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Post-stroke depression and lesion location: a systematic review

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Abstract Post-stroke depression (PSD) is a frequent problem in stroke rehabilitation. Several studies have evaluated association between the lesion location and the risk of depression. Different conclusions and contradictory findings have been published. The aim of the present study was to perform a systematic meta-analysis to evaluate the relationship between PSD and lesion location. We researched PubMed, ISI Web of Science, EMBASE, and systematically reviewed available publications reporting investigations on stroke location and risk of PSD. Subgroup analyses were performed according to the time since stroke onset to assessment for PSD or the source of patients. Odds ratios (ORs) and 95 % confidence intervals (CIs) were used for pooled analyses. Heterogeneity was assessed with Cochran's Q test and I^2 test. Begg's funnel plot and Egger's test were used to examine the publication bias. A total of 43 studies involving 5,507 patients suffering from stroke were included in this meta-analysis. The pooled OR with 95 % CI for the overall association of stroke location and depression risk was 0.99 (0.88–1.11). Subgroups analyses highlighted that only studies with subacute post-stroke group (1–6 months) showed a statistical association between right hemisphere stroke and risk of depression (OR = 0.79, 95 % CI 0.66–0.93). This systematic review offered no support for the hypothesis that lesion of the left hemisphere was associated with an increased risk of depression after stroke. We only find significant association between right hemisphere stroke and incidence of depression for studies within subacute post-stroke phase.

Keywords Post-stroke depression · Lesion location · Meta-analysis

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Introduction

Post-stroke depression (PSD) is of high clinical importance. Patients with PSD have more functional disability [1], poorer rehabilitation outcomes [2], and increased morbidity, and mortality in the first year after stroke onset [3]. Depression is often persistent after stroke, with high risk of relapse even after remission over a long period of time [4]. Reported prevalence of PSD varies widely, ranging from 25 to 79 %. Recently, a systematic review of observational studies indicated that depressive symptoms were present in approximately 33 % of all stroke survivors [5].

Although many studies of PSD have been reported, clinical association between the lesion location and the occurrence of depression remains a matter of debate. The possibility that the risk of depression after stroke is related to lesion location was developed more than 40 years ago at John Hopkins University and originated the concept of PSD [6]. Then, the same group's pooling results underlined that left hemisphere strokes may be associated with higher incidence of depression, especially the left anterior cerebral

lesions [7–9]. In contrast, some studies suggest the opposite results [10]. The attempts to systematically review studies of lesion location and PSD also have not served to clarify this association. Two meta-analyses did not support the hypothesis that the risk of PSD is due to a specific location of stroke [11, 12]. A systematic review by Bhogal et al. [13] sustained that depression was related to the left hemispheric stroke, while Yu et al. [14] suggest that there was a weak relationship between PSD and right hemisphere lesion. The lack of uniformity in definition and measurement of depression, highly variable time since stroke onset to assessment for PSD, sampling differences, and different study settings may partly explain these discrepancies.

In this article we not only expand the related literatures and explore the heterogeneity that might exist among results, but also rejudge and exclude some literatures that included in previous reviews, such as the studies with duplicate data, and studies that were not nonstandard for diagnosis of depression, especially studies that misdiagnosed depressive mood as depression. The major object is to investigate the relationship between stroke lesion location and the development of depression more precisely and completely.

Methods

Searching strategy

All studies that included an assessment of depression in patients who had stroke and examined the correlation between PSD and lesion location were initially eligible for inclusion.

Potential studies were identified by a comprehensive electronic search updated to 5 January 2014, via databases of PubMed, ISI Web of Science, and EMBASE. Our strategy used the keywords:

((stroke[MeSH Terms]) OR post-stroke[Title/Abstract]) OR post stroke[Title/Abstract])) AND (((depressive disorder[MeSH Terms]) OR depression[MeSH Terms]) OR mood disorders[MeSH Terms]).

Study selection

The inclusion criteria required: (1) the studies must have examined the association between depression after stroke and lesion location; (2) they must have provided information sufficient for the computation of effect sizes; (3) studies defining depression as a diagnosis made using DSM-IV criteria, a score above a cut-off point in a validated scale, or another validated method of diagnosis; (4) imaging using either CT or MR scanning; (5) the search

was restricted to studies published in English and involving human subjects.

Studies were excluded if they had any of the following: (1) studies limited to specific clinical characteristics (e.g., strokes in specific locations, strokes of a specific subtype); (2) they were limited to specific patient characteristics (e.g., patients of a specific age group); (3) studies of mixed populations (e.g., stroke and head injury) unless separate results for stroke patients were identified; (4) duplicate studies were excluded. These were defined as studies that shared a sampling frame, and had overlapping study dates, and similar or identical reported sample characteristics. Among duplicate studies, the study that gave original data on the largest number of participants was selected. If the studies were conducted on the same number of participants, the earliest one was used; (5) abstracts, review articles, case reports, retrospective recruitment studies or pharmacological intervention studies were excluded.

