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# Poststroke depression and risk of recurrent stroke
## A meta-analysis of prospective studies

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## Abstract

**Background:** Conflicting results have been reported on the association of poststroke depression with recurrent stroke events. This meta-analysis of prospective studies aims to evaluate whether poststroke depression is an independent predictor of stroke recurrence among stroke patients.

**Methods:** A systematic search of articles in PubMed and Embase databases from their inception to October 2018 was conducted. Prospective studies reporting risk estimates of stroke recurrence by depression status in stroke patients were included and pooled risk ratio (RR) with 95% confidence intervals (CIs) of stroke recurrence was calculated for patients with or without poststroke depression.

**Results:** Six studies with 4648 stroke patients were finally included, and the prevalence of poststroke depression was found to from 15.9% to 40.5%. The pooled adjusted RR for stroke recurrence in patients suffering from poststroke depression was 1.48 (1.22–1.79) in a fixed-effect model. Subgroup analyses indicated that poststroke depression significantly increased stroke recurrence (RR 1.64; 95% CI, 1.28–2.10) among ischemic stroke patients but not in total stroke patients (RR 1.28; 95% CI, 0.96–1.73).

**Conclusions:** This meta-analysis suggests that poststroke depression may be an independent predictor of stroke recurrence among ischemic stroke patients. Further studies are required to investigate whether treatment of poststroke depression can reduce the risk of stroke recurrence.

**Abbreviations:** CI = confidence intervals, NOS = Newcastle-Ottawa Scale, PSD = poststroke depression, RR = risk ratio.

**Keywords:** depression, meta-analysis, poststroke depression, recurrent stroke

## 1. Introduction

Stroke remains the main cause of morbidity and mortality worldwide.[1] Survivors of stroke, particularly the ischemic type, are known to be at high-risk for stroke recurrence. Common conventional risk factors for recurrent stroke include hypertension, diabetes mellitus, hyperlipidemia, sleep apnea, obesity, cardiac disease, and stroke subtype.[2] The cumulative risk of recurrent stroke at 1 year was estimated to be 6.7% in

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northeastern Greece[3] and 9.3% in the Black Afro-Caribbean population.[4] Globally, the risk of recurrent stroke is estimated to be approximately 11% within the first year after stroke.[5] As recurrent stroke is associated with high mortality and poor functional recovery, identification of additional risk factors of stroke recurrence is of great importance.

Poststroke depression (PSD) is the most common psychiatric problem after stroke.[6,7] Approximately one-third of all stroke survivors suffer from depression either in the early or late period after stroke.[8] PSD is considered a serious public health concern due to its negative influence on stroke outcomes. Stroke survivors with PSD are at greater risk of, poor functional recovery, recurrent vascular events, deterioration of quality of life, and high mortality than those without depression.[9] However, inconsistent findings[10–15] regarding the association between PSD and recurrent stroke risk have been reported. Despite a recently published systematic review and meta-analysis[16] assessing the predictive value of PSD in stroke recurrence, this outcome has only been analyzed in 2 studies.[11,13]

To the best of our knowledge, no other meta-analysis has yet focused on PSD in predicting of recurrent stroke. Therefore, we conducted a meta-analysis of prospective studies to evaluate whether PSD is an independent predictor of stroke recurrence among stroke survivors.

## 2. Materials and methods

### 2.1. Data source and search strategy

The present study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The Pubmed and Embase databases

were comprehensively searched from their inception to October 30, 2018. The search strategy included combinations of the following terms: "depression" OR "depressive" AND "recurrent" OR "recurrence" OR "relapse" AND "stroke" OR "cerebrovascular disease" AND "follow-up" OR "longitudinal." The articles were restricted to English and Chinese language publications. In addition, reference lists of all related articles were manually examined to identify any gray literature. Ethical approval was not required because this study reviewed the study-level data.

