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Review

Depression after Subarachnoid Hemorrhage: A Systematic Review

Wai Kwong Tang,[a] Lisha Wang,[a] George Kwok Chu Wong,[b] Gabor S. Ungvari,[c,d] Fumihiko Yasuno,[e] Kelvin K.F. Tsoi,[f,g] Jong S. Kim[h]

[a]Department of Psychiatry, Chinese University of Hong Kong, Hong Kong, China
[b]Department of Surgery, Chinese University of Hong Kong, Hong Kong, China
[c]University of Notre Dame Australia, Fremantle, Australia
[d]Division of Psychiatry, Medical School, University of Western Australia, Crawley, Australia
[e]Department of Psychiatry, National Center for Geriatrics and Gerontology, Obu, Japan
[f]Jockey Club School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China
[g]Stanley Ho Big Data Decision Analytics Research Centre, Chinese University of Hong Kong, Hong Kong, China
[h]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background and Purpose Depression is common and debilitating illness accompanying many neurological disorders including non-traumatic subarachnoid hemorrhage (SAH). The aim of this systematic review was to identify and critically appraise all published studies that have reported the frequency, severity and time course of depression after SAH, the factors associated with its development and the impact of depression on patients' quality of life after SAH.

Methods The PubMed database was searched for studies published in English that recruited at least 40 patients (>18 years old) after SAH who were also diagnosed with depression.

Results Altogether 55 studies covering 6,327 patients met study entry criteria. The frequency of depression ranged from 0% to 61.7%, with a weighted proportion of 28.1%. Depression remained common even several years after the index SAH. Depression after SAH was associated with female sex, premorbid depression, anxiety, substance use disorders or any psychiatric disorders, and coping styles. Comorbid cognitive impairment, fatigue, and physical disability also increased the risk of depression. Aneurysmal SAH and infarction may be related to depression as well. Depression reduces the quality of life and life satisfaction in patients after SAH.

Conclusions Depression is common after SAH and seems to persist. Further research is needed to clarify its time course and identify the neuroendocrine and neurochemical factors and brain circuits associated with the development of post-SAH depression. Randomized controlled treatment trials targeting SAH-related depression are warranted.

Correspondence: Wai Kwong Tang
Department of Psychiatry, Shatin Hospital, Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China
Tel: +852-2636-7760
Fax: +852-2647-5321
E-mail: tangwk@cuhk.edu.hk

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Introduction

Subarachnoid hemorrhage (SAH) is a relatively uncommon and severe type of stroke. As patients are affected by SAH at a mean age of 55 years, they can lose many years of productive life. The rupture of an intracranial aneurysm is the underlying cause in 85% of SAH cases.[1] Approximately 55% of patients survive SAH and regain independent functioning, whereas 19%

remain dependent and 26% die.[1] Many survivors of SAH have long-term deficits in cognition, and decreased quality of life.[2] Neuropsychiatric disturbances such as depression, anxiety, post-traumatic stress disorder, and fatigue are not uncommon, yet often neglected in patients with SAH.[3]

Depression is common in patients with neurological diseases such as Alzheimer's disease, Parkinson's disease, traumatic brain injury and stroke.[4] Depression is a frequent consequence of head injury, affecting up to 61% of patients. Depression is associated with worse global outcomes, impaired social functioning, difficulty performing activities of daily living, and a lower quality of life.[5]

Post-stroke depression contributes to disability and increased mortality following stroke. Depression is increasingly becoming a standard part of post-stroke assessment and rehabilitation.[6] However, there is still a lack of methodically sound psychopharmacological and psychosocial treatment trials on SAH-related depression.

The aims of this systematic review were as follows: (1) to determine the frequency, severity and time course of depression after SAH; (2) to identify the factors associated with the development of depression after SAH, including patients' demographic data, baseline characteristics of SAH, psychological factors including anxiety and cognitive impairment, somatic complications related to SAH (neuroendocrine changes, infarcts, and preexisting and post-SAH medical comorbidities); and (3) to evaluate the impact of depression on patients' quality of life following SAH.

Methods

Literature search

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The principal author (W.K.T.) searched the PubMed, EMBASE, PsycINFO, and Ovid Nursing databases on December 5, 2018, using the keywords "depression" or "mood" or "depressive" and "subarachnoid." Two authors (W.K.T. and L.W.) read every title and abstract, obtained the full texts of potentially relevant papers, and applied inclusion and exclusion criteria to each text. Any uncertainties were discussed. W.K.T. also scrutinized the reference lists of included papers to identify further studies.

Inclusion criteria

Studies were included in the review if they (1) were written in English, (2) were published in peer-reviewed journals, (3) included 10 or more patients who had survived non-traumatic SAH and were older than 18 years,[7] and (4) assessed patients for depression using a validated single or multiple item self-report instrument or diagnostic interview.

Exclusion criteria

Publications were excluded if they were (1) case reports, (2) pediatric studies (patients <18 years old), (3) dissertations, or (4) articles with no primary data (reviews, editorials letters, etc.), (5) sample size <40, (6) poor quality (a Strengthening the Report of Observational Studies in Epidemiology [STROBE] checklist score ≤13, i.e., 60% of maximum score).

Data extraction

Two authors (W.K.T. and L.W.) independently extracted the following data from the studies included in the review: study characteristics (aims/objectives, study design, inclusion and exclusion criteria, criteria for and measurement of depression), participants' characteristics (definition of the study population, age, gender, number, ethnicity, and socio-economic status of the patients at the beginning and end of the study, the number of deaths due to SAH, drop-outs, and patients lost to follow-up before the end of study, first or recurrent SAH, severity of SAH, comorbidities and complications) and results (characteristics of patients' subgroups, outcome data, and relationship between depression and patients' characteristics or SAH characteristics and/or outcomes).

Quality assessment

We used STROBE statement for quality assessment of the included papers.[8] It consists of 22 items. We scored each item 1 point. The maximum possible score is 22.

Data synthesis

Statistical analyses were performed in Software R (package metaphor & meta, R Foundation for Statistical Computing, Vienna, Austria). The results are presented as a narrative review and are also tabulated. Frist, the weighted proportion of the frequency of depression was calculated. We conducted a meta-analysis of frequency of depression, using the variance-stablizing double-arscine method transformation.[9] Pooled estimates in both the overall (and subgroup) analyses were calculated using the Hartung-Knapp-Sidik-Jonkman method, under the random effect model.[10] Statistical heterogeneity among the trials was assessed, and $P<0.1$ was considered as statistical significance.[11] Level of heterogeneity was assessed by I^2, which describes the percentage of total variation across studies because of heterogeneity rather than chance alone. A random-effects model for the trials with statistically significant heterogeneity was used. Subgroup analyses were performed according to data collection settings, i.e., interview and questionnaire.

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Second we conducted a meta-analysis of frequency of depression, using the variance-stablizing double-arscine method transformation.[9] Pooled estimates in both the overall (and subgroup) analyses were calculated using the Hartung-Knapp-Sidik-Jonkman method, under the random effect model.[10] Publication bias was examined by Funnel plot and Egger's regression test. Data from the identical cohorts was reported only once. Where depression was assessed with more than one method in a study, only the results with the most commonly used assessment method were considered. Where data from two or more time points after SAH were available, data from the earlier time point was included in the analysis.

Results

The electronic search identified 2,383 publications potentially eligible for the review. One hundred and six full texts were retrieved for detailed evaluation, of which 51 studies were excluded (Figure 1). Fifty-five studies covering 6,327 patients (range, 40 to 1,181) in 47 cohorts (data from five cohorts were used in 13 publications[12-24]) met the inclusion criteria (Table 1). The majority of studies (46 of 55) included more female than men. Quality of included studies was very different and the STROBE score varied from 14 to 22 (Supplementary Table 1).

Fifty-one of 55 studies (93%) used one of the following screening or rating scales to ascertain the presence of depression: Hospital Anxiety Depression Scale (HADS),[18,19,25-40] Beck Depression Inventory (BDI),[12-21,40-51] Center for Epidemiologic Studies Depression (CESD),[22-24,52,53] Montgomery Åsberg Depression Rating Scale (MADRS),[54,55] Geriatric Depression Scale (GDS),[56,57] International Classification of Diseases 10th Edition (ICD-10)-Symptom-Rating questionnaire,[58] Neuropsychiatric Inventory,[3] Emotional State Questionnaire,[59] Psychological General Well-Being Index,[60] and the Zung Depression Scale (ZDS).[61] Less commonly used measures of depression included the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) axis I disorders,[62] clinical interview,[63] Cornell personality questionnaire,[64] and Depression Skala[65] (Table 1).

Twenty-seven studies recruited patients early after SAH and assessed them for depression later. Twenty-six studies recruited patients and collected data at one or more defined time points after SAH (range, 4 days to 10 years) (Table 1).

