

# Effect of Depression on Stroke Morbidity and Mortality

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**Objectives:** This narrative review examines the evidence and discusses the clinical relevance of depression as a risk factor for stroke morbidity and mortality. It also proposes recommendations for future research.

**Methods:** We used the Medline computer database to search the relevant original studies published in English from January 1966 to December 2001. Our key words were as follows: depressive disorder, cerebrovascular disease, stroke, vascular risk factors, and mortality. Articles that investigated the relation between antecedent depression and subsequent stroke morbidity and mortality were collected and reviewed.

**Results:** Since 1990, 8 prospective studies have been published. Among these 8 studies, 6 addressed depression and stroke morbidity, 1 investigated the association of depression with stroke morbidity and stroke mortality, and 1 investigated the association with stroke mortality only. Of 7 studies examining the independent effect of depression on stroke morbidity, 6 were positive. With regard to stroke mortality, 2 studies found an independent association between depression and specific stroke mortality. The contributions and methodological limitations of these studies are discussed.

**Conclusions:** Emerging data suggest an association between depressive symptoms and increased risk for stroke morbidity and mortality. More methodologically sound studies are needed to elucidate causal pathways that link depression and cerebrovascular disease. They are also needed to determine the effect of depression intervention on reducing the risk of cerebrovascular events.

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## Clinical Implications

- Self-reported depressive symptoms may be a long-term risk factor for stroke morbidity and mortality.
- In stroke incidents, the relevance of depression in risk assessment and risk reduction needs to be considered.
- More studies are required to examine the causal relation between depression and stroke.

## Limitations

- This is a narrative review.
- A limited number of studies examine antecedent depression and stroke.
- Self-reported depressive symptoms are not equivalent to diagnosable clinical depression.

**Key Words:** *depression, vascular risk factors, stroke morbidity and mortality*

The association between depressive disorder and physical morbidity and mortality has been a topic of interest for many years. Although depression is unquestionably recognized as a cardiovascular risk factor (1,2), its contribution to stroke risk and survival has received little attention.

Identifying depression as a risk factor for cerebrovascular disease (CVD) may have implications for preventing stroke morbidity and mortality, because depression is a treatable condition. Recent prospective studies have reported a link between antecedent depression and subsequent stroke morbidity

and mortality (3–10). This review examines the evidence that depression is a cerebrovascular risk factor. It discusses the clinical relevance of depression in the risk assessment of stroke and proposes recommendations for future research.

### Cerebrovascular Outcome Studies of Depression

The existing body of literature on stroke morbidity and mortality and depression is small, compared with the numerous studies investigating cardiac morbidity and mortality (1,2,11). This literature review uncovered only 8 prospective studies examining antecedent depression and subsequent stroke risk or survival; the first of these papers was published in 1990 (3–10). Five studies investigated depression and general mortality (12–16) but were not included because they are beyond the scope of this review. Moreover, 4 of these (12–15) were reviewed elsewhere (17). Of the 8 studies included, 6 examined only the relation of depression and stroke morbidity risk (3–8), 1 examined the relation of depression and stroke mortality (10), and 1 examined the relation of depression and stroke morbidity and mortality risk (9). Table 1 outlines the essential details of each study, including subject characteristics, instruments used to define depression, study length, variables controlled, and summarized results.

Regarding depression and stroke morbidity risk, among 7 prospective epidemiologic studies (3–9), 6 have shown positive results (4–9). After controlling for confounding and potential risk factors, 3 studies have documented the independent effect of baseline depression on stroke morbidity in initially stroke-free subjects (6–8), as have 2 studies of high-risk elderly subjects with hypertension and cardiovascular and cerebrovascular diseases (4,9). In 1 study, baseline depressive symptoms did not predict subsequent stroke, but the increase in depressive symptoms over time was an independent predictor of stroke and cardiovascular death in elderly subjects with hypertension (5). With respect to stroke mortality outcomes, Everson and others provide the strongest evidence that baseline depressive symptoms and increased depressive scores from baseline independently predict stroke mortality after time-dependent and independent variables are controlled (10). Similarly, Simons and others have reported that baseline depressive scores in the upper tertile were independently associated with a higher risk of fatal stroke (9).

