

## Stroke and depression: A bidirectional link

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### Abstract

A number of studies have assessed the influence of depression on the risk of cardiovascular disease. A growing literature indicates a link between depression and cerebrovascular events, although the direction of this association remains unclear. Numerous data have emerged suggesting an association between depressive symptoms and subsequent risk of stroke, thus leading to the hypothesis that a direct causality between depression and stroke exists. Notwithstanding, how depression may act as a risk factor for stroke is still unclear. Depression might be linked to stroke *via* neuroendocrine and inflammation effects, through correlation with major comorbidities such as hypertension

and diabetes or by intervention of lifestyle behavioral mediators. Finally, antidepressant medications have recently drawn attention for a possible association with increased risk of stroke, although such findings remain uncertain. Depression has been also established as an important consequence after stroke, exerting a significant adverse impact on the course of motor recovery, social functioning and, overall, on quality of life. Post stroke depression occurs in nearly one third of stroke cases, but the exact mechanism leading to depression after stroke is still incompletely understood. In this article, we will review contemporary epidemiologic studies, discuss potential mechanisms and specific aspects of the complex relation between depression and stroke.

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**Key words:** Depression; Mood disorders; Stroke; Post-stroke depression; Antidepressant medications; Cerebrovascular disease

**Core tip:** A number of studies have assessed the influence of depression on the risk of cardiovascular disease. A growing literature indicates a link between depression and cerebrovascular events, although the direction of this association remains unclear. Numerous data have emerged suggesting an association between depressive symptoms and subsequent risk of stroke, thus leading to the hypothesis that a direct causality between depression and stroke exists. Depression has been also established as an important consequence after stroke, affecting functional recovery and quality of life. Contemporary epidemiologic studies, potential mechanisms and specific aspects of the complex relation between depression and stroke will be discussed.

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## INTRODUCTION

According to definition of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), major depressive disorder consists of two or more episodes of depressed mood, loss of interest or diminished sense of pleasure in usual activities for more than 2 wk, in addition to other depressive features sufficient to cause clinically important psychological or physical distress, or functional impairment, that is atypical for usual behavior and not attributable to a medical condition or bereavement<sup>[1]</sup>.

Depression is a highly prevalent condition worldwide, more common among women, with a lifetime prevalence of more than 16% in the general population, and a consequent impact on public health<sup>[2]</sup>. In the last decades, a number of studies have investigated the influence of depression on the risk of developing chronic condition such as diabetes<sup>[3]</sup> and hypertension<sup>[4]</sup>, and also cardiovascular disease<sup>[5]</sup>. Adding to these findings, a growing literature indicates a link between depression and cerebrovascular events, although the exact mechanisms of this association remain unclear.

The presence of depression has been established as an important consequence after stroke<sup>[6]</sup>, affecting functional recovery and quality of life<sup>[7]</sup>. In addition to this evidence, numerous data have emerged pointing toward a relation between depressive symptoms and subsequent risk of stroke as well as common predisposing conditions such as hypertension, diabetes or lifestyle behavioral factor<sup>[8]</sup>, thus leading to the hypothesis that a direct causality between depression and stroke exists<sup>[9]</sup>.

## IS DEPRESSION A RISK FACTOR FOR STROKE?

Several observational studies investigated the relation between depression and the risk of subsequent stroke, with conflicting results (Table 1).

Data from 10 studies published before 2005 were pooled in a first meta-analysis which detected an association between depression and risk of stroke, but with a significant heterogeneity among the studies included<sup>[38]</sup>. Subsequently, many other studies were published and recently summarized in two more detailed meta-analyses<sup>[39,40]</sup>, strengthening the evidence of a possible role of depression as a modifiable risk factor for stroke. According to the meta-analysis of Pan and coworkers, including prospective cohort studies, the pooled HR of stroke among patients with depression is 1.45 (95%CI: 1.29-1.63). Stratifying analysis by pathological stroke subtype, the pooled HR for ischemic stroke is 1.25 (95%CI: 1.11-1.40), while there is no significant influence of depression on the pooled risk of hemorrhagic stroke<sup>[39]</sup>. However, since very few studies have analyzed the association by stroke subtype we cannot draw any conclusion in this regard.

Likewise, a predisposing effect of depression was also observed by Dong *et al.*<sup>[40]</sup> in their meta-analysis (pooled

RR = 1.34; 95%CI: 1.17-1.54 in depressed subjects compared to non-depressed). Even, the INTERSTROKE study, an international multicenter case-control study designed to establish the association of traditional and emerging risk factors with stroke in countries of high, middle, and low income, reported a similar magnitude of the association between depression and an increased risk of all stroke and ischemic stroke (OR = 1.35; 99%CI: 1.10-1.66, and 1.47; 99%CI: 1.19-1.83, respectively), but not intracerebral haemorrhagic stroke<sup>[41]</sup>.

Both meta-analyses found no difference in pooled risk stratifying data by gender<sup>[39,40]</sup>. Although few studies reported age-stratified results, the age difference in the depression-stroke association was also evaluated, resulting in a increased risk in younger subjects [mean age < 65 years, HR = 1.77 (95%CI: 1.30-2.41); mean age ≥ 65 years, HR = 1.30 (95%CI: 1.18-1.44)]<sup>[39]</sup>. In this regard, the Framingham study was the first to find evidence of effect modification by age, examining the elderly and non-elderly groups separately and documenting the association between depressive symptoms and stroke risk in those aged ≤ 65 years<sup>[26]</sup>. Similarly, the Established Populations for Epidemiologic Studies of the Elderly (EPESE) which examined an older population with subgroups aged 65-74 years, and 75 years or older, observed this relation with age, with depression associated with increased stroke risk in younger but not in older participants<sup>[21]</sup>. Recently, in line with these data, the Intervention Project on Cerebrovascular Diseases and Dementia in the District of Ebersberg (INVADE trial), a population-based longitudinal study, corroborated the association between depression and the risk of ischemic stroke, particularly in women and patients younger than 65 years<sup>[35]</sup>. These findings suggest the hypothesis that differences may exist in the depression-associated stroke risk in sub-groups of subjects defined by age and sex, which needs to be investigated and confirmed in further studies.

