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# Fatigue and activity after stroke. Secondary results from the Life After Stroke study

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## Abstract

**Objectives:** The aim of this study was to describe how the prevalence of fatigue changed from the subacute phase to the chronic phase after stroke, and to investigate how activity was associated with fatigue among participants included in the randomized controlled multicentre-study Life After STroke (LAST).

**Methods:** The present study represents secondary analysis based on data from the LAST study. One-hundred-and-forty-five patients with mild and moderate stroke (mean (SD) age: 71.5 (10.5) years, 57.2% males) recruited from St. Olav's University Hospital were included. Fatigue was assessed by the Fatigue Severity Scale (FSS-7) at inclusion, 3 months after stroke, and at follow-up 18 months later. activPAL was used to measure activity at follow-up.

**Results:** A total of 46 (31.7%) participants reported fatigue at inclusion and 43 (29.7%) at follow-up ($p$ = .736). In the univariable regression analysis, sedentary behaviour, walking and sedentary bouts were significantly associated with fatigue ($p \leq .015$), whereas only time spent walking was significantly associated with fatigue in the multivariable regression analysis ($p$ = .017).

**Conclusions:** The present study showed that fatigue is a common symptom after stroke and that the prevalence of fatigue remained unchanged from the subacute to the chronic phase. The study also showed that increased time spent walking was strongly related to lower fatigue, while no such associations were found between the other activity categories and fatigue.

KEYWORDS
activity, fatigue, stroke, walking

## 1 | INTRODUCTION

Stroke is a common cause of disability and use of health care services (Benjamin et al., 2018). It is one of the medical conditions that leads to the highest disability-adjusted life years and years of life lost, both in Norway and globally (Stovner, Hoff, Svalheim, & Gilhus, 2014). Overall, stroke has a major impact on society, both economically and for affected individuals and their caregivers.

In the acute phase after stroke, both motor function and cognitive impairments can be present and can lead to a range of different symptoms, depending on the localization of the stroke (Dobkin, 2005). Following the acute phase, other symptoms like fatigue are more commonly reported (Miller et al., 2013; Naess, Lunde, & Brogger, 2012a). Fatigue can negatively affect both physical and psychological functioning (Ingles, Eskes, & Phillips, 1999). The reported prevalence of fatigue after stroke ranges from 30 to 72% in subacute and chronic phases (Appelros, 2006; Carlsson, Moller, & Blomstrand, 2003; Egerton, Hokstad, Askim, Bernhardt, & Indredavik, 2015; Miller et al., 2013; Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006). The aetiology is not known, but it probably involves biological, physiological and psychological factors (Duncan, Kutlubaev, Dennis, Greig, & Mead, 2012). Altered cortical excitability, lesion location, inflammation, immune responses and genetics have been proposed as possible factors explaining fatigue after stroke (Hinkle et al., 2017). It is not yet understood how these mechanisms are related to the subjective experience, and in order to identify intervention strategies, there is a need for an increased understanding of this field (Hinkle et al., 2017; Wu et al., 2015).

Poor pre-stroke health is shown to be associated with fatigue after stroke (Egerton et al., 2015). As fatigue has been found to be associated with stroke disability (measured by the modified Rankin scale [mRS]), but not stroke severity (measured by the National Institutes of Health Stroke Scale [NIHSS]), inactivity probably plays an important role in development of fatigue after stroke (Appelros, 2006; Ingles et al., 1999). In a longitudinal study from Duncan et al., a significant association between levels of fatigue and activity was reported in the acute, subacute and chronic phases after stroke (2015). A systematic review showed similar results (Thilarajah et al., 2017). The most common physical activity outcome reported was steps per day (Thilarajah et al., 2017). Research investigating other dimensions of activity in relation to fatigue after stroke is lacking.

