiety (HADS)		Depression (HADS)	
	Positives	**Negatives**	**Positives**	**Negatives**
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
A. Changes over time				
Pre-MRA	Ref	Ref	Ref	Ref
Post-MRA, before result	0.55 (-0.46–1.56)	-0.15 (-0.36–0.06)	0.27 (-0.94–1.48)	-0.04 (-0.24–0.16)
2 weeks post-MRA result	-0.22 (-1.25–0.81)	-0.27 (-0.50– -0.05)	-0.26 (-1.50–0.97)	0.01 (-0.20–0.23)
4 weeks post-MRA result	-0.06 (-1.09–0.97)	-0.41 (-0.63– -0.20)	-0.16 (-1.39–1.08)	0.03 (-0.18–0.24)
6 months post-MRA result	-0.22 (-1.25–0.81)	-0.32 (-0.53– -0.10)	0.74 (-0.50–1.97)	0.03 (-0.18–0.24)
1 year post-MRA result	-0.65 (-1.72–0.41)	-0.11 (-0.34–0.11)	-0.55 (-1.83–0.72)	0.28 (0.06–0.50)
B. Predictors				
Age at screening (continuous)	-0.02 (-0.14–0.11)	-0.02 (-0.04– 0.00)	-0.02 (-0.10–0.06)	-0.00 (-0.02–0.01)
Female sex	-0.16 (-4.80–4.48)	0.34 (-0.09–0.78)	-3.44 (-6.36– -0.52)	-0.61 (-1.04– -0.18)
Psychiatric history	1.02 (-1.96–3.99)	0.86 (0.15–1.56)	4.09 (2.23–5.94)	0.82 (0.12–1.53)
Anxiety history	-0.16 (-3.95–3.63)	-0.00 (-1.37–1.36)	-0.93 (-3.41–1.51)	-0.61 (-1.97–0.75)
Passive coping style[#]	0.87 (0.40–1.35)	0.53 (0.45–0.62)	0.38 (0.08–0.69)	0.44 (0.35–0.53)
Perceived stress previous year				
Never or sometimes	Ref	Ref	Ref	Ref
Always or often	-0.72 (-3.53–2.09)	1.22 (0.64–1.80)	-0.93 (-2.80–0.93)	0.50 (-0.08–1.08)

Supplementary Table 7. Results from linear mixed model analysis of quality of life over time (A) and according to predictors (B) for screen-positives vs. screen-negatives (I) *(continued)*

	Anxiety (HADS)		Depression (HADS)	
	Positives	**Negatives**	**Positives**	**Negatives**
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Perceived stress lifelong				
Never or sometimes	Ref	Ref	Ref	Ref
Always or often	-2.50 (-5.81–0.81)	0.94 (0.31–1.57)	0.60 (-1.63–2.83)	1.04 (0.41–1.67)
Physical complaints affecting mood	1.39 (-1.24–4.02)	0.80 (0.12–1.49)	1.99 (0.37–3.60)	0.74 (0.06–1.43)
Regular physical exercise	-2.46 (-7.13–2.20)	0.12 (-0.34–0.58)	-2.39 (-5.34–0.56)	-0.24 (-0.70–0.22)
Educational level				
Other	Ref	Ref	Ref	Ref
Primary school or lower secondary	-0.84 (-4.28–2.60)	0.84 (0.32–1.36)	2.00 (-0.12–4.12)	0.90 (0.38–1.43)
Recent smoking	-0.30 (-3.48–2.88)	-0.60 (-1.04– -0.16)	-0.62 (-2.62–1.37)	-0.50 (-0.94– -0.06)
Excessive alcohol consumption	3.33 (-3.04–6.69)	-0.63 (-1.76–0.51)	-1.56 (-5.54–2.42)	-0.32 (-1.46–0.82)
Hypertension	-1.70 (-4.16–0.77)	-0.13 (-0.43–0.69)	0.79 (-0.74–2.32)	0.35 (-0.21–0.91)

 # = per point increase UCL-P; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; MRA = magnetic resonance angiography; Ref = reference group.

Supplementary Table 7. Results from linear mixed model analysis of quality of life over time (A) and according to predictors (B) for screen-positives vs. screen-negatives (II)

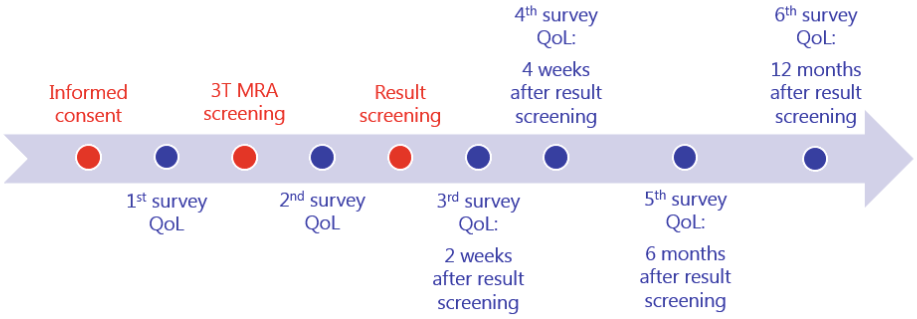
	HRQoL (EQ-5D)		Restrictions in daily activities (USER-P)	
	Positives	**Negatives**	**Positives**	**Negatives**
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
A. Changes over time				
Pre-MRA	Ref	Ref	Ref	Ref
Post-MRA, before result	1.87 (-3.42–7.16)	0.26 (-0.72–1.24)	-3.27 (-7.23–0.69)	0.11 (-0.60–0.83)
2 weeks post-MRA result	4.67 (-0.72–10.06)	1.12 (0.07–2.17)	-2.72 (-6.63–1.19)	-0.03 (-0.79–0.74)
4 weeks post-MRA result	4.64 (-0.74–10.03)	1.61 (0.59–2.62)	3.78 (-7.69–0.13)	-0.83 (-1.56– -0.10)
6 months post-MRA result	4.73 (-0.69–10.12)	0.71 (-0.30–1.72)	-6.83 (-10.81– -2.86)	-0.31 (-1.04–0.42)
1 year post-MRA result	5.34 (-0.22–10.91)	1.19 (0.15–2.22)	-5.90 (-9.94– -1.86)	-0.96 (-1.72– -0.21)
B. Predictors				
Age at screening (continuous)	-0.07 (-0.43–0.29)	-0.01 (-0.07–0.09)	-0.12 (-0.75–0.52)	-0.03 (-0.08–0.01)
Female sex	16.22 (3.26–29.18)	-1.48 (-3.42–0.46)	13.26 (-19.47–36.99)	0.02 (-1.08–1.11)
Psychiatric history	-5.62 (-13.90–2.62)	-2.77 (-5.94–0.39)	1.93 (-13.33–17.18)	-2.16 (-3.93– -0.39)
Anxiety history	-22.69 (-33.61– -11.77)	-8.86 (-14.99– -2.73)	-27.52 (-46.74– -8.30)	0.99 (-2.67–4.65)
Passive coping style[#]	-1.11 (-2.47–0.25)	-1.52 (-1.91– -1.12)	-0.47 (-2.89–1.95)	-0.43 (-0.66– -0.21)
Perceived stress previous year				
Never or sometimes	Ref	Ref	Ref	Ref
Always or often	18.61 (10.33–26.90)	0.06 (-2.54–2.66)	15.59 (1.43–29.75)	-0.36 (-1.85–1.12)

Supplementary Table 7. Results from linear mixed model analysis of quality of life over time (A) and according to predictors (B) for screen-positives vs. screen-negatives (II) *(continued)*

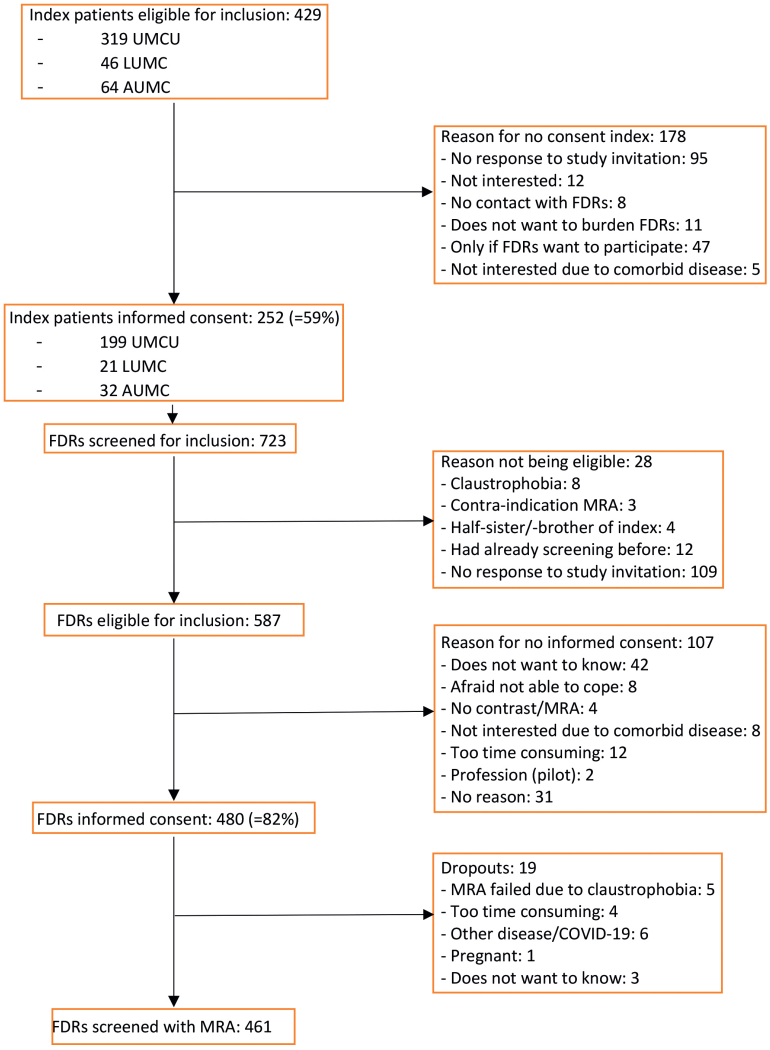
	HRQoL (EQ-5D)		Restrictions in daily activities (USER-P)	
	Positives	**Negatives**	**Positives**	**Negatives**
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Perceived stress lifelong				
Never or sometimes	Ref	Ref	Ref	Ref
Always or often	-14.11 (-24.02– -4.20)	-4.38 (-7.22– -1.55)	-11.28 (-27.92– -5.36)	-2.47 (-4.09– -0.84)
Physical complaints affecting mood	-16.63 (-23.82– -9.45)	-5.98 (-9.07– -2.89)	-9.42 (-22.93–4.10)	-3.19 (-5.00– -1.39)
Regular physical exercise	16.36 (3.25–29.47)	0.36 (-1.71–2.43)	19.34 (-4.46–43.15)	0.76 (-0.41–1.93)
Educational level				
Other	Ref	Ref	Ref	Ref
Primary school or lower secondary	0.75 (-8.68–10.18)	-3.23 (-5.59– -0.87)	0.29 (-17.37–17.94)	-0.47 (-1.81–0.87)
Recent smoking	3.18 (-5.67–12.02)	2.17 (0.19–4.15)	-0.53 (-16.81–15.76)	0.30 (-0.82–1.41)
Excessive alcohol consumption	12.37 (-5.31–30.06)	-2.80 (-7.92–2.31)	7.62 (-24.95–40.19)	1.55 (-1.51–4.62)
Hypertension	-10.26 (-17.06– -3.45)	-3.77 (-6.27– -1.26)	-10.63 (-23.25–1.99)	-1.85 (-3.26– -0.44)

[#] = per point increase UCL-P; CI = confidence interval; EQ-5D = EuroQol 5 Dimensions; MRA = magnetic resonance angiography; Ref = reference group; USER-P = Utrecht Scale for Evaluation of Rehabilitation – Participation.

Supplementary Figure 1. Time points of completion of e-questionnaires on quality of life

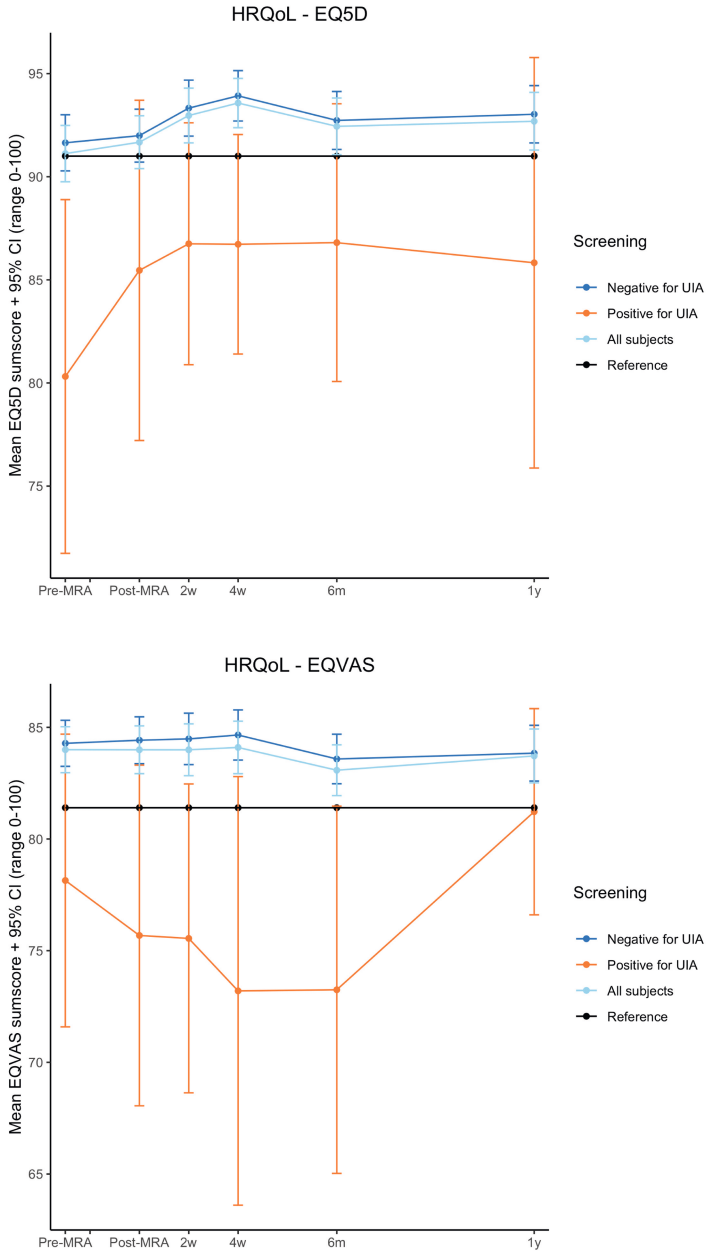


Supplementary Figure 2. Flowchart of screening and enrollment



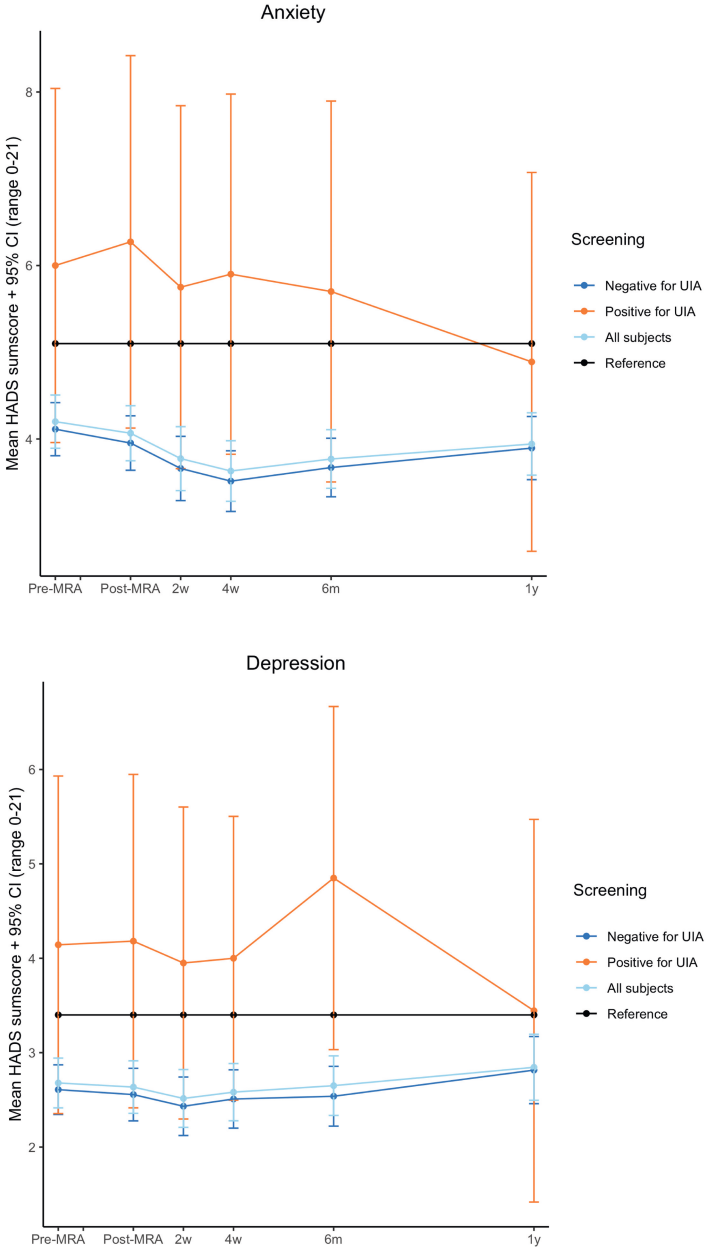
AUMC = Amsterdam University Medical Centre; FDR = first-degree relative; LUMC = Leiden University Medical Centre; MRA = magnetic resonance angiography; UMCU = University Medical Centre Utrecht

Supplementary Figure 3. Quality of life outcomes displayed as unadjusted mean sum scores with 95% CI

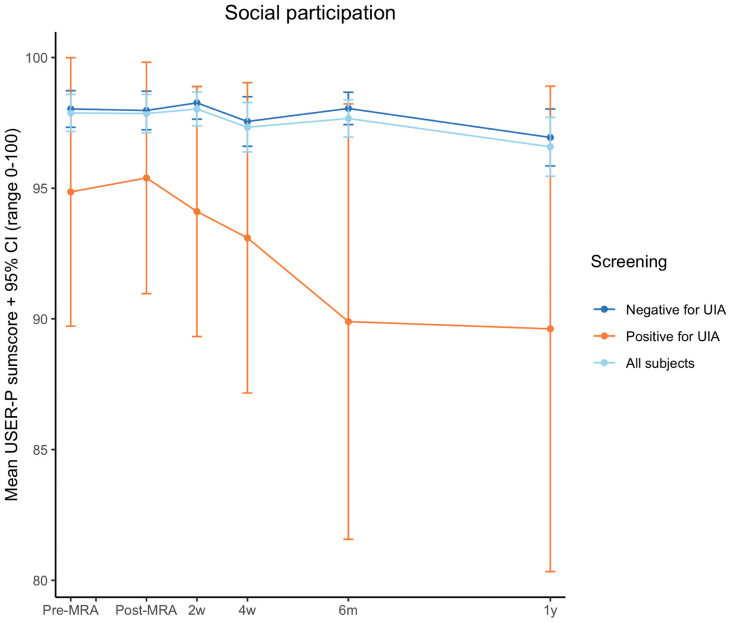


CI = confidence interval; HRQoL = health-related quality of life; m = months; MRA = magnetic resonance angiography; UIA = unruptured intracranial aneurysm; w = weeks; y = year

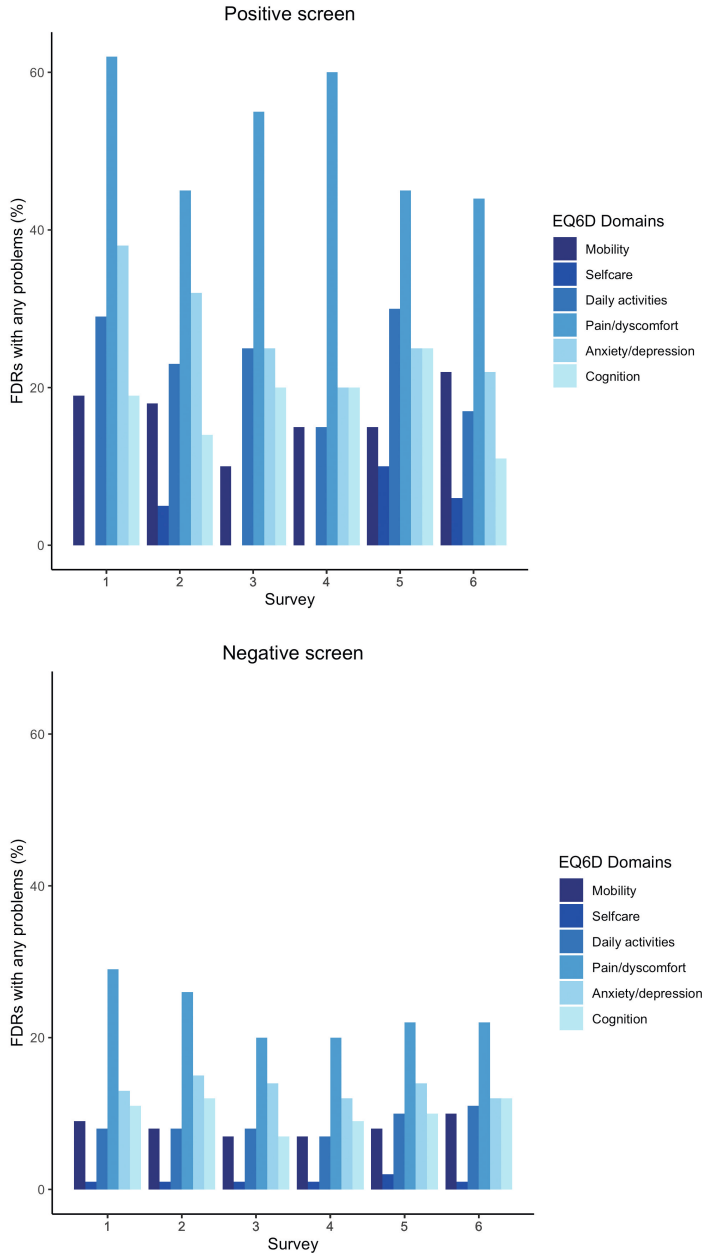
Supplementary Figure 3. Quality of life outcomes displayed as unadjusted mean sum scores with 95% CI *(continued)*



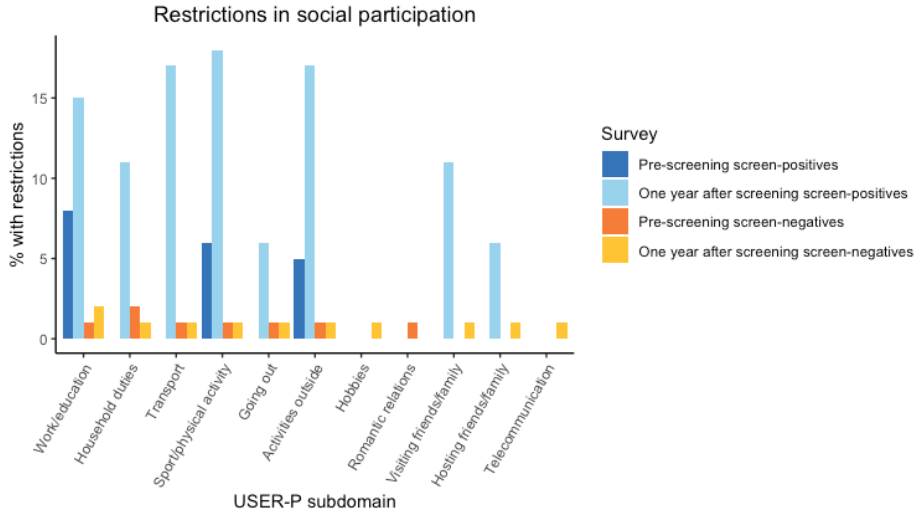
Supplementary Figure 3. Quality of life outcomes displayed as unadjusted mean sum scores with 95% CI *(continued)*



Supplementary Figure 4. Proportion (%) for screen-positives and screen-negatives reporting any problems per EQ-6D subdomain



Supplementary Figure 5. Proportion (%) for screen-positives and screen –negatives with restrictions in social participation per subdomain of the Utrecht Scale for Evaluation of Rehabilitation - Participation (USER-P), comparing pre-screening and one year after screening



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CHAPTER 3

Screening for unruptured intracranial aneurysms in persons ≥ 35 years with hypertension and atherosclerotic vascular disease who smoke(d)

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Submitted

ABSTRACT

Importance

Lifetime risk of aneurysmal subarachnoid haemorrhage (aSAH) is high in persons ≥35 years with hypertension and who smoke(d). In patients with clinical manifest atherosclerotic vascular disease hypertension and smoking are prevalent while they are at increased risk for subsequent ischemic and bleeding events. Whether screening for intracranial aneurysms (IAs) to prevent aSAH is effective in persons ≥35 years with hypertension, clinically manifest atherosclerotic vascular disease and who smoke(d) is unknown.

Objective

To determine the yield of screening in these persons and identify potential high-risk groups among them.

Design

Participants were retrieved from a cohort of patients with clinically manifest atherosclerotic vascular disease included between 2012 and 2019 at the University Medical Center Utrecht, the Netherlands (SMART-ORACLE, NCT01932671).

Setting

Single center.

Participants

Patients ≥35 years with hypertension who were current or past smokers in whom CT-angiography (CTA) of intracranial arteries was performed.

Exposure

CTAs were reviewed for the presence of IAs by experienced neuroradiologists. In patients with IAs follow-up imaging to detect aneurysmal growth was offered. The appropriate management (preventive treatment versus continued radiological follow-up) was determined by a multidisciplinary team.

Main Outcome and Measure

Aneurysm prevalence and a diagnostic model for IA risk at screening using multivariable logistic regression.

Results

IA were found in 25 of 500 patients (5.0% prevalence, 95% CI 3.3 – 7.3%). Median aneurysm size was 3mm (IQR 2 – 4mm); median 5-year risk of rupture assessed with the PHASES score was 0.9% (IQR 0.7 – 1.3%). After a median follow-up of 57 months (IQR 39–83 months) aneurysmal growth was detected in one patient and preventive

treatment was advised. Aneurysm risk at screening ranged between 1.6 – 13.4% with predictors being age at screening, female sex and current smoking (c-statistic 0.63, 95% CI 0.54 – 0.71).