## 2.2. Study selection

The selection criteria of the eligible studies included a prospective design, focus on patients with previous stroke, depression after stroke as exposure, and reported multivariate-adjusted risk estimates of stroke recurrence events among patients with and without PSD. Articles were excluded if depression was diagnosed before stroke onset, the study design was a case–control study or retrospective in nature, outcome reported was not of interest, and reviews or conference abstracts.

## 2.3. Data extraction and quality assessment

The first and second authors independently extracted the following data: first author's surname, year of publication, origin of study, study design, population, sample size, proportion of men, age, assessment method of depression, prevalence of PSD, duration of follow-up, number of recurrent stroke events, multivariate-adjusted risk ratio (RR) or hazard ratio (HR) and 95% confidence intervals (CIs) of stroke recurrence, and covariates adjusted in statistical model. Methodological quality was assessed according to the Newcastle-Ottawa Scale (NOS) for the cohort studies[17] with the following aspects: selection bias, detection bias, and attrition bias. Studies awarding 7 stars or over were deemed as good quality. In case of discrepancy between the 2 authors in terms of data extraction and quality assessment, consensus was achieved through discussion.

## 2.4. Statistical analysis

Data analyses applied the most fully adjusted risk estimate. HRs were directly considered equivalent to RR. The association of PSD with recurrent stroke risk was pooled for the PSD versus without depressed patients. Cochran's $Q$ test (significance level at $P < .10$) and $I^2$ statistic (significance level at $I^2 > 50\%$) were used to assess the heterogeneity across studies. We selected a random-effect model in the presence of significant heterogeneity; otherwise, a fixed-effect model was chosen. Publication bias was evaluated using a funnel plot, Begg's rank correlation test,[18] and Egger linear regression test.[19] To test for the robustness of the pooling results, we performed the sensitivity analyses by sequentially removing one study at each time. Subgroup analyses were performed based on follow-up duration, sample size, type of stroke, study region, study quality, and whether excluded patients with prestroke depression. All statistical analyses were conducted using the STATA 12.0 (Stata Corp LP, College Station, TX).

## 3. Results

### 3.1. Search results and study characteristics

Our preliminary literature search yielded 753 potential records. After removing duplicate publication and irrelevant articles,
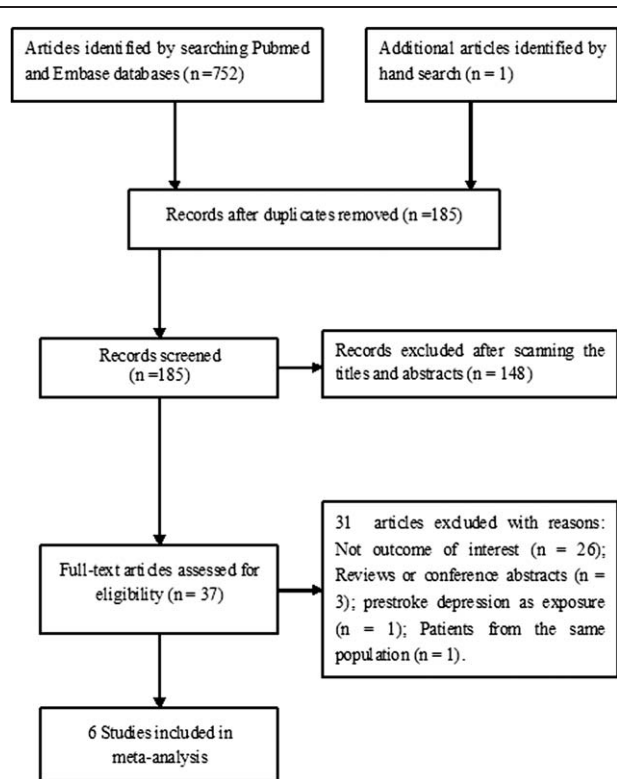


**Figure 1.** Flow chart of the study selection process.

37 articles were retrieved for full-text assessment. After reviewing the full-text articles, 31 studies were further excluded because they did not specify the outcome of interest, included prestroke depression as exposure, included populations overlapping those in other studies, or were designed as reviews and conference abstracts. Finally, 6 studies[10–15] were included in the current meta-analysis. A flow chart of the literature search and selection process is shown in Figure 1.

