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Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis

Wa Cai[a], Christoph Mueller[b,c], Yi-Jing Li[a], Wei-Dong Shen[a,*], Robert Stewart[b,c]

[a] Institute of Acupuncture and Anesthesia, Shanghai Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China
[b] South London and Maudsley NHS Foundation Trust, London, United Kingdom
[c] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

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ABSTRACT

Background: Post stroke depression is a significant neuropsychiatric manifestation, predicting a range of poor outcomes. There are several studies investigating the association between post stroke depression and stroke recurrence/mortality, but results have been inconsistent.
Objective: A systematic review, meta-analysis and meta regression of observational studies assessing the association between post stroke depression and risk of stroke recurrence and mortality.
Methods: A search of Medline (via PubMed), Web of Science databases, EMBASE, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews was conducted until August 2018. We extracted and pooled hazard ratios from observational studies that reported the risk estimates of stroke recurrence and mortality in stroke survivors with/without depression.
Results: The reviewed sample comprised 15 prospective cohort studies with 250,294 participants, 139,276 cases, and follow-up periods ranging from 1 to 15 years. The meta-analysis concluded a hazard ratio for post stroke depression and all-cause mortality of 1.59 (95% CI, 1.30–1.96), but research to date has been insufficient to determine the association between post stroke depression and stroke recurrence.
Conclusion and relevance: Post stroke depression is associated with a significantly increased risk of mortality in stroke survivors. More researches are required on the association with stroke recurrence.

1. Introduction

Stroke, a leading cause of long term disability and the fourth most common cause of death, has been reported to produce increased oxidative stress, which is closely associated with the development of psychiatric symptoms (Bolanos et al., 2009). Post-stroke depression (PSD), whose major symptoms are melancholia, dysphoria and vegetative signs such as sleep disorders, reduced libido and energy level (Whyte and Mulsant, 2002; Tateno et al., 2002; Paradiso et al., 2008), is a significant neuropsychiatric manifestation, predicting poor outcomes after stroke such as limitations in daily activities (Pohjasvaara et al., 2001), cognitive disorders (Chemerinski et al., 2001; Serrano et al., 2007), poor rehabilitation outcomes, social isolation (Boden-Albala et al., 2005), suicidal ideation (Bartoli et al., 2017) and suicide attempts (Eriksson et al., 2015). Two previous meta-analysis have concluded that PSD has a prevalence of approximately 30% among all stroke survivors (Hackett and Anderson, 2005; Ayerbe et al., 2013).

Several recent observational studies, including both prospective and retrospective cohort studies, have assessed the association between PSD and subsequent risks of stroke recurrence and mortality; however, the results of these studies have been inconsistent (Ayerbe et al., 2014; Sibolt et al., 2013; Kemper et al., 2011; Jia et al., 2006; Jorge et al., 2003). One previous meta-analysis concluded that PSD is closely related to an increased risk of all-cause mortality (Bartoli et al., 2013), and another later meta-analysis reported a significant association between depression occurred within 3 months after stroke and mortality (Bartoli et al., 2018). Since then many more high-quality studies have been published, but there is a lack of an up-to-date meta-analysis of the impact of PSD on mortality, and a review of impacts on stroke recurrence is also lacking, another important outcome. We sought to address these deficiencies in our study.

* Corresponding author at: Department of acupuncture, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Zhang Heng Road, Pu Dong New District, 201203, Shanghai, China.
E-mail addresses: 408346323@qq.com (W. Cai), christoph.mueller@slam.nhs.uk (C. Mueller), 1047282537@qq.com (Y.-J. Li), shenweidong_1018@163.com (W.-D. Shen), robert.stewart@kcl.ac.uk (R. Stewart).

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2. Materials and methods

2.1. Search strategy

The literature search was conducted using Medline (via PubMed), Web of Science databases, EMBASE, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, and articles published were searched up to and including August 2018. The search strategy was used as follows (eTable S1) : (1) Post stroke depression, combined exploded versions of Medical Subject Headings (MeSH) *post stroke depression, post stroke depressive disorder, depression after stroke or depressive disorder after stroke*; (2) Stroke, combined exploded versions of Medical Subject Headings (MeSH) *cerebrovascular accident, cerebrovascular disease, cerebral ischemia, ischemic stroke, hemorrhagic stroke, transient ischemic attacks*; (3) Mortality, combined exploded versions of MeSH terms *mortality, all-cause mortality, death or all-cause death*; (4) Observational study, combined exploded versions of MeSH terms *observational study, prospective cohort study, retrospective cohort study or population-based study*. We combined these terms as follows: 1 and (2 or 3) and 4.