Conclusions and Relevance

IA prevalence in persons ≥35 years with hypertension, clinically manifest atherosclerotic vascular disease and who smoke(d) was 5%. Given the very small proportion of preventively treated IA, we currently do not advise screening for this population in general. Whether screening may be effective for certain high-risk groups should be the subject of future studies.

KEY POINTS

Question

Is screening for intracranial aneurysms to prevent aneurysmal subarachnoid haemorrhage effective in persons aged ≥35 years with hypertension, clinically manifest atherosclerotic vascular disease and who smoke(d)?

Findings

Of 500 screened patients, who were retrieved from a prospectively collected cohort, aneurysms were detected in 25 (5.0% prevalence, 95% confidence interval 3.3 – 7.3%). After a median follow-up of 57 months (IQR 39 – 83 months), aneurysmal growth was detected in one patient and preventive treatment was advised.

Meaning

Based on current data, we do not advise screening in persons aged ≥35 years with hypertension, clinically manifest atherosclerotic vascular disease and who smoke(d).

INTRODUCTION

Subarachnoid haemorrhage (SAH) caused by rupture of an intracranial aneurysm is a devastating subset of stroke with an incidence of 8 per 100,000 persons-years and a lifetime risk of 0.3%.[1,2] It occurs at relatively young age, with a mean age of 50–55 years, and more often in women than in men with two-third of patients being women.[1,3] Since brain damage from the initial haemorrhage is a major cause of the poor outcome after aneurysmal SAH (aSAH),[4] prevention of aSAH has high potential to reduce the burden of aSAH. Non-invasive screening for intracranial aneurysms (IAs) with imaging can prevent future aSAH by early detection and preventive treatment of the identified IA.[5] Such screening is already proven to be cost-effective for the group of first-degree relatives of aSAH patients who are at high risk of aSAH with a lifetime risk of up to 26%[6] and with IAs identified in 11% at first screening.[5] To maximize the potential of aSAH prevention, additional groups with an increased aSAH risk in whom screening is also effective should be identified.

As persons ≥35 years with hypertension and (a history of) smoking also have a high lifetime risk of aSAH of up to 7%, these persons may also qualify as suitable candidates for screening.[2] In patients with clinically manifest atherosclerotic vascular disease, hypertension and smoking are prevalent and these patients are at increased risk for subsequent ischemic and bleeding events.[7] Therefore, we aimed to determine the yield of screening in persons ≥35 years with hypertension and (a history of) smoking, who were selected from a cohort of patients with clinically manifest atherosclerotic vascular disease, and to assess rupture risk, treatment decisions and follow-up of the IA found. In addition, we aimed to develop a diagnostic model to identify patients with a high risk for having an unruptured IA for whom diagnostic imaging of intracranial arteries would be appropriate.

METHODS

Study population

All patients aged 35 years or older with hypertension who smoked or had a history of smoking at the time of inclusion were retrieved from the SMART-ORACLE study (Clinicaltrials.gov Identifier 01932671) embedded in the UCC-SMART cohort at the University Medical Centre Utrecht (UMCU). The UCC-SMART cohort is an ongoing cohort study including patients aged 18 to 79 years referred to the UMCU with clinically manifest atherosclerotic vascular disease (coronary artery disease, cardiovascular disease, transient ischaemic attack, non-disabling stroke, peripheral artery disease, abdominal aortic aneurysm), or marked risk factors such as diabetes mellitus type 2 or hypertension.[8] In the SMART-ORACLE study, CT-angiography (CTA) visualizing the aortic arch to the intracranial arteries of the circle of Willis was performed between 2012 and 2019. Patients were excluded in case of known renal failure, previous allergic reaction to

contrast or other contra-indication for CT-scanning such as pregnancy. A more detailed description of the study protocol has been published previously.[8] For the current study we additionally excluded patients 1) with a past medical history of aSAH, unruptured IA (UIA), autosomal dominant polycystic kidney disease (ADPKD) or other disease known to predispose for aneurysm development such as Ehlers-Danlos or fibromuscular dysplasia (FMD), 2) with a positive family history for aSAH (defined as a first-degree relative (parent, sibling or child) with aSAH) at time of inclusion in the SMART-ORACLE cohort, and 3) who were previously screened for IA. The Medical Ethical Review Committee of the UMCU approved the study protocol, and all patients gave written informed consent.

Baseline characteristics

Baseline characteristics were assessed at time of inclusion in the SMART-ORACLE study. Images were acquired using a 256-slice MDCT-scanner (iCT, Philips Healthcare, the Netherlands) on the same day as the baseline characteristics were assessed.[8] Smoking was categorized as 'never', 'former' or 'current'. Excessive alcohol consumption was defined as consumption of ≥21 units per week. Hypertension was defined as a systolic blood pressure ≥140mmHg and/or a diastolic blood pressure ≥90mmHg and/or the use of antihypertensive medication. Other diseases in the medical history were defined as diagnosed by a physician and/or the use of the medication for the specific disease. Physical exercise per week was converted to Metabolic Equivalent Task units (METs) per week. Length and height at time of the CTA were used to calculate Body Mass Index (BMI).

CTA intracranial arteries

Main focus of the initial evaluation of the CTAs was the presence of abnormalities in the coronary and carotid arteries. The intracranial arteries were not assessed in detail, but if obvious abnormalities of the intracranial arteries were detected, these were discussed with the patients as well. For our present study three experienced neuro-radiologists (BKV, ICvdS, GAdK) evaluated the CTAs after a median period of 56 months (IQR 33 – 73 months) for the presence of intradural saccular UIAs. Each CTA was evaluated by one neuroradiologist and in case of uncertainty, the decision was reached by consensus among all three neuroradiologists. UIA were classified as 'definite' or 'possible'. Possible UIAs were either UIAs located near the ophthalmic artery where it was unclear if the location was truly intradural, or UIAs that could not be differentiated with certainty from a posterior communicating artery infundibulum. Aneurysm location and size were recorded. The PHASES score was calculated to estimate 5-year rupture risk of the identified IA.[9] All patients in whom definite or possible UIAs were discovered and who were aged <75 years and still alive at time of the diagnosis, were contacted and offered follow-up imaging to detect aneurysmal growth, since growth is a known risk factor for aneurysm rupture.[10] Follow-up imaging was performed with CTA or 3-Tesla TOF-MRA. Growth was defined as an increase in aneurysm diameter of ≥1mm.[11] After follow-up, the appropriate management of the UIAs (preventive treatment

versus follow-up imaging to determine potential aneurysmal growth) was determined by a multidisciplinary team consisting of vascular neurologists, neuro-interventional radiologists and vascular neurosurgeons and discussed with the patient. In case follow-up imaging was decided upon, follow-up data up to August 2022 were included in the present study.

Data analyses

For baseline characteristics, mean values with standard deviation (SD) or median values with interquartile range (IQR) were calculated depending on the distribution of data. We calculated the prevalence of IA in our cohort both before and after follow-up imaging, by dividing the total number of patients with a positive screen for IA by the total number of patients screened.

We performed multivariable logistic regression analysis to study the association between candidate predictors and the presence of an IA at screening. Candidate predictors were pre-specified based on literature: age at screening, female sex, current smoking, excessive alcohol consumption, hyperlipidaemia, diabetes, coronary artery disease, physical exercise, hypertension at physical examination and the interaction between female sex and current smoking.[12-15] All candidate predictors were considered for inclusion in the model, regardless of their association in the univariate analysis. There were no missing data. Backward selection was performed based on Akaike Information Criterion (AIC).[16] The resulting model was subsequently corrected for overfitting using bootstrapping. The amount of shrinkage was based on the full model with all candidate predictors to reflect the selection of predictors. We examined the performance of the final diagnostic model by determining its discrimination expressed by the C-statistic and corrected this for optimism. The C-statistic indicates to what extent the model could distinguish persons with a positive and a negative screen. We displayed the discrimination graphically with a receiver operating characteristic (ROC) curve. Subsequently, we generated a risk score by dividing the regression coefficients of the predictors in the final model by the smallest regression coefficient, resulting in points for each predictor from the final model. This risk score was displayed as a score chart accompanied by a table showing the mean estimated risk of finding an IA at screening for each score. The high-risk group was defined as an absolute probability of finding an IA at first screening ≥10%, based on the UIA prevalence of 11% in the group of persons with two or more affected first-degree relatives with aSAH and/or IA at first screening.[5] Statistical analyses were performed using R software (version 3.6.2 R Foundation).[17]

RESULTS

Study population

From all 532 patients aged 35 years or older with hypertension who smoked or had a history of smoking included in the SMART-ORACLE study between 2012 and 2019, 500 patients were included in our study. Patients were excluded because of a past medical history of aSAH (n=18) or UIA (n=1), FMD (n=2), ADPKD (n=1) or because no CTA of the circle of Willis was available (n=10). Mean age at time of CTA was 60.1 years (SD 8.6 years) and 19% were women. In 73% of patients, coronary artery disease was the cardiovascular event that led to inclusion in the SMART-ORACLE study. Other baseline characteristics are shown in Table 1.

Yield of screening

We identified 25 definite and 10 possible UIAs in 35 of the 500 screened patients, resulting in an UIA prevalence of 7.0% (95% CI 4.9 – 9.6%) when not taking into account the follow-up imaging data. Three of the 25 definite UIAs were already diagnosed at initial evaluation of the CTAs (i.e. directly after the CTA was performed). All patients had a single UIA with median size of these 35 UIAs being 2.5 mm (IQR 2.0 – 3.2 mm) and median 5-year risk of rupture according to the PHASES score being 0.9% (IQR 0.7 – 1.3%).[9] Of the 25 patients with a definite UIA, four had died (with a cause of death other than aSAH) and three were not invited for follow-up because of their age (≥75 years). Of the 10 patients with a possible UIA, three were not invited for follow-up because of their age (≥75 years). Thus, radiological follow-up was performed in 25 patients. After evaluation of this follow-up imaging, seven possible UIAs were now diagnosed as being definite infundibula. Thus, when also considering the follow-up data, in total 25 definite UIAs in 25 of the 500 screened patients were diagnosed, resulting in a 5.0% UIA prevalence (95% CI 3.3 – 7.3%). Median size of the 25 definite UIAs identified was 2.5 mm (IQR 2.0 – 3.5 mm) and median 5-year risk of rupture according to the PHASES score was 0.9% (IQR 0.7 – 1.3%) (Table 2).[9]

Table 1. Baseline characteristics

	Positive screen (n, %)	Negative screen (n, %)
Number of patients	25 (5)	475 (95)
Women	8 (32)	87 (18)
Age at screening in years, mean (SD)	64 (7)	60 (9)
Ethnicity		
North-American/European/African/Middle Eastern	25 (100)	475 (100)
Japanese/Finnish	0 (0)	0 (0)
Educational level		
Primary school	1 (4)	29 (6)
All types of secondary education	14 (56)	250 (53)
Higher vocational education and university	10 (40)	196 (41)
Current smoking	10 (40)	142 (30)
Excessive alcohol consumption (≥21U/week)	1 (4)	50 (11)
Medical history		
Hyperlipidaemia	24 (96)	468 (99)
Diabetes Mellitus	3 (12)	73 (15)
Coronary artery disease	21 (84)	373 (79)
Cerebrovascular disease	1 (4)	74 (16)
Peripheral artery disease	1 (4)	28 (6)
Abdominal aortic aneurysm	0 (0)	22 (5)
Kidney disease	0 (0)	11 (2)
Medication		
Blood pressure-lowering medication	25 (100)	454 (96)
Antiplatelet therapy	23 (92)	431 (91)
Anticoagulants	2 (8)	45 (9)
Lipid-lowering medication	24 (96)	432 (91)
Physical exercise in total MET per week, median (IQR)	36 (20–49)	49 (30–79)
Physical examination		
Systolic blood pressure in mmHg, mean (SD)	129 (16)	131 (15)
Diastolic blood pressure in mmHg, mean (SD)	77 (10)	79 (9)
Hypertension at physical examination	9 (36)	147 (31)
BMI in kg/m^2, median (IQR)	26 (25–28)[a]	27 (25–30)

[a] = ≤4% missing; BMI = Body Mass Index; IQR = inter quartile range; MET = metabolic equivalent of task; MRA = magnetic resonance angiography; n = number; SD = standard deviation; U = units

Table 2. Results of screening persons ≥ 35 years with hypertension who smoke(d)

	500 screened persons (n, %)
Patients with aneurysm identified	25 (5)
Patients with multiple aneurysms	0 (0)
Aneurysm size in mm, median (IQR)	3 (2–4)
Aneurysm location	
Internal carotid artery	2 (8)
Anterior communicating artery	5 (20)
Anterior cerebral artery	1 (4)
Pericallosal artery	1 (4)
Middle cerebral artery	9 (36)
Posterior communicating artery	4 (16)
Posterior circulation	3 (12)
PHASES, median % 5-year rupture risk (IQR)	0.9 (0.7–1.3)
Subjects with follow-up imaging	18 (72)
Follow-up imaging in months, median (IQR)	54 (40–83)
Detection of growth during follow-up	1 (4)
Treatment after follow-up	
Watchful waiting	12 (67)
Surgical clipping	1 (6)
Endovascular treatment	0 (0)
End of follow-up because of age	5 (28)

IQR = interquartile range; n = number

For all patients with a definite UIA who were invited for follow-up imaging (18/25), at least one radiological follow-up was available. After a median follow-up of 54 months (IQR 40 – 83 months), aneurysmal growth of 1mm was detected in 1 of these 18 (6%) patients and preventive aneurysm treatment (surgical clipping) was advised for this patient. For 12 of these 18 (67%) patients continuation of radiological follow-up was advised, and for the other 5 patients (28%) follow-up was discontinued because of their age.

High-risk groups

The full model had a C-statistic of 0.73 (95% CI 0.64 – 0.81) and univariate and multivariate ratios for risk of IA at screening for all candidate predictors are shown in Supplementary Table 1. Multivariable logistic regression identified three predictors for detecting an IA at screening: age at time of screening, female sex and current smoking (Table 3). After shrinkage, the model had a C-statistic of 0.63 (95% CI 0.54 – 0.71) (Figure 1). The regression equation is provided in the legend of Table 3.

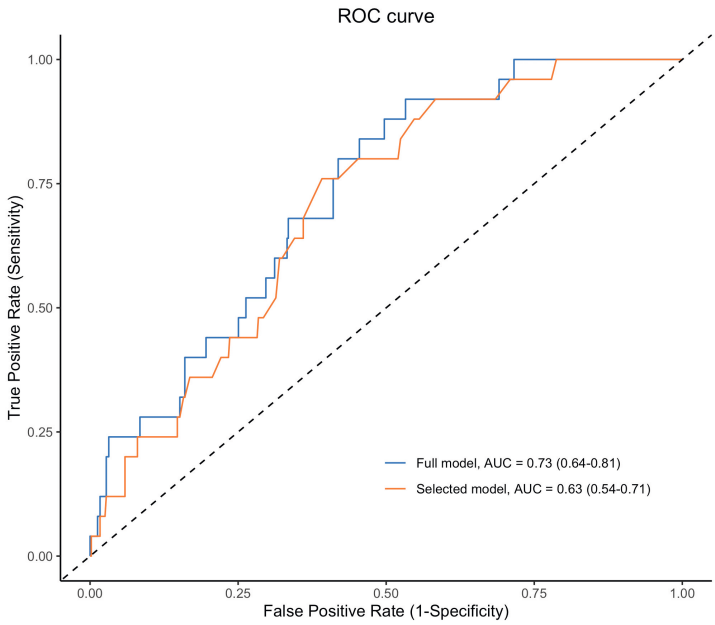
Table 3. Multivariable ratios for risk of unruptured intracranial aneurysms at first screening from the final model before and after shrinkage

	Multivariate OR (95% CI) before shrinkage	Multivariate OR (95% CI) after shrinkage[a]
Age per year	1.08 (1.03–1.14)	1.05 (1.00–1.11)
Female sex	2.25 (0.89–5.36)	1.70 (0.69–4.22)
Current smoking	2.12 (0.86–5.02)	1.64 (0.68–3.95)

[a] = adjusted for optimism with bootstrapping; CI = confidence interval; OR = Odds Ratio

*Regression equation: -6.361482 + 0.0510 * Age at time of screening + 0.5333 * Female sex + 0.4934 * Current smoking*

Figure 1. Receiver operating characteristic (ROC) curve for predicted probability of finding an unruptured intracranial aneurysm at screening

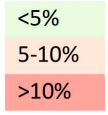


AUC = area under the curve; ROC = receiver operating characteristic

Regression coefficients were subsequently translated into a score chart (Supplementary Table 2) with the mean predicted probabilities per score shown in Supplementary Table 3. Figure 2 shows a risk chart with estimated probabilities of an IA at screening in patients aged 35 years or older with hypertension who smoke or had a history of smoking. The mean estimated absolute risk of an IA at screening ranged from 1.6% in men aged 35 to 44 years who never or formerly smoked to the highest estimated risk of 13.4% in men ≥75 years and women ≥65 years who currently smoke and in women ≥75 years who smoked in the past. The patient in whom follow-up imaging detected aneurysmal growth, had an estimated risk of finding an IA at screening of 5.5% (Figure 2).

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

	No current smoking	Current smoking	Age
Male	1.6	2.2	35-44y
	2.2	3.6	45-54y
	3.6	5.5	55-64y
	5.5	8.7	65-74y
	8.7	13.4	75-84y
Female	2.2	3.6	35-44y
	3.6	5.5	45-54y
	5.5	8.7	55-64y
	8.7	13.4	65-74y
	13.4	13.4	75-84y



y = year

DISCUSSION

In a cohort of patients with clinically manifest atherosclerotic vascular disease, a 5.0% UIA prevalence was found in persons aged 35 years or older with hypertension who smoke or have a history of smoking. All 25 IAs identified at screening had a low rupture risk, for which no preventive treatment was advised. Follow-up imaging in 18 patients in the initial years after screening (i.e. patients who were aged < 75 years and still alive at time of the UIA diagnosis), showed growth of the UIA in one (6%), and for this single patient preventive treatment was recommended. Predictors of a positive first screen for IA were age at time of screening, female sex and current smoking with predicted IA risk at screening ranging between 1.6% and 13.4% depending on the presence of these predictors**.**

No other studies on the prevalence of UIAs in persons aged 35 years or more who smoke(d), have hypertension and clinically manifest atherosclerotic vascular disease were identified to directly compare our findings with. However, in the present cohort of we did find a higher UIA prevalence was observed than the 3% prevalence in the general population.[15] A recent prospective pilot study in Finland in which 43 female smokers aged 50 to 60 years were screened with CTA, also found a higher UIA prevalence of 12% (5/43; 95% CI 2 – 22%) than the prevalence in the general population, with one of the UIAs found being treated preventively.[18] However, it cannot be concluded with certainty in this pilot study that the prevalence is higher given the small sample size and the relatively wide corresponding 95% CI.

Previous studies demonstrated female sex to be a risk factor for UIA development in healthy adults,[14,22,23] with UIA prevalence being especially high for women aged above 50 years.[15] A previous retrospective multicenter case-control study in women aged 30 to 60 years in whom a MRA was performed, demonstrated that both a history of smoking (OR 3.7, 95% CI 1.6 – 8.5) and of hypertension (OR 3.2, 95% CI 1.2 – 8.5) were associated with UIA, and that this association became stronger if both risk factors were present (OR 6.9, 95% CI 2.5 – 19.2).[20] In addition, a comparative study performed in Finland showed that hypertension treated with antihypertensive medication still associated with UIA development.[21] Our finding that current smokers have an additional risk of UIA development compared with ever smokers, has already been reported in previous prospective population-based studies,[14,23] and current smoking has also been shown to have an increased risk of aSAH.[24] Therefore, smoking cessation could be an effective preventive intervention in reducing UIA, and subsequent aSAH, risk. The degree of UIA risk reduction in relation to duration of smoking cessation requires further study. We found evidence that the yield of screening at an older age is probably higher as in our study all persons identified in the high-risk groups were aged over 65 years.

On the other hand, screening above the age of 65 has its downsides, because the benefit of preventive treatment of UIA is lower due to a shorter life expectancy and the increasing risk of complications of preventive treatment with age.[19] Consequently, it does not seem effective to start screening above that age.

A strength of the present study is the uniform data collection at one center, resulting in no missing data on potential predictors of IA development. To reflect clinical practice, the combined prevalence of definite and possible UIAs identified at screening are reported as the diagnosis of both types of UIAs have clinical consequences (i.e. radiological follow-up in possible UIAs). Next, the prevalence of UIAs were reported after integrating the radiological follow-up data which allowed us to exclude some possible UIAs, as these could now be diagnosed with certainty as infundibula.

A few limitations of the study need to be considered. First, our study population included relatively few women, probably because coronary artery disease was one of the events that led to inclusion in the SMART-ORACLE study in the majority of patients, and the prevalence of coronary artery disease in higher in men compared with women.[24] Also, the inclusion of relatively few women most likely resulted in an underestimation of UIA prevalence. In our cohort the prevalence in women was twice as high as in men, which is comparable to data in the literature.[14,15,18,22] If the male:female ratio would have been 1:1, the estimated UIA prevalence would have been 6% instead of 5%. Second, hypertension, defined as a systolic blood pressure ≥140mmHg and/or a diastolic blood pressure ≥90mmHg and/or the use of antihypertensive medication, was one of the inclusion criteria. As beta blockers are prescribed as a risk reduction therapy for patients with coronary vascular disease even in the absence of hypertension,[24] this may explain the relatively high proportion of patients with coronary artery disease included in this study.

Despite the 5.0% UIA prevalence in this study population, preventive treatment was only advised in 0.2% (i.e. in 1 patient). In 7.0% of the study population (i.e. 35 patients) follow-up imaging was advised after the first screening. This proportion decreased to 2.4% (i.e. twelve patients) for continued radiological follow-up, as after the first follow-up imaging some possible UIAs could then be diagnosed as being definite infundibula and in five patients follow-up was discontinued because of their age. Given the very small proportion of preventively treated IAs, we currently do not advise screening for IA in this population. However, this advice may change if more UIA grow during future follow-up imaging, necessitating preventive treatment of these UIAs. Even if we identified more aneurysmal growth in the subgroup with high prevalence, we would still need cost-effectiveness analysis to determine whether screening is effective in these high-prevalence groups. Last, future studies should assess the effect of smoking cessation on UIA risk.

In conclusion, a 5% IA prevalence was found in persons ≥35 years with clinically manifest atherosclerotic vascular disease, hypertension and who smoke(d). Given the very small proportion of preventively treated IA, we currently do not advise screening for this population in general. Whether screening is effective for certain high-risk groups depends on the risk of growth over time of these IAs and should be the subject of future studies.

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SUPPLEMENTARY CONTENT

Supplementary Table 1.	Univariate and multivariate ratios for risk of unruptured intracranial aneurysms at screening from the full model
Supplementary Table 2.	Score chart
Supplementary Table 3.	Predicted probability (%) of an unruptured intracranial aneurysm at first screening based on the prediction score

Supplementary Table 1. Univariate and multivariate ratios for risk of unruptured intracranial aneurysms at screening from the full model

Predictor	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age at screening, per year	1.06 (1.01–1.12)	1.08 (1.03–1.14)
Female sex	2.10 (0.88–5.02)	2.97 (0.87–9.10)
Current smoking	1.56 (0.69–3.56)	2.69 (0.90–7.68)
Excessive alcohol consumption	0.35 (0.05–2.67)	0.39 (0.02–1.87)
Hyperlipidaemia	0.36 (0.04–3.03)	0.40 (0.05–8.51)
Diabetes	0.75 (0.22–2.57)	0.66 (0.15–2.02)
Coronary artery disease	0.70 (0.23–2.07)	0.54 (0.14–1.61)
Physical exercise	1.00 (0.98–1.01)	1.00 (0.98–1.01)
Hypertension at physical examination	1.26 (0.54–2.91)	1.16 (0.46–2.78)
Female sex*Current smoking	1.89 (0.54–6.65)	0.50 (0.07–3.23)

CI = confidence interval; OR = Odds Ratio.

Supplementary Table 2. Score chart

	No current smoking	Current smoking	Age
Male	0	1	**35-44y**
	1	2	**45-54y**
	2	3	**55-64y**
	3	4	**65-74y**
	4	5	**75-84y**
Female	1	2	**35-44y**
	2	3	**45-54y**
	3	4	**55-64y**
	4	5	**65-74y**
	5	6	**75-84y**

y = year

Supplementary Table 3. Predicted probability (%) of an unruptured intracranial aneurysm at first screening based on the prediction score

Risk score	N	Mean predicted probability (%)
0	3	1.6
1	63	2.2
2	167	3.6
3	191	5.5
4	66	8.7
≥5	10	13.4

N = number of patients

CHAPTER 4

Serial quality of life assessment around screening for familial intracranial aneurysms: a prospective cohort study

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Submitted

ABSTRACT

Background and Objectives

Screening for intracranial aneurysms (IAs) is cost-effective in first-degree relatives (FDRs) of aneurysmal subarachnoid haemorrhage (aSAH) patients, but its psychosocial impact is largely unknown. We assessed the effects on quality of life (QoL) at six time points around screening for familial IA.

Methods

We approached a consecutive series of persons aged 20 – 70 years visiting the University Medical Centre Utrecht for first screening for familial IA between March 2017 and April 2020. For those consenting, we administered E-questionnaires consisting of the EuroQoL-6 Dimension for Health-Related QoL (HRQoL), Hospital Anxiety and Depression Scale for emotional functioning and Utrecht Scale for Evaluation of Rehabilitation-Participation for social participation. We compared QoL outcomes with the general population, and between participants with a positive and a negative screening for IA. We assessed predictors of QoL outcomes with a linear mixed effects model.

