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REVIEW

A meta-analysis of poststroke depression risk factors comparing depressive-related factors versus others

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ABSTRACT

Objectives: Poststroke depression (PSD) is a public health issue, affecting one-third of stroke survivors, and is associated with multiple negative consequences. Reviews tried to identify PSD risk factors with discrepant results, highlighting the lack of comparability of the analyzed studies. We carried out a meta-analysis in order to identify clinical risk factors that can predict PSD.

Design: PubMed and Web of Science were searched for papers. Only papers with a strictly defined Diagnostic and Statistical Manual of Mental Disorders depression assessment, at least 2 weeks after stroke, were selected. Two authors independently evaluated potentially eligible studies that were identified by our search and independently extracted data using standardized spreadsheets. Analyses were performed using MetaWin®, the role of each variable being given as a risk ratio (RR).

Results: Eighteen studies were included in the meta-analysis. Identified risk factors for PSD with RR significantly above 1 were previous history of depression (RR 2.19, confidence interval (CI) 1.52–3.15), disability (RR 2.00, CI 1.58–2.52), previous history of stroke (RR 1.68, CI 1.06–2.66), aphasia (RR 1.47, CI 1.13–1.91), and female gender (RR 1.35, CI 1.14–1.61). Fixed effects model leads to identification of two more risk factors: early depressive symptoms with an RR of 2.32 (CI 1.43–3.79) and tobacco consumption (RR 1.40, CI 1.09–1.81). Time bias was found for alcohol consumption. Sample size was significantly involved to explain the role of "alcohol consumption" and "cognitive impairment."

Conclusion: Five items were significantly predictive of PSD. It might be of clinical interest that depressive-related risk factors (such as past depressive episodes) were having the largest impact.

Key words: meta-analysis, stroke, post-stroke depression, depression, risk factors

Introduction

In developed countries, strokes are the third leading cause of death, after cardiovascular diseases and cancers according to World Health Organization data. In France, strokes are the first leading cause of acquired disability in adults according to INSERM data, leading to more quality of life issues when compared to myocardial infarction, another vascular disease. Poststroke depression (PSD) is also a public health issue, affecting one-third of stroke survivors, and is associated with multiple negative consequences such as higher mortality (Robinson and Jorge, 2016) and a poorer functional recovery. The recent "Stroke early management guideline" from the American Heart Association/American Stroke Association briefly mentioned PSD. There are nevertheless no specific and precise recommendation on optimal timing, standardized tool of screening, diagnosis, and specific treatment.

An extensive literature is available on this topic, and several reviews tried to identify PSD risk factors. The results are however contradictory and often highlight the lack of comparability in the performed studies. For example, Robinson and Jorge (2016) carried out several reviews showing results with an important variability. Gender is not a PSD risk factor in 13/21 studies, and heterogeneity of social support

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assessment does not allow to draw conclusion. The use of different procedures and instruments to assess depression in these studies is a frequently quoted detrimental issue (Robinson and Jorge, 2016). Depression is barely assessed with a face-to-face clinical interview using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria of depression but usually relies on different depression scales initially developed to assess depression intensity and not as a diagnostic tool. Moreover, even when studies are relying on the same instrument, different thresholds may have been used (Hackett and Pickles, 2014; Robinson and Jorge, 2016). The choice of DSM criteria as the best to assess PSD could be criticized: DSM criteria are specifically developed for research purpose and are used to validate many depression scales to diagnose PSD (Sagen *et al.*, 2009). It is difficult to affirm which assessment between DSM and depression scales is most relevant and valid, but DSM is universally acknowledged as the Gold Standard, and it seems essential to use a homogenous method. Besides, assessment issues due to aphasia do not differ between DSM-based interview and depression scales. To our knowledge, there are few meta-analyses evaluating PSD prevalence and its evolution (Hackett and Pickles, 2014). Shi *et al.* (2017) examine risk factors for PSD but do not use strictly DSM criteria for depression assessment, which seems an important issue. Furthermore, some risk factors like early depressive symptoms, pain, cognitive impairment, aphasia, and lesion location are not considered in this study. Ojagbemi *et al.* (2017) do not use strictly DSM depression assessment and focused on Sub-Saharan Africa population. For those reasons, and to overcome the significant difficulty of previous papers comparability, we propose a meta-analysis in order to identify and rank clinical risk factors of PSD, in order to help clinicians in the prevention of PSD. Only papers using a strictly defined depressive episode according to DSM criteria, assessed at least 2 weeks after stroke, were selected.

Methods

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. The study protocol was predefined but was not registered.

Search strategy

PubMed (MEDLINE) and Web of Science were searched in March 2017 for papers, using the keywords "post-stroke depression," "poststroke depression," and "risk factors." The exact request was ((poststroke depression) OR (post-stroke depression)) AND (risk factors). Two reviewers (L.M. and R.P.) independently evaluated potentially eligible studies that were identified by our search. Papers were screened for eligibility based on a review of the title and abstract only. We searched for papers published in English or French between January 2005 and March 2017. References of each study were screened to identify supplementary papers.

