Model of Understanding Fatigue After Stroke

Simiao Wu, MSc; Gillian Mead, FRCP; Malcolm Macleod, FRCP; Trudie Chalder, PhD

Fatigue is ubiquitous but it is more common and more severe in patients with acute and chronic conditions, including stroke. The reported proportion of people with fatigue after stroke ranges from 23% to 75%.

Fatigue is common immediately after stroke, and it tends to persist in most but not all patients. It contributes to lower quality of life and a higher risk of death. How to manage and prevent fatigue is ranked by stroke survivors and health professionals among the top 10 research priorities relating to life after stroke. However, there is no effective treatment, which is partly because of our lack of knowledge of its mechanisms.

Fatigue after stroke may share some common underlying mechanisms with other conditions. For example, Zedlitz and colleagues found that the psychosocial profiles of stroke patients with fatigue were similar to those reported in patients with cancer, multiple sclerosis, and chronic fatigue syndrome. Several fatigue models have been developed for patients with other conditions; a myriad of biological, psychosocial, and behavioral factors, as well as other symptoms, such as pain and sleep problems, are involved. In this review, we explored whether these factors contribute to fatigue after stroke.

We systematically reviewed studies of post-stroke fatigue (PSF) and discussed the definition of PSF, its natural history, and its associations. By drawing on literature of fatigue in other conditions alongside evidence from stroke studies, we propose a conceptual model of PSF. This model is potentially useful in understanding the mechanisms of PSF and informing the development of its treatment.

Definition of Post-Stroke Fatigue

In stroke studies, PSF is usually defined by cut-off scores on fatigue scales, which are often devised in nonstroke populations. Among over 50 fatigue scales used in research studies, only 7 have been tested for their psychometric properties in a stroke population, and all showed feasibility and validity in assessing PSF. Furthermore, dichotomizing patients by a single cut-off score does not fully characterize fatigue that matters to stroke survivors. To address this weakness, a case definition for PSF was developed, of which the criterion was self-reported significant fatigue that interfered with daily activities. This definition is valid and reliable in identifying clinically significant fatigue in stroke survivors. A study found that a third of stroke survivors met this case definition 1 month after stroke.

Natural History of Post-Stroke Fatigue

Five longitudinal studies (n=762) investigated the course of PSF in individual patients and found that more than one third of patients had fatigue at the initial assessment (usually within the first 3 months after stroke). Among patients with fatigue at the initial assessment, about two thirds of them had fatigue at a later stage (usually over 1 year after stroke), with perhaps one third of them recovering by this time. Among patients without fatigue at the initial assessment, fatigue developed in 12% to 58% of them during the course of follow-up.

These findings reveal 3 patterns of temporal course of fatigue after stroke, that is, persistent fatigue, recovered fatigue, and late onset fatigue (Figure 1).

Concept of Early Fatigue and Late Fatigue

Fatigue present early after stroke (ie, early fatigue) and fatigue present at a later stage after stroke (ie, late fatigue) could be viewed as part of an evolving process; in longitudinal studies of PSF, early fatigue is always associated with late fatigue. However, it is plausible that different factors contribute to PSF experienced at different times. Two studies investigated associations of fatigue at different time points after stroke. In one study, infratentorial stroke was associated with fatigue at 2 months but not 18 months after stroke; however, baseline depression and anxiety were associated with fatigue at both assessments. In another study, the 3 strongest correlates of fatigue at 6 months were initial stroke severity, disability, and depression, whereas at 1 year, the strongest correlates were depression, anxiety, and language impairments. These findings suggest that the nature of the stroke itself may be a more important determinant...
of early rather than late fatigue, with psychological factors important for both phases.

Factors Associated With Post-Stroke Fatigue
A myriad of biological, psychosocial, and behavioral factors might be associated with fatigue. Given the concepts of early and late fatigue after stroke and the observation in one study that lesion location was associated with early but not late fatigue, it is important to consider the time at which any related factor might exert most influence on PSF. Here we reviewed associations of PSF and explore their relationship with fatigue at early and later stages after stroke. (A summary of these associations is provided in Table I in the online-only Data Supplement of this review.)