Results

We included 105 participants from 75 families; in ten (10%) an IA was found. None of the IAs were treated preventively, all underwent follow-up imaging instead. During the first year after screening we found no negative effect on QoL compared with pre-screening, except for a temporary decrease in HRQoL six months after screening in participants with a positive screen (EQ-5D decrease -11.3 [95%CI -21.7 to -0.8]). Factors associated with worse QoL during the year after screening were a previous/current psychiatric disease (EQ-5D decrease -10.3 [95%CI -15.1 to -5.6]), presence of physical complaints affecting mood (EQ-5D decrease -8.1 [95%CI -11.7 to -4.4]), and a passive coping style (EQ-5D decrease per point increase on the Utrecht Coping List -1.1 [95%CI -1.5 to -0.6]).

Discussion

We did not find a lasting negative effect on QoL during the first year after screening for familial IA. Predictors for a worse QoL were a previous/current psychiatric disease, physical complaints affecting mood, and a passive coping style. This information can be used in counselling about familial IA screening. Future prospective research could study the effects on QoL in a larger group of persons with a positive screen, to provide more precise information on potential differences between persons with a positive and negative screening for familial IA.

INTRODUCTION

Non-invasive screening for unruptured intracranial aneurysms (UIAs) with Magnetic Resonance Angiography (MRA) can prevent future aneurysmal subarachnoid haemorrhage (aSAH) by early detection of intracranial aneurysms (IAs) followed by preventive treatment of these IAs. Such screening is proven cost-effective for first-degree relatives (FDRs) of aSAH patients.[1-3] The purpose of screening is to increase the number of life years in good quality. Therefore, the benefits of screening by preventing life years in good quality being lost by aSAH should be carefully weighed against the potential disadvantages of screening. Such disadvantages include the risk of complications of preventive IA treatment,[4] and the potential impact on quality of life (QoL) of screening, which may both lead to a decrease in the number of life years in good quality. One previous study showed a negative effect of screening for familial IA on QoL.[5] However, QoL was assessed many years (mean 8 years, standard deviation (SD) 1 year) after the initial screening, and therefore this study was subject to information bias.[5] Moreover, data on the course of QoL over time, including a comparison with QoL before first screening for IA, are needed but currently lacking.

To improve the counseling on the advantages and disadvantages of screening, we assessed the course and predictors of the effect of screening for familial IA on QoL during the first year around screening. We compared all screened persons to a reference group from the general population, and persons with a positive screen for IA to those with a negative screen.

METHODS

Study population

We approached a consecutive series of persons aged 20 – 70 years visiting the Neurology outpatient clinic of the University Medical Centre Utrecht between March 2017 and April 2020 for their first screening for IA because of a positive family history for aSAH. A positive family history was defined as at least one FDR with aSAH, with or without additional FDRs with UIA. We excluded persons with 1) a medical history of aSAH, UIA, autosomal dominant polycystic kidney disease (ADPKD), Ehlers-Danlos, fibromuscular dysplasia or other disease predisposing for UIA development, and 2) cognitive deficits or a language barrier. As a sample size calculation is difficult to perform for this type of study, we based our sample size on the previous retrospective study on 105 persons in which a statistically significant effect of screening on long-term QoL was found.[5]

Standard protocol approvals, registrations, and patient consents

The Institutional Research Ethics Board of the UMCU approved the study protocol (approval number 16-699). Eligible persons were included in the study after obtaining written informed consent.

Patient and aneurysm characteristics

After persons decided to undergo screening for familial IA, we approached them for information on the study and for informed consent to participate in our study. In case of consent, we derived baseline characteristics from the electronic patient record including age, sex, family history, smoking status and hypertension. Former smoking was defined as smoking stopped within the last 20 years. We defined hypertension as the use of antihypertensive medication and/or the diagnosis made by a physician. Additional baseline characteristics related to QoL such as a previous/current psychiatric disease, the presence of physical complaints affecting mood, highest level of education, current work and living situation, were assessed through a structured questionnaire directly after the visit at the outpatient clinic. We classified a previous or current psychiatric disorder as a psychiatric disease for which participants were treated by a psychiatrist and/or with medication. Physical complaints affecting mood were rated yes or no as indicated by the participant. We also assessed passive coping style as a baseline characteristic related to QoL, and for its assessment we used a subscale of the Utrecht Coping List (UCL-P).[6] This questionnaire consists of seven items that can be scored on a 4-point scale ranging from 1 (seldom) to 4 (very often), resulting in a sum-score between 7 (low level) and 28 (high level of passive coping).[6] We screened participants with MRA or with computed tomography angiography (CTA) in case of contraindications for MR. Screening results were derived from the electronic patient record and in case an IA was found we also derived information on aneurysm size and location, management of the IA (preventive treatment versus follow-up imaging to determine potential aneurysmal growth) and the detection of aneurysmal growth in case of follow-up imaging. We defined growth as an increase in aneurysm diameter of ≥1mm.[7] The PHASES score was calculated to estimate the 5-year rupture risk of the IAs identified.[8] We included follow-up data up to September 2022.

QoL outcomes

QoL was assessed through structured E-questionnaires that were sent to participants six times in a one-year period around screening (before screening, between screening and screening result, 2 and 4 weeks and 6 and 12 months after the screening result). If participants did not have email, questionnaires were sent by post instead. The E-questionnaires consisted of three validated questionnaires: 1. the EuroQol 6 Dimensions (EQ-6D) was used to measure health-related QoL (HRQoL);[9] 2. the Hospital Anxiety and Depression Scale (HADS) was used to measure emotional functioning in terms of anxiety and depression;[10] and 3. the Utrecht Scale for Evaluation of Rehabilitation - Participation (USER-P) restriction subscale was used to measure social participation.[11] The EQ-6D evaluates on a 3-point scale whether no, moderate or severe problems exist for the six domains mobility, self-care, daily activities, pain/discomfort, mood, and cognition. The EQ-6D is an extended version of the EQ-5D that additionally evaluates the cognitive domain. The EQ-5D and cognitive domain were analyzed separately. The EQ-5D produces a five-digit health profile from which a health index score can be

computed. This index score serves as a measure of HRQoL, ranging between 0 (worst) and 100 (best HRQoL). The cognitive domain of the EQ-6D was scored from 1 to 3 points, with higher scores indicating worse cognitive functioning. In addition, participants were asked to rate their health on a visual-analog scale (EQ-VAS), ranging from 0 (worst) to 100 (best imaginable health).[9] The HADS is a questionnaire consisting of 14 items with 7 items evaluating anxiety and 7 items evaluating depression. Each item can be scored from 0 to 3, with higher scores indicating higher levels of anxiety and/or depression. We used a sum-score of 8/21 as a cut-off point for either anxiety or depression.[10] The USER-P assesses participation in eleven activities such as vocational, leisure or social activities. Each item can be scored as '0' (not possible), '1' (with help), '2' (with difficulty), '3' (without difficulty) or as 'not applicable'. We defined the presence of restrictions in participation as scores ≤1 per activity.[11] Sum-scores can be converted to an overall score ranging from 0 (unfavorable) to 100 (favorable participation). In addition to the three validated questionnaires described above, the last E-questionnaire one year after screening also included a question about the occurrence of major life events during the past year and whether participants regretted their decision to screen for IA.

Statistical analysis

We calculated mean values with SD or median values with interquartile range (IQR) for the baseline characteristics. We calculated mean sum-scores with SD for the EQ-5D, EQ-VAS, HADS and USER-P at all survey moments. Per EQ-6D subdomain, we calculated the proportion of participants reporting any problems per survey moment. We compared the proportion of participants at baseline with anxiety levels ≥8 (which is the commonly used cut-off for an anxiety disorder)[12] with the proportion one year after screening. Also, the proportion of participants with restrictions per USER-P activity (scores ≤1) was calculated pre-screening and one year after screening. Mean values of a reference group from the general Dutch population were reported at all survey moments for all QoL outcomes,[13,14] except for the USER-P as no data on reference groups are available for this score. Linear mixed effect models (LME) with random intercept, random slope and fixed time effects were used to assess the course of QoL during the first year following screening and to assess variables associated with QoL outcome. Only variables available pre-screening were included in the model. These analyses were performed for all screened participants together and for the participants stratified by screening result. Changes were reported as mean adjusted difference with 95% confidence intervals (CI). Statistical analyses were performed using R software (version 3.6.2 R Foundation).[15]

RESULTS

Study population

Of 109 eligible persons who were contacted to participate in the study, 105 persons gave informed consent and were included, conferring to an inclusion rate of 96%. Baseline characteristics are shown in Table 1. Median age at time of screening was 47 years (IQR 33 – 55 years) and 66% of participants were women.

Table 1. Baseline characteristics

	All (n, %)	**Positive screen (n, %)**	**Negative screen (n, %)**
Number of patients	105 (100)	10 (10)	95 (90)
Women	69 (66)	8 (80)	61 (64)
Age at screening in years, median (IQR)	47 (33–55)	47 (40–55)	47 (33–55)
Number of affected FDRs			
1	61 (58)	5 (50)	56 (59)
2	33 (31)	4 (40)	29 (30)
≥3	11 (10)	1 (10)	10 (11)
Smoking			
Current	25 (24)	3 (30)	22 (23)
Former*	64 (61)	6 (60)	58 (61)
Medical history			
Hypertension	22 (21)	5 (50)	17 (18)
Psychiatric disease (ever)			
Depression	5 (5)	1 (10)	4 (4)
Anxiety	3 (3)	0 (0)	3 (3)
Other	2 (2)	0 (0)	2 (2)
Physical complaints influencing mood	22 (21)	2 (20)	20 (21)
Educational level			
Primary school	5 (5)	1 (10)	4 (4)
All types of secondary education†	56 (53)	8 (80)	48 (51)
Higher vocational education and university	44 (42)	1 (10)	43 (45)
Married/living with partner	75 (71)	9 (90)	66 (69)
Paid work	87 (83)	8 (80)	79 (83)
Passive coping style, median UCL-P (IQR)‡	10 (8–12)	11 (8–11)	10 (8–12)

** = stopped smoking <20 years ago; † = lower secondary education, higher secondary education, pre-university secondary education, secondary vocational education; ‡ = range sum-score between 7 (low level) and 28 (high level of passive coping); FDRs = first-degree relatives; IQR = interquartile range; n = number; SD = standard deviation; UCL-P = Utrecht Coping List Passive*

Ten of the 105 participants (10%) had a positive screening for IA. In all participants with a positive screening only one IA was found. Median aneurysm size was 2.3 mm (2.0 – 3.3 mm) and median 5-year risk of rupture according to the PHASES score[8] was 0.4% (IQR 0.4 – 0.7%) (Table 2). None of the identified IA were treated preventively but all were followed-up with imaging instead, with at least one radiological follow-up available for each UIA. After a median follow-up period of 27 months (IQR 25 – 36 months), no aneurysmal growth was detected (Table 2).

Table 2. Results of screening

	Screened persons 105 (n, %)
FDRs with positive screen	10 (10)
FDRs with multiple UIA	0 (0)
Aneurysm size in mm, median (IQR)	2.3 (2.0–3.3)
Aneurysm location	
Internal carotid artery	5 (50)
Ophthalmic artery	1 (10)
Anterior communicating artery	1 (10)
Middle cerebral artery	2 (20)
Pericallosal artery	1 (10)
PHASES, median % 5-year rupture risk (IQR)	0.4 (0.4–0.7)
Treatment UIA	
Follow-up imaging	10 (100)
Preventive treatment	0 (0)
Duration of follow-up in months, median (IQR)	27 (25–36)
Detection of growth during follow-up	0 (0)

FDRs = first-degree relatives; IQR = interquartile range; n = number; UIA = unruptured intracranial aneurysm

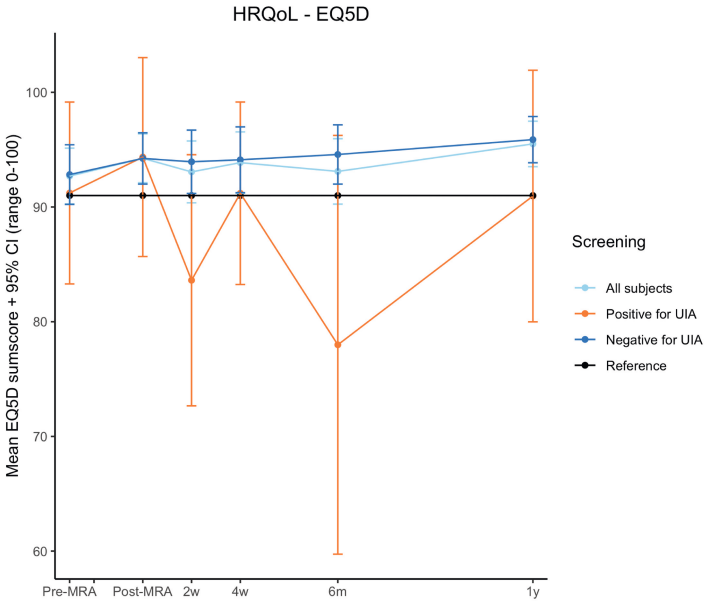
During the study, 87% (548/630) of all E-questionnaires were returned with return rates being comparable between participants with a positive (85%) and a negative screen (87%) for IA. All screen-positives who reported a major life event during the study period (4/4) described a negative major life event, while in the group of screen-negatives reporting a major life event this proportion was 87% (75/86). None of the screened participants who returned the E-questionnaire one year after screening and answered the question how they felt about their decision to be screened for IA (n=37), expressed regret about the screening.

At baseline, 22% (21/97) of all screened participants had a HADS anxiety sum-score of 8 points or more and one year after screening this proportion decreased to 13% (12/92). After adjusting for covariates in the mixed models, factors negatively influencing QoL outcomes were a previous/current psychiatric disease (EQ-5D decrease -10.3 [95%CI -15.1 to -5.6]), the presence of physical complaints affecting mood (EQ-5D decrease -8.1 [95%CI -11.7 to -4.4]), and a passive coping style (EQ-5D decrease per point increase on the Utrecht Coping List -1.1 [95%CI -1.5 to -0.6]) (Table 3).

QoL outcomes complete screening cohort

Analysis of the complete screening cohort showed better unadjusted HRQoL and emotional functioning at all survey moments during the first year after screening compared with a reference group from the general population (Figure 1).[13,14]

Figure 1. Quality of life outcomes displayed as unadjusted mean sum-scores with 95% confidence intervals



CI = confidence interval; HRQoL = health-related quality of life; m = months; MRA = magnetic resonance angiography; UIA = unruptured intracranial aneurysm; w = weeks; y = year

Figure 1. Quality of life outcomes displayed as unadjusted mean sum-scores with 95% confidence intervals *(continued)*

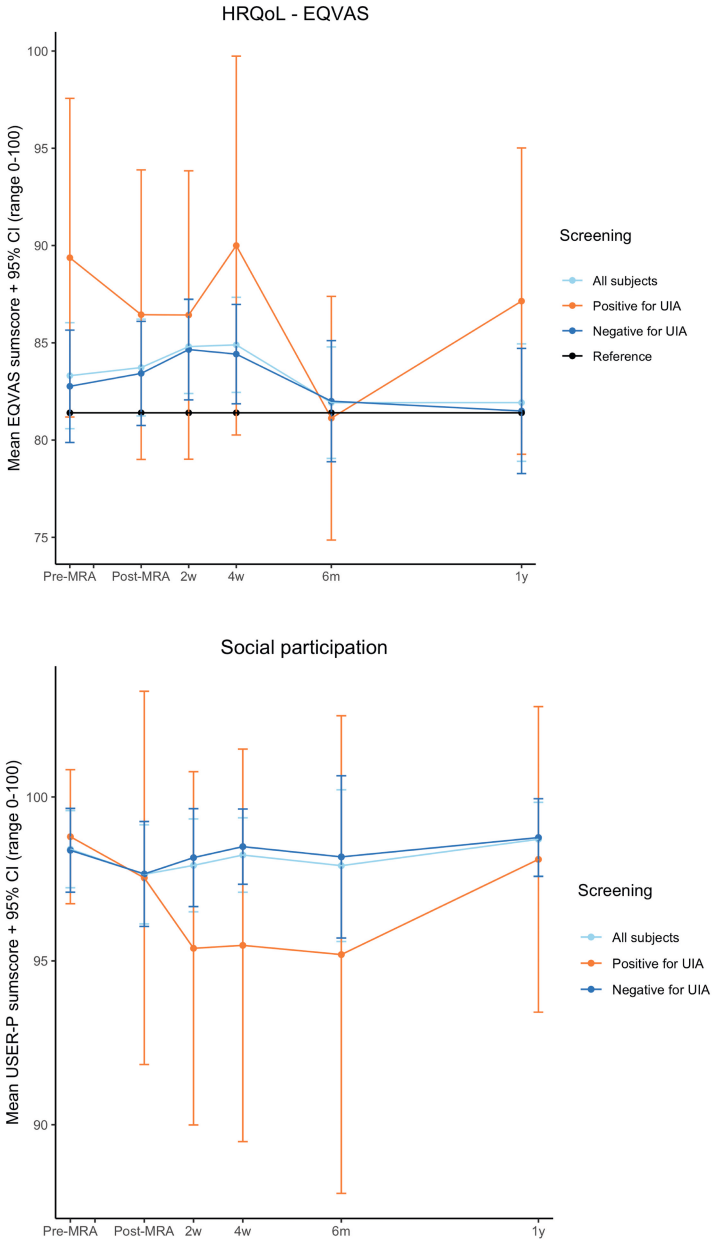
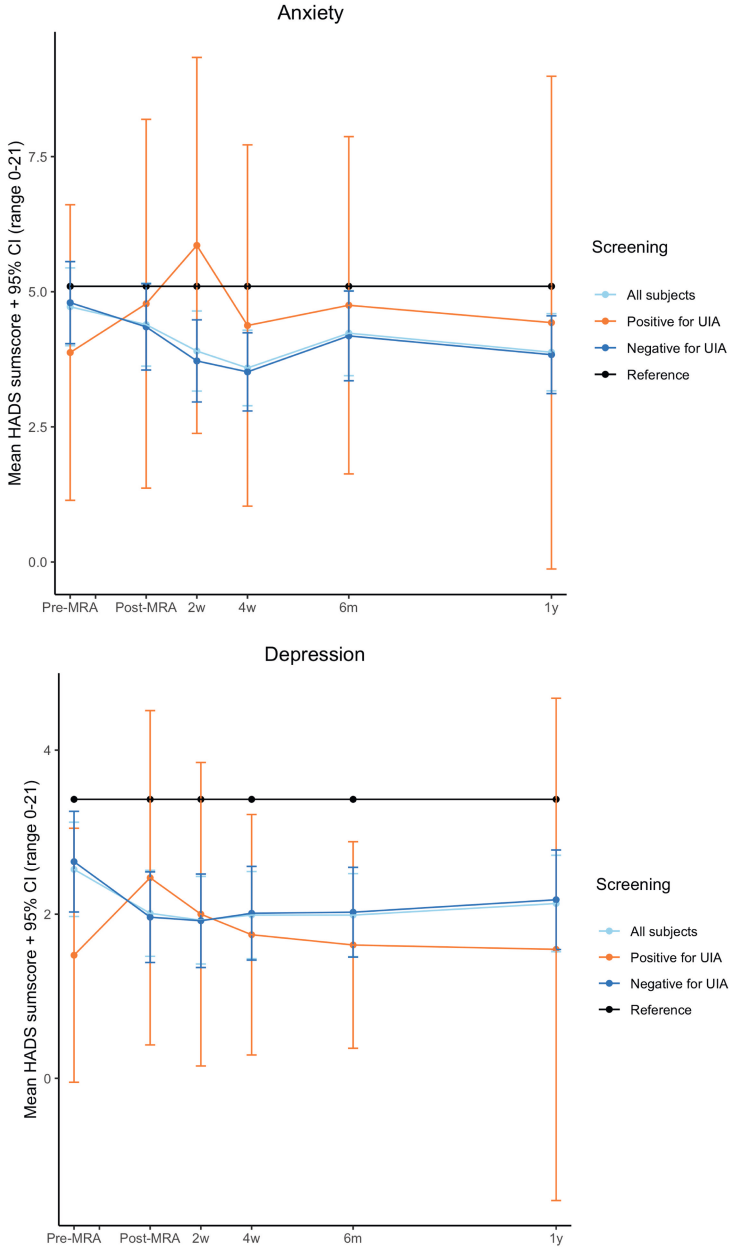


Figure 1. Quality of life outcomes displayed as unadjusted mean sum-scores with 95% confidence intervals *(continued)*



Changing the reference value for HRQoL of all age groups (EQ-5D index score 91) to the age group 45 – 54 years (EQ-5D index score 89), which is comparable to the median age in our study population, showed a larger difference in unadjusted HRQoL in favor of our screened cohort.[13] One year after screening, adjusted results on QoL from the mixed models showed a slightly improved HRQoL compared with pre-screening (mean adjusted EQ-5D sum-score improvement 2.8; 95% CI 0.4 – 5.1) and a slightly decreased level of anxiety (mean adjusted HADS anxiety sum-score decrease -0.7; 95% CI -1.2 – -0.2), while levels of depression and social participation remained the same as compared to pre-screening (Table 3; Supplementary Figure 1). The decrease in anxiety levels is observed from two weeks after receiving the screening result until one year after screening (Table 3).

Table 3. Results from linear mixed model analysis of quality of life over time (A) and according to predictors (B) for the complete screening cohort

	HRQoL (EQ-5D)	HRQoL (EQ-VAS)	Anxiety (HADS)	Depression (HADS)	Restrictions in daily activities (USER-P)
	Coefficient (95%CI)	Coefficient (95%CI)	Coefficient (95%CI)	Coefficient (95%CI)	Coefficient (95%CI)
A. Changes over time					
Pre-screen	Ref	Ref	Ref	Ref	Ref
Post-screen, before result	1.6 (-0.7–4.0)	0.1 (-2.6–2.8)	-0.3 (-0.8–0.2)	-0.4 (-0.8– -0.1)	-0.7 (-2.0–0.7)
2 weeks after screening result	0.9 (-1.5–3.4)	1.3 (-1.5–4.1)	-0.6 (-1.1– -0.1)	-0.4 (-0.8–0.0)	-0.5 (-1.9–0.9)
4 weeks after screening result	1.5 (-0.9–3.8)	1.7 (-1.0–4.4)	-0.9 (-1.4– -0.5)	-0.4 (-0.8– -0.0)	-0.7 (-2.0–0.7)
6 months after screening result	0.8 (-1.6–3.2)	-1.4 (-4.1–1.3)	-0.5 (-1.0–0.0)	-0.5 (-0.9– -0.1)	-0.6 (-1.9–0.8)
1 year after screening result	2.8 (0.4–5.1)	-1.9 (-4.6–0.8)	-0.7 (-1.2– -0.2)	-0.2 (-0.6–0.2)	-0.0 (-1.4–1.3)
B. Predictors*					
Age at screening (continuous)	-0.0 (-0.1–0.1)	0.1 (-0.1–0.2)	0.0 (-0.0–0.0)	0.0 (-0.0–0.0)	-0.1 (-0.2–0.0)
Female sex	-1.7 (-4.5–1.2)	0.1 (-3.1–3.4)	0.5 (-0.4–1.4)	-0.2 (-0.8–0.4)	-1.0 (-3.3–1.3)
Psychiatric disease	-10.3 (-15.1– -5.6)	-7.1 (-12.5– -1.7)	1.8 (0.2–3.3)	1.0 (-0.1–2.0)	-6.9 (-10.7– -3.0)
Passive coping style†	-1.1 (-1.5– -0.6)	-1.7 (-2.3– -1.2)	0.7 (0.6–0.9)	0.5 (0.4–0.6)	-0.7 (-1.1– -0.3)
Physical complaints affecting mood	-8.1 (-11.7– -4.4)	-6.2 (-10.3– -2.1)	1.7 (0.5–2.9)	2.2 (1.5–3.0)	-2.2 (-5.1–0.7)
Educational level					
Other	Ref	Ref	Ref	Ref	Ref
Primary school or lower secondary	1.6 (-1.7–4.9)	1.3 (-2.4–5.0)	-0.0 (-1.1–1.0)	0.7 (-0.1–1.4)	0.1 (-2.5–2.8)
Current smoking	-1.4 (-4.8–1.9)	2.3 (-1.4–6.1)	-0.7 (-1.8–0.4)	-0.4 (-1.1–0.4)	0.2 (-2.5–2.9)
Hypertension	-1.5 (-5.5–2.5)	-2.7 (-7.0–1.7)	1.0 (-0.3–2.2)	0.1 (-0.8–0.9)	0.1 (-3.0–3.2)

** = to estimate for example the HRQoL outcome for female sex at one year follow-up, you first add 2.8 to the reference value (the change in HRQoL over time) and subsequently subtract 1.7 (the influence of female sex); † = per point increase UCL-P; CI = confidence interval; EQ-5D = EuroQol 5 Dimensions; EQ-VAS = EuroQol Visual Analog Scale; HADS = Hospital Anxiety and Depression Scale; Ref = reference group; USER-P = Utrecht Scale for Evaluation of Rehabilitation - Participation.*

QoL outcomes positive versus negative screening

The subgroup of participants with a positive screen for IA was small (n = 10) resulting in relatively wide corresponding 95% CIs of QoL outcomes. There was no statistically significant difference in the unadjusted QoL outcomes comparing participants with a positive screen and participants with a negative screen for IA throughout the study period from pre-screening until one year after screening (Figure 1; Table 4). In participants with a positive screen for IA, we observed a trend towards a temporary increase of unadjusted anxiety levels two weeks after receiving the screening result (Figure 1) and a temporary increase in the proportion of participants reporting problems on the EQ-6D subdomain anxiety/depression after receiving the screening result (Figure 2).

