Prevalence and Predictors of 6-Month Fatigue in Patients With Ischemic Stroke

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Background and Purpose—Although persistent and significant fatigue affects the daily life of stroke survivors, there are no population-based studies examining the prevalence of fatigue in 6-month survivors of ischemic stroke and few studies of predictors of poststroke fatigue.

Methods—This article examined data from the Auckland Regional Community Stroke study conducted in Auckland, New Zealand, in 2002 to 2003. Presence of fatigue was evaluated at 6 months in 613 patients with ischemic stroke using a Short Form 36 Vitality Score (energy and fatigue) of ≤47. Multivariate logistic regression analysis was used to determine predictors of fatigue development 6 months poststroke.

Results—The prevalence of fatigue was 30% (28% in men and 33% in women). There was a clear association between increased prevalence of fatigue and advancing age. The only baseline variables independently associated with an increased risk of developing fatigue at 6 months poststroke were prestroke incontinence and being of New Zealand European ethnicity. Being independent and living alone at baseline were associated with significant reduction in the risk of being fatigued at 6 months poststroke. Severe depression at 6 months was significantly and independently associated with being fatigued.

Conclusions—The prevalence of fatigue found in our study is at the lower level of range reported in other studies. The prevalence of fatigue increased with advancing age, as found in most previous studies. Because fatigue can have a negative impact on stroke recovery, particular attention needs to be paid to those who are older, incontinent before stroke, and those who report severe symptoms of depression at 6 months after stroke. (Stroke. 2012;43:2604-2609.)

Key Words: epidemiology ■ outcomes ■ prognosis

A significant proportion of stroke survivors (39%–72%) have persistent and significant fatigue affecting their daily life.1–7 The frequency of self-reported fatigue is roughly twice as high in patients poststroke as in matched control subjects.2 Poststroke fatigue is known to persist for months to years.8,9 The time elapsed since the stroke occurred does not explain levels of fatigue.2,10 Two years after a stroke approximately 40% of patients report that they are “always” or “often” fatigued.1,2,10 Poststroke fatigue may be more prevalent in younger than in older patients1 probably because of their higher level of expectations, and fatigue in these patients may have a greater impact on functional outcomes such as return to work.

Poststroke fatigue has a central origin and is not the consequence of the stress of a recent acute cerebral event, comorbidities, medication, or other potential confounders.7,8 Fatigue, by its very definition, involves behavioral and work performance decrement and is characterized by distress and decreased functional status related to reduced energy.11 Poststroke fatigue often poses a barrier to return to work and reduced physical function, daily activities, quality of life, and rehabilitation potential.2,3,9,12–17 Fatigue is associated with profound deterioration of several aspects of everyday life1,18 and poor poststroke neurological recovery.19 In a population-based Swedish 2-year stroke follow-up study,18 fatigue independently predicted decreased functional independence, in-
stitutionalization, and case-fatality. Furthermore, poststroke fatigue may impede full participation in rehabilitation. Similarly, a case–control study in The Netherlands found that poststroke fatigue correlates significantly with functional disability and neuropsychological deficits. However, there are no population-based studies examining the prevalence of fatigue in ischemic stroke survivors and there is a paucity of studies determining predictors of poststroke fatigue.

Methods
The third Auckland Regional Community Stroke (ARCOS III) study population and method of case ascertainment has been described elsewhere. In brief, ARCOS was a population-based study (March 2002 through February 2003) in which all first-ever and recurrent stroke cases in people ≥16 years of age (hospitalized and nonhospitalized, fatal and nonfatal, and including all stroke subtypes) were registered and followed for 6 months. Pathological stroke subtype was documented by CT, MRI, or autopsy in 91% of events. In this report, only incident cases of CT/MRI-confirmed ischemic strokes that were alive 6 months poststroke and had completed the Short Form 36 (SF-36) evaluation were included. Participants with proxy responders were not asked to complete the SF-36.

The SF-36 Vitality Scale was selected as a measure of fatigue because this is a commonly used measure of broader outcomes of stroke, was scored according to standard guidelines, has good psychometric properties, and because New Zealand normative data standardized to the age and sex distribution in the previous population-based stroke incidence study population in Auckland (1991–1992) are available. Presence of fatigue at 6 months poststroke was defined as a SF-36 Vitality Score (energy and fatigue) of ≤47. This cutoff point was based on the New Zealand SF-36 norms. Patients were considered to have fatigue if they scored >1 SD (New Zealand norm SD 18.5) below the New Zealand norm mean (65.5). The interviews were carried out by a trained research nurse in a standard uniform manner and no proxy was allowed to be used to complete the SF-36 assessment.