Inclusion and exclusion criteria

Eligibility criteria accorded with the PICOS (participants, interventions, controls, outcomes, and studies) framework, as follows:

Participants: Participants were human adults, who have been hospitalized for an ischemic or hemorrhagic stroke, and not transient attack or lacunar infarcts.

Interventions: The intervention variable was defined as clinical risk factors and not only as biological or genetic risk factors for PSD.

Controls: The comparison groups consisted of participants with stroke but without depression.

Outcomes: The outcome is depression. The assessment of depression had to be performed based on DSM criteria, at least 2 weeks after stroke.

Studies: The study design was prospective cohort study, retrospective study, cross-sectional study, or case–control study.

We aimed to collect all clinical risk factors that authors assessed. When a risk factor was assessed in at least two studies, we conducted a meta-analysis: after data extraction, 13 variables were identified. Some risk factors could not be evaluated because of a lack of raw data: level of education, socioeconomic status, previous history of anxiety disorder, stressful life event, personality disorder, and previous family history of depression.

Data extraction

Two investigators (D.C. and R.P.) independently extracted data (information of the studies and baseline characteristics) and entered them into standardized spreadsheets. Data were finally collected for 13 variables: gender, social support, marital status, previous history of depression, early depressive symptoms, cognitive impairment, previous history of stroke, disability, aphasia, lesion side, pain, alcohol consumption, and tobacco consumption.

Statistical analysis

Analyses were performed using MetaWin®: Statistical Software for Meta-Analysis (Version 2; Sinauer Associates, Sunderland, MA, USA) (Rosenberg *et al.*, 2000).

When a clinical or radiological risk factor for PSD was assessed in at least two different studies, we ran

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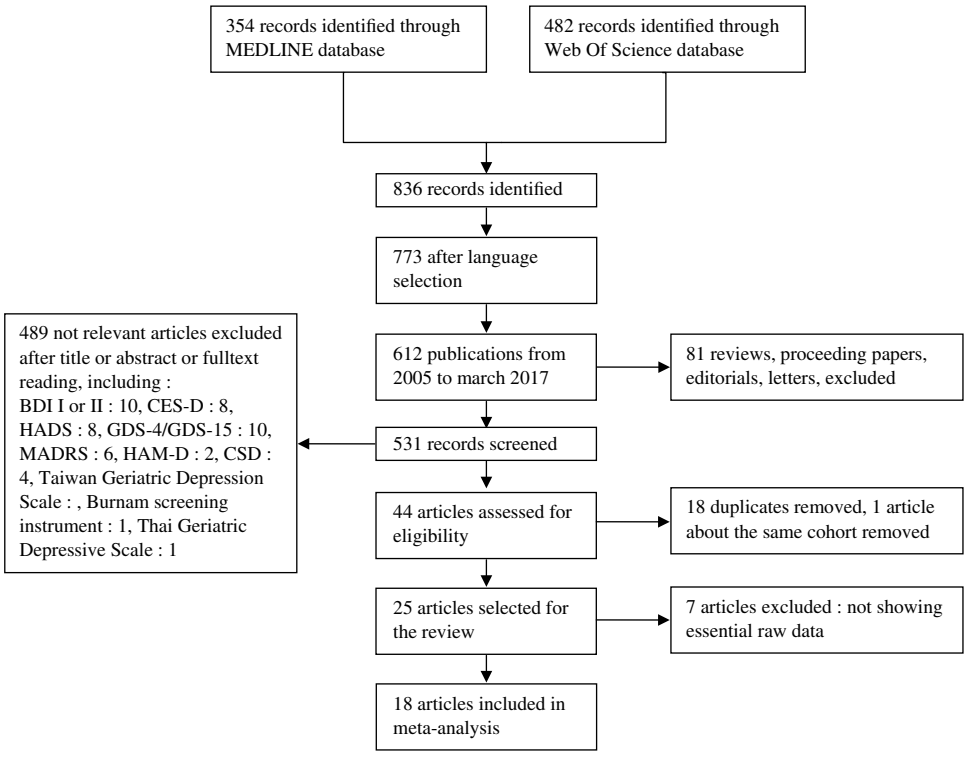

Figure 1. Flow chart for the meta-analysis. BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; GDS, Geriatric Depression Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; HAM-D, Hamilton Rating Scale for Depression; CSD, Cornell Scale for Depression.

meta-analyses. Relative rate was calculated for each study. As with most ratio metrics, the summary meta-analytic statistics are typically calculated for risk ratios (RRs): it is a measure of central tendency for a set of studies found as the weighted sum of effect sizes divided by the sum of the weights. We used a random effects model. However, the data were analyzed using a fixed effects model for "social support" and "marital status" because the estimate of the pooled variance was inferior or equal to zero.

