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Depression and the Risk of Stroke Morbidity and Mortality: A Meta-analysis and Systematic Review

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Abstract

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 PsychINFO 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 (n = 317540 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% confidence interval [CI], 1.29–1.63; *P*-for-

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heterogeneity <0.001; random-effects model) for total stroke, 1.55 (1.25–1.93; *P*-for-heterogeneity = 0.31; fixed-effects model) for fatal stroke (8 studies), and 1.25 (1.11–1.40; *P*-for-heterogeneity = 0.34; 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.

INTRODUCTION

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 over 16% in the general population.[3] Depression have 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 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 PsychINFO 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 papers published in English language were considered. Two search themes were combined using the Boolean operator “and”. The first theme, depression, combined exploded versions of 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: (1) the authors reported data from an original, peer-reviewed study (i.e., not review articles, or meeting abstracts); (2) the study was a cohort study (prospective cohort or historical cohort) consisting of non-institutionalized adults (>18 years old); and (3) the authors reported the risk estimates of stroke morbidity or mortality in depressed participants compared with non-depressed 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, gender), 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).

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, non-fatal 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 (CIs) 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 random-effects model otherwise,[12] 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 and visual inspection of a funnel plot.[13–14] The Duval and Tweedie nonparametric trim-and-fill procedure was used to further assess the possible effect of publication bias in our meta-analysis.[15] 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 9.2 (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×Pe(HR−1)/(Pe[HR−1]+1), where P_e is the prevalence of the exposure (depression) in the population and HR was derived from this meta-analysis.

RESULTS

Literature Search

The search strategy identified 7642 unique citations. After the first round screening based on titles and abstracts with the aforementioned criteria, 301 articles remained for further evaluation. After examining those articles in more detail, 276 articles were excluded for reasons shown in Figure 1. Another 2 studies were retrieved from the reference lists,[16–17] and one was from our recent publication.[18] In total, 28 articles were included.[16–43]

Among these 28 articles, 8 studies specifically reported results on fatal stroke,[16–17,21,26–27,29,33,38] 3 studies on non-fatal 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 paper[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 317540, with 8478 reported stroke outcomes (one 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: <65 and ≥65 years old (Salaycik et al.[34]), 65–74 and ≥75 years old (Avendano et al.[30]); two studies reported their results separately by baseline history of cardiovascular disease,[28,40] with one study providing unpublished data for the total sample;[40] three studies provided results stratified by gender 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] one in Australia,[16] and one in Taiwan,[36] and one was an international collaboration.[43] The study samples ranged from 401 to 93676, and the follow-up durations ranged from 2 to 29 years. Most of the studies comprised both men and women, while two studies included only men,[26,29] and three studies only women.[17–18,28]

In most of the studies, depression was measured by self-reported scales, such as Center for Epidemiologic Studies Depression Scale,[16,20,25,28–30,32,34–35,40–41] Zung's 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 (DIS) 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, while 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 one study relied solely on self-reported outcomes.[41] Three studies included outcomes comprised of 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 two studies reported the crude results without adjustment (eTable 2).[20,33] Most of the results were adjusted for age (25 studies), smoking status (20 studies), BMI (14 studies), alcohol intake (9 studies), physical activity (7 studies), and comorbidities (23 studies; such as diabetes, hypertension, and coronary heart disease).

Depression and Risk of Stroke Morbidity & Mortality

Among the 31 reports from the 28 studies of results on total stroke, the majority of studies reported a positive association (i.e., HR>1.00), with 14 of them being statistically significant. Only four studies reported HR<1.00 but 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 one study in each turn showed that Lee et al's study[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 other stroke outcomes (ischemic/non-fatal/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 3A). A modest heterogeneity was found with an I^2=15.8% (Cochrane Q statistic=8.32, *P*=.31). Most of the studies found a HR above 1.00 except one 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 non-fatal stroke and hemorrhagic 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 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 100000 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=273000) of stroke cases in the US were attributable to depression.

Stratified and Sensitivity analyses

Depression was associated with an increased risk of stroke in most subgroups (eFigure 2). 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), with participants in Asians, and lack of statistical control for BMI or smoking status. 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 pooled HR without smoking in the models (1.96; 95% CI, 1.28–2.86). Likewise, the pooled HR of 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.