Pre-Stroke Conditions
Three studies (n=471) asked about the presence of pre-stroke fatigue in stroke survivors, and all found that pre-stroke fatigue was associated with both early and late fatigue after stroke. These findings should be interpreted with caution though because pre-stroke fatigue was assessed retrospectively and there is a risk of recall bias.

In an underpowered study (n=108), no association was found between PSF and pre-stroke depression or age-related white matter changes at either 2 months or 18 months after stroke. However, the uncertainty regarding any association between PSF and lesion site might be attributed to 2 factors: the time of fatigue assessment and how lesion site was classified. In studies where a significant association between PSF and lesion site was reported, fatigue was usually assessed within the first few months after stroke, and the associations were found with specific brain structures, such as brain stem or basal ganglia. In contrast, in studies which reported no association, fatigue was often assessed during a later stage after stroke, and lesion site was classified more broadly as anterior or posterior circulation or by the affected hemisphere. Although another 2 studies (n=159) found an association between stroke severity at admission and fatigue within 6 months after stroke, this association was confounded by the effects of depression and anxiety.

Affective Factors
A systematic review reported a strong association between PSF and depressive symptoms (19 studies, 6712 patients; pooled odds ratio=4.14; 95% confidence interval, 2.73–6.27) and a trend toward an association between PSF and anxiety (4 studies, n=3884; pooled odds ratio=2.34; 95% confidence interval, 0.98–5.58). Furthermore, two longitudinal studies (n=204) reported that baseline depression and anxiety were both associated with follow-up fatigue. Finally, another study (n=108) found cross-sectional associations between PSF and depression and anxiety at both 2 months and 18 months and reported that depression and anxiety at 2 months were both independent predictors of fatigue at 18 months.

Other Associations
In addition to pre-stroke conditions, stroke lesions, and affective factors, we have identified several other factors associated with PSF. However, for some of these factors, there is limited data with which to claim a causal relationship with PSF, and some of these studies are of small sample size.

Biological Factors
Associations between PSF and inflammatory biomarkers were investigated in small studies. Associations were found with cytokines but not with cortisol or C-reaction protein. One study (n=45) found neuroendocrine changes within 3 days after stroke were associated with fatigue at 12 months but not 18 months.

Physical Impairments
Six studies (n=1295) found a cross-sectional association between PSF and residual neurological deficits or perceived
disability during the acute phase to several years after stroke.\(^{20,24,29,35,41,42}\) One study (n=108) reported that physical impairments at 3 months after stroke were associated with fatigue 1 year later.\(^{37}\) Furthermore, 2 studies (n=217) found a significant association between disability and fatigue within 6 months after stroke, but this association was no longer significant at 1 year after stroke or after controlling for the effects of depression and anxiety.\(^{18,18}\)

Cognitive Impairments
Eight studies (n=1184) investigated the association between PSF and global cognition (measured by the Mini-mental State Examination), but none found a significant association.\(^{15–17,24,29,30,34,43}\) However, one study (n=109) found a cross-sectional association between PSF and attentional deficits at both 6 months and 12 months\(^{16}\) and another study (n=108) reported that baseline cognitive impairments (including attentional deficits) was associated with fatigue 1 year later.\(^{37}\)

Psychosocial Factors
In addition to the affective factors discussed in the previous section, some other psychosocial associations of PSF were reported. One study (n=167) reported that locus of control directed to significant others was an independent baseline predictor of fatigue 1 year after stroke.\(^{15}\) Cross-sectional associations were found between PSF, and both lower level of self-efficacy of managing chronic diseases (one study, n=77)\(^{44}\) and lower level of social support (one study, n=46)\(^{45}\) in patients 6 months after stroke.

