ORIGINAL REPORT

FATIGUE IS ASSOCIATED WITH REDUCED PARTICIPATION AND HEALTH-RELATED QUALITY OF LIFE FIVE YEARS AFTER PERIMESENCEPHALIC SUBARACHNOID HAEMORRHAGE: A MULTICENTRE CROSS-SECTIONAL STUDY

Elisabeth A. DE VRIES[1,2], MSc, Wendy BOERBOOM[2], PhD, Rita J. G. VAN DEN BERG-EMONS[1], PhD, Fop VAN KOOTEN[3], MD, PhD, Johanna M. A. VISSER-MEILY[4,5], MD, PhD, Gerard M. RIBBERS[1,2], MD, PhD and Majanka H. HEIJENBROK-KAL[1,2], PhD

From the [1]Erasmus MC, University Medical Center Rotterdam, Department of Rehabilitation Medicine, [2]Rijndam Rehabilitation, Rotterdam, The Netherlands, [3]Erasmus MC, University Medical Center Rotterdam, Department of Neurology, [4]Department of Rehabilitation, Physical Therapy Science & Sports, UMC Utrecht Brain Center, University Medical Center Utrecht, [5]Center of Excellence for Rehabilitation Medicine, UMC Utrecht Brain Center, University Medical Center Utrecht and De Hoogstraat Rehabilitation, Utrecht, The Netherlands

Objective: **To determine whether fatigue is associated with participation and health-related quality of life 5 years after perimesencephalic subarachnoid haemorrhage.**

Design: **Multicentre cross-sectional study.**

Subjects: **Forty-six patients with perimesencephalic subarachnoid haemorrhage.**

Methods: **Fatigue was assessed with the Fatigue Severity Scale, participation (frequency, restrictions, satisfaction) with the Utrecht Scale for Evaluation of Rehabilitation-Participation, health-related quality of life with the Stroke-Specific Quality of Life Scale-12, symptoms of depression and anxiety with the Hospital Anxiety and Depression Scale, and coping with the Coping Inventory for Stressful Situations.**

Results: **A total of 46 patients were included (63% men, mean age 50.4 ± 9.4 years), with a mean time of 4.7 ± 1.6 years after perimesencephalic subarachnoid haemorrhage onset. Fatigued patients (33%) had worse participation ($p < 0.01$) and health-related quality of life ($p < 0.001$) than non-fatigued patients, and more often had hypertension, depression, anxiety and emotion-oriented coping ($p < 0.05$). Fatigue severity was inversely and independently ($p < 0.005$) associated with participation frequency (B = −3.62), satisfaction (B = −4.54), having restrictions (odds ratio = 2.48, 95% confidence interval 1.079–5.685), and health-related quality of life (B = −0.19), adjusted for depression, anxiety, and/or hypertension.**

Conclusion: **Five years after perimesencephalic subarachnoid haemorrhage, one-third of patients still reported fatigue, which was associated with worse participation and health-related quality of life. Future studies should examine whether these patients may benefit from rehabilitation aimed at fatigue.**

Key words: fatigue; participation; health-related quality of life; mood; coping; perimesencephalic subarachnoid haemorrhage; stroke; subarachnoid haemorrhage.

Accepted Jan 13, 2022; Epub ahead of Feb 22, 2022

LAY ABSTRACT

A subarachnoid haemorrhage (SAH) is a subtype of stroke. Of all patients with SAH, approximately 10% are diagnosed with non-aneurysmal perimesencephalic subarachnoid haemorrhage (PM-SAH). PM-SAH is generally considered a benign form of SAH; however we have previously found that one-third of patients with PM-SAH are still fatigued 5 years after PM-SAH. Fatigue may be related to reduced participation and health-related quality of life, both of which are considered important rehabilitation outcomes. Therefore, this study examined whether fatigue is associated with participation and health-related quality of life after PM-SAH. The results showed that, 5 years after PM-SAH, fatigued patients had worse participation and quality of life than non-fatigued patients. In addition, more severe fatigue was associated with worse participation, regarding frequency, satisfaction and restrictions, and with worse health-related quality of life. Further studies are necessary to determine whether patients with PM-SAH may benefit from rehabilitation aimed at fatigue.

J Rehabil Med 2022; 54: JRM00271

DOI: 10.2340/jrm.v54.212

Correspondence address: Elisabeth A. de Vries, Erasmus MC, University Medical Center, Department of Rehabilitation Medicine, PO Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail: e.a.devries@erasmusmc.nl

Of all patients with subarachnoid haemorrhage (SAH), approximately 10% are diagnosed with non-aneurysmal perimesencephalic subarachnoid haemorrhage (PM-SAH) (1). PM-SAH is characterized by the absence of an aneurysm and an accumulation of blood in the cisterns around the mesencephalon (2, 3). In terms of survival, clinical course and functional outcome (4), PM-SAH is generally considered a benign form of SAH (1, 2), with complications, such as hydrocephalus, delayed cerebral ischaemia and re-bleeds, seen only rarely (4). In addition, patients with PM-SAH do not need surgical or endovascular interventions with

long-term follow-up after treatment, and hence they often have a shorter hospital stay than patients with aneurysmal SAH (A-SAH) (4, 5). Because of their good prognosis, patients with PM-SAH are generally not referred to rehabilitation programmes. However, studies focusing on long-term neuropsychological outcome have shown that up to 7.5 years after onset, 26–62% of patients with PM-SAH report symptoms such as headaches, irritability, depression, forgetfulness, deconditioning and fatigue (6–8).