The following baseline variables were considered as potential predictors of fatigue: age, sex, 10-item modified Barthel Index (independent [score of 20] versus otherwise), prestroke dependency in activity of daily living, self-reported ethnicity (European versus other), living conditions before stroke (living alone versus otherwise), living at home versus other (eg, residential care, rest home, institution), education level (tertiary education versus other), history of stroke, smoking (current smoker versus current noncurrent smoker), prestroke urinary incontinence (yes or no), hypertension, diabetes mellitus, atrial fibrillation, other heart disease (yes or no), use of antidepressants, and sleepiness in the month before the index stroke (using Epworth Sleepiness Scale ≥10). We also looked at the effect of having ≥2 of the comorbidities mentioned versus <2 comorbidities at baseline. At 6 months poststroke, we measured the level of dependency in activities of daily living and presence or absence of severe depression (as suggested by the General Health Questionnaire depression subscore of ≥6).

Descriptive analysis was used for continuous variables (t tests) and chi-squared test for categorical variables. Logistic regression analysis was used to determine predictors of fatigue at 6 months poststroke. Predictive models were developed by first running univariate analyses between the outcome (presence or absence of fatigue) and each potential predictor. If the probability value was ≤0.2, the predictor was then considered for inclusion in the multivariate model. ORs with the corresponding 95% CIs were calculated. Correlations between each of the predictors were then checked and only the predictor with the most significant contribution to the model was included if there was a high correlation between the predictors. The remaining predictors were then entered in a stepwise manner until no variable excluded from the model made a significant (P ≤ 0.05) contribution. Age, sex, poststroke Barthel Index, and prestroke level of dependency in activities of daily living were forced in all models.

Sensitivity analyses were carried out with exclusion of stroke survivors who had a severe depression at 6-month follow-up. All analyses were conducted with SAS (Version 6.12) software.

Results
Nine hundred thirty-seven of a total 1172 (80%) stroke survivors at 6 months were diagnosed with ischemic stroke. Six hundred thirteen of the 937 (65%) ischemic stroke survivors had data available for analysis; 326 (34.79%) did not provide information on the SF-36 Vitality domain. Comparison of baseline characteristics between the 276 patients with ischemic stroke excluded from the analysis and the 613 patients with ischemic stroke who were included in the analysis showed that excluded patients were more dependent within the first few days after the event and at the prestroke period (Barthel Index <20; 77% versus 48% and 22% versus 7%, respectively; P < 0.0001), lived alone more often or were not married (49% versus 39%; P < 0.0001), were more dependent in activities of daily living at 6 months poststroke (66% versus 23%; P < 0.0001), were of non-European ethnicity more often (40% versus 16%; P < 0.001), and were more likely to be women (57% versus 46%; P < 0.001).

Of the 613 patients with ischemic stroke included in the analysis, there were 330 men (53.8%). Mean age of patients was 67.0 years (SD 12.9) in men and 73.2 years (SD 12.2) in women. Forty-five patients were diagnosed with large artery disease (7%), 146 patients with cardioembolic stroke (24%), 80 patients with small artery disease (13%), and 342 patients with other and undetermined causes of stroke (56%). Anterior circulation stroke was diagnosed in 376 patients (61%) and posterior circulation stroke in 145 patients (24%). Among hemispheric strokes, the left hemisphere was affected in 233 patients (38%). Fatigue was present in 183 of 613 (29.9%) patients 6 months after the ischemic stroke with no difference between men and women (27.6% in men versus 32.5% in women; P = 0.18). There was an association between increased prevalence of fatigue with advancing age (r = -0.12, P < 0.01). Trends for participants <45 years of age may be affected by the low numbers of participants (N = 26) in that age group (Figure 1).
Among 6-month ischemic stroke survivors included in the analysis, patients with poststroke fatigue were older (2.5 years), were more likely to be of New Zealand European ethnicity, were institutionalized prestroke, had a previous stroke, had prestroke urinary incontinence, and were more likely to be functionally dependent in the first month after stroke compared with those without poststroke fatigue (Table). Patients with fatigue were less often diagnosed with hypertension than those without fatigue. At 6 months poststroke, fatigued patients were more dependent in activities of daily living and had severe depression more frequently than those without fatigue.

Multivariate logistic regression analysis (Figure 2) revealed that the only baseline variables independently associated with an increased risk of development of fatigue were prestroke incontinence (OR, 2.44; 95% CI, 1.46–4.09) and being of New Zealand European ethnicity (OR, 2.50; 95% CI, 1.23–5.09). Being independent and living alone before stroke were associated with a reduced risk of fatigue (OR, 0.53; 95% CI, 0.35–0.80 and OR, 0.55; 95% CI, 0.34–0.89, respectively). Severe depression (OR, 12.42; 95% CI, 5.94–25.94) at the 6-month follow-up was independently associated with being fatigued. When excluding patients with severe depression at 6-month follow-up, sensitivity analysis showed that being of New Zealand European ethnicity (OR, 2.42; 95% CI, 1.14–5.14) and incontinent before stroke (OR, 2.47; 95% CI, 1.46–4.16) were associated with an increased risk of fatigue at 6 months poststroke, and being functionally independent at baseline (OR, 0.49; 95% CI, 0.32–0.76) was associated with the decreased risk of fatigue.

