Depression and Risk of Stroke Morbidity and Mortality

A Meta-analysis and Systematic Review

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Context Several studies have suggested that depression is associated with an increased risk of stroke; however, the results are inconsistent.

Objective To conduct a systematic review and meta-analysis of prospective studies assessing the association between depression and risk of developing stroke in adults.

Data Sources A search of MEDLINE, EMBASE, and PsycINFO databases (to May 2011) was supplemented by manual searches of bibliographies of key retrieved articles and relevant reviews.

Study Selection We included prospective cohort studies that reported risk estimates of stroke morbidity or mortality by baseline or updated depression status assessed by self-reported scales or clinician diagnosis.

Data Extraction Two independent reviewers extracted data on depression status at baseline, risk estimates of stroke, study quality, and methods used to assess depression and stroke. Hazard ratios (HRs) were pooled using fixed-effect or random-effects models when appropriate. Associations were tested in subgroups representing different participant and study characteristics. Publication bias was evaluated with funnel plots and Begg test.

Results The search yielded 28 prospective cohort studies (comprising 317 540 participants) that reported 8478 stroke cases (morbidity and mortality) during a follow-up period ranging from 2 to 29 years. The pooled adjusted HRs were 1.45 (95% CI, 1.29-1.63; *P* for heterogeneity <.001; random-effects model) for total stroke, 1.55 (95% CI, 1.25-1.93; *P* for heterogeneity = .31; fixed-effects model) for fatal stroke (8 studies), and 1.25 (95% CI, 1.11-1.40; *P* for heterogeneity = .34; fixed-effects model) for ischemic stroke (6 studies). The estimated absolute risk differences associated with depression were 106 cases for total stroke, 53 cases for ischemic stroke, and 22 cases for fatal stroke per 100 000 individuals per year. The increased risk of total stroke associated with depression was consistent across most subgroups.

Conclusion Depression is associated with a significantly increased risk of stroke morbidity and mortality.

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STROKE IS A LEADING CAUSE OF death and permanent disability, with significant economic losses due to functional impairments.[1] Depression is highly prevalent in the general population, and it is estimated that 5.8% of men and 9.5% of women will experience a depressive episode in a 12-month period.[2] The lifetime incidence of depression has been estimated at more than 16% in the general population.[3] Depression has been associated with increased risks of diabetes,[4] hypertension,[5] and cardiovascular disease.[6] However, whether depression increases the future risk of stroke remains unclear.

A number of studies have assessed the association between depression and subsequent risks of stroke morbidity and mortality, suggesting that depression could be a modifiable risk factor for stroke.[7,8] A previous meta-analysis that focused on cardiovascular outcomes pooled results from 10 studies published before 2005 as a secondary analysis and reported a positive association between depression and risk of stroke.[9] Since then many more studies have been published, which allow more detailed analysis of the association between depression and stroke morbidity and

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mortality. Therefore, we conducted a systematic review and a meta-analysis of prospective cohort studies to describe the association between depression and future risk of total and subtypes of stroke.

METHODS

Search Strategy

We conducted a systematic literature search (up to May 2011) of MEDLINE, EMBASE, and PsycINFO for studies describing the association between depression (defined by self-reported scales or clinician diagnosis) and stroke morbidity and mortality. In addition, we searched the reference lists of all identified relevant publications and relevant reviews.[7-9] Only articles published in the English language were considered. Two search themes were combined using the Boolean operator *and*. The first theme, depression, combined exploded versions of the Medical Subject Headings (MeSH) *depression*, *depressive disorder*, or *depressive disorder, major*. The second theme, stroke, combined exploded versions of MeSH terms *stroke*, *cerebrovascular disorders*, or *intracranial embolism,* and *thrombosis*.

Selection Criteria

Two investigators (A.P. and Q.S.) independently assessed literature eligibility; discrepancies were resolved by consensus. Articles were considered for inclusion in the systematic review if the authors reported data from an original, peer-reviewed study (ie, not review articles or meeting abstracts); the study was a cohort study (prospective cohort or historical cohort) consisting of noninstitutionalized adults (>18 years old); and the authors reported the risk estimates of stroke morbidity or mortality in depressed participants compared with nondepressed individuals. We used broad inclusion criteria for studies, including all types of stroke (total, fatal, nonfatal, ischemic, and hemorrhagic) and depression status (assessed by different scales or clinical diagnosis). We identified articles eligible for further review by performing an initial screen of identified titles or abstracts, followed by a full-text review.

