POST-STROKE FATIGUE: A SCOPING REVIEW [VERSION 1; PEER REVIEW: 1 APPROVED, 1 APPROVED WITH RESERVATIONS]

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ABSTRACT

Bacground: Post-stroke fatigue (PSF) is one of the most common and frustrating outcomes of stroke. It has a high prevalence and it can persist for many years after stroke. PSF itself contributes to a wider range of undesirable outcomes that affect all aspects of daily life. The aim of this review was to identify and summarise the most recent research on PSF, in order to update the evidence base.

Methods: We updated an existing review (Hinkle et al. 2017) systematically searching CINAHL, MEDLINE, PsycINFO, and PubMed to cover new research studies between 1st March 2016 and the search date (19th January 2020). We included interventional and observational research, and clinical practice guidelines that were not covered in the original review. After duplicate removal in EndNote, two reviewers screened the search results in Rayyan, and data from eligible full texts were extracted onto an Excel spreadsheet. Finally, we used RobotReviewer and a human reviewer to assess the risk of bias of randomised trials for this scoping review.

Results: We identified 45 records for 30 studies (14 observational, 10 interventional studies, and 6 guidelines). Apart from one, the interventional studies were single-centred, had high risk of bias and small sample size (median 50). They investigated exercise, pharmacotherapy, psychotherapy, education, and light therapy. Observational studies mainly reported the factors related to PSF including co-morbidities, depression and anxiety, quality of life, activities of daily living, stroke severity, medication use and polypharmacy, polymorphism, pain, apathy, limb heaviness, neuroticism, mobility, and thyroid-stimulating hormone. Guidelines either did not report on PSF or, when reported, their recommendations were supported by little or low level of evidence.

Conclusion: Although we identified a number of recent studies which have added to our current knowledge on PSF, none are robust enough to change current clinical practice.
Introduction
Post-stroke fatigue (PSF) has been defined as ‘overwhelming feeling of exhaustion or tiredness’, which is unrelated to exertion, and does not typically improve with rest. It is one of the most common outcomes of stroke and its prevalence varies between 25% and 85%; however, it is generally accepted that it affects 50% of people after stroke. PSF is linked to undesirable stroke outcomes and affects patients’ participation in studies, adherence to medication, and effectiveness of rehabilitation. This has a negative impact on patients’ quality of life and daily life activities, and also contributes to the burden on family members and carers.

Although researchers have attempted to explain PSF mechanisms, its aetiology still remains unclear. This is partly because there are many contributing factors to PSF, and each research team may focus only on some of the factors to find a route for preventing, treating or managing PSF. Any endeavour to find the most effective intervention in the research literature leads to a collection of heterogeneous interventions from physiotherapy and exercise to psychotherapy, pharmacotherapy, and recently laser therapy.

As a systematic effort to review these scattered interventions, a Cochrane review compared all the tested PSF treatments to a control group, to standard care, or to each other, through reviewing randomised controlled trials (RCTs). This review concluded that there was insufficient evidence of the efficacy of the tested interventions in trials, and more robust research with adequate sample sizes was required. Since then, more recent systematic reviews until 2019 have attempted to summarise the evidence of effectiveness of modafinil, mindfulness training, a traditional Chinese medicine, and smart technologies, but still came to a similar conclusion to that of the Cochrane review in 2015.

As a result of such uncertainty, current clinical practice guidelines rely on low levels of evidence, such as expert consensus, to make recommendations for PSF. However, the efforts to design and test treatments continue, which makes it necessary to keep up-to-date with new research and practice literature.

Objective
The objective of this review was to identify and summarise the most recent research literature related to PSF in order to update the evidence base. As there was an existing review covering the literature up until 2016, we only updated the literature not covered in this review.

Methods
Following methods from an existing review
In 2017, Hinkle et al. published a review covering emerging evidence relating to the management of PSF, up to and including February 2016. Because of the comprehensiveness of this review, we only searched for literature published after 1st March 2016. As the search methods of the Hinkle et al. review were not reproducible, and the search strategies and results were not available, we contacted the corresponding author and their librarian on 15th October 2019. Since we did not receive a reply, we designed the search methods for the reported databases in order to capture the majority of the literature included in Hinkle et al. ’s review.

Following scoping review methods
We followed Arksey and O’Malley framework for conducting this scoping review. We also used Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Extension for Scoping Reviews (PRISMA-ScR) for reporting. The relevant PRISMA-ScR checklist is available as Extended data and the flow diagram is reported in the Results section (Figure 1).

Search methods
We ran a search to include literature between 1st March 2016 and 19th January 2020 (search date) in CINAHL via EBSCOhost, MEDLINE via Ovid SP, PubMed (excluding MEDLINE), and PsycINFO via Ovid. There were no limitations to language, document type (e.g., thesis), study completion status (e.g., ongoing), and publication status (e.g., unpublished) at the search stage. We report the search strategies for all databases in Extended data.

Selection of studies
We imported the search results into EndNote X6 and de-duplicated them based on title, and additionally double-checked the automatically identified duplicates manually. Two reviewers (GA and FS) screened the results independently against the eligibility criteria using Rayyan, which is a recommended screening system. Discrepancies were resolved through discussions or asking a third reviewer (AD).

Two reviewers (GA and FS) also investigated the full texts of relevant search results against the same criteria involving a third reviewer (AD) in case of disagreement. At full text screening stage, we also investigated the reference lists of the relevant studies to identify additional relevant studies. Since one study may have multiple reports or publications, we kept a record and cited all the reports of a single study to provide a better overview of the new research evidence.