Is this enough to establish a causal association between depression and subsequent risk of stroke? As pointed out by many authors, most of the studies reported so far present several methodological limitations, and there is evidence of a significant heterogeneity.

First, this depends on differences in study design, sample size and population characteristics. Exclusion of patients with history of stroke is important to avoid the possibility of reverse causality and bias in risk estimation. Both meta-analyses observed a temporal relationship between depression and stroke by including only first-time stroke events that occurred after baseline assessments of depression<sup>[39,40]</sup>. However the possibility that undiagnosed stroke may have caused depression remains, despite efforts to exclude enrollment of participants with preexisting stroke at study entry. Furthermore, the reverse causality hypothesis might apply to the association with stroke as well, because depressive symptoms might be markers of preexisting cerebrovascular disease, as suggested by the vascular depression hypothesis<sup>[42]</sup>. In this regard, the results of two recent analyses from the Rotterdam

Table 1 Risk of stroke according to depression status in prospective studies

Ref.	Population	Follow-up years, (period)	No. of stroke cases	Risk of total stroke (95%CI)	Risk of ischemic stroke (95%CI)	Risk of hemorrhagic stroke (95%CI)	Adjustment for covariates and confounders	Depression assessment	Stroke ascertainment
Vogt <i>et al</i> <sup>[10]</sup>	2573 Men and women aged $\geq 18$ yr	15 (1970/71-1985)	NA	HR 0.84 (0.57-1.22)			Age, sex, socioeconomic status, length of health plan membership, subjective health status, smoking	Depressive index	Death index or vital records
Wassertheil-Smoller <i>et al</i> <sup>[11]</sup>	4367 Men and women aged $\geq 60$ yr	4.5 (1985-1990)	204	RR 0.85 (0.45-1.64)			Age, baseline depression, race, education, smoking, diabetes, history of CVD, activities of daily living	CES-D	Medical records
Everson <i>et al</i> <sup>[12]</sup>	6676 Men and women aged 16-94 yr	29 (1965-1983)	169	RR 1.54 (1.06-2.22)			Age, sex, race, education, hypertension, diabetes, smoking status, alcohol, BMI	HPL Depression Scale	Death certificates
Whoooley <i>et al</i> <sup>[13]</sup>	7518 Women aged $\geq 65$ yr	6 (1988-1994)	94	HR 1.7 (0.8-3.5)			Age, history of MI, stroke, hypertension, diabetes, smoking, perceived health, cognitive function	GDS	Medical records
Jonas <i>et al</i> <sup>[14]</sup>	6095 Men and women aged 25-74 yr	16 (1971/75-1992)	483	RR 1.73 (1.30-2.31)			Age, SBP, education, smoking, BMI, alcohol, physical activity, cholesterol, diabetes, history of heart disease	GWS	Hospital records and death certificates
Larson <i>et al</i> <sup>[15]</sup>	1703 Men and women aged $\geq 18$ yr	13 (1980/1983-1993/1996)	95	OR 2.67 (1.08-6.63)			Age, sex, race, educational attainment, smoking status, history of diabetes, heart problems, high blood pressure	DIS	Self-report and death certificates
Ohira <i>et al</i> <sup>[16]</sup>	879 Men and women aged 40-78 yr	10.3 (1985-1996)	69	RR 1.9 (1.1-3.5)	RR 2.7 (1.2-6.0)	RR 0.9 (0.3-3.1)	Age, sex, smoking status, alcohol use, BMI, SBP, serum total cholesterol level, current treatment with antihypertensive medication, and history of diabetes	Zung SDS	National insurance claims, medical records, clinical diagnosis and death certificates
Ostir <i>et al</i> <sup>[17]</sup>	2478 Men and women aged $\geq 65$ yr	6 (1986-1992)	340	RR 1.30 (0.85-1.99)			Age, sex, marital status, household income, education, smoking status, BMI, heart attack, diabetes, hypertension	CES-D	Self-report and death certificates
May <i>et al</i> <sup>[18]</sup>	2124 Men aged 45-59 yr	14 (1984/1988-1998)	130		HR 1.26 (0.85-1.85)		Age, social class, marital status, smoking status, alcohol use, BMI, SBP, comorbidity (ischemic heart disease, diabetes, respiratory disease, or retirement due to ill health)	GHQ	Medical records
Wassertheil-Smoller <i>et al</i> <sup>[19]</sup>	93676 Women aged 50-79 yr	4.1 (1993/1998-2000)	751	RR 1.01 (0.78-1.3) <sup>1</sup> ; 1.45 (1.11-1.9) <sup>2</sup>			Age, race, education, income, smoking status, BMI, physical activity, hormone use, high cholesterol level requiring medications, diabetes, and hypertension	CES-D and DIS	Self-report and medical records
Gump <i>et al</i> <sup>[20]</sup>	11216 Men aged 35-57 yr	18.4 (1979/1981-1999)	167	HR 1.48 (0.93-2.36)			Age, intervention group, race, educational attainment, smoking at baseline and visit 6, SBP, alcohol consumption, fasting cholesterol and the occurrence of nonfatal cardiovascular events during the trial	CES-D	Death certificates
Avendano <i>et al</i> <sup>[21]</sup>	2812 Men and women aged $\geq 65$ yr	12 (1982-1994)	270	HR age 65-74: 3.05 (1.63-5.7); age $\geq 75$ : 0.95 (0.46-1.98)			Age, sex, race, education and income	CES-D	Self report and medical records





