Exploratory Longitudinal Cohort Study of Associations of Fatigue After Stroke

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Background and Purpose—The pathogenesis of poststroke fatigue is unclear. In this prospective study, we explored whether reduced physical activity might contribute to poststroke fatigue or be a consequence of it.

Methods—Patients with a recent acute stroke were assessed at 1, 6, and 12 months with, Fatigue Assessment Scale (FAS), a fatigue case definition, Hospital Anxiety and Depression Score, sleepiness, quality of life, and accelerometry (ActivPAL). Bivariate analyses determined associations between fatigue and step count at each time point. Multiple linear regression tested whether 1-month step count independently predicted 6- and 12-month FAS.

Results—A total of 136 participants (mean age, 72 years; 64% men) attended ≥1 assessment. ActivPAL data were available for 84 (64%), 69 (66%), and 58 (64%) participants at 1, 6, and 12 months, respectively. At 6 and 12 months, a positive fatigue case definition was associated with lower daily step counts (P=0.014 and 0.013, respectively). At 1, 6, and 12 months, higher FAS (more fatigue) was associated with lower step count (P<0.001, 0.01, and 0.007), higher depression (P<0.001), anxiety scores (P<0.001) and sleepiness (P<0.001), and poorer quality of life (P<0.001). Lower daily step count (P<0.002 and 0.006) and greater anxiety (P<0.001 for both) at 1 month independently predicted higher FAS at 6 and 12 months.

Conclusions—Lower step counts at 1 month independently predicted greater FAS for ≤12 months. Physical activity might be a therapeutic target for poststroke fatigue. 

Key Words: fatigue ▶ physical activity ▶ stroke

Fatigue can be defined as a chronic and subjective feeling of lack of energy, weariness and aversion to effort. Fatigue after stroke affects around half of stroke survivors, it may persist, it can adversely affect physical and psychological functioning, social and family life, health-related quality of life, and return to paid employment.

The pathogenesis of poststroke fatigue is unclear. One hypothesis is that fatigue might be triggered by physical inactivity, which commonly occurs as a direct consequence of neurological deficits. Physical inactivity leads to physical deconditioning, thus making physical activity more fatiguing and leading to further avoidance of activity and persistence of fatigue. However, there is a paucity of evidence for or against an association between fatigue and either physical activity or physical fitness. If there is an association between poststroke fatigue and reduced physical activity, independent of other factors previously found to be associated with fatigue (ie, depression, anxiety, sleepiness, and quality of life), this would support the testing of physical activity–based treatments for fatigue.

This study had 3 main aims: first, to investigate whether fatigue is significantly associated with directly measured physical activity at 1, 6, and 12 months after stroke; second, to examine bivariate relationships between physical activity and other patient characteristics at or near baseline and fatigue at later time points; third, to discover whether physical activity remained a significant predictor of later fatigue controlling for other independent variables.

Materials and Methods

Study Design, Setting, and Participants

This prospective longitudinal cohort study recruited patients with an acute stroke (hemorrhagic or ischemic) within the previous month, admitted to hospital or seen in outpatient clinic, with postcodes in South Edinburgh, from September 1, 2009, to June 30, 2011. Exclusion criteria were subarachnoid hemorrhage (unless secondary to an intraparenchymal hemorrhage), medically unstable or dysphasia or cognitive impairment that was severe enough to prevent the patient from giving informed consent and completing questionnaires (as judged by the patient’s medical team and the researcher).
Standard Protocol Approvals, Registrations, and Patient Consents
Lothian Ethics committee approved the study. All participants gave written, informed consent.

Variables Recorded at Recruitment
Stroke subtype (Oxfordshire Community Stroke Project Classification) and patient characteristics were extracted from medical records. The researcher performed the Mini-Mental State Examination, the National Institute of Stroke Scale (NIHSS), Physical Activity Scale for the Elderly (PASE) questionnaire for prestroke physical activity and asked Did you have a problem with fatigue before your stroke?

Variables Recorded at Assessments
At 1, 6, and 12 months after stroke, participants were assessed in a clinical research facility, in a hospital ward (if still an inpatient) or at home, with the following measures

Fatigue Assessment Scale
The FAS is a 10-item self-report scale with 10 statements about different aspects of fatigue, each rated from 1 to 5 (1, never; 2, sometimes; 3, regularly; 4, often; and 5, always). A higher score indicates more fatigue.

