Cerebrovascular Diseases

Original Paper

Cerebrovasc Dis 2024;53:428–436
DOI: 10.1159/000534373

Received: May 27, 2023
Accepted: September 26, 2023
Published online: October 1, 2023

Serial Quality of Life Assessment around Screening for Familial Intracranial Aneurysms: A Prospective Cohort Study

Liselore A. Mensing Keneshka Atash Gabriel J.E. Rinkel Ynte M. Ruigrok

UMC Utrecht Brain Centre, Department of Neurology and Neurosurgery, University Medical Centre Utrecht, Utrecht, The Netherlands

Keywords
Subarachnoid haemorrhage · Intracranial aneurysm · Quality of life · Screening · Familial intracranial aneurysm

Abstract
Introduction: Screening for intracranial aneurysms (IAs) is cost-effective in first-degree relatives of aneurysmal subarachnoid haemorrhage patients, but its psychosocial impact is largely unknown. ***Patients and Methods:*** A consecutive series of persons aged 20–70 years visiting the University Medical Centre Utrecht for first screening for familial IA was approached between 2017 and 2020. E-questionnaires were administered at six time points, consisting of the EQ-5D for health-related quality of life (QoL), HADS for emotional functioning, and USER-P for social participation. QoL outcomes were compared with the general population and between participants with a positive and negative screening for IA. Predictors of QoL outcomes were assessed with linear mixed effects models. ***Results:*** 105 participants from 75 families were included; in 10 (10%), an IA was found. During the first year after screening, we found no negative effect on QoL, except for a temporary decrease in QoL 6 months after screening in participants with a positive screen (EQ-5D −11.3 [95% CI: −21.7 to −0.8]). Factors associated with worse QoL were psychiatric disease (EQ-5D −10.3 [95% CI: −15.1 to −5.6]), physical complaints affecting mood (EQ-5D −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 and Conclusion:*** 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 psychiatric disease, physical complaints affecting mood, and a passive coping style. This information can be used in counselling about familial IA screening.

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]

karger@karger.com
www.karger.com/ced

Correspondence to:
Liselore A. Mensing, L.A.Mensing-3@umcutrecht.nl

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, in that retrospective study, QoL was assessed many years (mean 8 years, standard deviation [SD] 1 year) after the initial screening; therefore, this study did not report on the short-term effects of screening on QoL and may be 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 counselling 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.

Patients and 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, 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].

Patient and Aneurysm Characteristics

We derived baseline characteristics from the electronic patient record; additional baseline characteristics related to QoL were assessed through a structured questionnaire directly after the visit at the outpatient clinic for definitions (see online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000534373) [6]. Former smoking was defined as smoking stopped within the last 20 years. If participants stopped smoking more than 20 years ago, they were considered never smokers. We screened participants with MRA or with computed tomography angiography 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 vs. 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 >1 mm between consecutive MRAs or computed tomography angiographys [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 6 times in a 1-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, 10]; (2). the Hospital Anxiety and Depression Scale (HADS) was used to measure emotional functioning in terms of anxiety and depression [11]; and (3). the Utrecht Scale for Evaluation of Rehabilitation – Participation (USER-P) restriction subscale was used to measure social participation [12]. Further details of the questionnaires used are described in online supplementary Table 1. In addition to the three validated questionnaires described above, the last E-questionnaire 1 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) [13] with the proportion 1 year after screening. Also, the proportion of participants with restrictions per USER-P activity (scores ≤1) was calculated pre-screening and 1 year after screening. Mean values of a reference group from the general Dutch population were reported at all survey moments for all QoL outcomes [14, 15], except for the USER-P as no data on reference groups are available for this score. Linear mixed effect models 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 for 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 (CIs). Statistical analyses were performed using R software (version 3.6.2, R Foundation) [16].