Peters <i>et al.</i> <sup>[31]</sup>	2656 Men and women aged ≥ 80 yr	2.1 (2001-2007)	97	HR 1.82 (1.19-2.78)		Age, sex, treatment group, treatment allocation, country area, educational level, living status, number of comorbidities, previous CVD, previous treatment for hypertension and hypertension	GDS	Self report and medical records
Pan <i>et al.</i> <sup>[34]</sup>	80574 Women aged 54-79 yr	6 (2000-2006)	1033	RR 1.29 (1.13-1.48)	RR 1.11 (0.91-1.35)	RR 1.20 (0.80-1.79)	MHI or self reported diagnosis or ADM use	Self report, medical records and death certificates
Seifert <i>et al.</i> <sup>[35]</sup>	3852 Men and women aged > 55 yr	6.1 (2001/2003-2009)	156	HR 1.3 (0.9-1.89)		Age, marital status, ethnicity, smoking status, alcohol consumption, BMI, physical activity level, menopausal status, postmenopausal hormone therapy, current aspirin or multivitamin use, Dietary Approaches to Stop Hypertension dietary score, parental history of MI	GDS or ADM	Medical reports
Majed <i>et al.</i> <sup>[36]</sup>	9601 Men aged 48-64 yr	10 (1991/1993-2003)	136	HR 1.41 (0.95-2.11)	HR 1.65 (1.07-2.55)	Age, sex, BMI, smoking, hypertension, diabetes, hyperlipidemia, previous MI, previous TIA, previous stroke, history of atrial fibrillation, physical activity		
Jackson <i>et al.</i> <sup>[37]</sup>	10547 Women aged 47-52 yr	12 (1998-2010)	177	OR 1.94 (1.37-2.74)		Age; study centers; socioeconomic factors, including marital status, education level, employment status, physical activity, smoking status, daily alcohol intake, SBP, use of anti-hypertensive drugs, BMI, total and high-density lipoprotein cholesterol, treatment for diabetes, ADM use. Age, education, homeownership, hypertension, diabetes mellitus, heart disease, hysterectomy/oophorectomy, smoking, alcohol use, physical activity, BMI	CES-D	Hospital records and general practitioner records
							CES-D or ADM use	Self report and death certificates

<sup>1</sup>No baseline CVD; <sup>2</sup>With baseline CVD; <sup>3</sup>Group with depression mean age 63 years, group without depression mean age 68 years. n Scale: Human Population Laboratory Depression Scale; GDS: Geriatric. CES-D: Center for Epidemiologic Studies Depression Scale; HPL Depression Scale; GWS: General Well-Being Schedule; Zung SDS: Zung Self-Rating Depression Scale; GHQ: General Health Questionnaire; ADM: Antidepressant medication; DSMMD: Diagnostic and Statistical Manual of Mental Disorders; HLEQ: Health and Life Experiences Questionnaire; PHQ: Patient Health Questionnaire; BDI: Beck Depression Inventory; MHI: Mental Health Index; CI: Confidence interval; NA: Not available; HR: Hazard ratio; RR: Relative risk; OR: Odds ratio; CVD: Cardiovascular disease; BMI: Body mass index; MI: Myocardial infarction; CHD: Coronary heart disease; CRP: C reactive protein; SBP: Systolic blood pressure; ECG: Electrocardiogram; PTCA: Percutaneous transluminal angioplasty; CABG: Coronary artery bypass graft.

Study<sup>[43]</sup> and the Health and Retirement Study<sup>[31]</sup> did not support this hypothesis.

Second, in most studies the influence of several confounders on the final results was not considered. These include, for example, behavioral and lifestyle factors such as alcohol consumption, dietary factors and physical activity, as well as socioeconomic status, which raise the possibility that residual confounders may be partially responsible for the relation between depression and stroke. In this regard, data from a prospective study including a cohort of 1017 subjects with stable coronary disease, aimed at evaluating the influence of baseline disease severity and potential biological or behavioral mediators on the association of depressive symptoms with subsequent cardiovascular events, point towards a role of poor health behaviors, particularly physical inactivity<sup>[8]</sup>.

Third, in most of the studies reported so far there are differences in stroke and depression measures. Stroke case ascertainment is based on a variety of sources, including medical records, death certificates, clinical diagnoses and self-reports. The assessment of depression is more often based on self-rating questionnaires than on a psychiatric structured interview and the DSM criteria.

Although the link between depression and stroke is evident using diagnostic measures of depression<sup>[15,28]</sup>, it is more consistent when using measures of depressive symptoms<sup>[14,16,17,26-27,30]</sup>. Most studies used the Center for Epidemiological Studies Depression scale (CES-D), a self-rating screening test for depression with an adequate internal consistency and reliability. The pooled RR for studies that used CES-D for depression assessment has been estimated to be 1.23 (95%CI: 1.13-1.34)<sup>[40]</sup>. However, we should also consider other types of mood disorder, such as bipolar disorder, which are not measured. In this regard, bipolar disorder has been suggested to be a potential risk factor for vascular disease<sup>[44]</sup> and stroke (HR = 1.24, 95%CI: 1.12-1.38) after adjusting for patients' demographic characteristics, comorbid medical disorders and socioeconomic status<sup>[45]</sup>.

These drawbacks support the need for further studies aimed at investigating the link between affective disorders and stroke. Moreover, both stroke and depression have a high prevalence and incidence. It was estimated that approximately 3.9% ( $n = 273000$ ) of stroke cases in the United States could be related to depression<sup>[39]</sup>. This raises important clinical and public health implications because of the potential of reducing stroke risk by prevention and treatment of mood disorders.