Fatigue is one of the most common and debilitating sequelae of SAH (9). In a previous study, we have found that 5 years post-PM-SAH onset, 33% of patients were still fatigued and that more severe fatigue was related to depression, comorbidity and worse cognitive functioning (8). In patients with A-SAH, the prevalence of fatigue 4–5 years after ictus was 60% (10) to 65% (11), respectively, and, in healthy subjects, 18% of people were found to be fatigued based on the same criteria as used in our previous study (12). Although the prevalence of fatigue is lower in patients with PM-SAH than in patients with A-SAH, fatigue is substantially more common in patients with PM-SAH than in healthy subjects. This endorses the importance of studying the possible negative consequences fatigue may have in this patient group.

Chronic fatigue may affect participation (13) and health-related quality of life (HR-QoL) (14), which are both considered important rehabilitation outcomes. Studies on participation and HR-QoL after PM-SAH are scarce, and studies that have been conducted have either a small sample size and/or did not assess outcome with validated questionnaires. Therefore, the results of these studies are difficult to compare and inconclusive: some studies have shown reduced HR-QoL (15, 16) and difficulties returning to work (6, 17), while others have reported good HR-QoL (18) and no problems returning to work (19, 20).

In patients with PM-SAH, it is not known what the role of fatigue is in participation and HR-QoL outcome. However, in patients with A-SAH, fatigue has been found to be related to worse HR-QoL (14, 21) and reduced participation in terms of functional performance and autonomy and restrictions in participation (13). Just as in patients with A-SAH, participation and HR-QoL might also be reduced in those patients with PM-SAH who experience long-term fatigue. If so, this may indicate that patients with PM-SAH could benefit from rehabilitation aimed at managing and coping with fatigue, since this may enhance their HR-QoL and participation. The aim of the current study was therefore to determine whether fatigue is associated with participation and HR-QoL in the long-term after PM-SAH, taking into account patient characteristics, depression, anxiety and coping as potential confounders. It was hypothesized that fatigued patients with PM-SAH would have lower levels of participation and HR-QoL than non-fatigued patients, and that fatigue severity would be independently associated with HR-QoL and participation.

METHODS

Participants and procedures

Patients diagnosed with PM-SAH, were identified from a data registry of all consecutive SAH patients who were hospitalized between 2006 and 2012 at the neurology or neurosurgery departments of Erasmus MC University Medical Centre Rotterdam or University Medical Center Utrecht. After screening for eligibility, patients were invited to participate in a cross-sectional study via a letter from their neurologist, sent by post, comprising information about study protocol, rationale and burden of participating in the study. Patients who were interested in participating were asked to return a reply form using a pre-paid envelope. Patients were included if they survived PM-SAH and were at least 18 years of age. Exclusion criteria were: serious (neurological) comorbidity and insufficient understanding of the Dutch language. PM-SAH was defined by an accumulation of blood in the cisterns around the mesencephalon on computed tomography (CT) and the absence of an aneurysm on 4-vessel angiogram (2, 3). Prior to inclusion, all patients signed an informed consent form. The study was approved by the medical ethics committee of Erasmus MC and UMC Utrecht.

Data collection

After patients provided informed consent, they were visited at home by a research psychologist to collect data on multiple outcome measures using validated questionnaires (8). In addition, patient characteristics, including years of education, employment status (paid job vs retired/no paid job), hypertension at time of home visit (yes/no), and discharge destination (home/home with outpatient rehabilitation vs rehabilitation centre/nursery home) were collected in a structured interview. In order to minimize fatigue during testing, the home visit was designed in such a way that fatigue was assessed in the first part of the test battery. In addition, all tests were provided in a fixed order with regular breaks between tests. Duration of the home visit varied, with a maximum of 150 minutes. If the tests were not completed after 150 minutes, participants were asked to return any remaining questionnaires by post the next day. In this study, a secondary analysis was conducted

on the data of the self-report questionnaires on fatigue, participation, quality of life, depression and anxiety, coping and comorbidity.

Measurement instruments

Fatigue was assessed with the Fatigue Severity Scale (FSS) (22), which consists of 9 statements on the impact of fatigue in daily life situations, which are rated on a 7-point Likert-scale, ranging from 1 (strongly disagree) to 7 (strongly agree). A cut-off score of 4 or higher was used to distinguish fatigued patients from non-fatigued patients. The FSS shows good internal consistency and test-retest reliability in patients with stroke (12, 22).