The main objective of the Life After Stroke (LAST) study—a randomized controlled multicentre study—was to evaluate the effects of a long-term follow-up programme after stroke, in maintaining motor function as high as possible for as long as possible (Askim et al., 2012). Despite neutral results concerning both primary and secondary outcomes, LAST provides an unique opportunity to explore the association between activity and fatigue among the participants in this high-quality trial (Askim et al., 2018). Hence, the overall aim of the present study was to investigate how the prevalence of fatigue changed from the subacute to the chronic phase after stroke, and how upright activity and sedentary behaviour were associated with fatigue in the chronic phase.

## 2 | METHODS

### 2.1 | Study design

The present study represents secondary analysis of data from the LAST study, which included 380 patients. The study lasted from October 2011 to January 2016. Only participants recruited at St. Olav's University Hospital took part in this sub-study.

The main study was approved by the Regional Committee of Medical and Health Research Ethics (REC no. 2011/1427) and registered with ClinicalTrials.gov (NCT01467206). An amendment for this sub-study was approved by REC in July 2017 (REC no 2011/1427).

### 2.2 | Subjects

Patients were recruited from the outpatient clinic at St. Olav's University Hospital and Bærum Hospital, 10 to 16 weeks after onset of stroke. Inclusion criteria in LAST were diagnosis of first-ever or recurrent stroke (infarction or intracerebral haemorrhage), age ≥18 years, discharged from hospital or inpatient rehabilitation at inclusion, community dwelling with mRS score <5 (Banks & Marotta, 2007) and cognitive function as evaluated by the Mini-Mental State Examination >20 points (>16 points for individuals with aphasia) (Folstein, Folstein, & McHugh, 1975). Exclusion criteria were serious medical comorbidity with short life expectancy or a condition contraindicating motor training. Additional inclusion criteria for the present study were patients recruited at St. Olav's University Hospital, responded to the seven-item version of the Fatigue Severity Scale (FSS-7) both at inclusion and at follow-up, and wore an activPAL accelerometer for at least two consecutive days or more at follow-up.

## 3 | PROCEDURE

Participants randomized to the control group received standard community-based treatment which is provided to all stroke patients in the municipality of Trondheim. In addition to usual care, participants in the intervention group were offered a long-term follow-up programme lasting 18 months. They were coached on physical activity and exercise by a physiotherapist each month. The programme aimed to include high-intensity exercise once a week (lasting 45–60 minutes), in addition to 30 minutes of daily physical activity related to the participants' own goals (Askim et al., 2018; Gunnes et al., 2019).

### 3.1 | Assessments

Age, sex, living condition and type of stroke were recorded at baseline. Severity of stroke was assessed by NIHSS (Meyer, Hemmen, Jackson, & Lyden, 2002), and degree of dependence was assessed by mRS.

Self-reported fatigue was assessed at inclusion and at the 18-month follow-up, measured by FSS-7 (Lerdal & Kottorp, 2011). The FSS-7 consists of seven items formulated as statements, scored on a 7-point Likert scale, ranging from "strongly disagree" to "strongly agree" for each item. The mean score of the seven items was used to estimate fatigue severity, with higher scores indicating higher fatigue levels (0–7) (Lerdal et al., 2011). According to previous studies, the fatigue score was also dichotomized into: ≥ 4 points, indicating fatigue, <4 points, indicating no fatigue (Egerton et al., 2015; Valko, Bassetti, Bloch, Held, & Baumann, 2008). Both the mean (SD) and the dichotomized score are presented in the current study.

To assess daily activity, a single-axis accelerometer (activPAL) was attached to the less-affected thigh at the 18-month follow-up assessment (PAL Technologies, 2019; Taraldsen et al., 2011). Participants were instructed to wear the sensor for at least four consecutive days, unless it became uncomfortable.

Depression was measured by the depression subscale of the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The HADS is a self-rating questionnaire with two subscales: HADS anxiety (HADS-A) and HADS depression, each with seven items scored from 0 to 3. The total score from each subscale ranges from 0 to 21, with higher scores indicating higher anxiety and depression levels.

