The time-course of post-stroke fatigue

Abstract

Objectives

To systematically review longitudinal studies to determine the prevalence and time-course of fatigue after stroke (post-stroke fatigue, PSF).

Materials and Methods

A study protocol was registered on PROSPERO. Five databases (PUBMED, MEDLINE, EMBASE, PSYCHINFO and CINAHL) were searched (10th to 13th June 2022). Citations were imported into Covidence software, abstracts screened by one author, full texts of potentially eligible studies retrieved, and one author applied inclusion criteria (longitudinal cohort studies of patients with acute stroke). Quality assessment of included studies was performed using the Joanna Briggs institute tool for observational studies. A meta-analysis was performed for the prevalence of PSF at different time-points after stroke onset, and changes over time. Subgroup analyses were performed by type of stroke and study location.

Results

A total of 13,991 records were returned from the searches. Nine studies were eligible and were included. Five studies were of strong and four of moderate quality. Of the studies suitable for meta-analysis, the prevalence of PSF was 42% (95% CI – 39-44%) at six months after ischaemic stroke; and 34% (95% CI – 28-40%) at one year in stroke survivors excluding subarachnoid haemorrhage. Subgroups analyses found no differences in PSF prevalence between Asian countries and others.

Of those with PSF at first assessment, 66% (95% CI – 61-71%) remained fatigued at follow-up; of those without PSF initially, 15% (95% CI – 11-20%) developed PSF at follow-up.

Conclusion

PSF is common and around two-thirds with fatigue remain fatigued. This justifies the development of new interventions for PSF treatment.

List of Figures and Tables

List of Abbreviations

AHA	American Heart Association
ASA	American Stroke Association
CFS	Chronic Fatigue Syndrome
CIS	Checklist Individual Strengths
COVID-19	Coronavirus Disease 2019
CNS	Central Nervous System
DALY	Disability Adjusted Life Year
FAI	Fatigue Assessment Inventory
FAS	Fatigue Assessment Scale
FSS	Fatigue Severity Score
GP	General Practice/General Practitioner
ICD-11	International Classification of Diseases, 11th Revision
ICH	Intracerebral Haemorrhage
JBI	Joanna Briggs Institute
NIHSS	National Institute for Health Stroke Score
OR	Odds Ratio
PSF	Post-stroke Fatigue
PHS	Public Health Scotland
SAH	Subarachnoid Haemorrhage
T1	Time of first measurement of fatigue
T2	Time of follow-up measurement of fatigue
UK	United Kingdom
WHO	World Health Organization

Introduction and Background

Defining Fatigue

Fatigue is a multidimensional and complex symptom [1]. It is a subjective experience and thus difficult to define. However, common themes are a feeling of tiredness and/or low energy - either mental or physical or both- which is distressing to the individual and affects their quality of life [2]. Fatigue was described as the worst or one of the worst symptoms by almost half of stroke survivors who were surveyed a few years ago [3], and remains a priority for research amongst stroke survivors and clinicians in the Stroke Association (UK) James Lind Alliance Priority setting partnership in 2022 [4].

The pathophysiology of fatigue is poorly understood and is further complicated by its association with the wider determinants of health such as socioeconomic status and social support [5]. A model of post-stroke fatigue (PSF) has been proposed-this includes a trigger (or triggers) at the time of the stroke, and then other factors that may cause it to perpetuate [6].

The prevalence of PSF can be assessed by applying a case definition [7], or by a range of different fatigue scales, which use cut-off points to categorise a person as having fatigue or not.

Stroke survivors who have PSF wish to know whether their fatigue is likely to improve with time [8]. Understanding the time course of PSF is also important for clinicians and researchers: if PSF resolves on its own, then arguably no treatments are needed; whereas if fatigue persists, this would justify the development and testing of new treatments.

The most recent systematic review of the time course of PSF was published in 2012; this review identified 9 studies; no firm conclusions could be drawn because of clinical and methodological heterogeneity, and a meta-analysis could not be performed [9]. Although there have been reviews of PSF since then[10, 11], none have addressed the specific question about the time course of fatigue after stroke. Thus, there is a need to perform a new systematic review of the literature in this area.

Aims and Objectives

Research Questions

What is the time-course of PSF?

In longitudinal cohort studies which have assessed the time-course of PSF after acute stroke, what is the prevalence of PSF at different time points after stroke?