The main characteristics of the selected studies are shown in Table 1. All of the included studies were published between 2012 and 2016, and the sample size ranged from 182 to 1713. The overall number of patients included in the current meta-analysis was 4648, with 537 recurrent stroke events. The follow-up period was between 6 months and 12 years. Depression was determined by and Hospital Anxiety and Depression Scale,[13,15] Diagnostic and Statistical Manual of Mental Disorders,[10,11] Beck Depression Inventory,[14] and Self-Rating Depression Scale.[12] The methodological quality of the included studies was quantified using the NOS (6–8 stars) and considered to be moderate to high.

### 3.2. Association of PSD with recurrent stroke

All the included studies reported recurrent stroke outcome. As shown in Figure 2, PSD was associated with an increased risk of recurrent stroke (RR 1.48, 95% CI, 1.22–1.79) than those without depressed patients in a fixed-effect model. No significant heterogeneity across studies was found ($I^2 = 23.8\%$, $P = .255$). Begg's rank correlation test ($P = .133$) and Egger's linear regression test ($P = .209$) did not observe evidence of publication bias.

**Table 1**

**Main characteristics of studies included in the meta-analysis.**

| First author, year | Country | Study type | Study population | Men, % | Age, y | Depression measure/ Prevalence | Follow-up duration | Recurrent number OR/HR (95% CI) | Covariates in multivariate analysis | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|
| Yuan 2012 [10] | China | Prospective cohort study | Total stroke 1713 (excluded predepression cases) | 65.6 | 60.4±12 | DSM-IV; 28.1%; 2 wk following stroke onset | 1.0 y | Recurrence: 158 1.49 (1.03–2.15) | Age, sex, hypertension, DM, smoking, alcohol, hyperlipidemia, CVD, NIHSS, history of stroke, ischemic stroke, anti-platelet, lower lipid drug, and anti-depressant drugs | 7 |
| Sibolt 2013 [11] | Finland | Prospective study | Ischemic stroke 223 | 52.0 | 65–77 | DSM-III; 37.0%; from 12 to 20 wk | 12 y | Recurrence: 85 1.68 (1.07–2.63) | Age, sex, DM, PAD, AF, smoking, hypercholesterolaemia, and hypertension | 8 |
| Mei 2013 [12] | China | Prospective study | Ischemic stroke 1074 | 51.0 | 63.7±8.9 | SDS ≥50; 40.5%; at 3 mo | 3.5 y | Recurrence:140 1.41 (0.99–2.01) | Age, sex, education, hypertension, DM, dislipidemia, cardiac disease, overweight or obesity, smoking, and drinking | 7 |
| Ayerbe 2014 [13] | UK | Prospective study | Total stroke 1101 | 54.0 | NP | HADS >7; 32.8% at 3 mo | 5.0 y | Recurrence:72 0.98 (0.60–1.62) | Age, sex, ethnicity, stroke severity, and disability | 7 |
| Jiao 2016 [14] | China | Prospective study | Ischemic stroke 355 (excluded predepression cases) | 57.7 | 52.6±12 | BDI-II ≥14; 23.1%; after discharge | 2.0 y | Recurrence:73 2.02 (1.12–3.64) | Age, sex, education, smoking, alcohol, marriage, hemisphere, stroke severity, infarct size, and sites | 6 |
| Yu 2016 [15] | Australia | Prospective study | Ischemic stroke 182 | 57.1 | 66–82 | HADS >8; 15.9%; 2 wk after discharge | 6 mo | Recurrence: 9 5.22 (1.08–25.12) | Age, sex, and Scandinavian Stroke score | 6 |

