

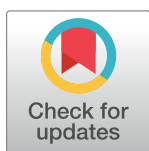
RESEARCH ARTICLE

Impact of depression on stroke outcomes among stroke survivors: Systematic review and meta-analysis

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Abstract

Background

Depression may negatively affect stroke outcomes and the progress of recovery. However, there is a lack of updated comprehensive evidence to inform clinical practice and directions of future studies. In this review, we report the multidimensional impact of depression on stroke outcomes.

Methods

Data sources. PubMed, PsycINFO, EMBASE, and Global Index Medicus were searched from the date of inception.

Eligibility criteria. Prospective studies which investigated the impact of depression on stroke outcomes (cognition, returning to work, quality of life, functioning, and survival) were included.

Data extraction. Two authors extracted data independently and solved the difference with a third reviewer using an extraction tool developed prior. The extraction tool included sample size, measurement, duration of follow-up, stroke outcomes, statistical analysis, and predictors outcomes.

Risk of bias. We used Effective Public Health Practice Project (EPHPP) to assess the quality of the included studies.

Results

Eighty prospective studies were included in the review. These studies investigated the impact of depression on the ability to return to work ($n = 4$), quality of life ($n = 12$), cognitive impairment ($n = 5$), functioning ($n = 43$), and mortality ($n = 24$) where a study may report on more than one outcome. Though there were inconsistencies, the evidence reported that depression had negative consequences on returning to work, functioning, quality of life, and mortality rate. However, the impact on cognition was not conclusive. In the meta-analysis,

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depression was associated with premature mortality (HR: 1.61 (95% CI; 1.33, 1.96)), and worse functioning (OR: 1.64 (95% CI; 1.36, 1.99)).

Conclusion

Depression affects many aspects of stroke outcomes including survival. The evidence is not conclusive on cognition and there was a lack of evidence in low-income settings. The results showed the need for early diagnosis and intervention of depression after stroke. The protocol was pre-registered on the International Prospective Register of Systematic Review (PROSPERO) (CRD42021230579).

Introduction

Stroke is a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause including cerebral infarction, intracerebral and subarachnoid hemorrhage [1]. They often face a range of problems including the inability to move some or whole parts of the body, problems with bladder and bowel control, numbness or strange sensations, trouble with judgment and memory, problems of understanding or forming speech, trouble in controlling or expressing emotions and, experiencing depressive symptoms [2].

Depression is one of the most common neuropsychiatric disorders that can happen before or in the early or late stages of a stroke. It affects approximately one-third of stroke survivors [3]. Post-stroke Depression (PSD) can occur as a continuation of pre-existing depression or may develop after the stroke. PSD is related to poor functional outcomes [5] and is associated with an increased mortality risk [4].

Kutlubaev and Hackett [5] conducted a systematic review of the predictors of depression after a stroke and the impact of depression on stroke outcomes. They reported a negative association between functional outcomes and PSD. Bartoli et al. [6, 7] and Cai et al. [8] also conducted a review and reported an increased mortality rate among survivors with depressive symptoms. Blöchl et al. [9] conducted a review on the impact of PSD on physical disability and reported poor functional outcomes among survivors with depressive symptoms.

Though these reviews included important studies and reported the impact of depressive symptoms on stroke outcomes they fail to review the other dimensions of stroke outcomes such as the ability to return to work. Our review included more studies and assessed more dimensions of stroke outcomes (the ability to return to work, cognition, and quality of life). Therefore, this systematic review and meta-analysis aimed to examine the relationship between depression and stroke outcomes (returning to work, functional recovery, cognition, quality of life, and mortality rate).

Methods

We were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [10] guidelines to report the review. The protocol was pre-registered on the International Prospective Register of Systematic Review (PROSPERO) (CRD42021230579).

Search strategy

We searched four databases from the date of inception until 1st August 2023: PubMed, Embase, Global Index Medicus, and PsycINFO. Forward and backward search was conducted

for the included studies. We have also searched University repositories and Google Scholar for grey literature. We used three big terms (terms for stroke, terms for depression, and terms for outcome) which were combined by the Boolean term AND ([S1 File](#)).

Eligibility criteria

We included longitudinal studies on depression conducted among adults diagnosed with various types of strokes. We included studies that reported both clinically diagnosed depression and studies that utilized screening tools. The outcomes we looked at were functioning, quality of life, returning to work, cognition, and mortality (rate and premature mortality)

Study selection process

The identified references were exported into EndNote reference manager software [11] and duplicates were removed. The references were reviewed using their title and abstracts. After that, the full body of the selected articles was checked for inclusion criteria. We then extracted the author, year of publication, sample size, measures used, and results of the articles. The article screening, selection, and extraction were done by two independent investigators (SS and WF). A third reviewer resolved discrepancies (YG).

Quality assessment

The quality of included studies was evaluated by the two investigators (SS and WF) independently using Effective Public Health Practice Project (EPHPP) [12]. EPHPP provides the means to assess study quality using its eight sections which include selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis. Results lead to an overall methodological rating as strong, moderate, or weak.

Data synthesis

We conducted a narrative synthesis to report the impact of depression on the ability to return to work, cognition, quality of life, functioning, and mortality rate. In the meta-analysis (homogeneous studies), we reported the pooled impact of PSD on functioning and mortality rate. For the mortality rate, we reported two pooled estimates as some studies reported hazard ratio (HR) while others reported odds ratio (OR). Since we expected heterogeneity we conducted a random effect meta-analysis. We used a funnel plot to see the risk of publication bias. We also conducted heterogeneity tests (I^2) to examine the variation in the outcomes among the studies. We used Comprehensive Meta-analysis Software 4 for the meta-analysis [13].

Patient and public involvement

No patient was involved.

Results

Study selection

Initially, we identified 25,646 articles. After removing 5,996 duplicates, 19,652 articles were screened using their title and abstract. Then, 150 full articles were reviewed, and we excluded studies which did not fulfil the inclusion criteria. Finally, eighty prospective studies that reported the relationship between depression and one or more stroke outcomes of interest