Eligibility criteria
We included the following studies:
- Studies of adult humans with PSF – any definition of PSF – at any stage of the stroke care continuum;
- Any interventional (clinical trial) or observational (cohort, case-control, and cross-sectional) studies, and clinical practice guidelines;
- Studies reporting findings that had not been included in the previous review;
- Studies included in relevant systematic reviews.

We excluded the following studies:
- Studies with case reports, case series, and qualitative design;
- Studies included in Hinkle et al. or results which repeated the summarised knowledge in that review;
- Studies of pre-clinical nature;
- Clinical studies where fatigue was reported only as a side effect of the treatment;
- Studies focusing on single muscle fatigue or muscle fatigue in general;
- Studies not focusing on fatigue and/or stroke or focusing on heat stroke, athletes’ fatigue or carers’ fatigue;
- Systematic or narrative or review papers;
- Ongoing studies or protocols with no results (listed and cited in this paper for further follow-up);
- Tool validation studies without reporting new findings on PSF.

**Data extraction methods**

One reviewer (GA) extracted and entered the data in Excel 2007 and the second reviewer (FS) checked the extracted and entered data against the full text and, if appropriate, corrected or amended the data.

For interventional studies, we extracted PICOS (participants, intervention, comparison, outcomes, and study design) and other data points:
- Study name and year;
- Clinical trial registration number (for further check on selective reporting bias);
- Country of origin;
- Number of centres;
- Patients: Number of patients, type of stroke, time passed after stroke;
- Intervention and controls: name of intervention and duration;
- Primary and secondary outcomes measures in general and fatigue measures in particular, outcome endpoints, and main findings related to PSF;
- Study design (single-arm clinical trial (CT), controlled clinical trial (CCT), or RCT);

For observational studies, we extracted:
- Study name and year;
- Clinical trial registration number (for further check on selective reporting bias);
- Country of origin;
- Number of centres;
- Patients: Number of patients, type of stroke, time passed after stroke;
- Primary and secondary outcomes measures in general and fatigue measures in particular, outcome endpoints, and main findings related to PSF;
- Study design (cohort, case-control, or cross-sectional).

For clinical practice guidelines, we extracted the following data:
- Study name and year;
- Country and organisation who produced the guideline;
- Recommendations on PSF;
- Evidence base reporting the level of evidence or study designs related to the level of evidence.

**Quality assessment methods**

We used RobotReviewer for assessing the risk of bias in the four categories of the Cochrane Risk of Bias tool for included RCTs. Although this automation system is reliable for checking the risk of bias for certain bias categories, one of the reviewers (GA) also double-checked and revised RobotReviewer’s assessment and corrected the data where necessary. We also added a ‘selective reporting of outcomes’ category to the list of biases to cover the main biases in Cochrane Risk of Bias tool.

**Synthesis methods**

We summarised the data from the new relevant literature in tables. We did not proceed to a meta-analysis for fatigue outcomes due to the heterogeneity of studies. We checked if any of the interventional studies considered following the CONSORT for reporting RCTs or TIDieR checklist to report the components of new interventions.

**Results**

The search identified 1021 results. After screening, we included 45 relevant records related to 24 studies and 6 guidelines (Figure 1).

The characteristics of included interventional studies have been charted in Table 1. The table shows eight RCTs some with multiple reports and one with a follow-up study, one CCT, and two single-arm trials. All studies were based on single centre studies, except for West et al. (2019) which had two centres. In studies that reported the intervention delivery details, the psychological interventions were delivered individually and face-to-face – rather than online – by psychologists. We also assessed the risk of bias for RCTs and reported the categories of risk in Table 2 with supporting statements in Extended data.

Most of the interventional studies have a medium to high risk of bias. Table 2 shows only two studies in green (indicating low risk of bias) but both have small sample size consisting of 34 (MIDAS study) and 64 randomised patients respectively.

We identified 14 observational studies of which half had a prospective cohort design and the other half were cross-sectional surveys. Three cross-sectional surveys were embedded within cohort studies. Only one of the studies (NOTFAST) had a follow-up report. Details of all studies are reported in Table 3 as well as the Extended data.

Table 4 summarises the main finding of each interventional study all of which either have high risk of bias or small sample size. Such limitations make it hard to transfer the research findings to practice.

The majority of observational studies investigated factors related to PSF including co-morbidities, physical and mental outcomes, illness characteristics, characteristics of interventions, and biomarkers (Table 5).

We identified six recent guidelines from three English-speaking countries including the UK and two North American countries (one from Canada and four from the USA). Among these, the Canadian guideline was the most recent and the only one with comprehensive recommendations on PSF. The UK guideline will be updated in 2021. Half of these guidelines, that is, all those from USA, have not provided specific recommendations on PSF, as reported in Table 6. In almost all the guidelines, the reliance on ‘experts’ consensus’ is apparent because of the limited evidence base for PSF.