Data collection and extraction

Two investigators (Wei N and Zhou Y) independently extracted the estimates on the basis of the inclusion and exclusion criteria. Disagreements were resolved by a group discussion, after which the primary investigators made the final decision. We extracted the following information from each included study: (1) first author, (2) year of publication, (3) demographic characteristics, (4) depression definitions and measures, (5) sample size, (6) the timing of interview for depression, (7) lesion localization, (8) exclude/include aphasia patients, (9) history of stroke or depression, (10) final conclusions. If a report did not include the data needed for the meta-analysis, the corresponding author was contacted in an effort to gather any required information not reported.

Assessment of quality of studies

The quality of included studies was evaluated independently by two investigators (Li X and Deng M) according to the Newcastle-Ottawa scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The third reviewer (Wei N) examined the results, and a consensus was reached. The NOS uses a 'star' rating system to judge quality based on three aspects of the study: selection, comparability, and exposure (case–control studies) or outcome (cohort studies). Scores were ranged from 0 (worst) to 9 stars (best). We specifically classified studies at low quality (1–3 stars), intermediate quality (4–5 stars), or high quality (6–9 stars). Study with a score equal to or higher than 4 was included in this meta-analysis.

Statistics analysis

We used Stata software (version 11.0; College Station, TX, USA) for statistical analysis and to derive forest plots showing the results of individual studies and pooled analysis. Heterogeneity among studies was examined by Cochran's Q test ($P_{heterogeneity}$) and then quantified by I^2 statistic. If the $P_{heterogeneity} < 0.10$ or $I^2 > 50\%$, the pooled ORs and 95 % CIs were estimated by a random-effects model because of significant heterogeneity; otherwise, they were evaluated by a fixed-effects model. Sensitivity analysis was used to assess the stability of results, in which each study was removed at a time and the rest were analyzed to recalculate the pooled OR to evaluate whether the results were affected statistically significantly. Publication bias was evaluated using the Begg's funnel plot and Egger's test [15, 16]. All P values were two-sided with a significant level at 0.05 expect for Cochran's Q test ($P_{heterogeneity} < 0.10$).

To explore the heterogeneity among study results, we conducted analyses in which subgroups were formed according to each study characteristic. The analysis was done in two stages. Firstly, all studies were included and the relationship of PSD and lesion location was calculated. For studies showing results at different follow-up periods, we included just the results at the first follow-up; secondly, we performed subgroups analyses based on the follow-up periods of the included studies: acute post-stroke phase (≤1 month), subacute post-stroke phase (1–6 months), and chronic post-stroke phase (>6 months); lastly, we performed subgroups analyses based on the source of patients (clinic, rehabilitation centre, and community).

Results

Characteristics for studies included

The initial search yielded 1,649 citations. 1,545 citations were initially excluded for not meeting the criteria outlined above, based on information garnered from their abstracts. After screening based on full text, 43 original reports were included in the review [7, 10, 17–57]. The process of the study search and detailed reasons for ineligibility are depicted in Fig. 1. The study characteristics and demographics are displayed in Table 1.

Diagnosis of depression

A variety of depression scales were used to assess depression or the degree of depressive symptoms. These depression scales were either self-completed by patients (in

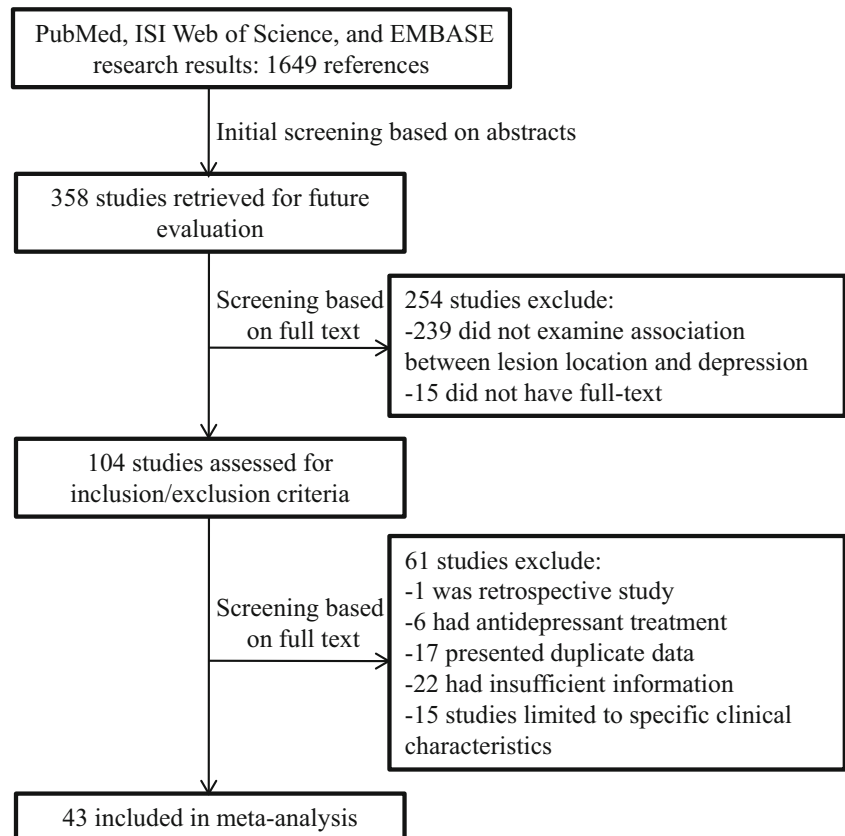**Fig. 1** Flow chart of study selection process