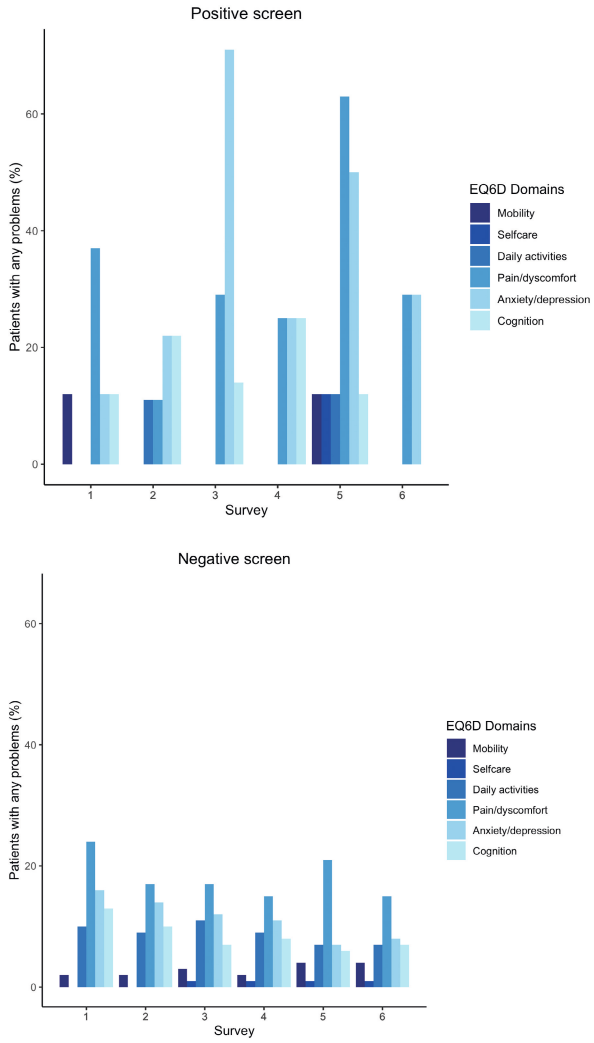
Table 4. Quality of life outcomes for persons with a positive and negative screening for unruptured intracranial aneurysms in unadjusted mean sum-scores with standard deviation

	HRQoL				Emotional functioning (HADS)				Restrictions daily activities	
	EQ-5D		EQ-VAS		Anxiety		Depression		USER-P	
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
Positive screen										
Pre-screen	9	92.2 (9.3)	9	88.3 (9.7)	9	4.3 (3.4)	9	1.7 (1.8)	9	98.9 (2.3)
Post-screen, before result	10	94.9 (10.8)	10	85.8 (9.4)	10	5.1 (4.3)	10	2.3 (2.5)	10	97.5 (7.0)
2 weeks after screening result	8	85.7 (12.4)	8	85.6 (7.8)	8	5.5 (3.6)	8	2.1 (1.9)	8	96.0 (5.6)
4 weeks after screening result	9	92.2 (9.4)	9	88.9 (11.4)	9	4.2 (3.8)	9	1.7 (1.7)	9	95.6 (6.7)
6 months after screening result	9	80.4 (21.7)	9	81.0 (7.0)	9	4.9 (3.5)	9	1.4 (1.5)	9	95.1 (8.2)
1 year after screening result	8	92.1 (11.4)	8	86.3 (8.3)	8	4.8 (4.7)	8	1.5 (3.1)	8	98.3 (4.7)
Negative screen										
Pre-screen	87	92.7 (12.3)	88	82.8 (13.8)	88	4.8 (3.6)	88	2.6 (2.9)	87	98.4 (6.1)
Post-screen, before result	83	94.2 (10.3)	80	83.5 (12.2)	82	4.3 (3.7)	82	2.0 (2.5)	82	97.7 (7.4)
2 weeks after screening result	74	93.9 (12.1)	74	84.7 (11.3)	74	3.7 (3.3)	74	1.9 (2.5)	74	98.1 (6.5)
4 weeks after screening result	85	94.0 (13.4)	85	84.5 (12.0)	86	3.5 (3.4)	85	2.0 (2.7)	85	98.5 (5.4)
6 months after screening result	81	94.5 (11.8)	81	82.0 (14.3)	81	4.2 (3.8)	81	2.0 (2.5)	80	98.2 (11.3)
1 year after screening result	84	95.8 (9.4)	84	81.5 (15.0)	84	3.8 (3.3)	84	2.2 (2.8)	83	98.7 (5.5)

EQ-5D = EuroQol 5 Dimensions; EQ-VAS = EuroQoL Visual-Analog Scale; HADS = Hospital Anxiety and Depression Scale; HRQoL = Health Related Quality of Life; n = number; SD = standard deviation; USER-P = Utrecht Scale for Evaluation of Rehabilitation – Participation

Also, a trend towards a lower unadjusted social participation was observed for participants with a positive screen for IA from receiving the screening result until one year after screening (Figure 1). Adjusted results from the mixed models showed a decrease in adjusted HRQoL in participants with a positive screen for IA six months after receiving the screening result (mean adjusted EQ-5D sum-score decrease -11.3; 95% CI -21.7–-0.8), which returned to baseline one year after screening (Supplementary Table 1). This decrease in HRQoL was mainly caused by an increase in reporting of moderate anxiety and pain (Figure 2).

Figure 2. Proportion (%) for screen-positives and screen-negatives reporting any problems per EQ-6D subdomain



DISCUSSION

We found no overall negative effect of screening for familial IA on QoL during the first year after screening compared with a reference group from the general population. One year after first screening there is even a slight increase in HRQoL and decrease in anxiety levels. The subgroup of participants with a positive screening for IA had a temporary decrease of 11 points in HRQoL (scale 0-100) six months after the initial screening, which was mainly caused by increased reporting of moderate anxiety and pain and which returned to the baseline level (i.e. pre-screening) after one year. Factors negatively influencing QoL after screening are a (history of) psychiatric disease, the presence of physical complaints subjectively affecting mood and a passive coping style.

One previous study assessed QoL in persons screened because of familial aSAH, using a structured telephone interview after a mean period of eight years (SD 1 year) after first screening for IA.[5] In that study a lower HRQoL was found in the 35 participants with a positive screen for IA compared both with 70 age and sex matched participants with a negative screen, and a healthy reference population.[5] This long-term negative effect of screening for IA on QoL, which was not confirmed in our current study, is probably explained by recall bias due to the retrospective design of that study. Another hypothetical explanation is that negative effects of screening on QoL develop only over a longer period of time.

This hypothesis is further supported by two other studies. A retrospective study from our centre assessing 173 patients with UIA after a mean period of 4 to 5 years after diagnosis of the UIA showed a reduced HRQoL, both for patients with treated and untreated UIA.[16] A recent prospective pilot study in Finland assessed HRQoL before and after screening for IA in 43 female smokers aged 50 to 60 years.[17] In that study, HRQoL did not deteriorate in the interval between screening and preventive IA treatment when compared with pre-screening.[17] Definitive conclusions about timing of reduced HRQoL cannot be drawn due to the different methods in the referenced studies and relatively small sample sizes in some of them. For patients with a chronic disease evidence points to the opposite effect of an improved QoL over time, caused by patients adapting to their new health status and reconstructing their perception of health with time.[18,19] The difference with our finding that overall screened participants report short-term improvement instead of deterioration of QoL, can be caused by the reassuring effect of screening as in the majority of our cohort screening did not identify an UIA and so those participants can be considered healthy. The temporary decrease in HRQoL for participants with a positive screening for IA is comparable to the transient reduction in QoL found in men with a positive screen for abdominal aortic aneurysms that returned to pre-screening levels after one year as shown in a prospective study performed in the United Kingdom.[20]

Psychiatric disease, the presence of physical complaints subjectively affecting mood and a passive coping style have a negative effect on QoL after screening for IA. This is in accordance with a study on QoL in patients with known UIA, with and without aneurysm treatment, which demonstrated that both a passive coping style and a history of psychiatric disease were predictors of worse QoL.[21] Although the extent to which an observed decrease in a QoL outcome actually has an effect in daily life is subjective, we consider the observed decreases to be clinically relevant as these decreases are larger than the minimally important difference for the EQ-5D.[22]

The most important strength of this study is the prospective assessment of QoL at multiple time points before and after first screening for IA, enabling us to study the course of QoL during the first year after screening. Also, the high proportion of 96% of eligible persons from a consecutive cohort agreeing to participate in our study, increases the validity of our results.

Some limitations need to be addressed as well. First, given the relatively small proportion of UIA identified, we had not enough participants with a positive screen for IA to reliably compare participants stratified by screening result. Second, we compared our findings on emotional functioning with references from the Dutch general population collected more than fifteen years ago.[14] As emotional functioning may change over time this could have resulted in an erroneous comparison of our screening cohort with the general population. We do not think this time difference between study and control cohorts has influenced our results to an important extent, because the prevalence of anxiety disorders or depression has not changed between 1990 and 2010.[23] Third, reference groups from the general population were not matched for age, while HRQoL is known to decline with increasing age.[13] However, we do not think this affects our results, since selecting a reference value for the general population based on the median age of our study population resulted in an even larger difference in HRQoL in favour of our screening cohort. Fourth, besides the screening for IA, other factors could have influenced QoL outcomes. We aimed to minimize this effect by collecting data on potential confounders and correcting for them in the analyses, and also by comparing the proportion of major life events during the study period between participants with a positive and a negative screen for IA. Last, one predictor of QoL outcome (the presence of physical symptoms subjectively affecting mood) was measured using a non-validated questionnaire.

In counselling persons with familial aSAH on screening for IA, lasting effects on QoL one year after screening do not need to be considered as a disadvantage of screening. However, it should be discussed that in case of a positive screen for IA a temporary decrease in HRQoL may occur, mainly caused by increased reporting of moderate anxiety and pain, which returns to pre-screening levels after one year. Also, it is important to identify persons with an increased risk for worse QoL around screening, e.g. persons with a (history of) a psychiatric disease, physical complaints affecting mood and a

passive coping style, and offer them additional counselling pre-screening about potential negative effects on quality of life. Future prospective studies on QoL in a larger group of persons with a positive screen for IA could provide more precise information on potential differences between persons with a positive and negative screening for familial IA.

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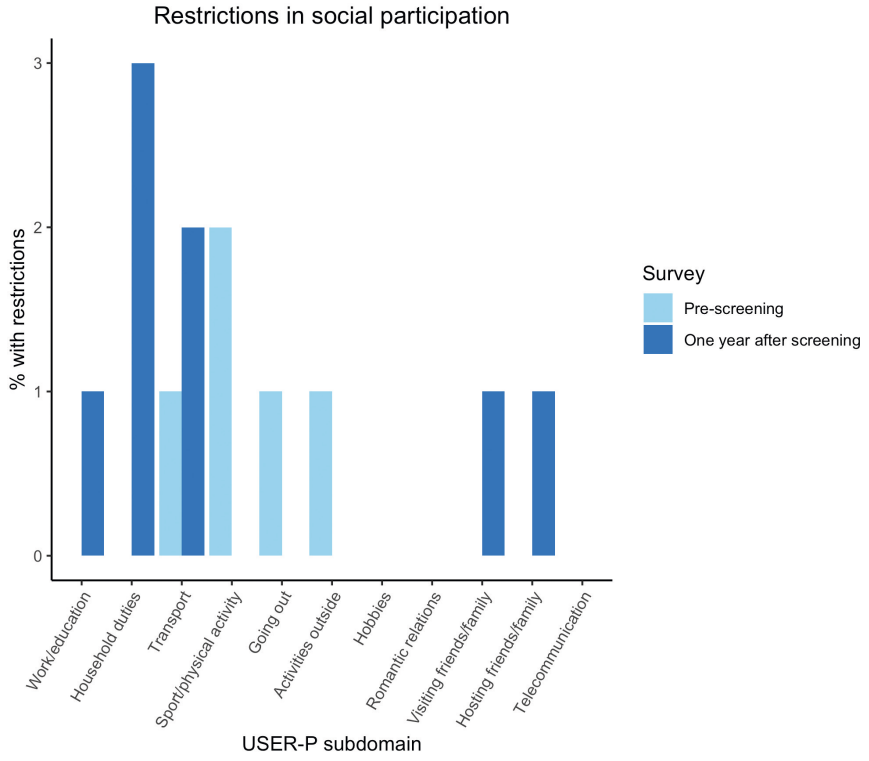
SUPPLEMENTARY CONTENT

Supplementary Figure 1. Proportion (%) of complete screening cohort with restrictions in social participation per subdomain of the Utrecht Scale for Evaluation of Rehabilitation - Participation (USER-P), comparing pre-screening and one year after screening

Supplementary Table 1. Results from linear mixed models analysis of quality of life over time (A) and according to predictors (B) for screen-positives vs. screen-negatives

Supplementary Figure 1. Proportion (%) of complete screening cohort with restrictions in social participation per subdomain of the Utrecht Scale for Evaluation of Rehabilitation - Participation (USER-P), comparing pre-screening and one year after screening



Supplementary Table 1. Results from linear mixed models analysis of quality of life over time (A) and according to predictors (B) for screen-positives vs. screen-negatives

	HRQoL (EQ-5D) Coefficient (95% CI)		Anxiety (HADS) Coefficient (95% CI)		Depression (HADS) Coefficient (95% CI)		Restrictions in daily activities (USER-P) Coefficient (95% CI)	
	Positives	**Negatives**	**Positives**	**Negatives**	**Positives**	**Negatives**	**Positives**	**Negatives**
A. Changes over time								
Pre-screen	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Post-screen, before result	2.2 (-8.0–12.3)	1.5 (-0.8–3.9)	0.7 (-1.5–2.9)	-0.4 (-0.9–0.1)	0.6 (-1.1–2.2)	-0.6 (-0.9– -0.2)	-1.7 (-6.5–3.1)	-0.6 (-2.0–0.8)
2 weeks after screening result	-4.3 (-15.2–6.6)	1.4 (-1.0–3.8)	0.6 (-1.8–2.9)	-0.7 (-1.2– -0.2)	0.2 (-1.6–1.9)	-0.4 (-0.8–0.0)	-3.0 (-8.2–2.2)	-0.3 (-1.7–1.2)
4 weeks after screening result	2.0 (-8.5–12.5)	1.4 (-1.0–3.7)	0.0 (-2.2–2.3)	-1.0 (-1.5– -0.6)	-0.1 (-1.8–1.6)	-0.5 (-0.8– -0.1)	-3.6 (-8.5–1.4)	-0.4 (-1.8–1.0)
6 months after screening result	-11.3 (-21.7– -0.8)	2.0 (-0.3–4.4)	0.2 (-2.0–2.5)	-0.5 (-1.0– -0.1)	-0.4 (-2.1–1.3)	-0.5 (-0.9– -0.2)	-4.3 (-9.2–0.7)	-0.2 (-1.6–1.2)
1 year after screening result	1.3 (-9.6–12.2)	2.9 (0.6–5.3)	0.5 (-1.8–2.9)	-0.8 (-1.3– -0.3)	-0.1 (-1.9–1.6)	-0.2 (-0.6–0.2)	-1.3 (-6.5–3.8)	0.1 (-1.3–1.5)
B. Predictors*								
Age at screening (continuous)	-1.3 (-2.9–0.3)	-0.0 (-0.1–0.1)	-0.2 (-0.9–0.6)	0.0 (-0.0–0.0)	0.0 (-0.1–0.2)	0.0 (-0.0–0.0)	-1.4 (-8.0–5.3)	-0.1 (-0.2–0.0)
Female sex	-11.6 (-38.0–14.8)	-0.8 (-3.7–2.1)	4.9 (-7.7–17.5)	0.4 (-0.6–1.3)		-0.2 (-0.8–0.5)	0.1 (-45.8–45.9)	-0.9 (-3.4–1.6)
Psychiatric disease	-17.4 (-58.7–24.0)	-12.5 (-17.4– -7.7)	1.9 (-94.6–98.4)	1.8 (0.1–3.4)	0.5 (-2.5–3.5)	1.0 (-0.1–2.2)	-21.0 (-127.9–85.9)	-7.9 (-12.1– -3.7)

Supplementary Table 1. Results from linear mixed models analysis of quality of life over time (A) and according to predictors (B) for screen-positives vs. screen-negatives *(continued)*

	HRQoL (EQ-5D) Coefficient (95% CI)		**Anxiety (HADS)** Coefficient (95% CI)		**Depression (HADS)** Coefficient (95% CI)		**Restrictions in daily activities (USER-P)** Coefficient (95% CI)	
	Positives	**Negatives**	**Positives**	**Negatives**	**Positives**	**Negatives**	**Positives**	**Negatives**
Passive coping style†	4.3 (-3.3–12.0)	-1.0 (-1.5– -0.6)	0.8 (-1.3–2.9)	0.7 (0.6–0.9)	0.2 (-0.3–0.8)	0.5 (0.4–0.6)	4.1 (-17.1–25.3)	-0.7 (-1.1– -0.3)
Physical complaints affecting mood	-36.5 (-80.2–7.1)	-8.1 (-11.8– -4.4)	0.4 (-12.7–13.6)	1.6 (0.3–2.8)	1.8 (-1.0–4.6)	2.3 (1.5–3.2)	-32.7 (-170.5–105.0)	-1.7 (-4.9–1.5)
Educational level								
Other		Ref		Ref		Ref		Ref
Primary school or lower secondary		1.4 (-1.9–4.7)		0.2 (-0.9–1.2)		0.7 (-0.1–1.4)		0.1 (-2.7–3.0)
Current smoking	-19.9 (-50.1–10.4)	-1.2 (-4.5–2.2)	-1.4 (-11.2–8.4)	-0.7 (-1.8–0.5)		-0.4 (-1.2–0.4)	-19.2 (-109.4–71.0)	0.4 (-2.5–3.3)
Hypertension		0.5 (-3.8–4.8)	3.1 (-9.1–15.3)	1.1 (-0.3–2.5)	0.8 (-1.5–3.2)	0.2 (-0.8–1.1)	11.8 (-56.1–79.7)	0.2 (-3.3–3.7)

** = to estimate for example the HRQoL outcome for female sex at one year follow-up in screen-positives, you first add 1.3 to the reference value (the change in HRQoL over time) and subsequently subtract 11.6 (the influence of female sex); † = per point increase UCL-P; EQ-5D = EuroQol 5 Dimensions; HADS = Hospital Anxiety and Depression Scale; USER-P = Utrecht Scale for Evaluation of Rehabilitation – Participation*

PART II

Characteristics of familial intracranial aneurysms

CHAPTER 5

Comparison of rupture risk of intracranial aneurysms between familial and sporadic patients

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ABSTRACT

Background and purpose

A much higher rupture rate for patients with familial intracranial aneurysms (IA) compared to patients with sporadic IA has been reported in a study with highly selected familial aneurysms using sporadic patients from other populations a controls. We aimed to validate these findings in a large independent series of Dutch patients with familial and sporadic IA.

Methods

We conducted a secondary analysis of our institutional cohort of patients who were screened for intracranial aneurysms between 1994 and 2016. We assessed the incidence of aSAH between familial, defined as ≥2 affected first-degree relatives with aneurysmal subarachnoid haemorrhage (aSAH) and/or unruptured IA (UIA), and sporadic patients with UIA with Cox regression analysis.

Results

We identified 62 familial IA patients with 91 UIA and 412 sporadic IA patients with 542 UIA. Despite familial aneurysms being smaller and more often located at low-risk sites than sporadic IA, three familial patients had aSAH (0.77 ruptures per 100 aneurysm-years [95% CI 0.20 – 2.09]) compared to seven sporadic patients (0.51 ruptures per 100 aneurysm-years [95% CI 0.22 – 1.01]). As compared to sporadic UIA, familial UIA seem to have a 3-fold higher risk of rupture (hazard ratio, 2.9 [95% CI 0.6 – 14]).

Conclusions

Our results suggest a slightly increased risk of aneurysm rupture for familial compared to sporadic IA, although we were not able to demonstrate this with statistical significance. However, the rupture risk seems less strongly increased than found in a previous study. Based on our results, we recommend to treat familial UIA more aggressively.

INTRODUCTION

A population-based study showed a large increased lifetime risk of aneurysmal subarachnoid haemorrhage (aSAH) for individuals with two or more affected first-degree relatives (FDRs).[1] It has not been settled yet if this increased risk of aSAH in persons with two or more affected FDRs is caused by a higher risk of aneurysm development, a higher risk of aneurysm rupture, or a higher risk of both. A meta-analysis of 83 study populations including 1450 unruptured intracranial aneurysms (UIA) reported a prevalence ratio of UIA in patients with a positive family history of 3.4 (95% confidence interval (CI) 1.9 – 5.9) compared with patients without a positive family history,[2] which suggests an increased risk of aneurysm development in persons with a positive family history. In addition, a previous study found a 17-times increased rupture rate for familial compared to sporadic UIA.[3] However, in this study patients with familial and sporadic UIA were recruited from different study populations (familial patients from the Familial Intracranial Aneurysm Study[3] and sporadic patients from the International Study of Unruptured Intracranial Aneurysms[4]), the patients with familial UIA were selected as they all smoked and/or had hypertension, and both patients with familial and sporadic UIA had aneurysms sized 7 mm or less.[3] Thus, additional studies are needed to further investigate the rupture risk of familial UIA.

We aimed to assess the rupture rate of familial UIA in a large independent series of Dutch patients, since confirmation of the previously reported very strongly increased risk of aneurysm rupture for familial UIA could warrant an aggressive treatment approach in patients with familial UIA.

METHODS

Study population

We included in this secondary analysis patients aged 18 years or older with a newly diagnosed, untreated UIA who visited the University Medical Centre Utrecht between 1994 and 2016. Patients with familial UIA were defined as patients having at least two affected FDRs with aSAH and/or UIA.[5] In these patients the UIA were most often identified by preventive screening because of a positive family history. Patients with sporadic UIA were defined as patients with an incidental UIA and no family history of aSAH and/or intracranial aneurysms (IA). In these patients the UIA were most often diagnosed as an incidental finding on brain imaging. Exclusion criteria were: 1) fusiform IA; 2) history of polycystic kidney disease; and 3) previous history of aSAH and/or UIA. The Medical Ethical Review Committee of the University Medical Centre Utrecht approved the study protocol and data collection used, and informed consent was obtained.

Data collection

UIA had to be identified on computed tomography angiography (CTA), magnetic resonance angiography (MRA) or conventional angiography, and imaging had to be available for review. As follow-up we used the time window between the first available imaging showing the UIA, and the occurrence of aSAH, or aneurysm treatment, or the last visit at the outpatient clinic. At the time of identification of the UIA, we recorded data on hypertension status (defined as a history of hypertension or the use of antihypertensive drugs), current smoking status, family history of aSAH and/or UIA and aneurysm size and location.

Statistical analysis

The incidence of rupture was assessed in both groups per patient and per aneurysm. Patients were censored at time of preventive aneurysm treatment, death or end of follow-up. When patients underwent a preventive aneurysm treatment, data from the period up to the time of the intervention were included in the analysis of risk of rupture. Although patients continued to be followed after the intervention, data from this period were not included in the analysis. We analyzed rupture risk per aneurysm rather than per patient. We calculated the effect of familial versus sporadic aneurysms for the following outcomes: aneurysm rupture and aneurysm rupture or growth >1mm. Strength of the effect was determined with hazard ratios (HR) using Cox regression analysis with adjustment for the PHASES score.[6] The PHASES score was developed to determine the 5-year risk of rupture of IA, taking into account several characteristics associated with aneurysm rupture, such as hypertension or a previous SAH from another intracranial aneurysm.[6] We checked the proportional hazards assumptions. Statistical analyses were performed using SPSS Statistics 22. Data are available from the authors on request.

RESULTS

Baseline characteristics

We identified 62 patients with 91 familial UIA and 391 aneurysm-years of follow-up (mean 4.3 years), and 412 patients with 542 sporadic UIA and 1373 aneurysm-years of follow-up (mean 2.5 years) (Table 1). The mean age was 48 (±9) years in the familial group, and 56 (±11) years in the sporadic group (Table 1). Comparing patients with sporadic and familial UIA, hypertension was observed more frequently in patients with sporadic UIA (49% vs 21%), while familial IA patients more often smoked than sporadic IA patients (52% vs 40%) (Table 1). Comparing aneurysm characteristics shows that familial UIA were more often small sized (size < 7mm: 85% vs 54%); were more often located in the internal carotid artery (24% vs 14%) and less often in the posterior circulation (13% vs 23%) as compared to sporadic UIA (Table 1). Of the familial IA patients, 45% was not treated preventively during follow-up compared to 52% of sporadic IA patients (Table 1). A slight increase in aneurysm size before preventive treatment was observed in both groups (Table 1). The mean PHASES score was 3 (±2) for familial IA patients and 5 (±3) for sporadic IA patients (Table 1).[6]

Table 1. Baseline characteristics

	Familial UIA (n, %)	Sporadic UIA (n, %)
Number of patients	62	412
Number of aneurysms	91	542
Mean age*, y (SD)	48 (9)	56 (11)
Age range*, y	27–73	22–81
Women	69 (76)	382 (70)
Hypertension*	19 (21)[a]	263 (49)[a]
Smoking*	47 (52)[a]	218 (40)[a]
Multiple aneurysms	48 (53)	220 (41)
Mean PHASES*, score (SD)	3 (2)	5 (3)
Aneurysm size*		
< 7.0 mm	77 (85)[a]	290 (54)
7.0 – 9.9 mm	9 (10)[a]	134 (25)
10.0 – 19.9 mm	3 (3)[a]	98 (18)
≥ 20.0 mm	0 (0)[a]	20 (4)
Aneurysm location		
Anterior circulation	20 (22)	135 (25)
Internal carotid artery	22 (24)	76 (14)
Middle cerebral artery	37 (41)	205 (38)
Posterior circulation	12 (13)	126 (23)
Aneurysm treatment during follow-up		
Clipping	39 (43)	121 (22)
Endovascular	11 (12)	140 (26)
Follow-up	41 (45)	281 (52)
Aneurysm size pre-treatment†		
< 7.0 mm	33 (66)[a]	74 (28)
7.0 – 9.9 mm	12 (24)[a]	89 (34)
10.0 – 19.9 mm	3 (6)[a]	84 (32)
≥ 20.0 mm	0 (0)[a]	14 (5)
Aneurysm growth pre-treatment		
0 mm	43 (86)[a]	250 (96)
1 mm	2 (4)[a]	3 (1)
2 mm	2 (4)[a]	5 (1)
3 mm	0 (0)[a]	2 (1)
6 mm	1 (2)[a]	1 (0)

** = at time of identification of UIA per aneurysm; † = clipping or endovascular treatment; [a] = data were missing on hypertension in 13 familial aneurysms (14%) and in 9 sporadic aneurysms (1.7%), on smoking in 17 familial aneurysms (19%) and in 51 sporadic aneurysms (9.4%), on size and growth pre-treatment in 8 familial aneurysms (8.8%) and in 17 sporadic aneurysms (3.1%); n = number; SD = standard deviation; UIA = unruptured intracranial aneurysm; y = year*

Incidence of aneurysm rupture

Of the 62 patients with familial UIA, three patients had rupture of their IA during 270 patient-years of follow-up (Table 2). The rupture rate was 1.11 ruptures per 100 patient-years (95% CI 0.11 – 8.94) or 0.77 ruptures per 100 aneurysm-years (95% CI 0.20 – 2.09). Another fourth familial patient had an aSAH from a de novo IA. This patient was screened for UIA because of a positive family history three years before the haemorrhage. At that time, screening was negative. Thus, the aSAH occurred during the five-year screening interval. As the aSAH occurred from a de novo IA this aSAH was not considered in our analysis. Of the 412 patients with sporadic UIA, aSAH occurred in seven patients during 1115 patient-years of follow-up. The rupture rate was 0.63 ruptures per 100 patient-years (95% CI 0.08 – 13.33) or 0.51 ruptures per 100 aneurysm-years (95% CI 0.22 – 1.01).