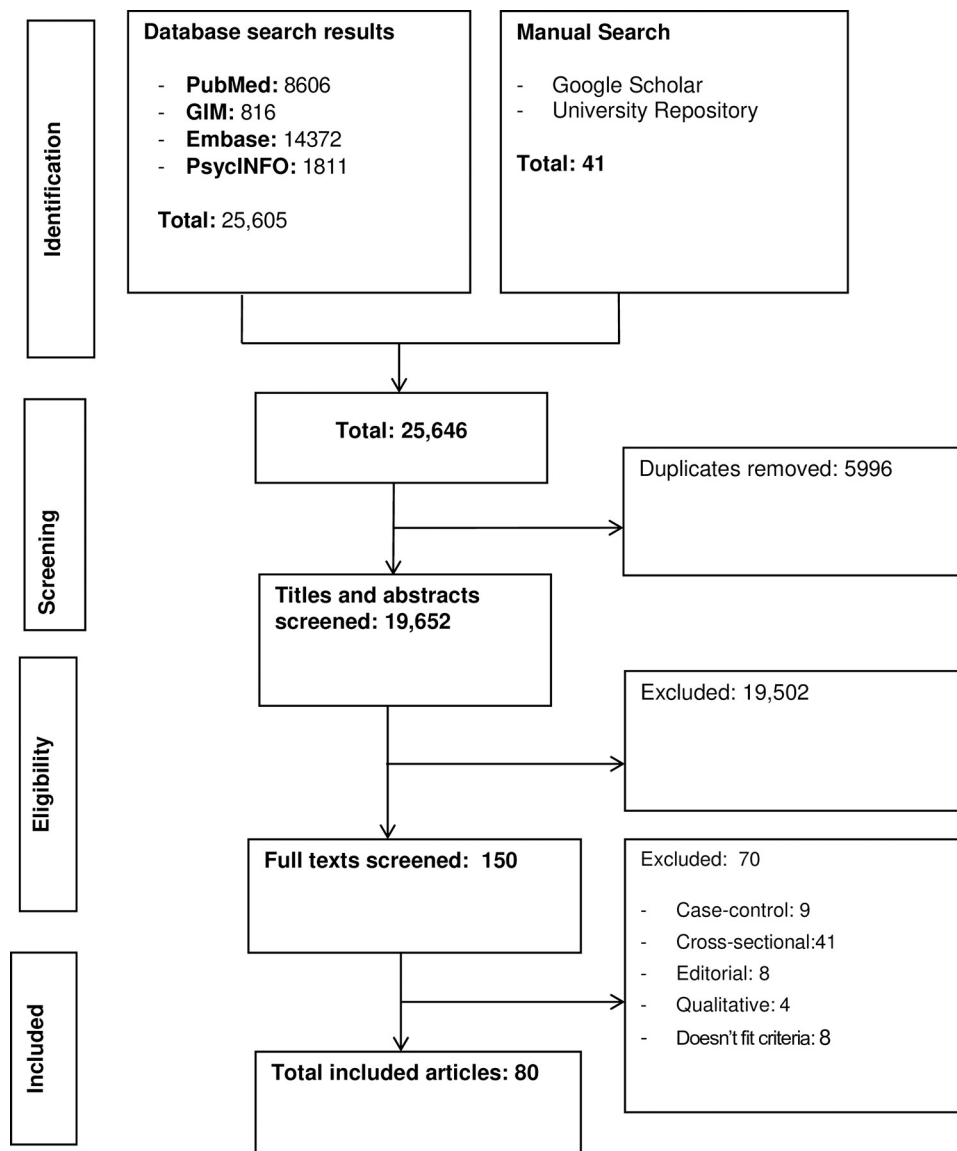


Fig 1. PRISMA flow diagram of the study selection process.

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(cognition, returning to work, quality of life, functional recovery, and mortality rate) were included (Fig 1).

Characteristics of the studies

Most of the studies ($n = 66$) were from high-income countries (HIC) (England, USA, Denmark, Norway, Korea, Australia, Canada, Poland, Finland, Singapore, Italy, Germany, Ireland, The Netherlands, Saudi Arabia, Japan, Scotland, and Singapore); and the rest ($n = 14$) were from middle-income countries (China, Nigeria, Brazil, Tunisia, Thailand, Lebanon, India and Serbia) and we did not come across studies from low-income countries which fulfilled the eligibility criteria.

Out of the eighty studies included in this review, four studies investigated the impact of depression on the ability to return to work, five on cognitive impairment, twelve on quality of

life, forty-three on functional recovery and twenty-four on mortality. The number of participants in the reviewed studies ranged from 49–152, 243 at baseline assessment.

Risk of bias within the studies

The global rating of the articles based on the EPHPPs resulted in thirteen strong, fifty-six moderate, and eleven weak quality studies. The papers that were categorized as weak lacked an assessment of different factors that may affect the main outcome ([S2 File](#)).

Impact of depression on returning to work (n = 4)

Four studies [[14–17](#)] assessed factors predicting the ability to return to work after a stroke. These studies were from Australia [[14](#)], Brazil [[15](#)], the United States of America (USA) [[16](#)], and the Netherlands [[17](#)]. The mean age of the participants was 50 years. They considered time up to one month from the stroke incident as a baseline and followed them up to two years ([Table 1](#)).

Stroke survivors who had worked for at least a month before the stroke incident were eligible to participate. Different types of professions were included from full-time to part-time jobs with different occupations including self-employed and non-manual jobs.

Out of the four studies, one study reported that depression affected the ability to return to work [[14](#)] while the other three reported no significant association between returning to work and depression. This study reported higher odds of returning to work within six months among survivors without depressive symptoms (AOR = 4.92, 95% CI, (1.92–14.37)) [[18](#)]. None of the studies reported treatment for depression ([Table 1](#)).

Impact of depression on quality of life (n = 12)

Twelve studies [[19–30](#)] reported the impact of depression on stroke survivors' quality of life; these studies were from the UK [[19](#)], Australia [[30](#)], Tunisia [[20](#)], Ireland [[22](#)], Nigeria [[23](#)], Brazil [[24](#)], Korea [[21](#), [25](#)], the Netherlands [[26](#)], China [[27](#), [29](#)], and Serbia [[28](#)]. The age range of the participants was 20–98 years; the sample size ranged from 49–1, 101 participants.

Ten studies found that depressive symptoms at various stages of recovery could affect the quality of life of a stroke survivor. The impact was true on both physical and mental components of quality of life.

In two studies that reported no association between depression and quality of life; one study reported that only 4% of the variance in the quality of life score was explained by depression while other predictors like economic status predicted 12% and activities of daily living predicted 19% of the variance [[31](#)] ([Table 1](#)).

Impact of depression on cognition (n = 5)

Studies conducted in England [[19](#)], Brazil [[32](#)], Finland [[33](#)], Lebanon [[34](#)] and South Korea [[35](#)] investigated the relationship between PSD and cognitive impairment. Baseline measures were taken one month after the stroke and followed up for 6 months in the South Korean study, and baseline measures were taken three months after the stroke and followed up for five years in the England study. Stroke survivors with severe cognitive impairment [[19](#)] or communication impairment due to dysphasia or dysarthria [[19](#), [33](#), [35](#)] and previous major depression with a history of suicide [[32](#)] were excluded from these studies.

Three of the studies reported no significant relationship between depression and cognitive impairment. Depression at 3 months was not associated with cognitive impairment at any point in time throughout the 5 follow-up years. Even though the mean Global deterioration

Table 1. Impact of depression on quality of life and returning to work.