Participation was assessed with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) (23). The USER-P assesses 3 aspects of participation, frequency of participation, restrictions in participation and satisfaction with participation. For all 3 aspects questions are related to work/education, household activities, sports/physical exercise, relationship with a partner and social and leisure activities. The frequency subscale is divided into 2 parts; the first part consists of 4 items about vocational activities in an ordinary week, scored on a scale from 0 (not at all) to 5 ($\geq$36 h). The second part consists of 7 items about participation in social and leisure activities in the last 4 weeks, scored on a scale from 0 (not at all) to 5 (19 times or more). The restrictions subscale consists of 11 items to assess whether the person experienced participation restrictions due to his/her health condition. Items are scored on a scale from 0 (not possible at all) to 3 (no difficulty at all). In case the experienced restrictions are not a result of the health condition, there is a "not applicable" answer option. Satisfaction with participation was assessed with 10 items, scored on a scale from 0 (not satisfied at all) to 4 (very satisfied), including a "not applicable" option for the items on work/education and relationship with a partner. Sum scores of the applicable questions are converted to a score ranging between 0 and 100 for all 3 subscales, where higher scores reflect better participation (higher frequency, less restrictions, higher satisfaction). In addition, the score on the USER-P Restrictions scale was dichotomized (USER-P-Restricted), where a score $<$100 indicates having restrictions and a score of 100 equals no restrictions. The USER-P has been found to be valid in patients who visited outpatient rehabilitation in the Netherlands, including stroke patients (23).

HR-QoL was assessed with the Stroke-Specific Quality of Life-12 (SS-QoL-12) scale and is expressed in a total, physical, and psychosocial score. The questionnaire contains 12 items, where 6 items relate to the physical scale and 6 items to the psychosocial scale. Items are rated on a scale from 1 (poor HR-QoL) to 5 (good HR-QoL). The physical scale encompasses domains of self-care, mobility, upper extremity function, language, vision, and work, and the psychosocial scale includes thinking, family roles, social roles, personality, mood, and energy domains. Mean scores are calculated for the total scale and the 2 subscales, with higher scores indicating better quality of life (24). The SS-QoL-12 has been validated in patients with stroke, including patients with SAH (24).

Symptoms of anxiety and depression in the past 4 weeks were assessed with the Hospital Anxiety and Depression Scale (HADS) (25), which consists of 7 questions related to anxiety and 7 questions related to depression. Patients rate all items on a 4-point scale ranging from 0 (no symptoms) to 3 (serious symptoms). The total sum score ranges between 0 and 21 for both the depression and anxiety scale. Higher scores reflect more depressive or anxiety symptoms. A cut-off score of 8 or higher indicates the presence of depression/anxiety (25). The Dutch version of the HADS has been validated in several (patient) groups (26).

Coping strategy was assessed with the Coping Inventory for Stressful Situations (CISS) (27). The CISS consist of 48 items, divided over 3 subscales each with 16 questions regarding a task-oriented, an emotion-oriented, or an avoidant coping strategy. Items are scored on a 5-point scale, ranging from 1 (not at all) to 5 (very much). Sum scores (range 16–80) are calculated and indicate to what extent people react in a certain way when they encounter a stressful situation. Higher scores on each subscale reflect using that coping strategy more often (27). The psychometric properties of the CISS have been found acceptable to good in a Dutch population of patients with acquired brain injury (including stroke patients) (28).

Comorbidity was assessed with the Cumulative Illness Rating Scale (CIRS), which measures impairments in 14 body systems on a scale from 0 (no impairments) to 4 (life-threatening impairments). Sum scores are calculated, ranging from 0 to 56, with higher scores indicating more severe comorbidity (29).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize patient characteristics and outcomes regarding depression and anxiety of the total study population and the fatigued and non-fatigued subgroups. Dependent on the assumption of normally distributed data, either independent t-tests or Mann–Whitney U tests were carried

out to examine differences in patient characteristics, and participation and quality of life outcomes between fatigued and non-fatigued patients. χ^2 tests were used for categorical variables.

Univariate and multivariate linear regression analyses were performed to examine the association of fatigue with participation (USER-P Frequency and USER-P Satisfaction) and HR-QoL (SS-QoL-12 total score), adjusting for patient characteristics, depression and anxiety, coping and comorbidity. In addition, univariate and multivariate logistic regression analyses were conducted to examine relationships of the aforementioned determinants with the dichotomized variable USER-P Restricted. Variables that were significant ($p<0.05$) in univariate regression analyses, were included in the multivariate regression using backward selection. Assumptions of linearity, multicollinearity, and normally distributed, homoscedastic and independent residuals, were met. A significance level of $p<0.05$ was used and a Bonferroni correction was applied to correct for multiplicity.