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% (online suppl. Fig. 1). 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* (%)
Patients, *n*	105 (100)	10 (10)	95 (90)
Women	69 (66)	8 (80)	61 (64)
Age at screening, 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)
>2	11 (10)	1 (10)	10 (11)
Smoking			
Current	25 (24)	3 (30)	22 (23)
Former*	64 (61)	6 (60)	58 (61)
Never	16 (15)	1 (10)	15 (16)
Medical history			
Hypertension	22 (21)	5 (50)	17 (18)
Stroke	1 (1)	1 (10)	1 (1)
Cancer	4 (4)	0 (0)	4 (4)
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[a]	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)[b]	10 (8–12)	11 (8–11)	10 (8–12)

FDRs, first-degree relatives; IQR, interquartile range; *n*, number; SD, standard deviation; UCL-P, Utrecht Coping List Passive. *Stopped smoking <20 years ago. [a]Lower secondary education, higher secondary education, pre-university secondary education, secondary vocational education. [b]Range sum-score between 7 (low level) and 28 (high level of passive coping).

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 IAs 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). 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 1 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.

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 (Fig. 1) [14, 15]. 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 favour of our screened cohort [14]. 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

Table 2. Results of screening

	Screened persons (n = 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.

(mean adjusted HADS anxiety sum-score decrease −0.7; 95% CI, −1.2 to −0.2), while levels of depression and social participation remained the same as compared to pre-screening (Table 3; online suppl. Fig. 2). The decrease in anxiety levels is observed from 2 weeks after receiving the screening result until 1 year after screening (Table 3). At baseline, 22% (21/97) of all screened participants had a HADS anxiety sum-score of 8 points or more, and 1 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: 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 1 year after screening (Fig. 1; Table 4). In participants with a positive screen for IA, we observed a trend towards a temporary increase of unadjusted anxiety levels 2 weeks after receiving the screening result (Fig. 1) and a temporary increase in the proportion of participants reporting problems on the EQ-6D subdomain anxiety/depression after receiving the screening result (Fig. 2). 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 1 year after screening (Fig. 1). Adjusted results from the mixed models showed a decrease in adjusted HRQoL in participants with a positive screen for IA 6 months after receiving the screening result (mean adjusted EQ-5D sum-score decrease −11.3; 95% CI, −21.7 to −0.8), which returned to baseline 1 year after screening (online suppl. Table 2). This decrease in HRQoL was mainly caused by an increase in reporting of moderate anxiety and pain (Fig. 2).

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) 6 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 1 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.