Author and year	Setting	Sample size	Age	Gender	Follow up	Depression Measures	Outcome measure	Depression treatment	Results
Ayerbe et al. 2014	England	1101	0-64-35.7% >64-64.3%	Male 54%	Up to 10 years	HADS	SF-36	Not reported	<ul style="list-style-type: none"> • Depression at 3 months and QOL in 5 years. <ul style="list-style-type: none"> ◦ $B = -8.16$ (- 10.23, 6.15) • Depression at 5 years and QOL in 10 years. <ul style="list-style-type: none"> ◦ $B = -8.16$ (- 10.23, 6.15)
Boudokhane et al. 2021	Tunisia	49	Mean 62.2	Male 60%	Up to 1 year	SF-36	HADS	Not reported	<ul style="list-style-type: none"> • Depression a 1 month and QOL at one year • $B = -0.54$ (-1.55,0.72) $p < 0.001$
Donnellan et al. 2010	Ireland	107	Range 20–98	Male 51%	Up to 1 year	SSQOL	HADS	Patients receiving treatment were excluded from the study	<ul style="list-style-type: none"> • Depressive symptoms and poorer quality of life ◦ T1 ($r = -0.56$, $p < 0.001$) and at T2 ($r = -0.41$, $p < 0.001$)
Gbiri et al. 2010	Nigeria	65	Mean 58.1	Male 33	Up to 6 months	SSQOL	ICD-10	Not reported	<ul style="list-style-type: none"> • Depression at baseline and QOL at 3 months <ul style="list-style-type: none"> ◦ $R^2 = 0.31$ $p = 0.00$ • Depression at baseline and QOL at 6 months <ul style="list-style-type: none"> ◦ $R^2 = 0.53$ $p = 0.00$
Guajardo et al. 2015	Brazil	75	Mean 51.6	Male 66.7%	Up to 3 months	GDS	BDI	Not reported	<ul style="list-style-type: none"> • Depressive and SF-36 subscale vitality <ul style="list-style-type: none"> ◦ $R = -0.319$, $P < 0.01$ • Depressive and SF-36 subscale mental health <ul style="list-style-type: none"> ◦ $R = -0.257$, $P < 0.05$
Hackett et al. 2012	Australia	271	Range 17–65	Male 68%	28 days, 6 and 12 months	HADS	-	Not reported	<ul style="list-style-type: none"> • Depression and returning to work. <ul style="list-style-type: none"> ◦ $OR = 2.31$ (0.87, 6.12)
Jet van der Kemp et al. 2019	Netherland	121	Mean 56.3	Female 27.3%	2 months and 1 year	HADS	-	Not reported	<ul style="list-style-type: none"> • Depression not predicting returning to work by 1-year post-stroke. <ul style="list-style-type: none"> ◦ $B = -0.094$ $P = 0.094$
Nascimento et al. 2019	Brazil	117	Mean 57	Male 68%	3 months 6 months	HADS	-	Not reported	<ul style="list-style-type: none"> • Depression did not predict returning to work
Kim et al. 2018	Korea	423	Mean 64.5	Male 57.7 5	Up to 1 year	WHOQOL	MINI	Depression was not treated.	<ul style="list-style-type: none"> • Depression had a significant and persistent impact on QOL at 2 weeks and 1 year after stroke.
Lam et al. 2019	Netherland	120	Mean 68.6	Male 64.2%	Up to 1 year	RAND-36	HADS	Not reported	<ul style="list-style-type: none"> • Depression at baseline and QOL at one year <ul style="list-style-type: none"> ◦ $B = -1.35$, $p < 0.001$
Li et al. 2019	Beijing, China	801	Mean 57.5	Female 30.6%	Up to 5 years	SF-12	DSM-IV	Not reported	<ul style="list-style-type: none"> • Persistent depression at one year and poor MSC score at 5 years. <ul style="list-style-type: none"> ◦ $OR = 48$, (0.29,0.81)
Orman et al. 2022	Australia	563	Mean 68.4	Male 64.5%	Up to 2 years	AQoL-4D	HADS	Not reported	<ul style="list-style-type: none"> • Depression associated with lower AQOL-4 scores. • $\beta = -0.058$ (-0.11,0.00), $p = 0.05$
Schulz et al. 2017	USA	159	Range 40–86	Male 74.8%	3,6, 9 and 12 months	GDS-15	-	Not reported	<ul style="list-style-type: none"> • Depression was not a predictor of SS's ability to return to work
Shi et al. 2016	China	747	Mean 61	Female 32.1%	Up to 1 year	SF-36	HDRS	Patients with antidepressant treatment were excluded from the study.	<ul style="list-style-type: none"> • Depression and PCS <ul style="list-style-type: none"> ◦ $OR = 0.43$ (0.30,0.62) • Depression and MCS <ul style="list-style-type: none"> ◦ $OR = 0.33$ (0.23,0.47)

(Continued)

Table 1. (Continued)

Author and year	Setting	Sample size	Age	Gender	Follow up	Depression Measures	Outcome measure	Depression treatment	Results
Smi et al. 2006	Korea	214	Mean 63	Male 61%	Up to 3 years	WHOQOL	DSM-IV	Not reported	• Depression and QOL ◦ $R^2 = 0.04$ $P < 0.05$
Zikic et al. 2014	Serbia	60			Up to 6 weeks	SF-36	HDRS	Not reported	• SF-36 mean scores were higher in patients without depression

AQoL-4D - Assessment of Quality of Life instrument, CI—Confidence Interval, MCS- Mental Component Summary, OR—Odds Ratio, PCS—Physical Component Summary, QOL—Quality Of Life, DSM-IV—Diagnostic Statistical Measure IV, HADS -Hospital Anxiety and Depression Scale, HDRS-Hamilton Depression Rating Scale, ICD-10- International Classification of Disease, MCS- Mental Component Summary, MINI—the Mini International Neuropsychiatric Interview, PCS—Physical Component Summary, PSD—Post-Stroke Depression, RAND-36 –Research and Development 36 Scale, SF-36 –the Short Form 36 health survey questionnaire, SS-Stroke Survivor, SSQOL- Stroke Specific Quality Of Life, QOL- Quality Of Life WHOQOL- World Health Organization's Quality Of Life Measure

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scale (GDS) score was lower among the mild to moderate depression (MMD) group compared to the moderate to severe depression (MSD) group; there was no significant difference in the change of GDS scores over time. While Finland [33], and Lebanon study [34], reported a significant association between depression and the degree of cognitive deficit (Table 2).

