

Research Article

The Course of Fatigue during the First 18 Months after First-Ever Stroke: A Longitudinal Study

Annors Lerdal,^{1,2} Kathryn A. Lee,³ Linda N. Bakken,^{4,5}
Arnstein Finset,⁵ and Hesook Suzie Kim⁴

¹ Department of Research, Lovisenberg Diakonale Hospital, Lovisenberggt. 17, 0440 Oslo, Norway

² Division of Medicine, Department of Gastroenterology, Oslo University Hospital, PB 4956 Nydalen, 0424 Oslo, Norway

³ Department of Family Health Care Nursing, University of California San Francisco, 2 Koret Way, San Francisco, CA 94143, USA

⁴ Department of Health Sciences, Buskerud University College, PB 7053, 3007 Drammen, Norway

⁵ Department of Behavioral Medicine, Faculty of Medicine, University of Oslo, PB 1111, Blindern, 0316 Oslo, Norway

Correspondence should be addressed to Annors Lerdal, annors.lerdal@lds.no

Received 7 June 2011; Revised 22 July 2011; Accepted 22 July 2011

Academic Editor: Gillian Mead

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Background. Little is known about the course of poststroke fatigue. **Objectives.** To describe the course of poststroke fatigue in relation to the patient's level of physical functioning, depressive symptoms, and self-reported history of prestroke fatigue. **Methods.** A longitudinal study using structured face-to-face interviews, questionnaires, and patients' medical records. Data were collected from 95 patients in Norway with first-ever stroke. Fatigue was measured with the Fatigue Severity Scale 7 item version and assessed for change between the acute phase, six, 12, and 18 months after stroke using 2-way ANOVA repeated-measures analyses. **Results.** The patients' level of fatigue did not change over time. However, those who reported prestroke fatigue showed a relatively high level of fatigue over time in the poststroke period, while patients with no history of pre-stroke fatigue showed a stable course of relatively low fatigue over time. **Conclusion.** Studies on poststroke fatigue should control for the patient's pre-stroke fatigue level.

1. Introduction

Fatigue is one of the most common complaints after stroke [1, 2]. Despite this, little is known about the development of poststroke fatigue, its development over time and how this development is related to other clinical factors. A few longitudinal studies have been conducted, but to our knowledge, no longitudinal studies have considered that patients with poststroke fatigue may have experienced fatigue for a long time before stroke. In fact, epidemiological studies report that approximately 20–25% of the general population experience current fatigue [3, 4]. A relationship between pre-stroke fatigue and poststroke fatigue has previously been reported in a cross-sectional study [5] 15 months after stroke (mean time after stroke) and in a study of stroke patients in the acute phase [6]. Thus, prestroke fatigue may confound the clinical covariates associated with poststroke fatigue reported in previous studies.

Fatigue can be defined as a sense of exhaustion, lack of perceived energy, or tiredness [7, 8] distinct from sadness or weakness [7]. Because of the subjective character of fatigue and the fact that no objective signs of the condition have been identified, self-report is seen as the most valid way to assess fatigue [9]. Although fatigue is understood as multidimensional with mental, physical, and motivational aspects [8], the Fatigue Severity Scale (FSS) is a one-dimensional self-report measure frequently used to assess fatigue in stroke populations [9].

In a previous published review of poststroke studies [9], poststroke fatigue was more common among women [10–12] and in those reporting a history of fatigue prior to their stroke [5]. Furthermore, poststroke fatigue was related to higher levels of depression [5, 13–19], sleep disturbance [5, 17], and dependency [5, 17, 18]. Some researchers have also observed a significant relationship between a patient's