Frequency, severity, and time course of depression after SAH

Frequency of depression after SAH

Thirty-seven studies (n=5,340) reported the frequency of depression after SAH. The frequency ranged widely depending on the assessment method and how long it was performed after the index SAH.

The frequency of depression reported in the 35 studies (n=5,217) that applied rating instruments/questionnaires was in the range of 0% to 61.7%, with a weighted frequency of 28.1%. Depression was assessed at 4 days to 10.1 years after ictus (Table 2). The weighted frequency of depression at ≤1 and >1 year after ictus were 32.2% and 27.3%, respectively. The frequency in the two studies (n=123) that used interviews to diagnose depression found 20% to 25% (weighted proportion=21.6%) of patients depressed (Table 2).[62,63]

In the meta-analysis, the overall pooled frequency of depres-

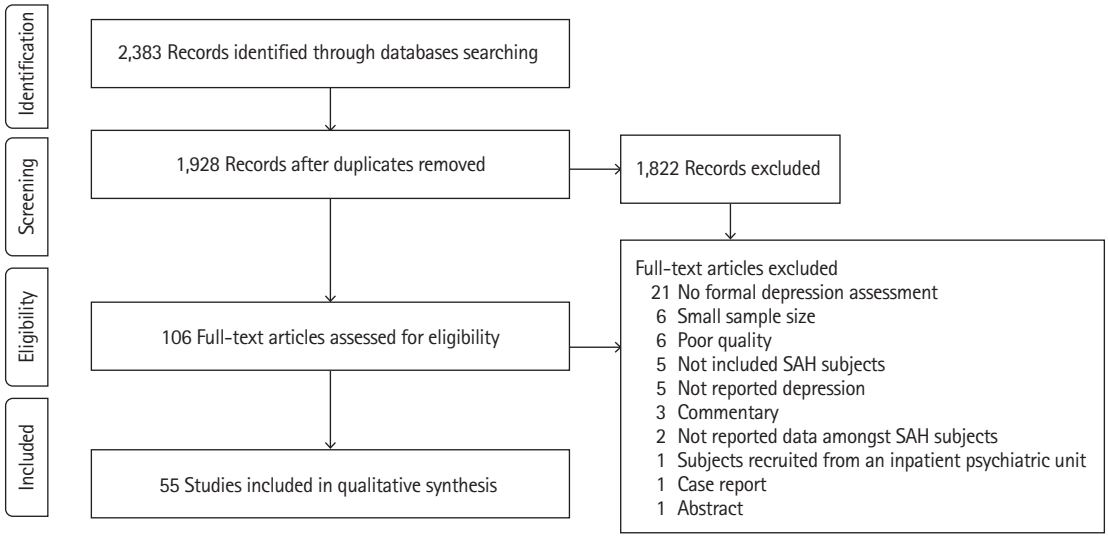

Figure 1. Flow-chart diagram presenting the selection of eligible studies. SAH, subarachnoid hemorrhage.

Table 1. Characteristics of the studies included in the systematic review

Study	Design	Participants			Aetiology of SAH	Timing after SAH	Tool used to diagnose depression
		No.	Age (mean±SD)	Male sex (%)			
Ljunggren et al. (1985)[63]	Cross	40	NR	42.5	Aneu	40–45 mo	Interview
Hütter et al. (1995)[20,21]	Cross	58	46 (median)	43	Aneu	1–5 yr	BDI
Hellawell et al. (1999)[39]	Long	44	49.7±14.6	45	Aneu	6 mo (T1) 1 yr (T2) 2 yr (T3)	HADS
Fertl et al. (1999)[51]	Cross	40	51 (SD NR)	40	Aneu	Average 22 mo (range, NR)	BDI
Carter et al. (2000)[61]	Cross	182	52 (SD NR)	NR	Aneu	1–5 yr	ZDS
Powell et al. (2002)[18] and Powell et al. (2004)[19]	Long	52	46.9±10.4	33	Aneu	3 mo (T1) 9 mo (T2) 18 mo (T3)	BDI & HADS
Fontanella et al. (2003)[50]	Long	37	55.3±8.8	35	Aneu	6 mo	BDI
Bellebaum et al. (2004)[49]	Long	32	54.4±12.5	NR	Aneu	23–28 mo	BDI
Morris et al. (2004)[40]	Cross	70	45.2±15.2	39	Aneu (81%)	14–23 mo	BDI & HADS
Salmond et al. (2006)[48]	Cross	20	58.6±2.1	20	Aneu	14–99 mo	BDI
Wermer et al. (2007)[38]	Cross	610	54.3±9.0	36	Aneu	2.3–18.8 yr	HADS
Kreitschmann-Andermahr et al. (2007)[47]	Cross	40	43.8 (SD NR)	NR	Aneu	12–66 mo	BDI
Preiss et al. (2007)[46]	Long	75	45.7 (SD NR)	33	Aneu	1 yr	BDI
Orbo et al. (2008)[45]	Long	42	48 (SD NR)	40.4	Aneu	1 yr	BDI
Visser-Meily et al. (2009)[36]	Cross	141	54.1±12.3	33.3	Aneu	2–4 yr	HADS
Haug et al. (2009)[55]	Long	46	53 (median)	37	Aneu	1 yr	MADRS
King et al. (2009)[37]	Long	178	54.7±12.6	26	Aneu	NR	HADS
Mukerji et al. (2010)[35]	Cross	77	54.3±10.8	32.5	Aneu (84%)	12–266 mo	HADS
Passier et al. (2010)[14], Passier et al. (2011)[15], Passier et al. (2012)[16]	Long	111	52.8±13.0	18	Aneu	3 mo	BDI
Meyer et al. (2010)[44]	Long	113	54.4±14.1	32.7	Aneu	At discharge (T1) 12 mo (T2)	BDI
Caeiro et al. (2011)[54]	Long	108	53.5±14.2	30	Aneu (56%)	≤4 day	MADRS
Alfieri et al. (2008)[17]	Long	38	44.3±13.7	42	Aneu (47%)	On admission (T1) 1 mo (T2) 1 yr (T3) 3 yr (T4) 5 yr (T5)	BDI
Hedlund et al. (2011)[62]	Long	83	52±9	36	NR	10 day (T1) 7 mo (T2)	Structured clinical interview for DSM-IV axis I disorders
Wong et al. (2012)[57]	Long	90	45±11	76	Aneu	3 mo	GDS
Latimer et al. (2013)[33]	Cross	23	52.7 (SD NR)	NR	Aneu	40–45 mo	HADS
von Vogelsang et al. (2013)[34]	Cross	217	50.6±12	29	Aneu	8.8–12 yr	HADS
Kreiter et al. (2013)[53]	Long	216	51.2±13.8	36	Aneu (87%)	3 mo (T1) 1 yr (T2)	CESD
Wong et al. (2013)[56]	Long	120	51 (median)	68	Aneu	1 yr	GDS
Vetkas et al. (2013)[59]	Cross	114	54±13	32	Aneu	1–10 yr	Emotional State Questionnaire
Noble et al. (2014)[32]	Cross	414	44.6 (SD NR)	25	Aneu (68.4%)	0–34 yr	HADS
Wong et al. (2014)[3]	Cross	103	55±10	29	Aneu	1–4 yr	Neuropsychiatric inventory
Gill et al. (2015)[31]	Cross	93	49.67±10.05	20.43	NR	2–58 mo	HADS
Hütter et al. (2014)[43]	Cross	45	47.1±10.7	44	Aneu (64%)	3–5 yr	BDI
Boerboom et al. (2014)[22] and Boerboom et al. (2016)[23,24]	Long	76	53.8±11.5	31.6	Aneu	0.4 yr (T1) 3.9 yr (T2)	CESD