Analysis of Publication Bias

Visual inspection of the funnel plot revealed asymmetry (eFigure 1A), and the Begg's 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, however, remained to be 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 the 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] where 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 (odds ratio, 1.35 [99% CI, 1.10–1.66]) in 3000 cases and 3000 matched controls from 22 countries. Several studies that did not met 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 incident rates were 2.3 to 2.7 times higher in most subgroups with high depressive symptoms compared with their non-depressed counterparts in a population of older adults with hypertension (n=3461); Nilsson and Kessing[49] found that patients with depression severe enough (n=11741) to be hospitalized was associated with an increased future risk of stroke (HR, 1.22; 95% CI, 1.06–1.41) compared with patients with osteoarthritis (n=81380) 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 (e.g., 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), interleukin (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 (*i.e.*, 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] between obesity and stroke (HR, 1.26; 95% CI, 1.07–1.48; from a meta-analysis).[57] Third, depression is correlated 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 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 a 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 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 publications, and the possibility of unpublished reports was not yet identified. 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 two investigators, and thus, the 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 significant clinical and public health importance. More studies are needed to explore the underlying mechanisms and elucidate the causal pathways that link depression and stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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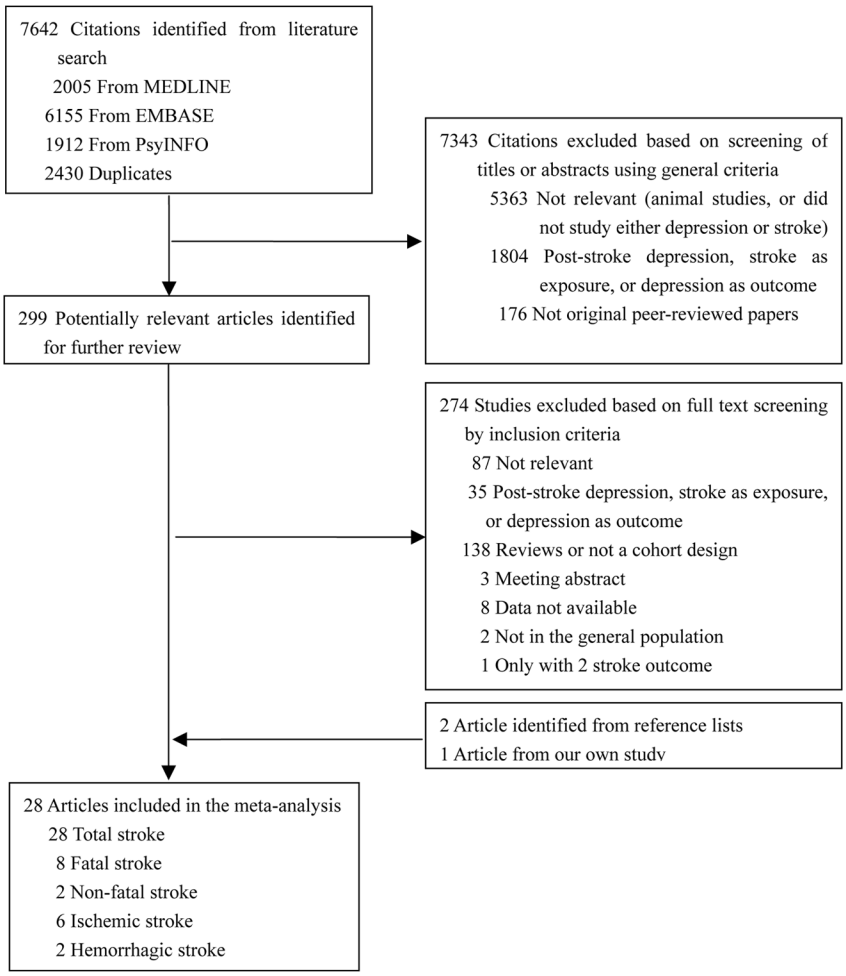