2.2. Selection criteria

Two researchers independently assessed literature eligibility. Any disagreement was resolved by a consultation with a third researcher or group discussion. All observational studies of the association between PSD and stroke recurrence/mortality that met the following criteria were included: (1) Prospective or retrospective observational studies; (2) Studies reported any of these outcomes including ischemic stroke, hemorrhagic stroke, TIA, stroke mortality and all-cause mortality; (3) The exposure was defined as depression; (4) Outcomes measured using univariate and multivariate Cox proportional hazards models; (5) Samples comprised adults aged ≥18 years; (6) Studies published in English. All the articles eligible for further review were identified by performing an initial screen of titles or abstracts, and a full-text review was made afterwards.

2.3. Data extraction

Two researchers independently extracted author information, publication year, country, follow-up years, number/age/gender of participants, the main exposure definition(s) (stroke history assessment methods, depression assessment methods), the main outcome definition (s) (stroke recurrence or mortality, types), the size of the association (hazard ratios with 95% confidence interval) and adjusted factors, multiple models, the account taken of important confounders including setting (institutionalized vs. community-dwelling) and depression measurement time points. Information about stroke severity and activities of daily living couldn't be accessed from most of the studies. Study quality was assessed by the Newcastle–Ottawa Quality Assessment Scale (NOS) to evaluate three quality parameters (selection, comparability, and outcome) divided across eight specific items. The length of follow-up that is long enough to assess the outcome is 7 years which is the mean follow-up length of all the included studies. Following Wells et al's methods (Wells et al., 2009), a study can be given a maximum of one star for each numbered item within the Selection and Outcome categories, and a maximum of two stars can be given for Comparability. Thresholds were respectively set for three levels: good quality (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain), fair quality (2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain) and poor quality (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain). All the included studies were evaluated and categorized to different levels (eTable S2). Use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was planned to evaluate the strength of the evidence, following our published protocol; however, we subsequently found that the four key factors in GRADE fully overlapped with those in the NOS for observational studies, and felt that the NOS assessed in more detail. As a result, NOS was used instead of GRADE to assess the risk of bias.

2.4. Data analysis

Statistical analyses were carried out using STATA (V.13) and Review Manager 5.3 software. Extracted HRs with 95% CIs were combined using a random-effects model. Heterogeneity of findings was measured with an I^2 value; values of < 25%, 25–50% and > 50% represented low, medium and high heterogeneity respectively (Melsen et al., 2014). Pooled HRs and 95% CIs were generated by meta-analysis. Publication bias was assessed by the funnel plot and the method proposed by Egger (Sterne et al., 2001). Sensitivity analysis, meta regression and subgroup analyses were performed in order to figure out the major factors of high heterogeneity. Subgroup analyses and meta regression were performed according to mean age, male proportion of study participants, sample size, the duration of follow-up, type of stroke history and depression assessment, study location. Since multiple HRs adjusted for different covariates were provided, subgroup analyses were also conducted to synthesize HRs of the same covariate in each subgroup.

3. Results

3.1. Literature search

Of a total of 1951 unique citations identified by the search strategy, 1176 studies remained after removing 775 duplicates. After the initial screening of titles and abstracts, 209 articles remained for full text review. After reviewing the full text of these articles, 190 were excluded for not meeting the inclusion criteria, and a further 4 studies were excluded due to the reasons described in Fig. 1. A total of 15 articles were included (Ayerbe et al., 2014; Sibolt et al., 2013; Hong et al., 2018; Freak-Poli et al., 2018; Razmara et al., 2017; Jorgensen et al., 2016; de Mello et al., 2016; Hornsten et al., 2013; Ried et al., 2011; Willey et al., 2010; Naess et al., 2010; Melkas et al., 2010; Ellis et al., 2010; Almeida and Xiao, 2007; Williams et al., 2004); 14 studies reported results for all-cause mortality, of which one study also reported total stroke recurrence outcome, and a further one study focused on ischemic stroke recurrence. No studies reported on stroke-specific mortality.