Fatigue Case Definition
This valid and reliable structured interview used 7 probe questions to identify clinically significant fatigue.13,17 The interviewer ascertains from the responses to these questions whether the participant had experienced fatigue or loss of energy or increased need to rest (as opposed to lack of motivation boredom), every day or nearly every day for ≥2-week period in the past month, for ≥50% of waking hours. The fatigue had to interfere with everyday problems or be perceived as a problem. Previous studies have shown that patients fulfilling the case definition have higher FAS scores.13,17

Free Living Physical Activity
Time spent sitting or lying, standing upright, stepping, and the number of steps/d were directly measured using an accelerometer (ActivPal) attached to the thigh unaffected by the stroke. The ActivPAL was chosen as we had previous experience using it in frail older people. After 7 days, the researcher removed it from inpatients. Patients at home returned it by post in prepaid envelope. Participants were asked to wear the ActivPAL even if they were unable to walk. The first and last days of recording which were incomplete 24-hour recordings were excluded, and data from the middle calendar days only were used. Mean number of steps/d for each participant was calculated.

Hospital Anxiety and Depression Scale
This self-report questionnaire has 7 items for anxiety and 7 for depression. Each item is scored from 0 to 3, and the scores added to give total scores for anxiety and for depression. Hospital Anxiety and Depression Scale was performed because depression and anxiety scores have been reported to be associated with poststroke fatigue.18

EuroQol
EuroQol (a quality of life scale)19 was performed because previous studies had demonstrated an association between quality of life and fatigue after stroke.5,6,19

Epworth Sleepiness Scale
This scale20 was used to determine the level of daytime sleepiness as 2 previous studies have demonstrated an association between the sleep disorders and poststroke fatigue.21,22 There are 8 items each scored 0 to 3. A score of ≥10 suggests a sleep disorder.

Diastolic and Systolic Blood Pressure
These were recorded for patients assessed in the clinical research facility or in hospital (but not at home) because a previous report had shown that fatigue was associated with either high or low blood pressure.21

Study Size
The proposed sample size was 170 at baseline and 120 at the 12-month follow-up, to have 92% power to detect a 10% difference in time upright between patients with and without fatigue, according to the case definition, assuming that 40% would have fatigue. The FAS was not used in sample size calculations.

Statistical Analysis
SPSS 14.0 and then 19.0 were used. Total FAS was positively skewed and so therefore transformed using logarithmic (base 10) distribution. Missing log FAS values in nonattendees at 6 and 12 months were replaced using the expectation maximization single imputation method. Little’s Missing Completely at Random test indicated that the data were missing completely at random (χ²=7.60; P=0.47). This increased the number of valid log FAS values from 105 to 136 at 6 months and from 91 to 136 at 12 months and thus the number of cases for regression analyses from 69 to 84 at 6 months and from 58 to 84 at 12 months.

Bivariate Relationships Between Fatigue (FAS and Case Definition) and Other Variables
Spearman correlation examined the relationships between log FAS and other patients characteristics at the same time point. For longitudinal relationships over time, Spearman correlation of log FAS at 6 and 12 months was performed with possible independent predictors (age, Mini-Mental State Examination, NIHSS, BP, EuroQol [UK population preferences, Time Trade Off value method], anxiety, depression, sleepiness, time per day stepping, steps/d) at baseline or 1 month. The relationships between log FAS and sex, stroke characteristics, and prestroke fatigue were examined with a t test.

The relationship between the fatigue case definition and sex, stroke characteristics, and prestroke fatigue was examined using Fisher exact test, and relationships with age, Mini-Mental State Examination, NIHSS, PASE, blood pressure, EuroQol, anxiety, depression, sleepiness, and step count was examined using Mann–Whitney U test.

Multivariate Analysis
We excluded the presence of nonlinearity and extreme outliers on scatterplots and tested the other assumptions for multiple linear regression for the final models.

Multiple regression analyses used log-transformed FAS with imputed missing values at 6 and 12 months as the dependent variables and the mean number of steps/d (in thousands) at 1 month as the baseline measure of physical activity. Multicollinearity was tested using variance inflation factor. Other potential independent variables were those with a significant bivariate relationship with log FAS at admission or recruitment (PASE) or at 1 month (anxiety, depression, and EuroQol). We adjusted models for age at recruitment, sex, and prestroke fatigue, although they were not statistically significant, as they were considered of fundamental importance.