Table 1 Characteristics of eligible studies

Reference	Year	Country	Source of patients	History of stroke excluded	History of depression excluded	Severe aphasia excluded	Quality assessment by NOS		
							Selection	Comparability	Exposure/outcome
Folstein et al. [17]	1977	USA	Rehabilitation	NG	Y	NG	****	**	***
Robinson et al. [7]	1983	USA	Clinic	N	NG	Y	***	**	***
Eastwood et al. [18]	1989	Canada	Rehabilitation	N	N	Y	***	*	**
Morris et al. [19]	1990	Britain	Clinic + rehabilitation	N	N	N	***	**	**
House et al. [20]	1990	Britain	Community	Y	Y	Y	****	**	**
Sharpe et al. [21]	1990	Britain	Community	Y	N	N	***	**	***
Starkstein et al. [22]	1991	USA	Clinic	NG	N	N	***	**	***
Schwartz et al. [23]	1993	USA	Rehabilitation	NG	N	Y	***	*	***
Astrom et al. [24]	1993	Sweden	Clinic	N	N	NG	***	**	**
Loong et al. [25]	1995	Singapore	Rehabilitation	Y	N	Y	***	**	**
Gonzalez-Torrecillas et al. [26]	1995	Belgium	Rehabilitation	N	N	Y	***	**	***
Andersen et al. [27]	1995	Denmark	Clinic	Y	Y	Y	****	**	**
Herrmann et al. [28]	1995	Germany	Clinic	Y	Y	N	***	*	**
Iacoboni et al. [29]	1995	Italy	Clinic	Y	Y	Y	****	**	***
Bjerg Bendsen et al. [30]	1997	Denmark	Rehabilitation	NG	Y	Y	****	*	***
MacHale et al. [10]	1998	Britain	Clinic	Y	Y	Y	****	*	**
Pohjasvaara et al. [31]	1998	Finland	Clinic	NG	N	Y	***	/	**
Kase et al. [32]	1998	USA	Community	Y	Y	N	****	**	***
Paolucci et al. [33]	1999	Italy	Rehabilitation	Y	Y	Y	****	**	**
Shimoda et al. [35]	1999	USA	Clinic	Y	Y	N	****	**	***
Singh et al. [36]	2000	Canada	Clinic	N	N	Y	***	*	**
Gainotti et al. [34]	2001	Italy	Rehabilitation	Y	Y	NG	***	**	**
Berg et al. [37]	2001	Finland	Clinic	Y	Y	Y	****	**	***
Desmond et al. [38]	2003	USA	Clinic	N	N	Y	***	**	**
Hsieh and Kao [39]	2005	China	Clinic	Y	Y	Y	****	**	***
Spalletta et al. [40]	2005	Italy	Clinic	Y	Y	Y	****	/	**
Nys et al. [41]	2005	Holand	Clinic	Y	Y	Y	***	**	**
Tang et al. [42]	2005	China	Clinic	N	N	Y	***	*	***
Glodzik-Sobanska et al. [43]	2006	Poland	Clinic	Y	Y	Y	****	**	**
Caeiro et al. [44]	2006	Portugal	Clinic	N	N	Y	**	**	***
Brodaty et al. [45]	2007	Australia	Clinic	N	N	Y	***	**	***
Provinciali et al. [46]	2008	Italy	Rehabilitation	Y	NG	Y	***	*	***
Oladiji et al. [47]	2009	Nigeria	Clinic	NG	N	Y	***	**	***
Fuentes et al. [48]	2009	Spain	Clinic	N	N	Y	***	**	***
Snaphaan et al. [49]	2009	Holand	Clinic	N	N	NG	***	**	***
Nidhinandana et al. [50]	2010	Thailand	Clinic	NG	NG	Y	***	**	**
Nishiyama et al. [51]	2010	Japan	Clinic	Y	Y	Y	****	*	**
Bour et al. [52]	2010	Holand	Clinic	Y	N	Y	***	*	***
Tennen et al. [53]	2011	Canda	Clinic + rehabilitation	Y	N	Y	***	**	**
Altieri et al. [54].	2012	Italy	Clinic	N	Y	Y	****	**	***
Choi-Kwon et al. [55]	2012	Korea	Clinic	N	Y	Y	****	/	***
Zhang et al. [56]	2013	China	Clinic	NG	Y	Y	****	**	**
Rajashekaran et al. [57]	2013	India	Clinic	Y	NG	NG	***	**	**