**Discussion**

We conducted this review to identify and summarise the most recent research studies on PSF since Hinkle et al.’s review (2017). We therefore documented the interventional and
<table>
<thead>
<tr>
<th>Study name</th>
<th>Country</th>
<th>Design</th>
<th># participants</th>
<th>Stroke type</th>
<th>Time after stroke</th>
<th>Interventions</th>
<th>Duration of intervention</th>
<th>Delivered by</th>
<th>Delivery mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. 2016</td>
<td>Taiwan</td>
<td>RCT</td>
<td>41</td>
<td>With CHF</td>
<td>64.95±53.07 D</td>
<td>Inspiratory Muscle Training + TAU v. TAU</td>
<td>10 W (5 D/W)</td>
<td>Respiratory Therapist</td>
<td>NR</td>
</tr>
<tr>
<td>Chen et al. 2019</td>
<td>Taiwan</td>
<td>RCT</td>
<td>72</td>
<td>Ischemic</td>
<td>NR</td>
<td>Mind-Body Exercise (Qigong) + TAU v. TAU</td>
<td>10 D</td>
<td>Researchers</td>
<td>Individual</td>
</tr>
<tr>
<td>Delva 2019</td>
<td>Ukraine</td>
<td>CCT</td>
<td>39</td>
<td>Ischemic/TIA</td>
<td>≥3 M</td>
<td>Acetylsalicylic Acid (Low Dose v. High Dose)</td>
<td>3 M</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Liu et al. 2016</td>
<td>Taiwan</td>
<td>RCT</td>
<td>64</td>
<td>Ischemic/TIA</td>
<td>≥3 M</td>
<td>Astragalus membranaceus v. Placebo</td>
<td>28 D</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Liu et al. 2018</td>
<td>China</td>
<td>RCT</td>
<td>140</td>
<td>NR</td>
<td>≥3 M</td>
<td>Vitamin C v. Wuling</td>
<td>12 W</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MIDAS</td>
<td>Australia</td>
<td>RCT</td>
<td>36</td>
<td>NR</td>
<td>≥3 M</td>
<td>Modafinil v. Placebo</td>
<td>6 W</td>
<td>Patients</td>
<td>Individual</td>
</tr>
<tr>
<td>Follow-Up 18/36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nguyen et al. 2019</td>
<td>Australia</td>
<td>RCT</td>
<td>15</td>
<td>//</td>
<td>NR</td>
<td>CBT v. TAU</td>
<td>8 W</td>
<td>Psychologists*</td>
<td>Individual</td>
</tr>
<tr>
<td>Van Heest et al. 2017</td>
<td>USA</td>
<td>1-Arm CT</td>
<td>49</td>
<td>NR</td>
<td>NR</td>
<td>Fatigue Management Course</td>
<td>6 W</td>
<td>Clinical Psychologist</td>
<td>Individual</td>
</tr>
<tr>
<td>West et al. 2019</td>
<td>Denmark</td>
<td>RCT</td>
<td>90</td>
<td>NR</td>
<td>7.6±8.3 (Treatment), 6.0±4.4 (Control) D</td>
<td>Naturalistic Lighting (Artificial Sunlight Spectrum) v. Standard Indoor Lighting</td>
<td>45.3±22.1 (Treatment), 33.7±12.7 (Control) D</td>
<td>NA</td>
<td>Group</td>
</tr>
<tr>
<td>Wu et al. 2017</td>
<td>UK</td>
<td>1-Arm CT</td>
<td>12</td>
<td>First/Recurrent</td>
<td>3±24 M</td>
<td>Manualised Psychological Intervention</td>
<td>7 S</td>
<td>Clinical Psychologist</td>
<td>Individual</td>
</tr>
</tbody>
</table>

* Psychologists with doctoral qualifications in clinical neuropsychology

RCT: Randomised Controlled Trial; CCT: CONTROLLED CLINICAL TRIAL; CT: Clinical Trial; NR: Not Reported; NA: Not Applicable; CHF: Congestive Heart Failure; TIA: Transient Ischaemic Attack; D: Day; W: Week; M: Month; S: Session
Despite the high prevalence of PSF\(^2\) and its obvious effects on treatment adherence\(^{102}\), in practice, only half of recent stroke guidelines have clinical recommendations on PSF. Of those that do, two guidelines provide only brief recommendations, and only one provides comprehensive recommendations, but these are based on low levels of evidence\(^48\). The weak evidence base and the need to rely on expert consensus is likely to be the main reason that PSF is generally not covered in the guidelines.

The dominance of single-centred interventional studies with small sample sizes and interventions delivered within a 12-week period may be the reasons for absence of follow-up studies. MIDAS (interventional)\(^{63-65}\) and NotFAST (observational)\(^{81-85}\) are the only recent studies with novel and potentially long-term findings with larger sample size (in case of MIDAS 2)\(^{103}\) or with the intention to design an intervention (NotFAST2)\(^{104}\).

While the observational studies reported the type of stroke, the interventional studies did not include this important data, which makes it difficult to summarise studies. Most of participants

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### Table 3. Characteristics of included observational studies.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Country</th>
<th># of centres</th>
<th>Design</th>
<th># participants</th>
<th>Stroke type</th>
<th>Time after stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCOS-IV</td>
<td>New Zealand</td>
<td>4</td>
<td>Cross-Sectional (in Cohort)</td>
<td>256/2096*</td>
<td>First/Ischemic/Haemorrhagic/Undetermined</td>
<td>4 Y</td>
</tr>
<tr>
<td>Blomgren et al. 2019</td>
<td>Sweden</td>
<td>1</td>
<td>Cohort</td>
<td>296/411</td>
<td>First/Recurrent/Ischemic</td>
<td>7 Y</td>
</tr>
<tr>
<td>Chen et al. 2018</td>
<td>USA</td>
<td>1</td>
<td>Cohort</td>
<td>128/203</td>
<td>Ischemic/Haemorrhagic</td>
<td>6 M</td>
</tr>
<tr>
<td>Choi-Kwon et al. 2017a</td>
<td>South Korea</td>
<td>1</td>
<td>Cross-Sectional</td>
<td>373/469</td>
<td>Ischemic</td>
<td>3 M</td>
</tr>
<tr>
<td>Choi-Kwon et al. 2017b</td>
<td>South Korea</td>
<td>1</td>
<td>Cohort</td>
<td>364/508</td>
<td>Ischemic</td>
<td>12 M</td>
</tr>
<tr>
<td>Douven et al. 2017</td>
<td>Netherlands</td>
<td>2</td>
<td>Cohort</td>
<td>243/250</td>
<td>First</td>
<td>3, 6, 12 M</td>
</tr>
<tr>
<td>Kuppuswamy et al. 2016</td>
<td>UK</td>
<td>3</td>
<td>Cross-Sectional</td>
<td>69</td>
<td>First</td>
<td>56.81±63 M</td>
</tr>
<tr>
<td>LAS-1</td>
<td>Sweden</td>
<td>1</td>
<td>Cross-Sectional (in Cohort)</td>
<td>349</td>
<td>NR</td>
<td>6 Y</td>
</tr>
</tbody>
</table>