All the prospective studies controlled for baseline confounding variables and vascular risk factors and then examined the independent effect of depression on stroke risk (3,4,6). Two studies used reasonably advanced analysis that allowed time-dependent changes in the risk-adjusted estimation (5,10). Everson and others and Wassertheil-Smoller and others used a time-dependent covariate model that allowed changes in some variables during the follow-up (that is,

changes in medical illnesses, depressive scores, and activities of daily living) and a time-independent covariate model (that is, sex and race) in their analyses (5,10). Interestingly, in the Dubbo study, well-established stroke factors such as coronary heart disease, diabetes mellitus, cholesterol levels, and cigarette smoking did not predict stroke outcome, whereas depression emerged as an independent risk factor for ischemic stroke (9). Since a significant proportion of elderly subjects had a history of stroke and vascular diseases at baseline, it is possible that vascular depression (that is, depression attributable to CVD) (18) may be a risk factor for stroke recurrence. This is discussed in more detail below.

Few studies have examined the effect of specific depressive symptoms, ethnicity, sex, and age on the association between depression and cerebrovascular outcomes. Among depressive symptoms, severely elevated levels of hopelessness were associated with stroke incidence in the follow-up of initially stroke free individuals (6). Anxiety symptoms did not predict the increased risk of stroke, and controlling for anxiety symptoms did not weaken the association between depression and stroke (6). With respect to ethnicity, blacks with higher depressive symptomatology had an increased risk of stroke, compared with whites (6). A sample of Japanese subjects also showed the independent effect of depressive symptoms on stroke risk, as did subjects of European descent (7). Regarding sex, the depressive measures seem to increase the risk of stroke morbidity more often in women than in men (5). Taking into account the higher proportion of stroke mortality among overall deaths in women, compared with men (19), it would be interesting to determine sex differences in depression-associated stroke mortality. Regarding age, in both predominantly middle-aged (25 to 59 years) and old-age (60 to 74 years) groups, higher depressive symptoms were found to be associated with increased stroke risk (6). Another study reported a similar significant interaction between depression score and age, suggesting that high depressive symptoms scores predicted stroke risk only in the old-age group (70 years or older) (9).

Consistent with the longitudinal data, a few cross-sectional studies have also shown evidence that depression has a causal role in CVD. Lenze and others demonstrated an independent effect of depression, as well as an interactive effect of advancing age and depression, for small white matter lesions in physically healthy subjects with depression but without cerebrovascular risk factors (20). Another recent study has shown decreased cerebrovascular reactivity to carbon dioxide challenge tests in elderly depression patients (21). Although decreased cerebrovascular reactivity may predict stroke, the absence of longitudinal observation of cerebrovascular reactivity during depression and remission may prevent any