Y yes, *N* no, *NG* not given

Asterisks indicate number of stars awarded for each item

6 studies) or administered and scored by interviewers (37 studies), and the psychiatric interviews were conducted either alone (in 21 studies) or in combination with a self-administered mood scale (16 studies). The cut-off points for the same scale used to assess depression across different studies were not consistent, such as multiple cut-points were used for the Beck Depression Inventory (BDI) ($\geq$10 [37, 46, 52], $\geq$13 [55]), Montgomery Åsberg depression rating scale (MADS) ($\geq$6 [31], $\geq$7 [36, 44], $\geq$8 [41]) and the Hamilton depression rating scale (HAMD) for depression ($\geq$7 [56], $\geq$8 [48], $\geq$10 [39, 45], $\geq$13 [27, 43]) and the HAMD for major depression ($\geq$15 [48], $\geq$17 [39], $\geq$18 [23, 27, 33]). Additionally, some studies did not describe the cut-off points to assess depression [7, 17, 18, 26, 30].

Risk effect of assessment

We firstly pooled all the studies to estimate the associations between stroke location and the prevalence of PSD. The studies ($n = 43$) involved 5,507 subjects: 2,743 with left hemisphere lesion and 2,764 with right hemisphere stroke. 898 cases of depression were detected from left hemisphere

lesion sample and 918 from right hemisphere lesion sample. Significant heterogeneity was observed ($P_{heterogeneity} = 0.00$, $I^2 = 55.9$ %, Fig. 2), thus, we chose the random-effects model to synthesize the data. The pooled OR with 95 % CI for the association of stroke location and depression risk was 0.99 (0.88–1.11) (Fig. 2). This result offered no support for the hypothesis that the risk of depression after stroke is affected by the location of the brain lesion.

Then, we did subgroups analyses according to the timing of interview for depression. Significant heterogeneity existed in acute post-stroke group ($n = 18$, $P_{heterogeneity} = 0.00$, $I^2 = 57.7$ %, Fig. 3a), and subacute post-stroke group ($n = 22$, $P_{heterogeneity} = 0.04$, $I^2 = 36.9$ %, Fig. 3b). Thus, we chose the random-effects model to synthesize the data. The heterogeneity of chronic post-stroke group was low ($n = 6$, $P_{heterogeneity} = 0.43$, $I^2 = 0.00$ %, Fig. 3c), so the fix-effects model was chose. A statistically significant association between right hemisphere stroke and PSD was found exclusively for studies with subacute post-stroke stroke phase (OR = 0.79, 95 % CI 0.66–0.93, Fig. 3b). Overall results suggested people with right hemisphere stroke may be more susceptible to depression during