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Table 1. Continued

Study	Design	Participants			Aetiology of SAH	Timing after SAH	Tool used to diagnose depression
		No.	Age (mean±SD)	Male sex (%)			
von Vogelsang et al. (2015)[29]	Long	88	52.6±14.2	34.1	Aneu	6 mo (T1) 1 yr (T2) 2 yr (T3)	HADS
Buunk et al. (2015)[30]	Cross	200	58.7 (SD NR)	36.5	Aneu	2–10 yr	HADS
Brand et al. (2015)[65]	Long	21	58.8 (SD NR)	19	Aneu	5–9 mo	Depression Skala
Scherfler et al. (2016)[28]	Long	14	46.1±12	43	Aneu (36%)	1 yr	HADS
Gerber et al. (2016)[42]	Cross	15	52.7±9.8	27	Aneu	44 mo	BDI
Taufique et al. (2016)[52]	Long	1181	52.3±12.8	NR	NR	1 yr	CESD
Kronvall et al. (2016)[60]	Long	51	NR	NR	Aneu	3–6 mo (T1) 6–12 mo (T2) 12–24 mo (T3)	Psychological general well-being
Pačić-Turk et al. (2016)[64]	Long	72	46±9.2	39	Aneu	11 mo (T1) 12–48 mo (T2)	Cornell personality questionnaire
Colledge et al. (2017)[12,13]	Cross	15	57.3±8.9	27	Aneu	44 mo	BDI
Ackermark et al. (2017)[41]	Long	93	50.3±11.8	19.4	Aneu	3 mo (T1) 1 yr (T2) 2–5 yr (T3)	BDI
Buunk et al. (2018)[26]	Cross	221	57.0±10.0 (Aneu group), 55.4±10.2 (other group)	31.3 (Aneu group), 58.2 (other group)	Aneu (75%)	3–10 yr	HADS
Tölli et al. (2018)[25]	Long	45	57.4±9.9	22.9	NR	3 mo (T1) 6 mo (T2) 12 mo (T3)	HADS
Bründl et al. (2018)[58]	Long	21	42.0–59.8 (mean)	33.3–50	Aneu (71%)	11–35 day (T1) 6 mo (T2)	ICD-10-Symptom-Rating Questionnaire

SD, standard deviation; SAH, subarachnoid hemorrhage; Cross, cross-sectional; NR, not reported; Aneu, aneurysmal; BDI, Beck Depression Inventory; Long, longitudinal; HADS, Hospital Anxiety Depression Scale; ZDS, Zung Self-rating Depression Scale; MADRS, Montgomery Åsberg Depression Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; GDS, Geriatric Depression Scale; CESD, Center for Epidemiologic Studies Depression; ICD-10, International Classification of Diseases 10th Edition.

sion was 26.3% (95% confidence interval [CI], 21.0% to 32.0%). The frequency of depression in the interview and questionnaire studies were 25.0% (95% CI, 12.6% to 39.7%) and 26.3% (95% CI, 20.8% to 32.3%), respectively (Figure 2). The Funnel plot did not suggest any publication bias (P=0.434) (Figure 3).

Severity of depression after SAH

Twelve studies (n=634) assessed the severity of depression using the BDI.[14-16,18-21,40,41,44,45,47] The weighted mean BDI value was 9.9 less than 1 year after SAH and 10.1 1-year or more after; these figures indicate mild to moderate depression.[15] Nine studies (n=1,280) evaluated the severity of depression using the HADS.[27-30,33,34,36-38] The weighted mean HADS value was 5 less than 1 year after SAH and 5.4 1-year or more after; according to a previous validation study,[66] both values can be interpreted as an absence of depression.[27] Less commonly used mood scales were the CESD,[22-24] MADRS,[54,55], GDS,[56,57] and one study each used the ZDS,[61] Depressions Skala,[65] Emotional State Questionnaire,[59] Cornell Personality Scale,[64] and the Psychological General Well-Being Scale[60] (Tables 1 and 2, Supplementary Table 2).

Time course of depression after SAH

Eight studies (n=539) assessed depression at more than one time point (Supplementary Table 3).[18,19,23,25,29,41,44,64] In one study (n=113), the proportion of patients with depression increased from 24.8% at discharge to 61.7% at the 12-month follow-up.[44] In another study, 72% of patients with depressive symptoms at 3 months still had symptoms at 2 to 5 years.[41] One study reported an increase in depressive symptoms from 11 months to 12 to 48 months follow-up.[64] On the contrary, five studies (n=261)

Table 2. Studies of frequency and/or severity of depression after SAH

Study	Study design and setting	Timing after SAH	Cut off point	Proportion of participants with depression (%)	Depressive symptom scores (mean±SD)	Limitations
Depression measured by rating instruments/questionnaires						
Alfieri et al. (2008)[17]	Longitudinal study, hospitalized patients	On admission (T1) 1 mo (T2) 1 yr (T3) 3 yr (T4) 5 yr (T5)	NR	NR	T1: 17.1±6.5 T2: 22.1±3.6 T3: 19.9±4.8 T4: 14.3±3.8 T5: 13.2±3.8	Small sample size
Caeiro et al. (2011)[54]	Prospective study, consecutive admissions to an academic neurosurgery center	≤4 day	MADRS ≥7	45	9.2±7.3	Sample biased towards SAH of mild severity, depression not assessed at subacute and chronic stage of SAH
Meyer et al. (2010)[44]	Longitudinal study	At discharge (T1) 12 mo (T2)	BDI >10	T1: 24.8 T2: 61.7	NR	Patients with aphasia excluded, possible confounders not measured.
Passier et al. (2010)[14], Passier et al. (2011)[15], Passier et al. (2012)[16]	Cross-sectional study, all subjects treated with clipping or coiling	3 mo	BDI ≥10	40	9.6±6.9	Nursing home patients not included.
Powell et al. (2002)[18] and Powell et al. (2004)[19]	Cross-sectional study, consecutive admissions to a neurovascular service	3 mo (T1) 9 mo (T2) 18 mo (T3)	BDI >10	T1: 9.1 T2: 11.4 T3: 16.3	T1: 9.6±6.2 T2: 9.2±6.9 T3: 9.4±7.3	Small sample size
Ackermark et al. (2017)[41]	Longitudinal study, subjects recruited from a clinic	3 mo (T1) 1 yr (T2) 2–5 yr (T3)	BDI ≥10	T1: 39 T2: 41 T3: 54	T1: 8.9±7.0 T2: 9.3±7.1 T3: 11.2±8.0	Nursing home patients not included, no data of previous mental health problems, locus of control, optimism or social support, self-report of depressive symptoms.
Kronvall et al. (2016)[60]	Prospective study in an academic neurosurgery unit	3–6 mo (T1) 6–12 mo (T2) 12–24 mo (T3)	NR	NR	T1: 15.0±3.5 T2: 15.3±2.9 T3: 15.8±2.9	Small sample size, validity of the mood assessment uncertain
Wong et al. (2012)[57]	Prospective multi-center study of consecutive admissions	3 mo	NR	NR	7 (median)	Lack of gold standard measure of depression
Kreiter et al. (2013)[53]	Prospective study, consecutive admissions to an academic neurosurgery center	3 mo (T1) 1 yr (T2)	CESD ≥16	T1: 38 T2: 33	NR	Less severely affected subjects more likely to complete follow-up, subjects treated for SAH a decade ago, confounders not considered.
Boerboom et al. (2014)[22] and Boerboom et al. (2016)[23,24]	Prospective study, consecutive admissions to an academic neurosurgery center	0.4 yr (T1) 3.9 yr (T2)	CESD ≥16	T2: 26.7	T1: 13.7±1.2 T2: 11.9±1.2	Subjects assessed at different time points following SAH.
Fontanella et al. (2003)[50]	Cross-sectional study, all subjects had treated anterior communicating artery bleeding aneurysm	6 mo	NR	NR	13.8 (SD NR)	Small sample size, limited generalizability to patients with other type of SAH
von Vogelsang et al. (2015)[29]	Longitudinal study, hospitalized subjects	6 mo (T1) 1 yr (T2) 2 yr (T3)	HADS ≥8	T1: 25.0 T2: 27.6 T3: 29.4	T1: 5.0 T2: 4.0 T3: 5.0 (median)	No data on previous history of depression or use of antidepressants during the follow-up period
Hellawell et al. (1999)[39]	Longitudinal study, subjects recruited from a neurosurgical unit	6 mo (T1) 1 yr (T2) 2 yr (T3)	NR	T1: 8 T2: 9 T3: 5	NR	Small sample size, high attrition rate
Brand et al. (2015)[65]	Case-control study, all subjects had treated SAH	5–9 mo	NR	NR	1.42±0.29	Small sample size, validity of the mood assessment uncertain, confounders not measured.

