Association between late-life depression or depressive symptoms and stroke morbidity in elders: A systematic review and meta-analysis of cohort studies

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Data availability statement:

The original data presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Abstract

Objective: Whether late-life depression or depressive symptoms are a risk factor of future stroke in elders is important for prevention measures. A systematic review and meta-analysis were used to investigate the association between depression or depressive symptoms and risk of stroke in elders.

Methods: Embase, MEDLINE, PsychINFO and Web of Science were searched for studies published from inception to January 6th 2023. Prospective cohort studies reporting quantitative estimates of the association between depression or depressive symptoms and stroke morbidity in participants aged over 60 years were included. Reviews, meta-analyses, case reports, retrospective, cross-sectional, and theoretical studies were excluded. Study screening and data extraction were conducted by two researchers independently. Random-effects meta-analysis was used to estimate pooled adjusted hazard ratios (HRs). Publication bias was evaluated via the symmetry of funnel plots and Egger tests. The Newcastle Ottawa Scale was used to assess the risk of bias. The quality of evidence of synthesis was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The primary outcome was any stroke, including non-fatal, fatal, ischemic and hemorrhagic sub-types.

Results: Seventeen studies of 57,761 patients in total were included in the meta-analysis. A positive association was found between depressive disorder or symptoms and stroke risk (HR: 1.39; 95% CI: 1.22-1.58; $P < 0.001$).

Conclusions: Late-life depression or depressive symptoms are a significant risk factor for stroke in older people. Regular assessment and more effective management of associated comorbidities are recommended to reduce stroke risk.

Keywords: Late-life depression; stroke; elders; systematic review; meta-analysis;

Introduction

Depression is one of the most prevalent psychiatric disorders in late life[1]. Depressive disorder in older age groups is often underrecognized and undertreated due to its subsyndromal features and

the complicated etiologies[2], which may account for the substantial burden[3]. One study[4] concluded that the median prevalence rate of clinical depressive disorders for the elderly population in the world was 10.3% (interquartile range [IQR], 4.7%-16.0%). Two other studies[5, 6] found that the overall prevalence of depressive symptoms of adults over 60 years old was 27.8%-31.8%. Stroke is a leading cause of permanent disability or death giving rise to significant economic losses[7]. It was reported that two thirds of strokes occurred in the population over 65 years old[8].

Many studies have investigated the association between depressive disorder or symptoms and risk of stroke morbidity, indicating that depression or depressive symptoms could increase the risk of stroke. Three previous meta-analyses[9-11], published before 2014, investigated the association of depression or depressive symptoms with incident stroke and have concluded positive associations in general population samples without age limitations; however, although both depression and stroke are common in later life, the association between depressive disorder/symptoms and stroke risk in older age remains inconclusive.

This study aimed to provide the first systematic review and meta-analysis of prospective cohort studies that have investigated the association of late-life depression or depressive symptoms with future risk of total and subtypes of stroke among individuals aged over 60.

Methods

This systematic review and meta-analysis was conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[12] and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[13] reporting guidelines.

Search Strategy, Study Selection, and Data Extraction

An independent researcher conducted the literature search from databases of MEDLINE, EMBASE, PsychINFO and Web of Science to identify all relevant literature on the longitudinal association between late-life depression and stroke from inception to January 6th 2023. Database search strategy was limited to English-written literature using the search filter. Searches used a combination of MeSH and keywords terms relating to depression, depressive symptoms, elders and stroke. The grey literature was screened from scientific depression/depressive symptoms and stroke related meetings, Google Scholar, and pre-publication reports. Title and abstract screening followed by a full-text review were performed by two researchers (CW and MW) independently. Disagreements were solved by discussion with a third researcher (SWD).

Studies were included if they fulfilled the following criteria: (1) prospective, cohort studies reporting quantitative estimates of the association between depression or depressive symptoms and stroke morbidity in participants aged over 60 years old were included; (2) investigated the association between all types of depression/depressive symptoms assessment (different scales or methods of diagnosis) and stroke (total, nonfatal, fatal, ischemic or hemorrhagic); (3) reported the outcomes measured using univariate and multivariate Cox proportional hazards models. Studies were excluded if they were reviews, meta-analyses, case reports, retrospective, cross-sectional, or theoretical studies.

Two researchers (CW and MW) independently conducted the data extraction, checked by a third researcher (SWD). Extracted information included the following: general study information (study name, authors, publication year, country, sample size, follow-up years), participants' characteristics (baseline age, gender), main exposure depression/depressive symptoms (assessed by self-reported scales or clinician diagnosis), main outcome stroke (type of stroke, assessed by self-report, medical records, or death certificates), and analysis strategy (statistical models and covariates). Discrepancies between the two researchers (CW and MW) were resolved by discussion with a third researcher (SWD).

Risk-of-Bias Assessment

Since only cohort studies were included, risk of bias was independently assessed by two researchers (CW and MW) using the Newcastle-Ottawa Quality Assessment Scale (NOS) [14] which evaluates three quality parameters: selection, comparability, and outcome. All the included studies were scored and categorized to three different levels (good, fair, and poor quality) (eMethod 1). Any discrepancy was resolved through discussion with the third researcher (SWD).

Data Synthesis and Data Analysis

Statistical analyses were performed using Stata, version 16.0 (StataCorp LLC) and Review Manager 5.4 software (Cochrane bespoke software). A 2-tailed $P < 0.05$ was considered to be statistically significant. We used a random-effects model to estimate the pooled adjusted hazard ratio (HR) with a corresponding 95% CI as common risk estimates across the included studies. The I^2 index was used to assess the heterogeneity among studies[15]: low (< 25.0%), moderate (25-50%), and high (>50%).

Sensitivity analyses and meta-regressions were necessary to conduct at first step to clarify heterogeneity[16]. Meta-regressions were performed to clarify associations with variables including study location, sample size, follow-up years, gender difference, type of depression/depressive symptoms assessment, and stroke or not at baseline. Since no significant results were found, subgroup analyses were performed later according to more variables including gender distribution, sample size, follow up years, study location, stroke or not at baseline, type of stroke outcome, type of depression/depressive symptoms assessment, type of stroke ascertainment, adjusted confounders in models. Publication bias was assessed by visual inspection of the symmetry of funnel plots and Egger tests[17]. Trim and fill analysis were performed if substantial publication biases were detected. The quality of evidence of synthesis with meta-analysis was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[18].

Results

Search Results

Seventeen studies[19-35] were included after screening 7413 articles and full-text review of 416. Figure 1 presents the PRISMA flow diagram of included studies. As displayed in eTable 1, five studies[24, 28, 30, 32, 34] specifically reported outcomes of fatal stroke, one study[28] specifically reported non-fatal stroke. Ischemic stroke was reported specifically in five studies[19, 21, 22, 30, 33], and hemorrhagic stroke in only one study[22].