Total heterogeneity was analyzed using chi square to measure the variation in RR for a set of studies, that is, inter-study heterogeneity.

Publication biases were detected in order to check if RR is independent from sample size, via the calculation of Spearman's rank correlation. The normal quantile plot was used considering the small number of studies. Time bias was investigated using nonparametric test (Spearman's ρ) to verify the absence of correlation between years of publication and RR, with IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Search results

A flow chart of the data search and study selection process is detailed in Figure 1. Three hundred and fifty-four papers were obtained with MEDLINE and four hundred and eighty-two with Web of Science. Papers reviewed were restricted to those in English or in French – that is, 773 papers – and to those available from 2005 to March 2017 – that is, 612 papers. Then, 81 reviews, proceeding papers, editorials, and letters were excluded. After this step, 489 irrelevant papers were removed after abstract or full-text reading. Forty-four papers were assessed for eligibility. Eighteen duplicates were removed. Two papers were related to the same cohort with the same features; the more recent was retained. Twenty-five papers were included in the review and selected for data extraction (Figure 1).

Twenty-two of the selected studies are prospective cohorts. One is a case–control study, another is a cross-sectional study, and the last is a medical files retrospective study. Among the selected papers, two refer to the same cohort but selection criteria, prevalence, and therefore results are not identical (Paolucci *et al.*, 2006; Provinciali *et al.*, 2008). For that reason, both papers have been maintained. After data extraction, seven papers were excluded not showing any essential raw data. Eighteen papers were finally included in the meta-analysis.

Time of depression assessment varies greatly between studies and sometimes in a same study as well: from 2 weeks to 6 months. Study characteristics are presented in Table 1.

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Table 1. Study characteristics

STUDY	DESIGN	*N*	STROKE TYPE	EXCLUSION/INCLUSION CRITERIA	EVALUATION TIME AFTER STROKE	PREVALENCE %
Volz *et al.* (2016), Germany	Prospective cohort study	88	First-ever ischemic stroke	*Inclusion*: first-ever ischemic stroke, formal education ≥ 8 years, sufficient comprehension (Token test > 12; fluent in German), age ≥ 40 years, <12 weeks deviation from planned 6 months interval of follow-up assessment	>4 weeks and 6 months	29.5
Vermeer *et al.* (2016), Canada	Medical files retrospective study	202	Ischemic and hemorrhagic	*Inclusion*: confirmed diagnosis of stroke, complete dataset for at least one consultation or follow-up visit *Exclusion*: Aphasia, first language different than English	1 month	36.0
Tsai *et al.* (2016), Taiwan	Prospective cohort study	91	Ischemic	*Inclusion*: first or recurrent ischemic stroke image-proven and occurred within the past 4 weeks *Exclusion*: TIA, impaired communication or cognitive function (MMSE < 15), history of depression, psychosis, or severe substance abuse, taking antidepressants within 2 weeks prior to the stroke, or possible concurrent depression	1, 3, 6, 9, and 12 months	11.0
Guiraud *et al.* (2016), France	Prospective cohort study	251	Ischemic	*Inclusion*: age ≥ 18, recent (<14 days) ischemic stroke confirmed by MRI or CT scan *Non-inclusion criteria:* unstable clinical status (altered consciousness), major psychiatric co-morbidities, ongoing depression at stroke onset, confirmed by psychiatric baseline evaluation, previously known moderate or severe dementia (MMSE ≤ 20), participation in another study testing antidepressants, uncertainty regarding compliance with follow-up	6 months	24.3
Gyagenda *et al.* (2015), Uganda	Cross-sectional study	73	Ischemic and hemorrhagic	*Inclusion*: age > 18 years, single episode of stroke confirmed by brain CT scan *Exclusion*: unstable concurrent systemic disease, prior diagnosis of depression or other psychiatric disorder that could affect cognition prior to the onset of stroke	>3 months	31.5