Impact of depression on functional recovery (n = 43)

Different terminologies such as activities of daily living, dependency, functioning, and motor function were used. Forty-three studies [19, 22, 28, 29, 35–73] reported the impact of depression on functional recovery. All except two studies from Serbia [28] and China [29, 72] (upper middle-income countries) were from high-income countries. The number of participants ranged from 40–1753 (Table 2).

Thirty-two studies reported a significant association between depression and functional outcomes. Depression at baseline predicted functioning after 6–24 months (OR:2.7–3.7). The severity of depression was also associated with poor outcomes at 6 months and one year after the stroke. Stroke survivors with MSD had poorer outcomes compared to those who were MMD [29, 35, 69].

Stroke survivors with depressive symptoms had a lower score on a motor assessment scale. For every point increase on the depressive symptom scale, there was a decrease of 0.82 points and 0.77 points on different motor outcome scales indicating poorer outcomes [50]. The crucial part of stroke rehabilitation, trunk control at discharge was also influenced by the presence of depression at admission into the rehabilitation center ($B = 9.057$ (1.03,17.08) $p = 0.027$) [59] (Table 2).

On the other hand, 11 studies reported depression not related to functional outcomes even though one study reported PSD predicting inactive lifestyle rather than functional outcome or performance [39]. And in a study conducted in Norway found that depression was not an independent predictor for modified Rankin scores [68]. In a study conducted in India, no significant difference in the functional outcomes between stroke patients with depression and those without depression with inpatient rehabilitation programs was reported [73].

Regarding depression treatment, out of the total 43 studies, 15 studies [38, 40, 43, 47, 51–54, 56, 57, 60, 62, 67, 72, 73] reported the number of participants who were on treatment for depression whether it was anti-depressant or psychological therapy while one study excluded patients who were on treatment for depression [22]. In a few of these studies [38, 51, 67], functioning improvement was not associated with treatment for depressive symptoms (Table 2).

Table 2. Impact of depression on cognition and functional recovery.

Author, year	Setting	Sample size	Follow up	Depression measures	Outcome measure	Depression treatment	Results
Adbdul-Sattar et al. 2013	Saudi Arabia	180	Up to 28 days	GDS-15	FIM	Not reported	<ul style="list-style-type: none"> • Presence of depression was negatively associated with FIM scores. <ul style="list-style-type: none"> ◦ $Beta = -3.73$ $SD = 0.85$
Ayerbe et al. 2014	England	1101	Up to 5 years	HADS	BI	Not reported	<ul style="list-style-type: none"> • Depression at 3 months and disability at 5 years <ul style="list-style-type: none"> ◦ $RR = 4.71$ (2.96, 7.48)
Ayerbe et al. 2015	England	1307	Up to 3 years	HADS	BI	Not reported	<ul style="list-style-type: none"> • Depression at 3 months and disability at 3 years <ul style="list-style-type: none"> ◦ $RR = 4.01$ (2.42–6.63) $P < 0.001$
Baccaro et al. 2019	Brazil	103	Up to 6 months	DSM IV	MMSE MoCA	Not reported	<ul style="list-style-type: none"> • Depression symptoms were not associated with cognition scores
Boutros et al. 2023	Lebanon	150		HADS	MMSE	Not reported	<ul style="list-style-type: none"> • Depression and cognitive impairment • $AOR = 2.536$, $CI = [1.004–6.403]$, $p = .049$
Cassidy et al. 2004	Ireland	50	Up to 2 months	HDRS	BI	6 patients were on antidepressant	<ul style="list-style-type: none"> • Depression was not related to functional disability.
Clark et al. 1998	Australia	125	Up to 1 year	ZSRS Australian	ADL	Not reported	<ul style="list-style-type: none"> • Depression was not related to functional status. • Depression is strongly a negative predictor of an inactive lifestyle at 6 and 12 months
Donnellan et al. 2010	Ireland	107	Up to 1 year	HADS	Nottingham Extended ADL scale	Patients receiving treatment were excluded from the studies.	<ul style="list-style-type: none"> • Depressive symptoms and poorer functional ability at • At T1 $r = -0.29$, $p < 0.01$ & T2 at one year $r = -0.19$, $p < 0.001$
El Husseini et al. 2017	USA	1444	Up to 1 year	PHQ-8	MRS	18.2% of participants were on antidepressant	<ul style="list-style-type: none"> • Persistent depression and worsening MRS • $OR = 0.85$ (0.53,1.34)
Gillen et al. 2001	USA	243	Up to 1 month	GDS	FIM	Not reported	<ul style="list-style-type: none"> • Higher level of depressive symptoms affects recovery outcome.
Gupta et al. 2022	India	30	Up to a year	HADS	BI, MRS	9 patients received antidepressant	<ul style="list-style-type: none"> • No significant difference in functional outcome between survivors with depression and without depression
Hama et al. 2007	Japan	237	Up to 5 months	SDS	FIM	Not reported	<ul style="list-style-type: none"> • SDS scores did not predict FIM scores
Herrmann et al. 1998	Canada	436	Up to 1 year	MADRS	FIM	19% of depressed patients were on antidepressant	<ul style="list-style-type: none"> • Higher depression scores and functional outcome <ul style="list-style-type: none"> ◦ $R^2 = 0.39$, $p < 0.0001$
Johnston et al. 2004	Scotland	40	Up to 3 years	HADS	BI	Not reported	<ul style="list-style-type: none"> • HADS depression score was not a significant predictor of recovery.
Kang et al. 2018	Korea	145	Up to 1 year	MINI	MRS	Not reported	<ul style="list-style-type: none"> • Depression at the acute phase predicted poor functional outcomes during both the acute and chronic phases of stroke
Kauhanen et al. 1999	Finland	106	Up to 1 year	DSM III R	MMSE	19/53 depressed patients used antidepressant	<ul style="list-style-type: none"> • significant association between the categories of depressive illness and the degree of cognitive deficits
Kijowski et al. 2014	Poland	423	Over a year	GDS	MRS	Not reported	<ul style="list-style-type: none"> • Depression limits gait recovery after stroke.
Koivisto et al. 1993	Finland	143	Up to 2 ½ months	DSM-III-R	MAS of Sivenius	Not reported	<ul style="list-style-type: none"> • SSs with depression performed worse compared to non-depressed SSs in ADL at follow up
Kotila et al. 1999	Finland	523	Up to 1 year	BDI	BI	18% of depressed patients were on antidepressant	<ul style="list-style-type: none"> • Depression at 3 months was associated with poor functional outcomes at 12 months.
Kuptniratsaikul et al. 2009	Thailand	271	Up to 1 month	HADS	BI	Not reported	<ul style="list-style-type: none"> • Depression was not a predictor of BI scores.
Lai et al. 2002	USA	459	Up to 6 months	GDS	BI	Not reported	<ul style="list-style-type: none"> • Depression and BADL • Risk ratio = 0.3 (0.23,0.50)