## HOW CAN DEPRESSION LEAD TO STROKE?

So far, various and no fully convincing evidence has been produced to explain how depression may act as a risk factor for vascular disease, including stroke.

A first hypothesis is based on the physiological disturbances linked with depression. These changes have mostly been investigated in relation to cardiovascular disease, and not specifically to stroke. Depression has known neuroendocrine effects, that is, an enhanced activity of the hypothalamic pituitary adrenocortical (HPA) axis and sympathoadrenal hyperactivity<sup>[46,47]</sup>. HPA axis disturbances predict increased circulating catecholamines, endothelial dysfunction, platelet activation and reduced heart rate variability, which could influence stroke risk<sup>[46,48]</sup>. The evidence for an involvement of autonomic cardiovascular dysregulation in depressed patients is revealed also by an increased heart rate response to physical stressors, baroreceptor sensitivity and ventricular instability<sup>[46,48]</sup>. Autonomic dysfunction is also known to influence the risk of atrial fibrillation and depression has been shown to predict atrial fibrillation recurrence after cardioversion<sup>[49]</sup>, suggesting a possible challenging link between depression and stroke that deserves further investigations.

Another mechanism whereby depression can affect the risk of stroke is an inflammation effect<sup>[50]</sup>. Inflammatory markers such as C-reactive protein, IL-1 and IL-6 have been suggested to be associated with depression<sup>[51,52]</sup>. Sparse results also pointed towards a role of some genetic<sup>[53]</sup> and biological markers of thrombotic risk, such as increased levels of fibrinogen<sup>[54]</sup> and increased serotonin and platelet activation<sup>[55]</sup>. The hypercoagulable, platelet-activating and inflammatory effects of depression may all be operant in increasing the risk of cardiovascular events in depressed patients. Notwithstanding, the degree to which these predisposing conditions might explain a significant alteration of the risk of stroke in depressed patients is unknown.

Since depression is correlated with major comorbidities, such as hypertension<sup>[4]</sup> and diabetes<sup>[3]</sup> probably through increased adrenergic activity, a third hypothesis is that depression influences stroke risk through the development of hypertension or diabetes or both. In this regard, some authors have suggested that depression may be a sign of preexisting cerebrovascular disease<sup>[56]</sup>. According to the vascular depression hypothesis, a small-vessel disease secondary to hypertension or diabetes might predispose or at least exacerbate depressive symptoms through impairment of brain regions involved in the regulation of emotions as a direct result of disruption of frontal-subcortical circuits<sup>[42]</sup>. Data from Rotterdam Study indicate an association between the presence of depressive symptoms and the risk of stroke in the general elderly population, but only in men and not in women and the authors discussed the possibility that depressive symptoms could be the expression of a cerebral vascular damage<sup>[27]</sup>. In this view, the association between depres-

sive symptoms and later onset ischemic stroke can be considered an epiphenomenon. The vascular depression hypothesis is also supported by the presence and severity of white matter hyperintensities in elderly groups with depression<sup>[57,58]</sup>. By contrast, data from the Health and Retirement Study, a large national study, provide evidence that depressive symptoms predicted an increased risk of stroke independently of memory impairment, considered a probable early manifestation of cerebral vascular injury<sup>[51]</sup>. This finding suggests that depression is independently associated with stroke rather than a marker of cerebrovascular damage, possibly through other mechanisms that increase stroke risk.

A fourth hypothesis is that the depression-stroke pathway is modulated by the intervention of behavioral mediators, such as smoking, physical inactivity, poor diet and lack of medication adherence, all of which are modifiable factors. In a prospective cohort study of more than 1000 outpatients with stable coronary heart disease, the association between depressive symptoms and cardiovascular events, including stroke, resulted non significant after adjustment for physical activity and other health behaviors (HR = 1.05; 95%CI: 0.79-1.40), suggesting that the increased risk of cardiovascular events associated with depression could potentially be prevented by behavior modifications, especially physical exercise<sup>[8]</sup>. Moreover, in depressed patients the control of vascular risk factors may be suboptimal because of non-adherence to medical treatment<sup>[59]</sup>. In this regard, a meta-analysis showed depression to be a risk factor for reduced medication compliance, with an OR = 3.03 (95%CI: 1.96-4.89)<sup>[59]</sup>.

Finally, depression and stroke might be linked *via* effects of antidepressant medications (ADM).

## ANTIDEPRESSANT MEDICATION USE AND STROKE RISK

The trend of antidepressant use has increased in many countries, including the United States and Europe<sup>[60,61]</sup>. ADM use has recently drawn attention for a possible association with increased risk of cardiovascular events, although such findings remain uncertain<sup>[62-65]</sup>. There is evidence that ADM exposure is correlated with bleeding complication<sup>[66]</sup>, increased inflammation<sup>[67]</sup>, weight gain<sup>[68]</sup>, cardiac toxic effects<sup>[69]</sup> and hypertension<sup>[70]</sup> thus resulting in a possible effects on vascular outcome. The link of antidepressants with stroke development has also been investigated in several studies, with different results. A 20% to 50% increased risk of stroke associated with ADM was shown in a large case-control study<sup>[71]</sup> and in a case-crossover study<sup>[72]</sup>. Recently, data from 6 prospective studies published before 2011 were pooled in a secondary analysis of the meta-analysis of Pan and coworkers, which showed a positive association between ADM use and stroke risk, with an estimated HR = 1.41 (95%CI: 1.25-1.59)<sup>[39]</sup>. Negative findings in randomized trials<sup>[73]</sup> and case-control studies<sup>[74,75]</sup> had also been reported. However, misclassification of depression and the absence of information on dose and duration of treatment in

many studies limit the possibility to understand the link between antidepressant use and stroke. A further confounder is the prescription of ADM for conditions other than depression such as insomnia, headaches and neuropathic pain.

