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Review

The Comorbidity and Associations between Depression, Cognitive Impairment, and Sleep after Stroke and How They Affect Outcomes: A Scoping Review of the Literature

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Abstract: Objectives: post-stroke depression (PSD), cognitive impairment, and sleep disturbances are the most common post-stroke conditions. To aid clinical practice for a highly confounded clinical problem, a clearer understanding of the associations between comorbid PSD, post-stroke cognitive impairment, and sleep disturbances is necessary. Materials and Methods: a scoping review of the literature was conducted according to the recommended guidelines using the search term ["stroke (mesh term) AND depression (in the abstract) AND cognitive (in the abstract) AND sleep (in the abstract)"]. Results: 10 studies met the criteria for inclusion. Only one study reported a co-occurrence of post-stroke emotional distress and sleep disturbances at a rate of 10.7%. Poor sleep and cognitive impairment are independent risk factors for PSD. The relationship between post-stroke poor sleep and cognitive impairment is ambiguous. None of the studies examined how PSD, cognitive impairment, and sleep disturbances interact to influence stroke outcomes. Conclusions: the dearth of studies indicates either a lack of awareness of the potential relationship between the three outcomes and the possible range of inter-related non-motor outcomes after stroke or the practical challenges in designing appropriate studies. The included studies had methodological weaknesses in their observational design and use of imprecise, subjective outcome measurements. Important knowledge gaps are identified for future research.

Keywords: post-stroke depression; post-stroke cognitive impairment; post-stroke sleep disorder; scoping review

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1. Introduction

Depression is one of the most frequent neuropsychiatric outcomes after stroke [1]. This is supported by a meta-analysis showing prevalence rates of 18% for major depression, with the rates rising to 33% when dysthymia, adjustment disorder, and minor depression are included [2]. Post-stroke depression (PSD) is, therefore, one of the most well-studied stroke outcomes. Its diagnosis is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) criteria for depressive disorder due to another medical condition, such as stroke. Essentially, the main criteria are the presence of depressed mood or anhedonia causing significant distress or impairment that is pathophysiologically related to the stroke and not better accounted for by other psychiatric disorders nor occurring exclusively in the context of delirium. The diagnosis can be further subtyped as major or minor depression depending on whether the number of symptoms in the criteria for major depressive disorder is met (minor if the criteria are not met) or as having mixed features if hypomanic or manic symptoms are present. PSD is different from major depressive disorder in non-stroke patients as there is an underlying structural brain injury that contributes to the etiology, and all the depressive symptoms, including cognitive difficulty, are more prevalent and more severe in stroke patients [3]. PSD patients may also report less frequent/severe sleep disturbances [4].

In clinical practice, the assessment of stroke patients referred for the evaluation of PSD is often challenging because of the concurrent presence of cognitive impairment and sleep disturbances. A patient who participates poorly in rehabilitation activities and is described as "moody" may, in fact, have episodic daytime sleepiness due to sleep problems at night, which affects their motivation, attention, and endurance in activities. In addition, they may have impairments in executive function, processing speed, and memory, which could also impair their ability to learn from the prescribed activities. Both these scenarios may mimic a clinical picture of PSD in silo or via the combined effect of PSD, cognitive impairment, and sleep disturbances.

Unsurprisingly, current evidence shows a prevalence rate of 38% of cognitive impairment in the first year after stroke, but such studies usually excluded subjects who had clinically significant depression [5]. A recent meta-analysis also showed a pooled prevalence of 40.7% of insomnia symptoms in individuals with stroke, with greater symptom severity among those who had comorbid depression and anxiety symptoms [6]. The relationship between stroke and sleep is further confounded by evidence that a specific sleep disorder, obstructive sleep apnea (OSA), increases the risk of both first and recurrent strokes [7] and can also be a post-stroke consequence that adversely impacts stroke outcomes [8]. OSA itself has also been associated with mood and cognitive problems [9].

To aid clinical practice in the diagnosis of and interventions for a highly confounded clinical problem, a clearer understanding of the nature of the associations between comorbid PSD, post-stroke cognitive impairment, and post-stroke sleep disturbances is necessary. Notwithstanding, there exist other non-motor stroke outcomes, such as apathy and fatigue, that need to be considered during clinical assessments, both of which have a growing body of literature. However, based on clinical experience, PSD, cognitive impairment, and sleep disturbances are by far the most common comorbid post-stroke conditions. Hence, a scoping review was deemed more appropriate for this purpose because the body of literature on non-motor stroke outcomes is likely to be too complex and heterogeneous for a systematic review. A similar scoping review was not found in the current literature, meaning this review is a novel one.

2. Objectives

This review focused on the specific post-stroke neuropsychiatric sequelae of depression, cognitive impairment, and sleep disturbances and was guided using the following research questions:

1. How often do studies in stroke populations include these three variables in their study design?
2. What are the rates of occurrences of these sequelae in post-stroke studies that included them as variables?
3. How are depression, cognitive impairment, and sleep disturbances associated with one another in post-stroke populations?
4. How do depression, cognitive impairment, and sleep disturbances interact with each other to influence stroke outcomes?

3. Method

As this work was not a systematic review, guidance for this work was drawn from "Guidance for conducting systematic scoping reviews" by The Joanna Briggs Institute [10], with every effort to comply where possible.