Data Extraction

We extracted the following information about the studies: study characteristics (study name, authors, publication year, journal, study site, follow-up years, and number of participants), participants' characteristics (mean age or age range, sex), main exposure depression (self-reported scales or clinician diagnosis, assessed at baseline or updated), main outcome stroke (morbidity or mortality, types, assessed by self-report, death certificates, or medical records), and analysis strategy (statistical models, covariates included in the models). Quality assessment was performed with consideration of the following aspects: study design, response rate, follow-up rate, follow-up years, exposure and outcome measurements, statistical analysis, and generalizability to other populations (eTable 1, available at http://www.jama.com).

Data Synthesis

The hazard ratios (HRs) were used as the common measure of association across studies, and the relative risks (RRs) were considered equivalent to HRs. If the result on total stroke were not available, we used data from ischemic stroke, nonfatal stroke, or fatal stroke (in the sequential order) as a surrogate for total stroke. Forest plots were produced to visually assess the HRs and corresponding 95% confidence intervals across studies. Heterogeneity of HRs across studies was evaluated by the Cochrane Q statistic ($P<.10$ was considered indicative of statistically significant heterogeneity) and the I^2 statistic (values of 25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively).[10,11] The HRs were pooled using the fixed-effect model if no or low heterogeneity was detected, or the DerSimonian and Laird[12] random-effects model otherwise, and the weights were equal to the inverse variance of each study's effect estimation. The possibility of publication bias was evaluated using the Begg test[13] and visual inspection of a funnel plot.[14] The Duval and Tweedie[15] nonparametric trim-and-fill procedure was used to further assess the possible effect of publication bias in our meta-analysis. Moreover, stratified analyses and sensitivity analyses were performed to evaluate the influences of selected study and participant characteristics on study results. The analyses were performed with Stata statistical software version 11.0 (StataCorp, College Station, Texas). P values were 2 sided with a significance level of .05.

We calculated absolute risk differences associated with depression by multiplying the background incidence rate of stroke in the general US population with (estimated HR–1). Population attributable risk (PAR) was calculated based on the following equation: $PAR\%=100\times P_e(HR-1)/(P_e[HR-1]+1)$, for which P_e is the prevalence of the exposure (depression) in the population and the HR was derived from this meta-analysis.

RESULTS

Literature Search

The search strategy identified 10 075 unique citations. After the first round of screening based on titles and abstracts with the aforementioned criteria, 302 articles remained for further evaluation. After examining those articles in more detail, 274 articles were excluded for reasons shown in FIGURE 1. Finally, 28 articles met the inclusion criteria and were included in the meta-analysis.[16-43] Among the included articles, 2 studies were retrieved from the reference lists,[16,17] and one was from our recent publication.[18]

Among these 28 articles, 8 studies specifically reported results on fatal stroke,[16,17,21,26,27,29,33,38] 3 studies on nonfatal stroke,[26,31,38] 6 studies on ischemic stroke,[16,18,24,26,32,35] and 2 studies on hemorrhagic stroke.[18,24] Six studies[18,28,32,37,40,42] reported the crude association between antidepressant medication use and total stroke risk (Wassertheil-Smoller et al[28] reported the results in a separate article[44]).

Study Characteristics

Characteristics of the 28 selected studies are shown in TABLE 1. The total number of participants included in this

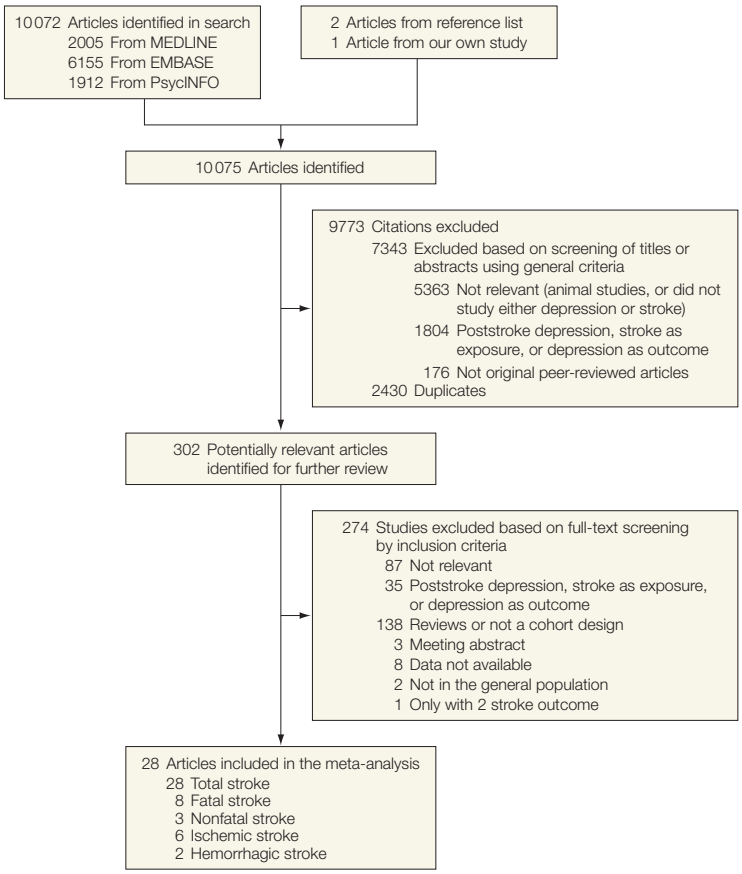
meta-analysis was 317 540, with 8478 reported stroke outcomes (1 study did not report the number of stroke cases[19]). The studies varied with regard to how results were presented. Two studies reported results separately by age group: younger than 65 and 65 years or older (Salaycik et al[34]), 65 to74, and 75 years or older (Avendano et al[30]); 2 studies reported their results separately by baseline history of cardiovascular disease,[28,40] with 1 study providing unpublished data for the total sample[40] and 3 studies providing results stratified by sex along with the results from total samples.[35,37,41] With regard to study location, most of the studies were from US or European countries. Three studies were conducted in Japan,[24,27,33] 1 in Australia,[16] and 1 in Taiwan,[36] and 1 was an international collaboration.[43] The study samples ranged from 401 to 93 676, and the follow-up durations ranged from 2 to 29 years. Most of the studies comprised both men and women, while 2 studies included only men,[26,29] and 3 studies only women.[17,18,28]