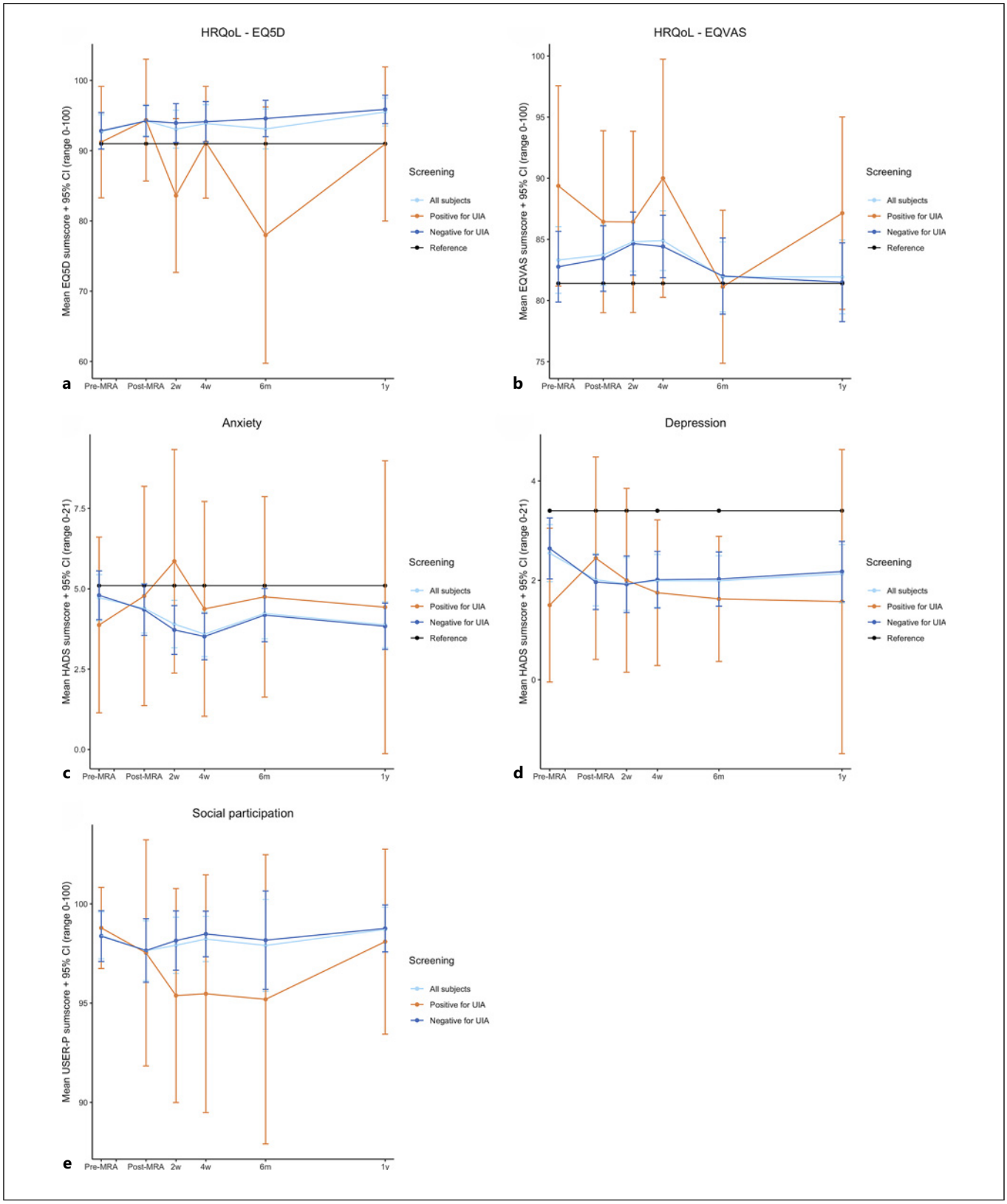

Fig. 1. a–e QoL outcomes displayed as unadjusted mean sum-scores with 95% confidence intervals.