AF = atrial fibrillation, BDI = Beck Depression Inventory, CVD = cardiovascular disease, DM = diabetes mellitus, DSM = Diagnostic and Statistical Manual of Mental Disorders, HADS = Hospital Anxiety and Depression Scale, HR = hazard risk, NIHSS = National Institute of Health, Stroke Score, NOS = Newcastle-Ottawa Scale, OR = odds ratio, PAD = peripheral arterial disease, SDS = Self-Rating Depression Scale.
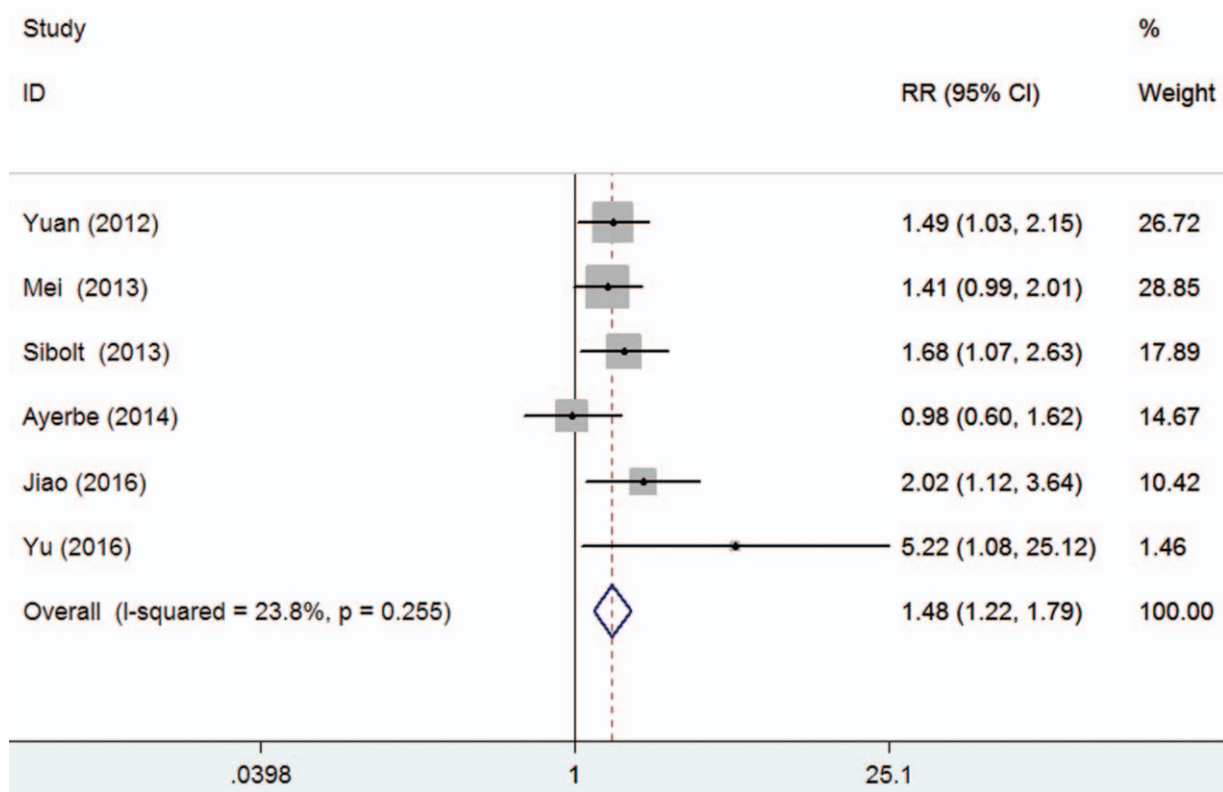
**Figure 2.** Forest plots showing risk ratio and 95% confidence interval of recurrent stroke event for poststroke depression versus without depressed stroke patients.