In most of the studies, depression was measured by self-reported scales, such as the Center for Epidemiologic Studies Depression Scale (CES-D),* Zung Self-Rating Depression Scale,[24,33] 30-item General Health Questionnaire,[26,27] Geriatric Depression Scale,[17,43] Beck Depression Inventory,[42] Human Population Laboratory Depression Scale,[21] 9-item Patient Health Questionnaire,[39] and 5-item Mental Health Index.[18] Four studies used the Diagnostic Interview Schedule to define depression as the exposure,[23,36-38] 2 studies included antidepressant medication use as a component of depression definition,[18,34] and 4 studies used combined methods.[18,33,34,40] The depression status was only measured at baseline in the majority of studies, whereas 3 studies used updated depression assessments.[18,21,33] In most of the studies, stroke was assessed by death certificates or medical records, and some studies combined self-reported measures with medical records; only 1 study relied solely on self-reported outcomes.[41] Three studies included outcomes comprising stroke and transient ischemic attack.[16,34,39] Baseline stroke cases were not excluded in 7 studies[16,17,20,27,28,39,43]; we included those studies in the main analysis, but conducted a stratified analysis by presence or absence of baseline stroke cases.

Adjusted HRs could be determined for most studies, except that 2 studies reported the crude results without adjustment (eTable 2 available at http://www.jama.com).[20,33] Most of the results were adjusted for age (25 studies), smoking status (20 studies), body mass index (BMI) (14 studies), alcohol intake (9 studies), physical activity (7 studies), and comorbidities (23 studies; such as diabetes, hypertension, and coronary heart disease).

*References 16, 20, 25, 28-30, 32, 34, 35, 40, 41.

Figure 1. Literature Search for the Meta-analysis



Depression and Risk of Stroke Morbidity and Mortality

Among the 31 reports from the 28 studies of results on total stroke, the majority of studies reported a positive association (ie, HR>1.00), with 14 of them being statistically significant. Only 4 studies reported an HR of less than 1.00 but these values were not statistically significant. A moderate to high heterogeneity was detected with an I^2=66.0% (Cochrane Q statistic=88.1, P<.001), the HR from random-effects model was 1.45 (95% CI, 1.29-1.63; FIGURE 2). A sensitivity analysis of omitting 1 study in each turn showed that the study by Lee et al[36] had the largest influence on the results: the pooled HR without this study was 1.36 (95% CI, 1.24-1.49). Another sensitivity analysis, in which we excluded studies that imputed the risk estimates from