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Question marks in red cells indicate unclear or high risk of bias and plus signs in green cells show low risk of bias.

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### Table 2. Risk of bias assessed by RobotReviewer and a human reviewer for randomised controlled trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Selective reporting of outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. 2016</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chen et al. 2019</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Liu et al. 2016</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MIDAS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nguyen et al. 2019</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>West et al. 2019</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
</tbody>
</table>

Question marks in red cells indicate unclear or high risk of bias and plus signs in green cells show low risk of bias.
## Table 4. Descriptive summary of findings from included interventional studies.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Country</th>
<th># of centres</th>
<th>Design</th>
<th># participants</th>
<th>Stroke type</th>
<th>Time after stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau et al. 2017</td>
<td>Hong Kong</td>
<td>1</td>
<td>Cross-Sectional</td>
<td>191</td>
<td>Ischemic</td>
<td>3 M</td>
</tr>
<tr>
<td>MacIntosh et al. 2017</td>
<td>Canada</td>
<td>4</td>
<td>Cross-Sectional</td>
<td>335</td>
<td>Ischemic/Haemorrhagic</td>
<td>Within 6 M</td>
</tr>
<tr>
<td>NotFAST</td>
<td>UK</td>
<td>4</td>
<td>Cohort</td>
<td>268/371</td>
<td>Fatigue was not significantly</td>
<td>4-6 W</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>263/371</td>
<td>associated with change in quality</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of life and was not different in</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>two groups.</td>
<td></td>
</tr>
<tr>
<td>Delva 2019</td>
<td>France</td>
<td>4</td>
<td>Cohort</td>
<td>153/179</td>
<td>Ischemic/Haemorrhagic</td>
<td>6 M</td>
</tr>
<tr>
<td>Liu et al. 2016</td>
<td>Netherlands</td>
<td>1</td>
<td>Cross-Sectional (in Cohort)</td>
<td>208</td>
<td>First/Ischemic/Haemorrhagic/Recurrent</td>
<td>3.3±0.5 M</td>
</tr>
<tr>
<td>Van Heest et al. 2017</td>
<td>UK</td>
<td>4</td>
<td>Cohort</td>
<td>191</td>
<td>Ischemic</td>
<td></td>
</tr>
<tr>
<td>West et al. 2019</td>
<td>China</td>
<td>1</td>
<td>Cohort</td>
<td>634/703</td>
<td>Ischemic</td>
<td></td>
</tr>
<tr>
<td>Wu et al. 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR: Not Reported; Y: Year; M: Month; W: Week; D: Day
*For cohort studies, the left number shows the number of participants who finished follow-up, and the right number is the number of participants who started and took part in the study; for cross-sectional studies within cohort studies, the left number shows the number of participants in cross-sectional study and the right number is the number of participants in cohort study.

FAS: Fatigue Assessment Scale; VAS: Visual Analogue Scale; BFI: Brief Fatigue Index; MFI: Multidimensional Fatigue Inventory; FSS: Fatigue Severity Scale; FACIT: Functional Assessment of Chronic Illness Therapy; W: Weeks; D: Day; M: Month; S: Session; TAU: Treatment As Usual; CBT: Cognitive Behavioural Therapy.