<b>Table 1 Stroke morbidity and mortality studies of depression</b>						
Author (year)	Study subjects	Instrument and method	Assessments	Total duration of follow-up	Variables controlled	Results
<b>Stroke morbidity</b>						
Colantonio (1992)(3)	Elderly subjects n = 2604 W/M = 59%/41% White subjects = 79% MA = 74 y	CES-D Dep ≥ 16	Baseline and 7 y	7 y	Age, sex, hypertension, diabetes, physical function, smoking, housing stratum	Depression scores but not baseline depression (≥ 16) predicted stroke morbidity in univariate analysis. No independent association between baseline depression scores and stroke risk was seen.
Simonsick (1995)(4)	Hypertensive elderly (≥ 65 y) n = 10294 W/M = 6256/4038 MA = na	CES-D High > 15 Low < 15	Baseline, 3 y, and 6 y	6 y	Age, disability, diabetes, angina, digitalis use, history of MI and stroke	Stroke morbidity is 2.3 to 2.7 times higher in group with high depression symptoms (15). Controlling for confounding variables reduced the significance. Men from Iowa Centre had low depression symptoms associated with increased stroke risk.
Wassertheil Smoller (1996)(5)	Elderly subjects (≥ 60 y) with systolic hypertension n = 4367 W/M = 53%/37% White subjects = 79% MA = 72 y	SCDSS CES-D Dep ≥ 16 CES-D as continuous measure	Baseline and semi-annually	4.5 y	Baseline depression and ADL, age, sex, race, randomization group, years of education, history of stroke, MI, diabetes, smoking, time-dependent variables: changes in ADL	5-point increases in CES-D scores over time increase the risk of stroke for all (RR = 1.21; 95%CI, 1.08 to 1.35) or for women (RR = 1.29; 95%CI, 1.13 to 1.48). No association between baseline depression (≥ 16) and stroke risk was seen.
Jonas (2000)(6)	Stroke-free adults n = 6095 White men = 2497 White women = 2860 Black subjects = 738 Age range 25–74 y	GWB-D High 0–12 Intermediate 13–18 Low 19–25	Baseline, 11–13 y, 15 y, 16 y, or 21 y and 8 months	16–21 y and 8 months	Age, race, sex, education, smoking status, body mass index, alcohol use, nonrecreational physical activity, serum cholesterol, history of diabetes or heart disease, systolic blood pressure	High depression (scores of 0–12) independently predicted stroke in all persons (RR = 1.73, 95%CI, 1.30 to 2.31), white men (RR = 1.68, 95%CI, 1.02 to 2.75), black persons (RR = 2.60, 95% CI, 1.40 to 4.80). Intermediate level depression (scores, 13 to 18) also increased stroke morbidity (RR = 1.25, 95%CI, 1.02 to 1.52)
Ohira (2001)(7)	Stroke free adults n = 879 W/M = 568/311 Age range 40–78 y	SDS Low ≤ 30 Medium 31–34 High ≥ 35	Baseline, 10.3 y	10.3 y	Age, sex, body mass index, systolic blood pressure, serum cholesterol, cigarette smoking, alcohol, history of diabetes, antihypertensive medications	High depression symptoms (≥ 35) independently predicted total stroke (RR = 1.9, 95%CI, 1.1 to 3.5) and ischemic stroke (RR = 2.7, 95%CI, 1.2 to 6.0)
Larson (2001)(8)	Adults (18 y) n = 1703 W/M=1071/632 White subjects = 1059 Black subjects = 588 Other = 56 MA = na	DIS Dysthymia Dep disorder (major dep and dep syndrome)	Baseline, 13 y	13 y	Age, sex, education, diabetes mellitus, heart problem, hypertension, tobacco use, antidepressant treatment	Depression disorder (major depression and dysphoria with 2 or more depression symptoms) independently increased the risk of stroke (RR = 3.08, 95%CI, 1.26 to 7.52). Dysthymia had a tendency to be a risk for stroke (RR = 2.65: 95%CI, 0.69 to 10.11).
<b>Stroke morbidity and mortality</b>						
Simons (1998)(9)	Elderly n = 2805 W/M = 56%/44% MA = 69 y	CES-D Dep scores in tertiles.	Baseline and postal surveys every 2 y	8 y and 2 months	Age, sex, marital status, prior history of stroke, body mass index, antihypertensive drugs, blood pressure, atrial fibrillation, HDL cholesterol, peak expiratory flow, physical disability	Baseline depression (tertile III) independently predicted all stroke (RR = 1.41, 95%CI, 1.01 to 1.96) and fatal stroke (RR = 2.30, 95%CI, 1.14 to 4.64).
<b>Stroke mortality</b>						
Everson (1998)(10)	Stroke free adults n = 6676 W/M = 54.2%/45.8% MA = 43.4 y	HPL-DS Dep ≥ 5 Non-dep < 5	Baseline, 9 y, and 18 y	29 y	Age, sex, race, education, alcohol, smoking, body mass index, history of hypertension and diabetes, time-dependent variables: changes in depressive symptoms and risk factors	Depression symptoms > 5 independently increased the risk of stroke mortality (HR = 1.54, 95%CI, 1.06 to 2.22).
W = women, M = men, MA = mean age, y = years, na = not available, HR = Hazard ratio, RR = relative risk, CES-D = Centre for Epidemiological Studies Depression Scale, HPL-DS = Human Population Laboratory Depression Scale, GWB-D = General Well Being Scale-Depression, SDS = Zung Self-Rating Depression Scale, SCDSS = Short Care Depression Symptoms Scale, ADL = Activities of daily living, HDL = high-density lipoproteins, Dep = depression, DIS = Diagnostic Interview Schedule. MI = myocardial infarction.						

definitive conclusions on depression's causal role in impaired cerebrovascular reactivity.