3.2. Study characteristics

Table 1 summarized the characteristics of the 15 selected studies. The total number of participants included in this meta-analysis was 250,294: 139,119 followed for mortality and 157 for recurrent stroke events. Study samples ranged from 223 to 51,119, and the follow-up durations ranged from 1 to 15 years. Most of the studies were from European countries or United States, but the selection included reports from South Korea (Hong et al., 2018), Brazil (de Mello et al., 2016) and Australia (Almeida and Xiao, 2007).

Depression was measured by various scales such as Diagnostic and Statistical Manual of Mental Disorders (DSM) (Sibolt et al., 2013; Hong et al., 2018; Melkas et al., 2010), Center for Epidemiologic Studies Depression Scale (CES-D) (Freak-Poli et al., 2018; Razmara et al., 2017; Ellis et al., 2010), Patient Health Questionnaire (PHQ-9) (de Mello et al., 2016), Hospital Anxiety and Depression Scale (HADS) (Ayerbe et al., 2014; Naess et al., 2010) and Hamilton Depression Rating Scale (HDRS) (Willey et al., 2010). Four studies used physician diagnosis to ascertain depression (Jorgensen et al., 2016; Ried et al., 2011; Almeida and Xiao, 2007; Williams et al., 2004). Depression status and history of stroke were measured at baseline in the majority of studies. Stroke was assessed by World Health Organization International Classification of

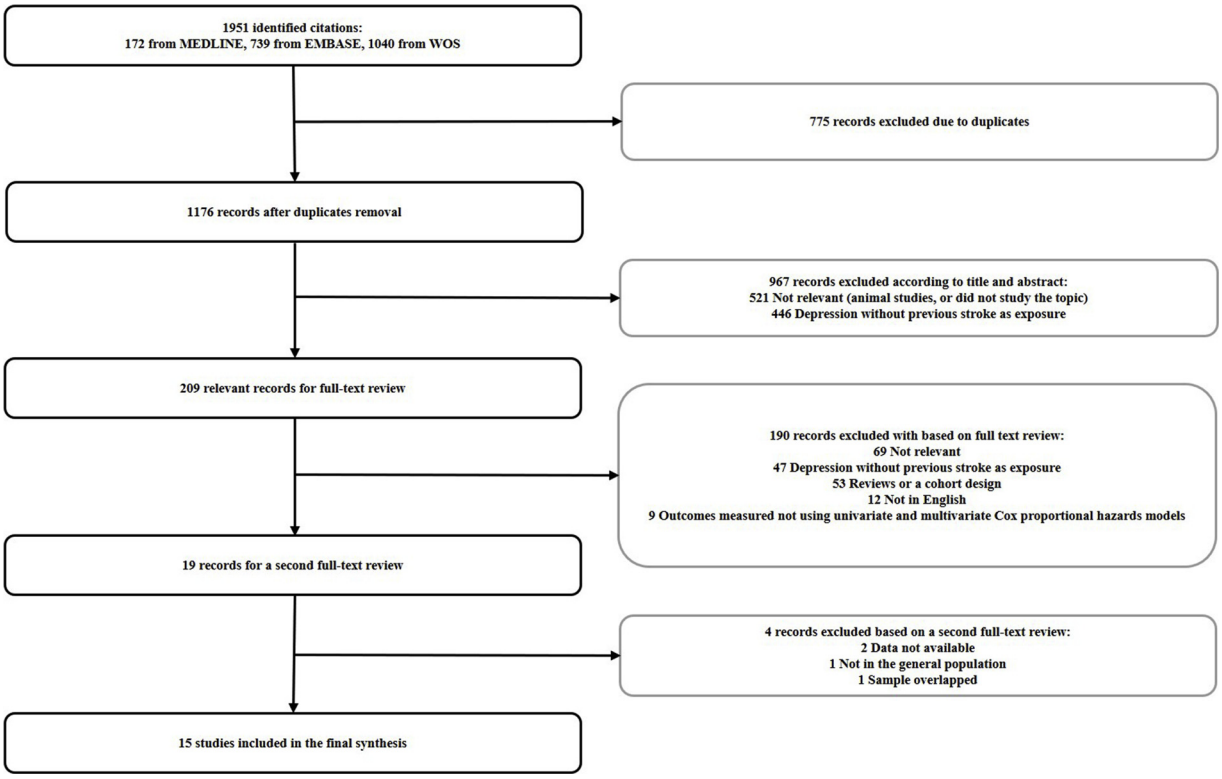

Fig. 1. Flowchart of search and selection.