### 3.3. Subgroup analyses and sensitivity analyses

PSD significantly increased the risk of recurrent stroke in most subgroups except the total stroke subgroup. Thin increase in risk appeared to be strongest in ischemic stroke, follow-up ≤2 years, and exclusion of the prestroke depression case subgroup. Details of the subgroup analyses are shown in Table 2. Sensitivity analyses showed a minimal influence on the quantitative pooled

risk estimate (RR ranged 1.43–1.59 and low 95% CI ranged from 1.18–1.29) when each of the studies was omitted one by one.

### 4. Discussion

This meta-analysis evaluated the impact of PSD on recurrent stroke in stroke survivors. The result of this meta-analysis demonstrated that PSD is associated with an increased risk of

**Table 2**

Subgroup analysis for recurrent stroke risk associated with poststroke depression.

| Subgroup | No. of studies | Pooled RR | 95% CI | Heterogeneity between studies |
|---|---|---|---|---|
| Type of stroke | | | | |
| Total stroke | 2 | 1.28 | 0.96–1.73 | $P=0.184$; $I^2=43.3\%$ |
| Ischemic stroke | 4 | 1.64 | 1.28–2.10 | $P=.352$; $I^2=8.3\%$ |
| Follow-up duration | | | | |
| >2 y | 3 | 1.36 | 1.07–1.73 | $P=.278$; $I^2=21.9\%$ |
| ≤2 y | 3 | 1.70 | 1.25–2.30 | $P=.250$; $I^2=27.9\%$ |
| Sample size | | | | |
| >1000 | 3 | 1.33 | 1.06–1.67 | $P=.382$; $I^2=0.0\%$ |
| <1000 | 3 | 1.89 | 1.34–2.68 | $P=.384$; $I^2=0.0\%$ |
| Geographic region | | | | |
| China | 3 | 1.53 | 1.21–1.93 | $P=.583$; $I^2=0.0\%$ |
| Others | 3 | 1.40 | 1.01–1.94 | $P=.071$; $I^2=62.3\%$ |
| Excluded prestroke depression cases | | | | |
| Yes | 2 | 1.62 | 1.19–2.22 | $P=.391$; $I^2=0.0\%$ |
| No | 4 | 1.40 | 1.10–1.78 | $P=.151$; $I^2=43.4\%$ |
| Study quality | | | | |
| NOS ≥7 | 4 | 1.40 | 1.14–1.71 | $P=.436$; $I^2=0.0\%$ |
| NOS <7 | 2 | 2.27 | 1.31–3.94 | $P=.268$; $I^2=18.5\%$ |

CI = confidence intervals, NOS = Newcastle-Ottawa Scale, RR = risk ratio.

recurrent stroke among stroke survivors. Stroke survivors with PSD had a 48% higher risk of recurrent stroke than those without. The prevalence of PSD varied from 15.9% to 40.5%. In addition, self-described prestroke depressive symptoms were associated with increased risk of stroke recurrence.[20] Early screening and treatment of depressive symptoms may thus present potential benefits in decreasing recurrent stroke rate.

Subgroup analyses showed that studies with the follow-up durations <2 years had a strong association between PSD and stroke recurrence risk. The risk of recurrent stroke weakened with increasing follow-up period, thus suggesting that this association is greatest after the initial stroke onset. Indeed, depressive symptoms most frequently developed within the first year after a stroke.[21] Nevertheless, PSD remained both a long- and short-term prognostic marker of stroke recurrence risk. The predictive significance observed persisted and remained statistically significant across several subgroups stratified by whether removal of prestroke depression cases at enrollment, geographic region, sample size, and study quality. However, subgroup analyses indicated that the pooled risk estimate (RR 1.28; 95% CI, 0.96–1.73) for studies with total stroke patients was not significant.