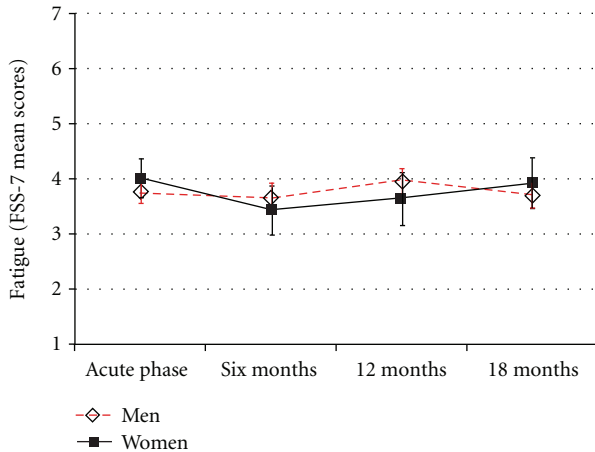


FIGURE 1: Time course for fatigue among men ($n = 56$) and women ($n = 39$). Adjusted for level of physical functioning, depressive symptoms, and prestroke fatigue. Bars are lower and upper 95% CI.

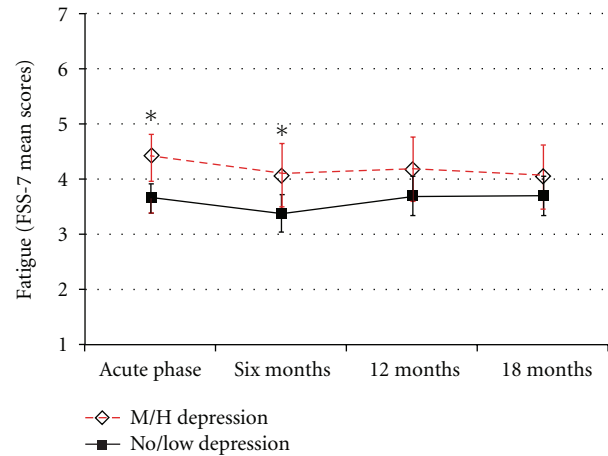
fatigue and neurological impairment [5, 18] while others have not [16, 17].

In a cross-sectional sample of stroke patients in the acute phase [6], we previously reported a higher proportion of cases of severe fatigue among women than among men, and that poststroke fatigue was related to current depressive symptoms, lower physical functioning in patients, and self-report history of prestroke fatigue. This paper reports on the findings from an 18 month follow-up of the participants of the cross-sectional study.

Based on previous findings, the aims of this study were to (1) describe the course of fatigue from the acute phase through six, 12, and 18 months in patients with first-ever stroke and (2) explore the time course related to the patient's level of physical functioning, depressive symptoms, and retrospective self-report of prestroke fatigue.

2. Methods

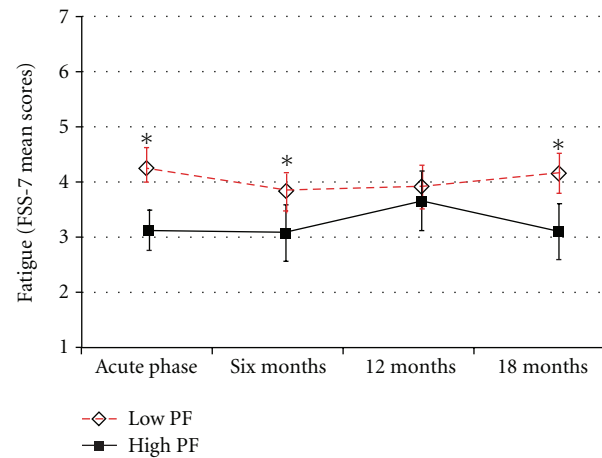
2.1. Participants and Procedures. Participants were recruited to a longitudinal poststroke fatigue study between March 2007 and September 2008 at a hospital in the southeastern region of Norway, and between September 2007 and June 2008 at a university hospital in Oslo. Upon admission to the hospital, patients with a clinical diagnosis of first-ever stroke were recruited for the study. Data were collected from medical records and in standardized interviews by three trained interviewers using validated questionnaires. When the patients were recruited to the study, they were informed that one of their significant others could be present during the interviews, but this occurred in very few cases. To ease the study participant burden in the acute phase, the interviews were conducted at two different times within 48 hours. Data on health-related quality of life (HRQoL) and fatigue were collected during the first interview, while data on sleep quality and depression were obtained during the second interview. At six, 12, and 18 months, data were collected by means of the same questionnaires used in the



* Significant differences ($P < 0.05$) in the FSS-7 scores between the groups at this time point shown in multivariate linear regression analyses.