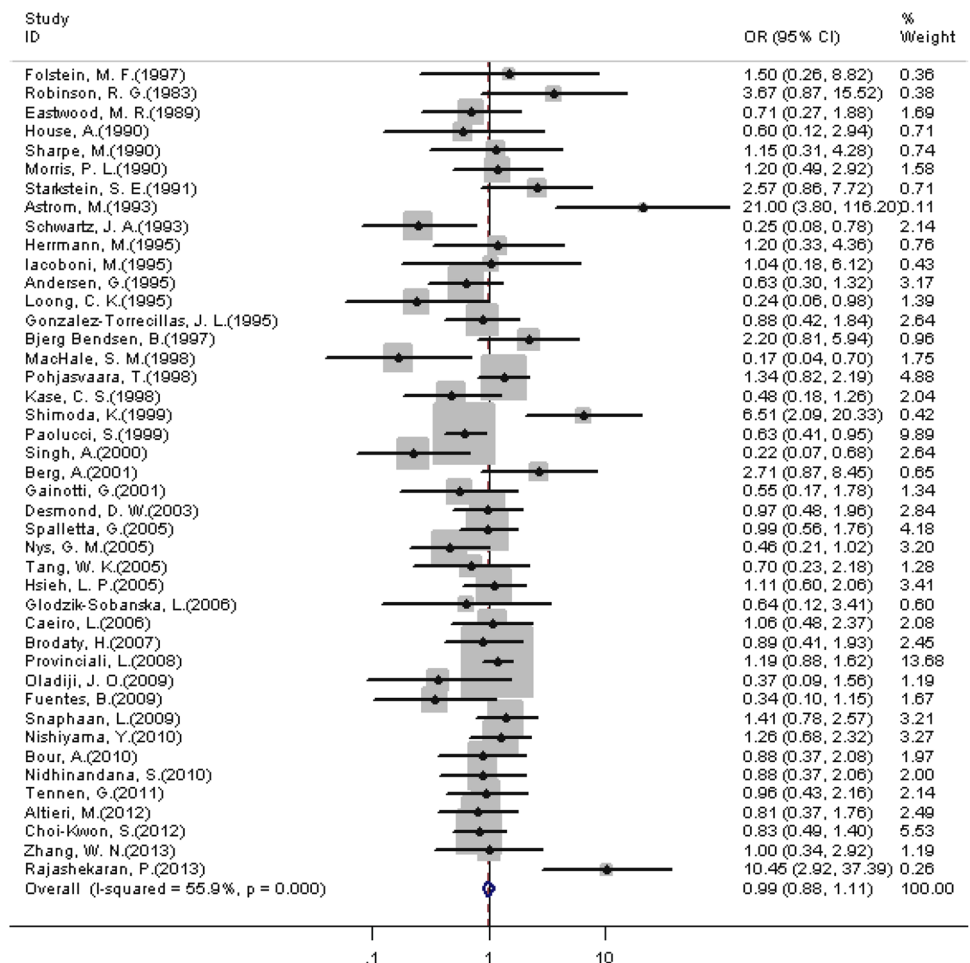Fig. 2 The forest plots of OR with 95 % CI for the overall association of stroke location and depression risk

Study ID	OR (95% CI)	% Weight
Folstein, M. F.(1997)	1.50 (0.26, 8.82)	0.36
Robinson, R. G.(1983)	3.67 (0.87, 15.52)	0.38
Eastwood, M. R.(1989)	0.71 (0.27, 1.88)	1.69
House, A.(1990)	0.60 (0.12, 2.94)	0.71
Sharpe, M.(1990)	1.15 (0.31, 4.28)	0.74
Morris, P. L.(1990)	1.20 (0.49, 2.92)	1.58
Starkstein, S. E.(1991)	2.57 (0.86, 7.72)	0.71
Astrom, M.(1993)	21.00 (3.80, 116.20)	0.11
Schwartz, J. A.(1993)	0.25 (0.08, 0.78)	2.14
Herrmann, M.(1995)	1.20 (0.33, 4.36)	0.76
Iacoboni, M.(1995)	1.04 (0.18, 6.12)	0.43
Andersen, G.(1995)	0.63 (0.30, 1.32)	3.17
Loong, C. K.(1995)	0.24 (0.06, 0.98)	1.39
Gonzalez-Torrecillas, J. L.(1995)	0.88 (0.42, 1.84)	2.64
Bjerg Bendsen, B.(1997)	2.20 (0.81, 5.94)	0.96
MacHale, S. M.(1998)	0.17 (0.04, 0.70)	1.75
Pohjasvaara, T.(1998)	1.34 (0.82, 2.19)	4.88
Kase, C. S.(1998)	0.48 (0.18, 1.26)	2.04
Shimoda, K.(1999)	6.51 (2.09, 20.33)	0.42
Paolucci, S.(1999)	0.63 (0.41, 0.95)	9.89
Singh, A.(2000)	0.22 (0.07, 0.68)	2.64
Berg, A.(2001)	2.71 (0.87, 8.45)	0.65
Gainotti, G.(2001)	0.55 (0.17, 1.78)	1.34
Desmond, D. W.(2003)	0.97 (0.48, 1.96)	2.84
Spalletta, G.(2005)	0.99 (0.56, 1.76)	4.18
Nys, G. M.(2005)	0.46 (0.21, 1.02)	3.20
Tang, W. K.(2005)	0.70 (0.23, 2.18)	1.28
Hsieh, L. P.(2005)	1.11 (0.60, 2.06)	3.41
Glodzik-Sobanska, L.(2006)	0.64 (0.12, 3.41)	0.60
Caeiro, L.(2006)	1.06 (0.48, 2.37)	2.08
Brodaty, H.(2007)	0.89 (0.41, 1.93)	2.45
Provinciali, L.(2008)	1.19 (0.88, 1.62)	13.68
Oladiji, J. O.(2009)	0.37 (0.09, 1.56)	1.19
Fuentes, B.(2009)	0.34 (0.10, 1.15)	1.67
Snaphaan, L.(2009)	1.41 (0.78, 2.57)	3.21
Nishiyama, Y.(2010)	1.26 (0.68, 2.32)	3.27
Bour, A.(2010)	0.88 (0.37, 2.08)	1.97
Nidhinandana, S.(2010)	0.88 (0.37, 2.06)	2.00
Tennen, G.(2011)	0.96 (0.43, 2.16)	2.14
Altieri, M.(2012)	0.81 (0.37, 1.76)	2.49
Choi-Kwon, S.(2012)	0.83 (0.49, 1.40)	5.53
Zhang, W. N.(2013)	1.00 (0.34, 2.92)	1.19
Rajashekaran, P.(2013)	10.45 (2.92, 37.39)	0.26
Overall (I-squared = 55.9%, p = 0.000)	0.99 (0.88, 1.11)	100.00