4. Search Strategy

The articles were searched using the OVID and EBSCO platforms, and the databases searched included MEDLINE (and Epub ahead-of-print, in process, in data review, and other non-indexed citations, daily, and versions), CINAHL, PsycINFO, EMBASE, and EBM reviews from inception until the present. The search parameter used was "stroke (mesh term) AND depression (in the abstract) AND cognitive (in the abstract) AND sleep (in the

abstract)". The mesh term was used only for "stroke" because the review aimed to focus on populations with any type of stroke and, at the same time, be broad in its scope of search for the possible relationships between the three outcome variables of interest.

5. Inclusion Criteria

1. Studies that included post-stroke adult individuals;
2. Studies that included variables of post-stroke depression, sleep, and objectively measured cognitive function in the data collection as well as in the results (all three must be present);
3. Research in the form of observational or epidemiological quantitative studies.

6. Exclusion Criteria

1. Animal studies;
2. Studies that specified including children or people aged < 18 with stroke (to reduce heterogeneity);
3. Studies reporting the psychometric properties of tools that screen for depression, cognitive impairment, and/or sleep;
4. Studies that only included two out of the three variables of interest (to limit heterogeneity);
5. Studies that used depression, cognitive impairment, or sleep as a subject exclusion criterion;
6. Studies that measured depression, sleep, or cognitive impairment pre-stroke;
7. Interventional trials (study samples and methods do not meet the review objectives);
8. Study protocols;
9. Qualitative studies;
10. Studies that measured cognitive impairment only using subjective reports;
11. Expert opinion and narrative review articles.

7. Study Selection

The abstracts of all the identified studies were reviewed to shortlist those that potentially met the inclusion criteria. The full texts of all the shortlisted studies were obtained where possible and reviewed to ensure their eligibility. The reference lists of the shortlisted studies and the excluded studies were also searched for additional studies. The studies that were not published in English were not excluded from the review.

The objective was to provide a broad picture of the existing literature on these post-stroke sequelae. Hence, the assessment of the methodological quality of the included studies was not performed.

The data were then extracted from the selected studies to be included in this review together with the specific details about the study design, objectives, subject inclusion and exclusion criteria, primary and secondary outcome measures, and salient study results. This information was necessary for the synthesis of the findings to meet the objectives of this review. A few studies were excluded because they marginally missed the criteria but were still worthy of discussion. Hence, they are qualitatively discussed to identify gaps in the literature and future research needs.

8. Results

An exploratory MEDLINE search using the parameter "stroke (mesh term) AND depression (title/abstract)" returned 3974 results. Using the parameter "stroke (mesh term) AND cognitive (title/abstract)", 7041 citations were found. A search for "stroke (mesh term) AND sleep (title/abstract)" returned 1446 results. Since the first two searches returned the most results, an attempt was undertaken with the parameter "stroke (mesh term) AND depression (title/abstract) AND cognitive (title/abstract)" and this returned 893 results. The exploratory search results are shown in Table 1.

Table 1. Results of the exploratory MEDLINE search in preparation for the scoping review.

MEDLINE Advanced Search Parameter	No. of Returned Citations
"stroke (mesh term) AND depression (title/abstract)"	3974
"stroke (mesh term) AND cognitive (title/abstract)"	7041
"stroke (mesh term) AND sleep (title/abstract)"	1446
"stroke (mesh term) AND depression (title/abstract) AND cognitive (title/abstract)"	893

Figure 1 shows the PRISMA [11] flowchart of our final search strategy ["stroke (mesh term) AND depression (in the abstract) AND cognitive (in the abstract) AND sleep (in the abstract)"] that yielded 109 citations, inclusive of two articles published in Chinese, one unpublished dissertation, and one conference abstract.

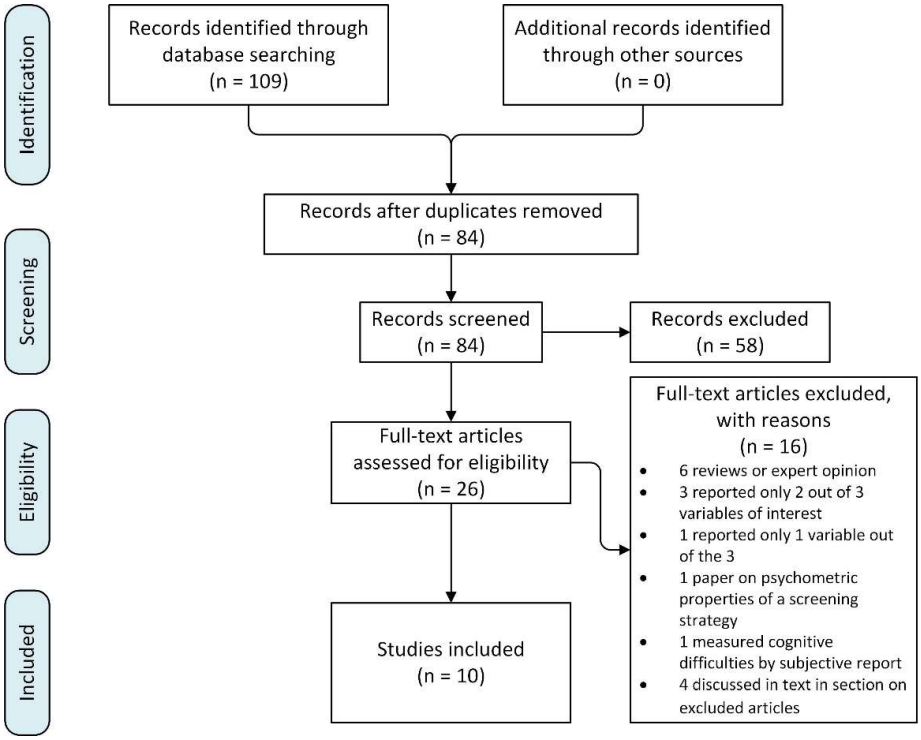

Figure 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram for this scoping review.