Objectives

- Identify eligible longitudinal studies reporting PSF published since 2011 by literature searching
- Review studies included in a systematic review by Duncan et al (2012) to decide whether they fulfil our current inclusion criteria
- Assess quality of included studies
- Synthesise results of those studies suitable for meta-analysis to determine the prevalence of PSF at different time points and its time-course

Methods

Systematic review of prevalence from observational studies

The use of systematic review for observational studies of prevalence is less well established than for reviews of intervention effects [12]. Researchers from the Joanna Briggs Institute (JBI) developed a modified format for conducting a systematic review of prevalence [12]. The conventional approach of defining: population, intervention, comparator and outcome (PICO) for inclusion criteria is replaced with the condition, context, population and design (CoCoPop) while broadly retaining the same principles of systematic review [12]. We followed this approach.

Study Protocol

A study protocol was developed using the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance [13] (appendix) and registered on PROSPERO on [14], on 29th of June 2022 (ID: CRD42022335540 [15].

Search Strategy

We ran the same search strategy devised previously (Duncan et al. (2012)) on 10th and 13th of June 2022 in: EMBASE, CINAHL, PSYCHINFO and MEDLINE, limiting results to 1st January 2011 onwards (appendix B).

Study Selection

Search results were uploaded to the Covidence platform [16], and duplicates were automatically deleted. CoCoPop inclusion and exclusion criteria for study selection, adapted from Munn et al. (2015) are shown in table 1. An amendment to the selection criteria from the study by Duncan et al. 2012 was to only include studies which recruited patients

prospectively, this was felt to give a more generalisable prevalence of PSF in stroke survivors.

One author screened all abstracts, obtained full texts of potentially eligible studies and applied eligibility criteria. If there was uncertainty about study inclusion, a second reviewer (GM) was consulted, and a consensus reached. Additionally, the nine studies included in the review by Duncan et al. (2012) were assessed and any meeting current criteria (table 1) were also included.

Data Extraction

A data extraction form was created in Microsoft Excel using a form adapted from the JBI manual for evidence synthesis [17]. The fields included are:

- Citation details
    - Year
    - Author
    - Title
    - Journal
- Study details
    - Study design
    - Country
    - Stroke type
    - Fatigue tool used
    - Study characteristics
    - Timing of fatigue assessments
    - Time-course of fatigue in individuals
    - Loss to follow up
    - Proportion of eligible individual recruited
    - Additional outcomes (sometimes fatigue was the secondary outcome)
    - Age of participants
    - Sex split of participants

This was piloted on two studies; no changes were necessary.

Data management and statistics

Data were synthesised narratively (table 2). Statistical meta-analysis was done in R version 4.2.0 [18] using RStudio 2022.02.0 [19] (appendix).

Prevalence for individual studies

Prevalence was extracted from the studies (table 3) and calculated for each time point with a 95% confidence interval (95% CI). [20] using the *prop.test* function in the base R package.

Pooled prevalence

To determine whether prevalence data were suitable for meta-analysis, assessment of both clinical (characteristics of participants) and methodological heterogeneity (methods and timing of PSF assessment) was performed narratively by one author (OM).

To minimise methodological heterogeneity, study results were pooled only if studies reported assessment of fatigue at similar time points. If clinical and methodological heterogeneity, such as participant characteristics or use of fatigue assessment tool, existed after taking account difference in timings of assessment, further subgroups were created prior to data extraction:

- Studies which used the Fatigue Severity Scale (FSS)
- Exclusion of studies investigating SAH
- Ischaemic stroke only
- Geographical area

If there was low methodological and clinical heterogeneity, for example participant characteristics were comparable, statistical heterogeneity was assessed visually by the prevalence and confidence intervals for each study in a forest plot using the *ggplot2* package [21], If there was poor overlap in the confidence intervals of the studies defined as the confidence intervals of two more studies not overlapping, this suggested statistical heterogeneity [22].

After visual inspection, the statistical test, I^2, was calculated to indicate the degree of statistical heterogeneity [23]. The *metaprop* function in the *meta* package [24] of R was used to calculate I^2.

When comparison between two proportions was suitable and heterogeneity was low, this was done using a two-sided z-test of proportions, using the *prop.test* function.

Time-course

For studies which reported the proportion of individuals with fatigue at initial assessment remaining fatigued or recovering; and/or those reporting the proportion of non-fatigued individual who went on to develop fatigue at the second (or subsequent assessments), the 95% confidence intervals of these proportions were calculated using the *prop.test* function.