Fig. 3 The forest plots of OR with 95 % CI for the association of stroke location and depression risk according to time since stroke onset (**a** acute group, **b** subacute group, **c** chronic group)
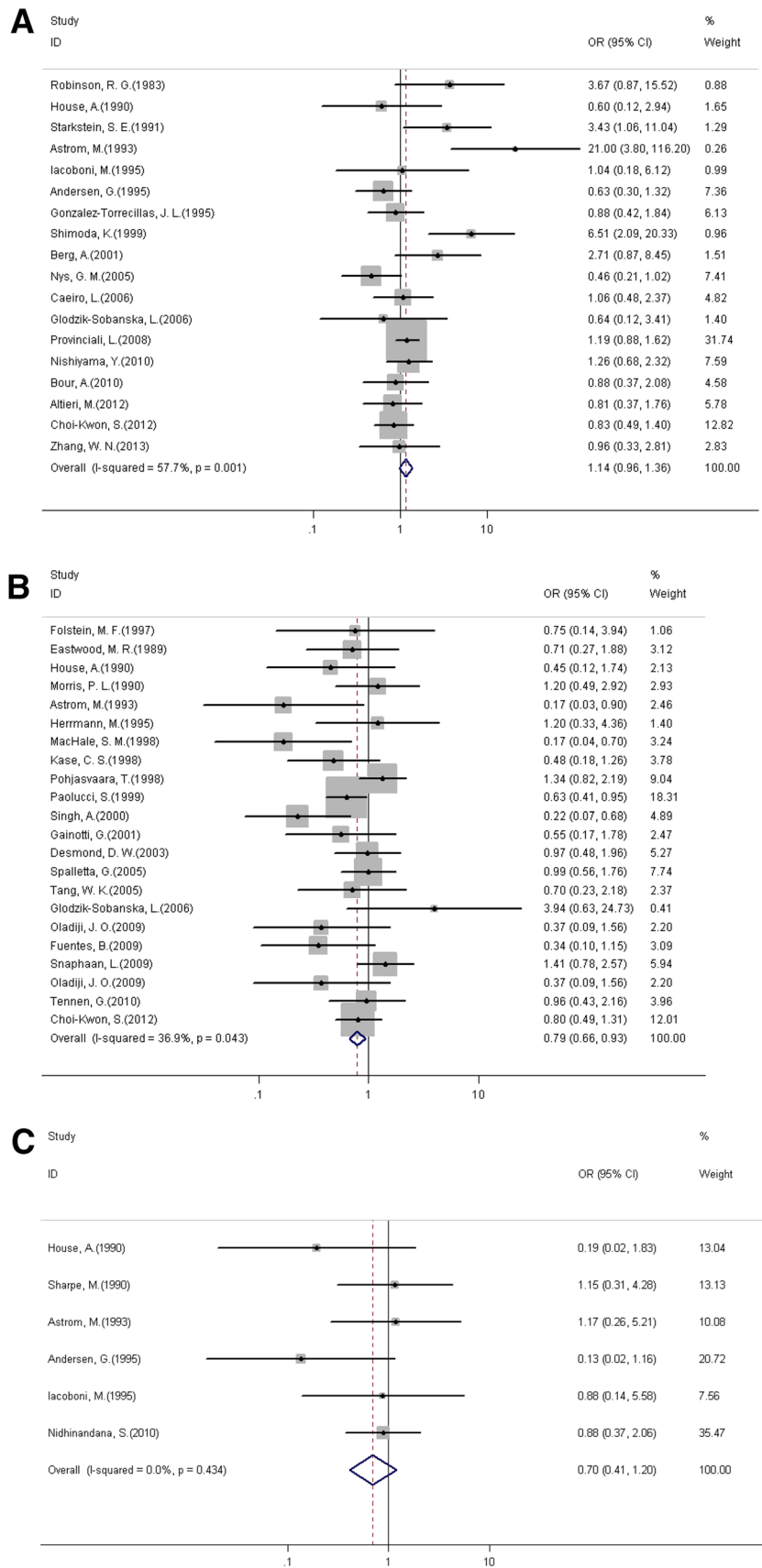
subacute phase of stroke. We also did subgroup analyses according to the source of patients, but no significant difference was found (Table S1).

