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RESEARCH ARTICLE

Aneurysm Prevalence and Quality of Life During Screening in Relatives of Patients With Unruptured Intracranial Aneurysms

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 patients with aneurysmal subarachnoid hemorrhage (aSAH). Whether screening is also effective for FDRs of patients with UIA 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 the effects of screening on quality of life (QoL).

Methods

In this prospective cohort study, we included FDRs, aged 20–70 years, of patients with UIA without a family history of aSAH who visited the Neurology outpatient clinic in 1 of 3 participating tertiary referral centers in the Netherlands. FDRs were screened for UIA with magnetic resonance angiography 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 6 times during the first year after 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). The median aneurysm size was 3 mm (interquartile range [IQR] 2–4 mm), and the median 5-year rupture risk assessed with the PHASES score was 0.7% (IQR 0.4%–0.9%). All UIAs received follow-up imaging, and 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% and 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 and emotional functioning were comparable with those in a reference group from the general population. One FDR with a positive screening result expressed regret about screening.

Discussion

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

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Glossary

aSAH = aneurysmal subarachnoid hemorrhage; **COVID-19** = coronavirus disease 2019; **EQ-5D** = EuroQoL 5 Dimensions; **EQ-VAS** = EuroQoL Visual Analog Scale; **HADS** = Hospital Anxiety and Depression Scale; **FDR** = first-degree relative; **HRQoL** = health-related QoL; **IQR** = interquartile range; **LME** = linear mixed-effect model; **MRA** = magnetic resonance angiography; **PCKD** = polycystic kidney disease; **QoL** = quality of life; **UIA** = unruptured intracranial aneurysm; **UMCU** = University Medical Center Utrecht; **USER-P** = Utrecht Scale for Evaluation of Rehabilitation—Participation.

Introduction

Aneurysmal subarachnoid hemorrhage (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 age 50–55 years)[2] and severity lead to a loss of productive life years similar to the far more common ischemic stroke.[3] Noninvasive 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. In addition, 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 performed in persons with a high lifetime risk of aSAH.

The prevalence of UIA in the general population is approximately 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 1 FDR with aSAH,[5] with 4% UIAs being identified at first screening[11] and a lifetime aSAH risk of approximately 3%.[5] Thus, the high lifetime aSAH risk in FDRs of patients with aSAH is caused by an increased risk of both UIA development and rupture.[5,8,10,11] For FDRs of patients with UIA, 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 a UIA, but no FDR with aSAH.

We aimed to determine the yield of screening in persons with ≥1 FDR with a 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 Center Utrecht (UMCU), Leiden University Medical Center, or Amsterdam University Medical Center 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, CT angiography, or conventional angiography and no family history of aSAH (defined as no FDR [parent, sibling, or child] with aSAH and no FDR with a sudden death, which may be caused by an 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) being younger than 20 years or older than 70 years during screening, (2) a medical history of UIA, PCKD, Ehlers-Danlos syndrome, 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 1 patient with aSAH performed more than 20 years ago,[11] the percentage of which 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 1 FDR with aSAH,[13] which may be extrapolated to a 2-fold increased UIA prevalence in these groups when compared with the general population.[7] With an expected sensitivity of MRA of 95%,[12] the target enrollment was set at 500 individuals, which is equivalent to the identification of 25 UIAs. Because recruitment was slow, partly due to the coronavirus disease 2019 (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 (please see eFigure 1, links.lww.com/WNL/C962 for the content of the patient information letter).

Data Collection

Baseline characteristics were assessed through a structured questionnaire. Smoking was defined as current smoking or smoking stopped within the past 20 years because 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 eTable 1 (links.lww.com/WNL/C962).