Table 1. Characteristics of Studies Included in the Meta-Analysis

Source	No. of Participants	No. of Cases	Follow-up Years	Male, %	Baseline Age, y	Depression Measures	Stroke Measures	Baseline Stroke Excluded
Vogt et al,[19] 1994 (United States)	2573	NA	15 (1970 and 1971-1985)	46	Range ≥18; mean <65	A depression index, top vs bottom tertile	Medical records and death certificates	Yes
Wassertheil-Smoller et al,[20] 1996 (United States)	4367	204	Mean 4.5 (1985-1990)	44	Range ≥60; mean 72	20-Item CES-D ≥16	Medical records	No
Everson et al,[21] 1998 (United States)	6676	169	29 (1965-1983)	46	Range 16-94; mean 43	18-Item HPLDS ≥5	Death certificates	Yes
Simons et al,[16] 1998 (Australia)	2805	306	Median 8.2 (1988-1997)	44	Range ≥60; mean ≥65	CES-D, top tertile vs bottom tertile	Medical records[a]	No
Whooley and Browner,[17] 1998 (United States)	7518	94	Mean 6 (1988 and 1990-1995)	0	Range ≥67; mean 72	15-Item GDS ≥6	Medical records	No
Jonas and Mussolino,[22] 2000 (United States)	6095	483	Mean 16 (1971 and 1975-1992)	40-50	Range 25-74; mean 49	GWB-D, score 0-12	Hospital records and death certificates	Yes
Larson et al,[23] 2001 (United States)	1703	95	Mean 13 (1980 and 1983-1993 and 1996)	38	Range ≥18; mean <65	DIS-diagnosed MDD	Self-report and death certificates	Yes
Ohira et al,[24] 2001 (Japan)	879	69	Mean 10.3 (1985-1996)	35	Range 40-78; mean <65	20-Item Zung SDS, top vs bottom tertile	Register database and death certificates	Yes
Ostir et al,[25] 2001 (United States)	2478	340	6 (1986-1992)	31	Range ≥65; mean ≥65	Modified 20-Item CES-D ≥9	Self-report and death certificates	Yes
May et al,[26] 2002 (United Kingdom)	2124	130	14 (1984 and 1988-1998)	100	Range 45-59; mean <65	30-Item GHQ ≥5	Medical records	Yes
Yasuda et al,[27] 2002 (Japan)	817	20	7.5 (1991-1998)	39	Range 65-84; mean 72	30-Item GHQ, depression subscale, ≥1 standard score	Death certificates	No
Wassertheil-Smoller et al,[28] 2004 (United States)	93676	751	Mean 4.1 (1993 and 1998-2000)	0	Range 50-79 mean <65	6-Item CES-D ≥5, self-reported depression history	Self-report and medical records	No
Gump et al,[29] 2005 (United States)	11216	167	Median 18.4 (1979 and 1981-1999)	100	Range 35-57; mean 46	20-Item CES-D ≥16	Death certificates	Yes
Avendano et al,[30] 2006 (United States)	2812	270	12 (1982-1994)	42	Range ≥65; mean ≥65	20-Item CES-D ≥21	Self-report and medical records	Yes
Stürmer et al,[31] 2006 (Germany)	3920	62	Median 8.5 (1992 and 1995, 2002-2003)	48	Range 40-65; mean 53	Standardized personality questionnaires, top tertile vs medium tertile	Medical records and death certificates	Yes
Arbelaez et al,[32] 2007 (United States)	5525	611	Median 11 (1989-2000)	42	Range ≥65; mean 73	10-Item CES-D ≥9	Self-report and medical records	Yes
Kawamura et al,[33] 2007 (Japan)	535	103	Mean 6.3 (1985-2000)	40	Range ≥65; mean ≥65	SDS or modified version, and physician diagnosis	Death certificates	Yes
Salaycik et al,[34] 2007 (United States)	4120	228	Mean 8 (1990 and 1998-1998 and 2006)	46	Range ≥29; mean 64	20-Item CES-D ≥16; or ADM use	Medical records[a]	Yes
Bos et al,[35] 2008 (the Netherlands)	4424	291	Mean 5.8 (1997 and 1999-2005)	40	Range ≥61; mean 72	20-Item CES-D ≥16	Medical records	Yes
Lee et al,[36] 2008 (Taiwan, China)	4962	98	Mean 5 (1998-2003)	44	Range 18-44; mean <65	Physician diagnosis	Medical records	Yes
Liebetrau et al,[37] 2008 (Sweden)	401	56	Mean 3 (1986 and 1987-1989 and 1990)	30	All 85 only	*DSM-III* diagnosed MDD and other types of depression	Self-report and medical records	Yes
Surtees et al,[38] 2008 (United Kingdom)	20627	595	Median 8.5 (1996 and 2000-2006)	43	Range 41-80; mean <65	HLEQ related to *DSM-IV* MDD	Medical records	Yes
Whooley et al,[39] 2008 (United States)	1017	47	Mean 4.8 (2000 and 2002-2008)	80	Mean 67	9-Item PHQ ≥10	Self-report and medical records[a]	No
Wouts et al,[40] 2008 (the Netherlands)	2965	176	Mean 7.7 (1992 and 1993-2001 and 2002)	48	Range ≥55; mean 71	CES-D ≥16; or DIS-diagnosed MDD	Self-report and medical records	Yes
Glymour et al,[41] 2010 (United States)	19087	1864	Mean 8.1 (1996-2006)	41	Range ≥50; mean 66	8-Item CES-D ≥3	Self-report	Yes
Nabi et al,[42] 2010 (Finland)	23282	129	7 (1998-2005)	41	Range 20-54; mean <65	21-Item BDI ≥10	Medical records	Yes
Peters et al,[43] 2010 (International)	2656	97	Mean 2.1 (2001-2007)	39	Range ≥80; mean ≥65	15-Item GDS ≥6	Self-report and medical records	No
Pan et al,[18] 2011 (United States)	80574	1033	Mean 6 (2000-2006)	0	Range 54-79; mean 66	MHI-5 ≤52; or self-reported diagnosis; or ADM use	Self-report and medical records and death certificates	Yes