Clinical, methodological and statistical heterogeneity was assessed as for prevalence. To assess whether the proportion of fatigued individuals remaining fatigued was suitable for meta-analysis an assessment of heterogeneity was made following the same process as detailed above.

Data synthesis

The intention was to perform a meta-analysis of pooled prevalence of PSF and of the proportion of individuals with PSF at baseline who remained fatigued at follow up. Meta-analysis was deemed to be appropriate if statistical heterogeneity was low, evidenced by the calculated I^2 statistic or its lower 95% confidence interval being less than 50%.

Meta-analysis

A random effects model using a generic inverse variance method was used [12].

Meta-analysis of was done using the *metaprop* function of the *meta* package [24].

Narrative synthesis

A narrative synthesis was also performed [25]. [26].

Quality and risk of bias assessment

The study protocol published on PROSPERO stated that the Newcastle Ottawa Scale would be used for assessment of quality and risk of bias. However, during the course of the project, a more appropriate tool was identified and the decision was taken to use the JBI critical appraisal checklist for studies reporting prevalence data [12]. [27].

This tool assesses a study on nine domains. For the purposes of this review, a binary score of 1 or 0 has been used for each domain allowing a total score of 9. For the purposes of stratifying stronger and weaker studies, a score of 8 or more was deemed a strong, 6-7 of moderate strength and a score of 5 or less deemed to be weak. Studies were included regardless of their quality though a sub-group analysis excluding the weak studies would have been undertaken if appropriate.

Reporting

Reporting of this systematic review followed the preferred reporting items for systematic reviews and meta-analyses: The PRISMA 2020 statement [28], a copy of this checklist can be found in appendix.

Funding and ethics

No funding was available for this project and no conflicts of interest are reported.

Results

Study selection

The search retrieved 13,991 reports, of which 5013 were duplicates, (figure 2) leaving 8,978 records for abstract screening. Of these 8,978 records, 62 were retrieved for full text review. Of the 62 records, 54 did not meet the inclusion criteria (3 had the wrong study design, 7 records did not report data on prevalence of fatigue at both time points adequately, full text was not available for 10 reports and one of the studies [29] was published in 2011 and had included in the initial systematic review by Duncan et al. 2012, these reports were assessed separately. This left 8 new reports for 8 studies.

Of the nine studies included in the systematic review by Duncan et al. (2012), only three studies met the new inclusion criteria for this review [29-31], the others had not recruited patients solely from an acute setting (appendix 1). Only one study Snaphaan et al. (2011) presented the information in a way which could be used for this systematic review.

This left a total of nine studies for the final analysis; these were published between April 2011 and March 2022. Included studies are listed in table 2. A table of excluded studies and a reason for exclusion can be found in the appendix J.

Study Characteristics

Study design including timing of assessments and fatigue measures, characteristics of those recruited and attrition are shown in table 2.

Two reports from a single study were identified. One report had been retracted [32], this was not due to methodological issues but rather, it was too similar to an article published by the same authors [33]. We included the retracted report as it provided data on fatigue.

The sample sizes of the nine studies ranged from 52 [34] to 1026 [35]. Three had the main aim of investigating PSF prevalence, time-course; Of the other included studies, one explored the association between obesity and PSF [35], one study explored the relationship between fatigue after subarachnoid haemorrhage and physical fitness [34], three explored risk factors

for PSF [29, 32, 36] and one explored the relationship between thyroid stimulating hormone and post-stroke fatigue [37].

At the first assessment of fatigue, there were a total of 3,245 participants across all nine studies. This fell to 2,889 at the time of final measurement, a loss of 11%. In individual studies, loss to follow up ranged from 9.2% [38] to 56.2% [39]. One study did not report the proportion lost to follow-up [29].

Population characteristics

Participants tended to be middle aged or older adults. Age and sex characteristics of individual studies can be found in table 3.

Four studies investigated participants with only cerebral ischaemic strokes [29, 32, 35, 37]. Four both ischaemic stroke and intracranial haemorrhage (excluding SAH) [36, 38-40]. In the studies reporting the proportion with cerebral ischaemic compared to ICH, the majority of strokes were cerebral ischaemic, with a range of 87% [39] to 96% [36]. One study recruited only people with SAH [34]. Information on stroke type of individual studies can be found in table 3.

Three studies included participants who had suffered a previous stroke and the others recruited only patients with a first ever stroke [32, 36, 37].

