Poststroke fatigue (PSF) is a distressing symptom that affects more than a third of stroke survivors. Currently, there is insufficient evidence to guide treatment. Psychological interventions improve fatigue in other conditions by targeting psychological factors such as mood. If psychological factors correlate with fatigue in stroke, this would justify the development of similar interventions for poststroke fatigue (PSF). We used systematic review and meta-analysis to determine psychological associations of PSF.

**Methods**—We systematically searched for studies that reported psychological associations of PSF. We used odds ratios (ORs) to estimate the strength of associations and random-effects modeling to calculate summary estimates of ORs. We used stratified meta-analysis to investigate the impact of study design and conducted sensitivity analyses limited to studies that excluded patients with clinical depression and to studies that used depression scales without fatigue items.

**Results**—Thirty-five studies (n=9268) reported the association between PSF and ≥1 psychological factor. For PSF and depressive symptoms, we identified 19 studies (n=6712; pooled OR=4.14; 95% confidence interval, 2.73–6.27); this association existed in patients without clinical depression (pooled OR=1.39; 95% confidence interval, 1.27–1.53) and in studies using depression scales without fatigue items (pooled OR=5.41; 95% confidence interval, 1.54–18.93). For PSF and anxiety, we identified 4 studies (n=3884; pooled OR=2.34; 95% confidence interval, 0.98–5.58). Two studies (n=123) found an association with poor coping styles and 1 study (n=167) with loss of control. Six studies (n=1978) reported other emotional or behavioral associations.

**Conclusions**—PSF is associated with depressive symptoms, anxiety, poor coping, loss of control, emotional, and behavioral symptoms. These factors are potential targets for treatment of PSF. (*Stroke*. 2014;45:1778-1783.)

**Key Words:** behavior ■ fatigue ■ rehabilitation ■ stroke

Poststroke fatigue (PSF) is a distressing symptom that affects more than a third of stroke survivors. Currently, there is insufficient evidence to guide treatment. Psychological interventions improve fatigue in cancer, multiple sclerosis, and chronic fatigue syndrome by targeting thoughts, mood, and behavior. To determine whether to develop and test similar interventions for PSF, we need evidence about associations between PSF and those factors that could be targeted as part of a psychological intervention.

Although several narrative reviews have reported psychological factors associated with PSF, their results are conflicting, for example, 3 reviews concluded that PSF was associated with depression and 6 reported that PSF could occur independently of depression. Three reviews reported that PSF was associated with anxiety and 1 review reported no association. One review reported that fatigue was associated with lower expectations for self-efficacy in performing physical activity. Importantly, none of these reviews used meta-analysis to estimate the strength of associations. Thus, we need more evidence about the nature of the association between PSF and psychological factors, including, but not limited to, depressive symptoms, anxiety, sense of control, and coping styles.

This systematic review and meta-analysis aimed to determine whether PSF is associated with psychological factors that could be targets for a psychological intervention.

**Methods**

We systematically searched electronic databases (MEDLINE, EMBASE, CINAHL Plus, AMED, and PsycINFO) using key words stroke and fatigue and their synonyms adapted from a Cochrane review of interventions for PSF.

One author (S.W.) screened all titles and abstracts on 2 separate occasions (to ensure that eligible studies were not missed) and obtained full texts of potentially eligible studies. S.W. read all full texts and 2 authors (G.M., A.B.) each read half of the full texts, independently of the first author. Any disagreement was discussed.
between authors. Reference lists of included articles and previous reviews were screened, and potentially relevant full texts were obtained.

We included observational studies reporting measures of both PSF and ≥1 psychological factor either as dichotomous variables (eg, the presence or absence of depressive symptoms) or as a continuous variable (eg, depression scales). For studies in which only qualitative data for the association were available, we included studies in the review but not in the meta-analysis. Studies were excluded if they (1) contained insufficient data to allow reporting of any association, (2) included any patients aged <18 years, (3) used unstructured assessment for PSF, or (4) provided data for patients with stroke that could not be disaggregated from other types of patients.

Two authors (S.W., A.B.) independently extracted data on demographics, presence of prestroke fatigue, how PSF and psychological factors were assessed, whether patients with a clinical diagnosis of depression were included or excluded, and statistics for associations. They independently applied the Strengthening the Reporting of Observational Studies in Epidemiology checklist to assess study quality.

Statistical Analysis

For each study in which raw data were provided, odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for associations between PSF and each psychological factor. ORs reported by study authors were accepted if raw data were unavailable. If studies reported only correlation coefficient, we used established methods to convert to ORs. If ORs could not be obtained by these methods, we summarized these studies qualitatively not quantitatively. Publication bias was assessed by funnel plotting.

For associations of PSF with depressive symptoms and with anxiety, we determined summary estimates of ORs using random-effects modeling. Between-study heterogeneity was assessed using the Cochran Q statistic, in which \( P < 0.05 \) implies significant heterogeneity. We had intended to perform meta-analysis for psychological associations other than mood, but this was not possible because these studies only reported regression coefficients and \( P \) values for the associations.