*Note: M/H depression = BDI score > 13 .

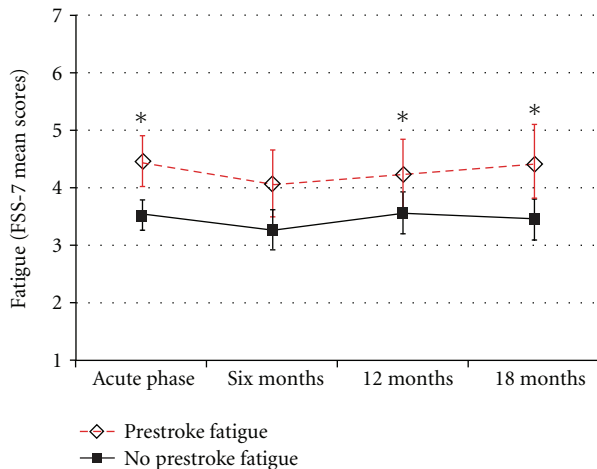
FIGURE 2: Time course for fatigue by patients with low depression scores ($n = 68$) versus those with medium-high depression scores ($n = 26$). Adjusted for level of physical functioning and prestroke fatigue. Bars are lower and upper 95% CI.



* Significant differences ($P < 0.05$) in the FSS-7 scores between the groups at this time point shown in multivariate linear regression analyses.

FIGURE 3: Time course for fatigue by patients with low physical functioning (PF) ($n = 61$) versus those with high PF ($n = 33$). Adjusted for level of depression and prestroke fatigue. Bars are lower and upper 95% CI.

acute phase. Interviews in the acute phase were usually performed in the hospital, either in the patients room if they were alone or in a secluded room onsite. At the follow-up times, most participants were visited in their homes by one of the interviewers. For those who were working or travelling abroad at the time of the follow-up data collection, the questionnaires were sent by mail and returned in a sealed envelope. Inclusion criteria for the study were that the patients had a first-ever clinical presentation of stroke



* Significant differences ($P < 0.05$) in the FSS-7 scores between the groups at this time point shown in multivariate linear regression analyses.

FIGURE 4: Time course for fatigue by patients with no prestroke fatigue ($n = 69$) and those with prestroke fatigue ($n = 26$). Adjusted for level of physical functioning and depressive symptoms. Bars are lower and upper 95% CI.

defined according to the ICD-10 (I 60, 61, 62, 63, and 64) [20] were 18 years or older and had adequate cognitive functioning to allow participation. Patients who were fully conscious or were somnolent but could be awakened to full consciousness (equivalent to a score of 4 or 6 on item number 1 in the Scandinavian Stroke Scale [SSS]) [21] and oriented for time, place, and person (equivalent to a score of 4 on item number 6 in the SSS) were eligible. At one hospital, those who did not meet the criteria for cognitive functioning were further assessed with the MiniMental State Examination (MMSE). Those with an MMSE score ≤ 10 and those with an MMSE score between 11 and 23, but who were found cognitively incompetent by a physician or a nurse, were excluded. At the second hospital, patients who did not meet the SSS criteria were clinically assessed by the stroke team. Patients who were found to be cognitively impaired were excluded from participation.