Table 1. Continued

STUDY	DESIGN	*N*	STROKE TYPE	EXCLUSION/INCLUSION CRITERIA	EVALUATION TIME AFTER STROKE	PREVALENCE %
Wichowicz *et al.* (2015), Poland	Prospective cohort study	105	First-ever ischemic stroke	*Inclusion*: symptoms present for at least 24 hours, presence/character/location of the lesion confirmed by CT and/or MRI *Exclusion*: TIA, hemorrhage strokes, stroke-like symptoms which turned out to be a glioma, additional serious medical condition (second stroke, myocardial infarction occurring at the period of observation, newly diagnosed or relapsed neoplasm), lost track of the patient, death	6 and 12 weeks, 6 and 12 months	27.6
Lewin-Richter *et al.* (2015), Germany	Prospective cohort study	71	Ischemic	*Inclusion*: at least 4 weeks after stroke, sufficient verbal comprehension (fluent in German, Token Test score > 12), no severe co-morbidities (diabetes), ≥ 8 years of education	>4 weeks, 6 months	27.0 MD, 16.0 mD
Schöttke and Giabbiconi (2015), Germany	Prospective cohort study	289	Ischemic and hemorrhagic	*Inclusion*: documentation of the presence of the neurological symptoms exceeding 24 hours, precise documentation of the lesion, physical capacity of the patient to attend facilities, capability to undergo a structured interview as an evaluation of affective disorders in German *Exclusion*: missing demographic or diagnostic data, major communication dysfunction	Median: 6 weeks, Q1, 25% = 4weeks, Q3, 75% = 9 weeks	31.1
Shi *et al.* (2015), China	Prospective cohort study	757	First-ever ischemic stroke	*Inclusions*: age > 18 years *Exclusion*: dementia, concomitant neurological disorder that might affect cognitive function, alcohol or drug abuse, communication dysfunction	3, 6, and 12 months	29.0, 1 year
Yang *et al.* (2015), China	Prospective cohort study	116	Ischemic	*Inclusion*: NIHSS ≤ 6, without conscious trouble, able to cooperate with the interview, severe aphasia, brain MRI scans (T1,T2, FLAIR and DTI), within 7 days of stroke onset, without history of schizophrenia, major depression, anxiety, dementia, drug abuse, antidepressant use at stroke onset, or a family history of mental disorders. *Exclusion*: severe drinkers (>42 drinks/week, where 1 drink equaled 8 g of alcohol)	1 month	12.1

Table 1. Continued

STUDY	DESIGN	*N*	STROKE TYPE	EXCLUSION/INCLUSION CRITERIA	EVALUATION TIME AFTER STROKE	PREVALENCE %
Jiang *et al.* (2014), China	Prospective cohort study	392	Ischemic and hemorrhagic	*Inclusion*: age > 18 years, brain MRI, without severe mental disease/cognitive or communication dysfunction, without aphasia/cardiopulmonary function failure or other serious somatic disease	2–6 weeks	4.2 MD
Rajashekaran *et al.* (2013), India	Prospective cohort study	62	First-ever ischemic and hemorrhagic stroke	*Inclusion*: consecutive patients with definite history of recent onset of stroke (>2 weeks but <6 months), ability to communicate verbally *Exclusion*: altered sensorium/aphasia/significant cognitive disturbances interfering with satisfactory communication, previous history of stroke or neurological disorders or psychiatric illness, disabling conditions and severe medical illnesses such as uncontrolled diabetes, recent myocardial infarction or severe metabolic disorders	Between>2 weeks and 6 months	45.0 depression 29.0 MD
Altieri *et al.* (2012), Italy	Prospective cohort study	105	Ischemic and hemorrhagic	*Inclusion*: stroke with NIHSS ≤ 5 *Exclusion*: severe comprehension dysfunction, severe aphasia, TIA, subarachnoidal hemorrhage, education level < 5 years, dementia, previous history of psychiatric disorder, concomitant neurological disorder that might affect cognitive function (e.g. Parkinson's disease), or a severe co-morbid medical illness (e.g. cancer) that would preclude follow-up for the duration of the study	1 month, and between 12 and 30 months	41 including 93 dysthymia
Zhang *et al.* (2012), China	Prospective cohort study	163	Ischemic	*Inclusion*: WHO criteria stroke with a maximum of 14 days from onset, age 18–80 years, no thrombolysis *Exclusion*: age <18 or >80 years, previous history of depression/dementia/neurologic disease, alcohol or drug abuse, not right hander, no MRI, communication dysfunction (e.g. reduced level of consciousness, severe hearing or visual impairment, severe aphasia or dysarthria and severe cognitive dysfunction), Clinical Dementia Rating ≥ 1 and Global Deterioration Scale ≥ 3	3 months	23.9