Diseases (WHO ICD) codes in most studies (Ayerbe et al., 2014; Sibolt et al., 2013; Freak-Poli et al., 2018; Jorgensen et al., 2016; de Mello et al., 2016; Ried et al., 2011; Almeida and Xiao, 2007; Williams et al., 2004), but three studies used the National Institutes of Health Stroke Scale (NIHSS) (Hong et al., 2018; Willey et al., 2010; Naess et al., 2010) and three other studies relied on self-reported outcomes Razmara et al., 2017; Melkas et al., 2010; Ellis et al., 2010). History of stroke at baseline was not described in one study(Hornsten et al., 2013).

Most studies determined adjusted HRs, although two studies reported the crude HRs without adjustment. No study reported HRs based on per-point increase in a depression scale score. Most of the results were adjusted for age (10 studies) (Ayerbe et al., 2014; Razmara et al., 2017; Jorgensen et al., 2016; de Mello et al., 2016; Hornsten et al., 2013; Willey et al., 2010; Melkas et al., 2010; Ellis et al., 2010; Williams et al., 2004), gender (9 studies) (Ayerbe et al., 2014; Freak-Poli et al., 2018; Razmara et al., 2017; Jorgensen et al., 2016; de Mello et al., 2016; Melkas et al., 2010; Ellis et al., 2010; Williams et al., 2004), race (6 studies) (Ayerbe et al., 2014; Razmara et al., 2017; Willey et al., 2010; Ellis et al., 2010; Williams et al., 2004), marital studies (7 studies) Freak-Poli et al., 2018; Razmara et al., 2017; Jorgensen et al., 2016; de Mello et al., 2016; Willey et al., 2010; Melkas et al., 2010; Ellis et al., 2010), education (7 studies) Freak-Poli et al., 2018; Razmara et al., 2017; Jorgensen et al., 2016; de Mello et al., 2016; Willey et al., 2010; Melkas et al., 2010; Ellis et al., 2010), and comorbidities (8 studies; such as coronary heart disease, diabetes and hypertension) Freak-Poli et al., 2018; Razmara et al., 2017; Jorgensen et al., 2016; de Mello et al., 2016; Willey et al., 2010; Melkas et al., 2010; Ellis et al., 2010; Williams et al., 2004), but only three studies adjusted for physical activity Freak-Poli et al., 2018; Willey et al., 2010; Ellis et al., 2010), and two studies for smoking status Freak-Poli et al., 2018; Ellis et al., 2010).

3.3. PSD and risk of stroke recurrence

Only two studies reported results on stroke recurrence using hazard ratios: One reported total stroke recurrence, and the other focused on ischemic stroke recurrence (eTable S3). Therefore, a narrative synthesis was taken instead of a meta-analysis. According to Sibolt et al. (2013), PSD was associated with increased ischemic stroke recurrence (HR: 1.68, 95% CI, 1.07–2.63); however, Ayerbe et al. (2014) reported that PSD at 3 months was not associated with higher risk of total stroke recurrence over a 5-year follow up (HR: 0.98, 95% CI, 0.60–1.62).

3.4. PSD and risk of mortality

3.4.1. Meta-analysis

Of the 14 studies of mortality outcome, the majority reported a statistically significant ($p < 0.05$) positive association, apart from two reporting associations with positive hazard ratios but not statistically significant (Willey et al., 2010; Almeida and Xiao, 2007) (HR: 1.15, 95% CI, 0.76–1.75; HR: 1.26, 95% CI, 0.71–2.23). Fig. 2A showed a high heterogeneity ($I^2 = 96.0\%$; $P < 0.001$) and a pooled HR from the random-effects model of 1.59 (95% CI, 1.30–1.96).

Considering the rather high heterogeneity, a sensitivity analysis following the approach proposed by (Patsopoulos et al. (2008)) to sequentially exclude a cluster of studies was performed to show that six studies (Hong et al., 2018; Razmara et al., 2017; Jorgensen et al., 2016; de Mello et al., 2016; Hornsten et al., 2013; Naess et al., 2010) had the largest influence on the heterogeneity and the pooled HR without these studies was 1.20 (95% CI, 1.11–1.30) with the I^2 value reduced to 36.0% (Fig. 2B).