Using the number of stroke studies in the exploratory search as the denominator, an estimated 1.2% (84/7041) to 5.8% (84/1446) of studies meeting the search criteria on at least one of the non-motor stroke outcomes of interest were identified to have included the three variables of depression, cognitive impairment, and sleep in the study design.

After reviewing all the 84 shortlisted articles for eligibility, only 10 met the criteria to be included in this review, and the summary of the studies is shown in Table 2. They were first grouped by the primary outcome measure before organizing them in chronological order. All the studies were observational studies, including one case-control, two retrospective chart reviews of medical record data (one cross-sectional and one cohort), and the rest were cross-sectional in design.

Table 2. Summary of studies included in this scoping criteria.

	Author/ Year	Study Title	Study Design/Main Objective	Inclusion/Exclusion Criteria	Primary Outcome Measure(s)	Other Measurements Used	Study Findings
1.	Chadwick 1992 (unpublished)	The effect of stroke on selected characteristics of depression in elderly nursing home residents	Observational (cross-sectional); To examine how selected characteristics of depression in elderly nursing home residents are affected by the presence of stroke	**Inclusion**: Aged > 65 Residents of 3 identified nursing homes Able to respond meaningfully to 75% of study instruments **Exclusion**: Dementia or too medically ill to respond Roommates of enrolled study subjects	**Depression** as defined by score of $\geq$11 on the Geriatric Depression Scale/Amended	**Cognitive Impairment:** MMSE **Sleep:** 4 questions developed by the author (Do you have problems sleeping? Going to sleep? Waking in the middle of the night? Waking up too early?)	n = 44 (**23 with stroke, of which 13 were depressed**; 21 non-stroke of which 11 were depressed). **Residents with stroke and depression had worse MMSE scores than residents with stroke and no depression** (mean 15.39 $\pm$ 6.63 vs. 19.30 $\pm$ 5.66, $p < 0.05$). **No difference in reported sleep problems regardless of presence of stroke and depression.**
2.	Taylor-Piliae et al., 2013	Predictors of Depressive Symptoms Among Community-Dwelling Stroke Survivors	Observational (cross-sectional); To examine the prevalence of depressive symptoms among community-dwelling chronic stroke survivors, and to examine potential independent predictors of depressive symptoms	**Inclusion**: Community-dwelling stroke survivors aged 50 years or older with mild to moderate disabilities **Exclusion**: Stroke survivors with no disability or severe disability, or a serious medical condition that interferes with study participation	**Depression:** CES-D $\geq$ 16	**Sleep**: PSQI > 5 **Cognitive Impairment**: MMSE	n = 100 **Prevalence of depressive symptoms was 35%** **Depressive symptoms correlated with poor sleep quality (r = 0.40, $p < 0.01$) but not cognitive score.** 64% of the variance in depressive symptoms could be explained by a model of 12 independent variables: quality of life physical and mental health, sleep quality, social support, cognitive function, functional disability, time since stroke, age, gender, history of major depression, and lesion location, but **sleep quality and cognitive function were significant independent predictors**.

Table 2. *Cont.*

	Author/ Year	Study Title	Study Design/Main Objective	Inclusion/Exclusion Criteria	Primary Outcome Measure(s)	Other Measurements Used	Study Findings
3.	Carrilo-Mora et al. 2020	Serum Kynurenines Correlate With Depressive Symptoms and Disability in Poststroke Patients: A Cross-Sectional Study	Observational (cross-sectional); To investigate if there is a correlation between serum kynurenines levels with poststroke anxiety and depression and disability scales	**Inclusion**: Patients aged at least 18 years with first ischemic or haemorrhagic stroke corroborated by neuroimaging, no history of neurological or psychiatric disorders, stroke at >1 month but <1 year, able to answer the evaluations of mood and cognition **Exclusion**: Patients with severe aphasia or acute complications that prevent objective assessment (e.g., delirium), current consumption of antidepressants, drugs of abuse, immunosuppressants, immunomodulators, or other drugs that affect mood or cognitive performance	**Significant depressive and/or anxiety symptoms** as measured by HADS (>6 on Anxiety or Depression subscales)	**Cognitive impairment**: MOCA < 24 **Sleep**: PSQI > 5	n = 60 55% male, mean age 57.3 ± 14 years, mean time since stroke 5.2 ± 3.5 months, 82% ischemic stroke, 55% on the right. **63% significant depressive symptoms. 53% significant anxiety symptoms. 45% had both. 50% had poor sleep quality. 68% cognitively impaired.** **PSQI score significantly higher in the depressed group** (11.7 ± 10.7 vs. 7.8 ± 9.8, $p = 0.0172$). **PSQI scores significantly correlated with HADS** subscale (HADS-A, $r = 0.6030$, $p < 0.0001$; HADS-D, $r = 0.4378$, $p = 0.0023$) and total scores ($r = 0.5789$, $p < 0.0001$). Significant positive correlation between 3HK levels with HADS-Total ($r = 0.30$, $p = 0.025$) and HADS-D ($r = 0.28$, $p = 0.039$). Significantly higher levels of 3HK ($p = 0.048$) and KYNA ($p = 0.0271$) in depressed patients Significantly higher 3HK levels in patients poor sleep ($p = 0.019$).