(Continued)

Table 2. (Continued)

Author, year	Setting	Sample size	Follow up	Depression measures	Outcome measure	Depression treatment	Results
Lin et al. 2020	USA	57	Up to 3 months	PHQ-9	MRS	Not reported	• Higher PHQ-9 scores were associated with worse motor outcome
Loong et al. 1995	Singapore	52	Up to 1 month	HDRS	MBS	10 patients were on antidepressant	• Depressive during admission were associated with functional impairment at discharge.
Matsuzaki et al. 2015	Japan	117	Up to 2 months and 20 days	SDS	FIM	10 patients were on antidepressant	• There was a marginal effect of depression on the FIM score.
Morris et al 1992	Australia	49	Up to 1 year	DSM III	BI	2 patients were on antidepressant	At follow-up, people with depression Improved less (mean change from baseline, 23% versus 48%) (P = 0.001)
Nannetti et al. 2005	Italy	117	Up to 3 months	GDS	BI	49 patients who were depressed were on antidepressant	• Depression and functional recovery • OR = 2.4 (1.1,5.1)
Novack et al. 1987	USA	134	At discharge	SDS	BI	Not reported	• Depression was not associated with BI scores
Paolucci et al. 1999,	Canada	508	-	HDRS	BI	All depressed patients were on antidepressant	• Depression and ADL • OR = 1.99 (1.14,3.46)
Parikh et al. 1990	USA	65	Up to 2 years	HDRS	ZSRS	2 patients were on antidepressants.	• Less impairment in ADL for non-depressed patients compared with the depressed group at 2 years follow up (t = 3.2; df = 61; p<0.01)
Park et al. 2015	Korea	180	Up to 6 months	BDI	BI	Not reported	• Unfavorable outcome in the MSD group versus the MMD group. • OR = 3.5 (1.28,9.97)
Park et al. 2016	Korea	91	Up to 6 months	BDI	mRS GDS	Not reported	• Depression was associated with poor disability outcomes. • OR = 1.37 (0.38–4.91) • GDS score between MMD Vs MSD groups. • Mean difference 1.0±0.2 Vs. 1.7±0.4
Pellicciari et al. 2021	Italy	241	-		TCT		• Depression and trunk control ◦ B = 9.057 (1.03,17.08) p = 0.027
Pohjasvaara et al. 2001	Finland	390	Up to 15 months	BDI	BI	32% of depressed patients were on antidepressant	• Depression and functional outcome • OR = 2.5(95% CI 1.60–3.75)
Saxena et al. 2007	Singapore	141	Up to 6 months	GDS	BI	Not reported	• Depressive associated with low functional recovery ($\beta = -1.31$, p = 0.02)
Schmid et al. 2011	USA	367	Up to 12 weeks	PHQ-9	MRS	Depressed patients were on either medication or psychological care	• Baseline stroke severity and independence at 12 weeks • OR = 1.06 (1.01,1.11)
Schubert et al. 1992	USA	21	Up to 1 month	BDI	BI	Not reported	• Depression was not significantly associated with BI score changes
Shi et al. 2016	China	747	Up to 1 year	HDRS	MRS	Not reported	• Depression and disability • AOR = 4.12 (2.13,7.90)
Spruit-van Eijk et al. 2012	Netherlands	175	At discharge	GDS	BI	Not reported	• No association between depression and BI scores
Tse et al. 2019	Australia	91	Up to 1 year	MADRS	ACS	Not reported	• Depression and an improvement in current activity participation • MADRS-SIGMA was associated with a change of 0.31 (95% CI 0.5 to 0.1, p ¼ 0.01) in current activity participation between 3- and 12 months post-stroke
Van de Weg et al. 1999	Australia	85	Up to 6 months	GDS	FIM	6/30 Depressed patients were on antidepressant	• Depression status and functional improvement were not associated.
Wagle et al. 2011	Norway	163	Up to 1 year and a month	MADRS	mRS	Not reported	• MADRS were not an independent predictor of MRS scores

(Continued)

Table 2. (Continued)

Author, year	Setting	Sample size	Follow up	Depression measures	Outcome measure	Depression treatment	Results
Willey et al. 2010	USA	340	Up to 5 years	HDRS	BI	Not reported	<ul style="list-style-type: none"> • Depression and severe disability at 1 year • OR = 2.91 (1.07 to 7.91) • Depression and severe disability at 2 years • OR = 3.72 (1.29 to 10.71).
Wilz et al. 2007	Germany	81	Up to 1 year	CDS	BI	Not reported	<ul style="list-style-type: none"> • Depression and functional impairment ◦ $B = 0.17$
Wulsin et al. 2012	USA	318	Up to 1 year	CESD	MRS	Not reported	<ul style="list-style-type: none"> • Depression was associated with functional outcomes. • OR = 2.4 (1.36–4.29)
Yuan et al. 2014	China	1753	Up to 1 year	HDRS	MRS	115 patients were on antidepressant	<ul style="list-style-type: none"> • Depression was associated with worse outcomes. • OR = 1.62 (1.18–2.23)
Zikic et al. 2014	Serbia	60	Up to 6 weeks	HDRS	BI	Not reported	<ul style="list-style-type: none"> • Depression and correlation between BI and HDRS score • $r = 0.052$ ($p = 0.784$)

ADL-Active Daily Living, B -Beta coefficient, BADL- Basic Activity of Daily Living, BI- Barthel Index, GDS-Global Deterioration Scale, HDRS- Hamilton Depression Rating Scale, MMD- Mild to Moderate Depression, MSD- Moderate to Severe Depression, OR- Odds Ratio, PSD-Post-stroke depression, SS-stroke survivor, ACS-active card sort, ADL-active daily living, BDI- beck depression inventory, BI- Barthel index, CDS- Cornell depression scale, DSM-III-R-diagnostic statistical manual of mental disorder, FIM-functional independence measure, GDS- geriatric depression scale, HADS- hospital anxiety and depression scale, HDRS-Hamilton depression rating scale, MADRS -Montgomery Rosberg depression rating scale, MBS- modified Barthel scale, MMD- mild to moderate depression, MSD- moderate to severe depression, MRS- modified Rankin scale, OR- odds ratio, PHQ-8 -patient health questionnaire, ZSRs- Zung self-rating scale, MMSE- Mini-mental status examination, MoCA-Montreal Cognitive Assessment, TCT- Trunk Control Test

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Impact of depression on mortality (n = 24)

Twenty-four studies [19, 69, 74–95] reported the impact of depression on the mortality rate. Of these, nine reported all-cause mortality while one study reported a suicide rate. The studies were from the USA [69, 77, 78, 83, 86, 89, 92–94], England [19, 82], Australia [74, 88], Denmark [84], Norway [90], Brazil [76], the Netherlands [79], Germany [85], Finland [87], Italy [91], Sweden and Finland [81], Lebanon [95], and South Korea [75, 80]. The sample size ranged from 84 to 152,243 participants and the age of the participants ranged from 18 to 74 years.