Table 3. Results from linear mixed models analysis of QoL 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 to −4.0)	0.1 (−2.6 to −2.8)	−0.3 (−0.8 to −0.2)	−0.4 (−0.8 to −0.1)	−0.7 (−2.0 to −0.7)
2 weeks after screening result	0.9 (−1.5 to −3.4)	1.3 (−1.5 to −4.1)	−0.6 (−1.1 to −0.1)	−0.4 (−0.8 to −0.0)	−0.5 (−1.9 to −0.9)
4 weeks after screening result	1.5 (−0.9 to −3.8)	1.7 (−1.0 to −4.4)	−0.9 (−1.4 to −0.5)	−0.4 (−0.8 to −0.0)	−0.7 (−2.0 to −0.7)
6 months after screening result	0.8 (−1.6 to −3.2)	−1.4 (−4.1 to −1.3)	−0.5 (−1.0 to −0.0)	−0.5 (−0.9 to −0.1)	−0.6 (−1.9 to −0.8)
1 year after screening result	2.8 (0.4–5.1)	−1.9 (−4.6 to −0.8)	−0.7 (−1.2 to −0.2)	−0.2 (−0.6 to −0.2)	−0.0 (−1.4 to −1.3)
B. Predictors*					
Age at screening (continuous)	−0.0 (−0.1 to −0.1)	0.1 (−0.1 to −0.2)	0.0 (−0.0 to −0.0)	0.0 (−0.0 to −0.0)	−0.1 (−0.2 to −0.0)
Female sex	−1.7 (−4.5 to −1.2)	0.1 (−3.1 to −3.4)	0.5 (−0.4 to −1.4)	−0.2 (−0.8 to −0.4)	−1.0 (−3.3 to −1.3)
Psychiatric disease	−10.3 (−15.1 to −5.6)	−7.1 (−12.5 to −1.7)	1.8 (0.2–3.3)	1.0 (−0.1 to −2.0)	−6.9 (−10.7 to −3.0)
Passive coping style[a]	−1.1 (−1.5 to −0.6)	−1.7 (−2.3 to −1.2)	0.7 (0.6–0.9)	0.5 (0.4–0.6)	−0.7 (−1.1 to −0.3)
Physical complaints affecting mood	−8.1 (−11.7 to −4.4)	−6.2 (−10.3 to −2.1)	1.7 (0.5–2.9)	2.2 (1.5–3.0)	−2.2 (−5.1 to −0.7)
Educational level					
Other	Ref	Ref	Ref	Ref	Ref
Primary school or lower secondary	1.6 (−1.7 to −4.9)	1.3 (−2.4 to −5.0)	−0.0 (−1.1 to −1.0)	0.7 (−0.1 to −1.4)	0.1 (−2.5 to −2.8)
Current smoking	−1.4 (−4.8 to −1.9)	2.3 (−1.4 to −6.1)	−0.7 (−1.8 to −0.4)	−0.4 (−1.1 to −0.4)	0.2 (−2.5 to −2.9)
Hypertension	−1.5 (−5.5 to −2.5)	−2.7 (−7.0 to −1.7)	1.0 (−0.3 to −2.2)	0.1 (−0.8 to −0.9)	0.1 (−3.0 to −3.2)

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. *To estimate for example the HRQoL outcome for female sex at 1-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). [a]Per point increase UCL-P.

One previous study assessed QoL in persons screened because of familial aSAH, using a structured telephone interview after a mean period of 8 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]. Preventive aneurysm treatment was performed in 28 of 35 participants (80%) with a positive screen in the previous study, while in our current study, there was no preventive aneurysm treatment in the 10 participants (0%) with a positive screen [5]. The long-term negative effect of screening for IA on QoL as found in the previous study, which was not confirmed in our current study, may be explained by recall bias due to the retrospective design of that study. Alternatively, the negative effects of screening on QoL may be caused by the higher number of participants with preventive aneurysm treatment in the previous study or by the fact that negative effects on QoL could develop only over a longer period of time.

This last hypothesis is further supported by two other studies, one reporting short-term and the other long-term HRQoL [17, 18]. Short-term data from a recent prospective pilot study in Finland assessed HRQoL before and after screening for IA in 43 female smokers aged 50–60 years [17]. In that study, HRQoL did not deteriorate in the interval between screening and preventive IA treatment when compared with pre-screening [17]. Long-term data from a retrospective study from our centre assessing 173 patients with UIA after a mean period of 4–5 years after diagnosis of the UIA showed a reduced HRQoL, both for patients with treated and untreated UIA [18]. 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 [19, 20]. 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 1 year as shown in a prospective study performed in the UK [21].

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.

Table 4. QoL outcomes for persons with a positive and negative screening for UIAs in unadjusted mean sum-scores with SD

	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.