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Table 2. Continued

Study	Study design and setting	Timing after SAH	Cut off point	Proportion of participants with depression (%)	Depressive symptom scores (mean±SD)	Limitations
Pačić-Turk et al. (2016)[64]	Prospective study in an academic neurosurgery unit	11 mo (T1) 12–48 mo (T2)	NR	NR	T1: 1.93 T2: 2.65	Modest sample size, validity of the mood assessment uncertain
Scherfler et al. (2016)[28]	Longitudinal study, subjects recruited from a neurological intensive care unit	1 yr	HADS >10	0	1 (median)	Small sample size, selected inclusion of patients without visually detectable structural lesions on MRI
Tölli et al. (2018)[25]	Longitudinal study, subjects recruited from a neruointensive care unit	1 yr	HADS ≥8	23	NR	Single center study, small sample size
Orbo et al. (2008)[45]	Longitudinal study, all subjects treated with clipping	1 yr	BDI ≥14	5	6 (SD NR)	Small sample size
Preiss et al. (2007)[46]	Longitudinal study, all subjects treated with coiling or clipping	1 yr	NR	NR	9.4	Relative small sample size, potential selection bias
Haug et al. (2009)[55]	Prospective study, all subjects treated for anterior or middle cerebral artery bleeding aneurysm	1 yr	NR	NR	5.5 (SD NR)	Small sample size, subjects with other locations of aneurysms excluded.
Taufique et al. (2016)[52]	Prospective study, consecutive admissions to an academic neurosurgery center	1 yr	CESD ≥16	33.3	NR	Poor grade patients more likely to be lost to follow-up.
Mukerji et al. (2010)[35]	Retrospective subject recruitment, all subjects received an angiogram	Median 13 mo (range, 12–266)	NR	13	NR	Subjects recruited at different time points following SAH, small sample size
Morris et al. (2004)[40]	Cross-sectional study, method and site of recruitment not reported	Average 16 mo (range, 14–23)	BDI ≥10	50	NR	Small sample size, opportunity samples, subjects recruited at different time points following SAH
Gill et al. (2015)[31]	Cross-sectional study, subjects recruited from neuropsychology services, charities and online support network	Average 21.1 mo (range, 2–58)	HADS ≥8	51	NR	No data on those refused to participate, self-report data of SAH, severity of injury not recorded, subjects, recruited at different time points following SAH.
Fertl et al. (1999)[51]	Cross-sectional study, all subjects treated for SAH	Average 22 mo (range, NR)	≥12	28	NR	Small sample size, subjects recruited at different time points following SAH
Kreitschmann-Andermahr et al. (2007)[47]	Cross-sectional study, method and site of recruitment not reported	Average 27.3 mo (range, 12–66)	BDI >10	37.5	8.33±5.85	Small sample size, subjects recruited at different time points following SAH
Wong et al. (2014)[3]	Cross-sectional four centers study, hospitalized subjects	Average NR (range, 1–4 yr)	-	13	NR	Attrition, subjects recruited at different time points following SAH, confounders not measured, reporting bias
Visser-Meily et al. (2009)[36]	Cross-sectional study, all subjects had been treated with coiling or clipping	Average 3 yr (range, 2–4)	HADS ≥8	23	4.8±3.9	Selection bias as only patients still alive included, subjects recruited at different time points following SAH.
Noble et al. (2014)[32]	Cross-sectional study, subjects recruited from support groups	Median 3 yr (range, 1–5)	HADS ≥8	45.2	NR	Only patients had access to internet included, no data on those refused to participate, lack of psychiatric interviews, self-report data of SAH details, subjects recruited at different time points following SAH.
Hütter et al. (1995)[20,21]	Cross-sectional study, all subjects operated for SAH	Median 3 yr (range, 1–5)	BDI >10	30	NR	Small sample size, subjects recruited at different time points following SAH, excluded subjects had worse SAH grading.

Table 2. Continued

Study	Study design and setting	Timing after SAH	Cut off point	Proportion of participants with depression (%)	Depressive symptom scores (mean±SD)	Limitations
Carter et al. (2000)[61]	Cross-sectional study, consecutive admissions to a tertiary medical center	Average NR (range, 1–5 yr)	ZDS ≥50	36	45.6 (SD NR)	Subjects recruited at different time points following SAH
Latimer et al. (2013)[33]	Retrospective subject recruitment, all subjects had anterior circulatory area SAH	40–45 mo	NR	NR	6.7	Retrospective subject recruitment, selective sample, small sample size
Colledge et al. (2017)[12,13] and Gerber et al. (2016)[42]	Cross-sectional study, almost all subjects treated with clipping	44 mo	NR	NR	8.9±6.6	Small sample size, subjects recruited at different time points following SAH, lack of psychiatric interview
Vetkas et al. (2013)[59]	Retrospective study of a single academic center	Average 4.5 yr (range, 1–10)	GDS ≥12	30	8.4±6.9	Retrospective study, subjects assessed at different time points following SAH
Buunk et al. (2015)[30]	Cross-sectional study, all subjects had been treated by coiling or clipping	Average 4.6 yr (range, 2–10)	HADS ≥8	23	4.2±4.3	Selective sample, subjects recruited at different time points following SAH
Boerboom et al. (2017)[27]	Cross-sectional study, hospitalized subjects	Average 4.7 yr (range, NR)	HADS ≥8	15.2	3.5 (SD NR)	Selection bias, small sample size, subjects recruited at different time points following SAH
Salmond et al. (2006)[48]	Cross-sectional study, method and site of recruitment not reported	Average 68 mo (range, 14–99)	NR	NR	6.5±1.4	Small sample size, subjects recruited at different time points following SAH
Wermer et al. (2007)[38]	Cross-sectional study, all subjects treated with clipping	Average 8.9 yr (range, 2.3–18.8)	HADS >10	9.4	6.2±3.1	Only patients treated with clipping and regained functional independence included, relative young age of the subjects, subjects recruited at different time points following SAH.
von Vogelsang et al. (2013)[34]	Retrospective subject recruitment, subjects recruited from a neurosurgical clinic	Average 10.1 yr (range, 8.8–12)	HADS ≥8	23.5	4.0 (median)	Subjects recruited at different time points following SAH, no data on previous history of depression or use of antidepressants during the follow-up period
King et al. (2009)[37]	Cross-sectional study, subjects recruited from neurosurgery clinics	NR	HADS >10	9	4.8±3.4	A single academic center study, some eligible patients not participated, Caucasians over-represented
Depression measured by interview						
Ljunggren et al. (1985)[63]	Cross-sectional study, all subjects had treated SAH and good neurological recovery	Average 3.5 yr (range, 14 mo–7 yr)	-	25	NR	Attrition, sampling bias, subjects recruited at different time points following SAH, self-report of depression
Hedlund et al. (2011)[62]	Prospective study, all subjects had treated SAH and good neurological outcome	7 mo	-	21	NR	Attrition, sampling bias

SAH, subarachnoid hemorrhage; SD, standard deviation; NR, not reported; MADRS, Montgomery Åsberg Depression Rating Scale; BDI, Beck Depression Inventory; CESD, Center for Epidemiologic Studies Depression; HADS, Hospital Anxiety Depression Scale; MRI, magnetic resonance imaging; ZDS, Zung Depression Scale; GDS, Geriatric Depression Scale.

found no change in depressive symptoms between the first assessment at 3, 6, or 9 months and subsequent follow-up(s) at 6, 9 months, 1, 1.5, 2, or 4 years after SAH.[18,19,23,25,29]

In a cross-sectional study, the proportion of patients with depression was not statistically different from patients 2 to 5, 5 to 10, and even more than 10 years after SAH, with 8.3%, 10.7%, and 8.6%, respectively.[37] The weighted frequency of depression was 33% up to a year after SAH and 28% a year or more after.[51,53] There was no relationship between length of follow-up and the severity of depressive symptoms at 39