In the study that looked into suicide, suicide risk was higher in stroke survivors with depression compared to those without depression (AOR = 4, 95% CI (1.8–9.5)) [96]. Nineteen studies reported that depression was independently associated with an increased risk of all-cause mortality. Depression at 3 months following stroke was a predictor of mortality at 5 years of survival [19] and even over the period of 29 years [78]. Three studies reported depression was not associated with all-cause mortality (adjusted hazard ratio 1.15, 95% CI (0.76–1.75)) [69] and also no significant association between depression at baseline (one month after stroke) and long-term mortality [93].

While most of the studies did not report the treatment of depression, eight studies [80–83, 90, 91, 93, 94] reported the percentage of participants who were on antidepressant or psychological treatment. These studies showed that the probability of survival was significantly greater in the patients assigned to receive antidepressant treatment ($\chi^2 = 4.7$, $df = 1$, $p = 0.03$, log-rank test) [93] and also protective (HR 0.31; 95% CI 0.11 to 0.86) [94] while compared with no depression treatment group. In another study, depression was a predictor of mortality at 12 months (OR 1.1, 95% CI (0.49, 2.6)) when compared to patients with depression who were given problem-solving therapy [82]. One study excluded patients who were on anti-depressant [76] (Table 3).

Table 3. Impact of depression on mortality rate.

Author and year	Setting	Sample size	Age	Gender	Follow up	Measures	Depression Treatment	Results
Almeida & Xiao et al. 2007	Australia	574	Mean 69.9	Male 55%	Up to 10 years	ICD-9 & ICD-10	Not reported	<ul style="list-style-type: none"> • Depression and mortality ◦ HR = 1.26 (0.71–2.23)
Ayereb et al. 2014	England	1101	0–64–35.7% >64–64.3%	Male 54%	Up to 10 years	HADS	Not reported	<ul style="list-style-type: none"> • Depression and mortality • HR = 1.27 (1.04,1.55)
Boutros 2022	Lebanon	150	Mean 74	Male 58.7%	Up to a year and 3 months	HADS	Not reported	<ul style="list-style-type: none"> • Depression and mortality • HR = 1.30 (1.027,1.65)
Choi et al. 2020	South Korea	128,286	Range 63–114	Male 42.6%	Up to 7 years	ICD-10	Not reported	<ul style="list-style-type: none"> • Depression and suicide • AHR = 4.1 (1.8,9.5)
De Mello et al. 2016	Brazil	191	Mean 63	Male 60.2%	Up to 1 year	PHQ-9	Patients who were on medication to treat depression were excluded.	<ul style="list-style-type: none"> • Depression and all-cause mortality • HR = 4.60 (1.36–15.55)
Ellis et al. 2010	USA	10,025	Range 24–74	Male 43.1%	Up to 10 years	CES-D	Not reported	<ul style="list-style-type: none"> • Depression and mortality • HR = 1.88 (1.27–2.79)
Everson et al. 1998	USA	6675	Mean 43.4	Male 45.8%	Up to 29 years	HPL	Not reported	<ul style="list-style-type: none"> • Depression and mortality • HR = 1.54 (1.06,2.22)
Freak-Poli 2018	Netherland	1344	55+	Male 46.1%	Up to 15 years	CES-D	Not reported	<ul style="list-style-type: none"> • Depression and Mortality • HR = 1.14 (1.06,1.22)
Hong 2018	Korea	210	Mean 62.4	Male 68.5%	Up to 8 years	ICD-10	Documentation of antidepressants for depression after stroke were taken as PSD	<ul style="list-style-type: none"> • Depression and Mortality • HR = 4.93 (1.61,15.08)
Hornsten 2013	Sweden and Finland	88	85>	-	Up to 5 years	GDS	28.9% of patients with depression were on antidepressant	<ul style="list-style-type: none"> • Depression and Mortality • HR = 1.90(1.15,3.13)
House et al. 2001	UK	448	Median 72	Male 54%	Up to 24 months	ICD-10	Patients with depression were given problem-solving therapy.	<ul style="list-style-type: none"> • Depression and mortality • OR = 1.7 (0.95–3.0)
Jia et al. 2006	USA	5825	Mean 67.7	Male 98%	Up to 12 months	ICD-9	15% of patients with depression received antidepressant	<ul style="list-style-type: none"> • Crude death rate among depression 11.0% versus no depression 12.0% • OR = 0.90[0.76, 1.06]
Jorge et al. 2003	USA	104	Range 25–84	Male 104	Up to 12 years	ICD-10	71 patients were on antidepressant	<ul style="list-style-type: none"> • Depression and mortality • OR = 0.74 (0.34, 1.61)
Jorgensen et al. 2016	Denmark	157,243	< 65 24.9%	Male 23.9%	Up to 2 years	Danish Psychiatry Registry	Not reported	<ul style="list-style-type: none"> • Depression and all-cause mortality • HR = 1.89 (1.83,1.95)
Kemper et al. 2011	Germany	977	>50	Male 71%	Up to 1 year	ICD-10	Not reported	<ul style="list-style-type: none"> • Depression and mortality • OR: 0.91 (0.55–1.52)
Melkas et al. 2010	Finland	257	Mean 71	Male 50.6%	Up to 12 years	DSM IIIR	Not reported	<ul style="list-style-type: none"> • Depression and mortality • HR = 1.63(1.05,2.52)
Morris et al. 1993	Australia	84	Mean 70.8	Male 54%	Up to 1 year and 3 months	DSM III	Not reported	<ul style="list-style-type: none"> • Depression and mortality • OR = 3.7 (1.1,12.2)
Morris et al. 1993	USA	91	Mean 60.9	Male 59%	Up to 10 years	HDRS	Not reported	<ul style="list-style-type: none"> • Depression and mortality • OR = 3.39 (1.4,8.4)
Naess et al. 2010	Norway	376	Mean 72.1	Male 60%	Up to a year	HADS	41.3% of patients with depression were on antidepressant	<ul style="list-style-type: none"> • Depression and Mortality • HR = 4.4, p = 0.002
Paolucci et al. 2006	Italy	1064	Range 18–92	Male 60%	Up to 2 years	BDI	44.2 5% of patients with depression were on antidepressant	<ul style="list-style-type: none"> • Prevalence of mortality: 5.48% versus 4.85% (depression versus no depression) • OR = 1.14 (0.65, 2.00)

(Continued)

Table 3. (Continued)