3.4.2. Meta regression

The results of univariate meta-regression analysis are presented in Table 2. In summary, none of the included covariates could explain the high heterogeneity: follow-up years (14 studies, P = 0.188), sample size (14 studies, P = 0.601), baseline mean age (10 studies, P = 0.656), male percentage of cases (14 studies, P = 0.449), study location (14 studies, P = 0.462), stroke history assessment (13 studies, P = 0.175) or depression assessment (14 studies, P = 0.992).

Table 1
Characteristics of Included Studies.

Author, Year	Country	Follow-up years	No. of participants	No. of cases	Study setting	Baseline age of cases	Male (%) of cases	Stroke history assessment	Depression assessment	Time points of depression assessment	Main outcome
Hong et al. (2018)	South Korea	7	7175	210	Not community-dwelling	Mean 63	69	NIHSS	DSM-IV	After stroke	Suicidal mortality
Freak-Poli et al. (2018)	Netherlands	15	6932	1344	Community-dwelling	Range > 55 Mean 70	46	WHO ICD	CES-D	Before and after CVD	All-cause mortality
Razmara et al. (2017)	United States	8	9919	121	Not community-dwelling	Range 25–64 Mean 55	61	Self-report	CES-D	After stroke	All-cause mortality
Jorgensen et al. (2016)	Denmark	2	157243	135417	Not community-dwelling	Range ≥15	24	WHO ICD	Other diagnosis standards	0-3 m, 3m-1y, 1y-2y after stroke	All-cause mortality
de Mello et al. (2016)	Brazil	1	284	191	Not community-dwelling	Range 35–94 Mean 63	60	WHO ICD	DSM-IV	Every 3 months during 1-year of follow-up	All-cause mortality
Ayerbe et al. (2014)	United Kingdom	10	3240	1458	Not community-dwelling	35.7% cases 0–64 64.3% cases > 64	54	WHO ICD	HADS	3 months, year 1, year 5 after stroke	Total stroke recurrence & All-cause mortality
Hornsten et al. (2013)	Sweden	5	452	88	Not community-dwelling	Range ≥85	N/A	N/A	GDS-15	After stroke	All-cause mortality
Sibolt et al. (2013)	Finland	12	223	83	Not community-dwelling	Mean 73	52	WHO ICD	DSM-III	After stroke	Ischemic stroke recurrence
Ried et al. (2011)	United States	7	870	790	Not community-dwelling	Mean 70	98	WHO ICD	WHO ICD	Within 12 months after stroke	All-cause mortality
Willey et al. (2010)	United States	5	655	340	Not community-dwelling	Range > 39	42	NIHSS	HDRS	Within 30 days after stroke	All-cause mortality
Naess et al. (2010)	Norway	Range 0.5–2.1 Mean 1	771	376	Not community-dwelling	Mean 72	60	NIHSS	HADS	After stroke	All-cause mortality
Melkas et al. (2010)	Finland	12	257	257	Not community-dwelling	Range 55–85 Mean 71	50.6	Self-report	DSM-IIIR	12-20 weeks after stroke	All-cause mortality
Ellis et al. (2010)	United States	8	10025	124	Not community-dwelling	Range 25–74 Mean 69	59	Self-report	CES-D	After stroke	All-cause mortality
Almeida and Xiao (2007)	Australia	10	1129	574	Not community-dwelling	Range 1–101 Mean 71	55	WHO ICD	Other diagnosis standards	After stroke	All-cause mortality
Williams et al. (2004)	United States	3	51119	197	Not community-dwelling	Mean 63	98	WHO ICD	WHO ICD and other diagnosis standards	Within 3 years after stroke	All-cause mortality

Abbreviations: DSM: Diagnostic and Statistical Manual of Mental Disorders; CES-D: Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; GDS, Geriatric Depression Scale; Hamilton Depression Rating Scale, HDRS; NIHSS, National Institutes of Health Stroke Scale; WHO ICD, World Health Organization International Classification of Diseases.
N/A, missing information.