Study Characteristics

Table 1 displays characteristics of the 17 included studies. The total sample size included in this meta-analysis was 57,761, with 5106 stroke outcomes. One study[20] reported results categorized to different age groups: 65-74 and > 74 years old. Another study[33] reported their results stratified by different ethnic groups (White and African American). Sample sizes of included studies ranged from 401 to 7518, with follow-up durations ranging from 2 to 12 years. Most studies were from US or Europe. Two studies[24, 34] were based in Japan, one[30] in Australia, and one[29] was from an international collaboration. Fifteen studies enrolled both male and female, while one study[23] included only male and another one[32] included only female.

Depression or depressive symptoms were ascertained by screening scales in most included studies including the Center for Epidemiologic Studies Depression Scale (CES-D)[19-22, 27, 28, 30, 31, 33, 35], Zung's Self-Rating Depression Scale (SDS)[23, 24], the depression subscale of the 30-item General Health Questionnaire (GHQ)[34], and Geriatric Depression Scale (GDS)[29, 32]. One study[26] used Diagnostic and Statistical Manual of Mental Disorders (DSM) to diagnose depression, and one study[24] combined SDS with psychiatrist diagnosis. Stroke was ascertained from medical records or death certificates in most studies, with some combining these with self-reported measures. One study[25] ascertained stroke as a self-reported outcome alone and four studies[30-32, 34] did not exclude baseline stroke cases.

All the included studies determined adjusted HRs (eTable 1), most of which were adjusted for age (all 17 studies), gender (13 studies), education (11 studies), smoking status (10 studies) and comorbidities (14 studies).

Risk-of-Bias Assessment

eTable 2 reports the results of Newcastle–Ottawa Quality Assessment Scale to assess the risk of bias. Apart from one study[25], all the other included studies received scores in the good quality range.

Synthesis With Meta-analysis

All the included studies had sufficient data to allow synthesis via meta-analysis. Of the included studies with results on total stroke, 15 reported HR>1.00, suggesting a positive association. Nine of these had statistically significant associations. The other three reported a negative association (HR<1.00) but without statistically significance. The pooled HR estimate was 1.39 (95% CI, 1.22-1.58; P < 0.001) with a substantial heterogeneity (I^2=55.0% (Figure 2). Figure 3 displays the 5 studies reporting fatal stroke results with a pooled HR of 1.96 (95% CI, 1.30-2.97; P=0.001) and a modest heterogeneity (I^2=40%). The pooled HR estimate of ischemic stroke results was 1.29 (95% CI, 1.14-1.45; P < 0.001) from 5 studies. No heterogeneity was found (I^2=0).

Sensitivity Analysis, Meta regression, and Subgroup Analysis

Considering the heterogeneity of studies reporting total stroke results, sensitivity analyses omitting one study in turn showed that no study had a substantial influence on the results (eTable 3). eTable 4 presents the results of univariate meta-regression analysis. None of the included covariates could explain the high heterogeneity (All P > 0.05). Subgroup analyses were conducted to investigate the high heterogeneity further (Table 2 & eFigure 1). The positive association between late-life depression/depressive symptoms and risk of stroke was more evident in several strata of study characteristic: male percentages of 0-60%, longer follow-up years (≥ 7), US studies, those excluding baseline stroke, those reporting outcomes of total or ischemic stroke, those using CES-D to assess depression, those ascertaining stroke by self-report or medical records, and those controlling age, gender, marital status, education, activity of daily living (ADL), comorbidities in models. Whereas, medium to high heterogeneities were detected in most subgroups.

Publication Bias

The funnel plot identified substantial asymmetry on visual inspection (eFigure 2) and the Egger test indicated substantial publication bias (P=0.008) (eTable 5). A trim and fill analysis was performed to assess the stability of the pooled estimates (eTable 6 & eFigure 3), but the recalculated pooled log HR (1.193; 95% CI, 1.034, 1.377; P=0.016) was still statistically significant.

Quality of Evidence

The overall strength of evidence is evaluated from the primary analysis in eTable 7. Sixteen out of seventeen studies had low risk of bias according to the Newcastle-Ottawa Quality Assessment Scale. Most studies had similar HRs with narrow 95% confidence intervals for the pooled estimate, thus there was no serious concern of inconsistency or imprecision. Since the evidence

directly answered the questions posed, indirectness was not detected. Despite evidence of publication bias, this did not have any apparent impact on the stability of the results. As a result, the overall strength of evidence for the association of late-life depression/depressive symptoms and stroke morbidity in elders was concluded to be moderate.

Discussion

This systematic review and meta-analysis found that late-life depression or depressive symptoms are prospectively associated with a significantly increased risk of future stroke in older adults (HR: 1.39; 95% CI: 1.22-1.58; P < 0.001). Moreover, the association remained statistically significant across several subgroups stratified by study characteristics. Positive associations of late-life depression or depressive symptoms with fatal stroke (HR: 1.96; 95% CI: 1.30-2.97; P=0.001) and ischemic stroke (HR: 1.29; 95% CI: 1.14-1.45; P < 0.001) were also concluded.

Although the studies included in the meta-analysis were purposefully limited to those with participants aged over 60 years, the results are consistent with three previous meta-analyses of studies without age limitations[9-11], indicating that depressive disorders or symptoms are associated with a raised risk of developing stroke for individuals of all ages. Another study[36] that did not met the inclusion criteria for the meta-analysis also found positive association that the stroke incident rates were 2.3-2.7 times higher in the subgroup with severe depressive symptoms compared with those non-depressed in a population of elders with hypertension.

A variety of mechanisms may contribute to the association of depression with stroke risk in older adults. Depression is related to unhealthy lifestyles such as smoking, physical inactivity, and obesity[37, 38], which are associated with higher risk of stroke[39, 40]. The results of our subgroup analysis indicated that controlling for smoking status, physical activity and BMI weakened the pooled P value, suggesting that these may confound or mediate the association of interest. Depression has also been found to be associated with increased risk of other comorbidities such as hypertension[41] and diabetes[42], which could further contribute. As a result, depression is associated with higher risk of poor daily behaviors and other major comorbidities that consequently increase risk of developing stroke. Furthermore, depressive disorder may lead to dysfunction of the HPA axis[43] and increased release of inflammatory cytokines[44], which could influence stroke risk and severity.

Substantial heterogeneity across studies was found for the pooled HR estimate of total stroke outcome. Neither sensitivity analysis nor meta-regression revealed a clear source of heterogeneity, although the gender subgroup strata had mild to modest heterogeneity, suggesting that different gender distributions may be an underlying factor. Zhao et al.[45] reported higher incidence of depression in women, which may lead to higher stroke incidence than in men. Besides, a cohort study based in Sweden[46] found that stroke incidence was 60% lower for female than male participants at age of 55-64 years, but women had a 50% higher incidence than men at

the age of 75 years. As a result, gender distributions may conceivably impact the HRs contributing to the observed heterogeneity.