Models using time spent stepping were similar to models with daily step count. We used step count in the final models because it is more often reported in studies of physical activity after stroke.24

A hierarchical exploratory approach was used initially for entry of predictors into the equations. In the final regression models, all predictors were entered during the same step.

Results
Participants
A total of 382 eligible patients were approached of whom 157 agreed to participate. Of these, 21 (13%) did not attend
any assessment visits, leaving 136 patients who are included (Table 1). The assessments at 1, 6, and 12 months after stroke onset were attended by 132 (97%), 105 (77%), and 91 (67%) participants, respectively (Figure).20 Twenty nine (21%) dropped out after the 1-month assessment (9 died, 9 dropped out and gave no specific reason, 5 reported being too ill, we were unable to contact 4, and 2 had returned to full time work), 16 (11%) dropped out after the 6-month assessment (3 died, 7 dropped out, 5 were too ill, and 1 returned to full time work). There were no significant differences in the characteristics of participants who attended all 3 assessments when compared with those who dropped out at 1 or 6 months.

**Descriptive Data**

The proportion of participants fulfilling the fatigue case definition was 43 of 132 (33%) at 1 month, 23 of 105 (22%) at 6 month, and 18 of 91 (20%) at 12 months. The median (interquartile range) FAS score was 23 (18–29) at 1 month, 21 (17–25.5) at 6 months, and 22 (17–28) at 12 months.20

ActivPal data were available from 84 of 132 (63.6%), 69 of 105 (65.7%), and 58 of 91 (63.7%) participants at the 1, 6, and 12 month assessments, respectively. Reasons for missing ActivPal data included participants declined (26 at 1 month, 25 at 6 months, and 23 at 12 months), participants attempted to use the device but were unable to, for example, because of skin irritation (6 at 1 month and 1 at 12 months), or devices not returned or malfunctioned (16 at 1 month, 11 at 6 months, and 10 at 12 months). There were ≥5 days of ActivPal data for 65 participants at 1 month, 48 at 6 months, and 44 at 12 months; in the remaining participants, there was ≥1 whole day of activity. The median (interquartile range) daily step count (thousands) was 2,841 (1,419–5,723; n=84) at 1 month, 4,047 (2,056–5,822; n=69) at 6 months, and 4,314 (1,657–6,890; n=58) at 12 months. Blood pressure was not obtained in 57 (43%), 49 (47%), and 47 (52%) participants at 1, 6, and 12 months, respectively, mainly because of assessments at home rather than in hospital.

**Table 1. Characteristics at Recruitment of Participants Who Attended ≥1 Assessment and Those Who Were Included in Multiple Regression Analyses After Replacement of Missing Fatigue Assessment Scale Data**

<table>
<thead>
<tr>
<th>Characteristic at Recruitment</th>
<th>Participants Who Attended ≥1 Assessment (n=136)</th>
<th>Participants Included in Regression Analyses (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Median age, y (IQR)</td>
<td>71.8 (62.6–79.2)</td>
<td>72.3 (65.2–80.5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>88 (64.7)</td>
<td>56 (66.7)</td>
</tr>
<tr>
<td>First ever stroke (%)</td>
<td>106 (77.9)</td>
<td>67 (79.8)</td>
</tr>
<tr>
<td>History of diabetes mellitus (%)</td>
<td>23 (16.9)</td>
<td>15 (17.9)</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>71 (52.2)</td>
<td>41 (48.8)</td>
</tr>
<tr>
<td>Median MMSE (IQR)</td>
<td>27 (25–28.5), n=121</td>
<td>27 (25–29), n=72</td>
</tr>
<tr>
<td>Median NIHSS (IQR)</td>
<td>2 (1–4), n=134</td>
<td>2 (1–3), n=82</td>
</tr>
<tr>
<td>Median PASE (IQR)</td>
<td>96 (57–158), n=135</td>
<td>96 (59–158), n=83</td>
</tr>
<tr>
<td>Mean systolic admission BP (SD)</td>
<td>147.6 (26.5), n=129</td>
<td>149.0 (28.6), n=79</td>
</tr>
<tr>
<td>Mean diastolic BP at admission (SD)</td>
<td>79.9 (14.9), n=129</td>
<td>78.2 (14.4), n=79</td>
</tr>
</tbody>
</table>