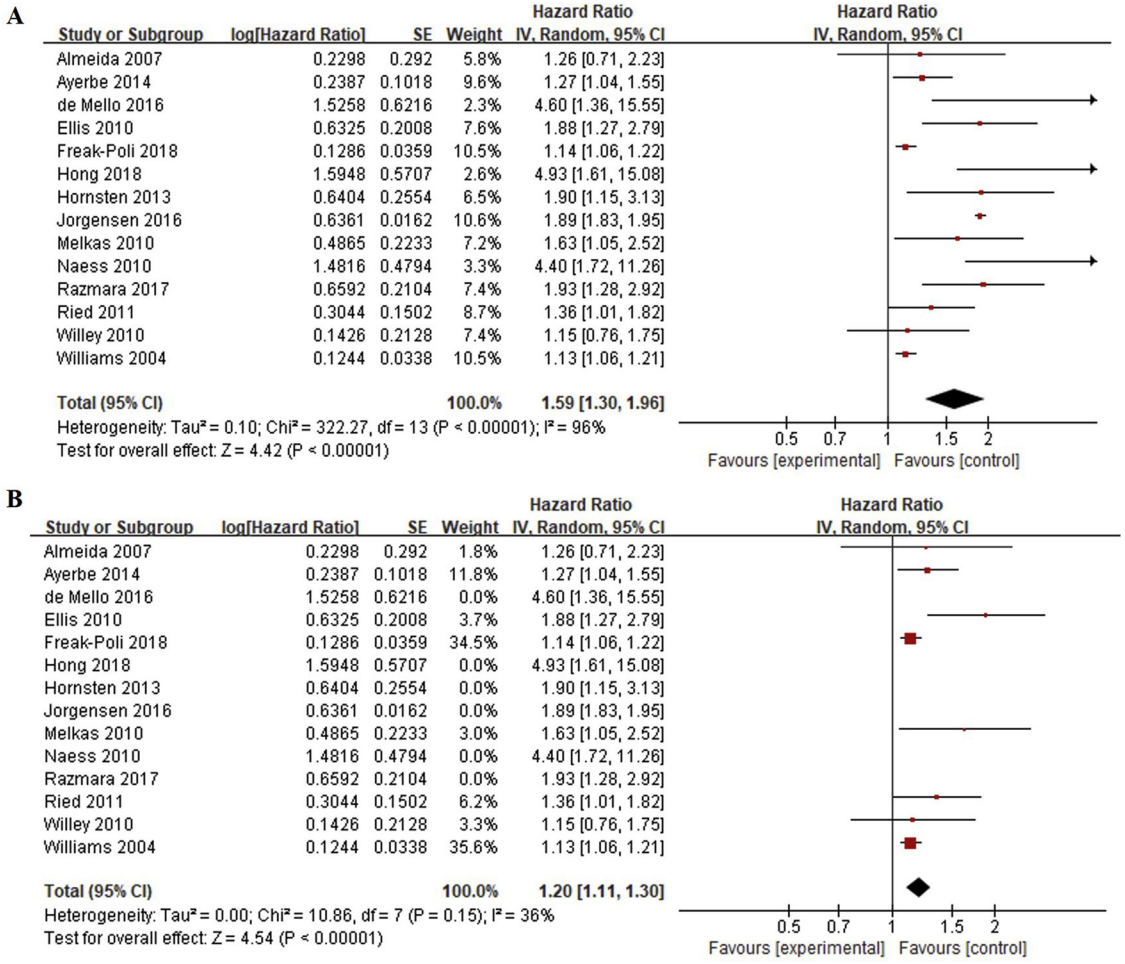

Fig. 2. Hazard ratios of mortality among subjects with post stroke depression before (2 A) and after (2B) the sensitivity analysis, excluding the study contributing most to heterogeneity.

Table 2
Results of the univariate meta-analysis regression for HRs.

Variable	No. of studies	B-Coefficient	95% Confidence Interval	*p*-Value
Follow-up years	14	−0.032	−0.080, 0.017	0.179
Sample size	14	7.85×10^{-7}	-3.66×10^{-6}, 5.23×10^{-6}	0.707
Mean age	10	−0.014	−0.083, 0.055	0.656
Male (%)	14	−0.003	−0.013, 0.007	0.519
Study location	14	0.158	−0.251, 0.567	0.417
Type of stroke history assessment	13	0.158	−0.101, 0.417	0.206
Type of depression assessment	14	−0.013	−0.205, 0.179	0.884

3.4.3. Subgroup analyses

In order to investigate the high heterogeneity further, 8 subgroup meta-analyses were conducted (Table 3). PSD was associated with an increased risk of mortality in most subgroups (eFig. S1). The increased risk was more significant in several strata of subgroup analyses: younger age, male percentages of 60%–90%, having a larger study sample (n ≥ 5000), having shorter follow-up period (< 7 years), using NIHSS to diagnose previous stroke, using DSM to diagnose depression, participants in Asia, and using crude models. Considering adjustments in the eighth subgroup analysis, the pooled HR in the 3 studies that controlled for physical activity (1.30, 95% CI, 0.97–1.75) was the lowest, while the pooled HR in the 7 studies that controlled for marital status and education was the highest (1.63, 95% CI, 1.22–2.19). Moreover, none of the pooled HRs from adjusted models was higher than the pooled HR from crude models without any adjustment for confounders (2.77, 95% CI, 1.05–7.36). Significant between-group differences were observed in gender and depression assessment subgroups.