In contrast to the positive studies, Colantino and his colleagues failed to demonstrate the significance of baseline depression scores on stroke morbidity when medical and other confounding variables were controlled (3). Methodological differences in duration of follow-up and in frequencies of baseline vascular diseases could account for this inconsistency. The total duration of follow-up in the Colantino and others study was 7 years (3), while the duration of follow-up in 3 other comparable positive studies involving stroke-free individuals at baseline was 16 years (with a maximum length of 21.8 years) (6), 10.3 years (7), and 13 years (8). However, a different set of 3 positive studies involving elderly subjects had a follow-up duration similar to that of the negative study (4,5,9). Nevertheless, the baseline frequency of vascular diseases (that is, hypertension, stroke, and myocardial infarction) in the elderly subjects of positive studies was higher than in the negative study. Further, participants in the negative study were nonrepresentative on sociodemographic variables (that is, education and income) and, hence, were not comparable with positive studies (3).

## Methodological Limitations

### *Use of Self-Report Instruments*

Most of the epidemiologic studies discussed above used self-report instruments to evaluate and quantify depressive symptoms (3–7,9,10). However, depressive symptomatology determined by self-report is not equivalent to diagnosable clinical depression, although it may reflect nonspecific, subjective psychological stress (22). In addition, the meaning of self-reported depressive symptoms in the context of severe comorbid medical illnesses remains unclear. More work is needed to clarify whether self-reported depressive symptoms reflect the severity of medical conditions or depressive illness, or both. Another issue is the validity and reliability of these depressive measures in elderly populations. Though the Centre for Epidemiologic Studies–Depression (CES-D) scale has been shown to have sound psychometric properties with high specificity, sensitivity, and predictive validity in a stroke population (23), it is not clear whether other depressive measures, such as the General Well-Being Depression (GWB-D) scale (24) and the Human Population Laboratory depressive scale (25), have been validated in elderly populations with medical diseases or stroke.

The use of self-report measures and a structured psychiatric interview in 2 stages would improve the accuracy of clinical depression diagnoses but may not be practical in large epidemiologic studies. Some studies have used structured psychiatric interview surveys. The Epidemiologic Catchment

Area (ECA) Study used the Diagnostic Interview Schedule (DIS), a structured survey instrument developed by the National Institutes of Mental Health (NIMH) to detect depression and its subtypes (8). The DIS appears to be a useful tool that can be used by trained lay interviewers to determine caseness of depression as well as its subtypes in large epidemiologic studies.

### *The Issue of Confounding Variables*

Reliance on self-report measures of medical comorbidities without corroborating medical record data is a major shortcoming in some studies. Everson and others used self-report measures of hypertension and diabetes as indicators of medical comorbidity (10). A better objective measure of physical comorbidity or medical sickness variables (such as physician or hospital report and medication review) might have further weakened the association between depression and CVD outcomes, or it might have strengthened the association between medical comorbidity and stroke incidence or mortality. In the study by Simonsick and others, marriage and education were 2 sociodemographic confounding variables between high- and low-depression groups; however, they were not adjusted to determine the independent effect of depression on stroke incidence (4). Further, 2 studies that used a time-dependent covariate model neglected to include time-dependent psychosocial variables, such as death of spouse; loss of significant others; changes in social support, marital, financial, and job situation; and changes in medications (5,10).

### *Data on Mechanisms*

The baseline chronological relation between depression and vascular diseases such as hypertension, diabetes mellitus, coronary artery diseases, and stroke was not known. Hence, it could be argued that depression may be a consequence of cerebral ischemic changes (that is, vascular depression) (18), or it may be secondary to vascular diseases; hence, depression may be an intervening variable between vascular diseases and stroke incidence. Further, vascular abnormalities or atherosclerosis may be a common etiologic factor for both depression and stroke. Simonsick and others (4) and Wassertheil-Smoller and others (5) acknowledge this limitation in their studies.

The mechanisms of association between baseline vascular diseases with depression and stroke outcome will be different from that of vascular diseases without depression. Most studies demonstrated that the effect of depression on stroke outcomes was independent of baseline vascular diseases (4–10); however, without baseline brain imaging and Doppler studies in depression patients with vascular diseases, it is not possible to completely rule out the impact on stroke outcomes of asymptomatic cerebral atherosclerosis, such as silent infarcts and white matter ischemic lesions. Further, almost all the

studies failed to collect data on the care process or on the progression of medical illnesses during follow-up, although poor medical management owing to depression-related self-neglect and noncompliance is a proposed mechanism linking depression and stroke. Another, related issue is that cognitive impairment associated with depression, medical illness, or medication in the elderly may affect compliance with medical management, thereby increasing morbidity and mortality (26). Some prospective studies of elderly subjects failed to examine or control the effect on the association of depression and stroke risk of cognitive deficits at baseline or during follow-up (4,5,9).