**Bivariate Associations With Fatigue at Each Time Point**

**Case Definition for Fatigue**

At 1 month, there were no significant differences between those with positive and negative case definition for age, Mini-Mental State Examination, NIHSS, PASE, blood pressure, anxiety and step count (Mann–Whitney U tests), sex, previous stroke, posterior circulation syndrome stroke (POCS/not POCS), fatigue before stroke, diabetes mellitus or hypertension, inpatient/outpatient, side of brain lesion, or ischemic/hemorrhagic stroke (Fisher exact tests). Those with a positive fatigue case definition had lower quality of life, greater depression, and more sleepiness than those with negative case definition (P<0.001, P<0.001, and P<0.001; Mann–Whitney U tests).

At 6 months, quality of life was significantly lower (P=0.003) and anxiety, and depression significantly higher (P=0.014 and P=0.010) in those with a positive case definition (Mann–Whitney U tests). This was also found at 12 months (P values <0.001, 0.020, and 0.015, respectively). More sleepiness was significantly associated with a positive case definition at 6 months but not at 12 months (P<0.001 and P=0.054). Step count was significantly lower in patients with a positive case definition at 6 and 12 months (median [interquartile range] step count [thousands]; Table 2).

**Fatigue Assessment Scale**

Associations between log FAS and activity, quality of life, sleepiness, anxiety, and depression are presented in Table 3. Blood pressure was not significantly related to log FAS at any time point (Spearman correlations). There were no significant differences in log FAS at any assessment for sex, side of brain lesion, history of diabetes mellitus or hypertension, ischemic/hemorrhagic stroke, inpatient/outpatient, previous stroke, or prestroke fatigue (t tests).
Bivariate Associations With Fatigue (Log FAS) Over Time

Less time spent stepping, lower step count, lower PASE and lower quality of life, higher anxiety, and higher depression scores were significantly associated with higher FAS at both 6 and 12 months (Table I in the online-only Data Supplement). The marginal significance for diastolic blood pressure should probably be disregarded as a large number of correlations were performed.

Multiple Regression Analyses

Scatter plots showed no extreme outliers and no evidence of nonlinearity. We intended to explore the influence of physical activity on fatigue, controlling for other patient characteristics using logistic regression with the fatigue case definition as the outcome variable and multiple linear regression with FAS as the outcome variable. There were insufficient events per covariate by 12 months (based on 10 events per covariate guidance) for logistic regression. We performed multiple linear regression with FAS as planned (Table 4).

Eighty-four participants were included. Fifty-two without activity data were excluded. The only significant differences between those with and without activity data were that the NIHSS was higher (more severe stroke) in those without activity data (Table 1).

In the final model, PASE and EuroQol were not significant because of multicollinearity with activity and anxiety and were not included. Sleepiness was also not significant. Lower daily step count at 1 month was significantly associated with higher FAS at 6 and 12 months, after controlling for age, sex, prestroke fatigue, and anxiety. Greater anxiety at 1 month was a significant predictor of higher FAS at 6 and 12 months. The model accounted for ≈30% of the variance in FAS (Table 4).

Depression is previously known to be related to fatigue. In bivariate analysis, depression was strongly associated with log FAS and highly correlated with anxiety. Multiple regression models that included depression, but not anxiety, had overall poorer fit and the step count was less significant. Depression was a less significant predictor of log FAS than anxiety in the 6-month model and it was not significant in the 12-month model. Adding depression to a model that included anxiety did not improve fit. These findings are because of the intercorrelation between depression and anxiety.

The first question of the EuroQoL questionnaire asks participants whether they have no problems walking about, moderate problems walking about, or whether they were unable to walk. The regression analyses were repeated with this question being added as a separate independent variable. Adding this variable had little effect on the model fit ($R^2$ changed from 31% to 32% at 6 months and from 27% to 28% at 12 months), walking ability was not a significant predictor of log FAS score at either 6 or 12 months and the variables steps taken per day and anxiety remained significant predictors at each of the time points. This suggests that measuring activity has substantial added value over walking ability in predicting fatigue at later time points.