Pain was measured by extracting the pain/discomfort dimension from EQ-5D-5L, which is a health-related quality of life measurement (Rabin & de Charro, 2001). In addition to pain/discomfort, it covers four dimensions: mobility, self-care, usual activities, and anxiety and

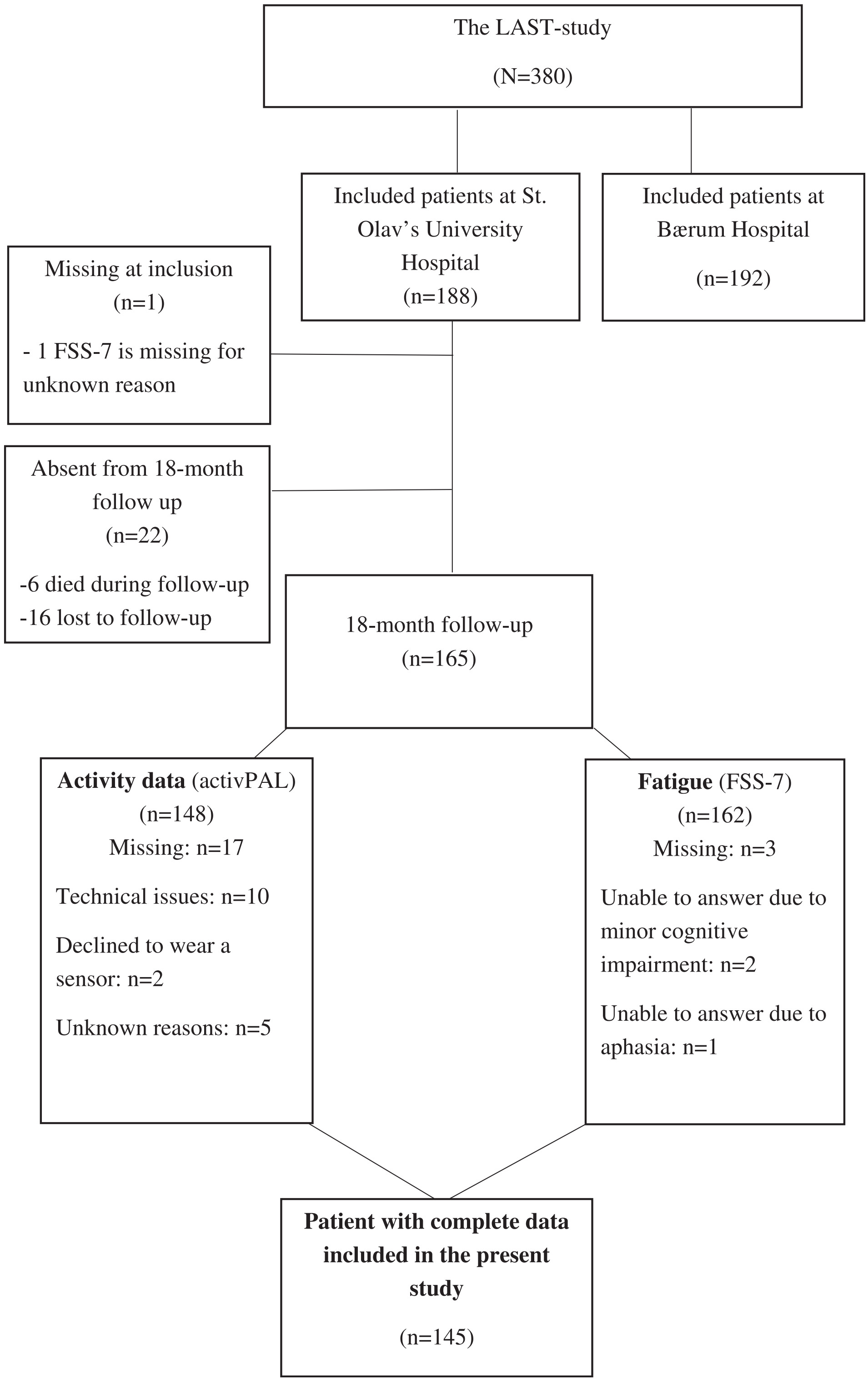


**FIGURE 1** Flow of participants through the study

depression (Rabin & de Charro, 2001). Each dimension is divided into five levels: no problem, slight problem, moderate problem, severe problem and extreme problem.