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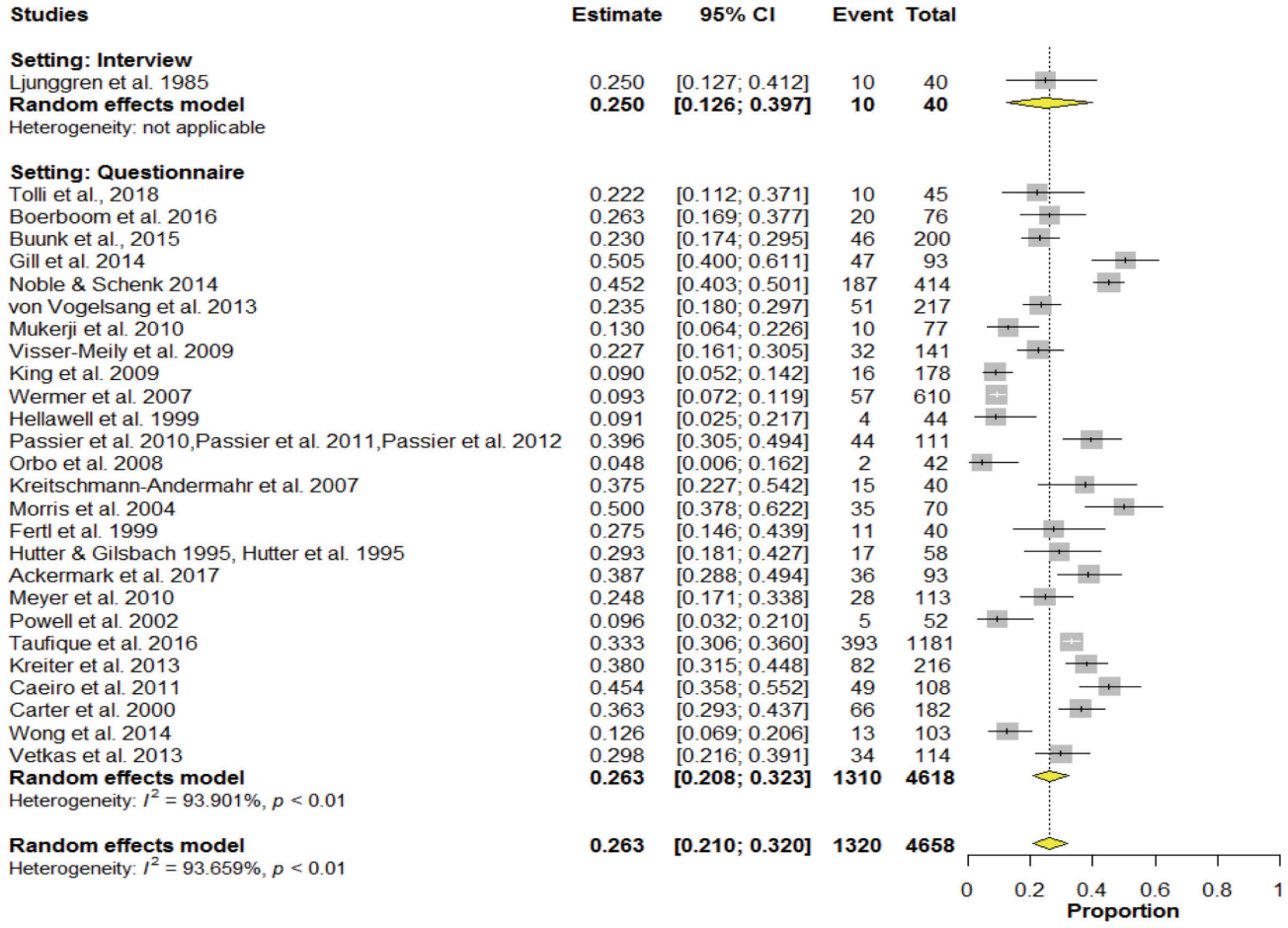

Figure 2. Meta-analysis of frequency of depression. CI, confidence interval.

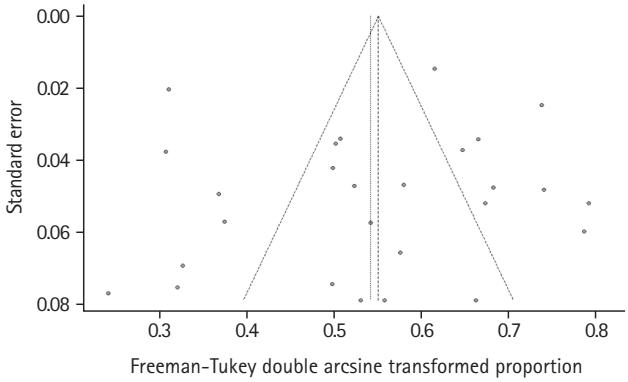

Figure 3. Funnel plot of included studies.

months after SAH in one study.[67]

Association between demographic factors, baseline characteristics of SAH, and depression

Demographic characteristics

Two studies explored the association between age and depression after SAH, all with negative findings.[20,40] One study reported a significant correlation between female sex and depression.[54] The association between sex and depression was not significant in the other three studies (n=314).[34,46] One study found no association between depression and educational level.[65] Another study reported that non-white ethnicity predicted depression (Table 3).[53]

Premorbid conditions

Three studies (n=411) examined the role of history of depression prior to SAH. Associations were found between depression and previous mood disorders;[54] lifetime history of major depression, or of anxiety or substance use disorder,[62] and self-reported history of depression.[53] One study reported that passive coping predicted post-SAH depressive symptoms (Table 3).[41]

Other premorbid conditions were examined in three studies. One found that depression was associated with lifetime psychiatric comorbidity.[62] The second reported that non-fluency in English and nicotine use predicted depression.[53] The third study observed a borderline association between depression and absence of pre-SAH dementia (Table 3).[54]

Table 3. Studies of associations between clinical features and complications of subarachnoid hemorrhage, comorbidities, biomarkers, and depression

Study	Risk factors	Associations with depression	Confounders controlled using multivariate analysis
Demographic characteristics			
Hütter et al. (1995)[20]	Age	No association	No
Morris et al. (2004)[40]	Age	No association	No
Caeiro et al. (2011)[54]	Sex	Female sex (P=0.003)	No
Preiss et al. (2007)[46]	Sex	No association	No
von Vogelsang et al. (2013)[34]	Sex	No association	No
Kreiter et al. (2013)[53]	Ethnicity	Non-white ethnicity, (OR, 2.7; 95% CI, 1.4–5.4; P=0.005); non-fluency in English (OR, 3.7; 95% CI, 1.7–8.2; P=0.001)	No
Brand et al. (2015)[65]	Education	No association	No
Premorbid conditions			
Caeiro et al. (2011)[54]	Psychiatric history	Past mood disorder (P=0.007), absence of pre-SAH dementia (P=0.05)	No
Kreiter et al. (2013)[53]	Psychiatric history	History of depression (OR, 3.1; 95% CI, 1.2–7.6; P=0.016)	Yes
Hedlund et al. (2011)[62]	Psychiatric history	Lifetime affective disorder (OR, 11.9; 95% CI, 3.0–46, P=0.001), anxiety disorder (OR, 6.5; 95% CI, 1.6–26; P=0.008), substance use disorder (OR, 9.8; 95% CI, 1.5–66; P=0.019), or any psychiatric disorders (OR, 14.1; 95% CI, 3.0–47; P=0.001)	Yes
Kreiter et al. (2013)[53]	Psychiatric history	Nicotine use (OR, 2.4; 95% CI, 1.3–4.5; P=0.006)	Yes
Ackermark et al. (2017)[41]	Premorbid personality traits	Passive coping was correlated with depressive symptoms (ρ=0.576, P<0.001).	Yes
Clinical features and complications of SAH			
Hütter et al. (1995)[20,21]	Neurological outcomes	No association	No
Morris et al. (2004)[40]	Neurological outcomes	No association	No
Bründl et al. (2018)[58]	subtypes of SAH	Depression symptoms were more common in aneurysmal SAH patients treated with microsurgury and endovascular aneurysm occlusion than those with perimensencephalic SAH (P=0.035 and P=0.016 respectively).	No
Boerboom et al. (2014)[22]	subtypes of SAH	Aneurysmal SAH patients had a higher mean CESD score (13.9±8.7 vs. 5.0±4.9, P=0.006) and higher rate of depression (44.4% vs. 0%, P=0.035) than perimensencephalic SAH.	No
von Vogelsang et al. (2013)[34]	Location of aneurysms	Rupture of posterior circulation aneurysms, compared to anterior circulation aneurysums, was related to a higher level of depression (P=0.036).	No
Hütter et al. (1995)[20]	subtypes of SAH	No association	No
Kreiter et al. (2013)[53]	Infarctions	SAH-related infarction predicted depression (OR, 2.1; 95% CI, 1.1–4.0; P=0.026).	Yes
Hütter et al. (1995)[21]	Infarctions	Parietal and/or frontal infarcts were negatively correlated with depression (n=58; F=5.03, t=2.57, P=0.03).	No
Bellebaum et al. (2004)[49]	SAH treatment	Patients treated with clips had more depressive symptoms than those treated with coils (U=73.50; P=0.039).	No
Preiss et al. (2007)[46]	SAH treatment	No difference between clips and coils	No
Fontanella et al. (2003)[50]	SAH treatment	No difference between clips and coils	No
Latimer et al. (2013)[33]	SAH treatment	No difference between clips and coils	No
Comorbidities			
Boerboom et al. (2017)[27]	Cognitive function	Self-rated cognitive function (r=0.372) and memory function (r=–0.427)	No
Fertl et al. (1999)[51]	Cognitive function	Cognitive impairment (P<0.01)	No
Passier et al. (2010)[14]	Cognitive function	depressive symptoms predicted cognitive complaints (β=0.40, P<0.001)	Yes
Wong et al. (2012)[57]	Cognitive function	MoCA (Kendall's tau b coefficient 0.191; P=0.027) and MMSE (Kendall's tau b coefficient 0.198; P=0.024)	No
Brand et al. (2015)[65]	Cognitive function	No association	No
Tölli et al. (2018)[25]	Cognitive function	No association	No