In addition, two patients had a ruptured IA after preventive treatment, the first was a basilar artery aneurysm with a known neck remnant after coiling with a wait-and-scan policy, and the second was an internal carotid artery aneurysm that was successfully clipped without further radiological follow-up after the surgery. These ruptured IA were not included in the analyses.

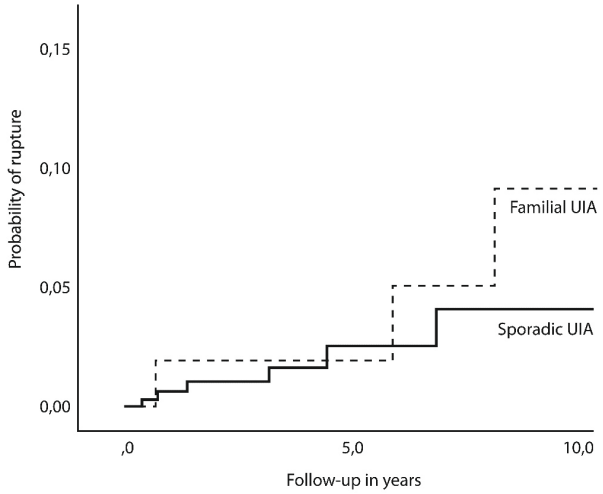
Table 2. Characteristics of subjects with aneurysmal subarachnoid haemorrhage from intracranial aneurysms

Subject	Age*	Sex	Time to rupture (years)†	SAH occurred in screening interval	IA size‡ (mm)	IA site	Affected FDR (n)	Smoking*	Hypertension*
Familial 1	65	F	5.9	Yes	3	ACA	3	No	No
Familial 2	45	M	8.4	Yes	4	ACOM	9	No	No
Familial 3	56	F	1.9	Yes	4	MCA	3	No	No
Sporadic 1	48	F	0.3	Yes; waiting for clipping	8	ACOM	NA	Yes	No
Sporadic 2	43	F	6.8	Yes	7	MCA	NA	No	No
Sporadic 3	53	F	4.4	No	9	MCA	NA	Unknown	Yes
Sporadic 4	65	F	0.5	No	5	ACOM	NA	Yes	No
Sporadic 5	71	M	0.7	Yes; waiting for clipping	21	ACOM	NA	Unknown	Yes
Sporadic 6	69	F	1.3	No	12	ACOM	NA	Yes	No
Sporadic 7	61	F	0.9	Yes	45	MCA	NA	Yes	Yes

** = at time of identification of unruptured IA; † = since identification of unruptured IA; ‡ = at last available imaging before SAH; ACA = anterior cerebral artery; ACOM = anterior communicating artery; BA = basilar artery; F = female; FDR = first-degree relative; IA = intracranial aneurysm; ICA = internal carotid artery; M = male; MCA = middle cerebral artery; n = number; SAH = subarachnoid haemorrhage*

Figure 1 shows the Kaplan Meier curves. The rupture rate of familial UIA was about 3-times higher than the rupture rate of sporadic UIA (adjusted HR 2.92, 95% CI 0.62 – 13.71). The combined outcome of aneurysm rupture and/or growth >1 mm of familial UIA was 2-times higher compared with sporadic UIA (adjusted HR 2.28, 95% CI 0.97 – 5.37).

Figure 1. Kaplan Meier curve of survival analysis



Familial UIA n = 91 aneurysms; Sporadic UIA n = 542 aneurysms

DISCUSSION

We could not confirm the very strongly increased risk of rupture of familial UIA that was previously reported.[3] However, our point estimates do suggest a slightly increased risk, although we were not able to demonstrate this with statistical significance. Our analysis showed a three-fold increased risk of IA rupture for familial compared to sporadic UIA. Remarkably, the observed rupture rate was high in both groups. This could be, partly, explained by the observation that patients on the waiting list for preventive treatment have a higher incidence of aneurysm rupture.[7]

The previous study that found a 17-times increased rupture rate for familial compared to sporadic UIA,[3] had a study population that differed in several aspects from ours. They used more stringent inclusion criteria: all included patients had IA sizes of 7 mm or less, and the patients with familial UIA were selected for being smokers and/or having hypertension.[3] We could not perform a sensitivity analysis in our cohort, as no aneurysm ruptures remained after excluding all familial IA patients that did not smoke and/or did not

have hypertension. We hypothesize that the higher rupture rate for familial IA established in the previous study might be explained by only including patients with familial UIA that smoked and/or had hypertension, which are both known risk factors for aneurysm rupture,[8] and comparing them to patients with sporadic UIA who did not all smoke and/or had hypertension. Furthermore, other studies comparing rupture risk of familial versus sporadic UIA (although in the Japanese population and in sub-analyses only) did not show an increased rupture risk for familial UIA.[9,10] One study investigating a Japanese cohort of 5720 patients found a hazard ratio of rupture for familial UIA of 0.71 (95% CI 0.37 – 1.36),[9] and another study on 2252 Japanese patients found a similar hazard ratio of 0.69 (95% CI 0.28 – 1.74).[10]

The strength of our study relies in the fact that familial and sporadic IA were recruited in a single centre from the same catchment area and thus received comparable treatment by the same treating physicians. A second strength of our study is the relatively long duration of follow-up for both the familial and sporadic UIA.

Our study has a few limitations. The first limitation concerns the study design, deriving information on the incidence of aneurysm rupture from electronic patient records. This could have led to missed aneurysmal ruptures if the patients were admitted with an aSAH in other hospitals and if we were not notified on this. Still, we do not think that might have influenced our results significantly, since most included patients visit our outpatient clinic regularly for follow-up and since we have no reasons to assume that missed aSAH differ between familial and sporadic patients. Second, selection by treatment occurred, with preventive aneurysm treatment changing the natural history of the identified UIA. However, in both groups preventive treatment was offered to patients considered at high risk of rupture with the proportion of aneurysms that were treated preventively being comparable between both groups. Also, the presumed risk of rupture for familial aneurysms is higher than indicated by the PHASES score, since this score was developed on cohorts with underrepresentation of familial aneurysms.[6] But, in our cohort the time until preventive treatment was even longer for familial patients than for sporadic patients implicating that familial patients were not treated more aggressively. Third, we did not correct for clustering of aneurysms within patients (e.g. patients having multiple UIA). Last, the number of events (e.g. aneurysm rupture) was low, especially in the familial group.

In conclusion, our results point to a slightly increased risk of aneurysm rupture for familial compared with sporadic UIA. Since this finding was not statistically significant, we conclude that if familial UIA indeed do have a higher risk of rupture, at least this risk seems less strongly increased than shown by a previous study showing a 17-times increased risk.[3] Further studies, including large cohorts with less selection, are needed to draw definite conclusions about the risk of rupture for familial compared with sporadic intracranial aneurysms. In the meantime, based on our results, we recommend to treat familial UIA more aggressively than sporadic UIA.

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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 haemorrhage and UIA; and 4) had aneurysm rupture as an outcome. Cohorts with available IPD were included. All studies included patients with newly diagnosed UIA visiting one of the study centres. 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 haemorrhage (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 centre 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 haemorrhage) AND (follow-up OR natural history OR natural course)" (Supplemental Figure 1). 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 eight studies that fulfilled the inclusion criteria[3,7-11,13,14], and seven research groups provided us with their individual patient data.[3,7-11,13] All studies included patients with newly diagnosed UIA visiting one of the study centres. 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 eight studies met our inclusion criteria (Figure 1).

In these studies 68 patients with polycystic kidney disease and two patients with moyamoya disease were excluded. In six studies first-degree relatives were defined as parents, siblings, or children,[3,7-10,15] while in two studies, only parents and children were referred to as first-degree relatives.[11,13] The eight cohorts are listed in Table 1 and the baseline characteristics of patients in all separate cohorts in Supplementary Table 1. Quality assessment of included cohort studies by QUIPS tool is shown in Supplementary Table 2.

Figure 1. Prisma flow diagram

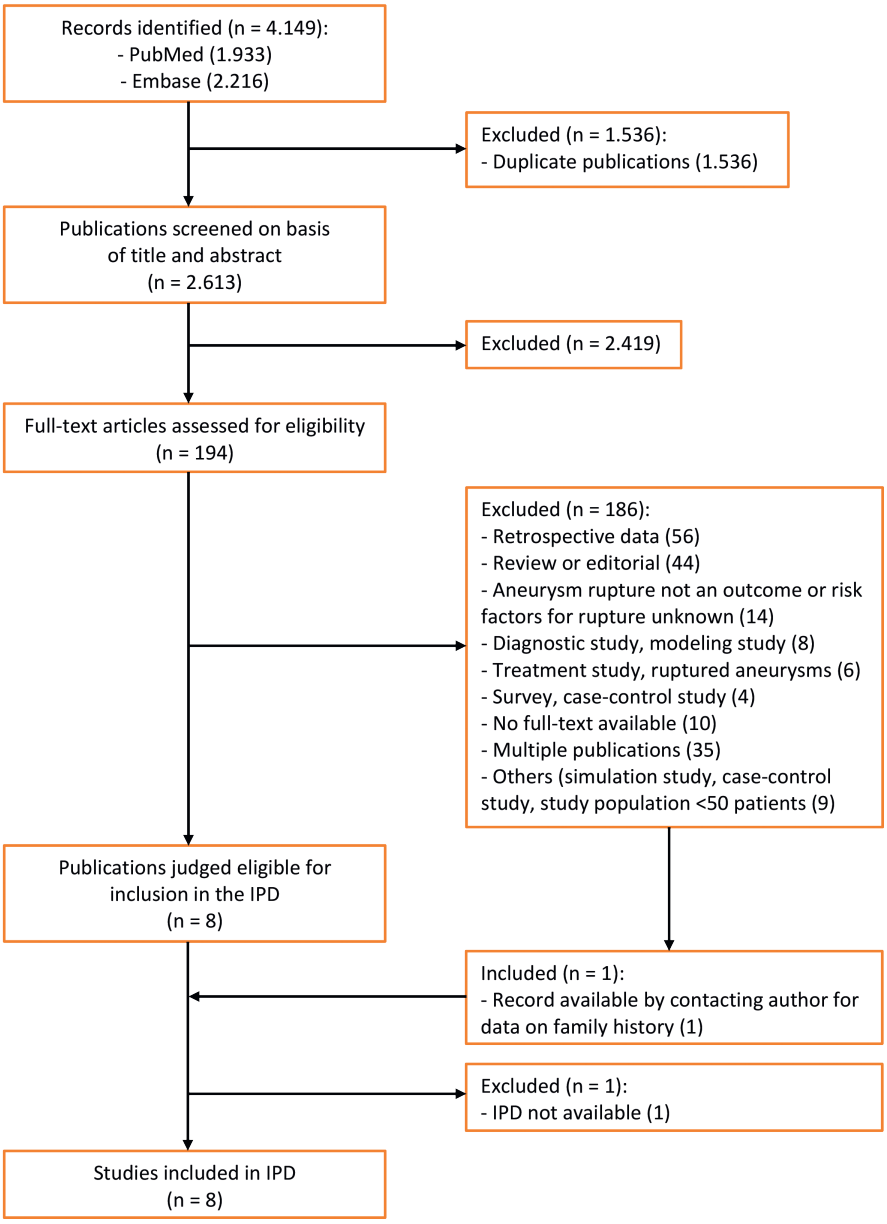


Table 1. Characteristics of included studies

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

[*] *= unpublished data; UIA = unruptured intracranial aneurysm; aSAH = aneurysmal subarachnoid haemorrhage*

The six cohorts that defined first-degree relatives as parents, siblings and children totalled 2,297 patients with 3,089 UIA and 7,301 person-years of follow-up. Baseline characteristics are shown in Table 2. The mean age was 56 ± 12 years, 399 patients (17%) had a positive family history 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 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 Supplementary Table 3.

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, y (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

aSAH = aneurysmal subarachnoid haemorrhage; y = years

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 Supplementary Table 4.

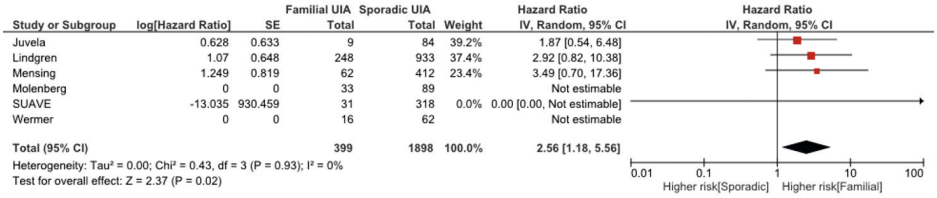
Table 3. Characteristics of ruptured intracranial aneurysms in cohorts defining first-degree relatives as parents, children, and siblings per aneurysm.

	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)
Dutch	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 haemorrhage * In case of multiple aneurysms, the largest aneurysm was used for analysis*

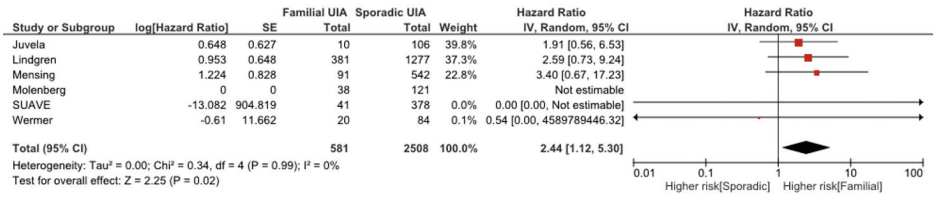
The unadjusted hazard rate (HR) of patients with familial compared to those with sporadic aneurysms was 1.49 (95% CI 0.73 – 3.07) in cohorts defining first-degree relatives as parents, children, and siblings. After adjustment for the PHASES score and smoking the adjusted HR was 2.56 (95% CI 1.18 – 5.56, 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 (Supplementary Figure 2). 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%; Supplementary Figure 3–5) 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, analysing the data per patient



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

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



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 analysed 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 analysing 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. Second, 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. Third, 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] Fourth, in our primary analysis patients from Finnish populations were overrepresented (55%) compared to Dutch (29%) and Japanese (15%) populations. Across all populations a higher risk of rupture for familial compared to sporadic UIA was found, with the highest HR in the non-Finnish and non-Japanese cohort, so we think that our results are generalizable to all populations. Fifth, 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 centres and that patients with a positive family history were referred to such centres 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. Sixth, we had no data on confirmed consanguinity for the different cohorts. Finally, the difference in definition for a positive family history in all available studies resulted in systematic differences in the rupture risk. In 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-analyse 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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SUPPLEMENTARY CONTENT

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Supplementary Figure 5. 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, analysing the data per patient and stratified for European populations and Japanese populations

Supplementary Table 1. Baseline characteristics of all separate cohorts

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

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[0]		Sonobe et al[1]		Morita et al[2]		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	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	4.0	5.0	6.0	7.0	7.0	6.0	7.0
(0-6)	(0-13)	(3-9)	(3-10)	(3-17)	(3-19)	(3-15)	(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	1.0	3.4	3.2	0.3	1.0	3.6	3.1
(0-2)	(0-2)	(1-6)	(0-7)	(0-8)	(0-9)	(0-11)	(0-11)
-	-	-	0.53	0.86	1.12	0.68	1.0
			(0.22- 1.11)	(0.27-2.06)	(0.91- 1.35)	(0.25- 1.51)	(0.75- 1.30)

Supplementary Table 2. 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 at al[12]	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

Supplementary Table 3. 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, y (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)	
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 haemorrhage; SD = standard deviation; y = years

Supplementary Table 4. 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)
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 haemorrhage; SD = standard deviation

Supplementary Figure 1. 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 "natural
course"[Title/Abstract]

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

Embase search string

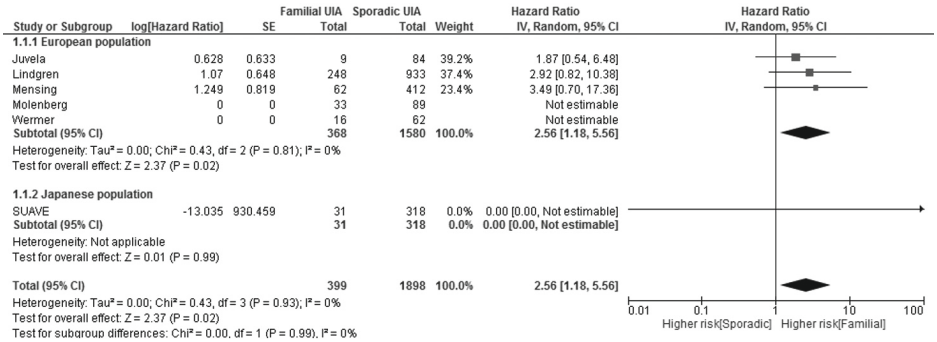
#1:
'intracranial aneurysm':ti:ab OR 'intracranial saccular aneurysm':ti:ab OR 'cerebral aneurysm':ti:ab OR
'intracranial aneurysms':ti:ab OR 'intracranial saccular aneurysms':ti:ab OR 'cerebral aneurysms':ti:ab

#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 – 339.423

#3:
'follow-up':ti:ab OR 'follow up':ti:ab OR 'natural history':ti:ab OR 'natural course':ti:ab - 688.714

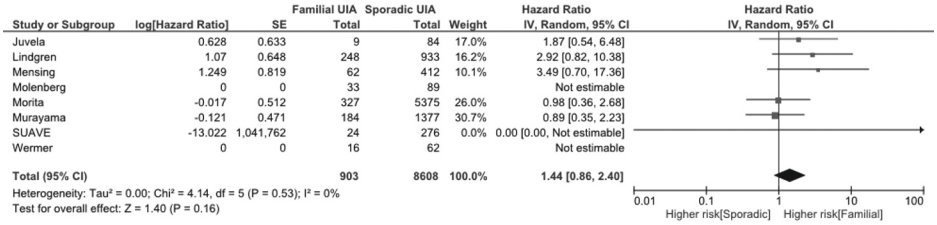
#1 AND **#2** AND **#3**

Supplementary 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, analysing the data per patient and stratified for European and Japanese populations

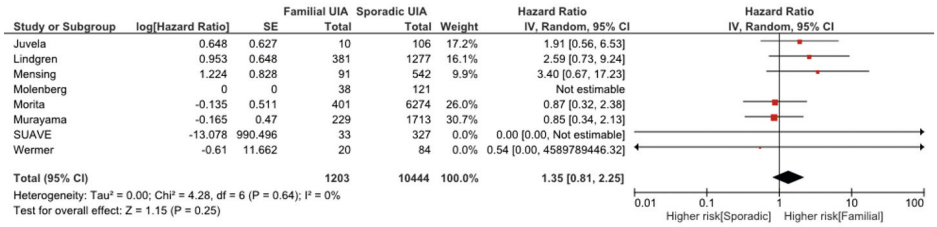


In the study from Wermer et al 1 aneurysm ruptured, in a patient with multiple aneurysms. The ruptured aneurysm was the smallest aneurysm and consequently this rupture was not included in the analysis per patient

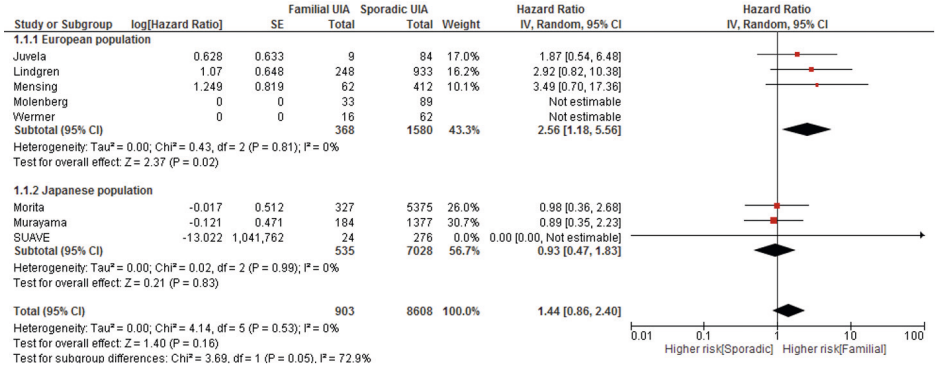
Supplementary Figure 3. Hazard ratio of the rupture rate in patients with familial aneurysms compared to sporadic aneurysms adjusted for the PHASES score and smoking in cohorts both including and excluding siblings in the definition of first-degree relatives, analysing the data per patient



Supplementary Figure 4. 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, analysing the data per aneurysm



Supplementary Figure 5. 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, analysing the data per patient and stratified for European populations and Japanese populations



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

CHAPTER 7

Correlation of age at time of aneurysmal subarachnoid haemorrhage within families

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ABSTRACT

Background & Purpose

The optimal preventive screening strategy for intracranial aneurysms in first-degree relatives (FDRs) of patients with aneurysmal subarachnoid haemorrhage (aSAH) remains unclear. We aimed to evaluate the correlation of age at time of aSAH in FDRs, to assess if age at time of aSAH may be a factor to consider in determining the optimal screening strategy.

Methods

In a series of Dutch, Finnish and French families with ≥2 relatives with aSAH, Intraclass Correlation Coefficients (ICCs) for age at time of aSAH and age differences at time of aSAH between FDRs were calculated. We performed sub analyses on siblings only and on Dutch and French families as different patient characteristics are reported for the Finnish.

Results

We included 146 families in total (87 Dutch, 43 Finnish and 16 French) with 319 FDRs with aSAH. The ICC of age at time of aSAH was 0.21 ($p<0.001$). The correlation slightly increased when analysing siblings only to 0.34 ($p<0.001$). On analysing the Dutch and French families only the ICC remained comparable (0.29, $p<0.001$). An age difference at time of aSAH of 20 years or less was observed in 84% of all FDRs, in 86% of siblings, and in 86% of FDRs of the Dutch and French families.

Conclusion

Our study shows a poor correlation of age at time of aSAH within families. We did not find evidence that age at time of aSAH is a contributing factor in determining the optimal screening strategy for intracranial aneurysm.

INTRODUCTION

First-degree relatives (FDRs) of patients with an aneurysmal subarachnoid haemorrhage (aSAH) are at increased risk of aSAH compared to the general population, with an absolute lifetime risk of aSAH in persons with two or more affected FDRs as high as 26%.[1] In these persons preventive screening for unruptured intracranial aneurysms, with subsequent treatment of detected aneurysms, has been proven cost-effective.[2] At first screening, an intracranial aneurysm is found in 10% of persons with two or more affected FDRs with aSAH or unruptured intracranial aneurysms.[3] If no aneurysm is found at initial screening, these persons have to undergo serial screening, because they have a 5% risk of developing new aneurysms per screening interval.[3] In a modelling study on the cost-effectiveness of several screening strategies, with different screening intervals appearing cost-effective, the optimal strategy was screening from age 20 to 80, every 7 years.[2,3] Currently, the same screening scheme is applied to all screenees and we are not able to give tailored screening.

We hypothesized that insight into the correlation of age at time of aSAH in affected FDRs may help to apply more tailored screening. If the correlation between age at time of aSAH in affected FDRs is high, it may justify to shorten the duration of the screening during life for screenees based on the age of the aSAH of the index case. Therefore, we evaluated the correlation of age and age difference at time of aSAH in affected FDRs in multicentre cohorts of Dutch, Finnish and French families.

METHODS

Study population

We included Dutch, Finnish and French families with familial intracranial aneurysms, defined by the presence of at least two affected first-degree relatives with aSAH or unruptured intracranial aneurysms. The Dutch families were acquired from the prospectively collected database of the University Medical Centre Utrecht (UMCU) between April 1993 and July 2016. For the Finnish families, the saccular intracranial aneurysm database of Neurosurgery of Kuopio University Hospital (KUH), Kuopio, Finland was used, which includes all sporadic and familial intracranial aneurysm patients admitted to KUH between 1980 and 2017. The KUH solely serves a defined catchment population in Eastern Finland. Last, for the French family's data of the ICAN project were used, which is a non-interventional nationwide and multicentre research program including large pedigrees with familial forms of intracranial aneurysms.[4] These families were recruited between 2015 and 2017. For the purpose of this study, we only included families with two or more relatives related in the first-degree with an aSAH. We included patients with both probable and definite aSAH, according to criteria previously described.[5] IRB approval was obtained for the different cohorts.

Data collection

Pedigrees were constructed for the included families. Subsequently, age at time of aSAH was obtained from the medical record.

Data analysis

First, normality of data was tested with the Kolmogorov-Smirnov normality test. Next, familial correlations of age at time of aSAH were calculated, by computing the ratio of between-family variance to the total variance using Linear Mixed Models. P-values of the Intraclass Correlation Coefficients (ICCs) were obtained with a Likelihood-ratio test. ICC agreement was classified into four different categories as follows: 1. no or poor agreement, defined as an ICC agreement less than 0.40; 2. fair, with values between 0.40 and 0.59; 3. good, with values between 0.60 and 0.74 and 4. excellent, with values between 0.75 and 1.00.[6] Second, age differences between FDRs at time of aSAH were calculated. In case of more than two affected FDRs, the largest age difference observed in that family was used. Finally, three sub analyses were performed for (1) patients with definite aSAH only, (2) siblings only, and (3) the Dutch and French families only, as a higher incidence of aSAH and different aneurysm and patient characteristics are reported for the Finnish population.[7,8]

RESULTS

We identified 146 families with two or more FDRs with a definite or probable aSAH (Table 1). These families included a total of 319 FDRs with aSAH, of whom 60% were women. Of those 319 FDRs, 278 FDRs were classified as having had a definite aSAH and 41 a probable aSAH. As a result, 118 families (including 252 patients) had two or more FDRs with a definite aSAH. The remaining 28 families only had one FDR with a definite aSAH. Mean age at time of aSAH of all 319 FDRs was 48.4 years (± 12.7 SD), with the ages at time of aSAH being normally distributed (Kolmogorov-Smirnov p=0.20).