RESULTS

Study population

In total, 46 patients were included, with a mean time post-onset of PM-SAH of 4.7 years (SD 1.6). Mean age was 50.4 years (SD 9.4) and 63% of subjects were men. Overall, the mean depression and anxiety scores were below the cut-off score of 8, indicating no symptoms of depression or anxiety. Mean fatigue score of the total group was 3.4 (SD 1.3) and 33% had long-term fatigue (8). No significant differences were found between fatigued and non-fatigued patients in patient characteristics, except for hypertension. Of all 46 patients, 1 patient received inpatient rehabilitation and 45 were discharged to their home. None of the patients who were discharged home received outpatient rehabilitation. The mean scores on the depression and anxiety subscales of the HADS differed significantly ($p<0.001$) between fatigued and non-fatigued patients. The proportion of patients with depressive ($p<0.05$) or anxiety ($p<0.001$) symptoms was also significantly larger in the fatigued group than in the non-fatigued group. Fatigued patients used an emotion-oriented coping strategy more often than non-fatigued patients ($p<0.05$) and had more comorbidity (Table I).

Participation and health-related quality of life in fatigued and non-fatigued patients

Fatigued patients scored significantly worse than non-fatigued patients on the frequency subscale ($p=0.001$), and the restrictions and satisfaction subscales ($p<0.001$) of the USER-P (Fig. 1). In addition, there were significantly ($p<0.001$) more patients who had restrictions in participation in the fatigued group ($n=13$, 86.7%) than in the non-fatigued group ($n=5$, 16.1%). Also regarding HR-QoL, fatigued patients scored significantly worse than non-fatigued patients on the total scale ($p<0.001$), and both the physical ($p<0.001$) and psychosocial scales ($p<0.001$) (Fig. 1). Correlations between participation and HR-QoL outcomes were: USER-P Frequency and SS-QoL-12: r = 0.341, $p=0.20$; USER-P Restrictions

Table I. Patient characteristics and outcome 5 years after perimesencephalic subarachnoid haemorrhage (PM-SAH) onset

	Total group ($n=46$)	Fatigued, FSS ≥ 4 ($n=15$)	Non-fatigued, FSS < 4 ($n=31$)
Patient characteristics			
Age at onset, years, mean (SD)	50.4 (9.4)	50.5 (9.3)	50.3 (9.6)
Sex, men, *n* (%)	29 (63.0)	10 (66.7)	19 (61.3)
Partner, yes, *n* (%)	39 (84.8)	11 (73.3)	28 (90.3)
Education, years, mean (SD)	14.4 (3.9)	13.2 (2.8)	15.0 (4.3)
Employed before SAH, *n* (%)	36 (78.3)	11 (73.3)	25 (80.6)
Hypertension, yes, *n* (%)	12 (26.1)	7 (46.7)	5 (16.1)*
Discharge destination, *n* (%)			
Home	45 (97.8)	15 (100)	30 (96.8)
Inpatient rehabilitation	1 (2.2)	0 (0)	1 (3.2)
Outcome after 5 years			
HADS Depression, mean (SD)	3.6 (3.6)	6.4 (3.0)	2.2 (3.0)**
HADS Anxiety, mean (SD)	5.5 (4.0)	8.9 (4.6)	3.9 (2.5)**
HADS Depression ≥ 8, *n* (%)	7 (15.2)	5 (33.3)	2 (6.5)*
HADS Anxiety ≥ 8, *n* (%)	11 (23.9)	9 (60.0)	2 (6.5)**
Coping strategy (CISS)			
Task-oriented, mean (SD)	55.9 (9.7)	52.3 (8.8)	57.5 (9.8)
Emotion-oriented, mean (SD)	36.7 (11.9)	42.2 (12.5)	34.4 (11.1)*
Avoidant, mean (SD)	36.3 (9.7)	35.2 (9.6)	36.7 (9.8)
Comorbidity (CIRS)	4.0 (3.0)	6.5 (3.5)	2.8 (1.7)**

*$p<0.05$; **$p<0.001$. HADS Depression and Anxiety range 0–21. CISS subscales range 16–80. HADS and CIRS: higher score means worse condition. CISS higher score reflects use of that coping strategy more often.

FSS: Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; CISS: Coping Inventory for Stressful Situations; CIRS: Cumulative Illness Rating Scale Missing; CISS total=2, 2 in fatigued group.