Overall, these findings point out a “paradox” related to the fact that depression is a potential risk factor for stroke, but so it appears to be the use of ADM prescribed to treat depression<sup>[76]</sup>. A key point is whether antidepressants exposure may be considered a surrogate for depression severity, rather than a causal mechanism. The drug-disease association may be expression of underlying differences in vascular risk factor, including depression, among the exposed patients. A recent population-based cohort study found a significant association between depression and risk of stroke regardless of exposure to antidepressant while in patients using only antidepressants an increased risk of stroke was not observed<sup>[77]</sup>. The authors suggested as explanation the possibility of “confounding by indication”, that is the situation in which “the indication for drug use could confound the drug-disease association so that it appears as if the drugs causes the disease”<sup>[77]</sup>.

Among the different classes of antidepressants, selective serotonin reuptake inhibitors (SSRIs) are the first line agents for management of depression today, owing to their relative safety in overdose, tolerability and well-established efficacy. Nevertheless, data from a well-characterized cohort of > 80000 United States middle-aged and elderly women of the Nurses’ Health Study during 6 years of follow-up showed that ADM use was associated with an increased stroke risk (HR = 1.30; 95%CI: 1.08-1.55), with a significant association for selective serotonin reuptake inhibitors (HR = 1.39; 95%CI: 1.13-1.72), but not for other ADM<sup>[34]</sup>, suggesting different effects for SSRIs on the risk of stroke in line with what observed in other studies<sup>[63,72]</sup>.

Despite the antiplatelet effect, SSRIs exposure was associated with an increased risk of ischemic stroke<sup>[71,72,77]</sup>. A possible biological explanation for this association is that serotonin receptors may act on smooth muscle cells leading to a vasoconstriction and, thus, favoring the thrombotic process in atherosclerotic cerebral arteries<sup>[78-80]</sup>.

Consistent with the evidence that SSRIs may increase the risk of bleeding complications owing to the blockade of serotonin reuptake and secondary depletion of platelet serotonin, which may inhibit platelet aggregation<sup>[81]</sup>, a possible association between SSRIs exposure and risk of hemorrhagic stroke has been also reported<sup>[63,72]</sup>, though with mixed results<sup>[71]</sup>. Recently, a systematic review and meta-analysis of 16 observational studies was performed to determine the association between SSRIs use and risk of brain hemorrhage, showing a significant association with both intracranial (RR = 1.51; 95%CI: 1.26-1.81) and intracerebral bleeding (RR = 1.42; 95%CI: 1.23-1.65)<sup>[82]</sup>. Moreover, SSRIs use increased significantly the risk of hemorrhagic stroke in patients concomitantly using oral

anticoagulants compared with patients receiving only oral anticoagulants (RR = 1.56, 95%CI: 1.33-1.83)<sup>[82]</sup>. This raises the issue, when considering SSRIs prescription, of an appropriate patient selection. In particular, caution should be used in those subjects with intrinsic risk factors for intracerebral hemorrhage, such as oral anticoagulant exposure, cerebral amyloid angiopathy or severe alcohol abuse<sup>[83]</sup>. However, more data are needed in this setting.

## POST-STROKE DEPRESSION

Mood disorders are common and important sequelae of stroke. Depression, anxiety disorder, apathy, catastrophic reactions and psychosis are frequently observed after stroke<sup>[84]</sup>. In stroke patients, neuropsychiatric complications may exert a significant adverse impact on the course of motor recovery, social functioning and, overall, on quality of life<sup>[84]</sup>.

## DIAGNOSIS OF PSD AND METHODOLOGICAL PROBLEMS

Post stroke depression (PSD) has been associated with increased disability<sup>[85,86]</sup>, impaired rehabilitation outcomes<sup>[87,88]</sup>, and mortality<sup>[88,89]</sup>. Although many studies have investigated the occurrence of depression among patients with stroke, a real estimate of its prevalence is difficult as a consequence of the wide variability across studies. This is due in part to methodological aspects, such as study population and timing of assessment, and in part to complexity in recognition, assessment, and diagnosis of depression. Furthermore, a contribution to reported differences in the prevalence of PSD may also arise from diagnostic tools used for detection of this disorder. The diagnosis of PSD was assessed on the basis of structured interviews using the diagnostic standards defined by the DSM, while in other studies the assessment is based on the use of cutoff scores in different rating scales. A recent review suggested that, among depression scales, the CES-D, the Hamilton Depression Rating Scale and the Patient Health Questionnaire-9 are adequate options, but they should not be used without a more detailed clinical assessment for an accurate identification of depression in stroke patients<sup>[90]</sup>. Moreover, there is an obvious risk of under or overestimation in the diagnosis of PSD<sup>[91,92]</sup>. In fact, stroke may produce somatic symptoms such as fatigue, sleep disturbance, appetite disturbances that might lead to an overdiagnosis of PSD, while post-stroke neurological disabilities, including aphasia or cognitive impairment, may cause under-recognition of PSD. An under-diagnosis of PSD may be also observed when its assessment is made by non-psychiatrists<sup>[93]</sup>.

As a consequence of this, the issue of how to diagnose depression in stroke patients has been the focus of a large number of studies. The presence of physiological symptoms such as psychomotor retardation, and disturbances in appetite, sleep, and sexual interest that can be



related either to stroke or PSD may affect the diagnosis. Stroke is one of the few conditions listed in the DSM-IV as “directly” causing depression. In this case, PSD is classified within the group of “Mood disorders due to stroke, with depressive features” or “with major depressive-like episode”<sup>[1]</sup>.