### Discussion

This is the first population-based study to report the prevalence and predictors of fatigue 6 months after an ischemic stroke. Fatigue occurred in approximately 30% of patients with ischemic stroke at 6 months and the prevalence of fatigue increased with advancing age. Those with severe poststroke depression 6 months after stroke were 12 times more likely to experience fatigue than those without severe depression.

### Table. Demographic and Clinical Characteristics of Patients With Ischemic Stroke Included in the Analysis, No. (%)

<table>
<thead>
<tr>
<th></th>
<th>Fatigued (n=183 [30%])</th>
<th>Not Fatigued (n=430 [70%])</th>
<th>Overall (n=613 [100%])</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>72.4 (12.6)</td>
<td>68.8 (13.0)</td>
<td>69.9 (13.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Female</td>
<td>92 (51)</td>
<td>191 (45)</td>
<td>283 (47)</td>
<td>0.18</td>
</tr>
<tr>
<td>European ethnicity</td>
<td>167 (92)</td>
<td>349 (82)</td>
<td>516 (84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Barthel Index: independent</td>
<td>64 (35)</td>
<td>230 (54)</td>
<td>294 (48)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Prestroke dependent in ADL</td>
<td>22 (12)</td>
<td>23 (6)</td>
<td>45 (8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Living alone</td>
<td>51 (28)</td>
<td>121 (28)</td>
<td>172 (28)</td>
<td>0.85</td>
</tr>
<tr>
<td>Live in institute prestroke</td>
<td>23 (13)</td>
<td>47 (8)</td>
<td>70 (22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Tertiary qualification</td>
<td>76 (42)</td>
<td>518 (83)</td>
<td>594 (97)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>49 (27)</td>
<td>72 (17)</td>
<td>121 (20)</td>
<td>0.01</td>
</tr>
<tr>
<td>Use of antidepressants prestroke</td>
<td>22 (12)</td>
<td>21 (5)</td>
<td>43 (7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>22 (12)</td>
<td>54 (13)</td>
<td>76 (13)</td>
<td>0.81</td>
</tr>
<tr>
<td>Prestroke urinary incontinence</td>
<td>50 (28)</td>
<td>47 (11)</td>
<td>97 (16)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>93 (51)</td>
<td>252 (59)</td>
<td>345 (57)</td>
<td>0.12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31 (17)</td>
<td>68 (16)</td>
<td>99 (17)</td>
<td>0.76</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>38 (21)</td>
<td>77 (18)</td>
<td>115 (19)</td>
<td>0.41</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>27 (15)</td>
<td>79 (19)</td>
<td>106 (18)</td>
<td>0.47</td>
</tr>
<tr>
<td>⩾2 comorbidities</td>
<td>95 (52)</td>
<td>188 (44)</td>
<td>283 (47)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sleepiness in month before stroke (using Epworth Sleepiness Scale ⩾10)</td>
<td>26 (15)</td>
<td>49 (12)</td>
<td>75 (13)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>6-mo follow-up</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dependent in ADL</td>
<td>69 (38)</td>
<td>76 (18)</td>
<td>145 (24)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SF-36: Vitality, mean (SD)</td>
<td>31.1 (12.4)</td>
<td>70.5 (13.4)</td>
<td>58.7 (22.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Severe depression*</td>
<td>41 (23)</td>
<td>13 (3)</td>
<td>54 (9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Severe depression subscore, mean (SD)</td>
<td>3.2 (3.7)</td>
<td>0.7 (1.9)</td>
<td>1.5 (2.8)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

P represents a difference between fatigued and not fatigued patients, as assessed by t test for continuous variables and χ² test for proportions.

ADL indicates activities of daily living; SF-36, 36-item Short Form.

*Severe depression was defined by the General Health Questionnaire-28 depression subscore of ⩾6. Fatigue was defined by a score of <47 on the Vitality subscale of the SF-36.
depression. The risk of developing poststroke fatigue was approximately 2½ times greater in people of New Zealand European ethnicity or who had prestroke incontinence and was seen in those with and without severe depression. That poststroke fatigue can occur in the absence of depression has been shown previously.2,10