The incidence rate of major depressive disorder in population of adults aged over 65 ranges from 1-5% in studies conducted in the United States and internationally[47]. Furthermore, about 15% of community-dwelling older adults are reported to have significant depressive symptoms[48]. However, older people with depression may misattribute their symptoms to medical illness or normal aging, which may reduce chances of effective treatment[49], compounded by potential stigma, and by anxiety about adverse effects of antidepressants[50]. All these may contribute to underreporting and missing treatment of depressive symptoms.

Even though most included studies in our meta-analysis reported scales assessing depressive symptoms as the exposure, the applied cut-off categories can be expected to identify older participants at great risk for clinical depression with high sensitivity, specificity, and consistency. Based on the consistent pooled estimates, the results of the meta-analysis were robust. Considering our finding that late-life depression or depressive symptoms are significantly associated with risk of stroke in elders, depressive disorder or tendency in late life needs more attention from families and clinicians to take effective actions, thus reducing future stroke.

Limitations

The meta-analysis still had several limitations that should be considered. First, as mentioned, substantial heterogeneity was found across studies. However, sensitivity analysis and meta-regressions showed no significant factors underlying this. After subgroup analysis, despite moderate to high heterogeneities in many subgroups, the pooled HRs in most subgroups still had consistent positive associations. Second, although we conducted the meta-analysis to investigate whether the depression-stroke association differed by stroke subtypes, more studies are clearly needed to investigate risk of hemorrhagic stroke as an outcome. Third, there existed different cut-offs in the same scale to ascertain depression/depressive symptoms in different included studies, which might be associated with the substantial heterogeneity that needs further study. Finally, all the included studies were limited to English language. Fourth, none of the included studies adjusted the pooled results for antidepressant use. Since the use of antidepressant is a marker of the severity of depressive symptoms, antidepressant use may partially mediate the association between depressive symptoms and stroke morbidity. For example, Pequignot et al.[28] found that the risk of fatal coronary heart disease and stroke increased across depressive symptoms and antidepressant treatments statuses, whereby those with depressive symptoms, who also received

an antidepressant, had the highest risk. Hence, more studies are needed to investigate the role of antidepressant use in the association between depression and stroke.

Conclusions

Our meta-analysis collated robust evidence that late-life depression or depressive symptoms are a significant risk factor for stroke in older people. Further high-quality studies are needed to fully control for confounding factors and to clarify underlying causal pathways between depressive disorder or symptoms and stroke in the late life. Considering that late life depressive disorder or tendency is often under detected, and the lack of timely treatment previously reported, regular assessment and effective management should be considered to reduce stroke risks amongst other outcomes.

Author Contributions: WC,WDS and JJ designed the study. WC was the principal investigator and guarantor. RS and CM gave statistical and epidemiological support. WC, WM and WDS conducted the study. WC drafted the manuscript.

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Figure 1. PRISMA Flow Diagram of Included Studies