The validity of DSM diagnostic criteria for depression among patients with stroke has been assessed in different studies. Depressive syndrome in patients with post-stroke major depression is similar to that observed in patients with major depression without a known medical cause<sup>[94]</sup>. Furthermore, all the symptoms used for the diagnosis of major depression following stroke are significantly more common among depressed patients compared with non-depressed<sup>[91,95,96]</sup>. However, differences between symptoms in major PSD and primary major depression were also described, with more likely catastrophic reactions, hyper-emotionalism, and diurnal mood variations in patients with PSD<sup>[97,98]</sup>. In a recent study, Cumming and coworkers confirmed that PSD has a phenomenological profile similar to that of depression unrelated to brain injury regarding psychological and somatic symptoms. This suggests that the diagnosis of depression based on DSM criteria is valid in patients with stroke<sup>[99]</sup>.

## EPIDEMIOLOGICAL ASPECTS AND COURSE OF PSD

According to the meta-analysis of Hackett *et al*<sup>[6]</sup> including studies published up to 2004, the pooled estimated frequency of depression was of 33% (95%CI: 29%-36%) at any time after acute stroke. The assessment of prevalence rates of PSD is complicated by a considerable variation across studies because of the variability in mood assessment, difference in the selection of cases (*i.e.*, variation in stroke features, clinical characteristics, source of patient recruitment), and timing of assessment. A lower prevalence rates has been generally observed in population studies than in studies conducted in acute hospital setting, rehabilitation hospitals or outpatients clinics, suggesting a potential selection bias. Moreover, the risk of depression is expected to be higher in the first few months after stroke. Quite surprisingly, the meta-analysis showed consistency in the overall frequency of depression across population-based, hospital-based and rehabilitation-based studies and different time intervals from stroke onset<sup>[6]</sup> (Table 2).

A more recent meta-analysis, including data from studies conducted between 1983 and 2011, confirmed that PSD occurs in nearly one third of cases and that this prevalence is independent of time-interval after stroke and study setting<sup>[100]</sup>. The incidence of PSD has been poorly investigated. Recent data from the South London Stroke Register showed an incidence of depression of 16% in the first year after stroke, of 7%-21% in the 15 years after stroke, and a cumulative incidence of 55%<sup>[101]</sup>. Moreover, the few studies comparing the incidence of depression in cohorts of stroke patients with that in

appropriately matched non-stroke cohorts reported a doubled risk in the former group<sup>[102,103]</sup>.

The natural course of PSD seems to be dynamic and dependent on the timing of onset. Longitudinal studies observed that most patients who have depression after stroke became depressed shortly after the acute event, with a greatest increase in the prevalence of PSD during the first months post-stroke despite the overall disability decreases over time<sup>[101,104-106]</sup>. Moreover, although a significant proportion of these patients recovered from depression, the occurrence of new cases made the overall prevalence of depression stable over time. About 15%-50% of patients with early onset PSD has been reported to recover in subsequent assessments within 1 year<sup>[100]</sup>, and to have a higher probability of remission in comparison to patients with later onset depressive episodes<sup>[106]</sup>. Data from a rehabilitation-based study indicates that, at 1 year, 60% of the patients with early depression (0 to 3 mo) had recovered and that those who had not recovered at this follow-up time had a high risk of developing chronic depression<sup>[107]</sup>. In line with these observations, data from a longitudinal study with a 15-year follow-up showed that half of the patients who were depressed at 3 mo had recovered from depression at 1 year, while the other half recovered gradually between years 2 and 9 and that the proportion of recurrent cases rose from 38% at 2 years to 100% at 15 years<sup>[101]</sup>. Therefore, depression is often persistent after stroke, with high risk of relapse even after remission over a long period of time.

Stroke survivors have more than six-fold higher risk of developing clinically overt depression even two or more years after index stroke compared to age-matched controls<sup>[108]</sup>. This suggests that stroke survivors remain at elevated risk for clinically significant depressive symptoms for years after the incident stroke.

According to the results of the Depression in Stroke patients multicenter observational study group, early onset depression appears to be distinct from later onset depression (after 6<sup>th</sup> month) regarding not only time course but also clinical features. Actually, patients with early occurrence of PSD presented more severe symptoms of depression, assessed using the Montgomery-Asberg Depression Rating Scale, than those developing PSD later<sup>[106]</sup>.

## WHAT IS THE PATHOGENESIS OF POSTSTROKE DEPRESSION?

The exact mechanism leading to depression after stroke is still incompletely understood (Figure 1).

In the mid-seventies, the hypothesis that PSD might depend on the anatomic location of brain lesions led to the view of this disorder as a clinical condition related to the interruption of specific pathways involved in mood regulation<sup>[109]</sup>. Subsequently, many reports suggested that left hemispheric lesions involving frontal region, basal ganglia and those the frontal pole are correlated with an increased risk of PSD<sup>[110-114]</sup>. The association between le-



**Table 2** Pooled prevalence of post stroke depression stratified by study setting and timing assessment in the meta-analysis of Hackett *et al*<sup>[6,147]</sup> and Ayerbe *et al*<sup>[100,101]</sup>