* Grey cells contain findings from low risk studies; however they have small sample size.
White cells report findings from studies with high or unclear risk of bias.
Table 5. Descriptive summary of findings from included observational studies.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Fatigue measure</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCOS-IV</td>
<td>FSS</td>
<td>Having hypertension, diabetes mellitus, and arrhythmia at the time of stroke were associated with increased PSF.</td>
</tr>
<tr>
<td>Blomgren et al. 2019</td>
<td>FIS</td>
<td>Fatigue was independently explanatory of worse outcome on FAI summary score and domestic chores.</td>
</tr>
<tr>
<td>Chen et al. 2018</td>
<td>FACIT-Fatigue</td>
<td>Early PSF appears to be largely attributable to stroke severity, while chronic fatigue occurs in the setting of medical co-morbidities and medication use.</td>
</tr>
<tr>
<td>Choi-Kwon et al. 2017a</td>
<td>FSS</td>
<td>Of the 6 polymorphisms examined, only one marker, that is, low-activity Monoamine Oxidase A was associated with PSF in female patients.</td>
</tr>
<tr>
<td>Choi-Kwon et al. 2017b</td>
<td>FSS</td>
<td>Musculoskeletal pain and central post-stroke pain was related to fatigue.</td>
</tr>
<tr>
<td>Douven et al. 2017</td>
<td>FSS</td>
<td>No association between apathy and fatigue was found at baseline and no interaction with time was found. Change in fatigue from baseline to 12-month follow-up was associated with change in depression and with change in apathy. Bidirectional associations were found between PSF and PSD.</td>
</tr>
<tr>
<td>Kuppuswamy et al. 2016</td>
<td>FSS</td>
<td>Those with high perceived limb heaviness also reported significantly higher levels of fatigue than those with no perceived limb heaviness, but there was no difference in weakness between the 2 groups.</td>
</tr>
<tr>
<td>LAS-1</td>
<td>FSS</td>
<td>In almost all Stroke Impact Scale domains the odds for PSF were higher in persons with a higher perceived impact. Fatigue is still present in one-third of persons six years after stroke onset.</td>
</tr>
<tr>
<td>Lau et al. 2017</td>
<td>FAS</td>
<td>Fatigue severity positively correlated with NEO Five-Factor Inventory neuroticism scores.</td>
</tr>
<tr>
<td>MacIntosh et al. 2017</td>
<td>FAS</td>
<td>Fatigue and depressive symptoms are related distinctly to cognitive and mobility impairments post-stroke. Fatigue was associated with poorer lower limb motor function, and with cognition indirectly via depressive symptoms.</td>
</tr>
<tr>
<td>NotFAST</td>
<td>FSS of FAI</td>
<td>Pre-stroke fatigue, having a spouse/partner, lower Rivermead Mobility Index score, and higher scores on both the Brief Assessment Schedule Depression Cards and Beck Anxiety Index were independently associated with PSF. Of those reporting fatigue initially 69% continued to report fatigue in follow-up. New PSF cases were reported by 38%. Lower Nottingham Extended Activities of Daily Living scores and higher Beck Anxiety Index scores were independently associated with fatigue at six months.</td>
</tr>
<tr>
<td>STROKDEM</td>
<td>CFS</td>
<td>Medication use was not a PSF predictor; however, polypharmacy increased PSF severity.</td>
</tr>
<tr>
<td>van Rijssbergen et al. 2019</td>
<td>FAS</td>
<td>Fatigue was associated with CLCE scores, independent of demographic, cognitive performance and stroke-related covariates. After including personality traits and coping styles in the model, independent associations with CLCE scores were found for fatigue and neuroticism.</td>
</tr>
<tr>
<td>Wang et al. 2018</td>
<td>FSS</td>
<td>The serum levels of thyroid-stimulating hormone were inversely associated with the risk of PSF in both the acute phase and at follow-up. Thyroid function profiles may be predictor of PSF after acute ischemic stroke.</td>
</tr>
</tbody>
</table>

FSS: Fatigue Severity Scale; FIS: Fatigue Impact Scale; FACIT: Functional Assessment of Chronic Illness Therapy; FAS: Fatigue Assessment Scale; FAI: Fatigue Assessment Inventory; PSD: Post-Stroke Depression; CFS: Chalder Fatigue Scale; CLCE: Checklist for Cognitive and Emotional consequences following stroke.

entered the interventional studies three-months after stroke. This is likely to be due to a number of reasons; for example, fatigue is not recognised immediately after a stroke, some studies want to ensure that participants have a stable fatigue, and there is competition for recruitment in the early stages to more acute trials.

The variety of the interventions tested in studies and trials underlines the complexity of PSF and is an indication to researchers that probably the most effective interventions need to target multiple aspects of fatigue. While current reporting practice of interventions in RCTs included in our review is of concern (none followed TIDieR and two followed CONSORT), future studies should consider following reporting guidelines such as CONSORT and TIDieR for interventional studies, STROBE for observational studies, and RIGHT\cite{105}, AGREE\cite{106}, or CheckUP\cite{107} for clinical practice guidelines.

Among the observational studies, the populations-based study from the stroke register in New Zealand\cite{91} and Sweden\cite{77} provides valuable insights about the link between co-morbidities and increased PSF in long-term (4–7 years). This, and other
similar register-based studies, represent the added value of having high-quality data in health system databases for long-term observational and register-based studies. Psychologists delivered the psychotherapies in RCTs to individual patients and there was no intervention using online platforms as the media of delivery. This may be due to a number of reasons: it is usual to test the efficacy of an intervention face to face before moving to another medium; participants with stroke may have other problems which mean it is more difficult to deliver treatments online, e.g. communication issue and cognitive problems.

Fatigue Severity Scale (FSS) was the main outcome measure for PSF in observational studies, whereas Fatigue Assessment Scale (FAS) was used more frequently than other measures in interventional studies. The main reason that the FSS has been used is probably because it is now seen as a way to compare different studies: in simple terms, researchers use it because other researchers have used it. It is also relatively straightforward to complete. Only one of observational studies and half of the interventional studies were registered in clinical trial registers, with the remaining unregistered trials potentially introducing bias in selective reporting of outcomes. One of the interventional studies was registered retrospectively with potential for the same bias.

### Limitations

It is possible that we overlooked studies which did not report PSF in the searchable part of the paper or if the report was not indexed in the searched databases. In such cases, we invite the audience of this review paper to contact us or comment on the paper online.

### Conclusion

The current trend of research on PSF shows the continued importance of this topic globally. Our review identified a weak evidence base that highlights the need for more research that could have the following characteristics: I) studies to design and test multi-component interventions for PSF; and II) Robust RCTs with adequate sample sizes to produce the evidence for recommendations in guidelines. From our current knowledge on PSF, none of the recent studies are robust enough to change current clinical practice.