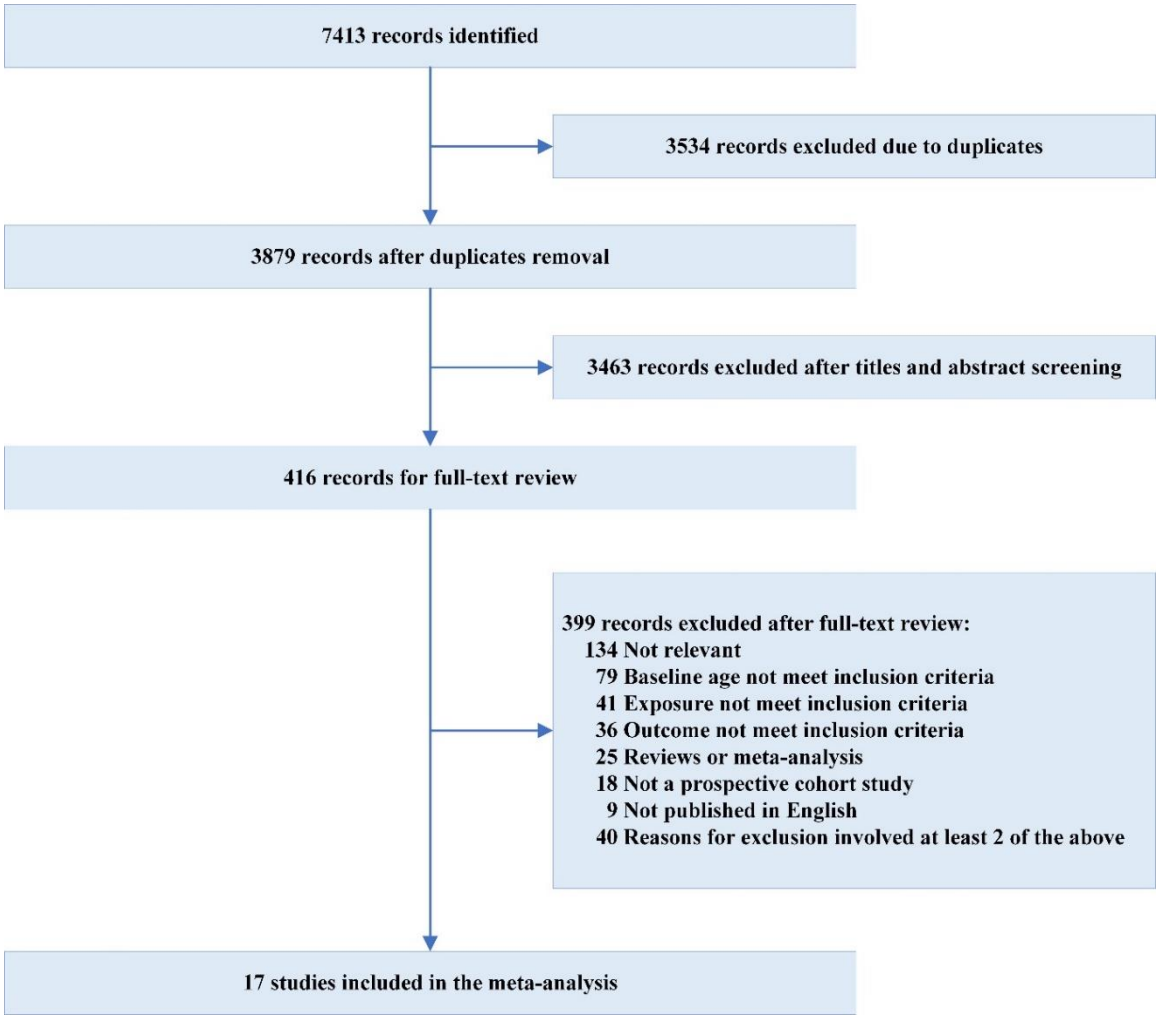


Figure 2. Adjusted Hazard Ratios of Total Stroke

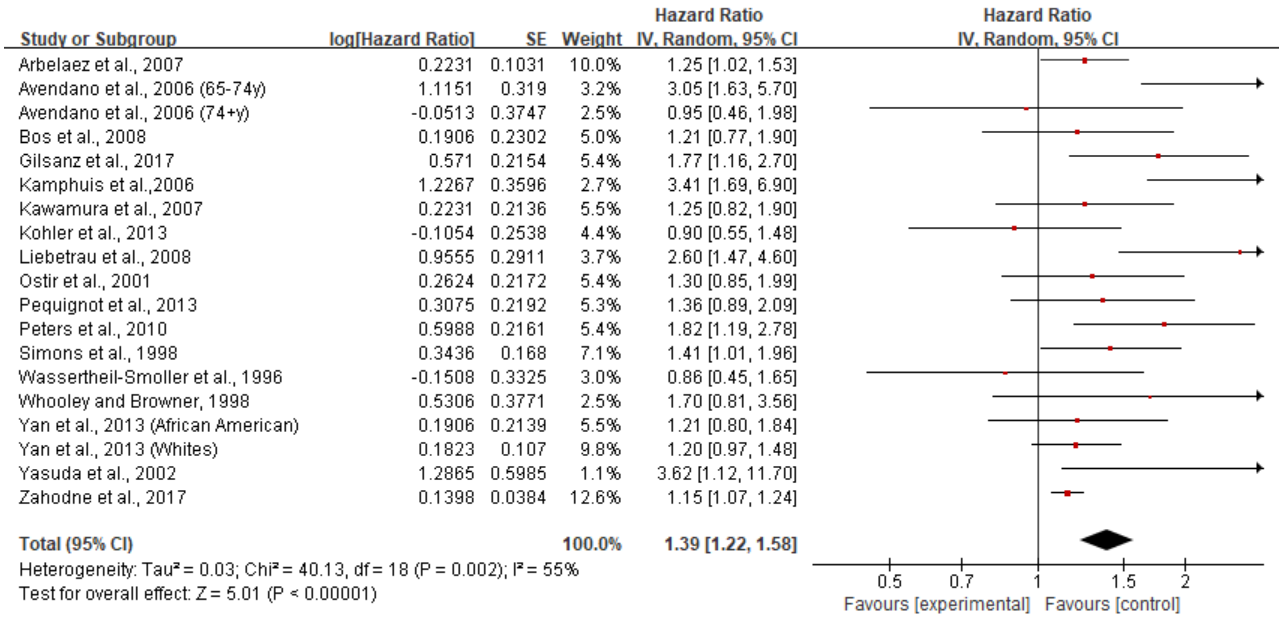
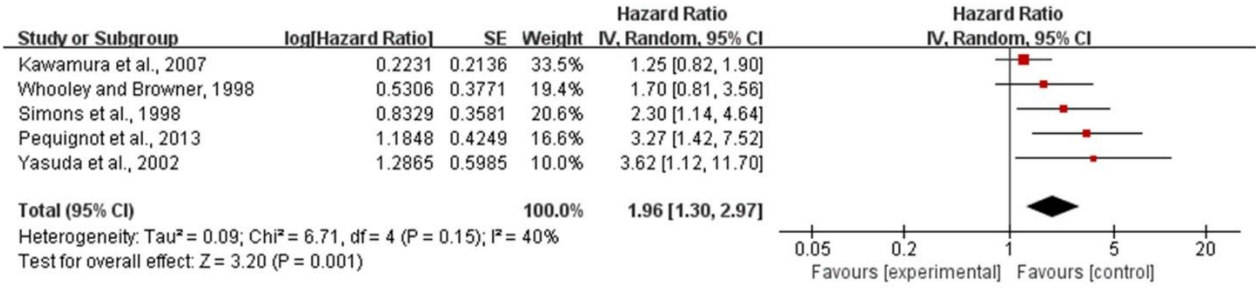


Figure 3. Adjusted Hazard Ratios of (A) Fatal Stroke and (B) Ischemic Stroke

A



B

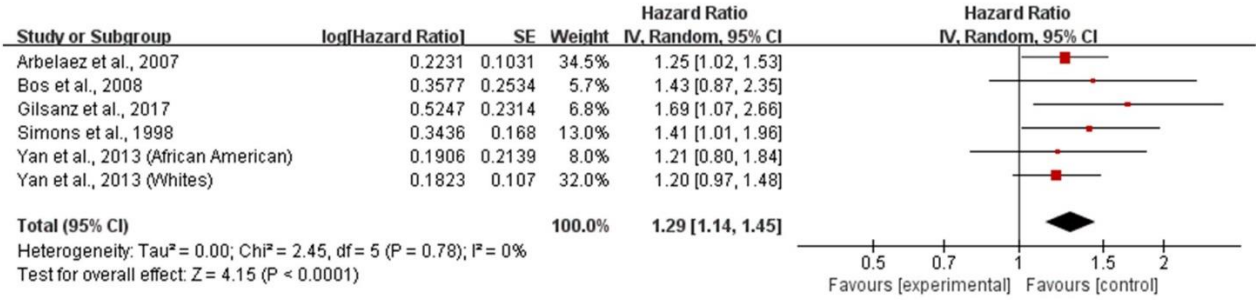


Table 1. Characteristics of Studies Included in the Meta-analysis

First author, Publication (yr)	Country	Sample size No.	Baseline age (yr)	Follow-Up duration (yr)	Male (%)	Depression assessment	Stroke ascertainment	No. of stroke cases	Baseline stroke excluded
Arbelaez et al., 2007[19]	United States	5525	Range ≥65; mean 73	Median 11	40	CES-D	Self-report &Medical records	611	Yes
Avendano et al., 2006[20]	United States	2812	Range ≥65; mean ≥65	12	42	CES-D	Self-report &Medical records	270	Yes
Bos et al., 2008[21]	The Netherland	4424	Range ≥61; mean 72	Mean 5.8	40	CES-D	Medical records	291	Yes
Gilsanz et al., 2017[22]	United States	4319	Range ≥65; mean72	Median 9.0	42	CES-D	Self-report & medical records	334	Yes
Kamphuis et al.,2006[23]	Finland, Italy, Netherlands	799	Range 70-90	Mean 7.4	100	SDS	Death certificates	66	Yes
Kawamura et al., 2007[24]	Japan	535	Range ≥65; mean ≥65	Mean 6.3	40	SDS or modified version, and psychiatrist diagnosis	Death certificates	103	Yes
Kohler et al., 2013[25]	Germany	2854	Range ≥75	6	34	GDS	Self-report	856	Yes
Liebetrau et al., 2008[26]	Sweden	401	All 85-year-old	Mean 3	30	DSM-III	Self-report &medical records	56	Yes
Ostir et al., 2001[27]	United States	2478	Range ≥ 65; mean ≥65	6	31	CES-D	Self-report &death certificates	340	Yes
Pequignot et al., 2013[28]	France	7308	Range 69–77	Median 5.3	37	CES-D	Medical reports & death certificates	141	Yes
Peters et al., 2010[29]	International	2656	Range ≥80; Mean ≥65	Mean 2.1	39	GDS	Self-report &medical records	97	Yes
Simons et al., 1998[30]	Australia	2805	Range ≥60; mean ≥65	Median 8.2	44	CES-D	Medical records	306	No
Wassertheil-Smoller et al., 1996[31]	United States	4367	Range ≥60; mean 72	Mean 4.5	44	CES-D	Medical records	204	No
Whooley and Browner, 1998[32]	United States	7518	Range ≥ 67; mean 72	Mean 6	0	GDS	Medical records	94	No
Yan et al., 2013[33]	United States	4619	Range ≥65	11.5	41	CES-D	Self-report & medical records	652	Yes
Yasuda et al., 2002[34]	Japan	817	Range 65–84; mean 72	7.5	39	30-item GHQ, depression subscale	Death certificates	20	No
Zahodne et al., 2017[35]	United States	3524	Range ≥65; mean74	Mean 6.4	42	CES-D	Medical records	665	Yes