Author and year	Setting	Sample size	Age	Gender	Follow up	Measures	Depression Treatment	Results
Razmara et al. 2017	USA	9919	24–74 years	Male 60.6%	Up to 8 years	CES-D	Not reported	<ul style="list-style-type: none"> Depression and mortality HR = 4.47 (1.21,16.49)
Ried et al. 2011	USA	790	Mean 70	Male 98%	Up to 7 years	ICD-9	32% of patients were on antidepressant	<ul style="list-style-type: none"> Depression and mortality HR = 1.87 (1.24, 2.82)
Willey et al. 2010	USA	340	Mean 68.8	Male 42%	Up to 5 years	HDRS	Treatment of depression was not assessed	<ul style="list-style-type: none"> Depression and all-cause mortality HR = 1.15 (0.76,1.75)
William et al. 2004	USA	51,119	Mean 65	Male 98%	Up to 8 years	ICD-9	Not reported	<ul style="list-style-type: none"> Depression and mortality HR = 1.13 (1.06,1.21)

AHR-adjusted hazard ratio, CES-D- Centre for Epidemiologic Studies Depression Scale, HADS -Hospital Anxiety and Depression Scale, HPL- Human Population Laboratory, HDRS-Hamilton Depression Rating Scale, HR- Hazard Ratio, ICD-10- International Classification of Disease, PSD-Post-Stroke Depression, SS- Stroke Survivor

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Pooled impact of depression on functioning and mortality rate

Eleven studies reported the impact of depression on functioning. Stroke survivors with depression reported higher functioning problems than stroke survivors without depression (pooled OR = 1.94; 1.38, 2.73). The I-squared statistic is 85%, which tells us that 85% of the variance in observed effects reflects variance in true effects rather than sampling error (Fig 2).

Regarding the studies that report the association of depression with mortality rate, we produced two pooled estimates. The first estimate included sixteen studies that reported effect size with HR. The result showed that the mortality rate was higher among survivors with depression (pooled HR = 1.61; 1.33, 1.96) compared to survivors without depression. The I-squared statistic is 95.4%, which tells us that 95.4% of the variance in observed effects reflects variance in true effects rather than sampling error (Fig 3).

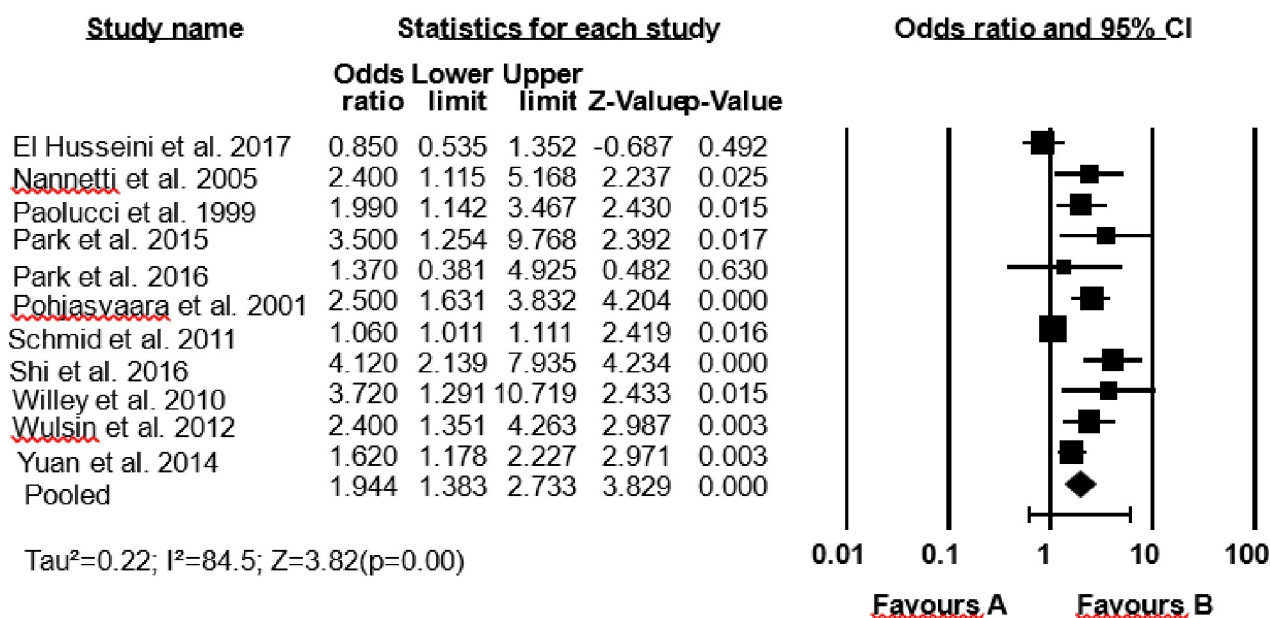


Fig 2. A pooled estimate of the impact of depression on functioning.

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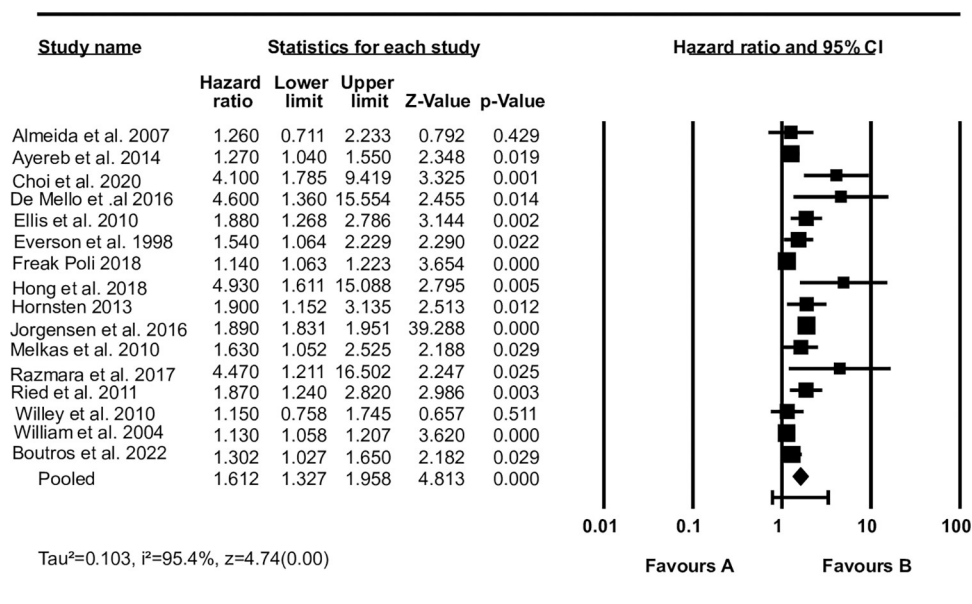


Fig 3. A pooled estimate of the impact of depression on mortality rate (hazard ratio).