The analyses were repeated omitting the nonsignificant independent variables (age, sex, and fatigue before stroke).

<table>
<thead>
<tr>
<th>Case Definition</th>
<th>Assessment 1 mo</th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigued, median (IQR)</td>
<td>2.48 (0.79–4.55), n=24</td>
<td>2.64 (0.53–3.39), n=11</td>
<td></td>
</tr>
<tr>
<td>Nonfatigued, median (IQR)</td>
<td>3.42 (1.64–5.95), n=60</td>
<td>4.75 (2.94–7.53), n=47</td>
<td></td>
</tr>
<tr>
<td>Mann-Whitney U test statistic</td>
<td>886.000</td>
<td>550.000</td>
<td>379.000</td>
</tr>
<tr>
<td>$P$ Value</td>
<td>0.096</td>
<td>0.014</td>
<td>0.013</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
There was little difference in the results for the other variables or for the overall model.

Repeating the analyses without imputing missing values for the outcome variable, log FAS, also gave similar results.

Casewise diagnostics identified 1 extreme outlier in the 12-month model, which was not an error in the data. Omitting this case improved the model fit (R² increased from 27% to 33%) and the step count became more significant (P value decreased from 0.006 to 0.001).

The variance inflation factor was within an acceptable range in the final models indicating no strong linear relationships among predictors. The Durbin–Watson test for serial correlation between errors found that the residuals were uncorrelated.

Plots of standardized residuals with standardized predicted values showed homoscedasticity and normally distributed errors.

**Discussion**

This is the largest study to investigate the association between poststroke fatigue and physical activity and the first longitudinal study to our knowledge to show that lower physical activity and higher anxiety at 1 month independently predicted greater fatigue at 6 and 12 months. Although this statistical prediction cannot prove causality, our findings are consistent with the hypothesis that physical inactivity and anxiety might contribute to greater fatigue over time. To be certain about direction of the relationship between fatigue and activity or anxiety, a randomized controlled trial of increasing physical activity and reducing anxiety after stroke would be needed, with fatigue as an outcome measure.

Three previous cross-sectional studies did not find associations between fatigue and activity,11 possibly because of limitations in statistical power. A meta-analysis of data from 19 observational studies reported significant associations between fatigue and low mood but a nonsignificant association with anxiety.26 Our observation that higher anxiety predicts subsequent increased fatigue supports a hypothesis that reducing anxiety might reduce fatigue. If physical activity improves fatigue, there are several putative mechanisms. It may improve aerobic fitness and muscle strength thus enabling a person to perform physical activity without feeling tired. It may improve self-esteem, self-efficacy, and social interactions.27–29 Exercise reduces cerebral infarct volume and improves neurobehavioral scores in animal models of focal ischemia30 and so exercise might be able to promote brain recovery and possibly improve fatigue.31

### Table 3. Spearman Correlation of Log Fatigue Assessment Scale With Other Variables at Individual Time Points

<table>
<thead>
<tr>
<th>Characteristic Recorded at 1, 6, and 12 mo</th>
<th>Coeff</th>
<th>P Value</th>
<th>n</th>
<th>Coeff</th>
<th>P Value</th>
<th>n</th>
<th>Coeff</th>
<th>P Value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time per day sitting and lying</td>
<td>0.35</td>
<td>0.001</td>
<td>84</td>
<td>0.19</td>
<td>0.12</td>
<td>69</td>
<td>0.23</td>
<td>0.08</td>
<td>57</td>
</tr>
<tr>
<td>Time per day upright</td>
<td>−0.31</td>
<td>0.004</td>
<td>84</td>
<td>−0.09</td>
<td>0.48</td>
<td>69</td>
<td>−0.10</td>
<td>0.47</td>
<td>57</td>
</tr>
<tr>
<td>Time per day stepping</td>
<td>−0.39</td>
<td>&lt;0.001</td>
<td>84</td>
<td>−0.31</td>
<td>0.009</td>
<td>69</td>
<td>−0.37</td>
<td>0.005</td>
<td>57</td>
</tr>
<tr>
<td>Steps/d (thousands)</td>
<td>−0.39</td>
<td>&lt;0.001</td>
<td>84</td>
<td>−0.31</td>
<td>0.01</td>
<td>69</td>
<td>−0.35</td>
<td>0.007</td>
<td>58</td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>0.50</td>
<td>&lt;0.001</td>
<td>132</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td>105</td>
<td>0.59</td>
<td>&lt;0.001</td>
<td>91</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>0.53</td>
<td>&lt;0.001</td>
<td>132</td>
<td>0.59</td>
<td>&lt;0.001</td>
<td>105</td>
<td>0.59</td>
<td>&lt;0.001</td>
<td>91</td>
</tr>
<tr>
<td>EuroQoL</td>
<td>−0.49</td>
<td>0.001</td>
<td>132</td>
<td>−0.54</td>
<td>0.001</td>
<td>105</td>
<td>−0.61</td>
<td>0.001</td>
<td>91</td>
</tr>
<tr>
<td>Walking ability</td>
<td>0.36</td>
<td>&lt;0.000</td>
<td>132</td>
<td>0.339</td>
<td>&lt;0.000</td>
<td>105</td>
<td>0.391</td>
<td>&lt;0.000</td>
<td>91</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>0.40</td>
<td>&lt;0.001</td>
<td>132</td>
<td>0.414</td>
<td>&lt;0.001</td>
<td>105</td>
<td>0.514</td>
<td>&lt;0.001</td>
<td>91</td>
</tr>
</tbody>
</table>