### Data availability

**Underlying data**

Registration DOI: https://doi.org/10.17605/OSF.IO/XJKCS
This project contains the following underlying data:
- Extracted data from included studies

Extended data
Open Science Framework: Post-Stroke Fatigue: A Scoping Review
https://doi.org/10.17605/OSF.IO/XJKCS

This project contains the following extended data:
- Full search strategies
- Risk of bias assessment

References


15. Delva I: Factors associated with post-stroke fatigue dimensions over the second year after acute cerebrovascular events. Bulletin of Problems Biology and Medicine. 2018; 42(2 (147)): 139–42. Publisher Full Text


Nicola Hancock
School of Health Sciences, University of East Anglia, Norwich, UK

Thank you for the invitation to review this interesting scoping review, focussing on an important area of current research highly relevant to multiple aspects of life after stroke- that of Post-Stroke Fatigue, PSF.

The current review updates the work of Hinkle et al. 2016, and the rationale for doing so is clearly stated by the authorship team. That the review here generated a further 24 studies (and six sets of guidelines including PSF) since 2016 further demonstrates the growing impetus of work in this area. The objective stated is rather non-specific, but this is acceptable in such a scoping review that serves as a summary of recent evidence. It is unsurprising that this review concludes that further research in this area is required, and the authors make relevant suggestions as to the characteristics of future research that are clearly based on the findings of this review.

The review is clearly written, and the methods used and ensuing findings have been reported with transparency and considerable attention to detail. Search strategies are available via an embedded link. This paper makes a very useful contribution and provides a foundation for further work.

The following minor comments and suggestions may be of use to the authors:

- The use of the word ‘following’ in the opening two section headings of the methods might be worth reconsidering, readability of this phrase in a title is challenging (page 3).

- In Figure 1, suggest clarifying ‘34 not new/covered’- does this mean 34 records removed as covered in the previous review? (page 4).

- Section on data extracted from clinical practice guidelines, please clarify ‘study name and year’- does this refer to the name and year of the guidelines or the included studies from which the guidelines was written? (page 5).

- Was any specific tool used to assess risk of bias in the non-randomised studies? If so,
should be stated in the methods text. If not, some justification would be helpful.

- In table 3, the final column is not entirely clear- is this mean time after stroke onset for included participants? Simple clarification in the column heading or legend would address this (page 7/8).

- Suggest rephrasing 'probably the most effective interventions' to deliver a clearer message here (page 9).

- In the discussion, the section on online platforms is somewhat unexpected- possible delivery via online mechanisms does not seem to have arisen prior to this point, though I apologise if I have missed this. Perhaps a line to place this paragraph in context might help the interpretation here? (page 10).

- As the authors focus on possible reasons for the use of the Fatigue Severity Score (FSS) in one section of the discussion, it might be helpful to include a line about the validity/reliability of this measure at this point.

- There are a few very minor typographical and grammatical errors.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**  
Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**  
Yes

**Is the statistical analysis and its interpretation appropriate?**  
Not applicable

**Are the conclusions drawn adequately supported by the results presented in the review?**  
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Stroke rehabilitation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 Jun 2020

Ghazaleh Aali, University of Nottingham, Nottingham, UK

We thank the expert reviewer for spending time on our review and for providing helpful comments. We have made amendments to the manuscript based on these comments.

**Comment:** The use of the word ‘following’ in the opening two section headings of the
methods might be worth reconsidering, readability of this phrase in a title is challenging (page 3).

**Reply:** Thank you. We have now changed these to ‘Methods from an existing review’ and ‘Scoping review methods’.

**Comment:** In Figure 1, suggest clarifying ‘34 not new/covered’- does these mean 34 records removed as covered in the previous review (page 4)?

**Reply:** We have now clarified this in the text. We excluded studies that had been covered in the previous review. We also excluded the new studies that were not covered in the previous review if they repeated the findings reported in the previous reviews. We included new studies that were repeating findings from the previous review if they had a larger sample size or a new factor or intervention so were adding to the existing knowledge. This is compatible with the ‘scoping’ element of this review.

**Comment:** Section on data extracted from clinical practice guidelines, please clarify ‘study name and year’- does this refer to the name and year of the guidelines or the included studies from which the guidelines was written (page 5).

**Reply:** The ‘Citation’ column refers to the reference publication and publication date of the guideline.

**Comment:** Was any specific tool used to assess risk of bias in the non-randomised studies? If so, this should be stated in the methods text. If not, some justification would be helpful.

**Reply:** Assessing risk of bias is not usually a feature of scoping reviews. However, because of availability of the automation tool (i.e. RobotReviewer) for RCTs and to provide additional training to two PhD students who were involved in this review, we added risk of bias assessment only for the RCTs. We did not assess non-RCTs for risk of bias because our resources were limited. We have now addressed this in the text: "Because of the 'scoping' nature of this review and lack of time and resources, we did not assess the risk of bias for non-RCTs."

**Comment:** In Table 3, the final column is not entirely clear- is this mean time after stroke onset for included participants? Simple clarification in the column heading or legend would address this (page 7/8).

**Reply:** It is both. Because of the lack of standards in reporting these data, some studies reported time period after stroke and some reported only mean and standard deviation. We have now detailed this under the table.

**Comment:** Suggest rephrasing ‘probably the most effective interventions’ to deliver a clearer message here (page 9).

**Reply:** We have changed ‘the most effective’ to ‘the future’.

**Comments:** In the discussion, the section on online platforms is somewhat unexpected- possible delivery via online mechanisms does not seem to have arisen prior to this point, though I apologise if I have missed this. Perhaps a line to place this paragraph in context might help the interpretation here (page 10)?