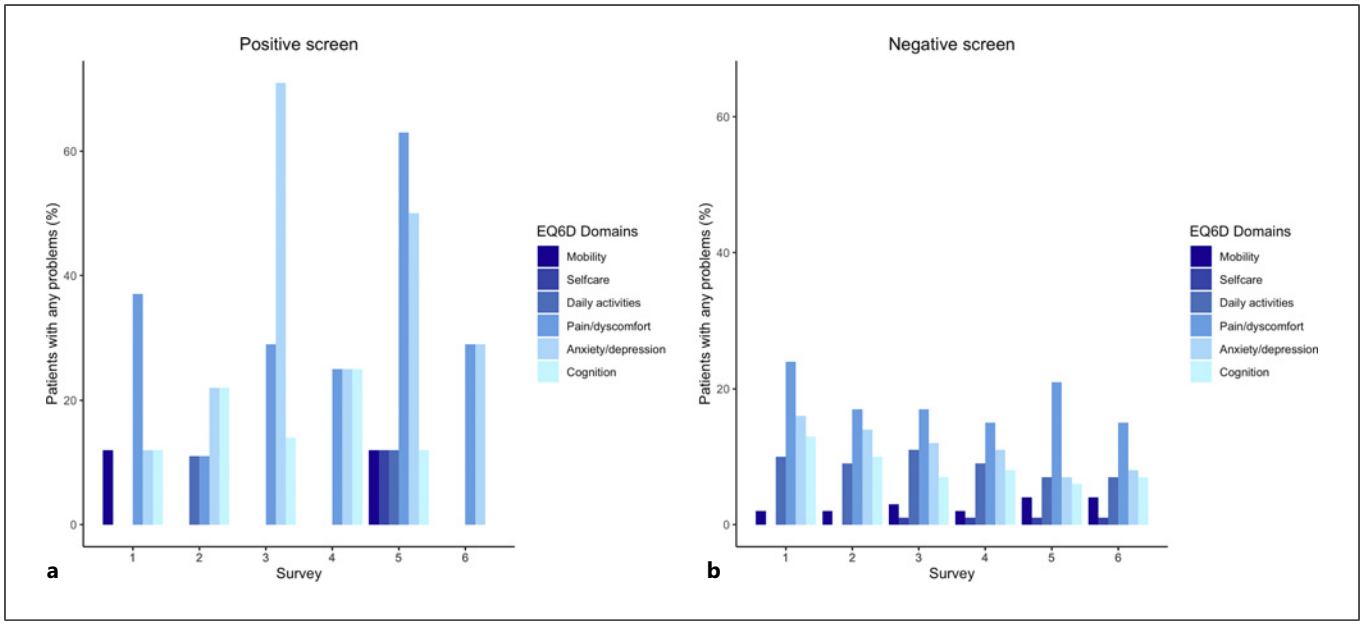

Fig. 2. Proportion (%) for screen-positives (**a**) and screen-negatives (**b**) reporting any problems per EQ-6D subdomain.

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 [22]. 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 [23].

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. Firstly, 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. However, for our primary outcome analysing the complete screening cohort, the sample size was sufficient. Secondly, all IA identified were small with a low estimated risk of rupture, and none were treated preventively which could have facilitated the observed improvement of QoL to the pre-screening level after 1 year. Thirdly, we compared our findings on emotional functioning with references from the Dutch general population collected more than 15 years ago [15]. 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 [24]. Thirdly, reference groups from the general population were not matched for age, while HRQoL is known to decline with increasing age [14]. 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. Fourthly, 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.

Conclusion

In counselling persons with familial aSAH on screening for IA, lasting effects on QoL 1 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 1 year. Also, it is important to identify persons with an increased risk for worse QoL around screening, e.g., persons with a (history of) psychiatric disease, physical complaints affecting mood, and a passive coping style, and offer them additional counselling pre-screening about potential negative effects on QoL. 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.

Statement of Ethics

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.

Conflict of Interest Statement

There are no conflicts of interest.

Funding Sources

This project has received funding from the Dutch Heart Foundation (CVON2015-08/ERASE) and the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement number: 852173).