In addition, patients who were assessed by the recruiting nurses to be unable to communicate (participate in a meaningful conversation with an interviewer or point to the response alternatives on questionnaires) were excluded. Of the 193 patients with a diagnosis of first-ever stroke, 14 were excluded because of poor cognitive functioning, 26 were excluded because of stroke-related difficulty in communicating, and one was excluded because of an inability to understand Norwegian. Of the 152 patients eligible to participate, 125 patients consented (82%) and 6 died or were transferred to hospitals in other regions before collection of the first set of data, resulting in the final sample of 119 patients. Data from 4 of the 119 patients were collected later than 15 days after admission and were excluded from analysis for acute phase findings. The study sample from the acute phase is described in detail in a previous report [6]. During the follow-up visits, 8 participants were excluded due to

death, 3 had other serious illnesses, and 4 did not wish to participate in further data collection. Five more participants were excluded for other reasons: three did not respond when they were contacted by the research team at the follow-up times and two were on holiday at the six-month follow-up. Thus, 95 participants had valid responses on the FSS and responded to all the items in the questionnaires at all four time points; these 95 were included in this analysis.

2.2. Measurements

2.2.1. Fatigue. The 9-item FSS is the most commonly used instrument to measure fatigue in stroke patients [9, 13, 22, 23]. It has shown high validity and reliability [24–26]. A recent published review of fatigue measures in people with chronic illness reported that the FSS had the best psychometric properties [27]. Participants are asked to respond to the statements about their fatigue on a 7-point Likert scale ranging from disagree to fully agree [24]. Higher scores indicate higher levels of fatigue. Findings from recent studies in patients with multiple sclerosis [28, 29] or stroke [30] and people living with HIV/AIDS [31] have shown that items number 1 and number 2 of the FSS did not show acceptable goodness-of-fit and should not be included in the FSS mean score. Given this finding, only the last seven of the original nine (FSS-7) items were included in computing the mean score, but scores still range from 1 to 7. Conceptually, the items in FSS-7 refer to fatigue interference with daily function [30]. Internal consistency of the FSS-7 baseline scores in the present study was adequate (Cronbach's alpha coefficient = 0.86). Mean FSS-7 scores at baseline did not differ by interviewer or by hospital site.

2.2.2. Sociodemographic Variables. Data on age (years), sex, and cohabitation (married/living with a partner) were collected from patients' medical records, while data on the level of formal education (less than 11 years versus 11 years or more) were collected from the questionnaire. Those in paid work or self-employed were categorized as working, while all others (full-time home-makers and those on disability or old-age pensioners) were categorized as not working.

Social class was defined as I (high), II (middle), or III (low) based on the grouping of professions in the international Erikson Goldthorpe Portocare social class schema [31, 32] using the Occupation Classification 2000 [32]. *Social class I* thus comprised high-level professionals, while *Social class II* consisted of midlevel professionals and administrators, and *Social class III* contained employees performing routine manual labour.

2.2.3. Stroke Type and Location. At admission to the hospital, computerized tomography (CT) scans were taken of all patients. Stroke type was categorized based on the radiologist's description as one of the following four groups: (a) ischaemic infarct, (b) haemorrhage, (c) chronic cerebral ischaemia, and (d) negative findings. If an additional CT scan was performed, the most recent description was used for categorizing the stroke. Stroke location was grouped as left,

right, or bilateral. If the CT scan showed signs of lesions from previous undiagnosed strokes, these lesions were included in the classification of stroke.

2.2.4. Stroke-Related Variables

(1) *Physical Function and Activities of Daily Living.* The level of physical functioning was self-rated using 10 physical functioning items from the *Short Form-36 Acute version (SF-36A)* [33]. The SF-36A is a questionnaire that measures physical and mental issues (one-week recall). Higher scores correspond to better-perceived quality of life. The SF-36 has demonstrated reliability and validity [33, 34] and has been suggested as the preferred instrument to measure disability in stroke patients [35]. Cronbach's alpha for scores in the acute phase of the present study was 0.93. The mean score for physical functioning from the normal population ($M = 81.2$) [33] was used to categorize patients as either low or high physical functioning.

Functional ability was assessed with the *activities of daily living personal activities (ADL-P)* Barthel Index (BI) [36]. Ten items were scored. The total score can range from 0 (ADL-P dependent) to 20 (ADL-P independent) [37]. The Norwegian version of the BI has demonstrated validity and reliability in stroke patients [38]. Cronbach's alpha for the BI for the scores in the acute phase was 0.92.