Timing of Fatigue Assessment

Four studies first measured fatigue at baseline [32, 35, 37, 39], one study at 4-6 weeks [40], one study at two months [29], one at 3 months [36], and two studies at 6 months [34, 38].

Two studies had a 3-month interval between fatigue assessments, [32, 39], one study a 4-5 month interval [40], four studies a 6-month interval [34, 35, 37, 38], one study a 9-month interval [36]; and one a 16-month interval [29].

Seven studies measured fatigue at two time points [29, 32, 34, 36-38, 40] and two studies measured at four time points [35, 39].

Results for the timing and frequency of fatigue assessment and the proportion of fatigued participants at each time point is presented in table 3.

Quality Assessment

Of the included studies; one scored 9 [37]; five scored 8[29, 32, 35, 36, 40]; two scored 7[34, 38] and one scored 6[39]. See table 4.

Results of Individual studies

Prevalence

Prevalence of PSF for each study at each time point is presented in table 3. The prevalence of fatigue at any time point ranges from 23.4% [32] to 66.7% [39].

Time-course

Six studies (table 5) reported the numbers of participants (n = 1,236) and whether or not individuals were fatigued at baseline and follow up in such a way that allowed calculation of the proportion remaining fatigued, fatigue resolving or developing fatigue [29, 32, 34, 36, 38, 39] see table 7. Three studies did not present data on the individual fatigue status of participants and therefore could not be included in the meta-analysis [35, 37, 40].

The proportion of fatigued patients at first measurement remaining fatigued at follow-up ranged from, 61.1% [36] to 77.3% [34]. The proportion of those who were not fatigued and went on to develop fatigue ranged from 5% [38] to 25% [34]. These results were suitable for meta-analysis.

Meta-analysis

Pooled Prevalence

There was too much clinical and methodological heterogeneity to pool the results of all nine studies. Thus the results were split into subgroups based on the timing of assessments. Even within these time-based subgroups, visual assessment of statistical heterogeneity was unsatisfactory, and was confirmed by high I^2, where I^2 or its confidence intervals were greater than 50%. Thus further subgroups were created with the aim of reducing clinical heterogeneity: a) included studies only with ischaemic stroke [32, 35, 37], b) removed the study which investigated SAH [34], c) comparing studies done in Asia to the rest of the World, as some studies have reported a lower prevalence of PSF in Asian countries; and d) reducing methodological heterogeneity (excluded Kirchberger et al. (2021), Radman et al. (2012) and Snaphaan et al. (2011) which used the FAS, FAI and CIS, respectively, rather than the FSS).

The subgroupings which had low statistical heterogeneity were:

- For cerebral ischaemic stroke only at 6 months, two studies with a combined sample size of 1,731 showed an I^2 of 0%, with pooled prevalence of PSF of 42% (95% CI 39-44%).
- Fatigue at 12 months excluding SAH had a sample size of 1,546 from four studies and showed an I^2 of 76% (95% CI 35-91%). Pooled prevalence of PSF was 34% (95% CI 28-40%)
- Prevalence of PSF at 6 months in Asian countries was suitable for comparison to studies in the rest of the World. The four rest of the world studies had a sample size of 437 and a pooled prevalence of PSF of 46% (95% CI 35-57%) with an I^2 of 80% (95% CI 47-93%) compared to two Asian studies which had a sample size of 1,731 and showed pooled prevalence of PSF of 42% (95% CI 39-44%). A difference in prevalence of 4.5% however, this was not statistically significant (95% CI for difference of proportions -0.8 to 9.9%, p = 0.094).

Forest plots illustrating the meta-analysis results are presented in figure 3.

Time-course

In the six studies which reported the fatigue status of individuals over time [29, 32, 34, 36, 38, 39] there were a total of 403 participants who were fatigued at baseline. There was low clinical, methodological heterogeneity and statistical heterogeneity; with an I^2 of 17% (95% CI 0-62%). The meta-analysis showed that 66% (95% CI 61-71%) of participants who were fatigued at initial assessment remained fatigued at follow up, see figure 5. A sub-group analysis was done which excluded the study by Harmsen et al. which investigated SAH, the results were similar. Of the 381 participants across five studies who were fatigued at baseline across five studies, 65% (95% CI 60-70%) remained fatigued at follow up, I^2 14% (95% CI 0-82%).