Behavioural Factors
Two studies investigated the association between PSF and coping patterns. A cross-sectional study (n=50) found that higher level of fatigue at 3 months after stroke was positively associated with emotional-oriented coping and negatively associated with task-oriented coping.\(^{33}\) A longitudinal study (n=108) reported that patients using passive coping at baseline were more likely to have fatigue 1 year later.\(^{37}\)

Two cross-sectional studies investigated the association between PSF and physical activity. One (n=84) found that higher level of fatigue was associated with less standing and stepping but more sitting and lying during the day in patients 1 month after stroke.\(^{46}\) Another (n=32) found no significant difference in scores of daily activities between fatigued and nonfatigued patients 3 months after stroke.\(^{47}\)

Other Symptoms
Five studies investigated the association between PSF and sleep problems, of which 4 (n=937) found a cross-sectional association between PSF and the presence of sleep disturbances (eg, insomnia or frequent waking during night).\(^{15,22,29,41}\) One study (n=115) found an association between poor sleep quality and higher level of fatigue.\(^{21}\) Sleep apnoea is common after stroke, but no study has directly investigated its association with PSF, apart from a small study (n=32), which used a scale of daytime sleepiness to evaluate symptoms of sleep apnoea and found the mean scores were not different between patients with and without PSF.\(^{47}\)

Five studies investigated the cross-sectional association between PSF and pain: 2 (n=4044) found an association\(^{2,22}\) and the other 3 (n=362) did not.\(^{29,44,47}\)

Potential Mechanisms of Post-Stroke Fatigue

Biological Mechanisms for Early Fatigue
Associations between PSF and inflammatory biomarkers, neuroendocrine changes, and attentional deficits were found in small studies in stroke. Together with the findings that stroke lesions at certain brain structures are associated with fatigue, a brain generator mechanism of cancer-related fatigue may apply to PSF where structural damages and consequent neuroendocrine changes of the reticular activating system might impair the ability to maintain attention and induce fatigue.\(^{6}\) However, this mechanism may only apply to early but not late fatigue after stroke. Ormstad and colleagues observed that the relationship between fatigue and cytokines found at 12 months disappeared at 18 months, whereas fatigue itself and depressive symptoms had not declined by this time. Thus, they speculated that psychosocial factors had contributed to sustained fatigue.\(^{38}\) This hypothesis was supported by Passier and colleagues who reported that in a subgroup of stroke survivors without physical or cognitive impairments, baseline depressive symptoms, anxiety, and passive coping were associated with follow-up fatigue.\(^{37}\)

Psychosocial, Behavioral, and Physical Mechanisms
Psychosocial and behavioral mechanisms of fatigue were reported in studies of chronic fatigue syndrome\(^6\) and multiple sclerosis.\(^9\) In this review, people with pre-stroke fatigued or those with pre-stroke depression\(^{22}\) were more likely to have fatigue after stroke, suggesting that they were already vulnerable to fatigue before stroke. Locus of control and self-efficacy are potential predisposing factors for PSF; and once fatigue develops, they may play a role in maintaining fatigue. There is robust evidence for the causal effects of depressive symptoms and anxiety on both early and late fatigue. Coping patterns, physical activity, and social support may be associated with both early and late fatigue, but there is limited data to illustrate a causal direction. Furthermore, residual neurological deficits or physical disability may maintain PSF over time,\(^{20,24,29,35,41,42}\) although this association may be confounded by psychological factors.\(^{16,18}\)

Pain and Sleep Problems
The interaction of sleep problems, pain, and fatigue has been reported in cancer studies.\(^{10}\) In stroke studies, PSF is associated with disturbed sleep patterns; however, the association between PSF and pain is inconclusive across studies, although pain is common after stroke and could coexist with fatigue in one third of stroke survivors.\(^{22}\)

Conceptual Model for Post-Stroke Fatigue
By drawing on literature of fatigue in other conditions alongside evidence from stroke studies, we propose a conceptual model of PSF (Figure 2). In this model, stroke lesions and related biological factors contribute to early but not late fatigue. Psychosocial and behavioral factors act as predisposing and perpetuating factors for PSF. Residual neurological deficits may influence PSF through the effects of psychological factors.

This model was based on the current available evidence from stroke studies. It is limited in that it may not cover all associations of PSF and other factors may be identified in
future. Furthermore, there are limited data for some factors in the model. Future studies should therefore explore the temporal relationship and causal directions between PSF and each of these factors. Finally, some factors in the model may interact with each other. For example, the association between PSF and anxiety may be confounded by the effect of depressive symptoms. Also some patients reported that the lack of external support would complicate their coping process and invoke emotional distress. Such interactions need to be clarified in patients with PSF.