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Table 3. Continued

Study	Risk factors	Associations with depression	Confounders controlled using multivariate analysis
Orbo et al. (2008)[45]	Cognitive function	No association	No
Ljunggren et al. (1985)[63]	Fatigue	Correlated with depressive symptoms (r=0.597)	No
Buunk et al. (2018)[26]	Fatigue	Correlated with depressive symptoms (r=0.58)	No
Hütter et al. (2014)[43]	Post-traumatic stress disorder	Severity of depression was correlated with scores on the IES avoidance and intrusion subscales (r=0.45 and r=0.52, respectively).	No
Gill et al. (2015)[31]	Post-traumatic stress disorder	Higher rate of depression predicted greater symptoms of post-traumatic stress disorder (β=0.38, t=5.74, *P*<0.001).	Yes
Boerboom et al. (2017)[27]	Physical comorbidity	Correlated with depressive symptoms (r=0.419)	No
Functioning			
Ackermark et al. (2017)[41]	Disability	Correlated with depressive symptoms (ρ=−0.343, *P*=0.001)	Yes
Fertl et al. (1999)[51]	Reduced working capacity	Depression was more frequent in patients with reduced working capacity (*P*<0.001).	No
Biomarkers			
Colledge et al. (2017)[13]	Hair cortisol level	Correlated with depressive symptoms (r=0.56)	No
Kreitschmann-Andermahr et al. (2007)[47]	Basal cortisol value	Correlated with (r=−0.56, *P*<0.01) and predicted depression (R^2=0.30)	Yes
Alfieri et al. (2008)[17]	APOE-ε4	Correlated with depressive symptoms (*P*<0.05)	No

OR, odds ratio; SAH, subarachnoid hemorrhage; CESD, Center for Epidemiologic Studies Depression; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; IES, Impact of Event Scale; APOE-ε4, apolipoprotein E ε4.

Association between clinical features and complications of SAH, comorbidities, biomarkers, and depression

Clinical features and complications of SAH

Two studies (n=128) examined the relationship between neurological outcomes and depression, with negative results (Table 3).[20,40]

Three studies (n=124) compared subtypes of SAH with respect to depression. Depressive symptoms were more common in patients with aneurysmal SAH treated by endovascular treatment or microsurgical clipping than in patients with perimesencephalic SAH.[58] Similarly, aneurysmal SAH patients had a higher mean CESD score and higher rate of depression than their perimensencephalic counterparts in a cohort study.[22] No difference in depressive symptoms between aneurysm versus other bleeding source was observed in a third study (Table 3).[20]

Two studies (n=274) examined the effect of infarction on the frequency of depression following SAH. SAH-related infarction predicted depression.[53] Parietal and/or frontal infarcts were negatively correlated with depression (Table 3).[20]

Four studies (n=167) investigated the effect of SAH treatment. Patients treated with clips had more depressive symptoms than those treated with coils.[49] The other three studies (n=135) reported no difference in depressive symptom scores between patients who were treated by surgical clipping and by endovascular coiling.[33,46,50] One study reported no significant association between measures of depression scores and time from admission until surgery.[40] In a second study, rupture of posterior circulation aneurysms was related to a higher level of depression (Table 3).[34]

Comorbidities

Seven studies (n=399) examined the impact of cognitive function on post-SAH depression. Two studies reported an association between depressive symptoms and objective and self-rated cognitive function and memory function.[27,57] Another study found depression to be more frequent in cognitively impaired patients.[51] In the fourth study, depressive symptoms were significant determinants of cognitive complaints.[14] In contrast, three studies found no association between depressive symptoms and cognitive performance or impairment.[25,45,65] Two studies explored the role of fatigue in post-SAH depression. Both reported a positive correlation between depressive symptoms and fatigue (Table 3).[13,63]

Other comorbid conditions were examined in five studies. Severity of depression was correlated with symptoms of post-traumatic stress disorder in two studies.[31,43] A third study found an association between depressive symptoms and overall physical comorbidity.[27] In the fourth study, disability predicted de-

Table 4. Summary of studies reporting impact of depression after subarachnoid hemorrhage on patients' lives

Study	Outcomes	Associations with outcomes	Confounders adjusted for
Work			
Buunk et al. (2015)[30]	Unemployment	Unemployed patients had higher level of depression (HADS-D score: 4.98±4.57 vs. 3.01±3.41, *P*<0.05).	None
Hedlund et al. (2011)[62]	Unemployment	Patients with a lifetime history of depression has higher rate of unemployment (χ^2=5.5, *P*=0.019).	None
Boerboom et al. (2016)[24]	Unemployment	Depression predicted unemployment (OR, 1.126; 95% CI, 1.01–1.25; *P*=0.031)	Age, gender, cognitive function
Carter et al. (2000)[61]	Unemployment	Depression predicted unemployment (OR, 10.5; 95% CI, 3.3–33.7; *P*<0.001)	Age, physical disability, neurological deficits
Fertl et al. (1999)[51]	Reduced work capacity	Depression was more common amongst patients with reduced work capacity (*P*<0.001).	None
HRQOL and related outcomes			
Passier et al. (2012)[16]	HRQOL	Depressive symptoms did not predict HRQOL.	Gender, education level, aneurysm location, discharge destination, cognitive function, level of impairment
Taufique et al. (2016)[52]	HRQOL	Depression predicted poor HRQOL (OR, 2.3; 95% CI, 1.7–7.3; *P*=0.02).	Age, ethnicity, education level, history of anxiety, neurological assessments, dmission CT scan grading, complications
Vetkas et al. (2013)[59]	HRQOL	Depressive symptoms were related to lower mental health component score of HRQOL (β=−8.8, SE=1.6, *P*<0.05).	Anxiety, agoraphobia-panic, fatigue and insomnia symptoms
Meyer et al. (2010)[44]	HRQOL	Depression predicted poor HRQOL (β=−1.80, 95% CI, −4.01 to −0.06, *P*=0.03).	Gender, marital status, education, clinical status on admission, functional disability
King et al. (2009)[37]	HRQOL	Depressive symptoms was correlated with lower HRQOL (ρ=−0.52, *P*<0.001).	Disability, anxiety symptoms
Brand et al. (2015)[65]	HRQOL	No association	None
Fertl et al. (1999)[51]	Satisfaction in life	Depressive symptoms was correlated with lower satisfaction in life (r=−0.46, *P*<0.01).	None
Functional outcomes			
Wong et al. (2013)[56]	Functional outcomes	Depression predicted unfavorable outcome (OR, 1.24; 95% CI, 1.1–1.3; *P*<0.001).	Cognitive deficits, neurological deficits
Buunk et al. (2018)[26]	Functional outcomes	No association	Fatigue and anxiety symptoms
Hütter et al. (1995)[20]	Functional impairment in daily life	Depression was correlated with functional impairment in daily life (r=0.63, *P*<0.001).	None
Other outcomes			
Buunk et al. (2015)[30]	Leisure and social activities	HADS-D score correlated with problems in leisure (r=0.45, *P*<0.01) and social (r=0.51, *P*<0.01) activities.	None
Carter et al. (2000)[61]	Reintegration to normal living	Depression predicted reintegration to normal living (OR, 15.2; 95% CI, 6.4–36.2; *P*<0.001).	Age, physical disability, neurological deficits
Passier et al. (2011)[15]	Fatigue	Depressive symptoms predicted severity of fatigue (F=4.10, *P*=0.046).	Level of impairment

HADS-D, Hospital Anxiety Depression Scale-depression subscale; OR, odd ratio; HRQOL, health-related quality of life; CT, computed tomography; SE, standard error.

pressive symptoms.[41] Depression was more frequent in patients with reduced working capacity in the fifth study (Table 3).[51]

Biological markers

Three studies (n=93) assessed the relationship between biological markers and depression following SAH. One reported an association between hair cortisol level and depressive symptoms.[13] Another found that depression was correlated with basal cortisol value, which also predicted depression.[47] The third study found a positive correlation between apolipoprotein E ε4 (APOE-ε4) levels and depressive symptoms (Table 3).[17]

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Impact of depression after SAH on patients' lives

Five studies (n=685) examined the impact of depression on work-related issues. Two studies reported that depression or depressive symptoms were more frequent in patients who were unemployed or with reduced working capacity.[30,51] Lifetime history of major depression and/or post-traumatic stress disorder reduced the likelihood of returning to gainful employment.[62] Two studies concluded that depression or depressive symptoms predicted unemployment (Table 4).[24,61]

Seven studies (n=1,642) looked at health-related quality of life (HRQOL) or life satisfaction. Two studies found a negative association between depressive symptoms and HRQOL or satisfaction with life.[16,51] Four studies found that depression and depressive symptoms predicted poor overall HRQOL or the mental health component of HRQOL.[37,44,52,59] One small-scale study reported no association between depression scores and quality of life (Table 4).[65]

Three studies (n=399) explored how depression influenced functional outcomes. Depression was correlated with self-rated functional impairment in daily life and with the impact of these impairments.[20] Depression predicted poor functional outcomes a year after SAH,[56] but this was not confirmed 3 to 10 years after SAH (Table 4).[26]

Other outcomes were assessed in three studies (n=489). Associations were found between depression and problems with leisure and social activities,[30] failure to resume previous level of daily life,[61] and fatigue (Table 4).[15]

Discussion

To the best of our knowledge, this was the first systematic review of depression after SAH. The weighted frequency of depression following SAH was 28.1%. The severity of depressive symptoms was mild to moderate. Depression after SAH seems to run a chronic course and its frequency does not decrease with time. A host of demographic variables, premorbid and comorbid conditions, as well as clinical features and complications of SAH are related to the risk of depression. Depression has negative impacts on the daily lives of patients with SAH.