Table 1. Continued

STUDY	DESIGN	*N*	STROKE TYPE	EXCLUSION/INCLUSION CRITERIA	EVALUATION TIME AFTER STROKE	PREVALENCE %
Chatterjee *et al.* (2010), Great Britain	Case–control study	182	Ischemic and hemorrhagic	*Inclusion*: no severe cognitive or communication dysfunction	9 months	21.9 MD
Zhang *et al.* (2010), China	Prospective cohort study	165	Ischemic	*Inclusion*: WHO criteria ischemic stroke with symptoms ≥ 24 hours, confirmed with CT or MRI and without intracranial hemorrhage *Exclusion*: age 18–85 years, not living in Beijing, dementia or other neurological disease known to affect cognition, alcohol or drug abuse, communication problems that preclude him from a psychiatric interview (e.g. reduced level of consciousness, severe hearing or visual impairment, severe aphasia or dysarthria and severe cognitive dysfunction MMSE < 12), TIA, recurrent stroke within 3 months	3 months	27.3
Fuentes *et al.* (2009), Spain	Prospective cohort study	85 then 59	Ischemic	*Inclusion*: cerebral infarction confirmed by neuroimaging techniques (CT) with a maximum of 10 days from onset, age 40–90 years *Exclusion*: TIA or hemorrhagic stroke, dementia, dyslexia, aphasia, sensory deficiency that interfered with neuropsychological evaluation, low consciousness (GCS < 14), impossibility of completing follow-up visits, history of prior diagnosis or treatment of depression in 3 months before the stroke	10 days and 3 months	28.8
Provinciali *et al.* (2008), Italy	Prospective cohort study	713	First-ever ischemic or hemorrhagic stroke	*Inclusion*: stroke confirmed by a CAT scan or MRI *Exclusion*: age < 18 years, subarachnoidal hemorrhage, TIA, mRS = 5, severe comprehension deficits, severe aphasia (visual analog mood scale not assessable)	Four visits: 2–6 weeks, 10–14 weeks, 22–26 weeks, 34–38 weeks, if PSD three more visits	37.3

Table 1. Continued

STUDY	DESIGN	*N*	STROKE TYPE	EXCLUSION/INCLUSION CRITERIA	EVALUATION TIME AFTER STROKE	PREVALENCE %
Brodaty *et al.* (2007), Australia	Prospective cohort study	164	Ischemic	*Inclusion*: stroke confirmed by a CAT scan or MRI *Exclusion*: age > 85 years, TIA, impairment of consciousness persisting >7 days at time of stroke, insufficient fluency in English, previous history of dementia or other neurological diseases known to affect cognition or current alcohol or drug abuse, possible dementia prior to the index stroke, DSM-IV diagnosis of mental retardation, severe aphasia	3–6 months and 15 months	20.7
Lee *et al.* (2007), Hong-Kong	Prospective cohort study	260 then 200	First-ever ischemic stroke	*Inclusion:* age ≥ 50 years, admitted to one of the two centers, from 1 June 2004 to 31 May 2005, first-ischemic stroke, diagnosis of stroke confirmed by documented cardinal sign and stroke symptoms and/or supported by a CAT scan or MRI reports *Exclusion*: documented history of depression and psychiatric disease before the onset of stroke, patients with a history of head or brain injury, TIA, or intra-cerebral hemorrhage, severe cognitive impairment (Abbreviated Mental Test < 6/10 or MMSE < 23), critical illness or comatose, stroke condition as an immediate complication of another health condition (e.g. stroke after a major operation, stroke during hemodialysis), severe aphasia GCS ≤ 3/5 (best verbal response category)	1 month	24.0
Leentjens *et al.* (2006), Holland	Prospective cohort study	190 then 165	First-ever ischemic stroke	*Inclusion*: stroke confirmed by CAT scan *Exclusion*: missing data, other health condition, previous family history of depression	1, 3, 6, 9, and 12 months	23.0
Paolucci *et al.* (2006), Italy	Prospective cohort study	1064	Ischemic and hemorrhagic	Age < 18 years, TIA, subarachnoid hemorrhage, MMSE ≤ 10, mRS = 5, severe aphasia, monitoring difficulty	1, 3, 6, and 9 months. If PSD three more visits	36.0 PSD 2.9 MD

Table 1. Continued

STUDY	DESIGN	*N*	STROKE TYPE	EXCLUSION/INCLUSION CRITERIA	EVALUATION TIME AFTER STROKE	PREVALENCE %
Aben *et al.* (2006), Holland	Prospective cohort study	190	First-ever ischemic stroke	*Inclusion*: ischemic nature of stroke verified by CT, no recurrent stroke, hemorrhage, or brainstem infarct *Exclusion*: death, severe physical morbidity, severe cognitive morbidity, combined physical/cognitive morbidity, concurrent major psychiatric disorder	1, 3, 6, 9, and 12 months	38.7 at 1 year 26.7 at 3 months
Carota *et al.* (2005), Switzerland	Prospective cohort study	273	First-ever ischemic stroke	*Inclusion*: stroke onset within 48 hours *Exclusion*: stay in the stroke unit ≤ 1 day, impaired vigilance or confusional state or delirium or epileptic crisis, systemic complications or diseases, concomitant Parkinson's disease, bilateral or multiple lesions, hemorrhagic stroke, leukoaraiosis graded 3 Fazekas, alcohol dependence, and loss of autonomy before stroke, severe comprehension deficits precluding verbal interviews	3 and 12 months	30.9 MD + mD
Tang *et al.* (2005), China	Prospective cohort study	189	Ischemic and hemorrhagic	*Inclusion*: Chinese ethnicity, well-documented (clinical and/or CT scan) first or recurrent acute stroke <7 days before admission, fluency in the Cantonese dialect *Exclusion:* TIA, subdural hematoma, or subarachnoidal hemorrhage, moderate or severe aphasia, MMSE < 19, history of any neurological disease other than stroke	3 months	16.4

mRS, Modified Rankin Scale; TIA, transient ischemic attack; MMSE, mini mental state examination; GCS, Glasgow Coma Scale; MD, major depression; mD, minor depression; CT, computerized tomography scan; MRI, magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery; DTI, diffusion tensor imaging; CAT, computer-assisted tomography.