However, moderate to high heterogeneities were observed in most subgroups. Of these, only two of the gender subgroups showed low to moderate heterogeneities.

3.4.4. Analysis of publication Bias

The funnel plot revealed asymmetry through visual inspection (eFig. S2A), but the results of Egger's test was not significant (P = 0.557, 95% CI, -4.42, 2.49) (eFig. S2B). There was no significant publication bias in the meta-analysis.

4. Discussion

4.1. Interpretation of findings

The meta-analysis of 14 studies confirmed that PSD is associated with a significantly increased risk of all-cause mortality. This association remained statistically significant across most of the subgroups analysed. However, only two studies with outcomes of stroke recurrence were eligible for the review based on our protocol (Cai et al., 2018). One of them had a significant association between PSD and recurrent stroke event (Sibolt et al., 2013), while PSD was not a predictor in another (Ayerbe et al., 2014).

Table 3
Subgroup analyses of hazard ratios (HRs) of mortality.

Sample characteristic	No. of studies	HR (95% CI)	*P* value for heterogeneity	I^2 value (%)	*P* value comparing groups
1. Mean age					
≥65	8	1.45 (1.20, 1.75)	0.004	66	
< 65	4	2.12 (1.14, 3.91)	< 0.001	83	0.25
2.Gender (% male)					
< 30%	1	1.89 (1.83, 1.95)	N/A	N/A	
30–59%	6	1.45 (1.17, 1.81)	0.15	39	
60–89%	4	3.14 (1.79, 5.51)	0.15	43	
90 + %	2	1.17 (1.02, 1.33)	0.24	27	< 0.001
3.Sample size					
≥5000	6	1.61 (1.19, 2.19)	< 0.001	98	
< 5000	8	1.50 (1.21, 1.86)	0.07	47	0.72
4.Follow-up years					
≥7	8	1.45 (1.21, 1.75)	0.003	67	
< 7	6	1.91 (1.23, 2.97)	< 0.001	98	0.26
5.Type of stroke history assessment					
WHO ICD codes	7	1.39 (1.06, 1.83)	< 0.001	98	
NIHSS	3	2.68 (0.91, 7.89)	0.005	81	
Self-reported	3	1.82 (1.43, 2.31)	0.83	0	0.24
6.Type of depression assessment					
Self-reported scales	7	1.51 (1.21, 1.89)	< 0.001	74	
DSM	3	2.86 (1.25, 6.58)	0.01	61	
WHO ICD codes	2	1.17 (1.02, 1.33)	0.02	27	
Other diagnosis standards	2	1.71 (1.22, 2.41)	0.002	48	0.02
7.Study location					
America	6	1.47 (1.14, 1.90)	0.003	72	
Europe, Australia	7	1.58 (1.18, 2.11)	< 0.001	97	
Asia	1	4.93 (1.61, 15.08)	N/A	N/A	0.12
8.Controlled-for cofounders in models					
Age	9	1.60 (1.24, 2.06)	< 0.001	96	
Gender	8	1.54 (1.19, 2.00)	< 0.001	98	
Race	5	1.35 (1.11, 1.65)	0.01	69	
Marital status	7	1.63 (1.22, 2.19)	< 0.001	97	
Education	7	1.63 (1.22, 2.19)	< 0.001	97	
Physical activity	3	1.30 (0.97, 1.75)	0.05	67	
Smoking status	2	1.41 (0.86, 2.29)	0.01	84	
Comorbidities	8	1.54 (1.18, 2.00)	< 0.001	98	
None	3	2.77 (1.05, 7.36)	0.02	74	0.82

Abbreviations: DSM: Diagnostic and Statistical Manual of Mental Disorders; NIHSS, National Institutes of Health Stroke Scale; WHO ICD, World Health Organization International Classification of Diseases.