Quality assessment and sensitivity analyses

Quality assessment was shown in Table 1 and Table S2. We then conducted sensitive analyses to assess the influence of each study on the pooled OR. As shown in Table S3, when any single study was omitted, the corresponding ORs were not materially changed, suggesting high stability of this meta-analysis. For subgroup's sensitive analyses we also get the same conclusion (Table S4).

Publication bias

Begg's funnel plot and Egger's linear regression were performed to assess the publication bias of the included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Fig. 4). The results of Egger's test also showed that there were not statistically

significant differences (total: $P_{\text{Egger's test}} = 0.931$; acute group: $P_{\text{Egger's test}} = 0.276$; subacute group: $P_{\text{Egger's test}} = 0.157$; chronic group: $P_{\text{Egger's test}} = 0.170$).

Discussion

PSD is thought to be a frequent complication of stroke associated with poorer outcomes. Available clinical data about the relationship between PSD and lesion location lacks strength and published results have been contradictory. Our meta-analysis revealed that there was a significant relationship between PSD and right hemisphere lesions when depression was assessed within 1–6 months after stroke.

Limitations of meta-analysis in this study

This study has several potential limitations. Firstly, the possibility of information and selection biases and unidentified confounders cannot be completely excluded because all of the included studies were observational.
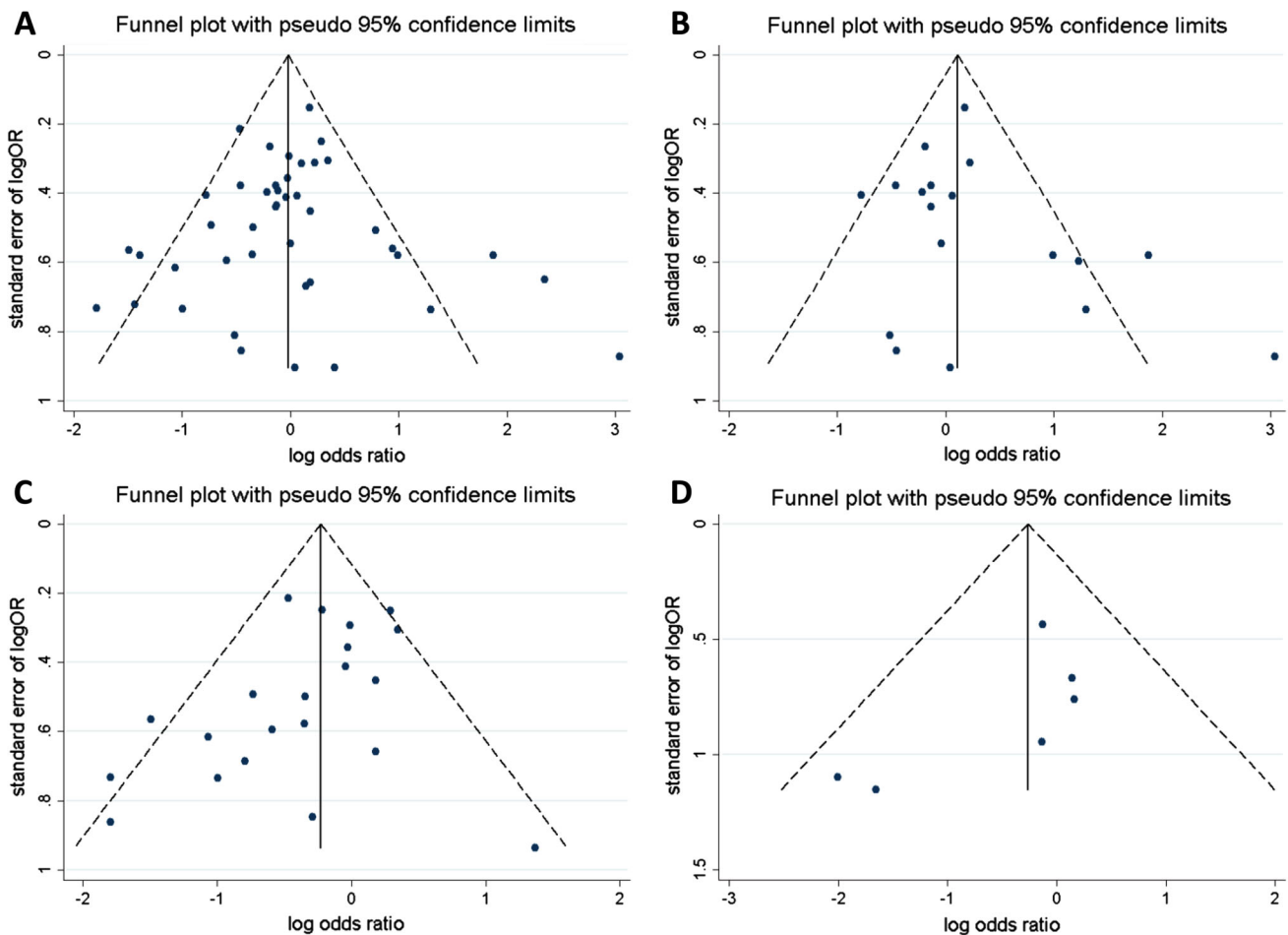