The weighted frequency of depression of 28% is similar to the frequency of depression after stroke in general (31%).[68] The frequency of depression in the included studies varied greatly, probably due to differences in the methods of assessment, patients' characteristics, and timing of the assessment. The variation in results was more prominent in studies that used questionnaires (0% to 62%) than in those that used interviews to detect depression (20% to 25%) (Tables 2 and 4).

Interviews give a clinical diagnosis whereas questionnaires will assess depressive symptomatology rather than clinical depression. Also, the number of interview studies was considerably smaller.

Longitudinal studies confirmed that depression and depressive symptoms in the later stages of SAH were at least as frequent and severe as in the early stage. Depressive symptoms persisted for long periods after SAH in 72% of patients.[41] Depression after stroke in general is also a chronic condition, with a prevalence and incidence of around 30% and 15% at 1 to 15 years post-stroke.[69]

The development of depression after SAH is associated with a variety of factors. The studies included in this review found relationships between depression and female sex, premorbid depression, anxiety, substance use, any psychiatric disorder, and coping styles. Comorbid cognitive impairment, fatigue, post-traumatic stress disorder, and physical disability also increased the risk of depression. The role of the features and complications of SAH in the development of depression was rarely explored, one study suggested that aneurysmal SAH and infarction may be related to depression. The findings on the impact of neurological deficits and treatment modalities for aneurysm repair on depression were inconclusive. Most of the above risk factors have also been found to be related to depression in stroke in general.[70] Further research on psychosocial factors such as pre-stroke life events and the quality of family and social support are warranted.[70]

Pituitary dysfunction may occur in up to one in three patients after SAH[71] and could contribute to the development of depression.[72] In support of this theory, an association between low basal cortisol levels and depression has been reported in patients after SAH.[47] One small-scale study reported a possible link between the APOE-ε4 allele and depression.[17] Interestingly, hypercortisolemia, blunted cortisol awakening response,[73] and APOE polymorphisms[74] increase the risk of post-stroke depression.

Post-SAH depression was significantly related to functional impairment, unemployment[75] or reduced working capacity, and poor HRQOL. Data on the impact of depression on the costs of hospitalization and mortality related to SAH are lacking.[70]

In terms of treatment of post-SAH depression, only one small-scale, open label trial of mindfulness-based psychotherapy has been published. Proper randomized control trials with antidepressants and other treatment modalities are clearly needed. Antidepressants seem to be commonly prescribed in patents with SAH, in a population-based cohort of 940 patients with SAH, 27% had continuous antidepressant use.[76] On the other hand, the use of selective serotonin reuptake inhibitors, a commonly prescribed antidepressant, in general population was associated with increased risk of intracranial hemorrhage, particularly in the first 30 days of use and when used currently

with anticoagulants.[77] Antidepressants are effective in the treatment[78] and prevention of post-stroke depression,[79] and non-pharmacological treatment modalities including ecosystem-focused therapy, life review therapy, problem solving therapy, meridian acupressure, transcranial magnetic stimulation, music therapy, exercise, light therapy, motivational interviewing, and robotic-assisted neurorehabilitation could also be trialed.[80]

This systematic review has several methodological strengths. An extensive search strategy was used so it is unlikely that relevant studies were missed. Two authors extracted pre-specified data independently, thus reducing the chance that any errors in data extraction would have gone undetected. A major limitation is the inclusion only of studies published in English.

There were several methodological shortcomings in the included studies that weakened the robustness of the review. First, the study design was heterogeneous, including longitudinal,[27] cross-sectional,[26] or retrospective[32] single site cohorts. Second, while most studies recruited hospitalized[26] subjects, some employed clinic,[33,38,42] population,[60] or support group[30,31] based sampling. Third, a number of studies involved bias sample, such as particular location,[32,54,81] investigation[3] or treatment received,[11,37,45] or neurological outcome[65,82] of SAH. Fourth, many studies had small sample size. Fifth, the timing of mood assessment various varied from acute[53,55] to chronic stage[33] of SAH recovery. In addition, most of them assessed depression only once; in cross-sectional studies, subjects were assessed at different time point following SAH. Sixth, most studies used scales to measure depression, whereas some employed, a single question,[83] or clinical interview.[61,62] Seventh, some authors described the baseline characteristics of SAH but did not relate them to the presence or severity of depression. Eighth, the majority of studies did not measure and adjust for potential confounders, such as personality, level of social support, recent life events, or previous depression with multivariate analysis. Future studies should consider prospective multi-center design, careful and non-selective sampling method, large sample size, assessment of depression at multiple time points with structural psychiatric interview, and detailed measurement and analysis of demographic and clinical characteristics and other possible confounding factors.

Implication for clinicians

Clinicians involved in the long-term care of SAH survivors need to be aware that post-SAH depression is common, runs a chronic course, and has a negative impact on patients' lives. Clinicians should routinely ask about depression when they review SAH patients and they should refer patients with suspected depression for psychological and/or psychiatric evaluation and treatment.

Directions for future research

More longitudinal studies are needed to determine the time course of depression after SAH using standardized diagnostic interviews. More studies assessing the relationship between depression and demographics, premorbid and comorbid conditions and complications of SAH are required to elucidate the relationship between depression and the consequences of SAH. Research on the association between depression and pituitary dysfunction, changes in neurotransmitter metabolism, and disruption of brain circuits after SAH is also warranted to clarify the pathogenesis of post-SAH depression. Finally, randomized controlled clinical trials on potential treatments for SAH-related depression are also needed.

Conclusions

Depression is common after SAH and seems to persist. The development of depression after SAH is associated with a variety of factors. Post-SAH depression had negative impacts on patients' daily life. Further research is needed to clarify its time course and identify the neuroendocrine and neurochemical factors and brain circuits associated with the development of post-SAH depression. Randomized controlled treatment trials targeting SAH-related depression are warranted.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2019.02103.

Disclosure

The authors have no financial conflicts of interest.

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Supplementary Table 1. Quality assessment of studies

Study	Introduction			Methods									Results					Discussion				Other information	Total
	Title and abstract	Background	Objectives	Study design	Setting	Participants	Variables	Data sources/ Measurement	Bias	Study size	Quantitative variables	Statistical methods	Participants	Descriptive data	Outcome data	Main results	Other analyses	Key results	Limitations	Interpretation	Generalisability	Funding	
Passier et al. (2011)[15]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	0	18
Passier et al. (2010)[14]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	0	19
Gerber et al. (2016)[42]	1	1	1	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	19
Ackermark et al. (2017)[41]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	21
Colledge et al. (2017) [13]	1	1	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	19
Colledge et al. (2017) [12]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	21
Hellawell et al. (1999)[39]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	0	1	16
Wermer et al. (2007)[38]	1	1	1	0	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	20
King et al. (2009)[37]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	20
Visser-Meily et al. (2009)[36]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	20
Mukerji et al. (2010)[35]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	21
von Vogelsang et al. (2013)[34]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	20
Latimer et al. (2013)[33]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	19
Noble et al. (2014)[32]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	20
Buunk et al. (2015)[30]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	20
von Vogelsang et al. (2015)[29]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	21

Supplementary Table 1. Continued

Study	Title and abstract	Introduction		Methods									Results					Discussion				Other information	Total
		Background	Objectives	Study design	Setting	Participants	Variables	Data sources/ Measurement	Bias	Study size	Quantitative variables	Statistical methods	Participants	Descriptive data	Outcome data	Main results	Other analyses	Key results	Limitations	Interpretation	Generalisability	Funding	
Boerboom et al. (2017)[27]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	20
Buunk et al. (2018)[26]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	18
Tölli et al. (2018)[25]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	21
Kreiter et al. (2013)[53]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	19
Boerboom et al. (2016)[24]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	1	19
Boerboom et al. (2016)[23]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	1	19
Boerboom et al. (2014)[22]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	1	18
Taufique et al. (2016)[52]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	19
Hütter et al. (1995)[21]	1	1	1	0	0	1	1	1	0	0	1	0	1	1	1	1	1	0	0	1	1	0	14
Hütter et al. (1995)[20]	1	1	1	0	0	1	1	1	0	0	1	0	1	1	1	1	0	0	1	1	1	0	14
Fertl et al. (1999)[51]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	0	0	0	17
Powell et al. (2004)[19]	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	0	1	17
Powell et al. (2002)[18]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	0	0	1	19
Fontanella et al. (2003)[50]	1	1	1	0	1	1	1	1	0	0	1	1	1	1	1	1	0	1	0	0	0	0	15
Morris et al. (2004)[40]	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	1	1	1	17
Bellebaum et al. (2004)[49]	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	0	0	16