Of participants 833 participants from six studies without fatigue at first measurement 15% (95% CI 11-20%) had developed fatigue at follow-up, I^2 50% (95% CI 0-80%).

This was repeated excluding the study by Harmsen et al. (2019) which investigated SAH leaving a sample of 813 participants from five studies. The results were similar with a risk of developing fatigue of 14% (95% CI 11-19%) with an I^2 of 54% (95% CI 0-80%).

Narrative Synthesis

The characteristics of the included studies are presented in table 2. These provide a description of the context of the studies. These elements can be compared to attempt to account for the variation in prevalence and time-course of PSF.

Stroke type and Location

Stroke type did not appear to explain the heterogeneity in prevalence of fatigue. The study by Harmsen et al. (2019) which studied individuals with SAH had relatively high prevalence of fatigue (48.1 and 52.4% at T1 and T2 respectively) however, the sample size was small and not dissimilar to other studies which reported a higher prevalence [39, 40]

The study which only reported on minor infarcts [38] reported prevalence of PSF on the lower end of the spectrum, 32.1 and 34.3% at 6 and 12 months respectively however, other studies which looked at a broader range of infarction size and impairment such as [32, 35] showed similar results.

None of the studies which looked at cerebral ischaemic stroke and ICH found a difference in prevalence of PSF between these groups [36, 38-40].

One study found an association between infratentorial infarction and an increased risk of PSF with an odds-ratio of 4.69 (95% CI 1.03–21.47) [29] but there were only 11 with infratentorial infarcts and thus very wide confidence intervals.

Time since stroke

Four studies [32, 34, 38, 40] showed and increased prevalence of PSF from baseline to follow-up and five a decrease [29, 35-37, 39].

Age

Snaphaan et al. (2011) found that younger age was associated with a higher risk of having PSF at baseline assessment. The other studies did not report age as associated with PSF prevalence. Across the studies, there are no obvious trends between age and PSF. The two studies with the youngest cohorts [38, 39] showed very different prevalence at 12 months, 34% and 54% respectively. The oldest cohorts [36, 40] had a prevalence of PSF of 51% at 6 months and 29% at 12 months, respectively.

Sex

One hypothesis identified from the literature is that women are more likely to experience fatigue than men. None of the included studies found this to be the case.

Employment status

Two studies recruited participants who were employed prior to their stroke [38, 39]. Radman et al. (2012) observed a prevalence of PSF of 34.3% and Rutkowski et al. (2021) 54.3% at 12 months. Rutkowski et al. (2021) removed participants from follow-up once they had returned to work and so remaining participants may be ones with a higher frequency of fatigue.

Geography

Two previous meta-analysis found that the prevalence of PSF was lower in Asia than other regions [10, 11]. These contrast with the findings of this review where there was no statistically significant difference in prevalence of PSF at six months between the studies conducted in Eastern and Western countries. An important consideration is that results from China are not generalisable to a region as diverse as Asia and only two studies were included.

Choice of fatigue tool

Six of the nine studies used the FSS [32, 34, 35, 37, 39, 40]. Kirchberger et al. (2022) used the FAS, Radman et al. (2012) used the FAI and Snaphaan et al. (2011) used the CIS; the choice of fatigue tool did not seem to influence PSF prevalence.

Duration of study period

Three studies had a follow up period of six months [34, 37, 38]; one study for three months [32]; one study for four months [40]; one for nine months [36]; one for 16 months [29]; one for two years [35] and one for one year [39]. There was no apparent pattern between length of follow up and PSF prevalence. The study with the longest follow-up [35] showed a statistically significant decrease in prevalence of PSF and it may be that other studies were not long enough to capture these changes.

Loss to follow up

Loss to follow up ranging from 10% [32] to 56% [39] Four studies showed differences between those lost to follow up and those who remained in the study [35, 36, 39, 40]. One study did not provide a description of the participants who were lost to follow up [37]. This attrition bias could influence the reported prevalence and time-course of PSF. If the fatigue status of an individual was a predictor of loss to follow-up, then the results of the study would be invalid. For example, if fatigued individuals were more likely to be lost to follow-up, then the prevalence of PSF would appear lower than it was and it would appear more individuals recovered from PSF.

Discussion

Summary of findings

To our knowledge, this is the first systematic review of the time-course of PSF which has included a meta-analysis. We identified nine longitudinal cohort studies of stroke which reported fatigue at least two time points. Statistical pooling of suitable studies showed a fatigue prevalence of between a third and half of stroke survivors. These findings are broadly similar to previous meta-analyses of fatigue prevalence which also included studies where fatigue was measured at a single time point e.g. [10, 11].