Yield of Screening

In all FDRs, 3T TOF-MRA was performed at the UMCU, and these scans were independently evaluated for the presence of intradural UIAs by 1 of 2 experienced neuroradiologists (B.K.V. and I.C.v.d.S.), 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 the 5-year rupture risk of the UIAs identified.[6] In case a UIA was identified, an advice on management (preventive treatment vs follow-up imaging to determine potential aneurysm growth) was determined by a multidisciplinary team, consisting of vascular neurologists, neurointerventional radiologists, and vascular neurosurgeons and discussed with the FDR. Follow-up data up to September 2022 were included.

Quality of Life

Coping style was assessed as a baseline characteristic related to QoL with a subscale of the Utrecht Coping List.[16] QoL was assessed through structured E-questionnaires that were sent to FDRs 6 times during 1 year (eFigure 2, links.lww.com/WNL/C962). If FDRs did not have an email address, questionnaires were sent by post instead. The E-questionnaires consisted of 3 validated questionnaires: (1) the EuroQoL 6 Dimensions were 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 eTable 1.

Statistical Analysis

We calculated UIA prevalence in our screening cohort by dividing the total number of FDRs with a positive screening result by the total number of FDRs screened. We performed multivariable logistic regression analysis to study the association between candidate predictors and the presence of a UIA at screening. Candidate predictors were prespecified 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] The number of affected relatives was not included as a candidate predictor because all FDRs had only 1 FDR with UIA(s) (the index patient) during 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.[25] The resulting model was subsequently corrected for overfitting using Ridge regression. The tuning parameter used in Ridge estimation for the 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 screening result. We displayed the discrimination graphically with a receiver operating characteristic 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 a UIA at screening for each score. The high-risk group was defined as an absolute probability of finding a 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 to be cost-effective.[10]

We calculated mean sum scores with SD for the EuroQoL 5 Dimensions (EQ-5D), EuroQoL Visual Analog Scale (EQ-VAS), HADS, and USER-P at all survey moments and expressed changes as mean differences with 95% CIs. QoL outcomes were compared between all screened FDRs and a reference group from the general Dutch population,[26,27] except for USER-P because 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 after screening and variables associated with QoL outcome. Time was included as a categorical variable based on survey moments, and all other variables were included as fixed effects. LMEs were performed for all screened FDRs and stratified by screening result. Only variables available prescreening 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) with those completed after its start to assess whether the pandemic had influenced QoL. Statistical analyses were performed using R software (version 3.6.2; R Foundation, Vienna, Austria).[28]

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator. Proposals should be directed to L.A.Mensing-3@umcutrecht.nl; to gain access, data requestors will need to sign a data access agreement.

Table 1 Baseline Characteristics

	Positive screening result, n (%)	Negative screening result, n (%)
No. of patients	23 (5)	438 (95)
Sex, female	15 (65)	239 (55)
Age at screening, y, 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[a]	8 (35)	85 (19)
Excessive alcohol consumption (≥18 units per week)	4 (17)	15 (3)
Drugs		
Current	0 (0)	28 (6)
Former	5 (22)	44 (10)
Medical history		
Hypertension	7 (30)	84 (19)
Hyperlipidemia	8 (35)	66 (15)
Diabetes	2 (9)	14 (3)
Migraine	3 (13)	41 (9)
Coronary artery disease	0 (0)	11 (3)
Hypertensive pregnancy complications[b]	3 (13)	46 (11)
Psychiatric history (ever)		
Depression	4 (17)	29 (7)
Anxiety	3 (13)	11 (3)
Other	1 (4)	17 (4)
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[c]	14 (61)	253 (58)
Higher vocational education and university	7 (30)	178 (41)
Married/living with partner	17 (74)	332 (76)[d]
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 during MRA		
Systolic blood pressure, mm Hg, mean (SD)	135 (19)	137 (19)[e]
Diastolic blood pressure, mm Hg, mean (SD)	83 (10)	83 (10)[e]
BMI, kg/m^2, mean (SD)	26 (4)	26 (4)[d]

Abbreviations: BMI = body mass index; FDR = first-degree relative; HELLP = hemolysis, elevated liver enzymes, low platelet count; IQR = interquartile range; UCL-P = Utrecht Coping List–Passive; UIA = unruptured intracranial aneurysm.
[a] Stopped smoking <20 years ago.
[b] Gestational hypertension and/or preeclampsia and/or HELLP syndrome.
[c] Lower secondary education, higher secondary education, preuniversity secondary education, and secondary vocational education.
[d] ≤0.5% missing.
[e] ≤2.5% missing.