**Reply:** Thank you. In the second paragraph of the Results we note that the delivery was mostly face-to-face and individually rather than online.
Comment: As the authors focus on possible reasons for the use of the Fatigue Severity Score (FSS) in one section of the discussion, it might be helpful to include a line about the validity/reliability of this measure at this point.

Reply: We have added a sentence about validity/reliability: "Bearing in mind that both these PSF measurement scales are valid and reliable...". We therefore tried to raise the other 'possible' reasons for the frequent use of this specific scale in this field.

Comment: There are a few very minor typographical and grammatical errors.

Reply: Thank you. We have now addressed these and apologise for overlooking these.

Competing Interests: None to declare.
The current manuscript is well written and easy to follow. It is clear that you have put in a lot of effort and made a great job. Even so, I have following minor comments/suggestions that could possibly improve your article:

**Method:**
- As written, I am uncertain about limitations to language. According to the manuscript, there were no limitations to language. However, in the *Extended data*, English language seems to be a limitation in the search strategies. Please, clarify so there is no doubt about this.
- Figure 1: Please, consider clarifying the number of excluded reports per each specified criterion regarding the 473 excluded reports; no clarification (in numbers) has been made for them as for the 86-excluded full-text reports.
- Figure 1: Please, give the readers more information about the nine additional sources. Which was your strategy, how did you found them? Did all arrived from the other articles’ reference lists?

**Results:**
- Are MIDAS (presented in Table 1), and ARCOS-IV and LAS-1 (presented in Table 3) examples of studies not yet published?
- (In Table 1, the fourth column, there is space available (two rows are already used) for you to write “Number of participants” or “No.” instead of using the symbol “#”.)
- Table 2: I like the use of different colours, and red and green are instantaneous to understand. However, in color blindness, the most common difficulty is to distinguish between red and green. Perhaps you can choose another colour combination. In the online version of Robot Reviewer report, I think that the table Risk of bias has a more easy to read layout than Table 2 in the main manuscript.
- (Table 3: Consider using “Number” or “Number of” or “No.” or “No. of” instead of “#” in the third and the fifth column?)
- Table 3, sixth column, “Stroke type”: Please, review the use of “/”. Should you use “and”, “,” or delete the “/” somewhere? Regarding Kuppuswamy and NotFAST: “First”, but which stroke type?
- (Table 4, fourth column: I suggest you to use “Post-stroke fatigue finding” instead of the use of the abbreviation “PSF finding”. Avoiding unnecessary abbreviations makes reading easier.)
- (In Table 5, consider if you should specify “Finding” to “Post-stroke fatigue finding” in the light blue heading (in line with the selected sub-heading in Table 4).)
- In the data commentary related to Table 6, you state that the Canadian guideline was the only one with comprehensive recommendations on post-stroke fatigue. In Table 6, under the heading “Recommendation” the reader is referred to page 15-16 of the guideline. I
suggest that you present vital parts of the content in Table 6, in addition to this reference.

○ I lack information on age and gender of the patients in the different studies from which the review is based. Is it possible to add this information?

○ Is it possible to give the reader even more specific information on which quantitative measures the post-stroke fatigue findings are based? (Although the level of significance is arbitrary set and statistically significance results does not need to be clinically meaningful for the patients.)

Discussion:

○ I suggest a sentence about time-dependent concerns regarding the construct (post-stroke fatigue) in the research studies conducted years after stroke and its potential significance for validity.

○ International recommendations regarding outcome measures related to, and time points for measuring, post-stroke fatigue in research studies on recovery after stroke would probably reduce the heterogeneity of studies and facilitate further summarises and updates. You could possibly include that post-stroke fatigue might be an issue for future Stroke Recovery and Rehabilitation Roundtable (SRRR) work.

○ You have a separate paragraph regarding limitations. Have you thought about including a sentence related to strengths of your study, in a paragraph in close proximity to “Limitations”?

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
reviewing this manuscript. We value their positive and thorough comments and have revised the manuscript accordingly.

Method
Comment: As written, I am uncertain about limitations to language. According to the manuscript, there were no limitations to language. However, in the extended data, English language seems to be a limitation in the search strategies. Please, clarify so there is no doubt about this.
Reply: Thank you for this comment. We initially intended to have no language restrictions but, as we followed the methods from an existing scoping review, we needed to apply a language limitation. This has now been corrected to: "We ran a search to include studies in English language only...".

Comment: Figure 1: Please, consider clarifying the number of excluded reports per each specified criterion regarding the 473 excluded reports; no clarification (in numbers) has been made for them as for the 86-excluded full-text reports.
Reply: We followed the PRISMA reported guideline and flow diagram which does not specify recording or reporting detailed reasons for exclusion at the Title/Abstract Screening step (Liberati et al. 2009; DOI 10.1136/bmj.b2700); however, as it is mandatory to report the reasons for exclusion in the Full Text Screening step, we have done this.

Comment: Figure 1: Please, give the readers more information about the nine additional sources. Which was your strategy, how did you found them? Did all arrive from the other articles' reference lists?
Reply: We have now included this statement under the Selection of studies section: "we also investigated the reference lists of the relevant studies to identify additional relevant studies ".

Results
Comment: Are MIDAS (presented in Table 1), and ARCOS-IV and LAS-1 (presented in Table 3) examples of studies not yet published?
Reply: No. These studies were completed and have reported their results, so they met our eligibility criteria. If a study was 'ongoing' at the time of our review, we did not report them in the table because "Ongoing studies or protocols with no results" was one of our exclusion criteria. If a study had no specific name, we used the last name of the first author and the year of publication as the study name in the tables.