Six studies in this review reported on the change in fatigue status of individuals over time; the meta-analysis showed that 66% (95% CI 61-71%) of individuals fatigued at the first assessment remained fatigued at follow-up; and 15% (95% CI 11-20%) of those who were not fatigued at first measurement developed fatigue at follow-up. These findings are consistent with a 2015 review which did not perform a meta-analysis which reported that about two-thirds of patients who were fatigued at baseline remained fatigued at follow up, and that 12 to 58% of patients developed new fatigue [6]

Strengths of included studies

The strengths of included studies were that recruitment was prospective and from an acute setting, thus reducing selection bias and recall bias. Only two of the nine studies had a follow-up period of less than six months [32, 40].

Limitations of included studies

Confounders such as pre-stroke fatigue, depression and other associated conditions were not controlled for in all studies and may have influenced the observed prevalence of fatigue. There was substantial loss to follow-up which can introduce attrition bias, and most studies included more men than women and this may make appreciation of role of sex differences in PSF more difficult to interpret. The majority were performed in single centres [29, 32, 34-39] and thus may not be generalizable. These results must be interpreted cautiously, as the calculation of the proportion of patients remaining in their fatigue status was based on

participants who had assessments at both T1 and T2, we cannot make any inferences about the fatigue status of those individuals lost between T1 and T2 who were not included in the analysis. The characteristics of the lost participants may influence the results, for example, if fatigued participants were more likely to withdraw from a study, this would affect the proportion of those seemingly remaining fatigued or developing fatigue.

Strengths of review process

We published our protocol in advance on PROSPERO, we tried to limit methodological heterogeneity by only including studies that recruited from an acute setting, and pre-specified the use of validated fatigue tools. We also systematically reported study quality using a validated method [12] in order to improve the rigour of our work.

Limitations of review process

Only one reviewer screened the abstracts, selected studies and performed quality assessment and the meta-analysis, as this was a Masters project, but the second author was consulted regularly about methodology including study selection, data extraction and analysis. For studies published only in abstract form, we did not have the resource to contact the authors to obtain further information-though if we had done, these data would probably not have been peer reviewed. By creating several subgroups, this reduced the sample sizes-and may have produced low statistical heterogeneity by chance.

Implications for further research

The studies in this review generally did not apply to people with severe stroke, aphasia/dysphasia and/or cognitive impairment, were of short duration, and there were no studies from low-income countries.

There was also variation in the timing of assessments and the fatigue tool used; this meant that we had to make judgements about methodological heterogeneity and the appropriateness of performing meta-analyses. Ideally, consensus is needed about the most appropriate fatigue tool to use in cohort studies, to enable studies to be pooled more easily.

This would require consideration of validity, reliability and feasibility. Also, consensus is needed about the most appropriate time points at which to assess fatigue.

We recommend that further cohort studies are needed, where attrition bias is minimised, and which assess fatigue at the same time points and with the same fatigue tool. Also, generalisability could be enhanced by ensuring that as many as possible eligible patients are recruited-we noted that more men than women were included in studies, which is a common finding in stroke studies. Researchers should consider working with others to develop common protocols, which would allow individual patient meta-analysis.

Two thirds of patients with fatigue at baseline continue to have fatigue. Further research is needed to explore the factors that predict resolution of PSF; a better understanding of these factors may help underpin intervention studies. Finally, because most PSF does not resolve on its own, this justifies the need for interventions to be developed to treat post-stroke fatigue.

Implications for future practice

Routine screening for fatigue when stroke survivors are followed up should be considered. When counselling stroke survivors with fatigue, a clinician might reasonably say that a third of patients with fatigue will improve spontaneously, whilst also making recommendations about physical activity, mood, pacing and sleep as suggested in guidelines [41].