A variety of mechanisms can be identified to explain positive associations of PSD with mortality/stroke recurrence. Depression after stroke has been reported to be associated with dysregulation of the HPA axis, which brings along abnormal cortisol secretion and elevated cortisol levels, inducing an inflammatory response with elevated levels of inflammatory cytokines, particularly IL-1β, TNF-α and IL-6 (Li et al., 2014; Chen et al., 2011; Ng et al., 2008), which could increase risk of stroke recurrence and mortality. PSD can also cause physical disability and a higher stroke severity, which leads to a higher likelihood of mortality (Hackett and Anderson, 2005). Of note, adjusting for physical activity had a lower pooled HR compared with an overall pooled HR, indicating that physical disability might mediate the association between PSD and mortality. PSD is frequently accompanied with such major comorbidities as diabetes, hypertension, and coronary heart disease (Barth et al., 2004), all of which can increase risk factors for stroke recurrence and mortality. As a marker of depression severity, the use of antidepressant medication has been found in several studies to increase mortality (Hansen et al., 2016; Bartoli and Paolucci, 2014; Juang et al., 2015; Krivoy et al., 2017; Lopponen et al., 2014).

However, in the process of the meta-analysis including studies with mortality outcome, we found high levels of heterogeneity across studies in the risk estimates cited, which was investigated further. The sensitivity analysis revealed that the I^2 value had reduced to 36.0% after excluding six studies: Four of the excluded studies had male percentages of 60%˜90%, another study had 24% which was the lowest proportion of male participants of all the included studies, and the remaining one lacked information on gender distribution. Furthermore, it was found in the subgroup analyses that only gender subgroup strata had low to moderate heterogeneities. Therefore, different gender distributions of different cohort studies may explain the high heterogeneity, at least in part. Based on a recently described French national dataset of patients hospitalized for stroke and stroke mortality (Lecoffre et al., 2017), females accounted for 58.5% of stroke mortality, and their in-hospital mortality rates were slightly higher than males' regardless of age. In our review, two included studies (Razmara et al., 2017; Jorgensen et al., 2016) found that depressed patients with previous stroke were more likely to be females, which could be an explanation for higher stroke mortality rate in females. On the contrary, Ellis et al. (2010) indicated that male gender is one of the factors associated with increased risk of death in PSD patients. To some extent, therefore, different gender distributions had impacts on the HRs, leading to a high heterogeneity.

4.2. Clinical implications

Our meta-analysis revealed that PSD is a significant predictor of all-cause mortality, which was consistent with two previous meta-analyses (Bartoli et al., 2013, 2018). Our findings support the need for a regular assessment of depressive symptoms in patients with a history of stroke. Lacking a gold standard for PSD assessment, depression after stroke often remains underdiagnosed (Meader et al., 2014; Esparrago Llorca et al., 2015), so PSD is frequently under-detected and less considered in routine practice as a complication than issues such as rehabilitation of nerve injury, motor dysfunction or cognitive impairment. Effective management of depression could potentially reduce stroke recurrence and mortality, although this requires empirical evaluation.

4.3. Limitations

There are limitations in this meta-analysis which should be borne in mind when interpreting findings. First, since the eligibility criteria were strict, only two studies of stroke recurrence outcome were included. Thus, the results lack statistical power and further research is required to clarify these associations. Second, the high heterogeneity in the meta-analysis of PSD and mortality lowers the quality of the pooled hazard ratio, although none of the factors considered in the meta regression significantly accounted for this heterogeneity. According to guidelines from the Cochrane Collaboration Handbook, the power of meta regression will be diminished if less than 20 studies are included; consequently, further subgroup analyses were required. Finally, all the included studies were limited to published research, and unpublished reports or ongoing studies were not considered in the review. Studies not providing HRs were also excluded; however, no evidence was found for significant publication bias.

5. Conclusion

This meta-analysis provides strong evidence that PSD is a risk factor for all-cause mortality following stroke, but research has been insufficient to date on the association with stroke recurrence. Considering the high prevalence and incidence of PSD, it is reasonable to recommend its regular assessment and management in patients who have a stroke history, although causal mechanisms underlying associations with adverse outcomes require further clarification, as does the extent to which interventions might modify risk elevation.

Author contributions

WC and WDS designed the study. WC was the principal investigator and guarantor. RS and CM gave statistical and epidemiological support. WC, YJL and WDS conducted the study. WC drafted the article.

Conflicts of interests

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.01.013.

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