Table 2. *Cont.*

	Author/ Year	Study Title	Study Design/Main Objective	Inclusion/Exclusion Criteria	Primary Outcome Measure(s)	Other Measurements Used	Study Findings
4.	Rabat et al. 2021	Association between neurological outcome and post-stroke comorbid mood and anxiety disorders: A real-life experience	Observational (retrospective chart review of cross-sectional data); To investigate the association between post-stroke mood and anxiety disorders and 3-month stroke outcome	**Inclusion**: Consecutive stroke patients who attended poststroke follow-up visit 3 to 4 months from time of stroke hospitalization. Age over 18. History of ischemic or haemorrhagic stroke confirmed on MRI or CT performed at symptoms onset. **Exclusion**: Missing data in the electronic health record for the variables of NIHSS, mRS, HADS or MOCA	**Comorbid mood and anxiety disorder defined as Poststroke Emotional Distress (PSED)**: >7 on both the anxiety and depression subscales of HADS	**Cognitive Impairment:** MOCA **Sleep:** Documented presence of sleep problems (Yes/No)	n = 2300 **28% met threshold for HADS-D** **34.7% met threshold for HADS-A** **19% had PSED. 26.7% had sleep problems.** **PSED subjects scored lower for MOCA** (24.92 $\pm$ 4.62 vs. 26.17 $\pm$ 4.02, $p < 0.001$), and **larger proportion of PSED reported sleep problems** (42.6% vs. 21.4%, $p < 0.001$). **Multivariate analysis showed that lower cognitive abilities (OR 0.953, $p < 0.001$) and experiencing sleep problems (OR 2.334, $p < 0.001$) were independently associated with presence of PSED on follow-up.** Other significant factors include younger age, female gender, smoking, higher functional disability, pain, fatigue, and abnormal movements.

Table 2. *Cont.*

	Author/ Year	Study Title	Study Design/Main Objective	Inclusion/Exclusion Criteria	Primary Outcome Measure(s)	Other Measurements Used	Study Findings
5.	Mandzia et al. 2016	Imaging and Baseline Predictors of Cognitive Performance in Minor Ischemic Stroke and Patients with Transient Ischemic Attack at 90 Days	Observational study (cross-sectional); To examine cognitive performance in minor stroke and TIA patients at 90 days and identify factors associated with cognitive dysfunction	**Inclusion**: Consecutive patients aged at least 18 years presenting with high-risk TIA or minor ischemic stroke (NIHSS $\leq$ 3). **Exclusion**: If received thrombolysis, had premorbid mRS score of $\geq$2, serious comorbidity with life expectancy <3 months, baseline dementia, could not complete neuropsychological testing, could not complete home sleep apnea testing.	**Mild cognitive impairment** as defined by $\geq$1 SD below normal composite score for executive function (EF), psychomotor processing speed (PS), and verbal memory-memory	**Depression**: CES-D $\geq$ 16 **Sleep**: Diagnosis of sleep apnea based on overnight home monitoring of oximetry	n = 92 76% male, 54% TIA, mean age 65.1 $\pm$ 12.0. **73% had OSA.** **20% impaired on memory, 16% on PS, 17% on EF.** **Cognitive scores did not differ by presence of OSA.** In multivariable analysis, **lower EF was associated with depression CES-D $\geq$ 16** (p = 0.0003), recurrent cortical stroke and greater disability. **Lower PS scores were associated with depression CES-D $\geq$ 16** (p = 0.03), recurrent cortical stroke and greater disability.
6.	Feng 2017 (published in Chinese, full text not available)	Relationship between sleep apnea syndrome and cognitive impairment and functional status after stroke	Observational (case-control); To analyse the correlation between obstructive sleep apnea syndrome and cognitive impairment and functional status after stroke	Inclusion and exclusion criteria not available in abstract	**Cognitive performance** in vigilance, attention, memory, working memory, executive, language, insight, mental activity, psychomotor and intelligence	**Depression and anxiety**: Not specified **Sleep quality and sleepiness**: Not specified	OSA cases = 86, controls = 70 **Cognitive performance of OSA cases significantly worse than control group** (t = 9.276, p = 0.012), specifically worse in attention, executive, insight, mental adjustment, and intelligence (p < 0.05). Functional status worse for cases (t = 38.094, p < 0.001). **No significant differences between groups for sleepiness, sleep quality, anxiety, and depression.**

Table 2. *Cont.*

	Author/ Year	Study Title	Study Design/Main Objective	Inclusion/Exclusion Criteria	Primary Outcome Measure(s)	Other Measurements Used	Study Findings
7.	Sandberg et al., 2001	Sleep Apnea, Delirium, Depressed Mood, Cognition, and ADL Ability After Stroke	Observational (cross-sectional); To investigate the presence of sleep apnea after stroke and its relationship to delirium, depressed mood, cognitive functioning, ability to perform activities of daily living (ADLs), and psychiatric and behavior symptoms	**Inclusion**: Consecutive stroke admissions to a geriatric stroke rehabilitation unit. **Exclusion (not stated a priori)**: Refusal to participate. Failed study procedure due to delirium.	**Sleep:** Overnight sleep apnea recording in hospital through monitoring of nasal and oral air flow, abdominal movements, respiratory and body movements, oxygen saturation and heart rate, body position and snoring	**Cognitive Impairment:** MMSE **Depression**: MADRS	n = 133 **59% fulfilled criteria for sleep apnea** with no difference between those with and without for age, gender, BMI, type of stroke and lesion location. **Those with sleep apnea had higher MADRS scores** (19.2 $\pm$ 11.3 vs. 14.0 $\pm$ 10.7, $p = 0.018$), and more ADL dependent, but **no difference in MMSE** (15.9 $\pm$ 8.5 vs. 17.8 $\pm$ 8.3, $p = 0.206$). Larger proportion of sleep apnea patients were delirious (75% vs. 56%, $p = 0.018$). Logistic regression shows **depressed mood to be significantly associated with sleep apnea**, together with high BMI, ADL dependency and presence if ischemic heart disease (OR 1.74, 95% CI 1.02-2.94, $p < 0.001$). **Central sleep apnea patients (26%) also had higher MADRS scores** (19.9 vs. 14.0, $p = 0.013$).