	Hackett <i>et al</i> <sup>[6,147]</sup>	Ayerbe <i>et al</i> <sup>[100,101]</sup>
Publication period of included studies	1977-2002	1983-2011
Number of included studies (population: <i>n</i> , 51 (population: 6, hospital: 16, rehabilitation: 29) hospital: <i>n</i> , rehabilitation: <i>n</i> )		43 (population: 6, hospital: 15, rehabilitation: 22)
Pooled prevalence		
Overall	33% (95%CI: 29%-36%)	29% (95%CI: 25%-32%)
Study setting		
Population-based	AP: 33% (95%CI: 29%-37%) MTP: 33% (95%CI: 0%-72%) LTP: 33% (95%CI: 29%-36%)	22% (95%CI: 17%-28%)
Hospital-based	AP: 36% (95%CI: 0%-73%) MTP: 32% (95%CI: 23%-41%) LTP: 34% (95%CI: 24%-45%)	30% (95%CI: 24%-36%)
Rehabilitation-based	AP: 30% (95%CI: 16%-44%) MTP: 36% (95%CI: 20%-39%) LTP: 34% (95%CI: 26%-42%)	30% (95%CI: 25%-36%)
Timing of assessment		
Acute phase (< 1 mo)	32% (95%CI: 19%-44%)	28% (95%CI: 23%-34%)
Medium-term phase (1-6 mo)	34% (95%CI: 20%-39%)	31% (95%CI: 24%-39%)
Long-term phase (6 mo or more) <sup>1</sup> (6 mo to 1 yr) <sup>2</sup>	34% (95%CI: 29%-39%)	33% (95%CI: 23%-43%)
Very long-term phase (> 1 yr)	n.d.	25% (95%CI: 19%-32%)

AP: Acute phase; MTP: Medium-term phase; LTP: Long-term phase; n.d.: Not determined.

sions involving these anatomic regions and depression was even stronger during the first months after an acute stroke<sup>[110,115]</sup>. Though interesting, these data have not been consistently replicated and some studies were also reported showing that depression might be associated with right-hemisphere lesions<sup>[106,115-118]</sup>. Moreover, the hypothesis that depression is influenced by the site of the cerebral lesion was not confirmed in a systematic review by Carson and coworkers. Thus, there is no definitive conclusion on the hypothesis of lateralization and risk for depression<sup>[119]</sup>.

Methodological limitations have been considered to explain these inconsistencies. Boghal and coworkers suggested that the heterogeneity of the results regarding lesions located in the left hemisphere and PSD might depend on whether patients were sampled as inpatients or from the community<sup>[120]</sup>. Moreover, a significant association of PSD with lesions located in the left hemisphere was found in the first month after stroke, in the right hemisphere after 6 mo<sup>[120]</sup>. Thus, it is possible that acute PSD and late PSD might be due to different mechanisms. In the acute phase variations in biogenic amines and modulations of serotonin (5HT) receptor may be involved, while in chronic phase PSD may reflect a failure to adapt to changes secondary to stroke, such as impairment in daily activities<sup>[121,122]</sup>.

Several studies have also explored the potential impact of small vascular lesions and chronic ischemic damage in triggering PSD. Based on the concept of vascular depression, chronic ischemic damage could predispose, precipitate or perpetuate depression in the elderly as a consequence of affecting frontal-subcortical circuits responsible for mood control<sup>[42]</sup>. White matter lesions are conceptualized as a marker of underlying cerebral vascular pathology and they have been described associated with late-onset depression, possibly affecting severity and outcome<sup>[123]</sup>. In line with this, Brodaty and coworkers

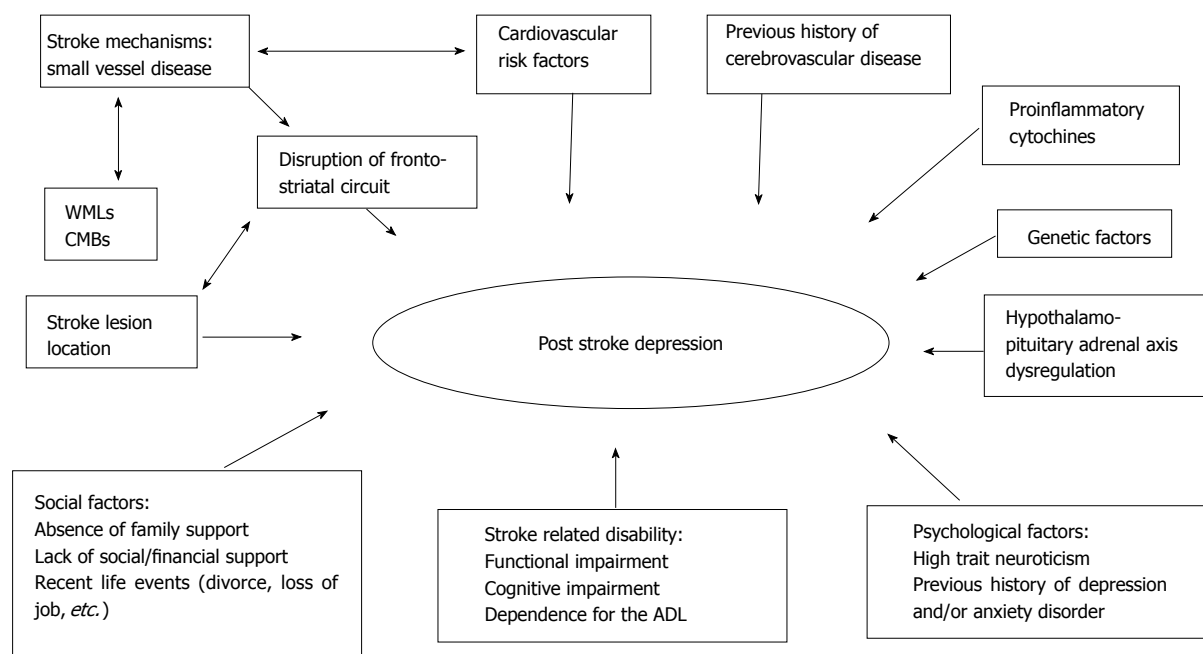
found that PSD may be related to accumulation of vascular lesions rather than site and severity of single stroke, supporting the view that biological factors might be an important determinant of PSD<sup>[124]</sup>. Moreover, in a neuropathological studies of 41 consecutive autopsy cases of patients with stroke it was observed that the vascular burden depending on progressive accumulation of lacunar infarcts within the thalamus and basal ganglia, and of microvascular lesions in deep white matter might have a role in the prediction of PSD<sup>[125]</sup>.