Results

Study Population

Seventy-nine percent of eligible FDRs (461/587) of 252 index patients were screened (eFigure 3, links.lww.com/WNL/C962). 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 a UIA," or "too time-consuming." Approximately 50% of FDRs who declined participation

Table 2 Results of Screening in FDRs of Patients With UIAs

	461 screened persons, n (%)
FDRs with a positive screening result	23 (5)
FDRs with multiple UIAs	1 (0)
UIA identified with screening	24 (5)
Aneurysm size, 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-y rupture risk (IQR)	0.7 (0.4–0.9)
Treatment UIA	
Follow-up imaging	24 (100)
Preventive treatment	0 (0)
Duration of follow-up, mo, median (IQR)	24 (14–38)
Detection of growth (≥1 mm) during follow-up[29]	0 (0)

Abbreviations: FDR = first-degree relative; MRA = magnetic resonance angiography; UIA = unruptured intracranial aneurysm.

were female 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. During inclusion, all FDRs had 1 affected relative, namely the index patient. The mean age during screening was 47 years (SD 13 years), and 55% were female. Baseline characteristics are summarized in Table 1.

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[a]
Age per year	1.05 (1.01–1.09)	1.02 (0.98–1.06)
Smoking[b]	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)

Abbreviation: OR = odds ratio.
[a] Adjusted for optimism using Ridge regression. Regression equation: −4.19333657 + 0.60054111 × smoking + 0.01819373 × age during screening + 1.11170844 × excessive alcohol consumption.
[b] Current smoker or stopped <20 years ago.

Yield of Screening

According to our sample size calculation, inclusion was stopped after 25 UIAs were detected. However, during follow-up, one of these UIAs 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 a UIA prevalence of 5.0% (95% CI 3.2%–7.4%). The UIAs identified had a median size of 3 mm (interquartile range [IQR] 2–4 mm) and a median 5-year risk of rupture according to the PHASES score of 0.7% (IQR 0.4%–0.9%) (Table 2).[6] Two UIAs were detected in 1 FDR; a 48-year-old female participant who smoked and had hypertension. Follow-up imaging was advised for all identified UIAs, and none of the FDRs were advised to undergo preventive treatment. For 96% (22/23) of FDRs with a positive screening, at least 1 radiologic follow-up was available; 1 FDR declined follow-up. After a median follow-up period of 24 months (IQR 13–38 months), no aneurysm growth or shape change was detected (Table 2). Incidental findings diagnosed on the brain sequences of the MRA are described in eTable 2 (links.lww.com/WNL/C962).