Abbreviations: ADM, antidepressant medication; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; DIS, diagnostic interview schedule; *DSM, Diagnostic and Statistical Manual of Mental Disorders*; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; GWB-D, General Well-Being Schedule-Depressed Mood Scale; HLEQ, Health and Life Experiences Questionnaire; HPLDS, Human Population Laboratory Depression Scale; LMHI, Langner Mental Health Index; MDD, major depressive disorder; MHI-5, 5-item Mental Health Index; NA, not applicable; PHQ, Patient Health Questionnaire; SDS, Zung Self-Rating Depression Scale.

[a]The outcome for this study is stroke plus transient ischemic attack.

other stroke outcomes (ischemic, nonfatal, fatal stroke) if data on total stroke were not available, revealed similar results (HR, 1.46; 95% CI, 1.26-1.69; 23 reports from 20 studies; I^2=73.7%; random-effects model). We conducted a secondary analysis to combine the unadjusted results on the association between antidepressant medication use and stroke risk, and the HR was 1.41 (95% CI, 1.25-1.59; I^2=0%; eFigure 1).

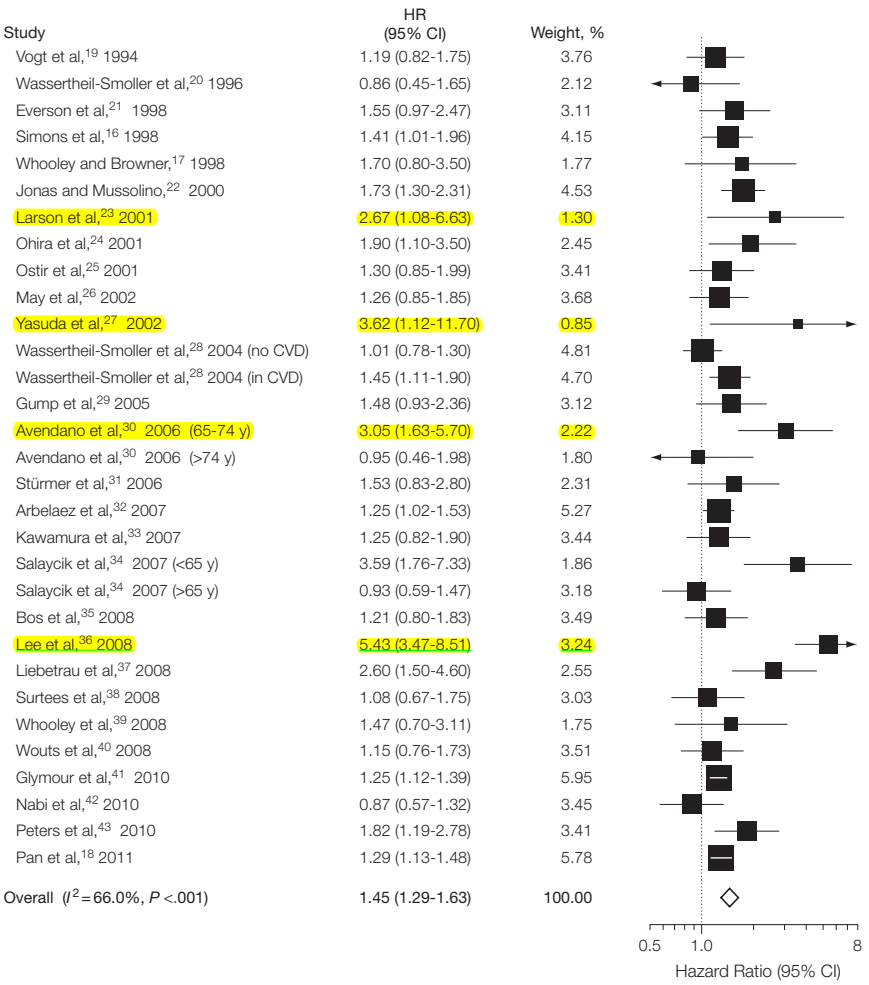
Fatal stroke results were available from 8 studies with a pooled HR of 1.55 (95% CI, 1.25-1.93) from fixed-effect model (FIGURE 3). A modest heterogeneity was found with an I^2=15.8% (Cochrane Q statistic=8.32, P=.31). Most of the studies found an HR above 1.00 except 1 study with an observed HR of 0.45.[38] Ischemic stroke results were available from 6 studies with a pooled HR of 1.25 (95% CI, 1.11-1.40; fixed-effect model). A low heterogeneity was found with an I^2=12.3% (Cochrane Q statistic=5.70, P=.34). Similar sensitivity analyses for fatal stroke and ischemic stroke did not appreciably change the results (data not shown). Results for nonfatal stroke and hemorrhagic stroke were not significant (1.21; 95% CI, 0.91-1.62 and 1.16; 95% CI, 0.80-1.70, respectively; both from fixed-effect model with I^2=0%; TABLE 2), however, the number of studies (n=3 and n=2, respectively) that separately addressed these stroke types was small.