Further support to these findings comes from the growing evidence supporting an association between cerebral microbleeds (CMBs) and occurrence of PSD<sup>[126-129]</sup>. CMBs are common in ischemic stroke and considered as an indicator of underlying small vessel vasculopathy<sup>[130]</sup>. There is some evidence indicating that CMBs could affect not only the risk of PSD but also its severity<sup>[128]</sup>. Furthermore in a recent study, the possibility of non-remission of depression at 1 year follow-up was associated to the presence of lobar CMBs in patients with well-established cerebrovascular disease, suggesting also an influence on outcome<sup>[129]</sup>. Research on the biology of CBMs may provide useful information on the mechanisms of PSD.

Vascular risk factors might also influence the risk of PSD. In particular, hypertension was found to impact significantly the development of post-stroke depressive symptoms<sup>[131,132]</sup>. In line with previous findings, hypertension may be linked to depression following stroke through a development of small vessel vasculopathy.

Additionally, several lines of evidence have shown that stroke determines a perturbation of proinflammatory cytokines, which might influence the inflammatory responses implicated in the pathophysiology of depression<sup>[133,134]</sup>, through a physiological dysfunction of brain structures involved in mood control, such as the limbic system<sup>[133,135]</sup>.

However, feeble and often contrasting results have



**Figure 1** Potential pathogenic pathways of post-stroke depression. WMLs: White matter lesions; CMBs: Cerebral microbleeds; ADL: Activities of daily living.

been reported for the association of PSD with a variety of inflammatory mediators, in particular interleukin (IL)-1 $\beta$ , IL-6, IL-18, tumor necrosis factor  $\alpha$  or C-reactive protein<sup>[136-139]</sup>. A significant association between high serum leptin levels and PSD have also been found at 1-month after stroke<sup>[138]</sup>.

Inconsistent results have also been reported for association between neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and the development of PSD at the acute stage of ischemic stroke<sup>[138,140]</sup>.

The contribution of genetic factors has been also investigated in PSD. A common genetic variant in the promoter region of the serotonin transporter (5-HTT) gene, the short variation length in the 5-HTT-linked polymorphic region (5-HTTLPR, s-allele) has been found to be significantly associated to PSD<sup>[141]</sup>. Patients carrying the s/s genotype have been also reported to have a better response to psychological intervention for PSD<sup>[142]</sup>. The val66met polymorphism of BDNF is another variant which may be implicated in PSD<sup>[143]</sup>.

Other predictive factors for PSD, including female gender<sup>[144]</sup> and previous stroke<sup>[118]</sup>, have been considered with inconsistent results.

Psychosocial factors have been reported to play a role in development of PSD. These include specific personality traits such as premorbid neuroticism<sup>[145]</sup>, previous history of depression<sup>[118]</sup>, living alone, and social isolation with lack of support<sup>[107,126]</sup>. Major recent life events seem to be a strong risk factor for PSD<sup>[118]</sup>. In these cases, the overwhelming psychological nature of stroke can trigger a depressive episode in predisposed individuals or in subjects with inadequate social relations. One year after stroke the persistence of few social contacts outside the immediate family contributes to depression<sup>[107]</sup>. Dependence in the activities of daily living is another important

predictor of depression after the first three months<sup>[107,146]</sup>. In a systematic review of observational studies, Hackett and coworkers found that, despite a wide range of predictive factors, only physical disability, stroke severity, and cognitive impairment resulted consistently associated to PSD<sup>[147]</sup>. As observed by the authors, however, methodological heterogeneity and the limited number of studies on this topic do not allow firm conclusions on how to identify those patients at the greatest risk of developing depression following a stroke. Depression and physical and cognitive impairment in stroke patients may be associated by a bidirectional causal link. Stroke-related disability may trigger depression which, in turn, may reduce patients' compliance to rehabilitation treatments leading to unfavorable functional outcome<sup>[126,147-149]</sup>.

## OUTCOME OF PSD

Depression can exert significant negative impacts on stroke recovery and impair outcome leading to a worsening of cognitive functions, motor abilities and quality of life. It also increases mortality. In a recent prospective population-based study, Ayerbe and coworkers recently reported that the occurrence of depression 3 mo after acute stroke was significantly associated with higher disability, anxiety and a lower quality of life up to 5 years after stroke<sup>[150]</sup>. Moreover, mortality rate during the 5 years following stroke was higher for patients depressed at 3 mo, and recovering from depression at 1 year did not improve prognosis. These patients, in fact, showed a higher mortality risk during the 5 years after stroke (HR = 1.69; 95%CI: 1.09-2.62) compared with those non-depressed<sup>[150]</sup>. Additionally, patients with acute PSD were 3.4 times more likely to die during a 10-year follow-up, compared to patients who were non-depressed after

acute stroke<sup>[151]</sup>.

## CONCLUSION

Strong evidence supports the view that depression and vascular diseases are deeply related, especially in the elderly. The link between depression and stroke observed in epidemiological analyses appears to be bidirectional, being depression both a precursor and an important consequence of stroke. In spite of a wide literature, the mechanisms underlying this association have not been completely clarified. In this regard, it is necessary that future studies use common methodological approaches, based on accurate description and validated scales for depression. Understanding how depression leads to stroke would allow the development of targeted prevention strategies and interventions aimed at reducing depression-related morbidity and mortality. Identifying the subgroup of stroke patients at highest risk of depression should be the first step. Early identification and treatment of PSD may improve stroke rehabilitation outcomes and decrease mortality.

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