## 3.2 | Statistical analyses

Data from baseline and from the 18-month follow-up were used in the statistical analyses. Demographic and clinical data were tested for normality using the Shapiro–Wilk test and QQ-plots and presented descriptively. To check for group differences, the independent samples *t*-test and Mann–Whitney *U* test were used on continuous variables, and the chi-square test and Fisher's exact test were used on categorical variables. To check for statistically significant change in the prevalence of fatigue and in the level of fatigue from inclusion to 18-month follow-up, McNemar's test and the paired sample *t*-test were used, respectively.

The activPAL software package (activPAL Professional Research Edition) was used to process the raw acceleration data signals from the activPAL accelerometers. activPAL provides information about time in sedentary (sitting/lying), standing, and walking positions, in addition to number of transitions from sitting to standing positions. The average daily time spent sitting/lying, standing, and walking, in addition to the number of transitions from sitting to standing (between 07.00 and 23.00), was calculated for each individual. From the average daily time spent sitting/lying and the average number of daily transitions from sitting to standing, the average length of sedentary bouts was calculated for each individual.

Regression analyses were used to investigate if participants' daily activity was associated with their level of fatigue 18 months after inclusion. Self-reported fatigue, measured by the FSS-7, was defined as the dependent variable. Sedentary behaviour (sitting/lying), sedentary bouts, standing and walking (all measured by activPAL) were defined as independent variables. Both univariable and multivariable regression analyses were carried out. Multicollinearity between the independent variables was assessed by correlation less than 0.7, tolerance value greater than 0.1 and variance inflation factor less than 10.

**TABLE 1** Baseline characteristics measured at inclusion, 3 months after acute stroke

| | Participants *n* = 145 | Non-participants *n* = 43 | Group differences (*p*-value) |
|---|---|---|---|
| Age, mean (SD) years | 71.5 (10.5) | 71.7 (12.1) | .930[a] |
| Age, *n* (%) | | | |
| >80 years | 31 (21.4) | 12 (27.9) | .371[b] |
| Sex, *n* (%) | | | .917[b] |
| Female | 62 (42.8) | 18 (41.9) | |
| Male | 83 (57.2) | 25 (58.1) | |
| Living condition, *n* (%) | | | .527[b] |
| Alone | 40 (27.6) | 14 (32.6) | |
| Together with someone | 105 (72.4) | 29 (67.4) | |
| Type of stroke, *n* (%) | | | .072[c] |
| Ischemic | 134 (92.4) | 43 (100.0) | |
| Haemorrhage | 11 (7.6) | 0 (0.0) | |
| NIHSS, median (IQR) points | 1.00 (0.00–2.00) | 1.00 (0.00–3.00) | .092[d] |
| NIHSS, *n* (%) | | | |
| Mild (0–7 points) | 141 (97.2) | 42 (97.7) | |
| Moderate (8–16 points) | 4 (2.8) | 1 (2.3) | |
| Severe > 16 points | 0 (0.0) | 0 (0.0) | |
| mRS, median (IQR) | 1 (1.00–2.00) | 2 (1.00–3.00) | |
| mRS, *n* (%) | | | .033[b] |
| 0–2 | 117 (80.7) | 28 (65.1) | |
| 3–4 | 28 (19.3) | 15 (34.9) | |

Abbreviations: IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
[a]Independent samples *t*-test.
[b]Chi-square test.
[c]Fisher's exact test.
[d]Mann–Whitney *U*-test.