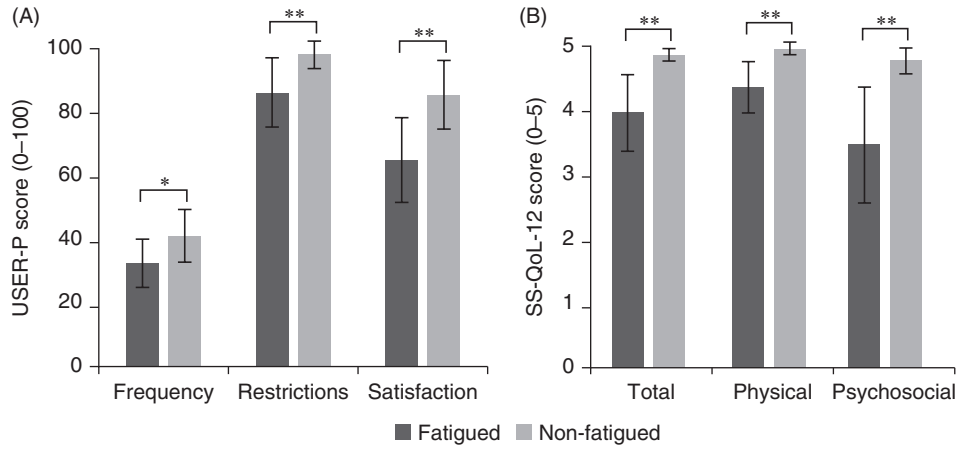

Fig. 1. (A) Participation and (B) health-related quality of life of fatigued and non-fatigued patients 5 years after perimesencephalic subarachnoid haemorrhage (PM-SAH). *$p = 0.001$; **$p < 0.001$. USER-P: Utrecht Scale for Evaluation of Rehabilitation-Participation; SS-QoL-12: Stroke Specific Quality of Life-12; FSS: Fatigue Severity Scale; Fatigued (FSS ≥ 4) $n = 15$; non-fatigued (FSS < 4) $n = 31$. USER-P and SS-QoL-12 higher score means better condition.

and SS-QoL-12: r = 0.697, $p < 0.001$; USER-P Satisfaction and SS-QoL-12: r = 0.681, $p < 0.001$. Outcomes of the total group and the non-fatigued and fatigued group are shown in Table SI.

Associations between fatigue, and participation and HR-QoL outcomes

Table II shows the outcomes of the univariate and multivariate linear regression analyses. In the univariate models, years of education, fatigue, depression, anxiety, comorbidity and emotion-oriented coping were significantly associated with participation in both the USER-P Frequency and Satisfaction domains, and with HR-QoL. In the multivariate model, fatigue severity remained significantly ($p < 0.005$) associated with the frequency of participation, ($R^2 = 0.257$), and with participation satisfaction, adjusted for depression ($R^2 = 0.594$). In addition, more severe fatigue was significantly ($p < 0.001$) associated with worse HR-QoL, adjusted for depression and anxiety ($R^2 = 0.791$) (Tables II and III).

Univariate logistic regression analyses showed that hypertension, fatigue, depression, anxiety and comorbidity were significantly ($p < 0.05$) associated with having restrictions in participation. In multivariate analysis more severe fatigue remained significantly ($p < 0.005$) associated with having restrictions in participation 5 years post PM-SAH onset, adjusted for anxiety, hypertension and comorbidity (Table SII).

DISCUSSION

The results of this study suggest that fatigue plays a key role in participation and HR-QoL after PM-SAH. This is supported by our finding that 5 years after PM-SAH fatigued patients participated less frequently in

Table II. Univariate and multivariate regression models for participation and health-related quality of life outcome 5 years after perimesencephalic subarachnoid haemorrhage (PM-SAH)

	USER-P Frequency				USER-P Satisfaction				SS-QoL-12 Total			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
Variables	B	*p*-value	B	*p*-value	B	*p*-value	B	*p*-value	B	*p*-value	B	*p*-value
Age at onset, per year	−0.17	0.235			−0.17	0.492			0.01	0.338		
Sex, men vs women	−1.22	0.662			−7.23	0.119			−0.04	0.805		
Partner, yes vs no	1.44	0.700			8.98	0.151			0.20	0.399		
Education, per year	0.85	0.011	–	NS	1.40	0.013	–	NS	0.04	0.040	–	NS
Pre-SAH employment status, employed vs unemployed	−0.85	0.795			−1.98	0.719			0.01	0.949		
Hypertension, yes vs no	−3.35	0.271			−6.00	0.242			−0.13	0.487		
FSS Fatigue	−3.70	0.000	−3.62	0.000	−7.99	0.000	−4.54	0.004	−0.36	0.000	−0.19	0.000
HADS Depression	−1.15	0.001	–	NS	−3.01	0.000	−2.07	0.000	−0.11	0.000	−0.03	0.075
HADS Anxiety	−0.87	0.007	–	NS	−2.40	0.000	–	NS	−0.11	0.000	−0.05	0.001
CISS Task-Oriented	0.18	0.217			0.14	0.564			0.01	0.174		
CISS Emotion-Oriented	−0.22	0.049	–	NS	−0.60	0.001	–	NS	−0.02	0.000	–	NS
CISS Avoidant	−0.17	0.237			0.01	0.985			−0.01	0.475		
CIRS	−1.04	0.020	–	NS	−2.11	0.004	–	NS	−0.078	0.005	–	NS

USER-P: Utrecht Scale for Evaluation of Rehabilitation-Participation; SS-QoL-12: Stroke Specific Quality of Life-12; FSS: Fatigue Severity Scale; HADS: Hospital Anxiety and Depression Scale; CISS: Coping Inventory for Stressful Situations; CIRS: Cumulative Illness Rating Scale.