Implications for Treatment of Post-Stroke Fatigue

This review identified several factors associated with PSF (Figure 2). Some of these factors are reversible and might be targets for treatment in PSF.

Early fatigue after stroke may be associated with damage to brain structures and neuroendocrine systems responsible for maintaining attention and wakefulness. Neuroendocrine regulators, for example, Modafinil and (−)-OSU6162, have been tested for PSF in small studies and exhibited tolerance in stroke survivors. Their efficacy needs to be investigated in randomized controlled trials and compared between patients with fatigue at early and later stages after stroke.

Psychosocial and behavioral factors may play an important role in triggering and maintaining fatigue symptoms. Although depressive symptoms have a direct effect on PSF, antidepressants showed no effect on reducing fatigue after stroke. One possible explanation is that PSF is a complex symptom that is influenced by different factors, and there are interactions between these factors. Complex interventions targeting these psycho-behavioral factors are effective in treating fatigue in other conditions and have shown feasibility in small studies with stroke survivors. Furthermore, a randomized controlled trial reported that the combination of cognitive–behavioral therapy (a psychotherapeutic approach which addresses emotional dysregulation, unhelpful behaviors, and cognitive processes) and graded activity training (COGRAT) was more effective than cognitive–behavioral therapy alone in treating PSF. However, the specific effect of either graded activity training or cognitive–behavioral therapy on PSF cannot be established because the trial did not include...
a usual medical care group. Therefore, effectiveness of psychological interventions and physical training on PSF should be investigated in future trials.

Conclusion

Fatigue is a common and distressing symptom in stroke survivors. Although early fatigue may be triggered by biological factors, late fatigue may be more attributable to psychological and behavioral factors. Prospective longitudinal studies are expected to clarify the temporal relationship and causal direction between PSF and these factors. Complex interventions targeting these psycho-behavioral factors are effective in treating fatigue in other conditions, and feasibility studies are promising in stroke survivors. Further studies are needed to test the efficacy of these interventions for PSF.

Disclosures

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References


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SUPPLEMENTAL MATERIAL

Online Supplemental Table I Factors associated with post-stroke fatigue (PSF).
Online Supplemental Table I Factors associated with post-stroke fatigue (PSF).

For each factor, we combined studies which reported the same result, by reporting the total number of studies with the total number of patients. For factors of which the results cannot be combined, we listed all existing studies and summarised the main findings of each study. For pre-stroke conditions and stroke lesions, all of them have longitudinal associations with post-stroke fatigue. For other factors, we discussed longitudinal studies separately from studies that reported cross-sectional associations. For factors where there were no longitudinal data, we indicated that there is ‘No relevant longitudinal studies’, for which future prospective studies are expected. Abbreviations were given at the end of the table.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Relevant studies (number of patients): main findings</th>
</tr>
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<tbody>
<tr>
<td><strong>Pre-stroke conditions</strong></td>
<td></td>
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<tr>
<td>Pre-stroke fatigue</td>
<td><strong>Lerdal 2011 (n=115)</strong>: PrSF was associated with scores of PSF in patients within 2 weeks after stroke.</td>
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<tr>
<td></td>
<td><strong>Duncan 2014 (n=136)</strong>: PrSF was associated with scores of PSF at both 6 months and 12 months but not at 1 month after stroke.</td>
</tr>
<tr>
<td></td>
<td><strong>Choi-Kwon 2005 (n=220)</strong>: PrSF was associated with the presence of PSF in patients who were at least 3 months after stroke (mean=15 months, range 3 to 27 months).</td>
</tr>
<tr>
<td>Pre-stroke depression and white matter changes</td>
<td><strong>Naess 2012 (n=377)</strong>: PrSD (n=46) and leucoaraiosis (n=101) were both associated with the presence of PSF in patients who were at least six months after stroke.</td>
</tr>
<tr>
<td></td>
<td><strong>Snaphaan 2011 (n=108)</strong>: neither PrSD (n=14) nor white matter changes (n=0) was associated with the presence of PSF at either 2 months or 18 months after stroke.</td>
</tr>
<tr>
<td><strong>Stroke lesions</strong></td>
<td></td>
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<tr>
<td>Left or right hemisphere stroke</td>
<td><strong>12 studies (n=1664)</strong>: the presence or severity of PSF was not associated with whether the stroke lesion occurred at right or left hemisphere (time of fatigue assessment ranged from 1 month to 18 months after stroke). (Appleros 2006, Carlsson 2003, Ingles 1999, Jaracz 2007, Kutlubaev 2013, Naess 2005, Ormstad 2011, Parks 2012, Radman 2012, Schepers 2006, Snaphaan 2011, van Eijsden 2011)(^{5-16}).</td>
</tr>
</tbody>
</table>
Anterior or posterior circulation stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appleros 2006, Carlson 2003, Christensen 2008, Ingles 1999, Kutlubaev 2013, Mead 2011, Naess 2012, Passier 2011</td>
<td>8 studies (n=2253)</td>
<td>the presence or severity of PSF was not associated with whether the stroke lesion occurred at anterior or posterior circulation or by the OCSP classification (time of fatigue assessment ranged from 1 month to over 2 years after stroke).</td>
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</tbody>
</table>