Table 1. Baseline characteristics of the first-degree relatives of the Dutch, Finnish and French families

Characteristic	All FDRs (n=319)	Dutch FDRs (n=196)	Finnish FDRs (n=87)	French FDRs (n=36)
Women, n (%)	192 (60)	130 (66)	44 (51)	19 (53)
Definite aSAH, n (%)	278 (87)	155 (79)	87 (100)	36 (100)
Mean age at time of aSAH, y (SD)	48.4 (12.7)	49.9 (12.7)	46.6 (12.6)	44.8 (11.7)

aSAH = aneurysmal subarachnoid haemorrhage; FDR = first-degree relative; n = number; SD = standard deviation; y = years

The ICC for age at time of aSAH in all 146 families (i.e., including the patients with a probable aSAH) was 0.21 (p<0.001, Table 2) which ICC value corresponds to poor agreement. The cumulative percentage of families per age difference at time of aSAH is demonstrated in Figure 1. Overall, FDRs had their aSAH within an age difference of 5 years in 21% (31/146), of 10 years in 45% (66/146), of 15 years in 67% (98/146), of 20 years in 84% (122/146), of 30 years in 92% (135/146), and of 40 years in 99% (145/146) of families. The remaining one FDR pair had an age difference at time of aSAH of 45 years.

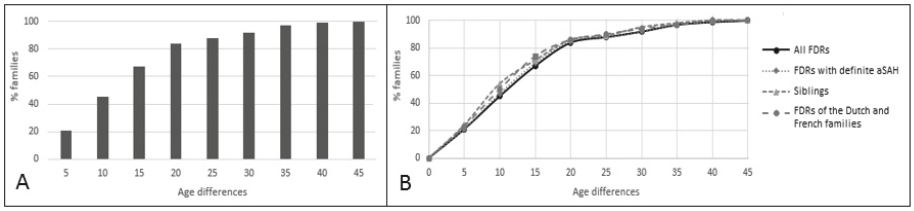
Table 2. Intraclass Correlation Coefficients for age at time of aneurysmal subarachnoid haemorrhage

Study population	ICC	p-value
All FDRs (including probable aSAH)	0.21	<0.001
FDRs with definite aSAH	0.22	<0.001
Siblings with aSAH	0.34	<0.001
FDRs of the Dutch and French families	0.29	<0.001

aSAH = aneurysmal subarachnoid haemorrhage; FDR = first-degree relative; ICC = Intraclass Correlation Coefficient

On excluding patients with probable aSAH the ICC for age at time of aSAH did not change (ICC=0.22, p<0.001) (Table 2). Also, the age differences between FDRs at time of definite aSAH remained essentially the same (equal or less than 5 years in 21%, 10 years in 47%, 15 years in 69%, 20 years in 85%, 30 years in 92% and 40 years in 99% of FDRs) (Figure 1). In the subgroup of siblings, the observed correlation was slightly higher but remained in the category of poor agreement (ICC=0.34, p<0.001) (Table 2). The age difference at time of aSAH between the sibling pairs also remained comparable (Figure 1). Finally, on analysing the Dutch and French cohort only a comparable ICC for age at time of aSAH was found (0.29, p<0.001). The age difference at time of aSAH between the FDRs remained again comparable.

Figure 1. Cumulative percentage of families per difference of age at time of aneurysmal subarachnoid haemorrhage.



Panel A shows the results for all first-degree relatives and Panel B for the sub-analyses including first-degree relatives with definite aneurysmal subarachnoid haemorrhage, siblings and first-degree relatives of Dutch and French families only.

FDR = first-degree relative; aSAH = aneurysmal subarachnoid haemorrhage

DISCUSSION

The correlation in age at time of aSAH within families is poor. The correlation slightly improved when analysing siblings with aSAH only, but remained poor. Moreover, less than half of the patients within these families had their aSAH within a time window of 10 years apart while even an age difference between FDRs at time of aSAH of up to 45 years was observed.

To the best of our knowledge, our study is the first to assess the correlation of age at time of aSAH within families. However, multiple previous studies focused on determining the optimal screening strategy for familial intracranial aneurysms. Several decision models evaluated the optimal screening strategy for individuals with a positive family history of aSAH, for most health benefit at acceptable costs (< €20.000 per QALY).[2,9] The best screening strategy for persons with two or more affected FDRs, was found to be screening from age 20 until 80 every 7 years, although the cost-effectiveness of any screening strategy in this group is likely to be acceptable.[3] Our study results cannot contribute to a tailored adjustment of the screening interval.

A strength of our study is that we approached the clinically relevant question on the concordance of age at time of rupture within a large international cohort of well phenotyped families with familial intracranial aneurysms. However, our study also has limitations that need to be addressed. First, as we do not have complete follow-up of the FDRs throughout their lives, we may have missed some episodes of aSAH, especially in the youngest generation. Second, information on age at time of aSAH of included patients was sometimes obtained through their relatives, which could have led to slightly different values. However, since we consider it unlikely that there would be systematic value errors over time, we think that the concordance analyses are valid.

Since we found no good correlation in age at time of aSAH within families with ruptured intracranial aneurysms, when counselling relatives of aSAH patients there is no reason to take age at time of aSAH of affected relatives into account in determining the optimal preventive screening strategy.

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CHAPTER 8

Difference in aneurysm characteristics between patients with familial and sporadic aneurysmal subarachnoid haemorrhage

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ABSTRACT

Object

Patients with familial intracranial aneurysms (IA) have a higher risk of rupture than patients with sporadic IA. We compared geometric and morphological risk factors for aneurysmal rupture between patients with familial and sporadic aneurysmal subarachnoid haemorrhage (aSAH) to analyse if these risk factors contribute to the increased rupture rate of familial IA.

Methods

Geometric and morphological aneurysm characteristics were studied on CT-angiography in a prospectively collected series of patients with familial and sporadic aSAH, admitted between September 2006 and September 2009, and additional patients with familial aSAH retrieved from the prospectively collected database of familial IA patients of our centre. Odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were calculated to compare the aneurysm characteristics between patients with familial and sporadic aSAH.

Results

We studied 67 patients with familial and 184 with sporadic aSAH. ORs for familial compared with sporadic aSAH were for oval shape 1.16 (95% CI 0.65 – 2.09), oblong shape 0.26 (95% CI 0.03 – 2.13), irregular shape 0.83 (95% CI 0.47 – 1.49), aspect ratio ≥ 1.6 0.94 (95% CI 0.54 – 1.66), contact with the perianeurysmal environment (PAE) 1.15 (95% CI 0.56 – 2.40), deformation by the PAE 1.05 (95% CI 0.47 – 2.35) and for dominance of the posterior communicating artery (PCoA) in case of PCoA aneurysms 1.97 (95% CI 0.50 – 7.83).

Conclusions

The geometric and morphological risk factors for aneurysm rupture do not have a higher prevalence in familial than in sporadic aSAH and thus do not explain the increased risk of IA rupture in patients with familial IA. We recommend further search for other potential risk factors for rupture of familial IA, such as genetic factors.

INTRODUCTION

Familial predisposition is the strongest risk factor for aneurysmal subarachnoid haemorrhage (aSAH).[1] A report from the Familial Intracranial Aneurysm (FIA) study found a 17-times higher rupture rate for patients with familial intracranial aneurysms (IA) compared to patients with sporadic IA matched for age, gender, location and size of the aneurysms.[2] The cause of this increased rupture rate of familial IA is as yet unknown.

Recently, a meta-analysis of six prospective cohort studies on risk of rupture showed that prognostic factors for IA rupture include age, hypertension, history of aSAH, geographical region and IA size and location, with IA > 7 mm and IA in the vertebrobasilar, anterior communicating and posterior communicating arteries carrying the highest risk of rupture.[3] Previous studies suggest that patients with familial IA are younger and have larger IA at time of rupture and more often have multiple IA and IA located at the middle cerebral artery.[4-7] The presence of hypertension does not differ between patients with familial and sporadic IA,[8] while no data on a possible difference in previous history of aSAH exist. Therefore, of the afore mentioned prognostic factors, only IA size may contribute to the higher risk of rupture of familial IA and a further search for risk factors contributing to the increased rupture rate is warranted.

Suggested additional geometric and morphological risk factors for IA rupture include aneurysmal shape, various size and shape ratio's, contact between the aneurysmal wall and surrounding anatomic structures and dominance of the posterior communicating artery (PCoA) in case of PCoA IA.[3,9,10]

In this study we compared geometric and morphological risk factors for aneurysmal rupture between patients with familial aSAH and patients with sporadic aSAH to analyse if these risk factors contribute to the increased rupture rate of familial IA.

METHODS

Study population

From a prospectively collected cohort of 250 consecutive aSAH patients admitted to the University Medical Centre Utrecht (UMCU) between September 2006 and September 2009, we compared patients with familial aSAH to patients with sporadic aSAH.[11] In addition, we used the cohort of familial aSAH patients admitted between January 2003 and September 2006 and between October 2009 and January 2014, retrieved from the prospectively collected database of familial IA patients of the UMCU. The Medical Ethical Committee of the University Medical Centre Utrecht approved the data collection used, and written informed consent was obtained. Familial aSAH was defined as two or more first-degree relatives with 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 CT compatible with a ruptured aneurysm and an aneurysm on CT-angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). Probable aSAH was defined as either sudden severe headache in combination with a normal neurological examination and hemorrhagic CSF, followed by sudden deterioration and death within 4 weeks (consistent with rebleeding), or as a history describing a second ictus followed by death within the first 4 weeks after "stroke" and age < 70 years.[12] Exclusion criteria were: 1) unavailable or poor quality CTA; 2) fusiform IA; 3) inability to identify the location of the ruptured IA in case of multiple IA; 4) previous history of conditions known to predispose to IA formation.[13]

Data extraction and imaging

The geometric and morphological aneurysm characteristics were reviewed on CTA images of the circle of Willis. The CTA scans were performed with a field of view of 160 mm and a slice thickness of 1.0 mm reconstructed at 0.5 mm. CTA source image data of all patients were transferred to an offline workstation (IntelliSpace Portal, v6.0.1.20250, Philips Healthcare) for interactive viewing and post-processing. CTA scans were reviewed blinded for family history by the same observer (LAM). Complex cases were discussed in a consensus meeting with an experienced neuroradiologist (ICvdS). A standardized window setting (window level and window width equal to the Hounsfield units within the aneurysm) was used to perform all measurements. The images could be rotated in three dimensions for all measurements and volume rendering was used for evaluation of the perianeurysmal environment (PAE).

Definitions of variables

Aneurysmal shape

Shape of the IA was divided into spherical (width > 80% of length) or elliptical (width < 80% of length), which was further divided into oval (width 50 – 80% of length) and oblong (width < 50% of length).[14] IA were considered to have an irregular shape when multiple lobes, a bleb or daughter sac were present.

Aspect ratio

Aspect ratio is used to describe the relation between the length and the neck of the IA and is calculated by dividing the maximal neck-to-dome-length by the neck-width using a 0.1-point scale. Aspect ratio was dichotomized into <1.6 and ≥1.6.[15-17]

Perianeurysmal environment

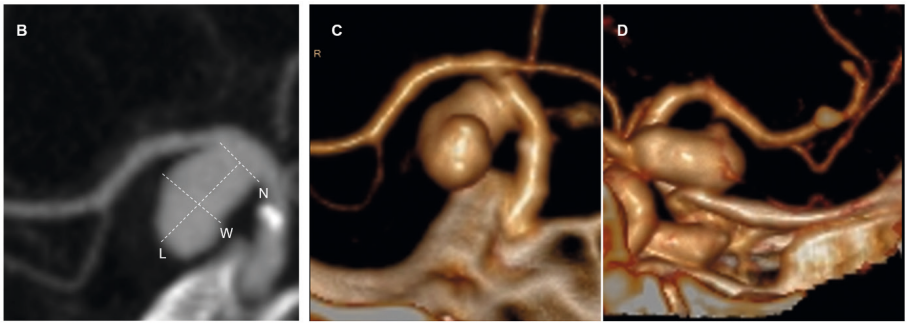
The aneurysm wall was evaluated for contact with bone or vessels in the PAE using volume rendering (Figure 1). Deformation of the aneurysm by the PAE was defined as a local change in contour of the aneurysm wall at the location of contact with a structure in the PAE or as a protrusion of the aneurysm wall contralateral of the location of contact with a structure in the PAE.[9] Three categories of PAE interaction were defined:

1) no contact with the PAE, 2) contact with the PAE without deformation of the IA and 3) deformation of the IA by contact with the PAE.

Dominance of the PCoA in case of PCoA aneurysms

For patients with familial or sporadic PCoA IA, dominance of the PCoA was studied on CTA. Vessel diameter of the PCoA and P1-segment of the posterior cerebral artery (PCA) were measured ipsilateral of the IA. The PCoA was considered dominant if the PCoA diameter exceeded the diameter of the P1-segment of the PCA with more than 33%.

Figure 1. Definitions of aneurysm-related risk factors



Panel A *Aneurysmal size of a right internal carotid artery aneurysm: N = neck (maximal length of the segment adjacent to the orifice), L = length (distance between neck centre and dome of the aneurysm), W = width (largest distance perpendicular to length);*
Panel B and C *Contact of a right internal carotid artery aneurysm with the perianeurysmal environment: coronal* **(B)** *and sagittal view* **(C)** *showing flattening of a right internal carotid artery aneurysm draping over the bony sella turcica.*

Data analysis

We calculated odds ratio's (ORs) with corresponding 95% confidence intervals (CI) to compare aneurysmal shape, aspect ratio ≥1.6, contact with or deformation of the IA by the PAE, and dominance of the PCoA in case of PCoA IA between patients with familial and sporadic aSAH. Multivariable logistic regression analysis was used to adjust for possible confounding by the six factors known to be associated with IA rupture: age, gender, previous aSAH, hypertension and IA size and location.[3] We did not adjust for IA location in the analysis of dominance of the PCoA. First, analyses were performed comparing all included patients with familial aSAH with patients with sporadic aSAH. Second, to test for possible selection bias, sensitivity analyses were performed using only the prospectively collected cohort of consecutive familial and sporadic aSAH patients[11] and thus excluding the additional cohort of familial aSAH patients from the prospectively collected database of familial IA patients.

RESULTS

In total, 22 patients with familial and 13 patients with sporadic aSAH were excluded for the following reasons: good quality CTA was not available for analysis (n=23), CTA showed a fusiform IA (n=6), the ruptured IA could not be identified in case of multiple IA (n=5) or the patient had a history of polycystic kidney disease (n=1). Baseline characteristics of the remaining 67 patients with familial aSAH and 184 patients with sporadic aSAH included in the analysis are summarized in Table 1.

Table 1. Baseline characteristics of the 67 patients with familial and 184 patients with sporadic aneurysmal subarachnoid haemorrhage.

	Familial aSAH (n=67) n (%)	Sporadic aSAH (n=184) n (%)
Women	54 (81)	135 (73)
Mean age*, y (SD)	55 (12)	54 (12)
Hypertension	18 (27)	41 (22)
Smoking*, (n=61/184)	39 (64)	111 (60)
Aneurysm size		
≥7 mm	27 (40)	98 (53)
Aneurysm location		
ACA/ACoA/PeriA	20 (30)	79 (43)
ICA	9 (13)	10 (5)
PCoA	11 (16)	37 (20)
MCA	16 (24)	38 (21)
BA/VA	11 (16)	20 (11)

** = at time of aSAH; ACA = anterior cerebral artery; ACoA = anterior communicating artery; BA = basilar artery; ICA = internal carotid artery; MCA = middle cerebral artery; n = number; PCoA = posterior communicating artery; PeriA = pericallosal artery; SD = standard deviation; VA = vertebral artery; y = years*

Of the 67 patients with familial aSAH, 38 were identified from the prospectively collected cohort of consecutive aSAH patients[11] and 29 from the prospectively collected database of familial IA patients.

Aneurysmal shape, aspect ratio ≥1.6, contact with or deformation of the IA by the PAE, and dominance of the PCoA in case of PCoA IA were not significantly associated with familial aSAH (Table 2).

Table 2. Geometric and morphological aneurysm characteristics in the 67 patients with familial and 184 patients with sporadic aneurysmal subarachnoid haemorrhage.

	Familial aSAH (n=67)	Sporadic aSAH (n=184)		
	(n, %)	(n, %)	OR (95% CI)	aOR (95% CI)
Shape				
Spherical	24 (36)	69 (38)	Reference	Reference
Elliptical – oval	42 (63)	104 (57)	1.16 (0.65–2.09)	1.29 (0.69–2.41)
– oblong	1 (2)	11 (6)	0.26 (0.03–2.13)	0.35 (0.04–3.20)
Shape				
Irregular shape	42 (63)	123 (67)	0.83 (0.47–1.49)	1.21 (0.63–2.35)
Aspect ratio				
≥1.6	38 (57)	107 (58)	0.94 (0.54–1.66)	1.36 (0.71–2.62)
Perianeurysmal environment				
No contact or deformation	44 (66)	125 (68)	Reference	Reference
Contact (without deformation)	13 (19)	32 (17)	1.15 (0.56–2.40)	1.27 (0.58–2.73)
Contact and deformation	10 (19)	27 (15)	1.05 (0.47–2.35)	1.28 (0.53–3.12)
PCoA aneurysms (n=48)				
PCoA dominance	5 (46)	11 (30)	1.97 (0.50–7.83)	0.40 (0.09–1.88)

(a)OR = (adjusted) Odds Ratio; aSAH = aneurysmal subarachnoid haemorrhage; CI = confidence interval; n = number; PCoA = posterior communicating artery

These results did not change after adjustment for age, gender, previous aSAH, hypertension, IA size and location. When comparing only patients with familial and sporadic aSAH from the prospectively collected cohort of consecutive aSAH patients[11] the results were essentially the same (data not shown).

DISCUSSION

Our study shows that geometric and morphological aneurysm characteristics associated with a higher rupture rate of IA, e.g. aneurysmal shape, aspect ratio ≥1.6, contact with or deformation by the PAE, and dominance of the PCoA in case of PCoA IA, do not differ between patients with familial aSAH as compared with patients with sporadic aSAH. Therefore, these characteristics do not explain the increased risk of IA rupture in patients with familial IA as compared to patients with sporadic IA.

First-degree relatives of patients with familial aSAH are advised to be screened for unruptured IA. In case an unruptured IA is discovered, knowledge on risk factors for rupture of familial IA is essential to select those relatives at high risk of IA rupture who could benefit from preventive treatment. Our results imply that the geometric and morphological aneurysm characteristics studied will not contribute in detecting these high-risk first-degree relatives of patients with familial IA. Thus far, only IA size has been found as an explanatory factor for the higher risk of rupture of familial IA,[6] although not all studies found a larger aneurysm size at rupture in familial than in sporadic IA.[4,5] Other potential risk factors include genetic factors. To date no genetic factors associated with IA rupture have been found, since most genetic studies performed thus far have not made a distinction between patients with unruptured and ruptured IA. Future studies should focus on the identification of genetic factors associated with rupture, their potential difference between patients with sporadic and familial IA, and the existence of gene-environment interactions[18] to clarify the increased risk of rupture of familial IA.

A strength of the current study is that all characteristics were studied on CTA images using the same structured approach. Furthermore, data collection and review of CTA scans was performed blinded for family history to prevent observer bias. Our study also has limitations that need to be addressed. First, we did not find a difference in prevalence of aneurysm characteristics associated with rupture studying a relatively small number of patients. Therefore, the results of this study should be considered preliminary. However, considering this number of included patients we were able to exclude a mean difference in the prevalence of aneurysm characteristics associated with rupture larger than 20% between sporadic and familial aSAH assuming a beta of 0.80. Second, patients and controls were not matched for IA size and location, which are important risk factors for rupture. Therefore, we adjusted for these characteristics in a multivariate analysis. Third, we restricted evaluation of the PAE to visible structures on CTA scans such as bone or vessels. This might have led to an underestimation of the actual interaction, as we might have missed other structures in the PAE modulating the shape of the IA and thereby causing the IA to rupture. But we do not expect to have missed a difference in interaction with the PAE between patients with familial and sporadic IA, since CTA scans were assessed in the same structured manner for both groups.

The geometric and morphological risk factors for aneurysm rupture do not have a higher prevalence in familial than in sporadic aSAH and thus do not explain the increased risk of IA rupture in patients with familial IA. We recommend further search for other potential risk factors for rupture of familial IA, such as genetic factors. Knowledge on these risk factors will help to identify those first-degree relatives of patients with familial IA at high risk of rupture of an IA, for whom preventive treatment should be considered.

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CHAPTER 9

General Discussion

GENERAL DISCUSSION

The research described in this thesis aimed to improve screening and prediction of rupture of intracranial aneurysms. We did this by studying the yield of screening for unruptured intracranial aneurysms and the effect of screening on quality of life in high-risk groups (Part I), and by studying the rupture risk of familial intracranial aneurysms and patient- and aneurysm-related characteristics contributing to this risk (Part II). In this chapter, the most important findings are put into perspective and implications for clinical practice and future studies are suggested.

Screening for unruptured intracranial aneurysms

Non-invasive screening with Magnetic Resonance Angiography (MRA) can prevent future aneurysmal subarachnoid haemorrhage by early detection and preventive treatment of the intracranial aneurysms identified. Preventive occlusion is only indicated for those aneurysms for which the risk of rupture outweighs the risk of complications of preventive treatment and the potential negative effect of screening on quality of life. To determine the cost-effectiveness of screening the following factors, among others, have to be taken into account: the prevalence of unruptured intracranial aneurysms in the screened population, the risk of rupture of the aneurysms identified with screening, the risk of complications of preventive treatment, the effects of screening on quality of life, the number of quality-adjusted life years (QALYs) gained, life expectancy of the persons screened, and associated costs. Types of costs that should at least be included are direct costs of screening, direct costs of preventive aneurysm treatment, direct costs of aneurysmal subarachnoid haemorrhage and indirect costs of aneurysmal subarachnoid haemorrhage. Since the factors mentioned above may vary between different healthcare systems and different populations eligible for screening, specific estimates of these factors are needed to determine cost-effectiveness.

Prevalence of unruptured intracranial aneurysms

The prevalence of intracranial aneurysms is known for the general population and for persons with a positive family history for aneurysmal subarachnoid haemorrhage.[1-3] For the general population, a prevalence of unruptured intracranial aneurysms of 3.2% (95% confidence interval (CI) 1.9 – 5.2%) was reported by a systematic review and meta-analysis, including persons from 21 countries worldwide up to 2011 (with a mean age of 50 years and consisting of 50% women).[1] In persons with two or more first-degree relatives with aneurysmal subarachnoid haemorrhage, intracranial aneurysm prevalence was 11% (95% CI 8.6 – 14.4%) at first screening.[2] In persons with one first-degree relative with aneurysmal subarachnoid haemorrhage, the prevalence was 4% (95% CI 2.6 – 5.8%).[3] In **Chapter 2 and 3**, we determined intracranial aneurysm prevalence in two new populations that may be good candidates for screening given

their increased lifetime risk of aneurysmal subarachnoid haemorrhage. In **Chapter 2** we showed in persons with at least one first-degree relative with an unruptured intracranial aneurysm and a negative family history for aneurysmal subarachnoid haemorrhage, that the prevalence of intracranial aneurysms is 5.0% (95% CI 3.2 – 7.4%). The screened population had a mean age of 47 years and consisted of 55% women, the distribution of these risk factors for aneurysm development (age and female sex) is comparable to the distribution in the meta-analysis that estimated the prevalence in the general population.[1] In **Chapter 3** we found in persons aged 35 years or more with hypertension and clinically manifest atherosclerotic vascular disease who smoke or had a history of smoking, that the prevalence of intracranial aneurysms is also 5.0% (95% CI 3.3 – 7.3%). Mean age of the study population was 60 years with only 19% women. If 50% of the study population would have been women, the estimated aneurysm prevalence would have been 6% instead of 5%. This prevalence is in the same range as the recently shown intracranial aneurysm prevalence of 4.7% in 2013 patients (50% women, 51% hypertension and 14% current smokers) who underwent MRA or Computed Tomography Angiography (CTA) because of suspected transient ischaemic attack or minor stroke between 2011 and 2020 in the OXVASC study, a longitudinal population-based cohort in the United Kingdom.[4] For both populations studied in **Chapter 2 and 3**, we demonstrated a higher intracranial aneurysm prevalence compared with the general population,[1] with a prevalence ratio of 1.56 (95% CI 1.05 – 2.33) for persons with at least one first-degree relative with an unruptured intracranial aneurysm and a negative family history for aneurysmal subarachnoid haemorrhage, and also 1.56 (95% CI 1.06 – 2.29) for persons aged 35 years or older with hypertension and clinically manifest atherosclerotic vascular disease who smoke or have a history of smoking.

The finding of a 5% prevalence of intracranial aneurysms for both populations described in **Chapter 2 and 3** raises the question whether this prevalence may more likely represent the current detection rate when screening the general population for intracranial aneurysms, instead of an increased prevalence in a high-risk population. This line of thinking is supported by the smaller mean size of the aneurysms identified in the studies described in **Chapter 2 and 3** compared to previous screening studies,[2,3] which might be caused by the increased sensitivity of MRA over the years resulting in a higher detection rate.[5] Since 2011, a few studies have been published that seem to support the hypothesis that the detection rate, and thereby the reported prevalence, of intracranial aneurysms in the general population has increased.[6,7] A cross-sectional population-based study in Norway reported a prevalence of intradural, saccular aneurysms sized 2 mm or more of 6.6% (95% CI 5.4 – 7.6%), screening persons with a mean age of 64 years that consisted of 53% women between 2016 and 2017 with 3T MRA.[6] However, this does not give definite proof of an increased detection rate because aneurysm prevalence in that study may be overestimated due to 1) the lack of information on additional risk factors for aneurysm development, e.g. no information on family history for intracranial aneurysms and/or subarachnoid haemorrhage was available, and 2) the presence of hypertension

as a known risk factor for aneurysm development in 54% of participants.[6] Another cross-sectional population-based study from China screening 4813 persons with a median age of 53 years and consisting of 51% women with 3T MRA between 2007 and 2011, found an intracranial aneurysm prevalence of 7.0% (95% CI 6.3 – 7.7%).[7] Only 25% of the screened population had hypertension and 22% were current or former smokers in that study, but no information on family history for unruptured intracranial aneurysms and subarachnoid haemorrhage was included to put those results into perspective.[7] In contrast to the studies reporting a higher prevalence in the general population than the generally assumed 3.2%, a review including relatively old autopsy studies published between 1958 and 1990 described a 0.3 – 4.0% intracranial aneurysm prevalence across all age groups.[8] Because a longitudinal study in one population with the same or different imaging modalities is lacking, proper assessment of a potential time-trend in intracranial aneurysm prevalence is limited. In conclusion, it cannot be discerned yet if there is an increased detection rate or an increased prevalence of unruptured intracranial aneurysms.