Table III. Model selection and performance

	USER-P Frequency			USER-P Satisfaction			SS-QoL-12 Total	
Model	R^2 Change	*p*-value		R^2 Change	*p*-value		R^2 Change	*p*-value
1 Education, FSS, HADS-D, HADS-A, CISS-E, CIRS	0.352	0.010	Education, FSS, HADS-D, HADS-A, CISS-E, CIRS	0.624	0.000	Education, FSS, HADS-D, HADS-A, CISS-E, CIRS	0.796	0.000
2 Education, FSS, HADS-D, CISS-E, CIRS	−0.001	0.832	Education, FSS, HADS-D, HADS-A, CIRS	−0.001	0.821	Education, FSS, HADS-D, HADS-A, CIRS	0.000	0.842
3 Education, FSS, HADS-D, CIRS	−0.004	0.739	Education, FSS, HADS-D, HADS-A	−0.004	0.512	Education, FSS, HADS-D, HADS-A	−0.000	0.791
4 Education, FSS, CIRS	−0.014	0.242	FSS, HADS-D, HADS-A	−0.014	0.235	FSS, HADS-D, HADS-A	−0.005	0.338
5 Education, FSS	−0.033	0.168	FSS, HADS-D	−0.011	0.295			
6 FSS	−0.044	0.118						
	R^2 total	0.257		R^2 total	0.594		R^2 total	0.791

USER-P: Utrecht Scale for Evaluation of Rehabilitation-Participation; SS-QoL-12: Stroke Specific Quality of Life-12; FSS: Fatigue Severity Scale; HADS: Hospital Anxiety and Depression Scale; HADS-D: Depression; HADS-A: Anxiety; CISS-E: Coping Inventory for Stressful Situations Emotion-oriented coping; CIRS: Cumulative Illness Rating Scale.

daily life activities, had more participation restrictions and were less satisfied with their participation than non-fatigued patients. In addition, fatigue severity was associated with both participation and HR-QoL outcomes, independent of depression, anxiety, hypertension or comorbidity.

Overall, 5 years post-PM-SAH patients have a rather good participation regarding frequency, restrictions and satisfaction. However, strikingly, both frequency of participation and perceived restrictions in participation in the subgroup of fatigued patients in the current study were comparable to patients 1 year post-stroke (75% ischaemic) (30) and to patients up to 4 years post-stroke (92% ischaemic) (31), respectively. In addition, satisfaction with participation in fatigued patients with PM-SAH was only slightly higher than in patients 1 year post-stroke (30). Thus, although, in general, patients with PM-SAH seem to have a benign course regarding long-term participation outcome, the current results suggest that a subgroup of patients with PM-SAH who experience fatigue have a comparable level of problems in participation as patients post-stroke.

Regarding HR-QoL, patients with PM-SAH overall reported a rather good HR-QoL as assessed with the SS-QoL-12. This is in agreement with studies in patients with PM-SAH, who used the Short-Form-36 (SF-36) (15, 16, 20) and the Sickness Impact Profile (SIP) (18) to assess HR-QoL. In the current study, fatigued patients had worse HR-QoL than non-fatigued patients, and the psychosocial domain was most affected. This is in agreement with a previous study in patients with SAH, which found that HR-QoL, also assessed with the SS-QoL-12, was lowest in the psychosocial domain and primarily regarding the items fatigue and memory (32). Apparently, patients with PM-SAH, and especially those who are fatigued, mainly experience a lower quality of life in domains regarding thinking, memory and social roles and less in domains regarding self-care, mobility and work.

This study found that the severity of fatigue was inversely associated with the level of participation in the 3 domains of frequency, restrictions and satisfaction and with HR-QoL, 5 years after PM-SAH. This agrees with studies in patients with A-SAH, that showed that fatigue is related to reduced HR-QoL (21) and reduced participation in terms of functional performance and autonomy and restrictions in participation (13). Other psychological variables related to participation and HR-QoL in the current study included depression, anxiety and emotion-oriented coping. These factors are known to be associated with participation, HR-QoL and fatigue after A-SAH and stroke (13, 14, 21, 33–36). Interestingly, the associations between fatigue and satisfaction with participation, between fatigue and having restrictions in participation, and between fatigue and HR-QoL, remained significant, even after adjusting for depression, and/or anxiety, respectively. Emotion-oriented coping dropped out of the multivariate models, probably because this coping style is also associated with depression and anxiety, which had a stronger association with participation and HR-QoL (28, 37).

Patients with PM-SAH are generally not referred to inpatient or outpatient rehabilitation programmes, which is also reflected in the current study sample, where only 1 patient received rehabilitation. The current results indicate that it would be useful to screen patients with PM-SAH for fatigue in outpatient rehabilitation centres or at the general practitioner, using, for example, the FSS as screening tool, with the cut-off score of 4. In addition, it seems important to be aware of additional psychological characteristics of fatigued patients, such as symptoms of depression or anxiety, which may also be related to an emotion-oriented coping strategy (28, 37). For this subgroup, especially, it should be considered to refer them to rehabilitation programmes aimed at reducing fatigue and coping with fatigue, since this may improve not only the frequency

of participation, but also the experienced restrictions and satisfaction with participation, and HR-QoL in the long-term.