Specific lesion site

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leegaard 1983 (n=44)</td>
<td>Leegaard 1983 (n=44)</td>
<td>the presence of diffuse cerebral symptoms (including PSF) was not associated with infarct site (the classification of infarct site and the time of fatigue assessment were not reported).</td>
</tr>
<tr>
<td>Choi-Kwon 2005 (n=220)</td>
<td>Choi-Kwon 2005 (n=220)</td>
<td>the presence of PSF was not associated with any specific lesion site (cortex, subcortex, lenticulocapsular area, thalamus, brainstem or cerebellum) in patients who were at least 3 months after stroke (mean=15 months, range 3 to 27 months).</td>
</tr>
<tr>
<td>Naess 2005 (n=192)</td>
<td>Naess 2005 (n=192)</td>
<td>fatigue scores were not associated with basilar artery stroke in patients who were more than 6 months after stroke.</td>
</tr>
<tr>
<td>Radman 2012 (n=109)</td>
<td>Radman 2012 (n=109)</td>
<td>the presence of PSF was not associated with any specific lesion site (cortical, subcortical, cortical-subcortical, cerebellar, and brainstem) at either 6 months or 12 months after stroke.</td>
</tr>
<tr>
<td>Staub 2001 (n=42)</td>
<td>Staub 2001 (n=42)</td>
<td>the proportions of patients with PSF were significantly different between brainstem stroke (6/11) &gt; subcortical stroke (6/15) &gt; cortical stroke (1/16) in patients between 3 months to 3 years after stroke.</td>
</tr>
<tr>
<td>Manes 1999 (n=25)</td>
<td>Manes 1999 (n=25)</td>
<td>subjective anergia and tiredness within 2 weeks after stroke were significantly more frequent in patients with insular stroke than those with non-insular stroke (i.e. parietal, temporal or occipital stroke; patients with frontal stroke were excluded at recruitment from this study).</td>
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<tr>
<td>Ormstad 2011 (n=45)</td>
<td>Ormstad 2011 (n=45)</td>
<td>mean scores of Fatigue Severity Scale in patients with supratentorial stroke (n=30) vs infratentorial stroke (n=4) were 4.1 vs 4.6 at 6 months, 4.0 vs 3.5 at 12 months, and 4.2 vs 4.1 at 18 months, but significance of the difference was not calculated due to small sample size of patients with infratentorial stroke.</td>
</tr>
<tr>
<td>Tang 2010a (n=334)</td>
<td>Tang 2010a (n=334)</td>
<td>presence of PSF at 3 months after stroke was positively associated with internal capsule or basal ganglia stroke, negatively associated with brainstem or cerebellum stroke, but no association with frontal lobe, temporal lobe, parietal lobe, occipital lobe or thalamus.</td>
</tr>
<tr>
<td>Tang 2013 (n=500)</td>
<td>Tang 2013 (n=500)</td>
<td>presence of PSF at 3 months after stroke was positively associated with caudate or putamen stroke, negatively associated with pons stroke, but no association with frontal lobe, temporal lobe, parietal lobe, occipital lobe, subcortical white matter changes, globus pallidus, thalamus, medulla, or cerebellum.</td>
</tr>
<tr>
<td>Snaphaan 2011 (n=108)</td>
<td>Snaphaan 2011 (n=108)</td>
<td>infratentorial stroke was an independent predictor of PSF at 2 months but not 18 months after stroke; PSF was not associated with other lesion site (cortex, subcortex, basal ganglia or thalamus) at either time point.</td>
</tr>
</tbody>
</table>
Stroke severity