The corresponding absolute risk difference associated with depression based on the most recent stroke statistics for the United States[45] was estimated to be 106 cases for total stroke, 53 cases for ischemic stroke, and 22 cases for fatal stroke per 100 000 individuals per year. According to the most recent statistics, 9.0% (21 million) of US adults meet the criteria for current depression.[46] Using the risk estimates from our meta-analysis, we estimated that 3.9% (n=273 000) of stroke cases in the United States could be attributable to depression.

Stratified and Sensitivity Analyses

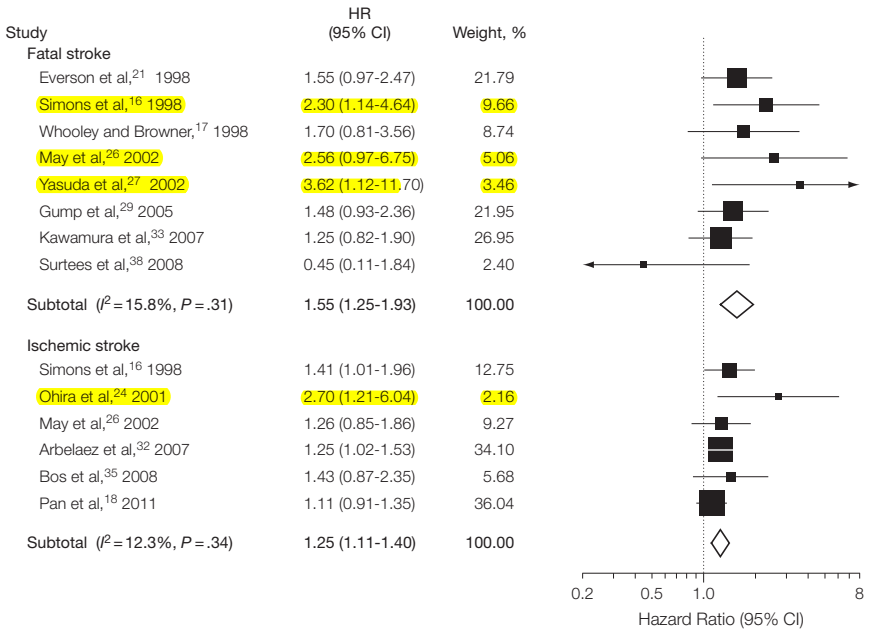
Depression was associated with an increased risk of stroke in most subgroups (eFigure 2 available at http://www.jama.com). The increased risk was more evident in several strata of study characteristics (Table 2): using clinical diagnosis to define depression, with a high study quality (more than the median score), having shorter follow-up (≤10 years), featuring younger participants (mean age <65 years), having a relatively small study sample (n<5000), among Asian studies, and lack of statistical control for smoking status or BMI. Twenty-two reports (7334 cases) adjusted for smoking in the multivariate models, whereas 9 reports (1144 cases) did not. The pooled HR controlling for smoking (1.28; 95% CI, 1.21-1.36) was lower than the pooled HR without smoking in the models (1.92; 95% CI, 1.28-2.86). Likewise, the pooled HR controlling for BMI (1.28; 95% CI, 1.20-1.36; 15 reports, 6718 cases) was lower than pooled HR without BMI in the models (1.76; 95% CI, 1.33-2.32; 16 reports, 1760 cases). No between-group differences were observed for other variables (eTable 3). Nevertheless, moderate to high heterogeneities were observed in most of the subgroups.

Figure 2. Adjusted Hazard Ratios of Total Stroke for Depressed Participants Compared with Nondepressed Participants



The summary estimates were obtained using a random-effects model. The data markers indicate the adjusted hazard ratios (HRs) in depressed participants compared with nondepressed individuals. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond data marker indicates the pooled HR.