The 30% prevalence of fatigue found in this study is at the lower level of 29% to 72% range reported in most other studies1–7,18,32 but higher than reported in Sweden (17%).1 However, most these earlier studies were not population-based and were therefore susceptible to selection bias. In addition, fatigue prevalence for all stroke subtypes combined was reported, whereas our analysis was limited to those with ischemic stroke. The only other population-based study that reported prevalence of fatigue was the Oxford Vascular Study in the United Kingdom.7 This showed a 56% prevalence of fatigue in patients with minor stroke at 6 months. The difference in findings may reflect the use of different measurement tools between the 2 studies; for example, the Oxford Vascular Study used the Chalder fatigue scale. It is also possible that the perception of fatigue in patients with minor strokes, which has been defined as full recovery within the first 3 to 4 weeks after stroke onset, is systematically different (higher) than in patients with disabling strokes.2,33,34

The finding of increased prevalence of fatigue with advancing age is consistent with other studies.24,35,36 This is likely to be related to the accumulation of comorbid medical conditions with age,1 although this association has not been found in all studies.10 Urinary incontinence is commonly regarded as a measure of stroke severity37 so that the independent effect of prestroke incontinence on the occurrence of fatigue is not surprising. The same reasoning applies to our findings of the protective effect of living alone and being independent in activities of daily living. Others have also reported direct associations between disability,4,7,10,16 depression,4,5,35,36 and the subsequent risk of fatigue. Although studies support the separate existence of poststroke fatigue and depression, this is complicated by fatigue also being a symptom of depression.

One of the unexpected findings of our study was the increased risk of developing of fatigue in New Zealand Europeans. The finding that fatigue was associated with European ethnicity raises the question of whether there are ethnic differences in the perception of fatigue or a greater willingness to endorse symptoms of fatigue, although this was not explored further.21 Stroke survivors with less severe physical or cognitive disability tend to rate fatigue as a more severe symptom,2,33,34 which may be due to a relative lack of other sequelae,38,39 greater expectation for full recovery, and differing demands of daily life in these patients.39 Previous stroke per se did not appear to be an independent predictor of fatigue at 6 months, although it is likely that prestroke dependency, which is shown to be independently associated with the risk of fatigue, is an approximation of the effects of previous stroke.

This study has a number of strengths. The major strength is the study’s population-based design means that it is unaffected by selection bias and all estimates of fatigue prevalence and characteristics reflect the true extent of the problem at the population level. Second, we limited the analysis to ischemic stroke because the prevalence and characteristics fatigue may differ between different pathological stroke subtypes. Third, we did not allow information about fatigue to be collected from proxies. Only patients with ischemic stroke who personally provided information about their energy and fatigue levels (compared with national SF-36 Vitality norms) were included in the analysis, thus allowing the minimization of diagnostic misclassification bias.

This study has a number of limitations. The most important limitation is that there are no standard, universally accepted criteria of poststroke fatigue. As such, results from this study may not be entirely comparable with other population-based studies that use different criteria for fatigue (eg, exertion fatigue as opposed to chronic fatigue; general versus physical fatigue, reduced activity, reduced motivation, peripheral/neuromuscular, and central/cognitive or mental fatigue).8,40–43 There is also evidence that poststroke exertion fatigue and chronic (central) fatigue are 2 distinct entities associated with different contributing factors. For example, exertion fatigue is independently associated with peak oxygen uptake, whereas central fatigue is independently associated with depression.40 The choice of the SF-36 Vitality subscore to assess fatigue was largely driven by practical and convenience reasons, although it has previously been used to study fatigue.24,44–46 The SF-36 Vitality subscore has been shown to have good psychometric properties for measuring fatigue19 and strongly correlates with some more specific and commonly used fatigue measurement tools such as the Fatigue Severity Scale.27 Another limitation of our study is that we did not measure prestroke fatigue or cognitive functioning and were limited in the number of potential predictors (eg, urinary incontinence at baseline, site of stroke) and confounders (eg, medications, Barthel Index at 6 months), because these are post hoc analyses. Excluding 276 patients who did not complete the fatigue rating scale at 6 months poststroke may have lessened the generalizability of the results and may have resulted in selection bias. However, the effect of this selection bias on the prevalence estimates is likely to be minimal because...
among excluded stroke survivors, there were more people of non-European ethnicity, a factor shown to be associated with lower risk of fatigue 6 months poststroke in our study population. In addition, the effect of that selection bias on the observed cause-and-effect associations is likely to be toward underestimation of the true cause-and-effect associations because among excluded participants, there were significantly more people with inversely related predictors of fatigue such as being non-Europeans and living alone before stroke. It is acknowledged that the assessment of fatigue is a complex area and further work is needed to determine an agreed working definition and comprehensive assessment of fatigue.

In conclusion, our data on the prevalence and determinants of fatigue in 6-month ischemic stroke survivors is important for healthcare planning and development of future interventions to prevent and control this common and debilitating condition. Because fatigue is a relatively common problem during the first 6 months poststroke and has a negative impact on various outcomes, it deserves more attention in clinical practice and scientific research, including interventional studies to manage this serious condition.

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None.

References
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