HADS indicates Hospital Anxiety and Depression Scale.

### Table 4. Multiple Linear Regression Models for the Analysis of the Relationship Between Physical Activity (Mean Steps/d) at 1 Month and Fatigue at 6 and 12 Months, Controlling for Age, Sex, Fatigue Before Stroke, and Anxiety

<table>
<thead>
<tr>
<th>Predictor</th>
<th>FAS (Log 10) at 6 mo (n=84)</th>
<th>FAS (Log 10) at 12 mo (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1.27 (1.06, 1.49)</td>
<td>1.25 (1.01, 1.49)</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.000 (−0.002, 0.003)</td>
<td>0.001 (−0.001, 0.004)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.014 (−0.043, 0.072)</td>
<td>−0.005 (−0.069, 0.058)</td>
</tr>
<tr>
<td>Fatigue before stroke</td>
<td>−0.014 (−0.067, 0.039)</td>
<td>−0.031 (−0.09, 0.028)</td>
</tr>
<tr>
<td>Thousands of steps/d at 1 mo</td>
<td>−0.013 (−0.021, −0.005)</td>
<td>−0.012 (−0.021, −0.004)</td>
</tr>
<tr>
<td>Anxiety (HADS) at 1 mo</td>
<td>0.015 (0.008, 0.022)</td>
<td>0.014 (0.007, 0.022)</td>
</tr>
<tr>
<td>R</td>
<td>0.31</td>
<td>0.27</td>
</tr>
</tbody>
</table>