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The second estimate included seven studies that reported effect size with OR. The result showed that the mortality rate was not significantly higher among survivors with depression (pooled OR = 1.26; 0.88, 1.80) compared to survivors without depression (Fig 4).

Discussion

In this systematic review and meta-analysis, we have synthesized the impact of depression on stroke outcomes from the results of eighty prospective studies. Five main stroke outcomes

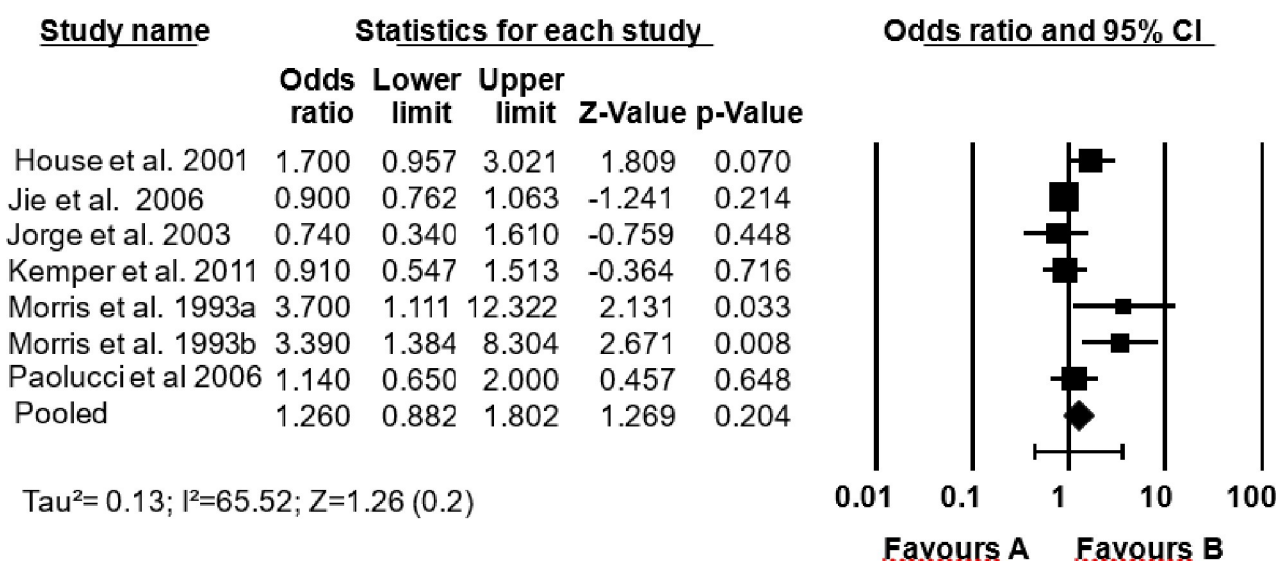


Fig 4. A pooled estimate of the impact of depression on mortality rate (odds ratio).

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were identified: cognitive impairment, quality of life, ability to return to work, functional recovery, and mortality. We presented a comprehensive narrative report on other outcome measures and reported the pooled impact of depression on functional recovery and mortality rate which were not fully addressed in previous reviews.

Three out of the four studies that investigated the impact of depression on the ability to return to work [15–17] reported that depression was not related to the stroke survivor's ability to return to work. This finding may not be true as the survivors in these studies had mild to moderate stroke severity, and they were in the 'younger' age group. Other studies also refuted this conclusion [14, 16]. The inability to return to work is also associated with other factors such as cognitive status [17] and health insurance [14]. The inability to return to work may be different across different settings. These included the socioeconomic status and the available social welfare system which warrants the need for primary studies in low-resource settings to fully understand the impact and find ways to address these issues.

Our finding on the impact of depression on cognitive impairment is not to our expectation [19, 32, 35]. The no association result may be due to lower stroke severity and the exclusion of people with severe cognitive impairment from the studies. Previous studies reported cognitive impairment among both people with depression [97] and stroke [98]. We expect a multiplicative effect when a person had both depression and stroke. However, the results of these studies show the need for more studies to establish the relationship between depression and cognition among stroke survivors.

The association between depression and quality of life after stroke seems conclusive though two out of the twelve studies reported no association in a multivariable analysis. This might be because of the low rate of depression in those studies, and study participants had mild to moderate stroke severity. In these studies, stroke survivors who received treatment for depression were not included in the analysis [22, 29]. Patients who were treated in outpatient clinics and aphasic stroke survivors were also not included in the studies.

Regarding functional recovery, most of the studies indicated the impact of depression on this outcome while few studies reported low to no impact of depression on functional recovery. In these studies, participants who received immediate pharmacological treatment for depression showed better functional improvement by 30% compared to those who did not get treatment for depression [99]. This was also supported by our meta-analysis where depression was significantly associated with poorer functioning though the result needs to be interpreted with caution since the heterogeneity among studies is high.

Our pooled estimate of the impact of depression on mortality rate had significant implications for policy and practice, as shown in previous meta-analyses [6, 7, 9]. Depression increases both all causes, and suicide-related death compared to those without depression. Studies also suggested that early intervention with antidepressant treatments could be associated with the probability of longer survival [93, 94].

Though our review can be considered a comprehensive systematic review with a meta-analysis which synthesized a significantly higher number of prospective studies compared to previous reviews, it is not free from limitations. The first limitation was the definition of post-stroke depression. Stroke is mainly associated with chronic health conditions such as hypertension and diabetes. Depression is a common health problem among people with these chronic health conditions [100, 101]. These indicated the depression after stroke may be a continuation of pre-stroke depression. Nevertheless, the data shows that depression remains a significant issue that needs to be addressed for all stroke patients regardless of when it occurs. The second limitation was the heterogeneity of the studies. The heterogeneity was related to illness duration, the severity of the stroke, the setting and the measures used to assess depression. It's important to consider all these factors while reading the finding.

The third limitation was related to the small sample size of the studies included in the meta-analysis which prevented us from sub-group analysis. The fourth limitation comes from the fact that most of the studies were conducted in high-income countries with better rehabilitation services.

Conclusion

Depression affects many aspects of stroke outcomes including survival. The evidence is not conclusive on some outcomes such as cognition. This review indicated the need for longitudinal studies with higher sample size especially in low-resource settings since the treatment for depression and stroke is not well-established and there is no well-established social welfare system. It also showed the need to provide mental health support for stroke survivors as it is related to better overall health and recovery.

Supporting information

S1 File. Search strategy for impact of depression on stroke outcomes.
(DOCX)

S2 File.
(PDF)

S1 Table. Quality assessment for impact of depression on stroke outcomes.
(DOCX)

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