Table 2. *Cont.*

Author/ Year	Study Title	Study Design/Main Objective	Inclusion/Exclusion Criteria	Primary Outcome Measure(s)	Other Measurements Used	Study Findings
8. Davis et al., 2019	Examining the Inter-relations of Depression, Physical Function, and Cognition with Subjective Sleep Parameters among Stroke Survivors: A Cross-Sectional Analysis	Observational (cross-sectional); To examine the association of subjective sleep parameters with depression, health related quality of life, physical function, and cognition among stroke survivors.	**Inclusion:** Community-dwelling survivors of ischemic or haemorrhagic stroke confirmed by CT or MRI. Aged 55 years and over. History of single stroke of at least 1 year prior to study enrolment. MMSE score of greater than or equal to 20/30 on screening. Living in Greater Vancouver area. Able to comply with study procedures. Read, write, and speak English with acceptable visual and auditory acuity. Not expected to start or are stable on a fixed dose of cognitive medications. Able to walk for a minimum of 6 m with rest intervals with or without assistive devices. Have an activity tolerance of at least 60 min with rest intervals. Not currently participating in any regular therapy or progressive exercise. **Exclusion**: Diagnosed dementia. Diagnosis of another neurodegenerative or neurological condition that affects cognitive function and mobility. At high risk for cardiac complications during exercise and/or unable to self-regulate activity or to understand recommended activity level. Have clinically significant peripheral neuropathy or severe musculoskeletal or joint disease that impairs mobility. Taking medications that may negatively affect cognitive function. Aphasia.	**Sleep**: PSQI $\geq$ 5	**Cognitive Impairment**: MOCA MMSE ADAS-Cog Trail Making Tests A and B Digits Forward minus Backwards **Depression**: CES-D $\geq$ 4	n = 72 **68% rated as having depressive symptoms (CES-D $\geq$ 4).** **47% rated significant poor sleep quality (PSQI $\geq$ 5).** **Global PSQI associated with depression (r^2 = 0.21, p < 0.001) but not with cognition** or physical function. **In bivariate analysis, subjective sleep quality** (r^2 = 0.06, p = 0.038), **sleep latency** (r^2 = 0.10, p = 0.007)**, daytime dysfunction (r^2 = 0.18, p < 0.001) associated with depression.** **In multivariate analysis, daytime dysfunction was associated with depression after adjusting for age and Functional Comorbidities Index. Sleep quality was associated with depression after adjusting for age.** **No significant predictors of cognition were identified.**

Table 2. *Cont.*

	Author/ Year	Study Title	Study Design/Main Objective	Inclusion/Exclusion Criteria	Primary Outcome Measure(s)	Other Measurements Used	Study Findings
9.	Katzan et al., 2020	Sleep disturbance predicts future health status after stroke	Observational (retrospective cohort, analysis of extracted electronic health data); To evaluate factors associated with the presence of sleep disturbances in stroke patients, and to determine the role of patient-reported sleep disturbances in patient-reported outcomes after stroke	**Inclusion**: Age > 18 years, clinical diagnosis of ischemic stroke, intracranial haemorrhage (ICH), subarachnoid haemorrhage (SAH, or transient ischemic attack (TIA), completion of Patient-Reported Outcomes Information Measurement System (PROMIS) sleep disturbance scale at 1 or more ambulatory visits during the study period **Exclusion**: Nil	**Sleep**: PROMIS sleep disturbance scale by computer adaptive testing	**Depression:** PHQ-9 and an equivalent cross-linked PROMIS depression score **Cognitive Impairment:** Computer adaptive testing version of the Quality of Life in Neurological Disorders (NeuroQoL) cognitive function v1.0 scale	n = 2190, of which 476 had follow-up data. **14.5% had depression.** **Sleep score highly correlated with depression score** (r = 0.57;95% CI 0.50, 0.63). In separate multivariate models examining the effect of outcomes of physical function, anxiety, fatigue, pain interference, social role satisfaction and cognitive function on sleep score as the dependent variable and adjusting for depression score and other clinical and demographic variables, **poorer outcomes were significantly associated with worse sleep scores even after adjusting for depression.** **Depression, pain, and fatigue were associated with sleep disturbance in all stroke types.** **Cognitive function and anxiety were associated with sleep disturbance in all stroke types except SAH.** Social role satisfaction was associated with sleep disturbance in all stroke types except ICH. Physical function was associated with sleep disturbance in the TIA group only. Younger age was associated with worse sleep disturbance in ischemic stroke and TIA. In ICH group, men had more sleep disturbance than women after adjusting for depression. **Worse baseline sleep scores were associated with worse follow-up scores for depression**, fatigue, social role satisfaction and physical function after adjusting for each outcome's baseline score, baseline depression score and other clinical variables.