Depression and pain, recorded at the 18-month follow-up, were included as covariates in the analyses. Additionally, age, sex, mRS and grouping factor (intervention or control) were included as covariates. Statistical analyses were run in IBM Statistical Packages for the Social Sciences (SPSS), version 25.0. A significance level of $p < .05$ was chosen.

**TABLE 2** Fatigue at inclusion and at 18-month follow-up ($n$ = 145)[a]

| | | Fatigue at follow-up, *n* | | |
|---|---|---|---|---|
| | | Yes | No | Total |
| Fatigue at inclusion, n | Yes | 27 | 19 | 46 |
| | No | 16 | 83 | 99 |
| | Total | 43 | 102 | 145 |

[a]McNemars test showed no difference in the prevalence of fatigue from inclusion to follow-up ($p$ = .736).

**TABLE 3** Hours of activity, from 07.00 to 23.00 per day, unless otherwise stated

| Activity category | Mean | (SD) |
|---|---|---|
| Standing | 3.7 | (1.7) |
| Sedentary behaviour (sitting/lying) | 10.9 | (2.2) |
| Sedentary bouts | 0.4 | (0.7) |
| Walking | 1.3 | (0.8) |
| Number of sit-to-stand transitions per day | 43.8 | (16.9) |

## 4 | RESULTS

In total, 145 participants were included in the present study (Figure 1). Participants had a mean (SD) age of 71.5 (10.5) years. Eighty-three (57.2%) were males, and 105 (72.4%) were living with someone. One-hundred-and-thirty-four (92.4%) were diagnosed with ischemic strokes, while 141 (97.2%) participants were affected by mild stroke (0–7 points on NIHSS), assessed at inclusion (Table 1).

Participants had a mean (SD) HADS-D score of 3.4 (3.2). One-hundred-and-seven (73.8%) reported no or slight pain/discomfort, 26 (17.9%) reported moderate pain/discomfort, and 12 (8.3%) reported severe or extreme pain/discomfort, assessed at the 18-month follow-up.

Table 2 shows that 46 (31.7%) participants reported fatigue at inclusion, and 43 (29.7%) reported fatigue at the 18-month follow-up ($p$ = 0.736). Twenty-seven (18.6%) reported fatigue both at inclusion and at follow-up. The mean (SD) FSS-7 score was 3.05 (1.61) and 2.97 (1.77) at inclusion and after 18 months, respectively ($p$ = .536).

Most participants (n = 132) wore the activPAL for 4 days as prescribed per protocol. However, 10 individuals wore the activPAL for 3 days, and three participants wore it for 2 days. Between 07.00 and 23.00, the participants spent an average of 3.7 hours (SD 1.7) standing and 1.3 hours (SD 0.8) walking (Table 3). Total sedentary time averaged 10.9 hours (SD 2.2) per day, and the sedentary bouts lasted on average 0.4 hours (SD 0.7).

Sedentary behaviour, walking, sedentary bouts, pain, depression, sex and mRS were significantly associated with fatigue in the univariable regression analysis (Table 4). In the multivariable regression analysis, walking was significantly associated with fatigue (B: −0.70, 95% CI: −1.26 to −0.13, $p$ = .017), along with depression and pain ($p$ = .001 and $p$ = .032, respectively). The standing variable was excluded because of