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A. Search strategy

PUBMED – 13/06/2022

1. cerebrovascular disorders or basal ganglia cerebrovascular disease or brain ischaemia or carotid artery diseases or cerebrovascular accident or brain infarction or cerebrovascular trauma or hypoxia–ischemia, brain or intracranial arterial diseases or intracranial arteriovenous malformations or “Intracranial Embolism and Thrombosis” or intracranial haemorrhages or vasospasm, intracranial or vertebral artery dissection
2. stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc* or cva or apoplex* or SAH - tw
3. (brain* or cerebr* or cerebell* or intracran* or intracerebral) and (ischaemi* or infarct* or thrombo* or embol* or occlus*) tw
4. (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) and (haemorrhage* or haemorrhage* or haematoma* or bleed*) tw
5. Hemiplegia or paresis
6. hemipleg* or hemipar* or paresis or paretic – tw
7. 1-6
8. fatigue or fatigue syndrome, chronic or asthenia or mental fatigue or muscle fatigue or lethargy – mesh
9. fatigue* or asthenia* or neurastheni* or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg* or apath* or malaise – tw
10. (low or lack) and energy – tw
11. 8-10
12. 7 and 11
13. 2011 – present
14. English

MEDLINE – 10/06/2022

1. cerebrovascular disorder.af. or basal ganglia cerebrovascular disease.xs. or brain ischaemia.xs. or carotid artery diseases.xs. or cerebrovascular accident.xs. or brain infarction.xs. or cerebrovascular trauma.xs. or brain hypoxia ischemia.xs. or intracranial arterial diseases.xs. or intracranial arteriovenous malformations.af. or (Intracranial Embolism and Thrombosis).xs. or intracranial haemorrhages.xs. or intracranial vasospasm.af. or vertebral artery dissection.af.

2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.

3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or haemorrhage$ or haematoma$ or haematoma$ or bleed$)).tw.

5. hemiplegia/ or exp paresis/

6. (hemipleg$ or hemipar$ or paresis or paretic).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. fatigue/ or fatigue syndrome, chronic/ or asthenia/ or mental fatigue/ or muscle fatigue/ or lethargy/

9. (fatigue$ or asthenia$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw.

10. ((low or lack) adj5 energy).tw.

11. 8 or 9 or 10

12. 7 and 11

13. limit 12 to (english language and yr="2011 -Current")

PSYCHINFO – 10/06/2022

1. cerebrovascular disorders/ or cerebral haemorrhage/ or cerebral ischemia/ or cerebrovascular accidents/

2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc $ or cerebral vasc$ or cva$ or apoplexy$ or SAH).tw.

3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or haemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

5. Hemiplegia/

6. (hemipleg$ or hemipar$ or paresis or paretic).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. Fatigue/ or chronic fatigue syndrome/ or hypersomnia/ or sleepiness/ or asthenia/ or neurasthenia/ or apathy/ or dysthymic disorder/

9. (fatigue$ or asthenia$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or lassitude or letharg$ or apath$ or malaise).tw.

10. ((low or lack) adj5 energy).tw.

11. 8 or 9 or 10

12. 7 and 11

13. 12 and "Journal".sa_pubt.

14. 13 and 2011:2022.(sa_year).

EMBASE – 10/06/2022

1. cerebrovascular disease/ or basal ganglion haemorrhage/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or exp carotid artery disease/ or exp brain hematoma/ or exp brain haemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/

2. stroke unit/ or stroke patient/

3. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc $ or cerebral vasc$ or cva$ or aploplex$ or SAH).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.

5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or haemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

6. hemiplegia/ or paresis/

7. (hemipleg$ or hemipar$ or paresis or paretic).tw.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. fatigue/ or chronic fatigue syndrome/ or exhaustion/ or lassitude/ or muscle fatigue/

10. lethargy/ or listlessness/ or malaise/ or apathy/ or dysthymia/ or asthenia/ or neurasthenia/

11. (fatigue$ or astheni$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw.

12. ((low or lack) adj5 energy).tw.

13. 9 or 10 or 11 or 12

14. 8 and 13

15. (hepatitis or dialysis or cancer or carcinoma or meningitis or heat stroke or cerebral palsy).ti.

16. (Parkinson$ or sclerosis or myeloma or tumour$ or tumour$ or transplant$).ti.

17. exp neoplasm/

18. (kidney or renal or heat or cardiac or migraine).ti.

19. 15 or 16 or 17 or 18

20. 14 not 19

21. 20 and 2011:2022.(sa_year).

22. 21 and "Article".sa_pubt.