Abbreviations: CES-D: Center for Epidemiologic Studies Depression Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; GDS: Geriatric Depression Scale; GHQ: General Health Questionnaire; SDS: Self-rating Depression Scale;

Table 2. Subgroup Analyses of Hazard Ratio (HR) of Stroke morbidity

Sample characteristic	No. of studies	HR (95% CI)	*P* value for heterogeneity	I^2 value (%)	*P* value comparing groups

1. Gender (male %)					
0-30%	2	2.22 (1.41, 3.49)	< 0.001	0	
31-60%	16	1.29 (1.16, 1.44)	< 0.001	38	
61-100%	1	3.41 (1.69, 6.90)	N/A	N/A	0.003
2.Sample size					
≥ 4000	8	1.26 (1.12, 1.42)	< 0.001	0	
< 4000	11	1.56 (1.24, 1.98)	< 0.001	71	0.11
3.Follow-up years					
≥ 7	9	1.53 (1.23, 1.90)	< 0.001	61	
< 7	10	1.30 (1.10, 1.53)	0.002	42	0.25
4.Study location					
America	10	1.27 (1.11, 1.45)	< 0.001	42	
Europe, Australia	6	1.59 (1.21, 2.09)	0.001	53	
Asia	2	1.84 (0.67, 5.00)	0.23	64	
International	1	1.82 (1.19, 2.78)	N/A	N/A	0.22
5.Baseline stroke included					
Yes	15	1.39 (1.21, 1.59)	< 0.001	59	
No	4	1.43 (0.95, 2.15)	0.08	39	0.89
6.Type of stroke outcome					
Total stroke	19	1.39 (1.22, 1.58)	< 0.001	55	
Non-fatal stroke	1	1.36 (0.89, 2.09)	N/A	N/A	
Fatal stroke	5	1.96 (1.30, 2.97)	0.001	40	
Ischemic stroke	6	1.29 (1.14, 1.45)	< 0.001	0	
Hemorrhagic stroke	1	1.77 (1.16, 2.70)	N/A	N/A	0.24
7.Type of depression assessment					
CES-D	11	1.31 (1.16, 1.49)	< 0.001	21	
SDS	2	1.98 (0.74, 5.28)	0.17	83	
GDS	3	1.39 (0.86, 2.25)	0.18	58	
GHQ	1	3.62 (1.12, 11.70)	N/A	N/A	
DSM	1	2.60 (1.47, 4.60)	N/A	N/A	0.08
8.Type of stroke ascertainment					
Self-report	10	1.43 (1.18, 1.73)	< 0.001	56	
Medical records	13	1.37 (1.19, 1.58)	< 0.001	55	
Death certificates	5	1.64 (1.14, 2.35)	0.007	54	0.66
9.Controlled-for cofounders in models					
Age	17	1.34 (1.18, 1.52)	< 0.001	49	
Gender	13	1.26 (1.11, 1.44)	< 0.001	45	
Race	6	1.32 (1.06, 1.65)	0.01	65	
Marital status	6	1.16 (1.09, 1.24)	< 0.001	0	
Education	11	1.29 (1.13, 1.47)	< 0.001	49	
Physical activity	5	1.96 (1.08, 3.53)	0.03	82	
ADL	3	1.14 (1.06, 1.23)	< 0.001	0	
Cognitive function	6	1.31 (0.99, 1.74)	0.06	58	
Smoking status	10	1.37 (1.09, 1.72)	0.007	54	
BMI	6	1.45 (1.12, 1.87)	0.005	73	
Comorbidities	14	1.38 (1.19, 1.61)	< 0.001	57	0.09

Abbreviations: ADL, Activity of Daily Living; BMI: Body Mass Index; CES-D: Center for Epidemiologic Studies Depression Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; GDS: Geriatric Depression Scale; GHQ: General Health Questionnaire; SDS: Self-rating Depression Scale;

Supplementary Content

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethod 1. Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort

a) Truly representative (one star)

b) Somewhat representative (one star)

c) Selected group

d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort (one star)

b) Drawn from a different source

c) No description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) Secure record (e.g., surgical record) (one star)

b) Structured interview (one star)

c) Written self report

d) No description

e) Other

4) Demonstration that outcome of interest was not present at start of study

a) Yes (one star)

b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders

a) The study controls for age, sex and marital status (one star)

b) Study controls for other factors (list) _____ (one star)

c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome

a) Independent blind assessment (one star)

b) Record linkage (one star)

c) Self report

d) No description

e) Other

2) Was follow-up long enough for outcomes to occur

a) Yes (one star)

b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above:_____

3) Adequacy of follow-up of cohorts

a) Complete follow up- all subject accounted for (one star)

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)

c) Follow up rate less than 80% and no description of those lost

d) No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain

eTable 1. Hazard Ratio (HR) and Adjusted Confounding Factors of The Included Studies

Reference	Adjusted confounders	Total stroke HR (95% CI)	Non-fatal stroke HR (95% CI)	Fatal stroke HR (95% CI)	Ischemic stroke HR(95% CI)	Hemorrhagic stroke HR(95% CI)
Arbelaez et al., 2007[17]	Age, gender, race, occupation, income, education level, marital status, hypertension status, diabetes status, smoking, coronary heart disease status, cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and BMI	1.25 (1.02,1.53)			1.25 (1.02,1.53)	
Avendano et al., 2006[18]	Age, gender, race, hypertension, smoking, diabetes, alcohol consumption, BMI and physical activity, depressive symptoms, social networks, difficult life events, physical and cognitive function	3.05 (1.63,5.70)-65-74y 0.95 (0.46,1.98)-74+y				
Bos et al., 2008[19]	Age, gender, systolic blood pressure, diabetes mellitus, cigarette smoking (ever), cigarette smoking (current), intima–media thickness, history of myocardial infarction, history of PTCA or CABG, history of TIA, antithrombotic drug use, antihypertensive drug use, cholesterol lowering drug use, psycholeptic drug use and psychoanaleptic drug use	1.21 (0.82,1.90)			1.43 (0.87,2.35)	