**8 studies (n=1502):** stroke severity (e.g. NIHSS scores or SSS scores) at admission were not associated with either presence or severity of PSF (time of fatigue assessment ranged from within 2 weeks to over 10 years after stroke). (Appleros 2006, Christensen 2008, Ingles 1999, Kutlubaev 2013, Naess 2005, Snaphaan 2011, Tang 2012a, Wu 2014).

Jaracz 2007 (n=50): SSS scores at admission was associated with fatigue scores in patients who were 3 months after discharge; however, this association was no longer significant in multivariate regression in controlling of age, dependency, depression scores, and coping patterns.

Radman 2012 (n=109): NIHSS scores at admission were associated with fatigue scores at 6 months but not 12 months after stroke; but the association was no longer significant in multivariate regression in controlling of scores of depression and anxiety.

**Biological factors**

**Inflammatory biomarkers**

McKechnie 2010 (n=21): C-reaction protein levels were not different between patients with and without fatigue in patients who were 3 months after stroke.

**Longitudinal studies:**

Ormstad 2011 (n=45): cytokine changes within 3 days after stroke were associated with fatigue scores at 6 months and 12 months but not at 18 months; no association between C-reaction protein and PSF.

Radman 2012 (n=109): no association between PSF and cortisol, ACTH, T4, or TSH at either 6 months or 12 months after stroke.

**Neuroendocrine changes**

Ormstad 2014 (n=45): reduced serotonin synthesis bioavailability within 3 days after stroke was associated with fatigue scores at 12 months but not 18 months.

**Cognitive deficits**

5 studies (n=727): no cross-sectional association between global cognition (measured by MMSE) and PSF (time of fatigue assessment ranged from 1 year to more than 10 years after stroke) (Appleros 2006, Carlsson 2003, Naess 2005, Park 2009, Schepers 2006).
### Longitudinal studies:

**Residual neurological impairments or disability**

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 studies (n=1295)</td>
<td>Cross-sectional associations were found between the presence of residual neurological deficits or perceived disability (by mRS or SIP-7) and PSF (time of fatigue assessment ranged from within 2 weeks to over 10 years after stroke). (Appleros 2006, Choi-Kwon 2005, Naess 2005, Parks 2012, van der Werf 2001, Wu 2014)3, 6, 11, 13, 25, 29.</td>
</tr>
</tbody>
</table>

**Longitudinal studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passier 2011 (n=108)19</td>
<td>Presence of physical impairments at 3 months was associated with PSF 1 year after stroke.</td>
</tr>
<tr>
<td>Snaphaan 2011 (n=108)5</td>
<td>mRS scores were associated with PSF at 2 months but not 18 months after stroke; but this association was not significant in multivariate regression in controlling of depression and anxiety.</td>
</tr>
<tr>
<td>Radman 2012 (n=109)14</td>
<td>mRS scores were associated with PSF at 6 months but not 12 months after stroke; but this association was not significant in multivariate regression in controlling of scores of depression and anxiety.</td>
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</table>

**Psychosocial factors**

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
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<tbody>
<tr>
<td>Hoang 2012 (n=32)42</td>
<td>Depression scores were not different between patients with and without PSF at least 3 months after stroke.</td>
</tr>
<tr>
<td>Zedlitz 2012a (n=88)43</td>
<td>Depression scores were not associated with fatigue scores in patients who were more than 4</td>
</tr>
</tbody>
</table>
Months after stroke.

**Longitudinal studies:**
- **Passier 2011 (n=108)**: patients with baseline depressive symptoms had higher fatigue scores at 1 year than those without baseline depressive symptoms.
- **Lerdal 2013 (n=96)**: acute phase depression scores were associated with fatigue scores at both baseline and 18 months after stroke.
- **Snaphaan 2011 (n=108)**: depression scores at 2 months were associated with the presence of PSF at both 2 months and 18 months; in multivariate regression, depression scores at 2 months was an independent predictor of PSF at both 2 months and 18 months.