Comment: In Table 1, the fourth column, there is space available (two rows are already used) for you to write "Number of participants" or "No." instead of using the symbol ".
Reply: We have corrected this now to "No. of".

Comment: Table 2: I like the use of different colours, and red and green are instantaneous to understand. However, in colour blindness, the most common difficulty is to distinguish between red and green. Perhaps you can choose another colour combination. In the online version of Robot Reviewer report, I think that the table Risk of bias has a more easy to read layout than Table 2 in the main manuscript.
Reply: We followed Cochrane's Risk of Bias tool and therefore also followed their reporting
method. However we recognise that some of our readers might be colour-blind and so we are using plus signs and question marks in addition to the colour coding. We have also now changed the colours from red/green to grey/white.

**Comment:** Table 3: Consider using "Number" or "Number of" or "No." or "No. of" instead of "#" in the third and the fifth column?

**Reply:** We have corrected these to "No. of".

**Comment:** Table 3, sixth column, "Stroke type": Please, review the use of "/". Should you use "and", ",," or delete the "/" somewhere? Regarding Kuppuswamy and NotFAST: "First", but which stroke type?

**Reply:** We replaced "/" with ",". We used type of stroke as reported in the studies. Thus, although 'First' does not refer to a specific stroke type, this was what was reported and therefore what we presented under 'type'. Since this is a scoping review, we did not contact specific researchers to clarify these details.

**Comment:** Table 4, fourth column: I suggest you to use "Post-stroke fatigue finding" instead of the use of the abbreviation "PSF finding". Avoiding unnecessary abbreviations makes reading easier.

**Reply:** We have now corrected this to 'post-stroke fatigue'.

**Comment:** In Table 5, consider if you should specify "Finding" to "Post-stroke fatigue finding" in the light blue heading (in line with the selected sub-heading in Table 4).

**Reply:** We have now added 'post-stroke fatigue'.

**Comment:** In the data commentary related to Table 6, you state that the Canadian guideline was the only one with comprehensive recommendations on post-stroke fatigue. In Table 6, under the heading "Recommendation" the reader is referred to page 15-16 of the guideline. I suggest that you present vital parts of the content in Table 6, in addition to this reference.

**Reply:** We did consider this approach initially. However, for the following reasons we decided not to report the text for this guideline: 1. there are two pages of content that could be paraphrased and summarized into the table but because of the volume of the content (even after summarizing and paraphrasing) it would require official copyright permission from the publisher of the guideline. Aside from the process of obtaining such permission, this will require payment to the publisher which is not included within our grant. 2. We found the content of these two pages relevant, well-written, and important, and we have consequently intentionally referred the reader to this source, rather than paraphrasing and losing important detail.

**Comment:** I lack information on age and gender of the patients in the different studies from which the review is based. Is it possible to add this information?

**Reply:** If it is not reported in our review, it means that this information was missing from the primary study. Since this is a scoping review, we did not consider contacting each researcher separately. However, we have highlighted the fact that even very basic but important demographic information has not been reported by researchers of the primary studies. Not including key demographic information is an important issue to highlight,
because it needs to be addressed in future studies

**Comment**: Is it possible to give the reader even more specific information on which quantitative measures the post-stroke fatigue findings are based? (Although the level of significance is arbitrary set and statistically significance results does not need to be clinically meaningful for the patients.

**Reply**: Reporting/calculating effect sizes is not routine practice or part of reporting guidelines for conducting scoping reviews. However, we thought this revision could add to the value of the interventional studies so we reported these statistics in Table 4. Since this is not a systematic review, we did not consider contacting the researchers for complete information and we did not calculate or combine the effect sizes. Instead we reported the statistics as they were reported in the original studies.

**Discussion**

**Comment**: I suggest a sentence about time-dependent concerns regarding the construct (post-stroke fatigue) in the research studies conducted years after stroke and its potential significance for validity.

**Reply**: Thank you. We have added the following: "One issue worth considering is whether the construct of PSF holds for fatigue experienced in research participants recruited years after their stroke, and whether this fatigue is a function of other issues. Future systematic reviews could address this issue by conducting sensitivity analyses comparing studies that include participants many years after their stroke with those including participants immediately after their stroke."

**Comment**: International recommendations regarding outcome measures related to, and time points for measuring, post-stroke fatigue in research studies on recovery after stroke would probably reduce the heterogeneity of studies and facilitate further summaries and updates. You could possibly include that post-stroke fatigue might be an issue for future Stroke Recovery and Rehabilitation Roundtable (SRRR) work.

**Reply**: Thank you for this suggestion. We have made a comment about this being an important area for future research but do not want to identify an individual group or organization to take this forward. We added: "In addition, harmonisation of studies requires standard international guidelines regarding outcome measurements and time points for measuring PSF in a standard way to create homogenous and collective body of evidence."

**Comment**: You have a separate paragraph regarding limitations. Have you thought about including a sentence related to strengths of your study, in a paragraph in close proximity to "Limitations"?

**Reply**: Thank you for this comment. We have changed the heading to 'Limitations and Strengths' and added three strengths of the review in this section: A. Public and open sharing of our methods so that anyone can update our review, B. Utilizing automation tools such as Rayyan and RobotReviewer to save time and resources and C. The fact that this was A multi-disciplinary review team.
Competing Interests: None to declare.

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