We used partitioning of heterogeneity to compare studies that reported adjusted ORs with those that reported unadjusted ORs. For the association with depressive symptoms, only 3 studies reported adjusted ORs by controlling for potential confounders (age, sex, lesion site, and dependence in daily life) for PSF in multiple logistic regression, whereas the remaining 16 studies reported unadjusted ORs (Figure 1). We conducted sensitivity analyses (1) for studies that had excluded people with a clinical diagnosis of depression and (2) by excluding studies that had used a depression measure that contained an item of fatigue.

Results

A total of 5863 citations were identified, and 288 full texts were retrieved. Three studies (2 conference abstracts and 1 not published in English) were excluded because they contained insufficient data for analysis and study authors did not provide further data on our request. Thirty-five studies fulfilled inclusion criteria (Figure 1).

Mean age of patients ranged from 51 to 75 years. The proportion of women ranged from 19% to 67%. Five studies recruited patients with ischemic stroke, 2 with subarachnoid hemorrhage, 18 studies included both ischemic and hemorrhagic stroke, and the other 10 studies did not specify stroke type.

The median number of Strengthening the Reporting of Observational Studies in Epidemiology checklist items scored (out of 22) was 19 (interquartile range, 18–20). No study provided sample size calculations. Other common weaknesses included not describing details of recruitment, not addressing potential bias, or not declaring sources of funding.

Depressive Symptoms

Overall Meta-Analysis

Of 31 studies that provided data on the association between PSF and depressive symptoms, ORs could be obtained, and used in meta-analysis, from 19 studies; from these we calculated ORs from raw data of 7 studies, extracted ORs from 4 studies, and converted ORs from correlation coefficients from 8 studies. Summary estimate of OR was 4.14 (95% CI, 2.73–6.27; Figure 2), with no significant between-study heterogeneity (\( Q = 15.58; \text{df} = 18; P = 0.62 \)).

Stratified Meta-Analysis

The use of adjusted ORs or unadjusted ORs explained a significant portion of heterogeneity between studies (\( Q = 4.91; \text{df} = 1; P = 0.03 \)). The strength of the association in 16
studies of unadjusted ORs (n=6171; pooled OR=5.46; 95% CI, 3.58–8.32) was higher (P<0.01) than the association in 3 studies in which ORs were adjusted (541 patients; pooled OR=1.36; 95% CI, 1.26–1.46). This heterogeneity might have contributed to an asymmetrical funnel plot (Figure 3) because the 3 studies reporting adjusted ORs were located in the upper left-hand corner of the plot away from the other 16 studies.

Sensitivity Analyses
Of the 19 studies included in meta-analysis, one study (n=334) excluded patients with major depression at recruitment24 and another study (n=99) provided data for patients without depression33; pooled estimate of these 2 adjusted ORs was 1.39 (95% CI, 1.27–1.53, which was not statistically different from the summary estimate of all 3 adjusted ORs; P=0.91). The other 17 studies did not specify whether they had distinguished patients with current clinical depression.

Thirteen studies assessed depression using a measure that contained a single item for fatigue, 19,22,24,25,30,32–34,36,43,45,49 and 2 of them also assessed fatigue using this fatigue item of the depression measure.22,49 For the remaining 6 studies (n=4554) that used depression measures without any fatigue item, the pooled OR was 5.41 (95% CI, 1.54–18.93), which was not significantly different from either the summary estimate for the other 13 studies (pooled OR=3.45; 95% CI, 1.82–6.57; P=0.53) or from that of the total 19 studies (pooled OR=4.14; 95% CI, 2.73–6.27; P=0.84).

Qualitative Analysis
Twelve studies did not report sufficient data to be included in meta-analysis. Nine studies (n=1043) reported an association between PSF and depression,18,21,28,31,38,41,42,51,52 whereas one study (n=32) reported no significant difference in depression scores between fatigued and nonfatigued groups23; another study (n=100) reported that depressive symptoms were associated with mental fatigue but not with other fatigue domains26; and one further study (n=88) used 2 measures for PSF and 2 measures for depression, but reported 4 conflicting results of the association.29
Anxiety

Seven studies reported the association between PSF and anxiety,23,29,31,33,39,44,52 and data from 4 studies (n=3934)23,33,39,44 could be included in meta-analysis. The summary estimate of the OR was 2.34 (95% CI, 0.98–5.58) with no significant between-study heterogeneity (Q=2.36; df=3; P=0.50). Stratified meta-analysis indicated that the strength of association between PSF and anxiety in 2 studies23,30 not controlling the effect of depression (n=217; pooled OR=5.34; 95% CI, 4.70–6.07) was higher (P<0.01) than that in the other 2 studies39,44 having controlled the effect of depression (n=3717; pooled OR=1.25; 95% CI, 1.14–1.38).