Supplementary Table 1. Continued

Study	Title and abstract	Introduction		Methods									Results					Discussion				Other information	Total
		Background	Objectives	Study design	Setting	Participants	Variables	Data sources/ Measurement	Bias	Study size	Quantitative variables	Statistical methods	Participants	Descriptive data	Outcome data	Main results	Other analyses	Key results	Limitations	Interpretation	Generalisability	Funding	
Kreitschmann-Andermahr et al. (2007)[47]	1	1	1	0	0	1	1	1	0	0	1	1	1	1	1	1	0	1	1	0	0	1	16
Preiss et al. (2007)[46]	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	19
Orbo et al. (2008)[45]	1	1	1	0	0	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0	0	1	16
Alfieri et al. (2008)[17]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	19
Meyer et al. (2010)[44]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	20
Passier et al. (2012)[16]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	19
Wong et al. (2013)[56]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	19
Hütter et al. (2014)[43]	1	1	1	1	1	0	1	1	0	0	1	1	1	1	1	1	0	1	0	1	0	0	15
Salmond et al. (2006)[48]	1	1	1	0	0	0	1	1	0	0	1	1	1	1	1	1	0	1	1	1	1	1	16
Scherfler et al. (2016)[28]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	19
Wong et al. (2012)[57]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	20
Gill et al. (2015)[31]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	0	17
Ljunggren et al. (1985)[63]	1	1	1	1	0	1	1	1	0	0	0	0	1	1	1	1	0	1	0	1	0	1	14
Hedlund et al. (2011)[62]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	20
Vetkas et al. (2013)[59]	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	0	1	17

Supplementary Table 1. Continued

Study	Title and abstract	Introduction		Methods									Results					Discussion				Other information	Total
		Background	Objectives	Study design	Setting	Participants	Variables	Data sources/ Measurement	Bias	Study size	Quantitative variables	Statistical methods	Participants	Descriptive data	Outcome data	Main results	Other analyses	Key results	Limitations	Interpretation	Generalisability	Funding	
Wong et al. (2014)[3]	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	1	1	19
Brand et al. (2015)[65]	1	1	1	0	0	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	18
Pačić-Turk et al. (2016)[64]	1	1	1	0	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	0	0	16
Kronvall et al. (2016)[60]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	1	0	1	0	1	0	0	15
Bründl et al. (2018)[58]	1	1	1	0	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	1	0	17
Carter et al. (2000)[61]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	1	0	17
Haug et al. (2009)[55]	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	0	1	1	1	0	1	18
Caeiro et al. (2011)[54]	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	19

Each item was scored 1, maximum score for the quality assessment tool was 22 points.

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Supplementary Table 2. Severity of depression after subarachnoid hemorrhage

Study	Timing after SAH	Measurement	Depressive symptom scores (mean±SD)
Studies using BDI			
Alfieri et al. (2008)[17]	On admission (T1) 1 mo (T2) 1 yr (T3) 3 yr (T4) 5 yr (T5)	BDI	T1: 17.1±6.5 T2: 22.1±3.6 T3: 19.9±4.8 T4: 14.3±3.8 T5: 13.2±3.8
Passier et al. (2010)[14], Passier et al. (2011)[15], and Passier et al. (2012)[16]	3 mo	BDI	9.6±6.9
Powell et al. (2002)[18] and Powell et al. (2004)[19]	3 mo (T1) 9 mo (T2) 18 mo (T3)	BDI	T1: 9.6±6.2 T2: 9.2±6.9 T3: 9.4±7.3
Ackermark et al. (2017)[41]	3 mo (T1) 1 yr (T2) 2–5 yr (T3)	BDI	T1: 8.9±7.0 T2: 9.3±7.1 T3: 11.2±8.0
Fontanella et al. (2003)[50]	6 mo	BDI	13.8 (SD NR)
Orbo et al. (2008)[45]	1 yr	BDI	6 (SD NR)
Preiss et al. (2007)[46]	1 yr	BDI	9.4
Kreitschmann-Andermahr et al. (2007)[47]	Average 27.3 mo (range, 12–66)	BDI	8.33±5.85
Colledge et al. (2017)[12,13] and Gerber et al. (2016)[42]	44 mo	BDI	8.9±6.6
Salmond et al. 2006[48]	Average 68 mo (range, 14–99)	BDI	6.5±1.4
Studies using HADS			
von Vogelsang et al. (2015)[29]	6 mo (T1) 1 yr (T2) 2 yr (T3)	HADS	T1: 5.0 T2: 4.0 T3: 5.0 (median)
Scherfler et al. (2016)[28]	1 yr	HADS	1 (median)
Visser-Meily et al. (2009)[36]	Average 3 yr (range, 2–4)	HADS	4.8±3.9
Latimer et al. (2013)[33]	40–45 mo	HADS	6.7
Buunk et al., 2015[30]	Average 4.6 yr (range, 2–10)	HADS	4.2±4.3
Boerboom et al. (2017)[27]	Average 4.7 yr (range, NR)	HADS	3.5 (SD NR)
Wermer et al. (2007)[38]	Average 8.9 yr (range, 2.3–18.8)	HADS	6.2±3.1
von Vogelsang et al. (2013)[34]	Average 10.1 yr (range, 8.8–12)	HADS	4.0 (median)
King et al. (2009)[37]	NR	HADS	4.8±3.4
Studies using other scales			
Boerboom et al. (2014)[22] and Boerboom et al. (2016)[23,24]	0.4 yr (T1) 3.9 yr (T2)	CESD	T1: 13.7±1.2 T2: 11.9±1.2
Caeiro et al. (2011)[54]	≤4 day	MADRS	9.2±7.3
Haug et al. (2009)[55]	1 yr	MADRS	5.5 (SD NR)
Wong et al. (2012)[57]	3 mo	GDS	7 (median)
Vetkas et al. (2013)[59]	Average 4.5 yr (range, 1–10)	GDS	8.4±6.9
Carter et al. (2000)[61]	Average NR (range, 1–5 yr)	ZDS	45.6 (SD NR)
Brand et al. (2015)[65]	5–9 mo	Depression Skala	1.42±0.29
Pačić-Turk et al. (2016)[64]	11 mo (T1) 12–48 mo (T2)	Cornell personality questionnaire	T1: 1.93 T2: 2.65
Kronvall et al. (2016)[60]	3–6 mo (T1) 6–12 mo (T2) 12–24 mo (T3)	Psychological General Well-Being	T1: 15.0±3.5 T2: 15.3± 2.9 T3: 15.8±2.9

SAH, subarachnoid hemorrhage; SD, standard deviation; BDI, Beck Depression Inventory; NR, not reported; HADS, Hospital Anxiety Depression Scale; CESD, Center for Epidemiologic Studies Depression; MADRS, Montgomery Åsberg Depression Rating Scale; GDS, Geriatric Depression Scale; ZDS, Zung Depression Scale.

Supplementary Table 3. Time course of depression after subarachnoid hemorrhage

Study	Timing after SAH	Findings
Meyer et al. (2010)[44]	Upon discharge, 6 and 12 mo	The proportion of patients with depressive symptoms (BDI >9) increased from 24.8% at discharge to 61.7% at the 12-mo follow-up (P<0.001).
Pačić-Turk et al. (2016)[64]	11 mo and 12–48 mo	Depressive symptom score increased with time (t=–2.417, P=0.019).
Ackermark et al. (2017)[41]	3 mo, 1 yr, 2–5 yr	Of patients with depressive symptoms at 3 mo, 72% still had symptoms at 2–5 yr.
Tölli et al. (2018)[25]	3, 6, and 12 mo	No difference in HADS depression scores between 3, 6, 12 mo follow-up
Boerboom e al. (2016)[24]	0.4 and 3.9 yr	Depressive symptoms remained relative stable over time.
Powell et al. (2002)[18] and Powell et al. (2004)[19]	3, 8 and 18 mo	No change in depressive symptoms from 3–9 mo, and from 9–18 mo
von Vogelsang et al. (2015)[29]	6 mo, 1 and 2 yr	No significant change in depressive symptoms during the 2-year observation period

SAH, subarachnoid hemorrhage; BDI, Beck Depression Inventory; HADS, Hospital Anxiety Depression Scale.

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