Some studies did not periodically assess the change during follow-up in baseline depression severity and medical illnesses (3,7,8). This lack of assessment prevents evaluation of dose–response relations between chronicity or recurrence of depression and stroke outcomes. It also means that the impact of the time-dependent progression of medical illness on the association between depression and stroke outcome cannot be evaluated. Importantly, in epidemiologic studies examining the long-term effects of risk exposure, the time-dependent covariates are often both potential confounders and intermediate variables or effect modifiers. The above-mentioned studies used conventional statistical approaches to adjust for time-dependent covariates, but these approaches are not considered appropriate for control of variables that could be both confounders and intermediate. Some authors have suggested the G-estimation method to adjust for both confounding and intermediate causal effects (27).

#### *Shortcomings in Outcome Measures*

The report on depression and stroke mortality did not have data on the types of stroke mortality (10). This information would be useful, because depression may have differential effects or different mediating factors on ischemic or hemorrhagic stroke events. In some studies, stroke outcome was determined by self-report, which may not be as sensitive as medical records (4). Moreover, elderly persons with depression are more likely to express somatic symptoms, which might result in differential or higher self-report of stroke, compared with elderly persons not suffering from depression. Further, more attention was given to macrovascular outcomes, while other cerebrovascular outcomes, such as microvascular disease, vascular dementia, and transient ischemic attacks, were neglected. Only 1 study included transient ischemic attack as a stroke outcome (9). The exclusion of transient ischemic attacks in other studies may have reduced the effect sizes; it also limited our understanding of depression's role in the evolution of stroke.

#### *Missing Data*

In the Everson and others study, only 50% of the data from 1 of 2 follow-up assessments (1974 and 1983: 50% sample) were available for analysis. Further, data from 2 follow-up time points (1994 and 1995) were not included in the analysis (10). It is possible that including all the follow-up data would have changed the results or effect sizes. Moreover, if people with depression are more likely to be lost to follow-up, it will lead to underestimating the association (nonresponse bias). Variables of great significance that were missing from almost all these studies include psychostimulant abuse (for example, cocaine and amphetamines), use of psychotropic medication, antidepressant treatment, and hormonal treatment (for example, estrogen and progesterone).

#### **Discussion**

Several limitations related to this review process need to be acknowledged. First, although this paper represents the most comprehensive review to date of studies on depression and stroke morbidity and mortality, the existing body of literature is small. Second, this is a narrative review that falls short of metaanalysis in scientific merit. However, as noted, the data are limited, and effect sizes are not comparable across studies because they were computed with different methods. Third, methodological variations in sample composition, depressive measures, duration of follow-up, periodic assessments, and statistical analysis pose problems when comparing the results of these studies; therefore, it is difficult to synthesize the evidence. Fourth, this review does not include studies published in non-English literature. Fifth, negative results concerning cerebrovascular outcomes may not have been reported in earlier physical morbidity and mortality studies of depression. Nevertheless, despite the shortcomings in these studies and in this review process, the inferences drawn from population-based prospective epidemiologic studies using large cohorts allows us to address the issue of a causal relation between depression and stroke outcomes, as well as the importance of depression in cerebrovascular risk assessment. Further, most of the observed shortcomings are inherent in large epidemiologic studies; they should be considered as opportunities for future studies, rather than as major failures of the previous studies.