Of the 3 studies that provided insufficient data to be included in the meta-analysis, 2 (n=90) reported a significant association between fatigue and anxiety,11,32 whereas 1 (n=88) excluded patients with depression at recruitment and found a nonsignificant association between PSF and anxiety.29

Sense of Control and Coping Styles

One study (n=167) reported that patients who were not confident in their own ability to control their health had more severe fatigue (P=0.002).37 Associations between PSF and coping styles were investigated by 2 studies. One (n=50) reported that patients focusing on personal emotions and self-blame were more likely to have a higher level of PSF (P<0.01).30 Another study (n=73) found that maladaptive coping (eg, denial and self-distraction) was the main cause of post-traumatic stress disorder (P<0.0001), and the latter was associated with PSF (P<0.0001).37

Other Psychological Factors

Six studies reported other psychological associations of PSF. Three studies (n=1527) assessed mental health and emotional role by Short Form-36, and all reported that poor outcomes of mental or emotional subscales were associated with PSF.25,40,46 Such an association was also reported by another study (n=141) using the emotional subscale of stroke-specific quality of life.26 PSF was also associated with inappropriate laughing (1 study, n=220)43 and alertness behavior (measured by Sickness Impact Scale in 1 study, n=90).51

Discussion

This is, to our knowledge, the first meta-analysis to report associations between PSF and mood or other psychological factors. We found a statistically significant association between PSF and depressive symptoms and a trend toward an association between PSF and anxiety. Two studies reported associations with inadequate coping styles, 1 study with loss of control, and 6 studies with emotional or behavioral symptoms. The named psychological factors, that is, depressive symptoms, anxiety, locus of control and coping, have already been targeted by psychological interventions for fatigue in other conditions such as cancer and multiple sclerosis. This review provides the necessary evidence to justify the development of a similar intervention for fatigue in stroke survivors. However, our findings should be interpreted with caution because only a small number of studies investigated each factor except for depressive symptoms. Also, there are some weaknesses in the quality of the included studies in that most of them did not report how patients were recruited and how study size was achieved; thus, it is difficult to determine whether the sample is representative of the entire stroke population.

PSF is associated with depressive symptoms, even in patients not meeting clinical criteria for depression. A previous study reported the presence of depressive symptoms in patients with stroke without clinical depression, where 41% of the patients reported depressed mood but only half of them met clinical criteria for depression.53 This suggests that clinicians should be aware of depressive symptoms in patients with stroke and screen for them in patients with PSF, even in those without a clinical depression. We also noticed that some of the included studies had measured depression by using scales or criteria that contain a single item of fatigue. We therefore performed a sensitivity analysis to determine whether this might result in an overestimation of the strength of association between fatigue and depression. The result indicated that this association remained significant even after excluding studies that had used a depression measure containing a fatigue item. In fact, in these depression measures, fatigue only contributes a small proportion to the total score of depression (from 1/9 to 1/66). Thus, the association that we identified was not because of the overlap between fatigue and depression measures.

In some of the included studies, age, sex, lesion site, and dependence in daily life were considered as confounders for the association between PSF and depressive symptoms. Based on the current data, however, we could not analyze the effect of each individual factor on the association. Previous studies reported that age and sex are associated with fatigue40 but not with depression.54 There is insufficient evidence for the association between lesion site and either fatigue54 or depression.6 The association between PSF and dependence has been widely reported in the studies included in this review. Dependence was also reported to be associated with poststroke depression.39 Future research is expected to investigate the effect of these confounders.

There is a trend toward an association between PSF and anxiety, but the association was weaker after controlling the effect of depressive symptoms. One study (included in our systematic review but not in meta-analysis) that had excluded patients with depression reported no significant association between PSF and anxiety.29 It is reported that anxiety is strongly correlated with depression after stroke.58 To better clarify whether depressive symptoms are confounders, the association between PSF and anxiety needs to be compared between patients with stroke with and without depressive symptoms.

Our study has several strengths. It is the first systematic review to pool the results from studies that reported the associations between PSF and depressive symptoms or anxiety. We performed a comprehensive search, had a pre-specified protocol, and used a well-established statistical approach. We also used a funnel plot to detect publication bias, in which the asymmetrical plot might indicate certain publication bias caused by the missing studies in the bottom left-hand corner of the plot. These studies are likely to be of small sample size and reported less significant results.
A possible source for this publication bias might be the exclusion of conference abstracts and studies not published in English, although we have attempted to obtain further data by contacting the study authors but did not get a reply. One limitation of our study is that only 1 author read all the abstracts to identify potentially eligible studies. However, this was done on 2 separate occasions to reduce the possibility of missing any relevant studies.

Conclusions
This review provides robust evidence for the association between PSF and depressive symptoms. This implies the screening and treatment of PSF in patients with stroke needs to integrate strategies targeting mood. PSF is also associated, either directly or indirectly, with anxiety, loss of control, poor coping styles, emotional, and behavioral symptoms; these factors are potential targets for treatment of PSF.

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Disclosures
None.

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