Figure 3. Adjusted Hazard Ratios of Fatal Stroke and Ischemic Stroke for Depressed Participants Compared With Nondepressed Participants



The summary estimates were obtained using a fixed-effect model. The data markers indicate the adjusted hazard ratios (HRs) in depressed participants compared with nondepressed individuals. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond data markers indicate the pooled HRs.

Analysis of Publication Bias

Visual inspection of the funnel plot revealed asymmetry (eFigure 1A), and the Begg test was significant (z=2.33; P=.02). A sensitivity analysis using the trim-and-fill method was performed with 6 imputed studies, which produced a symmetrical funnel plot (eFigure 1B). The pooled HR incorporating the 6 hypothetical studies was smaller than the original results, but it remained statistically significant (HR, 1.28; 95% CI, 1.12-1.47; P<.001). No significant publication bias was observed for fatal stroke (P=.22), and a moderate bias for ischemic stroke (P=.04; HR, 1.19; 95% CI, 1.03-1.38 after trim-and-fill method).

COMMENT

The results of this meta-analysis demonstrate that depression is prospectively associated with a significantly increased risk of developing stroke. Furthermore, the association persisted and remained statistically significant across several subgroups stratified by various study and participant characteristics. We also found a positive association of depression with fatal stroke and ischemic stroke.

Our results are consistent with a previous meta-analysis of 10 studies published before 2005 (HR, 1.43; 95% CI, 1.17-1.75).[9] Our current meta-analysis, with 5 times more cases, provides strong evidence that depression is associated with increased risks of total stoke, fatal stroke, and ischemic stroke. The result is also consistent with a large case-control study, the INTERSTROKE study,[47] for which the investigators found that self-reported depression (for ≥2 or more weeks in the last year) was associated with a significantly increased risk of stroke (OR, 1.35; 99% CI, 1.10-1.66) in 3000 cases and 3000 matched controls from 22 countries. Several studies that did not meet the inclusion criteria for the meta-analysis also found a positive association between depression and stroke. For example, Simonsick et al[48] found that the stroke incidence rates were 2.3 to 2.7 times higher in most subgroups with high depressive symptoms compared with their nondepressed counterparts in a population of older adults with hypertension (n=3461); Nilsson and Kessing[49] found that patients with depression severe enough (n=11 741) to be hospitalized had an increased future risk of stroke (HR, 1.22; 95% CI, 1.06-1.41) compared with patients with osteoarthritis (n=81 380) in Denmark. Using a continuous variable of 20-item CES-D score, Ostir et al[50] found that depressive symptoms were associated with an increased stroke risk (HR, 1.01 per score increase; 95% CI, 1.00-1.02) in 2682 Mexican Americans aged 65 years and older.

Depression may contribute to stroke through a variety of mechanisms. First, depression has known neuroendocrine (eg, sympathetic nervous system activation, dysregulation of the hypothalamic-pituitary-adrenocortical axis, platelet aggregation dysfunction)[6] and immunological/inflammation effects,[51] which could influence stroke risk. A recent meta-analysis suggests that depression is positively associated with C-reactive protein (CRP), IL-1, and IL-6 in clinical and community samples,[52] and these inflammatory factors have been associated with an increased risk of stroke.[53] Second, depression is associated with poor health behaviors (ie, smoking, physical inactivity, poor diet, lack of medication compliance)[54] and obesity,[55] which might increase the risk of stroke. Adjusting for smoking or BMI somewhat attenuated the association between depression and stroke, suggesting that smoking and obesity may confound or mediate the association between depression and stroke. The magnitude of the depression-stroke association observed in this study is similar to the associations between smoking and stroke (HR, 1.51; 95% CI, 1.45-1.58; from a meta-analysis),[56] and between obesity and stroke (HR, 1.26; 95% CI, 1.07-1.48; from a meta-analysis).[57] Third, depression is corre-

lated with other major comorbidities, such as diabetes[4] and hypertension,[5] both of which are major risk factors for stroke. Finally, antidepressant medication use may contribute to the observed association. We found a positive association between the medication use and stroke risk; however, the results should be interpreted cautiously because medication use can be a marker of depression severity, and many studies lacked information on dose and duration of medication use.