#### *Causal Nature of the Relation*

The prospective studies provided evidence for a temporal relation between antecedent depression and stroke morbidity (4–9), and the strength and consistency of the relation has been demonstrated by the predominance of positive studies (6 of 7) examining depression and stroke morbidity (4–9). With respect to the dose–response relation, several studies using depression self-report instruments showed that, compared with low depressive scores, baseline high depressive scores

predicted stroke morbidity (4,6,7). Similarly, another study showed that depressive disorders (that is, the group comprising major depression and subthreshold major depression), but not dysthymia, were an independent risk factor for stroke (8). Further, a growing body of literature illustrates the biological plausibility of the association: major depressive disorder is associated with postmyocardial infarction arrhythmia (28), platelet activation and increased propensity for platelet adhesion (29), heart-rate variability (30), and insulin resistance (31). The reported activation in major depression of the hypothalamus–pituitary–adrenal axis (32), the sympathomedullary system (33), and the immunological system (34), as well as a decrease in cerebrovascular reactivity (21), might also contribute to the development and progression of vascular diseases. Finally, evidence pointing to the effect of antidepressant treatment or clinical recovery on cerebrovascular risk reduction would confirm a causal relation, but owing to insufficient data, it is difficult to comment on the effect of depression recovery on stroke outcomes. In conclusion, the observed strength and consistency in the data supporting an independent effect of antecedent depression on subsequent stroke risk, and the emerging data on a dose–response relation, as well as the illustrated biological plausibility of this association, suggest a causal relation.

#### *Depression in Cerebrovascular Risk Assessment*

Risk assessment may be considered as premature, owing to limited data. To change the outcome, however, it will be important for future research to estimate risk potency and risk management. Statistical measures of potency (odds ratios, risk ratios, relative risk, and hazard ratios) can be used to determine the potency of depression as a risk factor for defining groups at high and low risk for stroke morbidity and mortality (see Table 1). The 5 positive studies on depression and stroke risk suggest an average relative risk of 1.86—a significant effect, but one difficult to generalize, owing to the small number of studies (5–9). Hence, the characterization of depression as a high or major risk factor for stroke is incomplete without further empirical evidence. As an alternative, risk classification for stroke can be developed using multiple risk factors to define high and low risk groups. Some risk factors, such as hypertension and cardiovascular disease, may be more potent than depression, but the combined use of several risk factors simultaneously increases the potency when risk factors interact synergistically or additively. Significant interactions of depression with ethnicity, sex, age, and social ties have been reported. More studies examining the interactive effect of depression with other stroke risk factors in a multivariate risk model are needed. Further, on the basis of multiple risk factors, a mathematical function of several risk factors (a risk score) can be developed.

In risk management, the typology of risk factors needs to be defined. Depression can be considered as a variable risk factor, because changes in depression can occur spontaneously or by intervention (35). If clinical recovery from depression can be shown to change the risk of stroke outcome, then depression can be regarded as causal risk factor; otherwise, it can be viewed as a variable marker (35). Without data concerning the effect on cerebrovascular outcomes of treatment-induced clinical recovery from depression, our understanding of depression risk management is limited. Policy recommendations for developing a cost-effective structure to identify and treat depression as a preventive strategy for stroke outcome may require substantial evidence suggesting that treating depression has a beneficial effect on stroke risk reduction. However, even if depression emerges as a variable marker or an epiphenomenon of atherosclerosis, treating it may improve quality of life and functioning in high-risk populations.

#### **Conclusions and Future Directions for Research**

This review suggests that self-reported depressive symptoms are probably a long-term prospective risk factor for ischemic stroke. Future studies should be methodologically sound and rigorous. The recommended investigative strategies include using a prospective, longitudinal, case control or cohort design and structured clinical interviews or surveys with a symptom-severity scale. In addition, it will be important to control for objectively measured baseline medical and socio-demographic variables, as well as for time-varying and time-constant variables. Finally, future studies should use both well-defined specific and broader cerebrovascular outcomes. Since the causal relation is critical to the clinical and policy decision-making process in risk assessment and management, a complete and clear understanding of whether depression is a causal cerebrovascular risk factor is essential.

Sophisticated statistical analysis, such as the G-computation algorithm, should be considered for separating the direct effect of depression from the indirect effect of intermediate variables (27,36). Time-dependent variables such as hypertension and cardiovascular disease can be simultaneously confounders and intermediate variables; therefore, future studies should use G-estimation methods that allow variables to be appropriately adjusted for both confounding and intermediary effects (27). Understanding both direct and indirect causal effects of depression may have implications for preventing stroke morbidity and mortality. If increased stroke risk in patients with depression is partly due to the indirect or interactive effects of medical illness (an intermediate variable), treating depression may reduce stroke risk by improving the management of medical illnesses through increased compliance with medication and exercise. Clinical recovery from

depression may also reduce the progression of vascular diseases, and thereby the stroke risks, because depression may also contribute to the initiation and progression of vascular risk factors (37–41).