### Anxiety

5 studies (n=3916): cross-sectional association was found between the presence or severity of anxiety and the presence or severity of PSF (time of fatigue assessment ranged from within 2 weeks to 2 years after stroke). (Glader 2002, Harbison 2009, Lynch 2007, Radman 2012, Vuletic 2011)

- **Zedlitz 2012a (n=88)**: anxiety scores were not associated with fatigue scores in patients who were more than 4 months after stroke.

**Longitudinal studies:**
- **Passier 2011 (n=108)**: patients with baseline anxiety had higher fatigue scores at 1 year than those without baseline depressive symptoms.
- **Snaphaan 2011 (n=108)**: anxiety scores at 2 months were associated with the presence of PSF at both 2 months and 18 months; in multivariate regression, anxiety scores at 2 months was an independent predictor of PSF at both 2 months and 18 months.

### Self-efficacy or sense of control

**Miller 2013 (n=77)**: self-efficacy scores (CDSES) were associated with fatigue scores in patients who were more than 6 months after stroke.

**Longitudinal studies:**
- **Schepers 2006 (n=167)**: patients with a locus of control more directed to significant others at admission were more likely to have PSF 1 year after stroke.
Social support  
**Michael 2006 (n=46)**⁴⁶: higher level of PSF was associated with lower level of social support in patients who were at least 6 months after stroke.

*No relevant longitudinal studies*

**Behavioural factors**

**Coping patterns**  
**Jaracz 2007 (n=50)**⁹: higher level of fatigue was positively associated with emotional-oriented coping and negatively associated with task-oriented coping at 3 months after stroke.

*Longitudinal studies:*

**Passier 2011 (n=108)**¹⁹: people with a passive coping pattern at 3 months after stroke were more likely to develop PSF 1 year after stroke.

**Physical activities**  
**Duncan 2012 (n=84)**⁴⁷: higher level of fatigue was associated with less standing and stepping but more sitting and lying during the day in patients one month after stroke.

**Hoang 2012 (n=32)**⁴²: no significant difference in scores of daily activities between 11 non-fatigued patients vs 21 fatigued patients at 3 months after stroke.

*No relevant longitudinal studies*

**Other symptoms**

**Sleep problems**  
5 studies (n=1013): cross-sectional associations were found between PSF and the presence of sleep disturbances (e.g. insomnia or frequent awakening during night) and poor sleep quality (time of fatigue assessment ranged from within 2 weeks to over 2 years after stroke). (Appleros 2006, Lerdal 2011, Naess 2012, Park 2009, Schepers 2006)¹, ⁴, ⁶, ¹⁵, ²⁸.

**Hoang 2012 (n=32):** scores of scale of daytime sleepiness were not different between patients with and without PSF at 3 months after stroke.

*No relevant longitudinal studies*
Pain

2 studies (n=4044): cross-sectional association was found between PSF and pain in patients who were more than 6 months after stroke (Naess 2012)\textsuperscript{4} or those who were 2 years after stroke (Glader 2002)\textsuperscript{33}.

3 studies (n=362): no significant association was found between PSF and presence or severity of pain in patients who were at least 3 months after stroke (Appleros 2006, Hoang 2012, Miller 2013)\textsuperscript{5,42,45}.

No relevant longitudinal studies

Abbreviations: PSF, post-stroke fatigue. PrSF, pre-stroke fatigue. PrSD, pre-stroke depression. OCSP, the Oxford Community Stroke Project classification (also known as Bamford or Oxford classification). NIHSS, National Institute of Health Stroke Scale. SSS, Scandinavian Stroke Scale. MMSE, Mini-mental State Examination. ACTH, adrenocorticotropic hormone. TSH, thyroid-stimulating hormone. mRS, modified Rankin scale. SIP-7, Sickness Impact Profile-7. CDSES, Chronic Disease Self-efficacy Scale.
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<th>References for Online Supplemental Table I</th>
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