Fig. 4 Funnel blot was designed to visualize a potential publication bias (a overall studies, b acute group, c subacute group, d chronic group)

Secondly, the time interval between stroke and depression assessment varied widely from several weeks to years. Thirdly, depression scales across different studies were various, even for the same scale the cut-off points used to assess degree of depressive symptoms were not consistent. Fourthly, studies used different methods of reporting results: some provided raw data from which OR could be calculated, while others provided either adjusted/unadjusted OR or other forms of statistical measures. This variability presented compatibility problems for analysis, and led to the inability to include certain studies in the analysis due to a lack of usable data. Lastly, we restricted our search strategy to articles published in English. Articles with potentially high-quality data that were published in other languages were not included because of anticipated difficulties in obtaining accurate medical translation.

Development of an appropriate and standardized measure of depression

The diagnosis of depression in stroke patients is a difficult task. The phenomenology of PSD is different from non-comorbid depression. Most instruments used to assess PSD were not originally developed for stroke populations therefore they have never been specifically validated in stroke patients. For example, as a direct consequence of stroke, patients may suffer from symptoms such as insomnia and loss of appetite, which may lead to an increase in false-positive depression scores. So it may get different conclusions for scales that include somatic items (e.g., BDI, HAMD) and others that seek to avoid such items [e.g., hospital anxiety and depression scale (HADS) and MADS]. Recent meta-analysis suggests that Center of Epidemiological Studies-Depression Scale (CES-D), HAMD or the Patient Health Questionnaire-9 (PHQ-9) as the most promising options to screen for PSD [58].

In most of the studies that we reviewed, many patients with severe aphasia were excluded from samples because patients with substantially impaired comprehension have difficulties completing most standardized interviews and scales. In fact, aphasia is a common consequence for patients with left hemispheric lesion. Consequently, the existence and severity of depression in patients with left hemisphere damage may be underestimated. To better research the relation between PSD and stroke location, evaluation methods for depression which are suitable for aphasic patients were needed.

Optimal time since stroke onset to assessment for PSD

Several studies have suggested that PSD over different terms may have different mechanisms, so the time interval between stroke onset and diagnosis of depression was an important confounder to confirm the association of PSD occurrence and stroke location. During the acute post-stroke period ($\leq$3 months), depression has been associated with left anterior lesions, owing to a disruption in biogenic amine neurotransmission. However, during the post-acute period (3–6 months post-stroke), the proximity of the lesion to the frontal pole in both hemispheres influences the occurrence of post-stroke depression. For chronic stroke (1–2 years post-stroke), the occurrence of depression among survivors with left hemisphere lesions is mostly determined by severity of disability, whereas among those with right hemisphere damage, it is associated with lesion size and proximity to the occipital pole [35, 59]. In Carson's study, no evidence supported the hypothesis that lesion location was associated with depression no matter when the depressive symptoms after stroke were assessed [11]. However, Yu et al. showed that depression was statistically associated with right hemisphere lesions when depression was assessed within 4–9 months after stroke. In our review, in the beginning we tried to group studies into acute post-stroke group ($\leq$3 months), subacute post-stroke group (3–6 months), and chronic post-stroke group (>6 months) according to the biological mechanism as mentioned earlier, but no statistical association was found. Considering the average hospitalization time for most stroke patients was less than 1 month, then they would move back home or rehabilitation center to continue treatment, and authors of almost all of the studies that included in this review cut the time interval of follow-up into 1 month, 3 months, 6 months, 1 year or longer, we classify the subgroup into acute post-stroke group ($\leq$1 month), subacute post-stroke group (1–6 months), and chronic post-stroke group (>6 months). Our conclusion showed risk of depression was associated with right hemisphere stroke when depression was assessed within 1–6 months after stroke.

Conflicts of interest The authors declare that there is no conflict of interest.

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