To determine whether depression has a direct effect on stroke risk, we require more focused research on dose–response relations, biological and psychosocial causal pathways, and the effects of treatment (for example, antidepressants and psychosocial interventions) on prevention and reduction of cerebrovascular risk. With regard to dose–response relations, prospective studies should examine the relation between depression severity, type, chronicity, and recurrences or relapses and stroke morbidity and mortality. Ceiling effects or biological compensatory mechanisms need to be examined if the dose–response relation fails to establish causal effects of depression on cerebrovascular outcomes. Baseline and periodic evaluation of the common biological markers of depression and atherosclerotic vascular diseases (that is, hypercortisolism, sympathoadrenal system hyperactivity, insulin resistance, immune activation, and platelet adhesion) might allow us to determine biological pathways that mediate depression-related cerebrovascular morbidity and mortality. Vascular challenge studies examining cerebrovascular reactivity during depression and remission, together with the prospective follow-up of the same cohorts, would help to determine whether depression has a direct effect on cerebrovascular reactivity and whether clinical recovery from depression improves cerebrovascular reactivity and reduces the long term stroke risk (42). The possible compounding effect of antidepressant medications on cerebrovascular reactivity and on depression-associated increased CVD morbidity or mortality also needs to be determined prior to validating depression as the causal cerebrovascular risk factor. Animal models can be used to examine the effect of antidepressants on cerebrovascular reserve or reactivity.

Future studies should also focus on psychosocial causal pathways that connect depression with cerebrovascular outcomes. The documented association of feelings of hopelessness with the prevalence and progression of carotid atherosclerosis (41) and stroke incidence (6), as well as the association between poor social support or ties and general mortality in stroke patients with depression (12), may require replication, because these findings may have major implications in risk management. More studies are needed to examine the effect of age, sex, and race on this relation and also to examine age-, sex-, and race-specific causal pathways, because these interactions may have implications for identifying and managing risk groups. The comparative effectiveness of various treatment modalities (that is, psychosocial interventions vs psychopharmacological treatment, or a combination of these) in reducing or preventing depression-related stroke risk remains to

be determined. In summary, research on depression risk factors for cerebrovascular outcomes is very important from both a clinical and public health point of view. More rigorous research reporting in this area is warranted to guide depression risk assessment and management to reduce the risk for stroke morbidity and mortality.

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### Résumé : Effet de la dépression sur la morbidité et la mortalité de l'ACV

**Objectifs :** Cette étude narrative examine les preuves et discute de la pertinence clinique de la dépression comme facteur de risque de la morbidité et de la mortalité des accidents cérébrovasculaires (ACV). Elle propose également des recommandations pour la future recherche.

**Méthodes :** Nous avons utilisé la base de données informatique Medline pour chercher les études originales pertinentes en anglais, de janvier 1966 à décembre 2001. Nos mots clés étaient les suivants : trouble dépressif, maladie cérébrovasculaire, accident cérébrovasculaire, facteurs de risque vasculaire, et mortalité. Les articles portant sur la relation entre la dépression antécédente et la morbidité et la mortalité d'un ACV subséquent ont été recueillis et étudiés.

**Résultats :** Depuis 1990, 8 études prospectives ont été publiées. Sur ces 8 études, 6 abordaient la dépression et la morbidité de l'ACV, 1 étudiait l'association de la dépression avec la morbidité de l'ACV et la mortalité de l'ACV, et 1 examinait l'association avec la mortalité de l'ACV seulement. Des 7 études examinant l'effet indépendant de la dépression sur la morbidité de l'ACV, 6 étaient positives. En ce qui concerne la mortalité de l'ACV, 2 études ont constaté une association indépendante entre la dépression et la mortalité spécifique à l'ACV. Les contributions et les limitations méthodologiques de ces études ont été discutées.

**Conclusions :** Les données trouvées suggèrent une association entre les symptômes dépressifs et le risque accru de morbidité et de mortalité de l'ACV. Il faut des études plus solides sur le plan méthodologique pour clarifier les voies causales qui lient la dépression et la maladie cérébrovasculaire. Elles seront aussi nécessaires pour déterminer l'effet de l'intervention en dépression sur la réduction du risque d'accidents cérébrovasculaires.