FAS indicates Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; and VIF, variance inflation factor.
Our data are generalizable to medically stable patients with a mild stroke. There were some limitations. Just under a half of eligible patients agreed to take part, we recruited 93% of our target and our dropout rate was higher than expected. Some patients declined to use the ActiV PAL and of those who used it, data were not obtained in all participants. NIHSS scores were higher in participants without activity data. Severity of stroke may confound the relationship between fatigue and inactivity and so our results may not apply to the whole stroke population. There were insufficient patients fulfilling the fatigue case definition to perform logistic regression, partly because the proportion with fatigue was lower than expected. Consequently comparisons between those who were fatigued and not fatigued should be interpreted with caution especially at the 12 month time point where the case definition was fulfilled in only 18 participants. As planned, we also used FAS as the dependent variable in a multiple regression analysis. We did not specify a cutoff score on the FAS to define the presence or absence of fatigue; however, a relationship between FAS score and clinically significant fatigue has been shown in previous studies suggesting that a higher FAS has relevance for a clinical diagnosis. ActiV PAL would not have detected swimming or cycling, may have undercounted steps in patients with slow or shuffling gaits, and would not have differentiated walking at different inclines (requiring different energy expenditure). However, these factors should not have introduced bias unless the amount of unrecorded or more strenuous activity was influenced by the level of fatigue. Participant may have increased their activity levels because they knew they were being monitored. However, it is unlikely this would have influenced activity levels for more than a day or so, and we followed the standard practice for monitoring activity. The median step count/d was similar to a recent meta-analysis of which activity might be associated with less fatigue. We also should record physical activity and explore mechanisms by causal influence, it is reasonable for health professionals to consider the proportion with fatigue was lower than expected. Consequently comparisons between those who were fatigued and not fatigued should be interpreted with caution especially at the 12 month time point where the case definition was fulfilled in only 18 participants. As planned, we also used FAS as the dependent variable in a multiple regression analysis. We did not specify a cutoff score on the FAS to define the presence or absence of fatigue; however, a relationship between FAS score and clinically significant fatigue has been shown in previous studies suggesting that a higher FAS has relevance for a clinical diagnosis. ActiV PAL would not have detected swimming or cycling, may have undercounted steps in patients with slow or shuffling gaits, and would not have differentiated walking at different inclines (requiring different energy expenditure). However, these factors should not have introduced bias unless the amount of unrecorded or more strenuous activity was influenced by the level of fatigue. Participant may have increased their activity levels because they knew they were being monitored. However, it is unlikely this would have influenced activity levels for more than a day or so, and we followed the standard practice for monitoring activity. The median step count/d was similar to a recent meta-analysis of step counts after stroke and is lower than in a healthy older population. Our single question for prestroke fatigue may have been subject to recall bias and does not measure the severity of fatigue or whether their fatigue had been clinically significant. We are aware of only 3 previous studies of poststroke, which reported the presence of prestroke fatigue, so our data, albeit reported the presence of prestroke fatigue, so our data, albeit recent study demonstrated an association between fatigue and attentional deficits. Other potentially relevant causal factors such as coping style, locus of control, poor sleep, and systematic inflammation should be explored in future studies. There are implications for clinical practice and future research. Further work to enhance compliance rates of accelerometer in stroke would be useful, although our compliance rates were substantially higher than has been previously reported. Although this longitudinal study cannot establish causal influence, it is reasonable for health professionals to encourage patients to increase activity to reduce later fatigue, particularly as the health benefits of physical activity are well established. Longitudinal cohort studies of poststroke fatigue should record physical activity and explore mechanisms by which activity might be associated with less fatigue. We also need to better understand the nature of anxiety after stroke and how this might relate to the onset of fatigue. Randomized controlled trials of interventions to reduce anxiety and increase activity should be tested for poststroke fatigue.

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**Disclosures**

G.E. Mead produced training materials on exercise after stroke for Later Life Training and received a payment of £4000 for 4 years. This money was paid into her research fund and she did not receive it personally. She also contributed to a book on exercise after stroke and was paid £1000 by Elsevier. This money was paid into her university account to support further research. She was also a speaker at the World Stroke Organization (2014) and UK Stroke Forum (2014) on Fatigue after stroke but received no compensation for either talk. The other authors report no conflicts.

**References**


Exploratory Longitudinal Cohort Study of Associations of Fatigue After Stroke
Fiona Duncan, Susan J. Lewis, Carolyn A. Greig, Martin S. Dennis, Michael Sharpe, Alasdair M.J. MacLullich and Gillian E. Mead

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Supplemental Table I

Spearman’s correlation of log FAS (missing values replaced) at 6 & 12 month with possible independent variables at baseline or one month

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<th>Characteristic recorded at baseline or one month</th>
<th>Assessment</th>
<th>6 months</th>
<th></th>
<th>12 months</th>
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<td></td>
<td></td>
<td>coeff</td>
<td>p</td>
<td>n</td>
<td>coeff</td>
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<tr>
<td>Time per day stepping at one month</td>
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<td>.&lt;.001</td>
<td>84</td>
<td>- .31</td>
<td>.004</td>
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<tr>
<td>Steps per day (thousands) at one month</td>
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<td>EuroQoL at one month</td>
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<td>- .32</td>
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<td>&lt;.001</td>
<td>132</td>
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<td>&lt;.001</td>
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<td>--------</td>
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<td>------</td>
<td>--------</td>
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<tr>
<td>Depression (HADS) at one month</td>
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<tr>
<td>PASE before stroke</td>
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<td>0.01</td>
<td>135</td>
<td>-0.30</td>
<td>&lt;.001</td>
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<td>134</td>
<td>0.12</td>
<td>0.19</td>
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</tbody>
</table>

NIHSS: National Institute of health Stroke Scale

MMSE: Mini Mental State examination