Table 2. Risks factors for PSD, and figure of effect sizes and 95% CI plots

RISK FACTORS	MEAN RR	CI 95%	REFERENCES
Previous history of depression	2.19	1.52–3.15	Carota *et al.* (2005), Guiraud *et al.* (2016), Paolucci *et al.* (2006), Schöttke and Giabbiconi (2015), Tang *et al.* (2005), Zhang *et al.* (2010)
Disability	2.00	1.58–2.52	Fuentes *et al.* (2009), Guiraud *et al.* (2016), Gyagenda *et al.* (2015), Jiang *et al.* (2014), Paolucci *et al.* (2006), Zhang *et al.* (2010)
Previous history of stroke	1.68	1.06–2.66	Chatterjee *et al.* (2010), Fuentes *et al.* (2009), Guiraud *et al.* (2016), Jiang *et al.* (2014), Paolucci *et al.* (2006), Tang *et al.* (2005), Zhang *et al.* (2010)
Aphasia	1.47	1.13–1.91	Carota *et al.* (2005), Gyagenda *et al.* (2015), Paolucci *et al.* (2006), Schöttke and Giabbiconi (2015)
Gender	1.35	1.14–1.61	Altieri *et al.* (2012), Brodaty *et al.* (2007), Carota *et al.* (2005), Chatterjee *et al.* (2010), Fuentes *et al.* (2009), Guiraud *et al.* (2016), Gyagenda *et al.* (2015), Jiang *et al.* (2014), Paolucci *et al.* (2006), Rajashekaran *et al.* (2013), Schöttke and Giabbiconi (2015), Shi *et al.* (2015), Tang *et al.* (2005), Tsai *et al.* (2016), Vermeer *et al.* (2016), Zhang *et al.* (2010)
Early depressive symptoms	2.46	0.97–6.25	Carota *et al.* (2005), Guiraud *et al.* (2016), Zhang *et al.* (2010)
Social support	2.44	0.10–62.54	Brodaty *et al.* (2007), Jiang *et al.* (2014)
Pain	2.15	0.10–44.82	Lee *et al.* (2007), Vermeer *et al.* (2016)
Cognitive impairment	1.52	0.59–3.96	Guiraud *et al.* (2016), Shi *et al.* (2015), Vermeer *et al.* (2016)
Tobacco consumption	1.36	0.86–2.16	Altieri *et al.* (2012), Brodaty *et al.* (2007), Chatterjee *et al.* (2010), Shi *et al.* (2015), Vermeer *et al.* (2016), Zhang *et al.* (2010)
Marital status	1.23	0.93–1.63	Brodaty *et al.* (2007), Gyagenda *et al.* (2015), Rajashekaran *et al.* (2013), Schöttke and Giabbiconi (2015), Shi *et al.* (2015), Tang *et al.* (2005), Tsai *et al.* (2016), Zhang *et al.* (2010)
Left hemisphere lesion	1.07	0.87–1.32	Altieri *et al.* (2012), Brodaty *et al.* (2007), Carota *et al.* (2005), Chatterjee *et al.* (2010), Fuentes *et al.* (2009), Jiang *et al.* (2014), Paolucci *et al.* (2006), Rajashekaran *et al.* (2013), Schöttke and Giabbiconi (2015), Shi *et al.* (2015), Tang *et al.* (2005), Tsai *et al.* (2016), Wichowicz *et al.* (2015)
Alcohol consumption	0.83	0.49–1.42	Altieri *et al.* (2012), Brodaty *et al.* (2007), Shi *et al.* (2015), Vermeer *et al.* (2016), Zhang *et al.* (2010)

Prevalence

The pooled prevalence of PSD was 27.96% (time frame between 2 weeks and 6 months), in line with previous reviews and meta-analyses.

Identification of PSD risk factors

Results with random effects model are detailed in Table 2. Identified risk factors for PSD were previous history of depression (RR 2.19, confidence interval (CI) 1.52–3.15) with 6 studies, disability (RR 2.00, CI 1.58–2.52) with 6, previous history of stroke (RR 1.68, CI 1.06–2.66) with 7 studies, aphasia (RR 1.47, CI 1.13–1.91) with 4 studies, and female gender (RR 1.35, CI 1.14–1.61) with 16 studies.

We propose a ranking of those risk factors sorted by magnitude of each RR. We assume that there are some overlap in CI.

When using a fixed effects model, we identified two more risk factors for PSD: early depressive disorder (RR 2.32, CI 1.43–3.79) and tobacco consumption (RR 1.40, CI 1.09–1.81).