Figure 1.
Flowchart of the Meta-analysis

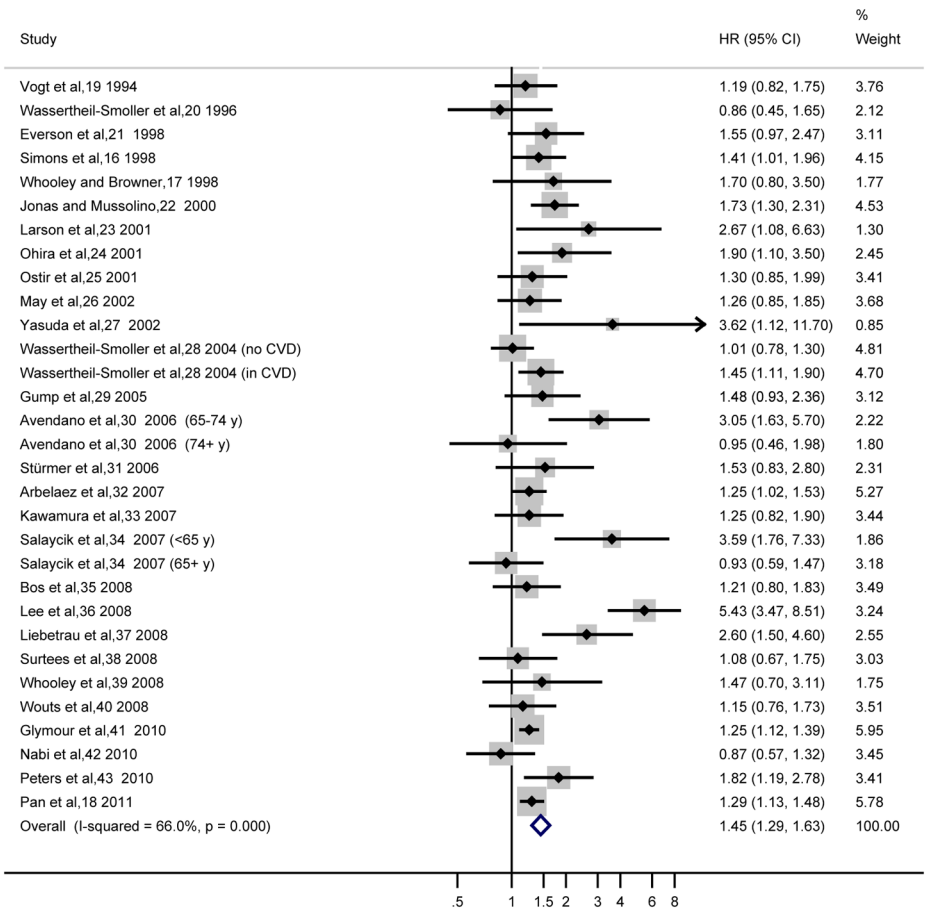

Figure 2.

Adjusted Hazard Ratios of Total Stroke for Depressed Participants Compared with Non-depressed Individuals

The summary estimates were obtained using a random-effects model. The data markers indicate the adjusted hazard ratios (HRs) in depressed participants compared with non-depressed 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. CI indicates confidence interval.

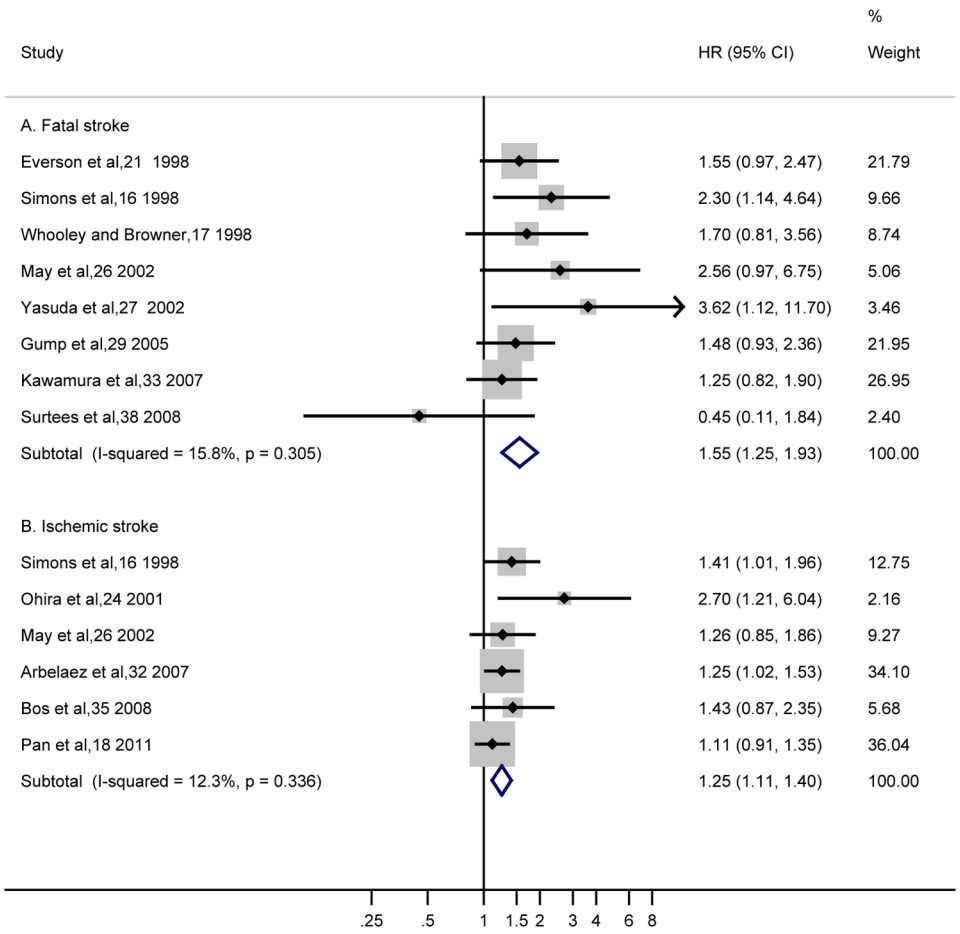

Figure 3.