Table 2. *Cont.*

	Author/ Year	Study Title	Study Design/Main Objective	Inclusion/Exclusion Criteria	Primary Outcome Measure(s)	Other Measurements Used	Study Findings
10.	Park et al., 2009	Functional Outcome in Poststroke Patients With or Without Fatigue	Observational (cross-sectional); To evaluate the influence of fatigue on functional outcomes after stroke	**Inclusion:** Consecutive stroke patients receiving outpatient rehabilitation at study site **Exclusion**: <3 months after stroke onset. <18 years old. Previous history of stroke. Multiple or bilateral lesions. Communication problems due to aphasia or dementia. History of diagnosed depression. Rapidly progressive medical disease.	**Fatigue:** Fatigue Severity Scale score > 4	**Cognitive Impairment:** MMSE **Depression**: BDI > 15 **Sleep:** Single question asking whether study subjects experience any sleep disturbances	n = 40 30% had FSS score $\geq$ 4. **55% had BDI > 15.** **30% had sleeping problems.** **No difference in MMSE score between fatigued group and non-fatigued group.** **More fatigued stroke patients had sleep problems (50% vs. 17.9%, $p < 0.05$).** **BDI score was significantly correlated with FSS score ($r = 0.47$, $p < 0.05$)** even though the mean BDI score was not significantly different between groups (22.4 $\pm$ 12.08 vs. 12.9 $\pm$ 9.2). No difference in scores of ADL independence and motor function.

Abbreviations (in alphabetical order): ADAS-Cog—Alzheimer's Disease Assessment Scale; BDI—Beck Depression Inventory; BMI—Body Mass Index; CES-D—Centre for Epidemiological Studies-Depression; CI—Confidence Interval; CT—Computed Tomography; HADS—Hospital Anxiety and Depression Scale; HADS-A—HADS Anxiety subscale; HADS-D—HADS Depression subscale; HADS-Total—sum total of HADS-A and HADS-D scores; MADRS—Montgomery Asberg Depression Rating Scale; MMSE—Mini-Mental State Examination; MOCA—Montreal Cognitive Assessment; MRI—Magnetic Resonance Imaging; mRS—modified Rankin Scale; NIHSS—National Institute of Health Stroke Severity; OR—Odds Ratio; OSA—Obstructive Sleep Apnea; TIA—Transient Ischemic Attack; PSQI—Pittsburgh Sleep Quality Index.

8.1. Rates of Occurrence

There was a wide range of the prevalence rates of post-stroke depression reported, depending on the chronicity of the stroke and the measurement tool that was used. For chronic stroke survivors, the prevalence rate was 35% in the community setting using the Centre for Epidemiologic Studies Depression scale (CES-D) threshold of ≥16 [12], 68% using a CES-D threshold of ≥4 [13], and 56.5% in the long-term care setting (using the geriatric depression scale/amended) [14]. For the subacute stroke patients in the ambulatory or rehabilitation setting, the reported rates ranged from 14.5% using the patient health questionnaire-9 (PHQ9) [15] to 55% using Beck's depression inventory (BDI) [16] and to 63% using the hospital anxiety and depression scale-depression (HADS-D) threshold of >6 [17]. However, in another outpatient sample at three to four months post-stroke, only 28% of the patients met the HADS-D threshold of >7, with 19% of patients meeting the thresholds of both hospital anxiety and depression scale-anxiety (HADS-A) > 7 and HADS-D > 7, a condition the authors termed as post-stroke emotional distress (PSED) [18]. Mandzia et al. reported a rate of 17.4% using CES-D ≥ 16 90 days post-stroke [19]. It appears that there is a higher prevalence among chronic stroke survivors, especially in the long-term care setting. The difference in prevalence from the subacute setting requires further study and explanation.

The common methods for measuring cognitive performance in patients with subacute stroke were the Montreal cognitive assessment (MoCA), mini mental state examination (MMSE) and specific neuropsychological tests. Using a threshold of MOCA < 24, 68% of the study population were cognitively impaired at >1 month but <1 year after a stroke [17]. With specific neuropsychological tests, 20% of the patients were impaired in memory, 16% in processing speed, and 17% in executive function 90 days post-stroke [19]. The disparity in the reported prevalence is likely due to the specificity of the measurements used, with MOCA being more sensitive but less specific than neuropsychological tests as it is a bedside screening measure.

For the studies that used objective measurements for sleep, the use of overnight oximetry monitoring in the home setting <90 days post-stroke identified a 73% prevalence rate of OSA [19], and the other study that employed overnight sleep apnea monitoring in the hospital setting reported an overall 59% prevalence of sleep apnea and 26% prevalence of central sleep apnea [20]. The studies that measured sleep using subjective reports had PSQI-reported prevalence rates of between 47% (in chronic stroke survivors) [13] and 50% (in patients with subacute stroke) [17]. Other studies that used single-question identification and clinical chart documentation reported rates of poor sleep quality in subacute stroke patients of 30% [16] and 26.7% [18], respectively. It appears that subjective measurements may under-detect post-stroke sleep problems.

A co-occurrence between post-stroke emotional distress (PSED) and sleep problems could be computed only in one study by Rabat et al. [18] at a rate of 10.7%.

8.2. Inter-Relationships

The next objective was the characterization of the nature of the association between PSD, cognitive impairment, and sleep. A consistent finding in the four studies [12,14,17,18] using depressed mood with or without anxiety as a primary outcome was that depressive symptoms were associated with sleep disturbance and cognitive impairment. In fact, two studies showed that sleep disturbance and cognitive function were independent predictors of the presence of depressive symptoms, both with and without comorbid anxiety symptoms, through multivariate analyses [12,18].