Even with a fixed effects model, the other assessed items were not identified as risk factors for PSD.

Potential biases

Inter-study heterogeneity was not significant for any risk factor with all p values > 0.05 (Table 3). Possible publication bias was assessed using normal quantile plot, for all risk factors (Figure 2, Extended data). Sample size was significantly involved to explain the role of "alcohol consumption" in the meta-analysis with, Spearman's $\rho = -0.90$; $p = 0.04$ (Table 4). A "new finding effect" (time bias) was found for alcohol consumption with Spearman's $\rho = -0.90$ with $p = 0.04$ (Table 4)

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Table 3. Total heterogeneity for each risk factor – interstudy heterogeneity

RISK FACTOR	TOTAL HETEROGENEITY	DEGREE OF FREEDOM	PROBABILITY (χ^2 TEST)
Early depressive symptoms	1.77	2	0.41
Social support	0.02	1	0.90
Previous history of depression	8.70	5	0.12
Pain	1.00	1	0.32
Disability	5.18	5	0.39
Previous history of stroke	12.22	6	0.06
Cognitive impairment	1.84	2	0.40
Aphasia	2.21	3	0.53
Tobacco consumption	4.89	5	0.43
Gender	16.39	15	0.36
Marital status	4.14	6	0.66
Left hemisphere lesion	14.96	12	0.24
Alcohol consumption	3.56	4	0.47

Table 4. Time bias and publication bias

	SPEARMAN'S ρ		SPEARMAN'S ρ	
RISK FACTOR	TIME BIAS	p	PUBLICATION BIAS	p
Early depressive symptoms	0.50	0.67	− 0.50	0.67
Previous history of depression	0.73	0.10	− 0.26	0.62
Disability	0.43	0.40	− 0.54	− 0.27
Previous history of stroke	0.11	0.82	0.21	0.65
Cognitive impairment	0.87	0.33	− 1.00	0.33
Aphasia	− 0.11	0.89	− 0.80	0.20
Tobacco consumption	0.29	0.58	0.31	0.54
Gender	− 0.04	0.90	− 0.10	0.70
Marital status	− 0.04	0.94	0.21	0.65
Left hemisphere lesion	0.24	0.42	0.08	0.80
Alcohol consumption	− 0.90	0.04	− 0.90	0.04

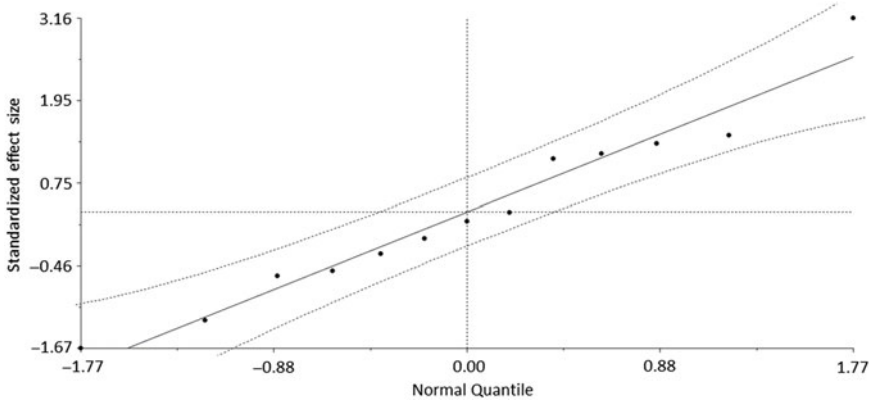

Figure 2. Extended data: normal quantile plot of effect sizes for 13 studies assessing stroke lesion side.

Mean RR had no time effect and were not explained by a single study. All risk factors were retested after removing the retrospective study data, and RR remained significant.

Discussion

We found that five studied risk factors had a significant capacity to predict PSD, which confirms

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previous tendencies. These risk factors could be clustering into four groups: Depressive related, neurological and other medical risk factors, socio-demographic and use disorders items.

Depressive-related risk factors

Early depressive symptoms and previous history of depression are associated with PSD. These results are in line with previous reviews and not surprising regarding the similarity of physiopathology (Robinson and Jorge, 2016; Shi *et al.*, 2017).

To assess depressive symptoms, several scales were used. Hamilton Depression Rankin Scale is used in one study (Zhang *et al.*, 2010), Carota *et al.* (2005) assessed "crying," "expressed sadness," and "apathy" and Guiraud *et al.* (2016) assess "pathological crying". Obviously, it is difficult to prioritize a specific scale, but a systematic early assessment of mood after stroke can be proposed as a top priority.

Neurological and other medical risk factors

We identified three neurological and other medical risk factors for PSD: disability, previous history of stroke, and aphasia.