(2) *Depressive Symptoms.* Depressive symptom severity was measured by using the Beck Depression Inventory Version II (BDI-II) [39]. The instrument consists of 21 groups of four statements by severity of the symptom (0–3), where the patient is required to select one in each group. The best possible score is 0. Cronbach's alpha for the BDI-II in the acute phase was 0.85. The BDI-II has been found to be an acceptable screening instrument for depression in stroke patients [40]. A cut-off value of 13 was used to categorize participants in this study as not depressed ($BDI \leq 13$) or depressed (classified as mild, moderate, or severe) [40].

(3) *Other Clinical Characteristics.* The patient's weight and height were measured in the hospital. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. The patients' use of sleep medication during the last three days in hospital, their past or present illnesses and medical diagnoses, and the date of hospital admission were collected from their medical records.

(4) *Prestroke Fatigue.* Prestroke fatigue was measured retrospectively by two items: "did you experience fatigue before you had your stroke" (yes/no), and if yes, "how long did you experience fatigue" (less than a week, less than three months, 3–6 months, and more than six months). Patients who reported fatigue lasting longer than three months before the stroke were defined as having prestroke fatigue.

2.3. *Statistical Analysis.* Differences between groups were assessed by chi-square (χ^2) for categorical variables or by *t*-test

for continuous variables. One-way and two-way repeated-measures analysis of variance (ANOVA) was used to assess the course of fatigue for the whole sample, for the two groups with low or high physical functioning, for groups with and without depression (BDI-II scores >13 versus those with BDI-II scores ≤ 13) and groups with and without prestroke fatigue lasting more than three months. In the two-way ANOVA analyses, the statistical model controlled for level of physical functioning (continuous variable), for depressive symptoms (continuous variable), and for prestroke fatigue (yes/no). For each time point, the fatigue scores were analysed for possible differences between the groups by a linear regression controlling for similar covariates as in the two-way ANOVA analyses. A Rasch measure of the FSS-7 [30] was used when FSS-7 scores were treated as a continuous variable; the mean scores are presented in the text and figures for ease of interpretation. The level of significance was set at $P < 0.05$ and all tests were two tailed. The data were analysed using SPSS for Windows Version 17.0 (SPSS Inc., Ill, USA).

2.4. *Ethics.* The study was approved by the Regional Medical Research Ethics Committee of Health East of Norway, the Norwegian Data Inspectorate, and the hospital units for approval of security of personal data. Informed written consent was obtained from all patients.

3. Results

Among the 95 patients in the sample, 56 (59%) were men and 39 (41%) were women. The mean age for the whole cohort was 67.8 years (standard deviation [SD] = 13.3) and did not differ significantly between men (66.0 years [SD = 12.8]) and women (70.4 years [13.0], $t = 1.64$, $P = 0.10$). Compared with the women, the men were more likely to have higher education, be in a paired relationship, and belong to a higher social class (see Table 1). Clinical characteristics at baseline are shown in Table 2 for the 95 participants who completed all four time points.

A previous report from the baseline data on the entire sample [6] showed that, except for a higher proportion of circulatory diseases and higher proportion of cases with severe fatigue among women, there were no differences in clinical profiles between men and women. The level of physical functioning at baseline ranged from 0 to 100, and 34.7% ($n = 33$) had high physical functioning. The depression scores ranged from 0 to 22 and 26 participants (27.4%) were depressed. Twenty-six of the patients (27.4%) retrospectively reported that they had prestroke fatigue lasting more than three months.