Adjusted Hazard Ratios of (A) Fatal Stroke and (B) Ischemic Stroke for Depressed Participants Compared with Non-depressed Individuals

The summary estimates were obtained using a fixed-effect model. The data markers indicate the adjusted hazard ratios (HRs) in depressed participants compared with non-depressed 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. CI indicates confidence interval.

Table 1

Characteristics of Studies Included in the Meta-analysis

Reference, study location	No. of participants	No. of cases	Follow-up years	Male (%)	Baseline age	Depression Measures	Stroke Measures	Baseline stroke excluded?
Vogt et al,[19] 1994; United States	2573	NA	15 (1970/71–1985)	46	Range ≥18; mean <65	A depression index, top tertile vs. bottom tertile	Medical records & 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	CESD, Top tertile vs. bottom tertile	Medical records[a]	No
Whooley and Browner,[17] 1998; United States	7518	94	Mean 6 (1988/90–1995)	0	Range ≥ 67; mean 72	15-item GDS ≥6	Medical records	No
Jonas and Mussolino,[22] 2000; United States	6095	483	Mean 16 (1971/75–1992)	40–50	Range 25–74; mean 49	GWB-D, score 0–12	Hospital records & death certificates	Yes
Larson et al,[23] 2001; United States	1703	95	Mean 13 (1980/83–1993/96)	38	Range ≥18; mean <65	DIS-diagnosed MDD	Self-report & 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's SDS, top tertile vs. bottom tertile	Register database & 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 & death certificates	Yes
May et al,[26] 2002; United Kingdom	2124	130	14 (1984/88–1998)	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 (1993/98–2000)	0	Range 50–79 mean <65	6-item CES-D ≥5, self-reported depression history	Self-report & Medical records	No
Gump et al,[29] 2005; United States	11216	167	Median 18.4 (1979/81–1999)	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 & Medical records	Yes
Stürmer et al,[31] 2006; Germany	3920	62	Median 8.5 (1992/95–2002/03)	48	Range 40–65; mean 53	Standardized personality questionnaires, top tertile vs. medium tertile	Medical records & death certificates	Yes

Reference, study location	No. of participants	No. of cases	Follow-up years	Male (%)	Baseline age	Depression Measures	Stroke Measures	Baseline stroke excluded?
Arbelaez et al,[32] 2007; United States	5525	611	Median 11 (1989–2000)	42	Range ≥65; mean 73	10-item CESD ≥9	Self-report & 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 (1990/98–1998/2006)	46	Range ≥29; mean 64	20-item CESD ≥16; OR ADM use	Medical records[a]	Yes
Bos et al,[35] 2008; The Netherland	4424	291	Mean 5.8 (1997/99–2005)	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 (1986/87–1989/90)	30	All 85-year-old	DSM-III diagnosed MDD and other types of depression	Self-report & medical records	Yes
Surtees et al,[38] 2008; United Kingdom	20627	595	Median 8.5 (1996/2000–2006)	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 (2000/02–2008)	80	Mean 67	9-item PHQ ≥10	Self-report & medical records[a]	No
Wouts et al,[40] 2008; The Netherland	2965	176	Mean 7.7 (1992/93–2001/02)	48	Range ≥55; mean 71	CESD ≥16; OR DIS-diagnosed MDD	Self-report & 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 (2001/07–2007)	39	Range ≥80; Mean ≥65	15-item GDS ≥6	Self-report & 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 & medical records & 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, five-item Mental Health Index; SDS, Zung's Self-Rating Depression Scale;

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

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	
Non-fatal 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]						
Male	5	1.38 (1.18–1.61)	2.1	.71	0	
Female	7	1.34 (1.14–1.58)	15.5	.02	61.2	.45
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	
Physician-diagnosis	4	2.52 (1.15–5.53)	23.2	<.001	87.1	<.001
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	
Medical records	16	1.47 (1.16–1.87)	57.9	<.001	74.1	.30
Combined	14	1.46 (1.26–1.68)	27.8	.01	53.2	
Mean age						
<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	

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	No. of reports[a]	HR (95% CI)	Q-Statistic	*P* value for heterogeneity	I^2 value	P value between groups
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						
America	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	

[a] Three studies reported their results by age groups or baseline cardiovascular disease status, therefore, there are 31 reports from 28 papers for total stroke.

[b] Three studies provided stratified results by gender, and three studies reported their results by age groups or baseline cardiovascular disease status, therefore, there are 34 reports from 28 papers.