One of the strengths of the current study is that different aspects of participation and HR-QoL were assessed with validated questionnaires in a relatively large group of patients with PM-SAH, particularly considering the rather low incidence of PM-SAH (1). In addition, the current study not only considered participation and HR-QoL of the total group, but also of the fatigued group and non-fatigued group separately. This revealed that the FSS and the cut-off score of 4 can be a useful and appropriate tool to distinguish fatigued from non-fatigued patients in clinical practice. Finally, depression, anxiety, coping, and patient characteristics were taken into account, thereby enabling analysis of the independent role of fatigue in participation and quality of life outcome.

One of the limitations of the study is that it is not known whether fatigue is causally related to participation and HR-QoL, since the study had a cross-sectional design. It would be of interest to examine a possible causal relationship in future longitudinal cohort studies. In addition, it was necessary to preselect possible predictors for the multivariate analysis, since the number of predictors to take into account in the multivariate analysis was limited due to the sample size of 46 patients. Finally, other personality factors, such as self-efficacy and neuroticism, are known to be associated with fatigue, quality of life and participation after SAH or stroke (14, 35, 38, 39). These variables were not taken into account in the current study, but this would be of interest in future studies.

To summarize, 5 years after non-aneurysmal PM-SAH, fatigued patients had worse participation and HR-QoL than non-fatigued patients, and fatigue severity was related to multiple aspects of participation and HR-QoL. Future studies should examine whether patients with PM-SAH may benefit from rehabilitation aimed at fatigue, in terms of enhanced participation and HR-QoL.

The authors have no conflicts of interest to declare.

REFERENCES

1. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. Lancet 2017; 389: 655–666.
2. van Gijn J, van Dongen KJ, Vermeulen M, Hijdra A. Perimesencephalic hemorrhage: a nonaneurysmal and benign form of subarachnoid hemorrhage. Neurology 1985; 35: 493–497.
3. Rinkel GJ, Wijdicks EF, Vermeulen M, Ramos LM, Tanghe HL, Hasan D, et al. Nonaneurysmal perimesencephalic subarachnoid hemorrhage: CT and MR patterns that differ from aneurysmal rupture. Am J Neuroradiol 1991; 12: 829–834.
4. Mensing LA, Vergouwen MDI, Laban KG, Ruigrok YM, Velthuis BK, Algra A, et al. Perimesencephalic hemorrhage: a review of epidemiology, risk factors, presumed cause, clinical course, and outcome. Stroke 2018; 49: 1363–1370.
5. Boerboom W, Heijenbrok-Kal MH, Khajeh L, van Kooten F, Ribbers GM. Differences in cognitive and emotional outcomes between patients with perimesencephalic and aneurysmal subarachnoid haemorrhage. J Rehabil Med 2014; 46: 28-32.
6. Marquardt G, Niebauer T, Schick U, Lorenz R. Long-term follow-up after perimesencephalic subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 2000; 69: 127–130.
7. Greebe P, Rinkel GJ. Life expectancy after perimesencephalic subarachnoid hemorrhage. Stroke 2007; 38: 1222–1224.
8. Boerboom W, van Zandvoort MJ, van Kooten F, Khajeh L, Visser-Meily JM, Ribbers GM, et al. Long-term fatigue after perimesencephalic subarachnoid haemorrhage in relation to cognitive functioning, mood and comorbidity. Disabil Rehabil 2017; 39: 928–933.
9. Kutlubaev MA, Barugh AJ, Mead GE. Fatigue after subarachnoid haemorrhage: a systematic review. J Psychosom Res 2012; 72: 305-310.
10. Boerboom W, Heijenbrok-Kal MH, Khajeh L, van Kooten F, Ribbers GM. Long-term functioning of patients with aneurysmal subarachnoid hemorrhage: a 4-year follow-up study. Am J Phys Med Rehabil 2016; 95: 112–120.
11. Western E, Sorteberg A, Brunborg C, Nordenmark TH. Prevalence and predictors of fatigue after aneurysmal subarachnoid hemorrhage. Acta Neurochir 2020; 162: 3107–3116.
12. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. Sleep 2008; 31: 1601–1607.
13. de Vries EA, Boerboom W, van den Berg-Emons R, van Kooten F, Ribbers GM, Heijenbrok-Kal MH. Fatigue in relation to long-term participation outcome in aneurysmal subarachnoid haemorrhage survivors. J Rehabil Med 2021; 53.
14. Passier PE, Visser-Meily JM, Rinkel GJ, Lindeman E, Post MW. Determinants of health-related quality of life after aneurysmal subarachnoid hemorrhage: a systematic review. Qual Life Res 2013; 22: 1027–1043.
15. Beseoglu K, Pannes S, Steiger HJ, Hanggi D. Long-term outcome and quality of life after nonaneurysmal subarachnoid hemorrhage. Acta Neurochir 2010; 152: 409–416.
16. Konczalla J, Schmitz J, Kashefiolasl S, Senft C, Seifert V, Platz J. Non-aneurysmal subarachnoid hemorrhage in 173 patients: a prospective study of long-term outcome. Eur J Neurol 2015; 22: 1329–1336.
17. Krajewski K, Dombek S, Martens T, Koppen J, Westphal M, Regelsberger J. Neuropsychological assessments in patients with aneurysmal subarachnoid hemorrhage, perimesencephalic SAH, and incidental aneurysms. Neurosurgical Review 2014; 37: 55–62.
18. Brilstra EH, Hop JW, Rinkel GJ. Quality of life after perimesencephalic haemorrhage. J Neurol Neurosurg Psychiatry 1997; 63: 382–384.
19. Rinkel GJ, Wijdicks EF, Hasan D, Kienstra GE, Franke CL, Hageman LM, et al. Outcome in patients with subarachnoid haemorrhage and negative angiography according to pattern of haemorrhage on computed tomography. Lancet 1991; 338: 964–968.
20. Alfieri A, Gazzeri R, Pircher M, Unterhuber V, Schwarz A. A prospective long-term study of return to work after non-traumatic nonaneurysmal subarachnoid hemorrhage. J Clin Neurosci 2011; 18: 1478–1480.
21. Visser-Meily JM, Rhebergen ML, Rinkel GJ, van Zandvoort MJ, Post MW. Long-term health-related quality of life after aneurysmal subarachnoid hemorrhage: relationship with psychological symptoms and personality characteristics. Stroke 2009; 40: 1526–1529.
22. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46: 1121–1123.