CINAHL – 13/06/2022

1. (MH “Cerebrovascular Disorders+”) OR (MH “Carotid Artery Diseases+”) OR (MH “Carotid Artery Dissections”) OR (MH “Cerebral Arterial Diseases+”) OR (MH “Intracranial Arterial Diseases+”) OR (MH “Arterial Occlusive Diseases+”) OR (MH “Cerebral Aneurysm”) OR (MH “Intracranial Embolism and Thrombosis+”) OR (MH “Cerebral Ischemia+”) OR (MH “Hypoxia–Ischemia, Brain”) OR (MH “Stroke”) OR (MH “Stroke Patients”) OR (MH “Stroke Units”) OR (MH “Cerebral Vasospasm”) OR (MH “Intracranial Haemorrhage+”) OR (MH “Subarachnoid Haemorrhage”) OR (MH “Basal Ganglia Haemorrhage”) OR (MH “Vertebral Artery Dissections”) OR (MH “Cerebral Haemorrhage+”) OR (MH “Basal Ganglia Cerebrovascular Disease+”) OR (MH “Basal Ganglia Diseases+”) OR (MH “Arteriovenous Malformations+”)

2. TX stroke or TX poststroke or TX post-stroke or TX cerebrovasc* or TX brain vasc* or TX cerebral vasc* or TX cva* or TX apoplex* or TX SAH

3. TX brain* n5 isch?emi* or TX brain* n5 infarct* or TX brain* n5 thrombo* or TX brain* n5 emboli* or TX brain* n5 occlus*

4. TX cerebr* n5 isch?emi* or TX cerebr* n5 infarct* or TX cerebr* n5 thrombo* or TX cerebr* n5 emboli* or TX cerebr* n5 occlus*

5. TX cerebell* n5 isch?emi* or TX cerebell* n5 infarct* or TX cerebell* n5 thrombo* or TX cerebell* n5 emboli* or TX cerebell* n5 occlus

6. TX intracran* n5 isch?emi* or TX intracran* n5 infarct* or TX intracran* n5 thrombo* or TX intracran* n5 emboli* or TX intracran* n5 occlus*

7. TX intracerebral n5 isch?emi* or TX intracerebral n5 infarct* or TX intracerebral n5 thrombo* or TX intracerebral n5 emboli* or TX intracerebral n5 occlus*

8. TX brain* n5 haemorrhage* or TX brain* n5 haemorrhage* or TX brain* n5 haematoma* or TX brain* n5 hematoma* or TX brain* n5 bleed*

9. TX cerebr* n5 haemorrhage* or TX cerebr* n5 haemorrhage* or TX cerebr* n5 haematoma* or TX cerebr* n5 hematoma* or TX cerebr* n5 bleed*

10. TX cerebell* n5 haemorrhage* or TX cerebell* n5 haemorrhage* or TX cerebell* n5 haematoma* or TX cerebell* n5 hematoma* or TX cerebell* n5 bleed*

11. TX intracerebral n5 haemorrhage* or TX intracerebral n5 haemorrhage* or TX intracerebral n5 haematoma* or TX intracerebral n5 hematoma* or TX intracerebral n5 bleed*

12. TX intracranial n5 haemorrhage* or TX intracranial n5 haemorrhage* or TX intracranial n5 haematoma* or TX intracranial n5 hematoma* or TX intracranial n5 bleed*

13. subarachnoid n5 haemorrhage* or subarachnoid n5 haemorrhage* or subarachnoid n5 haematoma* or subarachnoid n5 hematoma* or subarachnoid n5 bleed*

14. (MH “Hemiplegia”)

15. TX hemipleg* or TX hemipar* or TX paresis* or TX paretic*

16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. (MH “Fatigue+”) OR (MH “Fatigue (Saba CCC)”) OR (MH “Fatigue Syndrome, Chronic”) OR (MH “Muscle Fatigue”) OR (MH “Fatigue (NANDA)”)

18. (MH “Asthenia”)

19. TX fatigue* or TX astheni* or TX neurastheni* or TX tired or TX tiredness or TX weary or TX weariness or TX exhaust* or TX lassitude or TX listlessness or TX letharg* or TX apath*

20. TX malaise

21. TX low n5 energy or TX lack n5 energy

22. 17 or 18 or 19 or 20 or 21

23. 16 and 22

24. 22 Limiters – Publication Year: 2011-2022

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	i
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	21
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	31
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4

Topic	No.	Item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A

Topic	No.	Item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	40
Study characteristics	17	Cite each included study and present its characteristics.	25
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	27
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	26
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	15

Topic	No.	Item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	16
	23c	Discuss any limitations of the review processes used.	16
	23d	Discuss implications of the results for practice, policy, and future research.	16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	7
Competing interests	26	Declare any competing interests of review authors.	7
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	No
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org