3.1. *The Course of Fatigue.* The mean FSS-7 scores by sex for the different time points are shown in Figure 1. The within-subject analysis showed that the patient's level of fatigue did not vary over time (Wilks' lambda = 0.99, $F [3, 87] = 0.38$, $P = 0.77$), and the slope did not differ by sex ($F [1, 89] = 0.01$, $P = 0.96$, partial $\eta^2 = 0.04$) after adjusting for level of physical functioning and prestroke fatigue. No sex difference in fatigue scores was found when separate analyses

TABLE 1: Sociodemographic characteristics of the sample at baseline.

Sociodemographic variables	Total sample N = 95	Men n = 56	Women n = 39	Statistics	P
Age, years, mean (SD)	67.8 (13.0)	66.0 (12.79)	70.41 (13.0)	$t = 1.64$	0.10
	N (%)	n (%)	n (%)	χ^2	
Level of formal education				4.78	0.04
<11 years	69 (72.6)	36 (86.4)	33 (84.6)		
≥11 years	26 (27.4)	20 (35.7)	6 (15.4)		
In paired relationship (yes)	65 (68.4)	43 (76.8)	22 (56.4)	4.42	0.05
Work status				1.88	0.23
Working	24 (25.3)	17 (30.4)	7 (17.9)		
Not working	71 (74.7)	39 (69.6)	32 (62.1)		
Social class (n = 91)				17.42	0.97
High (class I)	17 (18.7)	13 (24.1)	4 (10.8)		<0.001
Middle (class II)	13 (14.3)	1 (1.9)	12 (32.4)		
Low (class III)	61 (67.0)	40 (74.1)	21 (56.8)		

TABLE 2: Clinical characteristics at baseline of the study sample (N = 95).

Clinical variables	Mean (SD)
SF-36—Physical function (1–100)	61.8 (31.5)
ADL-P (Barthel Index) (1–20) (n = 87)	17.9 (3.9)
Depression (BDI-II sum score) (n = 94)	9.4 (7.4)
Body mass index (n = 85)	26.5 (5.2)
Stroke characteristics	n (%)
Stroke type	
Infarct	74 (77.9)
Haemorrhage	7 (7.4)
Unknown	14 (14.7)
Location (n = 72)	
Right	32 (33.7)
Left	26 (27.4)
Bilateral	14 (14.7)
Comorbidity (past or present)	
Prestroke fatigue	26 (27.4)
Endocrine	21 (22.1)
Circulatory	55 (57.9)
Respiratory	12 (12.6)
Digestive	9 (9.5)
Muscular	18 (18.9)
Other disease	38 (40.0)

of fatigue scores for each time point was assessed in separate multivariate linear regression analyses.

The course of fatigue among patients with low versus high scores on depressive symptoms is shown in Figure 2. There was no within-subject change over time (Wilks' lambda = 0.98, $F [3, 88] = 0.58$, $P = 0.63$). However, the patients without depression showed less fatigue than those with symptoms of depression ($F [1, 88] = 3.81$, $P = 0.05$, partial $\eta^2 = 0.04$) after adjusting for level of physical functioning and prestroke fatigue.

When fatigue was assessed in groups with and without depression by multivariate linear regression analysis, patients without depression reported less fatigue only at the six-month time point ($\beta = 0.19$, $P = 0.05$) compared with the acute phase ($\beta = 0.16$, $P = 0.08$). Results showed a similar trend at 12 months ($\beta = 0.15$, $P = 0.15$), but at 18 months there was no difference between the groups ($\beta = 0.05$, $P = 0.65$).

When the course of fatigue was compared between patients with low and high levels of physical functioning, there was no within-subject change in fatigue over time (Wilks' lambda = 0.94, $F [3, 88] = 1.91$, $P = 0.13$), as shown in Figure 3. However, there was a significant between-group difference ($F [1, 88] = 10.46$, $P = 0.002$, partial $\eta^2 = 0.10$) after controlling for depressive symptoms and prestroke fatigue. The scores differed significantly in the acute phase ($\beta = 0.39$, $P < 0.001$), at six-month ($\beta = 0.21$, $P = 0.04$) and 18-month ($\beta = 0.22$, $P = 0.04$) follow-up, but not at 12 month follow-up ($\beta = 0.11$, $P = 0.30$).