23. Post MW, van der Zee CH, Hennink J, Schafrat CG, Visser-Meily JM, van Berlekom SB. Validity of the utrecht scale for evaluation of rehabilitation-participation. Disabil Rehabil 2012; 34: 478–485.
24. Post MW, Boosman H, van Zandvoort MM, Passier PE, Rinkel GJ, Visser-Meily JM. Development and validation of a short version of the Stroke Specific Quality of Life Scale. J Neurol Neurosurg Psychiatry 2011; 82: 283–286.
25. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67: 361–370.
26. 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: 363–370.
27. Endler NS, Parker JD. Coping Inventory for Stressful Situations (CISS) manual. Toronto, Canada: Multi-Health Systems; 1990.
28. Brands IMH, Köhler S, Stapert SZ, Wade DT, van Heugten CM. Psychometric properties of the Coping Inventory for Stressful Situations (CISS) in patients with acquired brain injury. Psychol Assess 2014; 26: 848–856.
29. Linn BS, Linn MW, Gurel L. Cumulative Illness Rating Scale. J Am Geriatr Soc 1968; 16: 622–626.
30. Groeneveld IF, Goossens PH, van Meijeren-Pont W, Arwert HJ, Meesters JJL, Rambaran Mishre AD, et al. Value-based stroke tehabilitation: feasibility and tesults of patient-teported Outcome measures in the first year after stroke. J Stroke Cerebrovasc Dis 2019; 28: 499–512.
31. Stiekema APM, Nijsse B, de Kort PLM, Spikman JM, Visser-Meily JMA, van Heugten CM. The relationship between social cognition and participation in the long term after stroke. Neuropsychol Rehabil 2019: 1–15.
32. Murgo M, Cavanagh K, Latham S. Health-related quality of life and support needs for sub-arachnoid haemorrhage survivors in New South Wales Australia. Aust Crit Care 2016; 29: 146–150.
33. Passier PE, Post MW, van Zandvoort MJ, Rinkel GJ, Lindeman E, Visser-Meily JM. Predicting fatigue 1 year after aneurysmal subarachnoid hemorrhage. J Neurol 2011; 258: 1091–1097.
34. Huenges Wajer IM, Visser-Meily JM, Greebe P, Post MW, Rinkel GJ, van Zandvoort MJ. Restrictions and satisfaction with participation in patients who are ADL-independent after an aneurysmal subarachnoid hemorrhage. Top Stroke Rehabil 2017; 24: 134–141.
35. de Graaf JA, Schepers VPM, Nijsse B, van Heugten CM, Post MWM, Visser-Meily JMA. The influence of psychological factors and mood on the course of participation up to four years after stroke. Disabil Rehabil 2020: 1–8.
36. Visser MM, Aben L, Heijenbrok-Kal MH, Busschbach JJ, Ribbers GM. The relative effect of coping strategy and depression on health-related quality of life in patients in the chronic phase after stroke. J Rehabil Med 2014; 46: 514–519.
37. Visser MM, Heijenbrok-Kal MH, Spijker AV, Oostra KM, Busschbach JJ, Ribbers GM. Coping, problem solving, depression, and health-related quality of life in patients receiving outpatient stroke rehabilitation. Arch Phys Med Rehabil 2015; 96: 1492–1498.
38. van Mierlo ML, Schröder C, van Heugten CM, Post MW, de Kort PL, Visser-Meily JM. The influence of psychological factors on health-related quality of life after stroke: a systematic review. Int J Stroke 2014; 9: 341–348.
39. Aarnes R, Stubberud J, Lerdal A. A literature review of factors associated with fatigue after stroke and a proposal for a framework for clinical utility. Neuropsychol Rehabil 2020; 30: 1449–1476.