Several limitations of this meta-analysis should be considered. First, we found significant heterogeneity across studies, which may result from differences in study designs, sample sizes, depression and stroke measures, analysis strategies, and participants' characteristics. Although moderate to high heterogeneities still remained in many subgroups, the pooled HRs showed consistent positive associations in most subgroups. Second, the funnel plot indicated a possible publication bias; however, the trim-and-fill sensitivity

Table 2. Stratified Analyses of Hazard Ratio (HR) of Stroke According to Depression Status

	No. of Reports[a]	HR (95% CI)	*Q* Statistic	*P* Value for Heterogeneity	I^2 Value	P Value Between Groups
Overall studies						
Total stroke	31	1.45 (1.29-1.63)	88.1	<.001	66.0	
Fatal stroke	8	1.55 (1.25-1.93)	8.32	.31	15.8	
Nonfatal stroke	3	1.21 (0.91-1.62)	0.77	.62	0	
Ischemic stoke	6	1.26 (1.10-1.44)	5.70	.34	12.3	
Hemorrhagic stroke	2	1.16 (0.80-1.70)	0.21	.65	0	
Subgroup analyses for total stroke						
Baseline stroke excluded or not						
Excluded	24	1.44 (1.26-1.65)	80.5	<.001	71.4	.21
Included	7	1.48 (1.25-1.75)	6.07	.42	1.1	
Sex[b]						
Men	5	1.38 (1.18-1.61)	2.1	.71	0	.45
Women	7	1.34 (1.14-1.58)	15.5	.02	61.2	
Mixed	22	1.53 (1.27-1.84)	72.1	<.001	70.9	
Type of depression measure						
Self-reported scale	22	1.31 (1.22-1.40)	31.0	.07	32.3	<.001
Physician diagnosis	4	2.52 (1.15-5.53)	23.2	<.001	87.1	
Combined	5	1.31 (1.00-1.72)	10.2	.04	60.8	
Type of stroke measure						
Self-reported	1	1.25 (1.12-1.39)	NA	NA	NA	.03
Medical records	16	1.47 (1.16-1.87)	57.9	<.001	74.1	
Combined	14	1.46 (1.26-1.68)	27.8	.01	53.2	
Mean age, y						
<65	11	1.77 (1.30-2.41)	47.0	<.001	78.7	.001
≥65	20	1.30 (1.18-1.44)	27.4	.06	35.4	
Study quality						
High, score >14	13	1.31 (1.18-1.45)	19.0	.09	36.8	.03
Low, score ≤14	18	1.62 (1.30-2.01)	64.6	<.001	73.3	
Sample size						
<5000	20	1.63 (1.32-2.02)	65.6	<.001	71.0	.003
≥5000	11	1.27 (1.19-1.36)	13.9	.18	28.0	
Study location						
United States	18	1.35 (1.21-1.51)	32.2	.01	47.2	.001
Europe, Australia	8	1.27 (1.09-1.48)	10.9	.15	35.5	
Asian	4	2.54 (1.15-5.61)	23.1	<.001	87.0	
International	1	1.82 (1.19-2.78)	NA	NA	NA	
Controlling BMI in models						
Yes	15	1.28 (1.20-1.36)	15.7	.33	10.8	<.001
No	16	1.76 (1.33-2.32)	60.0	<.001	75.0	
Controlling smoking status in models						
Yes	22	1.28 (1.21-1.36)	29.1	.11	27.8	<.001
No	9	1.92 (1.28-2.86)	41.7	<.001	80.8	

Abbreviations: BMI, body mass index; NA, not applicable.
[a] Three studies reported their results by age groups or baseline cardiovascular disease status; therefore, there are 31 reports from 28 articles for total stroke.
[b] Three studies provided stratified results by sex, and 3 studies reported their results by age groups or baseline cardiovascular disease status; therefore, there are 34 reports from 28 articles.

analysis did not materially change the results (although the pooled HR was modestly attenuated). Nevertheless, the possibility of publication bias could not be fully excluded by this method. Moreover, the meta-analysis was limited to English-language publications, and there is the possibility of unidentified unpublished reports. Data extraction and analyses were not blinded to the authors, journals, or institutions of the publications; however, the literature screening and data extraction were conducted independently by 2 investigators, and thus, selection bias was unlikely. Furthermore, most studies did not have information on depression treatment and antidepressant medication use. The role of depression treatment in modulating subsequent risk of stroke needs to be studied further. Finally, further studies are needed to determine whether depression is associated with hemorrhagic stroke.

In conclusion, this meta-analysis provides strong evidence that depression is a significant risk factor for stroke. Given the high prevalence and incidence of depression and stroke in the general population, the observed association between depression and stroke has clinical and public health importance. More studies are needed to explore the underlying mechanisms and elucidate the causal pathways that link depression and stroke.

Author Contributions: Drs Pan and Hu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Pan, Rexrode, Hu.
Acquisition of data: Pan, Sun.
Analysis and interpretation of data: Pan, Sun, Okereke, Rexrode, Hu.
Drafting of the manuscript: Pan.
Critical revision of the manuscript for important intellectual content: Sun, Okereke, Rexrode, Hu.
Statistical analysis: Pan, Sun.
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Study supervision: Hu.
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