Future directions

A direct comparison of intracranial aneurysm prevalence between studies has its limitations, mainly due to differences in imaging modality, time period reported on and study design that may result in selection bias. An updated review and meta-analysis of individual patient data, only analysing more recent population-based studies that incorporated known risk factors for aneurysm development including family history, should determine if the intracranial aneurysm prevalence found in **Chapter 2 and 3** is higher compared with the prevalence in the general population. If the groups studied in **Chapter 2 and 3** indeed have an increased intracranial aneurysm prevalence compared with the general population, their increased lifetime risk of aneurysmal subarachnoid haemorrhage can be (partly) explained by this increased aneurysm prevalence. If, however, intracranial aneurysm prevalence in the groups studied in **Chapter 2 and 3** is not increased compared with the general population, the increased lifetime risk of aneurysmal subarachnoid haemorrhage in these groups might be explained by 1) an increased risk of rupture of the aneurysms identified with screening, or 2) an increased risk of rupture shortly after the aneurysm has developed. The first scenario will make screening more effective in these groups, because the identified aneurysms can be treated in time to prevent rupture. In the second scenario screening will be less effective, because aneurysms will have ruptured before they can be detected with screening. In that case, strategies to prevent aneurysm development will be more effective to prevent aneurysmal subarachnoid haemorrhage.

For persons without a positive family history for intracranial aneurysms and/or aneurysmal subarachnoid haemorrhage, the highest prevalence of intracranial aneurysms is expected in women aged over 50 years with hypertension who smoke.[1,4,9,10] This is supported by our finding in **Chapter 3** that, in persons aged 35 years or older with hypertension who smoke or have a history of smoking, the highest prevalence is observed in women

who currently smoke and that this prevalence is increasing with age. Therefore, future prospective screening studies are warranted to determine the aneurysm prevalence in women who currently smoke. Also, future research could determine whether smoking cessation results in a decreasing prevalence, and whether former smokers ever return to the intracranial aneurysm prevalence of never smokers.

Clinical consequence of screening

Besides the prevalence of intracranial aneurysms identified with screening, the clinical consequences of identifying these aneurysms are decisive in determining whether or not to screen in a certain population. Clinical consequences in case of an unruptured intracranial aneurysm detected by screening, could be preventive aneurysm occlusion or radiological follow-up to determine aneurysmal growth or other morphological changes. In the future, non-invasive treatments such as aspirin or intensive blood pressure lowering may be shown to be effective in reducing the risk of aneurysm rupture.[11] These treatments are expected to increase the benefit of screening, by reducing risk of aneurysm rupture without introducing risk of significant complications. As a result, more persons will benefit from screening for intracranial aneurysms. Screening is only beneficial if it ultimately results in more years in good quality of life compared with not screening. However, studies comparing outcome in terms of years in good quality of life by randomizing persons between screening and not screening for intracranial aneurysms will not be performed. First, given the relatively low incidence of aneurysmal subarachnoid haemorrhage, a large sample size and extensive follow-up time are needed. Second, randomization to not screening will be difficult as the study population knows that they might have an increased risk of aneurysmal subarachnoid haemorrhage. Therefore, observational data on the number of aneurysms identified with screening that have been treated preventively, directly or after detection of aneurysmal growth with follow-up imaging, can be used as a surrogate marker of the number of subarachnoid haemorrhages that can be prevented by screening. To date, for none of the aneurysms identified in **Chapter 2** preventive treatment has been indicated, and in none growth has been detected or aneurysm rupture has occurred. Based on these results, we currently do not advise screening in persons with a first-degree relative with unruptured intracranial aneurysms and a negative family history for aneurysmal subarachnoid haemorrhage. In the cohort of persons who smoke(d) and have hypertension screened in **Chapter 3**, thus far preventive aneurysm treatment was advised to one patient. Therefore, we currently do not advise screening in this population in general. We suggest to first extend follow-up, to evaluate the occurrence of aneurysmal growth and rupture, before developing a decision-model to decide whether or not to advise screening in this population. The number of observed clinical consequences during this extended follow-up that is needed to then decide that it has additional value to develop a decision-model to study cost-effectiveness of screening is arbitrary. Aneurysmal growth can be used as a surrogate marker for rupture.[12] Previous cost-effectiveness studies of screening in persons with a positive family history for aneurysmal subarachnoid haemorrhage used

a probability of growth of 3% per year.[13,14] Extrapolating this probability would mean that three of the average 25 aneurysms identified in **Chapter 2 and 3** would grow during four years of follow-up.

Future directions

Future studies with extended follow-up should assess aneurysmal growth in the cohorts screened in **Chapter 2 and 3**, and in case additional clinical consequences of screening are identified the cost-effectiveness of screening should be studied further in a decision-model with various estimates of risks of aneurysmal growth and rupture. Cost-effectiveness of screening for intracranial aneurysms has been previously studied with cohort-level Markov models,[13,14] and more recently with a microsimulation study (an individual-level Markov model),[15] with the main advantage of a microsimulation study being that transition probabilities can change over time which may better reflect the natural course of intracranial aneurysms. This type of model has been used more widely in, and is recommended to assess cost-effectiveness of, screening programs for various types of cancer.[16]

For persons with at least one first-degree relative with an unruptured intracranial aneurysm but a negative family history for aneurysmal subarachnoid haemorrhage, predictors of a positive first screen for intracranial aneurysms as identified in **Chapter 2**, e.g. age, smoking and excessive alcohol consumption, should be validated externally in cohorts from different countries including low- and high-risk populations. Unfortunately, these cohorts are not available at this time. Future studies could also assess if number of affected relatives with unruptured intracranial aneurysms is an additional predictor of a positive first screen for intracranial aneurysms, since number of affected relatives is a known predictor of a positive screen in persons with a positive family history for aneurysmal subarachnoid haemorrhage.[17] Because we included only 26 persons with multiple affected first-degree relatives with unruptured intracranial aneurysms in **Chapter 2**, we were not able to study this factor.

Despite the underrepresentation of women in **Chapter 3**, we identified female sex to be a risk factor for aneurysm development in this cohort of persons who have hypertension, clinically manifest atherosclerotic vascular disease and who smoke(d), which is in accordance with other studies.[18] Female sex has also been shown to be an independent risk factor for aneurysm rupture,[19] but the reason for this increased risk for women is still unknown. An association with female-specific hormones is suggested from observational and genetic studies,[20-22] as well as with anatomical differences of the circle of Willis.[23] Thus, future studies should aim to identify additional women-specific risk factors for aneurysm development and rupture. Next to female sex, we also found that current smoking and increasing age are predictors of a positive screen for intracranial aneurysms in **Chapter 3**. Based on this finding and previous literature,[18,24,25] the effect of screening could be studied prospectively in a cohort of women aged 50 years or more

with hypertension who smoke, for example derived from the general population, with standardized collection of risk factors, imaging, and quality of life data. In case multiple of these cohorts will be collected in the future, research groups should collaborate in setting up a multinational, individual patient data meta-analysis to determine the yield of screening in this population.

Effect screening for intracranial aneurysms on quality of life

Time-course of quality of life around screening for intracranial aneurysms

Screening for intracranial aneurysms could have negative effects on quality of life, such as anxiety around screening moments or fear of aneurysm rupture in case radiological follow-up imaging is advised after a positive screening. To determine the cost-effectiveness of screening and to better inform persons eligible for screening, information on the effect of screening on quality of life is needed. The effect of screening for intracranial aneurysms because of a positive family history for aneurysmal subarachnoid haemorrhage on quality of life has been investigated by one previous study, showing a negative effect of a positive screening for intracranial aneurysms on quality of life as compared with a negative screening or the general population.[26] However, this study assessed quality of life after a mean period of eight years after the initial screening, and therefore was subject to information bias.[26] In **Chapter 4**, we studied effects of screening on quality of life in a similar population,[26] e.g. persons screened because of a positive family history for aneurysmal subarachnoid haemorrhage, but now data on quality of life were collected prospectively before and at five moments after first screening. One year after first screening, we found no negative effect of screening on quality of life in the complete screened cohort described in **Chapter 4** nor for the persons with a positive screen for intracranial aneurysms. We did observe a clinically relevant temporary decrease in reported health-related quality of life (measured with the EQ5D) in persons with a positive screen six months after screening. This decrease in quality of life was mainly caused by increased reporting of moderate anxiety and pain by these patients. The persons screened in **Chapter 4** were aware of their increased lifetime risk of aneurysmal subarachnoid haemorrhage at time of quality of life assessment, because they had seen the consequences of an aneurysmal subarachnoid haemorrhage in a first-degree relative. Whereas in **Chapter 2**, we studied effects of screening on quality of life in participants who did not know if they had an increased risk of developing an intracranial aneurysm compared with the general population, which makes them different from the participants screened in **Chapter 4**. Using a prospective cohort design with standardized survey moments to assess quality of life similar to **Chapter 4**, we described in **Chapter 2** that one year after first screening no clinically relevant negative effect on quality of life is observed in persons screened because of a first-degree relative with an unruptured intracranial aneurysm. Reported quality of life outcomes pre-screening and after one year were comparable between both cohorts described in **Chapter 2 and 4**.

We therefore conclude for both cohorts that lasting effects on quality of life one year after first screening do not need to be considered as a disadvantage of screening when counseling these persons. This finding is comparable with previous studies on screening for abdominal aortic aneurysms, that showed a transient decrease in mental quality of life six weeks after a positive screen with quality of life improving up to pre-screening levels after one year.[27,28] Interestingly, we found reported emotional functioning and social participation of persons with a positive screening for intracranial aneurysms studied in **Chapter 2 and 4** to be better compared with a previous study.[29] That study reported on quality of life in persons in whom an intracranial aneurysm was identified accidentally, but in whom this aneurysm was not treated preventively.[29] The difference in reported quality of life may be caused by the active choice to be screened in our study population compared with the unexpected confrontation with the presence of an intracranial aneurysm in that other study.[29] After an active choice to be screened you could consider the identification of an intracranial aneurysm as an incidental finding, but still these screened persons did expect that they might have an unruptured aneurysm. In 1984, Calman formulated quality of life as 'the discrepancy between our expectations and our experience'.[30] Applying this definition provides an explanation for the observation that an incidental finding (unexpected) may result in a more pronounced decrease in quality of life compared with a positive screening result (expected), despite that in both patients an aneurysm is detected.[30]

It may be questioned whether the validated questionnaires used to assess quality of life are sensitive enough to detect potential effects of screening. Because the screening itself and the presence of an intracranial aneurysm do not result in physical symptoms in the majority of persons, questionnaires should focus particularly on psychosocial consequences. The observation of a temporary decrease in reported quality of life in patients with a positive screening for intracranial aneurysms, even despite the small sample size in **Chapter 4**, supports the discriminative value of the questionnaires used in the studies described in this thesis. Also, questionnaires used in our studies are recommended by the guidelines for Common Data Elements in intracranial aneurysm research.[31] Common Data Elements are standards for the collection and exchange of data.[31] Another point to consider, is that only persons who wanted to know if they had an intracranial aneurysm and consequently decided to be screened were included in the studies described in **Chapter 2 and 4**. I do not consider the selection bias introduced as a consequence of this inclusion criterion as a limitation, since results will be only applicable to persons who want to be screened and those are the persons who visit our outpatient clinic.

Predictors of quality of life around screening for intracranial aneurysms

In order to early identify persons eligible for screening who are at increased risk of having a negative effect of this screening on quality of life, it is crucial to determine predictors of a negative effect on quality of life around screening. In **Chapter 2 and 4**,

factors negatively influencing quality of life were a psychiatric history, a passive coping style, and the presence of physical complaints that subjectively affect mood. Additionally, perceived stress throughout life rated as always or often was also identified as a predictor of worse quality of life in persons screened because of a first-degree relative with an unruptured intracranial aneurysm in **Chapter 2**. These factors are consistent with previous studies.[29,32]

Future directions

Future prospective studies on the time-course and predictors of quality of life in a larger group of persons with a positive screen could provide more precise information on potential differences between persons with a positive and a negative screening for familial intracranial aneurysms. Increasing the number of patients with a positive screening in those studies could be achieved by collaborating with other institutions experienced in screening for intracranial aneurysms within the same healthcare system. Also, prospectively evaluating quality of life in persons undergoing serial screening, can add valuable information. For example, quality of life may change close to the next screening moment, or in the long-term as was reported by a previous retrospective study in persons screened because of a positive family history for aneurysmal subarachnoid haemorrhage.[26] It is possible that reassurance prevails after an initial negative screening, while the repeated confrontation with serial screening results in a negative impact on quality of life in the long-term. In addition, implementing annual quality of life questionnaires at the outpatient clinic will result in the possibility to collect real-world data, optionally also evaluating the years when no radiological follow-up is scheduled. If this approach is chosen, response rates should be monitored carefully, because the expected decrease in response rate over time could introduce selection bias. In case a decreased response rate is observed, non-response patterns over time should be assessed for different subgroups to determine if it increased the risk of selection bias.[33] A decrease in response rate could be prevented by limiting the number of survey moments and questions, by personally reminding patients of these questionnaires, and by emphasizing its importance to elicit a sense of duty and personal value in participants.[34] Last, quality of life outcomes obtained could be integrated in the electronic patient record, enabling the treating physician to incorporate this information in shared-decision making on the management of the identified aneurysm and to identify persons in need of additional counseling. Effects of interventions to improve quality of life such as cognitive behavioral therapy or computer-assisted training programs could be further evaluated in a randomized study.[35]

Characteristics of familial intracranial aneurysms

Estimating risk of aneurysm rupture

In management decisions on intracranial aneurysms that are identified with screening, the risk of rupture has to be weighed against the risk of complications of preventive aneurysm treatment and effects of this treatment on quality of life. To predict the risk of complications of preventive aneurysm treatment, the SAFETEA scores were developed.[36] The effects of preventive aneurysm treatment on quality of life were comparable between patients with and without preventive aneurysm occlusion one year after detection of the intracranial aneurysm.[29,37] Two risk scores have been developed to predict the absolute risk of aneurysm rupture: the PHASES and UCAS score.[38,39] These scores are based on individual patient data from prospective cohort studies, resulting in the same inevitable limitations for both cohorts namely selection bias and censoring of patients during follow-up because of preventive aneurysm treatment. The PHASES score was developed in patients from the United States, Canada, Europe (including Finland) and Japan, and predicts the absolute 5-year risk of rupture based on six patient and aneurysm characteristics: Population, Hypertension, Age, Size of the aneurysm, Earlier subarachnoid haemorrhage from another aneurysm, and Site of the aneurysm.[38] The UCAS score was developed and validated in Japanese patients and predicts the absolute 3-year risk of rupture based on six patient and aneurysm characteristics: Age, Sex, Hypertension, Size of the aneurysm, Location of the aneurysm, and the presence of a Daughter sac.[39]

Rupture risk of familial intracranial aneurysms

In the multidisciplinary meeting at our institution where we discuss the management of unruptured intracranial aneurysms, we currently use the PHASES score to estimate 5-year risk of rupture because our population is represented in the cohorts used to develop that score.[38] However, the majority of aneurysms identified with screening are small with a low estimated risk of rupture using the PHASES score. Yet, some of these small aneurysms will rupture and the increased risk of rupture in those aneurysms is probably explained by factors that are not included in the PHASES score. Thus, additional predictors of aneurysm rupture are needed to better identify intracranial aneurysms at high risk of rupture. One of these factors could be a positive family history. The lifetime risk of aneurysmal subarachnoid haemorrhage in the general population is highest for persons with a positive family history for aneurysmal subarachnoid haemorrhage.[40,41] A previous study reported a 17-times higher risk of aneurysm rupture for patients with familial compared to sporadic unruptured intracranial aneurysms who smoke and/or have hypertension.[42] However, the PHASES score does not include family history of aneurysmal subarachnoid haemorrhage as a potential predictor of aneurysm rupture, since data on family history was not available for all cohorts included.[38] These data will be difficult to collect, due to the relatively low prevalence of familial intracranial aneurysms and the observation that, as one can imagine, persons with a positive family history for

aneurysmal subarachnoid haemorrhage are more likely to opt for preventive aneurysm treatment because they have seen the consequences of a subarachnoid haemorrhage in a first-degree relative. To improve prediction of risk of aneurysm rupture for patients with familial intracranial aneurysms, we compared risk of rupture between patients with familial and sporadic intracranial aneurysms that were followed at our institution between 1994 and 2016 in **Chapter 5**. We found a not statistically significant 3-times increased risk of aneurysm rupture for patients with familial intracranial aneurysms.[4] This finding pointed to the direction of a less strongly increased risk of aneurysm rupture for familial patients than the 17-times increased risk that had been suggested until then.[42,43] As the number of events (three familial and seven sporadic patients with aneurysm rupture) was low in this study, we subsequently performed an individual patient data meta-analysis in **Chapter 6**. We included six prospective cohorts from the Netherlands, Finland and Japan that defined affected first-degree relatives as parents, siblings or children, and found a 2.5-times (95% CI 1.2 – 5.6) higher risk of aneurysm rupture for patients with familial compared with sporadic intracranial aneurysms.[44] The number of events increased to 10 patients with ruptured familial intracranial aneurysms and 43 patients with sporadic intracranial aneurysms,[44] resulting in more statistical power to demonstrate an effect. When including an additional two cohorts from Japan that excluded siblings from the definition of a first-degree relative, the risk of aneurysm rupture decreased to a 1.4-times (95% CI 0.9 – 2.4) higher risk of aneurysm rupture for patients with familial compared to sporadic intracranial aneurysms.[44]

Additional risk factors for rupture of familial intracranial aneurysms

It is unknown what may cause the additional risk of rupture of familial intracranial aneurysms. Several potential patient and aneurysm related characteristics have been identified that might influence the risk of rupture of familial intracranial aneurysms. First, the observation of a different risk of aneurysm rupture between cohorts in- and excluding siblings in the definition of first-degree relatives,[44] was confirmed in another study demonstrating that siblings have a 1.6-times higher risk of aneurysmal subarachnoid haemorrhage and a 2.3-times higher risk of unruptured intracranial aneurysms, compared with children.[45] Second, a meta-analysis showed that familial intracranial aneurysms tend to rupture at a younger age of the patient than sporadic aneurysms, however heterogeneity between included studies was high.[46] In **Chapter 7**, however, we showed that there is a poor correlation of age at time of aneurysmal subarachnoid haemorrhage within families with at least two affected first-degree relatives with aneurysmal subarachnoid haemorrhage from 87 Dutch, 43 Finnish and 16 French families.[47] This poor correlation remained the same when only analysing 1) families with definite aneurysmal subarachnoid haemorrhage,[48] 2) siblings or 3) Dutch and French families.[47] We concluded that age of a person with a positive screen for familial intracranial aneurysms does not help to identify aneurysms at high risk of rupture within families.

Next, we compared geometric and morphological aneurysm characteristics on CTA that are known to be associated with aneurysm rupture in **Chapter 8**, to assess if these factors contribute to the increased risk of rupture of familial intracranial aneurysms. We did not find a higher prevalence of these risk factors (oval shape, oblong shape, irregular shape, aspect ratio ≥1.6, contact with the perianeurysmal environment, deformation by the perianeurysmal environment and dominance of the posterior communicating artery in case of aneurysms of the posterior communicating artery) in familial compared with sporadic aneurysmal subarachnoid haemorrhage.[49] In summary, we did not identify any additional clinical patient or aneurysm related characteristics besides type of kinship that increase the risk of rupture specifically for familial intracranial aneurysms. Future studies should reveal whether other patient or aneurysm related characteristics explain the increased risk of rupture of familial intracranial aneurysms. To further explain risk of rupture of intracranial aneurysms in general, other aneurysm related characteristics are suggested. For example, the absence of vessel wall enhancement on MRI is associated with aneurysm stability.[50,51] Next to imaging markers, the increased risk of development and rupture of intracranial aneurysms in case of a positive family history for this disease suggests a genetic predisposition. The largest genome-wide association study (GWAS) of intracranial aneurysms in 10.754 cases and 306.882 controls identified 17 common variant risk loci with an explained polygenic heritability of 21.6% and a high correlation between ruptured and unruptured intracranial aneurysms.[52] There was a strong overlap with the genetic risk for smoking and hypertension, which are established risk factors for intracranial aneurysm development and rupture.[52] Besides for smoking and hypertension, the pathway between genetic factors and risk of rupture is unknown. A genetic risk score was developed that showed an association between younger age at time of aneurysm rupture and higher genetic risk.[52] Family studies additionally identified rare variants with a large effect, that did not show a correlation with the presence of sporadic intracranial aneurysms and are probably specific for single families.[53]

Future directions

Based on the increased rupture risk compared with sporadic intracranial aneurysms, a more aggressive treatment approach is justified in patients with unruptured familial intracranial aneurysms. However, in current clinical practice, it is unsure how the 2.5-times increased risk of rupture of familial aneurysms should be weighed in relation to the rupture risk as estimated by the PHASES score.[38] Therefore, family history of aneurysmal subarachnoid haemorrhage should be included as a candidate predictor when developing an updated prediction model for risk of aneurysm rupture in a pooled analysis of large cohorts representing different populations. In defining a positive family history, it is important to distinguish number of affected relatives with unruptured intracranial aneurysms and number of affected relatives with aneurysmal subarachnoid haemorrhage, to further study potential differences between these definitions of a positive family history and thereby improve implementation in daily practice.

Worldwide, research groups studying intracranial aneurysms should already adhere to the proposed unified definitions of Common Data Elements to facilitate pooling of this data on an individual level in the future.[54] Risk prediction of familial intracranial aneurysm rupture can be further improved by introducing additional clinical patient related (family history, type of kinship)[44,45] and genetic (polygenic risk scores)[52] factors as candidate predictors and determine their additional predictive value. Suggested associations of aneurysm related characteristics with rupture risk in sporadic intracranial aneurysms, such as irregular shape and vessel wall enhancement, require further study in familial intracranial aneurysms.[50,51,55]

Conclusions

The prevalence of intracranial aneurysms at first screening is 5%, both in persons with a family history positive for unruptured intracranial aneurysms and negative for aneurysmal subarachnoid haemorrhage, and in persons aged 35 years or more with hypertension and clinically manifest atherosclerotic vascular disease who smoke or have a history of smoking. Within these populations, risk scores have been developed to identify groups with highest risk of finding an intracranial aneurysm at screening. Since all intracranial aneurysms detected with screening had a low estimated risk of rupture, we currently do not advise screening in these groups, even though no negative effect on quality of life one year after screening was observed. The course of quality of life in persons with a positive screen for intracranial aneurysms requires further study. Familial intracranial aneurysms have a 2.5-times increased risk of rupture compared with sporadic intracranial aneurysms. Age at time of aneurysm rupture of the affected relative or aneurysm related characteristics studied in this thesis did not contribute to this increased rupture risk. Future studies could identify additional predictors of rupture of familial intracranial aneurysms and this information can be used to further improve early recognition of persons at high risk of aneurysmal subarachnoid haemorrhage.

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APPENDICES

SUMMARY

The prevalence of unruptured intracranial aneurysms in the general adult population is around 3%. Most intracranial aneurysms remain asymptomatic, but some can rupture, causing an aneurysmal subarachnoid haemorrhage (aSAH). This is a devastating subset of stroke with a poor outcome, occurring at a relatively young mean age of 50 to 55 years. Important risk factors for the development of intracranial aneurysms and aSAH are smoking, hypertension and a positive family history for aSAH. A positive family history is defined as two or more affected first-degree relatives (parents, children or siblings) with aSAH. The best opportunity to reduce the burden of aSAH is by prevention of aSAH, since brain damage from the initial haemorrhage is a major cause of the poor prognosis. Non-invasive screening with Magnetic Resonance Angiography (MRA) can prevent future aSAH by early detection of intracranial aneurysms, followed by preventive treatment of those aneurysms with a high estimated risk of rupture. Screening should ideally only be done in persons in whom a high lifetime risk of aSAH outweighs the risk of complications of preventive aneurysm treatment and the potential negative effects of screening on quality of life (QoL). The lifetime aSAH risk is highest for persons with a positive family history for aSAH and screening has been shown effective for this group of persons. However, since this group constitutes only a minority of all aSAH patients, more information on additional high-risk groups and predictors of aneurysm rupture is needed to further improve prevention of aSAH.

The first part of this thesis assesses the yield of screening for intracranial aneurysms in two groups of persons that could benefit from screening given their potentially high lifetime risk of aSAH. In addition, it describes the course and predictors of the effect of screening for intracranial aneurysms on QoL. The second part of this thesis focuses on the rupture risk of familial intracranial aneurysms, and patient and aneurysm related characteristics contributing to this risk. The overall aim of this thesis is to reduce the number of life years in good quality being lost through aSAH, by improving screening for and prediction of rupture of intracranial aneurysms.