PSD could be triggered by the neurological event or constitute a reaction to the associated disability (motor disability, aphasia, cognitive impairment, etc.). Nevertheless, the present meta-analysis confirms previous tendencies (Shi *et al.*, 2017) and reinforces the importance of appropriate functional physiotherapy with specific health professionals, to improve disability and to allow early detection of depressive symptoms, as already shown.

Lastly, aphasia is identified as PSD risk factor – even though the most severe aphasic patients were excluded from one of these studies. Though, aphasia could constitute a risk factor for PSD via the left lesion location.

Lesion location was widely studied and remarkably, the only previous meta-analysis found a correlation between right hemisphere lesions and PSD (Wei *et al.*, 2015), while our results could not strictly identify left hemisphere as a risk factor, possibly due to exclusion of most severe aphasic patients, knowing that aphasia is a frequent consequence when left hemisphere stroke occurs. Clinical selection criteria could explain the difference of results: depression was not assessed with strictly DSM criteria. Moreover, in most of the included studies, patients with aphasia were excluded which leads to an underestimation of depression in patients with left neurological lesion. Finally, our results are in line with the idea that left frontal region could lead to PSD which is well formulated by Robinson and Jorge (2016), and supported by the fact that there is strong scientific evidence of brain lateralization of emotion.

In our meta-analysis, cognitive impairment could not be strictly identified as a risk factor for PSD. However, cognitive functions can be impacted not only by stroke but also by major depressive disorder (Gorwood *et al.*, 2008). It seems therefore difficult to specify the role of this marker as a risk factor, as it could testify the stroke event or just accompany a depressive episode. Indeed, Ayerbe *et al.* (2013) reminded that cognitive impairment and PSD can be either cause or consequence and share common risk factors.

Socio-demographic risk factors

Only female gender is identified as a risk factor of PSD. This replicates the results of a recent meta-analysis (Shi *et al.*, 2017) and allows identification of female gender as a PSD risk factor, while a lot a previous reviews did not (Kutlubaev and Hackett, 2014). Interestingly, this risk factor is already known for depression, independent of stroke event. Authors wrote about the complex relationship between gender and depression, and several explanatory models are involved in a multifactorial perspective: psychological, socio-cultural, and biomedical models (Hammarström *et al.*, 2009). There is a lack of scientific evidence of specific mechanism explaining PSD among women.

For social support and marital status, Robinson and Jorge (2016) and Shi *et al.* (2017) suggested the importance of a great social support. We did not confirm these results, possibly due to too few data.

Risk factors related to tobacco and alcohol consumption

Among our 25 selected papers, 7 excluded patients with addictive behavior (alcohol, tobacco, and other drugs). Substance use disorders could not be studied because of the lack of data. However, tobacco and alcohol consumption were assessed, and correlation was found between tobacco consumption and PSD with fixed effects model. The association between PSD and smoking could be mediated by high National Institute of Health Stroke Scale (NIHSS) score and disability (Shi *et al.*, 2015).

Strengths and limitations

Despite an accurate selection, there are still methodological biases. There is a significant variation in depression assessment time among a clinical population (from 2 weeks to 6 months in the same study). Yet, early and late PSD equally lead to functional impairment and higher mortality. Variety of assessment time reflects clinical reality and reminds us that psychiatric monitoring should be close from 2 weeks to 6 months after stroke.

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We select papers since 2005 in order to highlight most recent data. We assume that it could constitute a bias.

The striking result of this meta-analysis is that risk factors related to depression seem to have a higher capacity to predict PSD than any others.

Conclusion

This meta-analysis led to identify PSD clinical risk factors from the psychiatric, neurological and other medical features, socio-demographic fields, and factors related to tobacco and alcohol use. Further research is needed to confirm other items such as previous family history of depression, stressful life event, anxiety disorder, neurotic personality as PSD risk factors. We observed that some PSD risk factors are similar to those for depressive disorder independently of stroke, including gender, pain, substances use, and social support. It confirms that PSD epidemiology, mechanisms, and physiopathology are a way to better understand depressive disorder in general.

Such conclusion could help clinicians to focus more on previous affective disorder story and early depressive symptoms and their related risk factors. Based on these results, specific recommendations could emerge as early assessment of depressive symptoms (in the days following stroke), whatever the depression scale is used. Then, a systematic psychiatric assessment of depression for patients with previous history of depression should be performed and repeated over the first 6 months after stroke. This could help clinicians to detect earlier PSD.

Conflict of interest

None.

Description of authors' roles

R. Perrain designed the study, screened for papers, extracted data, conducted the statistical analysis, analyzed the data, and wrote the manuscript. L. Mekaoui designed the study, screened for papers, analyzed the data, and proofread the manuscript. D. Calvet extracted data, analyzed the data, and proofread the manuscript. J.L. Mas proofread the manuscript. P. Gorwood designed the study, analyzed the data, and proofread the manuscript. All authors contributed to and have approved the final manuscript.

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