**TABLE 4** The association between fatigue and activity, 18 months after inclusion

| Fatigue ($n$ = 145) | Univariable regression | | | Multivariable regression[a] | | |
|---|---|---|---|---|---|---|
| | B | 95% CI for B | *p*-value | B | 95% CI for B | *p*-value |
| Standing | −0.11 | −0.28 to 0.06 | 0.189 | | | |
| Sedentary behaviour | 0.12 | 0.03 to 0.29 | 0.015 | −0.16 | −0.35 to 0.03 | 0.095 |
| Sedentary bouts | 0.50 | 0.10 to 0.90 | 0.015 | 0.20 | −0.18 to 0.58 | 0.297 |
| Walking | −0.85 | −1.21 to −0.50 | <0.001 | −0.70 | −1.26 to −0.13 | 0.017 |
| Depression (HADS-D) | 0.26 | 0.17 to 0.34 | <0.001 | 0.16 | 0.07 to 0.26 | 0.001 |
| Pain (EQ-5D-5L) | 0.70 | 0.43 to 0.97 | <0.001 | 0.31 | 0.03 to 0.60 | 0.032 |
| *Age* | 0.02 | −0.01 to 0.05 | 0.188 | −0.02 | −0.04 to 0.01 | 0.176 |
| *Female gender* | −0.63 | −1.21 to −0.05 | 0.033 | 0.04 | −0.54 to 0.63 | 0.888 |
| *mRS* | 0.76 | 0.46 to 1.06 | <0.001 | 0.26 | −0.09 to 0.60 | 0.149 |
| *Intervention group* | 0.00 | −0.58 to 0.59 | 0.989 | −0.14 | −0.66 to 0.38 | 0.599 |

Abbreviations: B, beta (unstandardized coefficients); CI, confidence interval; EQ-5D-5L, EuroQol-5 dimension-5 level version (pain dimension); HADS-D, Hospital Anxiety & Depression Scale – Depression subscale (range of scores 0–21); mRS, modified Rankin Scale (range 0–6).
[a]Each variable is adjusted for all other variables.

multicollinearity (a variance inflation factor of 27.8). Thirty-three per cent of the variation in fatigue score (R = 0.33) was explained by the variables included in the regression analysis (Table 4).

## 5 | DISCUSSION

The main results from the present study showed no significant difference in prevalence of fatigue from inclusion 3 months after stroke onset until 18 months later, while increased time spent walking was associated with lower fatigue at follow-up.

The reported prevalence of fatigue (about 30% at inclusion and follow-up) was in the lower range of previously reported prevalence data on post-stroke fatigue (Appelros, 2006; Carlsson et al., 2003; Egerton et al., 2015; Miller et al., 2013; Schepers et al., 2006). Choice of outcome measurements and the use of different cut-off scores to define fatigue may explain some of the differences (Appelros, 2006). Nevertheless, the prevalence reported by other studies using the FSS also varied from 35% 3 months post-stroke (Egerton et al., 2015) to 70% 6 to 12 months after stroke (Miller et al., 2013; Schepers et al., 2006). The cut-off score of >4 on the nine-item version of the FSS might explain the high prevalence in the latter studies (Miller et al., 2013; Schepers et al., 2006). Furthermore, the low level of disability in our study sample may also be a reason for the low prevalence of fatigue (Appelros, 2006).

In contrast to a recent meta-analysis (Cumming et al., 2018), our results showed no change in fatigue over time. However, it is worth noting that only 27 of the 47 participants with fatigue at inclusion were still fatigued at 18 months, indicating that about 40% improve from fatigue while almost the same amount became fatigued over time. Physical deconditioning and a negative cycle of inactivity have been suggested as potential reasons for the increasing number of people suffering from post-stroke fatigue (Cumming et al., 2018). The activity data in the present study showed that participants spent 10% less time on sedentary behaviour and 15% more time standing compared to findings among people with stroke in previous studies (Fini, Holland, Keating, Simek, & Bernhardt, 2017; Janssen et al., 2010; Mudge, Barber, & Stott, 2009). Even though we cannot assume a causal relationship inference based on our analysis, the higher activity levels might have led to a lower chance of developing deconditioning and fatigue over time.

Sedentary behaviour, sedentary bouts and walking were significantly associated with fatigue in the univariable regression analysis, but only walking remained significant in the multivariable analysis. The finding that less time spent walking was associated with higher levels of fatigue is in line with findings in other studies (Duncan et al., 2015; Thilarajah et al., 2017). It would have been of interest to know the intensity of the walking sessions because a close association between cardiorespiratory fitness (CRF) and fatigue has been reported in different populations; specifically, those with high CRF were less fatigued (Egerton, Chastin, Stensvold, & Helbostad, 2016; Heine, van de Port, Rietberg, van Wegen, & Kwakkel, 2015). Hence, future research should include an activity monitor that also can objectively measure intensity of the activity.