Part I: Screening for unruptured intracranial aneurysms in high-risk groups
The high lifetime risk of aSAH of persons with a positive family history for aSAH is caused by an increased risk of both aneurysm development and rupture. Screening has been shown effective in case of a positive family history for aneurysm rupture (i.e. aSAH), but has not been investigated in case of a positive family history for aneurysm development (i.e. unruptured intracranial aneurysms). **Chapter 2** presents the results of a multicentre prospective cohort study that we performed to determine the yield and effects on QoL of screening for unruptured intracranial aneurysms in first-degree relatives of patients with unruptured intracranial aneurysms and a negative family history for aSAH. 461 first-degree relatives were screened with MRA between 2017 and 2021. We detected 24 intracranial aneurysms in 23 of these 461 first-degree relatives, resulting

in a 5.0% prevalence (95% CI 3.2 – 7.4%). All identified aneurysms were small with a relatively low estimated 5-year risk of rupture of 0.7% (IQR 0.4 – 0.9%). As a result of this low estimated risk of rupture, none of the identified aneurysms were treated preventively. All received follow-up imaging to detect aneurysmal growth or change in aneurysm shape, because these are known risk factors for aneurysm rupture. After a median follow-up of two years (IQR 13 – 38 months), no aneurysmal growth or change in aneurysm shape had been detected. Subsequently, we developed a model for predicting the probability of detecting an intracranial aneurysm at first screening. This risk ranged between 2.3% and 14.7%, with the highest risk increasing with age in first-degree relatives who smoke and have excessive alcohol consumption. We evaluated QoL with E-questionnaires six times during the first year following screening, and found no evidence that QoL is negatively influenced by the screening. However, we currently do not advise screening in first-degree relatives of patients with unruptured intracranial aneurysms and a negative family history for aSAH, because none of the identified aneurysms had a high estimated risk of rupture necessitating preventive treatment. If aneurysmal growth or change in aneurysm shape will be detected with follow-up imaging, preventive treatment of the identified aneurysms may be indicated in the future. This requires further study. Our advice not to screen in this population should be reconsidered if during extended follow-up aneurysmal growth or even rupture occurs.

The lifetime risk of aSAH is also high for persons aged 35 years or more with hypertension who smoke or have a history of smoking. We therefore investigated the yield of screening for intracranial aneurysms in this population in **Chapter 3**. Computed Tomography Angiographies (CTAs) of 500 patients with clinically manifest atherosclerotic vascular disease performed between 2012 and 2019 were reviewed and 25 intracranial aneurysms were identified, resulting in a prevalence of 5.0% (95% CI 3.3 – 7.3%). All identified aneurysms were small with a relatively low estimated 5-year risk of rupture (0.9%, IQR 0.7 – 1.3%). After a median follow-up of almost five years (IQR 39 – 83 months), aneurysmal growth was detected in one patient and preventive aneurysm treatment was advised. Given this small proportion of detected intracranial aneurysms that needed preventive treatment (4%), we currently do not advice screening for this population in general. We did develop a model to identify potential high-risk groups that could benefit from screening. The risk of identifying an intracranial aneurysm at first screening ranged between 1.6% and 13.4%, with predictors of a positive screen being age, female sex and current smoking. Whether screening may be effective for certain high-risk groups depends on the risk of growth of the identified aneurysms over time, and should be the subject of future studies.

The benefits of screening for intracranial aneurysms in terms of preventing life years in good quality being lost as a consequence of aSAH by preventive aneurysm treatment should be carefully weighed against the disadvantages of screening. Such disadvantages include the potential negative psychosocial impact which may lead to a decrease in

number of life years in good quality. Screening has been shown cost-effective for persons with a positive family history for aSAH, but its psychosocial impact is largely unknown. Therefore, in **Chapter 4**, we describe a prospective cohort study on the effects of the current screening for familial intracranial aneurysms on QoL. In a consecutive series of 105 persons from 75 families, aged 20 to 70 years, QoL was evaluated with E-questionnaires at six fixed time points during the year following their first screening for familial intracranial aneurysms. We found no negative effect of screening on QoL, except for a temporary decrease in QoL six months after screening in persons in whom an intracranial aneurysm was identified. This decrease in QoL was mainly caused by increased reporting of moderate anxiety and pain, and returned to the pre-screening level one year after screening. Overall, one year after first screening there was even a slight increase in health-related QoL and decrease in anxiety levels. This new information can be used in counselling about screening for familial intracranial aneurysms. Factors associated with worse QoL after screening were the presence of a psychiatric disease, physical complaints subjectively affecting mood and a passive coping style. It is important to identify persons with such an increased risk of worse QoL following screening, and offer them additional counseling pre-screening.

Part II: Characteristics of familial intracranial aneurysms

A previous study reported a 17-times higher rupture rate for patients with familial intracranial aneurysms compared to patients with sporadic intracranial aneurysms. This increased rupture rate could warrant a more aggressive treatment approach for unruptured familial intracranial aneurysms. However, as the previous study included highly selected familial aneurysms and sporadic patients from a different population, this finding needed to be validated in an independent population. In **Chapter 5**, we assessed the rupture rate of familial compared with sporadic intracranial aneurysms retrieving patients from our institutional cohort, which was prospectively collected between 1994 and 2016. We identified 91 familial aneurysms in 62 patients with 391 aneurysm-years of follow-up, and 542 sporadic aneurysms in 412 patients with 1,373 aneurysm-years of follow-up. We observed 0.77 ruptures per 100 familial aneurysm-years (three familial patients with aSAH) and 0.51 ruptures per 100 sporadic aneurysm-years (seven sporadic patients with aSAH), resulting in a 3-fold higher risk of rupture for familial as compared to sporadic intracranial aneurysms (hazard ratio 2.9 [95% CI 0.6 – 14]). Since we were not able to demonstrate this slightly increased risk of rupture with statistical significance, we further assessed the risk of rupture of familial as compared to sporadic intracranial aneurysms in an individual patient data meta-analysis. In **Chapter 6** we describe the results of this meta-analysis using data from eight prospective cohorts from the Netherlands, Finland and Japan. We included 3,089 intracranial aneurysms in 2,297 patients with 7,301 person-years of follow-up from six cohorts and found a 2.6-times higher risk of rupture for familial compared with sporadic intracranial aneurysms (hazard ratio 2.6 [95% CI 1.2 – 5.6]). We conclude that patients

with familial unruptured intracranial aneurysms have a higher risk of rupture and therefore a more aggressive treatment approach is justified.

To improve the current screening strategy for familial intracranial aneurysms, and thereby the prevention of aSAH, additional patient and aneurysm related factors that contribute to the increased risk of rupture of familial intracranial aneurysms need to be identified. In **Chapter 7**, we present a multicentre cohort study to evaluate whether age at time of aSAH of first-degree relatives may be a factor to consider in determining the optimal screening strategy. We hypothesized that if the correlation of age at time of aSAH within families is high, the duration of the screening during life could be shortened to an interval around the age at time of aSAH of the affected relative. We included 319 first-degree relatives with aSAH from 146 families (87 Dutch, 43 Finnish and 16 French). We found a poor correlation of age at time of aSAH within families, with an Intraclass Correlation Coefficient (ICC) of 0.21 ($p<0.001$). When analysing siblings with aSAH only, the observed correlation was slightly higher (ICC 0.34 [$p<0.001$]) but remained poor. An age difference at time of aSAH of 20 years or less was observed in 84% of first-degree relatives with aSAH, for siblings with aSAH this increased to 86%. Based on these results, age at time of aSAH of affected first-degree relatives is not a factor to consider in developing a more tailored screening approach.

Next to patient related factors such as age, aneurysm related factors could also contribute to the increased rupture rate of familial intracranial aneurysms. In **Chapter 8**, we describe whether geometric and morphological risk factors for aneurysm rupture have a higher prevalence in patients with familial intracranial aneurysms. We reviewed CTAs of 67 patients with familial and 184 patients with sporadic intracranial aneurysms from a prospectively collected cohort for the presence of the following aneurysm related factors: oval shape, oblong shape, irregular shape, an aspect ratio of ^{3} 1.6 (used to describe the relation between the length and the neck of the aneurysm), contact with the perianeurysmal environment (PAE), deformation by the PAE, and dominance of the posterior communicating artery in case of aneurysms of the posterior communicating artery. None of these factors had a higher prevalence in familial compared with sporadic intracranial aneurysms, and therefore these factors do not explain the increased risk of rupture of familial intracranial aneurysms. Future studies should elucidate whether other patient or aneurysm related characteristics explain the increased risk of rupture of familial intracranial aneurysms.

SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

Intracraniële aneurysma's zijn uitstulpingen van de slagaders in de hersenen, die in de loop van het leven kunnen ontstaan. Ze komen bij ongeveer 3% van de bevolking voor. Het merendeel van de intracraniële aneurysma's zal nooit klachten geven, maar sommigen kunnen barsten (ook wel ruptureren genoemd) en een aneurysmatische subarachnoïdale bloeding (aSAB) veroorzaken. Deze bloeding zit in de subarachnoïdale ruimte: de ruimte tussen twee hersenvliezen (de arachnoïdea en pia) die tussen de hersenen en de schedel liggen en waar de bloedvaten naar de hersenen zich bevinden. Een aSAB is een ernstige vorm van beroerte met een slechte prognose, aangezien ongeveer een derde van de mensen met dit type hersenbloeding aan de gevolgen overlijdt. Het komt bovendien op een relatief jonge gemiddelde leeftijd van 50 tot 55 jaar voor. De belangrijkste risicofactoren voor het ontstaan van intracraniële aneurysma's en aSAB zijn roken, hoge bloeddruk en een positieve familieanamnese voor aSAB. Dit laatste betekent dat tenminste twee eerstegraads familieleden (ouders, kinderen, broers en/of zussen) zijn aangedaan. Aangezien de schade aan de hersenen direct na de bloeding de belangrijkste oorzaak is van de slechte prognose, kun je de gevolgen van een aSAB het beste beperken door het barsten van intracraniële aneurysma's te voorkomen.

Nog ongebarsten intracraniële aneurysma's kunnen opgespoord worden door de slagaders in het hoofd af te beelden met Magnetische Resonantie Angiografie (MRA) of Computed Tomografie Angiografie (CTA), ook wel screening genoemd. Omdat intracraniële aneurysma's in de loop van het leven ontstaan, moet de screening gedurende het leven herhaald worden. Wanneer vervolgens de gevonden aneurysma's waarvan ingeschat wordt dat ze een hoog risico hebben om te barsten worden behandeld, kan een toekomstige aSAB worden voorkomen. Deze preventieve behandeling kan zowel via de slagader in de lies (endovasculair) als via een botluik in de schedel (neurochirurgisch) plaatsvinden. Het doel is om het aneurysma af te sluiten van de bloedsomloop; bij endovasculaire behandeling gebeurt dit door het aneurysma op te vullen met platina spiraaltjes (coils) en bij neurochirurgische behandeling door een klem (clip) om de hals van het aneurysma te zetten. Idealiter worden alleen personen gescreend voor wie het risico om gedurende het leven een aSAB te krijgen opweegt tegen het risico op complicaties van de preventieve behandeling en de potentieel nadelige effecten van de screening op kwaliteit van leven. Deze voor- en nadelen van screening moeten dus telkens worden afgewogen, voordat besloten wordt om een groep personen te screenen. Het risico om gedurende het leven een aSAB te krijgen is het hoogst voor personen met een positieve familieanamnese voor aSAB (afhankelijk van de aanwezigheid van andere risicofactoren kan dit oplopen tot 20%), en het is dan ook bewezen effectief om in deze groep te screenen op ongebarsten intracraniële aneurysma's. Echter, deze groep met een positieve familieanamnese voor aSAB maakt maar een minderheid uit van alle mensen die een dergelijke bloeding krijgen. Daarom is meer kennis nodig over aanvullende groepen met een hoog risico op een aSAB en voorspellers voor aSAB.

De studies beschreven in dit proefschrift adresseren drie doelen. Het eerste doel van dit proefschrift is om de opbrengst van screening op ongebarsten intracraniële aneurysma's in kaart te brengen voor twee groepen personen die baat kunnen hebben bij screening, doordat ze mogelijk een hoog risico hebben om gedurende hun leven een aSAB te krijgen. Het tweede doel van dit proefschrift is om inzicht te krijgen in het verloop en de voorspellers van het effect van screening op intracraniële aneurysma's op kwaliteit van leven. Het derde doel van dit proefschrift is om het ruptuurrisico van familiaire intracraniële aneurysma's te bepalen, en patiënt en aneurysma karakteristieken die bijdragen aan dit risico te identificeren. Het overkoepelende doel van dit proefschrift is om het aantal levensjaren in goede kwaliteit dat verloren gaat door een aSAB te verlagen, door de screening en het voorspellen van aneurysma ruptuur te verbeteren.

Deel I: Screening op ongebarsten intracraniële aneurysma's in hoog-risico groepen

Het verhoogde risico voor personen met een positieve familieanamnese om gedurende het leven een aSAB te krijgen, wordt veroorzaakt door zowel een verhoogd risico op het ontstaan als een verhoogd risico op ruptuur van intracraniële aneurysma's. Screening is bewezen effectief bij een positieve familieanamnese voor gebarsten aneurysma's, maar het is nooit onderzocht bij een positieve familieanamnese voor ongebarsten aneurysma's. **Hoofdstuk 2** beschrijft de resultaten van een onderzoek dat we hebben uitgevoerd om de opbrengst en de effecten op kwaliteit van leven in kaart te brengen van screening op ongebarsten intracraniële aneurysma's. Hierbij onderzochten we eerstegraads familieleden van patiënten met een ongebarsten intracranieel aneurysma en een negatieve familieanamnese voor aSAB. Er werden 461 eerstegraads familieleden gescreend met MRA in een periode van 2017 tot 2021, geworven in drie Nederlandse ziekenhuizen. Hierbij werden 24 intracraniële aneurysma's gevonden bij 23 van deze 461 eerstegraads familieleden, wat erop neerkomt dat bij 5% een aneurysma werd gevonden. Alle aneurysma's die ontdekt zijn waren klein met een relatief laag ingeschat 5-jaars ruptuurrisico van 0.7%. Omdat het laag ingeschatte ruptuurrisico niet opwoog tegen het ingeschatte complicatierisico van preventieve behandeling, werd geen van de gevonden aneurysma's preventief behandeld. In plaats daarvan werden deze aneurysma's gevolgd met herhaalde MRA's om eventuele groei of vormverandering van het aneurysma op te sporen, aangezien dit risicofactoren zijn voor het barsten van een intracranieel aneurysma. Na een mediane follow-up duur van twee jaar, was er geen sprake van groei of vormverandering van een van de aneurysma's. Daaropvolgend hebben we een model ontwikkeld om de kans op het vinden van een intracranieel aneurysma bij screening te voorspellen. Dit risico varieerde tussen 2.3% en 14.7%, met het hoogste risico toenemend met de leeftijd voor eerstegraads familieleden die roken en overmatig alcohol (≥18 eenheden per week) gebruiken. We evalueerden kwaliteit van leven met behulp van elektronische vragenlijsten op zes vaste momenten gedurende het eerste jaar na de screening, en vonden geen negatief effect van de screening op kwaliteit van leven.

We keken hierbij naar gezondheid gerelateerde kwaliteit van leven, angst, depressie en sociale participatie. En op basis van deze resultaten adviseren wij niet om eerstegraads familieleden van patiënten met een ongebarsten intracranieel aneurysma en een negatieve familieanamnese voor aSAB te screenen. De reden hiervoor is dat er geen van de gevonden aneurysma's een dermate hoog ingeschat ruptuurrisico had dat preventieve behandeling nodig was. Als toekomstige follow-up beeldvorming groei of vormverandering van een van de aneurysma's laat zien, kan preventieve behandeling alsnog geïndiceerd zijn. Hiervoor is verder onderzoek nodig. Ons advies om deze groep personen niet te screenen moet dus heroverwogen worden als in de toekomst groei of zelfs het barsten van een van de gevonden aneurysma's optreedt.

Het risico om gedurende het leven een aSAB te krijgen is ook hoog voor personen ouder dan 35 jaar met een hoge bloeddruk die roken of in het verleden gerookt hebben. Daarom hebben we de opbrengst van screening op intracraniële aneurysma's in deze groep onderzocht in **Hoofdstuk 3**. De CTA's van 500 patiënten met symptomatisch vaatlijden op basis van slagaderverkalking werden beoordeeld, waarbij 25 intracraniële aneurysma's werden gevonden. Ook in deze groep werd dus (net als in de groep beschreven in Hoofdstuk 2) bij 5% een ongebarsten intracranieel aneurysma gevonden. Deze aneurysma's waren klein met een relatief laag ingeschat 5-jaars ruptuurrisico van 0.9%. Na een mediane follow-up duur van bijna vijf jaar, werd bij één patiënt groei van het aneurysma aangetoond. Omdat het risico op ruptuur was toegenomen door deze groei, werd preventieve behandeling van dit aneurysma geadviseerd. Aangezien maar één van de gevonden aneurysma's preventief behandeld hoefde te worden, adviseren wij op dit moment niet om deze hele groep te screenen. Om binnen deze groep die personen te identificeren met een hoog risico op een aneurysma bij screening, hebben we vervolgens een model ontwikkeld. Het risico om een intracranieel aneurysma te vinden bij eerste screening varieerde van 1.6% tot 13.4%, waarbij onafhankelijke voorspellers voor het vinden van een aneurysma bestonden uit: toenemende leeftijd, vrouwelijk geslacht en huidig roken. Of screening wel effectief is voor een van deze hoog-risico groepen hangt af van het risico op groei van de gevonden aneurysma's in de loop van de tijd. Dit zal in toekomstige studies verder onderzocht moeten worden.

Het belangrijkste voordeel van screening op intracraniële aneurysma's (het voorkomen dat er levensjaren in goede kwaliteit verloren gaan door een aSAB) moet zorgvuldig afgewogen worden tegen de nadelen. Hieronder valt bijvoorbeeld de mogelijk negatieve psychosociale consequenties van screening met een afname van het aantal levensjaren in goede kwaliteit tot gevolg. Screening is bewezen kosteneffectief voor personen met een positieve familieanamnese voor aSAB, maar de psychosociale impact van deze screening is grotendeels onbekend. Daarom hebben we in **Hoofdstuk 4** de resultaten van een onderzoek beschreven dat de effecten op kwaliteit van leven weergeeft van de huidige screening op familiair voorkomende intracraniële aneurysma's. Bij een opeenvolgende reeks van 105 personen afkomstig uit 75 families in de leeftijd van 20 tot 70 jaar, werd op zes vaste

momenten gedurende het jaar na hun eerste screening kwaliteit van leven geëvalueerd met elektronische vragenlijsten. We hebben hierbij geen negatief effect gevonden van de screening op kwaliteit van leven, behalve een tijdelijke afname van kwaliteit van leven zes maanden na de screening bij personen bij wie een aneurysma was ontdekt. Deze afname in kwaliteit van leven werd voornamelijk veroorzaakt door een toegenomen rapportage van matige angst en pijn, en herstelde zich na een jaar weer tot het niveau van voor de screening. In de gehele onderzochte groep werd een jaar na de eerste screening juist een kleine toename in kwaliteit van leven en een afname in angst geobserveerd. Deze nieuwe informatie kan gebruikt worden bij de voorlichting over screening op intracraniële aneurysma's, zodat familieleden een betere individuele afweging kunnen maken of zij screening wel of juist niet willen. Factoren die geassocieerd waren met een slechtere kwaliteit van leven na de screening waren de aanwezigheid van een psychiatrische ziekte, lichamelijke klachten die de gemoedstoestand negatief beïnvloedden, en een passieve coping stijl. Het is belangrijk om deze personen met een verhoogde kans om een slechtere kwaliteit van leven te ervaren te herkennen. Hen zou bijvoorbeeld aanvullende begeleiding aangeboden kunnen worden voorafgaand aan de screening.

Deel II: Karakteristieken van familiaire intracraniële aneurysma's

Een eerder onderzoek vond een zeventien keer verhoogd ruptuurrisico voor patiënten met familiaire intracraniële aneurysma's in vergelijking met patiënten met sporadische intracraniële aneurysma's. Er is sprake van een sporadisch aneurysma zodra er geen eerstegraads familieleden zijn met een ongebarsten aneurysma of een aSAB. Het verhoogde ruptuurrisico van familiaire intracraniële aneurysma's zou een goede reden kunnen zijn om deze aneurysma's in een vroeger stadium preventief te behandelen dan sporadische aneurysma's. Maar dit eerdere onderzoek bekeek alleen een geselecteerde groep patiënten met familiaire aneurysma's, namelijk mensen die daarnaast rookten en een hoge bloeddruk hadden, en de sporadische patiënten kwamen uit een andere populatie. Hierdoor moest de uitkomst van dit onderzoek eerst in een onafhankelijke groep personen gevalideerd worden voordat ze in de praktijk gebruikt kon worden. In **Hoofdstuk 5** bestuderen we het ruptuurrisico van familiaire in vergelijking met sporadische intracraniële aneurysma's in het cohort van patiënten met een intracranieel aneurysma in ons ziekenhuis. Dit cohort is prospectief verzameld tussen 1994 en 2016. We identificeerden 91 familiaire aneurysma's bij 62 patiënten met een follow-up duur van 391 aneurysmajaren, en 542 sporadische aneurysma's bij 412 patiënten met een follow-up duur van 1,373 aneurysmajaren. Er waren 0.77 rupturen per 100 familiaire aneurysmajaren (drie familiaire patiënten hadden een aSAB) en 0.51 rupturen per 100 sporadische aneurysmajaren (zeven sporadische patiënten hadden een aSAB). Dit leidt tot de observatie van een drie keer verhoogd ruptuurrisico voor familiaire in vergelijking met sporadische intracraniële aneurysma's. Aangezien we dit licht verhoogde ruptuurrisico niet met statistische significantie konden aantonen, besloten we het ruptuurrisico van familiaire aneurysma's verder te onderzoeken in **Hoofdstuk 6.** Hierbij gebruikten we individuele patiëntengegevens uit acht onderzoeken uit Nederland,

Finland en Japan. We includeerden 3,089 intracraniële aneurysma's bij 2,297 patiënten met 7,301 persoonsjaren follow-up uit zes cohorten en vonden een 2.6 keer verhoogd ruptuurrisico voor familiaire in vergelijking met sporadische intracraniële aneurysma's. Hieruit concluderen wij dat patiënten met een ongebarsten familiair intracranieel aneurysma een hoger ruptuurrisico hebben en dat er bij hun derhalve een agressievere behandelstrategie van het aneurysma gerechtvaardigd is.

Om de huidige screeningstrategie en daarmee het voorkomen van aSAB te verbeteren, moeten nieuwe factoren gevonden worden die bijdragen aan het verhoogde ruptuurrisico van familiaire intracraniële aneurysma's. In **Hoofdstuk 7** beschrijven we de resultaten van een cohortonderzoek waarin werd bekeken of leeftijd ten tijde van aSAB bij eerstegraads familieleden een factor zou kunnen zijn die meegenomen moet worden om de optimale screeningstrategie te bepalen. Als er een hoge correlatie wordt gevonden van de leeftijd ten tijde van de aSAB binnen families, kan de periode waarin screening geadviseerd wordt mogelijk verkort worden tot een bepaald interval rond die leeftijd ten tijde van aSAB bij de aangedane familieleden. Correlatie hebben we onderzocht met de zogenaamde Intraclass Correlation Coefficient (ICC) waarbij 0 geen correlatie betekent en 1 perfecte correlatie. We onderzochten 319 eerstegraads familieleden met aSAB uit 146 families (87 Nederlandse, 43 Finse en 16 Franse families). We vonden een slechte correlatie van leeftijd ten tijde van aSAB binnen families, met een ICC van 0.21. Als we alleen de leeftijden ten tijde van aSAB van aangedane broers en zussen bekeken, was de correlatie iets hoger maar nog steeds slecht (ICC 0.34). Bij 84% van de eerstegraads familieleden met aSAB werd een onderling verschil in leeftijd ten tijde van de bloeding van 20 jaar of meer gevonden, bij broers en/of zussen met aSAB was dit 86%. Op basis van deze bevindingen is leeftijd ten tijde van aSAB bij eerstegraads familieleden geen factor om mee te nemen in het ontwikkelen van een meer gepersonaliseerde screeningstrategie.

Naast patiënt gerelateerde factoren zoals leeftijd, zouden ook aneurysma gerelateerde factoren kunnen bijdragen aan het verhoogde ruptuurrisico van familiaire intracraniële aneurysma's. In **Hoofdstuk 8** onderzoeken we of bij patiënten met familiaire intracraniële aneurysma's bepaalde vormkenmerken van aneurysma's, waarvan we weten dat ze het ruptuurrisico verhogen, vaker voorkomen in vergelijking met patiënten met sporadische intracraniële aneurysma's. We beoordeelden op CTA's de intracraniële aneurysma's van 251 patiënten op de aanwezigheid van de volgende factoren: de vorm (ovaal, langwerpig, onregelmatig), de verhouding tussen de lengte van het aneurysma en de breedte van de hals (aspect ratio), of het aneurysma contact maakt met of vervormd wordt door structuren in de omgeving, en de aanwezigheid van bepaalde variaties in de aanleg van de bloedvaten in het hoofd. Geen van deze factoren kwam vaker voor bij familiaire in vergelijking met sporadische intracraniële aneurysma's. Daarom verklaren deze factoren het verhoogde ruptuurrisico van familiaire intracraniële aneurysma's niet. Toekomstig onderzoek zal moeten uitwijzen of andere patiënt en aneurysma gerelateerde factoren het verhoogde ruptuurrisico van familiaire intracraniële aneurysma's kunnen verklaren.

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Liselore Adelinde Mensing was born on January 28, 1990 in Amsterdam. In 2008, she graduated from secondary school (Gymnasium, Willem de Zwijger College Bussum) and started medical school at Utrecht University. As part of her medical training, she went abroad for clinical internships in Curaçao, Malaysia and Boston. During her studies, she developed a special interest in neurology and started her first project as a student researcher on perimesencephalic haemorrhage at the department of neurology of the University Medical Center (UMC) Utrecht in 2011.

After obtaining her medical degree, she started working as a neurology resident at the UMC Utrecht in January 2015 (under supervision of prof. dr. John Wokke, prof. dr. Tatjana Seute and prof. dr. Geert Jan Biessels). Since 2016, she combines her clinical training with a PhD on intracranial aneurysms at the department of neurology of the UMC Utrecht (under supervision of dr. Ynte Ruigrok and prof. dr. Gabriël Rinkel), resulting in this thesis. She also performed research projects on ischaemic stroke under supervision of dr. Ynte Ruigrok, prof. dr. Jaap Kappelle and prof. dr. ir. Gerhard Zielhuis. Liselore received an Investigator Award from the European Academy of Neurology in 2017 for her research described in Chapter 5 of this thesis.

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Currently, she is still working as a neurology resident and expects to complete this program in February 2024. Liselore lives in Utrecht, and in her free time she loves playing field hockey and other sports, travelling, and enjoying the good company of friends and family.

LIST OF PUBLICATONS

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