The two studies that measured cognitive performance on a neuropsychological battery as a primary outcome both compared the results using OSA status but had opposing findings. Mandzia et al.'s study showed that cognitive performance was not differentiated by the presence of OSA [19], while Feng's study (2017) showed that OSA cases demonstrated worse cognitive performance compared with the controls and were also worse in post-

stroke functional status [21]. Interestingly, Mandzia et al. also showed that poorer cognitive performance was also associated with depression, but this was not found in Feng's study.

Looking at the studies that examined sleep as the primary outcome, Sandberg et al.'s study showed that objectively diagnosed sleep apnea was associated with higher depression scale scores [20]. Both Davis et al. and Katzan et al. demonstrated that subjectively reported sleep disturbance was associated with depression [13,15]. However, all three studies failed to show an association between sleep disturbances and cognitive performance regardless of the measure used for cognitive performance, i.e., MMSE, MOCA, or neuropsychological battery.

Finally, the last study included in this review measured post-stroke fatigue as a primary outcome and found that sleep disturbance and depression, but not MMSE scores, were significantly associated with post-stroke fatigue [16].

In summary, sleep disturbance and cognitive impairment are associated with and are also independent risk factors for PSD. However, the relationship between post-stroke sleep disturbance and cognitive impairment is less clear, perhaps because of the heterogeneity of the measures used. Additionally, the duration and severity of the post-stroke sleep problems, as well as the underlying causes of the sleep disturbances, may not have been measured well and controlled for in the reviewed studies.

Nonetheless, these conclusions were drawn purely from observational studies, and a unifying theory about the underlying neurological mechanisms is lacking. This adds an imperative factor to this review so that a framework for future scientific investigation into this area may be constructed.

On the other hand, the clinical implication is that while a PSD patient is highly likely to be sleeping poorly and cognitively impaired at the same time, an objective evaluation for other underlying causes of poor sleep is warranted to intervene more specifically and effectively. A simplistic causal attribution to PSD and limiting treatment to PSD treatment would prevent the optimization of stroke recovery outcomes.

8.3. Impact on Stroke Outcomes

Five out of the ten studies measured the impact of the variables of interest on global stroke outcomes. Of the three studies on sleep apnea, Mandzia et al. showed that poorer cognitive performance (not OSA) was associated with greater disability [19], while Feng showed that functional status was worse in the OSA group [21], and Sandberg et al. showed that patients with sleep apnea were more ADL-dependent [20]. The adverse effect of sleep apnea on physical function post-stroke cannot be concluded with confidence.

Even though Davis et al. showed that global PSQI score was not associated with post-stroke physical function [13], baseline and follow-up data from the electronic records of a cohort of stroke clinic patients showed that poor sleep at the baseline was associated with poorer quality of life scores in several domains, including pain, fatigue, physical function, and social role satisfaction both at the baseline and follow-up, even after appropriate statistical adjustments were performed [15]. This analysis of real-world data suggests the important role of sleep in the quality of life after stroke.

9. Excluded Articles

Out of the sixteen articles that did not meet the criteria, six were reviews or expert opinion articles, and one of them did not have a full text available. Three studies were excluded because they only reported two out of the three variables of interest, and one paper was excluded because it only reported one of the variables. The remaining two papers were excluded because one reported the psychometric properties of a clinical screening strategy, and the other measured cognitive difficulties using subjective reports.

The remaining four excluded papers were worthy of some discussion even though they narrowly missed being included in this review [22–25]. Grouped by primary outcome measure, sleep was the primary outcome measure for three of the papers [22–24], while fatigue was the primary outcome measure for the remaining study [25].

In a case-control study by Zhang et al. (published in Chinese, full text not available), 11.1% of 199 ischemic stroke patients were diagnosed with restless legs syndrome (RLS) after a polysomnography. Compared with stroke patients without RLS, patients with RLS had higher depression scores on the patient health questionnaire (PHQ9) by 2.17 (95% CI 0.39–3.94, $p < 0.05$), more severe daytime sleepiness scores on the Epworth sleepiness scale (ESS), and poorer stroke recovery as measured using the NIHSS score at three months post-stroke. There were also higher odds of having moderate-severe depression on the PHQ in the stroke RLS group (OR = 4.27, 95% CI 1.40–13.10, $p < 0.05$). This study was eventually excluded because the cognitive outcomes were not reported [22], but it is noteworthy because it highlights that there are other non-OSA primary sleep disorders that could be associated with PSD.

Kim et al. (2010) was excluded because it was a prospective interventional trial that examined the effects of pharmacological treatments for insomnia in hospitalized stroke patients. At the baseline, the stroke insomnia group (n = 15) showed poorer performance in tests of attention but were not significantly different from the non-insomnia group (n = 15) in MMSE, Beck's depression inventory (BDI), and Barthel index scores. At follow-up after three weeks, there were no significant differences between the groups in the sleep patterns or cognitive and functional status, leading the authors to conclude that active treatment helped stroke patients with insomnia achieve outcomes equivalent to those without insomnia [23]. This small study suggests that the impact of sleep disturbance on mood and cognitive performance may not be clinically apparent when the follow-up duration is short, hence possibly explaining the heterogeneity of the results in the reviewed studies.