Gilsanz et al., 2017[20]	Age, race, clinic site, enrollment cohort, education, selective survival, participation, and prior exposure to depressive symptoms	1.77(1.17,2.70)			1.69 (1.07,2.66)	2.01 (0.68,5.97)
Kamphuis et al.,2006[21]	Country, education, BMI, smoking, alcohol intake, systolic blood pressure, total and high-density lipoprotein cholesterol levels and physical activity	3.41 (1.69,6.90)				
Kawamura et al., 2007[22]	Age	1.25 (0.82,1.90)		1.25 (0.82,1.90)		
Kohler et al., 2013[23]	Age, gender, marital status, level of education, smoking, hypertension, myocardial infarction, diabetes, peripheral artery disease, TIA, hypercholesterolemia, hyperlipidemia and ApoE status, mobility, ADL impairment, level of alcohol consumption and MCI status	0.90 (0.55,1.48)				
Liebetrau et al., 2008[24]	Age	2.60 (1.50,4.60)				
Ostir et al., 2001[25]	Age, income, education, marital status, BMI, smoking, heart attack, diabetes, systolic blood pressure	1.30 (0.85,1.99)				
Pequignot et al., 2013[26]	Age, study center, gender, smoking status, alcohol consumption, high blood pressure, impaired fasting glycemia or diabetes, hypercholesterolemia, living alone, education level, Mini Mental State Examination (MMSE) score	1.36 (0.89,2.09)	1.36 (0.89,2.09)	3.27 (1.42,7.52)		
Peters et al., 2010[27]	Age, gender, treatment allocation, country area, educational level, living alone, number of comorbidities, previous	1.82 (1.19,2.78)				

	cardiovascular disease, previous treatment and previously diagnosed hypertension					
Simons et al., 1998[28]	Lipoprotein, alcohol intake, ECG evidence of left ventricular hypertrophy, and family history of premature CHD	1.41 (1.01,1.96)		2.30 (1.14, 4.64)	1.41 (1.01,1.96)	
Wassertheil-Smoller et al., 1996[29]	Age, gender, race, baseline depression, randomization group, years of education, history of stroke, MI, or diabetes, smoking, baseline ADL, and ADL as a time-dependent covariate	0.86 (0.45,1.65)				
Whooley and Browner, 1998[30]	Age, history of myocardial infarction, stroke, chronic obstructive pulmonary disease, hypertension, diabetes, smoking, perceived health and cognitive function	1.70 (0.80,3.50)		1.70 (0.81,3.56)		
Yan et al., 2013[31]	Age, gender, marital status, income, education	1.20 (0.97,1.48)-Whites 1.21 (0.79,1.84)-African American			1.20 (0.97,1.48)-Whites 1.21 (0.79,1.84)-African American	
Yasuda et al., 2002[32]	Age, gender, chronic conditions under treatment, regular physical activity and availability of close or casual neighbors	3.62 (1.12,11.70)		3.62 (1.12,11.70)		
Zahodne et al., 2017[33]	Age, gender, race, education, marital status, self-rated health, ADL, exercise, cognitive status, BMI, and Framingham Risk Score	1.15(1.06,1.24)				

Abbreviations: ADL, Activity of Daily Living; ApoE, Apoenzyme; BMI, Body Mass Index; CABG, Coronary Artery Bypass Grafting; CHD, Coronary Heart Disease; ECG, Electrocardiograph; MCI, Mild cognitive impairment; MI, myocardial infarction; PTCA, Percutaneous Transluminal Coronary Angioplasty; TIA, Transient Ischemic Attacks;

eTable 2. Risk of Bias Assessment of Included Studies according to the Newcastle–Ottawa Quality Assessment Scale (NOS)

Reference	Selection				Comparability	Outcome			Study quality
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Arbelaez et al., 2007[17]	★	★	★	★	★★	★	★	★	Good
Avendano et al., 2006[18]	★	★	★	★	★	★	★	★	Good
Bos et al., 2008[19]	★	★	★	★	★	★	☆	★	Good
Gilsanz et al., 2017[20]	★	★	★	★	★	★	★	★	Good
Kamphuis et al.,2006[21]	★	★	★	★	★	★	★	★	Good
Kawamura et al., 2007[22]	★	★	★	★	★	★	☆	★	Good
Kohler et al., 2013[23]	★	★	★	★	★★	☆	☆	★	Poor
Liebetrau et al., 2008[24]	★	★	★	★	★	★	☆	★	Good
Ostir et al., 2001[25]	★	★	★	★	★	★	☆	★	Good
Pequignot et al., 2013[26]	★	★	★	★	★	★	☆	★	Good
Peters et al., 2010[27]	★	★	★	★	★	★	☆	★	Good
Simons et al., 1998[28]	★	★	★	★	★	★	★	★	Good
Wassertheil-Smoller et al., 1996[29]	★	★	★	★	★	★	☆	★	Good
Whooley and Browner, 1998[30]	★	★	★	★	★	★	☆	★	Good
Yan et al., 2013[31]	★	★	★	★	★★	★	★	★	Good
Yasuda et al., 2002[32]	★	★	★	★	★	★	★	★	Good
Zahodne et al., 2017[33]	★	★	★	★	★★	★	☆	★	Good

eTable 3. Results of Sensitivity Analysis by excluding Study One by One

Removed studies	No. of studies	No. of participants	HR (95% CI)	I^2-value (%)	*P*-value
Before	17	57761	1.39 (1.22, 1.58)	55	< 0.001
Arbelaez et al., 2007[17]					
After	16	52236	1.42 (1.23, 1.63)	58	< 0.001
Avendano et al., 2006[18]					
After	16	54949	1.35 (1.20, 1.53)	49	< 0.001
Bos et al., 2008[19]					
After	16	53337	1.40 (1.23, 1.60)	58	< 0.001
Gilsanz et al., 2017[20]					
After	16	53442	1.37 (1.20, 1.56)	54	< 0.001
Kamphuis et al.,2006[21]					
After	16	56962	1.34 (1.19, 1.51)	47	< 0.001
Kawamura et al., 2007[22]					
After	16	57226	1.40 (1.22, 1.60)	58	< 0.001
Kohler et al., 2013[23]					
After	16	54907	1.42 (1.24, 1.62)	56	< 0.001
Liebetrau et al., 2008[24]					
After	16	57360	1.35 (1.19, 1.52)	49	< 0.001
Ostir et al., 2001[25]					
After	16	55283	1.40 (1.22, 1.60)	58	< 0.001
Pequignot et al., 2013[26]					