Author Contributions

L.M., Y.R., and G.R. conceived the study and were involved in protocol development, gaining ethical approval and patient recruitment. L.M., K.A., and Y.R. were involved in data analysis. L.M. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

References

1 Bor ASE, Koffijberg H, Wermer MJH, Rinkel GJE. Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis. Neurology. 2010;74(21):1671–9.
2 Takao H, Nojo T, Ohtomo K. Screening for familial intracranial aneurysms: decision and cost-effectiveness analysis. Acad Radiol. 2008;15(4):462–71.
3 Hopmans EM, Ruigrok YM, Bor ASE, Rinkel GJE, Koffijberg H. A cost-effectiveness analysis of screening for intracranial aneurysms in persons with one first degree relative with subarachnoid haemorrhage. Eur Stroke J. 2016;1(4):320–9.
4 Algra AM, Lindgren A, Vergouwen MDI, Greving JP, van der Schaaf IC, van Doormaal TPC, et al. Procedural clinical complications, case-fatality risks, and risk factors in endovascular and neurosurgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis. JAMA Neurol. 2019;76(3):282–93.
5 Wermer MJH, van der Schaaf IC, van Nunen P, Bossuyt PMM, Anderson CS, Rinkel GJE. Psychosocial impact of screening for intracranial aneurysms in relatives with familial subarachnoid hemorrhage. Stroke. 2005;36(4):836–40.
6 Schreurs P, Willige G, Brosschot J, et al. Handleiding utrechtse coping lijst UCL (herziene versie). Lisse: Swets & Zeitlinger; 1993.
7 Backes D, Rinkel GJE, Greving JP, Velthuis BK, Murayama Y, Takao H, et al. ELAPSS score for prediction of risk of growth of unruptured intracranial aneurysms. Neurology. 2017;88(17):1600–6.
8 Greving JP, Wermer MJH, Brown RD Jr, Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol. 2014;13(1):59–66.
9 Hoeymans N, van Lindert H, Westert GP. The health status of the Dutch population as assessed by the EQ-6D. Qual Life Res. 2005;14(3):655–63.
10 van Reenen M, Oppe M, Secnik Boye K, et al. EQ-5D-3L user guide. EuroQoL Research Foundation; 2021. p. 2018. Version 6.0).
11 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
12 Post MWM, Van der Zee CH, Hennink J, Schafrat CG, Visser-Meily JMA, Van Berlekom SB. Validity of the Utrecht scale for evaluation of rehabilitation-participation. Disabil Rehabil. 2012;34(6):478–85.
13 Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale: an updated literature review. J Psychosom Res. 2002;52(2):69–77.
14 Janssen MF, Szende A, Cabases J, Ramos-Goñi JM, Vilagut G, Konig HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. Eur J Health Econ. 2019;20(2):205–16.
15 Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363–70.
16 R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019. https://www.R-project.org/.
17 Huhtakangas J, Numminen J, Pekkola J, Niemelä M, Korja M. Screening of unruptured intracranial aneurysms in 50 to 60-year-old female smokers: a pilot study. Sci Rep. 2021;11(1):23729.
18 Buijs JE, Greebe P, Rinkel GJE. Quality of life, anxiety, and depression in patients with an unruptured intracranial aneurysm with or without aneurysm occlusion. Neurosurgery. 2012;70(4):868–72.
19 Blome C, Augustin M. Measuring change in quality of life: bias in prospective and retrospective evaluation. Value Health. 2015;18(1):110–5.
20 Due-Christensen M, Zoffmann V, Willaing I, Hopkins D, Forbes A. The process of adaptation following a new diagnosis of type 1 diabetes in adulthood: a meta-synthesis. Qual Health Res. 2018;28(2):245–58.
21 Bath MF, Sidloff D, Saratzis A, Bown MJ; UK Aneurysm Growth Study investigators. Impact of abdominal aortic aneurysm screening on quality of life. Br J Surg. 2018;105(3):203–8.
22 Algra AM, Greving JP, Wermer MJH, van Walderveen MAA, van der Schaaf IC, van der Zwan A, et al. Quality of life outcomes over time in patients with unruptured intracranial aneurysms with and without preventive occlusion: a prospective cohort study. Neurology. 2022;99(16):e1715–24 Online ahead of print.
23 Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005;14(6):1523–32.
24 Baxter AJ, Scott KM, Ferrari AJ, Norman RE, Vos T, Whiteford HA. Challenging the myth of an "epidemic" of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. Depress Anxiety. 2014;31(6):506–16.