The independent variables and the covariates in the multivariable regression analysis only explain 33% of the variation in fatigue scores. This indicates that there may be other more important factors contributing to fatigue. In addition to pain, depression and post-stroke disability (mRS), pre-stroke fatigue has been shown to be associated with post-stroke fatigue (Appelros, 2006; Egerton et al., 2015; Naess, Lunde, & Brogger, 2012b; Ponchel, Bombois, Bordet, & Henon, 2015), and an inclusion of this variable might have improved the model. Sleep disturbances, coping skills, and social support, may also be factors that influence the level of fatigue after stroke (Hinkle et al., 2017). In addition, it has been shown that medical comorbidities, like hypertension and obstructive sleep apnoea, and medication use are associated with increased fatigue scores in the chronic phase after stroke (Chen & Marsh, 2018). Future studies should include some of these variables to improve the explained variation of the model.

When comparing results between studies, the lack of (and the need for) a gold standard measuring fatigue becomes evident (Skogestad, Kirkevold, Gay, Indredavik, & Lerdal, 2019). However, creating a gold standard is challenging, as fatigue is a subjective phenomenon and can be closely related to other symptoms. So far, researchers and clinicians both rely on subjective measurements, mostly self-report questionnaires (Lerdal & Kottorp, 2011). The FSS is one of the questionnaires most commonly used in the stroke population (Hinkle et al., 2017; Lerdal & Kottorp, 2011), and the use of FSS-7 is therefore considered a strength in the present study. It is a valid and reliable measure, and it has better psychometric properties for patients with stroke than the original nine-item version (Lerdal & Kottorp, 2011). However, fluctuating factors may have affected participants' answers, for example, a bad night's sleep, nervousness, an uncomfortable setting or misunderstanding the question.

In the present study, the minimum accelerometer wear time of 2 days could be considered a limitation, as other studies support a minimum wear time of 3 days when investigating complex measures of physical activity (Fini, Burge, Bernhardt, & Holland, 2019; Tinlin et al., 2018). However, only three of the 145 participants had a wear time of 2 days. A weighted average could have been calculated, making the wear time for those participants with 2 or 3 days count less, but because this only involved 13 of 145 participants, and the reason for fewer days was missing at random, it is unlikely that this would have noticeably influenced the results.

As the intervention in the LAST study primarily targeted physical function, there was a chance of selection bias, meaning that the most well-functioning patients may have been more interested in participating. This was reflected in the baseline characteristics showing that the participants were mainly affected by non-severe stroke and were mildly disabled (Table 1). However, according to the annual report from the stroke register in Norway, 80% of those having a stroke in 2018 had mild or moderate stroke severity (NIHSS 0–10) (Fjaertoft et al., 2018). This means that the study sample is fairly representative. Nevertheless, more severe strokes were not represented, and the results should therefore be interpreted with caution regarding the transferability to this part of the stroke population.

## 6 | CONCLUSION

The present study showed that one third of the patients suffered from fatigue 3 months after stroke, and that the prevalence remained unchanged 18 months later. The study also showed that time spent walking was significantly associated with fatigue, while no such associations were found between the other activity categories and fatigue in the chronic phase after stroke. Hence, future research should investigate if a walking intervention could reduce fatigue after stroke.

### 6.1 | Implications for physiotherapy practice

To be able to provide patients the best possible treatment and follow-up after suffering from stroke, an increased understanding of the prevalence of fatigue after stroke, how it develops with time from stroke, and possible associated factors are essential pieces of information for physiotherapists. It is also of clinical importance to know that fatigue can both improve and become worse over time, and that lower fatigue is associated with increased time spent walking. This knowledge is particularly useful for physiotherapists when planning and implementing a rehabilitation programme for patients suffering from stroke.

## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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