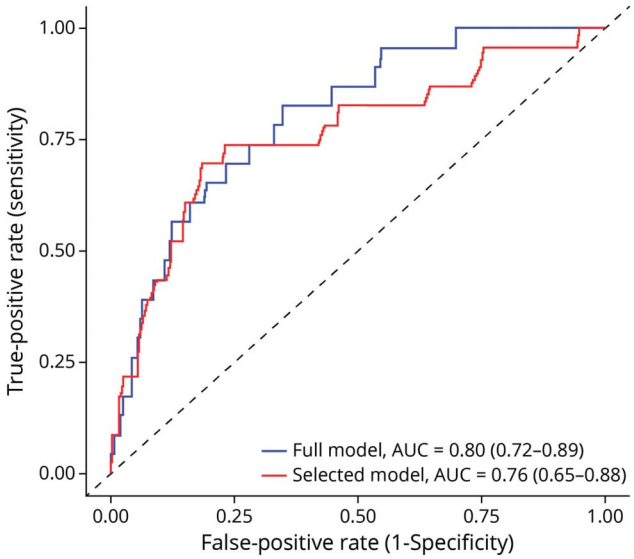
High-Risk Groups

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), and univariate and multivariate odds ratios for risk of UIA at screening for all candidate predictors are summarized in eTable 3 (links.lww.com/WNL/C962). These odds ratios are mainly shown for illustrative purposes and should be interpreted with caution because the multivariate model resulted in severe overestimation of the effect due to the small number of events (24 aneurysms identified at screening) and the large number of candidate predictors included. Multivariable logistic regression identified 3 predictors for finding a UIA at screening: higher age during 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. Regression coefficients were subsequently translated into a score chart (eTable 4) with mean predicted probabilities per score summarized in eTable 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).

Quality of Life

Eighty-nine percent (2,460/2,766) 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 those with a positive screening result (6/19 [32%]) and those with a negative screening result (124/374 [33%]). Of all FDRs who returned the E-questionnaire 1 year after screening and answered the question how they felt about their decision to be screened for UIA (n = 129), 1 FDR with a positive screening result expressed regret about screening (1/129 [0.8%]).

Figure 1 ROC Curve for Predicted Probability of Finding an Unruptured Intracranial Aneurysm at Screening



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

Analysis of the complete screening cohort showed similar unadjusted HRQoL and emotional functioning compared with that of the general population (eFigure 4, links.lww.com/WNL/C962).[26,27] One year after screening, HRQoL improved slightly compared with prescreening (mean adjusted EQ-5D sum score improvement 1.38; 95% CI 0.36–2.40), levels of anxiety remained the same, and 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 to −0.47) (eTable 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 (eTable 6).

Figure 2 Risk Chart With Absolute Probabilities (%) of Finding an Unruptured Intracranial Aneurysm at Screening

	No smoking*	Smoking*	Age (years)
No excessive alcohol consumption	2.3	4.0	20–29
	2.8	4.8	30–39
	3.3	5.9	40–49
	4.0	6.9	50–59
	4.8	8.0	60–69
Excessive alcohol consumption	6.9	14.7	20–29
	8.0	14.7	30–39
	14.7	14.7	40–49
	14.7	14.7	50–59
	14.7	14.7	60–69

*Current smoker or stopped <20 years ago.

FDRs with a positive screening result for UIA already reported a lower HRQoL before the screening (positive screening result mean EQ-5D 80.3 [95% CI 72.3–88.3] compared with negative screening result mean EQ-5D 91.6 [95% CI 90.2–93.0]) (Table 4 and eFigure 4, links.lww.com/WNL/C962). FDRs with a positive screening result reported a higher level of depression 6 months after screening, a lower HRQoL (EQ-5D) 4 weeks after receiving the screening result, and rated their health lower on the EQ-VAS 2 weeks, 4 weeks, and 6 months after the screening result (eFigure 4 and 5) when compared with FDRs with a negative screening results. One year after screening, FDRs with a positive screening results reported a lower social participation (mean adjusted USER-P sum score change −5.90; 95% CI −9.94 to −1.86) when compared with prescreening (eTable 7 and eFigure 6). 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, approximately 5% of FDRs of patients with UIA and a negative family history for aSAH has a UIA at initial screening with MRA. Predictors for finding UIA at screening were higher age during screening, smoking, and excessive alcohol consumption with predicted UIA risk ranging between 2.3% and 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 1 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 1 FDR with aSAH performed >20 years ago.[11] However, we identified smaller UIAs (mean size 3 mm [range 1–7 mm]) compared with those observed in this previous study (mean size 4.5 mm [range 2–11 mm]).[11] Small aneurysms may have been missed in that previous study because the sensitivity of MRA has increased over the years[12]; thus, the previously reported UIA prevalence of 4% in persons with 1 FDR with aSAH could be an underestimation. We found lower predicted probabilities of identifying a 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 this study, most persons had only 1 FDR with UIA vs ≥2 FDRs with aSAH in the previous study). Predictors of a positive screening result 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 screening result, but not hypertension and number of affected relatives. The latter is