After	16	50453	1.39 (1.22, 1.59)	57	< 0.001
Peters et al., 2010[27]					
After	16	55105	1.36 (1.20, 1.55)	54	< 0.001
Simons et al., 1998[28]					
After	16	54956	1.39 (1.21, 1.59)	57	< 0.001
Wassertheil-Smoller et al., 1996[29]					
After	16	53394	1.41 (1.24, 1.61)	56	< 0.001
Whooley and Browner, 1998[30]					
After	16	50243	1.38 (1.21, 1.58)	57	< 0.001
Yan et al., 2013[31]					
After	16	53142	1.44 (1.24, 1.68)	60	< 0.001
Yasuda et al., 2002[32]					
After	16	56944	1.37 (1.21, 1.55)	54	< 0.001
Zahodne et al., 2017[33]					
After	16	54237	1.43 (1.24, 1.66)	48	< 0.001

eTable 4. Results of the Univariate Meta-Analysis Regression for HR

Variable	Coefficient	Standard error	95% Confidence Interval	*P*-Value
Study location	0.009	0.124	-0.262, 0.279	0.945
No. of participants	7.95×10^{-6}	5.47×10^{-5}	-0.001, 0.001	0.887
Follow up years	0.021	0.034	-0.054, 0.097	0.544
Male (%)	0.011	0.007	-0.005, 0.027	0.173
Type of depression assessment	0.207	0.107	-0.026, 0.441	0.077
Baseline stroke excluded	-0.071	0.218	-0.545, 0.403	0.750

eTable 5. Results of the Egger Test

Standard Efficiency	Coefficient	Standard error	95% Confidence Interval	*P*-Value
slope	0.081	0.057	-0.039, 0.202	0.172
bias	1.287	0.427	0.387, 2.187	0.008

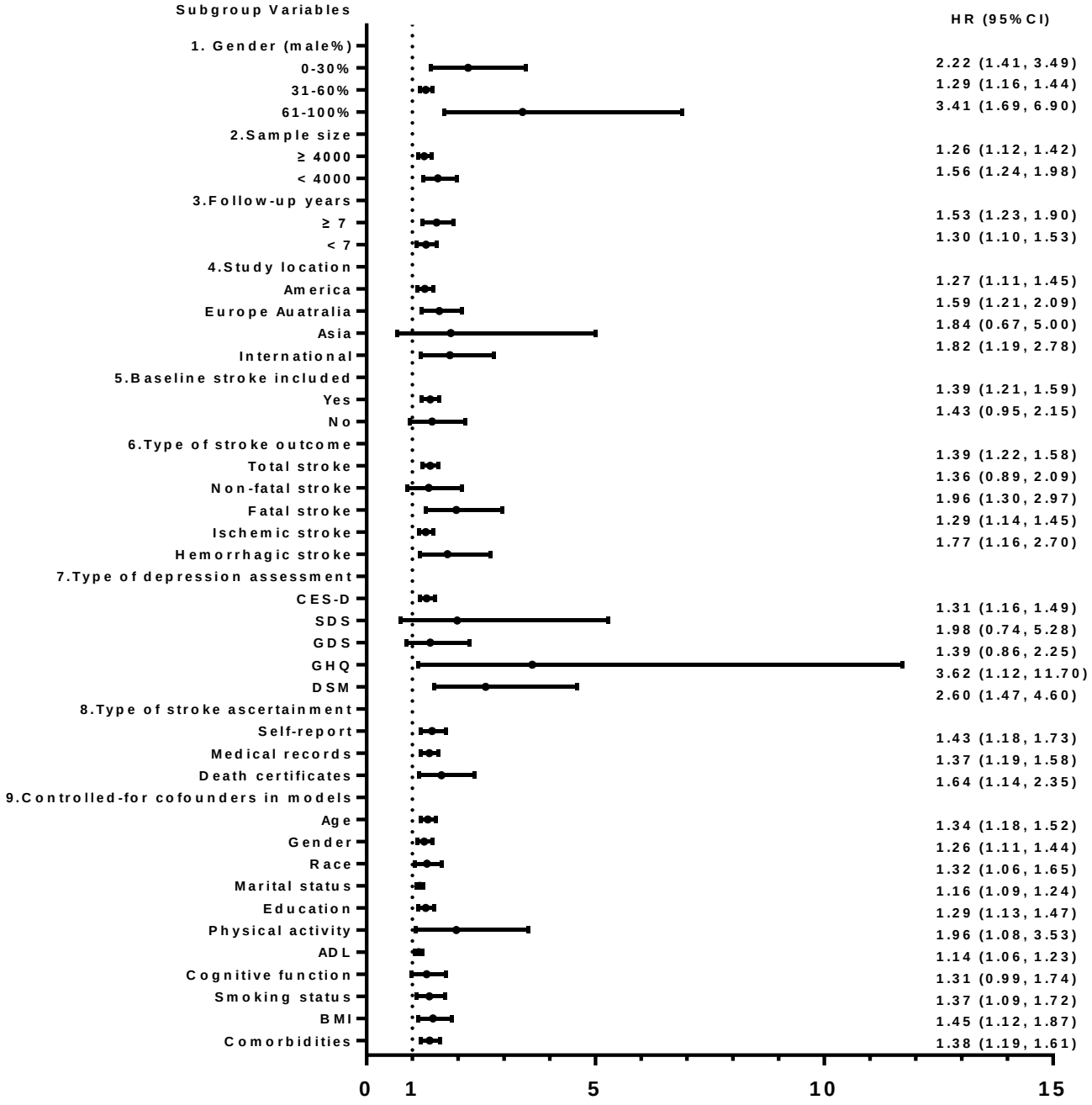
eTable 6. Results of Trim and Fill Analysis

Before				
Method	Pooled Log HR	95% Confidence Interval	*P*-value	No. of studies
Fixed	0.210	0.149, 0.270	< 0.001	19
Random	0.329	0.200, 0.457	< 0.001	
After				
Method	Pooled Log HR	95% Confidence Interval	*P*-value	No. of studies
Fixed	1.178	1.111, 1.248	< 0.001	25
Random	1.193	1.034, 1.377	0.016	