A study examining post-stroke apathy by Cosin et al. (2015) was excluded from this review because the study excluded stroke patients with a MOCA score of less than 20 and those with a HADS score of $\geq$8 on either one or both subscales at the time of study enrolment. The primary outcome parameters were apathy, sleep, depression, and cognitive measures that were compared between the apathy and non-apathy groups three months after a stroke. The apathy group had significantly lower MOCA (26.00 ± 0.50 vs. 28.00 ± 1.50, $p = 0.024$) and sleep efficiency ($p = 0.002$) scores and higher HADS-D scores (3.50 ± 2.63 vs. 1.00 ± 1.00, $p = 0.038$), with more sleep fragmentation ($p = 0.001$) on actigraphy [24]. These results suggest that there may be other non-motor stroke outcomes associated with depression, cognitive impairment, and sleep disturbance.

Post-stroke fatigue may be one such outcome. The study by Drummond et al. (2017) was excluded from this review because those who exceeded the threshold score of 7 on the brief assessment schedule depression cards were excluded from the study. Out of the 268 stroke patients studied, 71 (26.5%) developed post-stroke fatigue as measured using the fatigue severity scale (FSS). Higher FSS scores were correlated with poor sleep hygiene on the sleep hygiene index ($r = 0.29$, $p < 0.001$), higher scores on brief assessment schedule depression cards ($r = 0.33$, $p < 0.001$), and Beck's anxiety index ($r = 0.50$, $p < 0.001$), but was not correlated with performance on a cognitive battery. A multivariate analysis showed that higher depression and anxiety scores were independently associated with post-stroke fatigue [25].

10. Discussion

Unsurprisingly, the exploratory MEDLINE search showed a dearth of studies examining the relationship between post-stroke depression, cognitive impairment, and sleep disturbances. This likely indicates either a lack of awareness in researchers on the potential range of inter-relationships between non-motor outcomes after stroke or the practical challenges in designing appropriate studies that adequately investigate such clinical complexities as they likely require large sample sizes, a long duration of follow-up, or tedious assessments, etc.

The main conclusion from this review is that sleep disturbances and cognitive impairment are independent predictors of PSD. In patients without stroke, sleep disturbance

and cognitive difficulties are part of the diagnostic criteria for major depression. In the post-stroke patient, however, neurological damage from stroke leads to additional challenges in clinical assessment, management, and therapeutic monitoring. For example, the cognitively impaired stroke patient may have communication or processing speed impairments and may not have valid self-reports of depressive symptoms. In addition, psychiatric pharmacotherapy may not produce the same extent of therapeutic benefits seen in a non-stroke depressed patient and may even cause a paradoxical worsening of the symptoms [26]. From the author's clinical experience, an example is that mirtazapine often causes excessive daytime fatigue, interfering with rehabilitation activities when prescribed for depressed mood and insomnia. Nevertheless, the high prevalence of PSD, cognitive impairment, and sleep disturbance does justify routine and comprehensive assessments in clinical practice, with early interventions to optimize rehabilitation potential. However, this review has also shown that significant knowledge gaps still exist regarding the optimal methods of clinical assessments and understanding the relationships between common non-motor stroke outcomes.

Our review revealed an ambiguous relationship between sleep disturbances and cognitive impairment. The findings regarding the specific effects of sleep apnea are inconsistent between studies, and the studies showed a lack of relationship between subjective sleep quality and cognitive performance, regardless of the cognitive test used. Juxtaposed with the findings from Kim et al. (a study that was excluded) [23], that treatment of post-stroke insomnia has the benefit of optimizing stroke recovery, it is clear there is a need for a deeper understanding of how sleep disturbance after stroke mediates outcomes before it can be regarded as a therapeutic target and before clinical trials of the different types of sleep interventions can be conducted. A detailed appraisal of the studies using subjective sleep quality reports revealed that sedative medications and the duration and severity of sleep symptoms post-stroke were not adjusted for in the analysis, and this may have accounted for the negative findings.

As most of the studies in this review were cross-sectional in design, a conclusion on the impact of the three variables of interest on future global stroke outcomes could not be produced. However, the overall summary of the findings suggests that sleep disturbances can predict poorer overall health for stroke patients during follow-up assessments.

A consistent limitation of the studies in this review was the potential methodological weakness of the studies using self-reported mood questionnaires to diagnose PSD. None of the studies stated whether the chosen scale was validated for use in the study population. Moreover, not all stroke patients are capable of self-reporting symptoms, adding to the high risk of classification bias for studies that relied on such measures for determining the primary outcomes, leading to inconsistent findings among the studies.

Similarly, the use of brief cognitive screening instruments like the MoCA is also likely to be an important limitation that explains the lack of strong conclusions. While the MoCA is touted to be sensitive in detecting mild impairments and in detecting changes over time, cognitive impairment may occur in single, specific domains that are not apparent in a global MoCA score or even in the domain scores because of the standard scoring method. Hence, the internal validity of studies using such brief cognitive measures may be affected.

Other notable limitations are that the screening and review of the articles were performed by a single author, and the review protocol was not recorded in a database like Prospero.

This review has also highlighted a few interesting points. Firstly, no significant associations were found between any of the variables and stroke characteristics/locations so far, or rather, no attempts were executed to investigate this. Secondly, none of the studies examined the differential impact of hyperacute stroke treatments on these non-motor outcomes as a group.

Some knowledge gaps identified from this review are the following:

1. What are the trajectories of different non-motor stroke outcomes?
2. How does the inter-relationship between these outcomes change over time?

3. What is the magnitude of the impact of each outcome on the global health outcomes, and does the relative magnitude change over time?
4. What stroke characteristics are predictive of these non-motor outcomes?
5. Do hyperacute stroke treatments influence the answers to the above questions?

It is hoped and anticipated that with information technology-enabled careful, structured, systematic, and comprehensive assessments in clinical settings and the use of big data analytics, all these questions can be answered in the foreseeable future.

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