Table 4 Quality-of-Life Outcomes for First-Degree Relatives With a Positive and Negative Screening Result for Unruptured Intracranial Aneurysms in Unadjusted Mean Sum Scores With SD

	HRQoL				Emotional functioning		Restrictions daily activities	
	EQ-5D		EQ-VAS		HADS		USER-P	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Positive screening result								
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 wk post-MRA result	20	86.8 (12.5)	20	75.6 (14.8)	20	9.7 (7.3)	20	94.1 (10.2)
4 wk post-MRA result	20	86.7 (11.4)	20	73.2 (20.5)	20	9.9 (7.3)	20	93.1 (12.7)
6 mo post-MRA result	20	86.8 (14.4)	20	73.3 (17.6)	20	10.6 (8.2)	19	89.9 (17.3)
1 y post-MRA result	18	85.8 (20.0)	18	81.2 (9.3)	18	8.3 (8.3)	18	89.6 (18.7)
Negative screening result								
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 wk post-MRA result	347	93.3 (12.9)	346	84.5 (10.9)	347	6.1 (6.0)	336	98.3 (5.8)
4 wk post-MRA result	392	93.9 (12.3)	391	84.7 (11.3)	389	6.0 (6.0)	383	97.6 (9.4)
6 mo post-MRA result	394	92.7 (14.2)	391	83.6 (11.2)	392	6.2 (6.1)	386	98.1 (6.2)
1 y post-MRA result	365	93.0 (13.5)	363	83.8 (12.1)	363	6.7 (6.4)	354	97.0 (10.3)

Abbreviations: 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; USER-P = Utrecht Scale for Evaluation of Rehabilitation—Participation.

because all our included FDRs had 1 affected FDR during screening. Results of previous studies on hypertension as an additional risk factor of UIA development in familial patients with UIA are conflicting. A previous retrospective analysis of a prospectively collected database in the Netherlands identified hypertension as an additional risk factor of 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 of 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 screening result, independently of and even to a greater extent than smoking, whereas previous studies showed excessive alcohol consumption to be a risk factor of aSAH but not of 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 8 years after first screening, and a lower HRQoL was found in persons with a positive screening result for UIA compared with both persons with a negative screening result 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 observed only a slight increase in depression levels and decrease in social participation 1 year after screening, but the depression levels were still lower than those from the general population.[27] Because 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] Of interest, we found reported HRQoL prescreening to be lower for FDRs who later had a positive screening result for UIA compared with FDRs who later had a negative screening result. What causes this difference is unknown and requires further study. Hypothetically, there could be an overlap in risk factors of lower HRQoL and UIA development because 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. In addition, 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 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, there was some collinearity between predictors. Both the relative high number of predictors and collinearity result in a large amount of shrinkage in Ridge estimation and a noticeable change in odds ratios. Third, we were not able to externally validate our model predicting UIA risk at first screening because, to the best of our knowledge, there are no comparable prospective cohorts available. Because we currently do not recommend to apply the prediction model, we did not implement any resampling techniques in model development. Before clinical use, the model performance should be evaluated in new independent data. Fourth, to assess the rupture risk of identified UIA, we used the PHASES score, but this score did not incorporate the known additional rupture risk of familial UIA.[6] Fifth, we included relatively few persons with multiple FDRs with UIA, making it unable to draw definite conclusions on the number of affected FDRs as a potential predictor of UIA risk. Last, 2 potential predictors of QoL were measured using nonvalidated questionnaires, for example, perceived stress and the presence of physical complaints affecting mood.

Because 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, though we found no evidence that QoL is negatively influenced by screening. Because UIAs may grow over a longer period of time and growth is a known risk factor of 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 patients with UIA 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 patients with UIA with a negative and a positive screening result. At present, such FDRs should be informed on the negative effect of smoking and excessive alcohol consumption on their risk of developing a UIA.

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Continued

Appendix *(continued)*

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