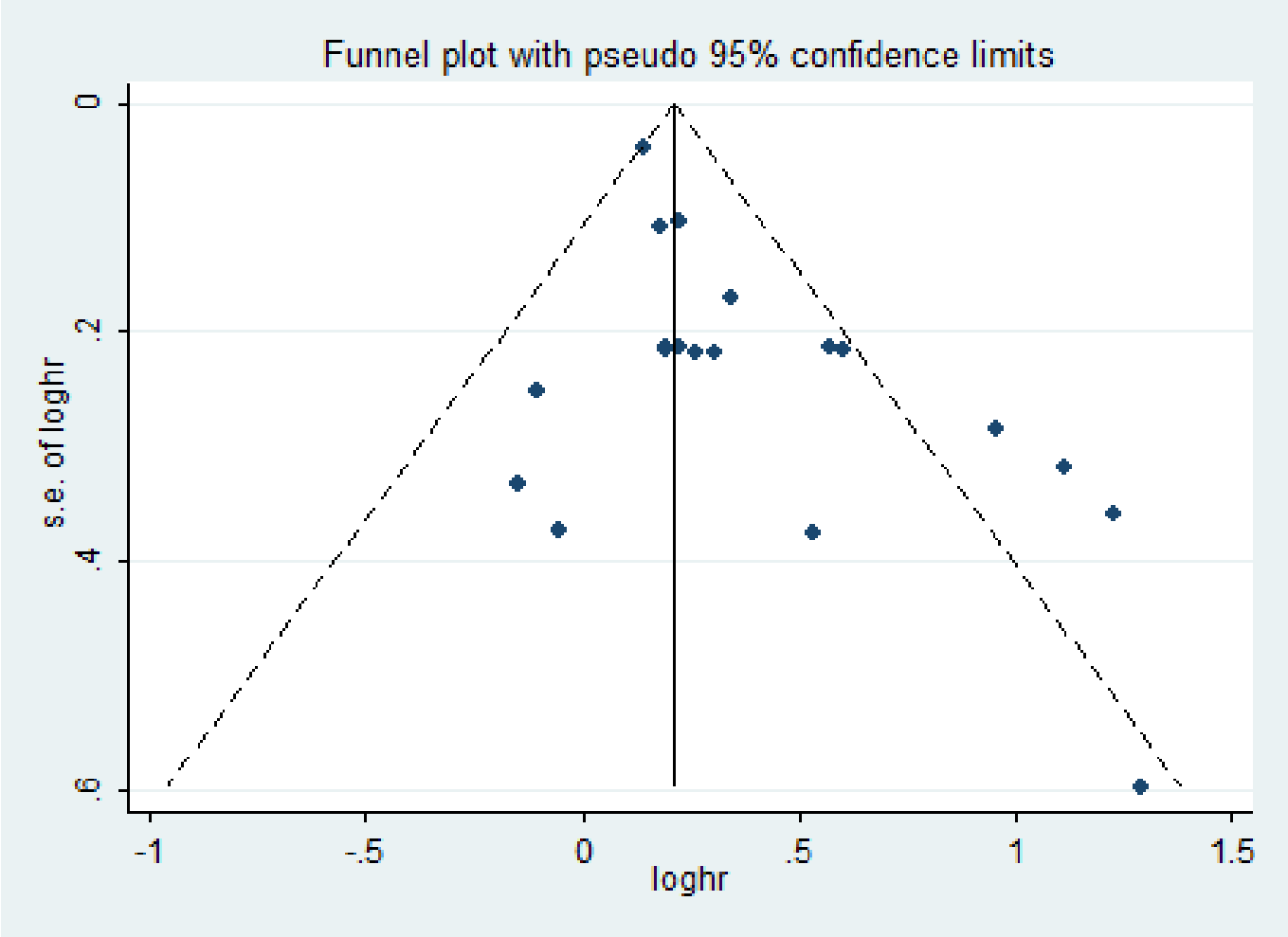
eTable 7. Quality of Evidence Synthesis and GRADE Evidence Profile of Outcomes

Outcome	Total stroke
No. of studies (Participants)	17 (57761)
Risk of bias	Low
Consistency	Consistent
Precision	Precise
Directness	Direct
Other limitations	No randomized controlled trials
Overall strength of evidence	Moderate

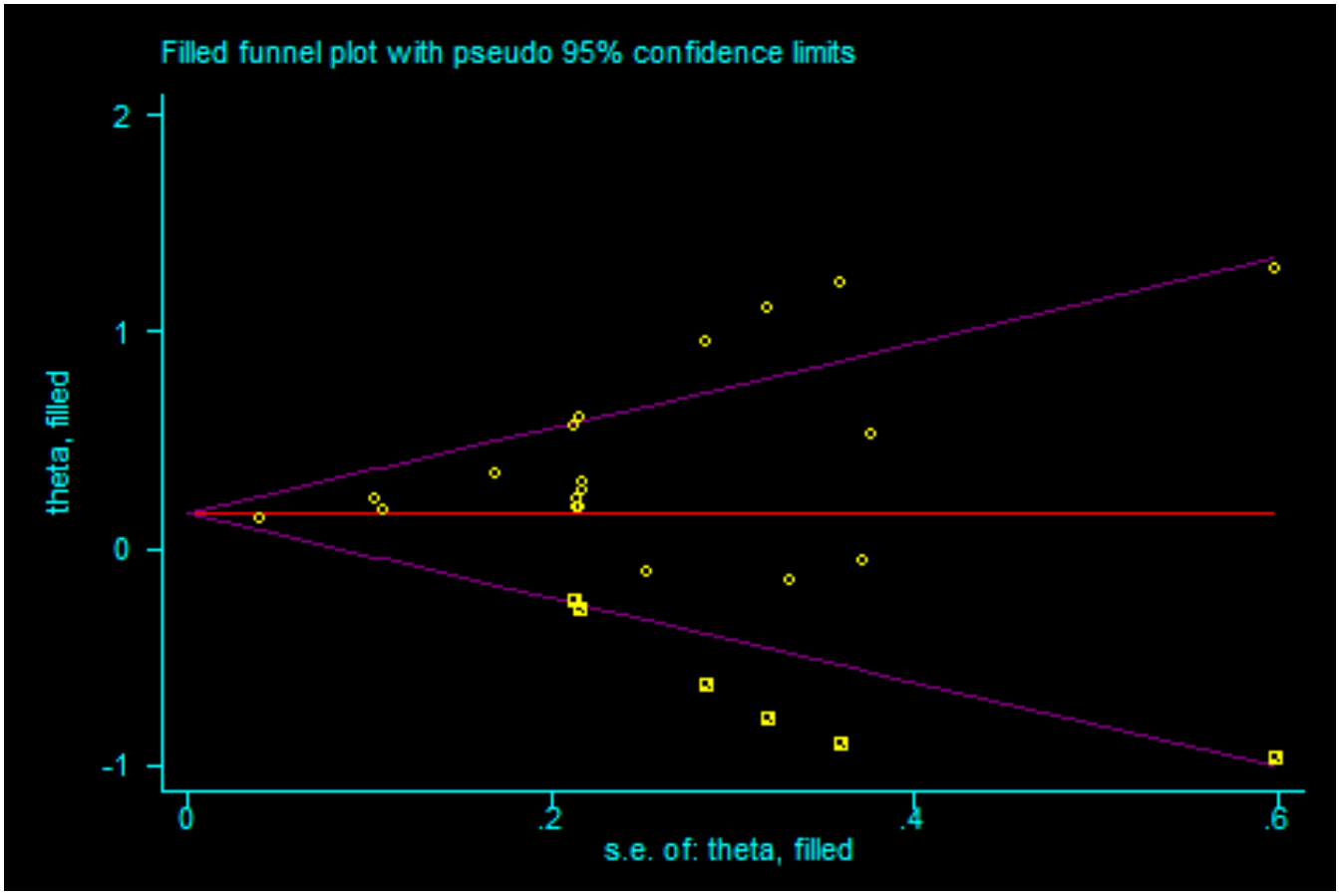
eFigure 1. Summary Forest Plot for the Subgroup Analyses of Stroke Morbidity



eFigure 2. Funnel Plot for HR



eFigure 3. Funnel Plot of Trim and Fill Analysis


Filled funnel plot with pseudo 95% confidence limits
theta, filled
2
1
0
-1
0
.2
.4
.6
s.e. of: theta, filled