Avoiding stroke recurrence is the primary target of secondary stroke prevention in order to improve long-term patient prognosis.[22] Apart from recurrent stroke outcome, previous meta-analyses have suggested that besides recurrent stroke outcomes, patients suffering from PSD had a 22% higher risk of mortality than those who do not suffer from depression.[23] Stroke recurrence may further increase morbidity and mortality risk. Therefore, PSD deserves more clinical and research attention.

Given the negative impacts of PSD, whether antidepressant therapy could prevent recurrent stroke outcomes is an interesting subject. One-quarter of 15747 Swedish stroke survivors reported using antidepressant agent at 3 months.[24] Antidepressant use may reflect more severe depression. However, only one included study[10] considered the use of antidepressant drugs in the multivariable statistical models and this study showed a lack of statistical significance (OR 1.96, 95% CI, 0.95–4.04) in the association between PSD and recurrent stroke risk among patients receiving antidepressant drugs. As for individual studies have yielded conflicting evidence on the long-term survival of antidepressant therapy,[25,26] the impact of antidepressant agents in preventing stroke recurrence requires further investigation.

The association between particular lesion location after stroke and the development of PSD remains under debate.[27] A more recent published meta-analysis suggested that left-hemisphere lesions were more susceptible to PSD than right-hemisphere lesions during the subacute phase of stroke.[28] The underlying mechanisms linking PSD with stroke recurrence have not been fully elucidated. Possible explanations include depression is more common in patients with severe stroke than in those with mild stroke, stroke survivors suffering from PSD may be less compliant with treatment than those who do not suffer from depression, and PSD can affect stroke outcomes via the multitude of variables, including as those associated with cerebellar metabolism,[29] cerebral perfusion,[30] inflammatory response,[31] and immune reaction.[32]

Depressive symptoms are common among stroke survivors.[33] The pathogenesis of PSD involves biological and social psychological factors, such as hypothalamic–pituitary–adrenal axis abnormalities, monoamine neurotransmitter change, immunological changes, inflammation, and genetic variants.[34,35] Therefore, management of stroke patients will increasingly require a comprehensive assessment of both laboratory and clinical factors, which would help to improve clinical decision-making and outcome prognostication.

In interpreting the findings of this meta-analysis, several potential limitations should be mentioned. First, the included studies used self-reported scales to determine depression, which may lead to selection bias and underestimate the risk associated with recurrent stroke. Second, depression subtypes were not reported in the included studies and we failed to distinguish the impacts of minor or major depression. Third, information on antidepressant agent use was not reported in most of the original studies, and antidepressant drugs may affect the association between PSD and stroke recurrence. Fourth, the results of subgroup analysis may be unreliable due to the small number of studies analyzed. Fifth, despite the absence of significant heterogeneity in our pooled risk of stroke recurrence, determination of PSD based on different scales and time points presents obvious clinical heterogeneity, which may overestimate or underestimate the actual risk summary. Finally, the predictive significance of recurrent stroke associated with hemorrhagic type of recurrent stroke remains remained unclear. Future studies are warranted to investigate whether the impact of PSD on recurrent stroke is similar for patients with ischemic and hemorrhagic stroke.

## 5. Conclusions

This meta-analysis indicates that PSD may be an independent risk factor of recurrent stroke among stroke survivors. Thus, clinicians should routinely assess depressive symptoms after stroke. Future studies are warranted to investigate the impact of antidepressant agents on recurrent stroke among stroke survivors.

## Author contributions

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**Investigation:** Quan-e Wu, Ai-min Zhou.
**Methodology:** Ai-min Zhou, Xin Shi.
**Project administration:** Xin Shi.
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**Software:** Yun-peng Han, Yan-ming Liu.
**Supervision:** Xin Shi.
**Validation:** Xin Shi.
**Visualization:** Quan-e Wu.
**Writing – original draft:** Yang Yang.
**Writing – review and editing:** Xiao-meng Wang.
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