Mean scores for the course of fatigue among patients with and without prestroke fatigue are shown in Figure 4. Again, fatigue did not show any overall within-subject change over time (Wilks' lambda = 0.92, $F [3, 88] = 0.62$, $P = 0.60$). However, the main effect for the between-group comparison was significant, $F (1, 90) = 10.54$, $P = 0.002$, partial $\eta^2 = 0.105$. The fatigue scores differed in the acute phase ($\beta = 0.27$, $P = 0.01$), and at six months ($\beta = 0.20$, $P = 0.05$) and at 18 months ($\beta = 0.29$, $P = 0.008$), but was not significant at 12 months ($\beta = 0.16$, $P = 0.11$).

4. Discussion

To our knowledge, this is among the first studies describing the course of fatigue in patients with first-ever stroke. Longitudinal studies on poststroke fatigue have mainly reported the prevalence of poststroke fatigue at different time points [13, 41], and findings from previous studies are contradictory. While an increase in prevalence of fatigue during

the 18 months after a stroke has been reported [13], other studies find a lower prevalence [41]. A recently published longitudinal study [42] showed that the proportion of patients with fatigue in the acute poststroke phase (35%, $n = 38$) was similar to the proportion of patients with fatigue 1.5 years later (33%, $n = 36$).

The important new finding from our study is that patients report different trajectories of fatigue depending on their experience of prestroke fatigue and their level of physical functioning in the acute phase. These two clinical factors independently predicted the long-term course of fatigue in our sample.

The relationship between prestroke fatigue and poststroke fatigue has previously been reported in cross-sectional studies [5, 6]. However, a new finding from our study is that patients who reported prestroke fatigue showed a relatively high level of fatigue over time in the poststroke period, while patients with no history of prestroke fatigue showed a stable course of relatively low fatigue over time. When studying poststroke fatigue, it is important to take into consideration that the prevalence of fatigue in the general population is relatively high, and that fatigue measured in the early period after a stroke may not necessarily be caused by the stroke. Studies of the general population have found prevalence rates of current severe fatigue ranging from 14% to 38% [3, 43, 44]. A prevalence of 23% severe fatigue for the general population in Norway was reported using the same instrument (FSS reported) [4].

When the course of fatigue among patients with or without depression was assessed in our study, the differences in fatigue levels observed at the acute phase and at six-month follow-up were not evident 12 months after stroke. Another study [17] showed that depressive symptoms had a tendency to predict fatigue at one year after stroke. However, in that study, depressive symptoms were only borderline significant as a predictor ($P = 0.07$). Direct comparison between these studies is complicated because one of the studies included patients with recurrent stroke [42], while the other study had patients from a rehabilitation clinic [13] where the patients might have more impairment. Although several studies have shown that depression is related to high levels of fatigue [10, 13–15, 23], this association does not seem to be evident from a longitudinal perspective. Difference in fatigue levels in the acute phase between patients with no/low depression versus those with mild/high depression seems to disappear during the period between the acute phase and 18-month follow-up, although the difference in fatigue between patients with and without depression remains at six months after stroke. This would support Kirkevold's proposal [45] that the recovery from stroke occurs in three phases: stabilization, adjusting for the long-term effects of the stroke, and getting on with life. It is possible that both fatigue and depression are common responses to the experiences of the acute phase of stroke, with a positive relationship between them, while poststroke experience in the later stages may have an independent effect on fatigue and depression with no observable relationship.

In the acute phase, we found a higher proportion of women than men with severe fatigue [6], but no significant

differences between sexes in mean fatigue. This study showed that mean fatigue did not differ over time in relation to sex. Similar findings are reported in most other studies of poststroke fatigue [5, 15–18, 46]. However, other studies [11, 12] have shown that vitality is inversely associated with fatigue. Because female stroke patients reported lower vitality than men, it is possible that the observed effect of sex on fatigue may need to be examined further in terms of vitality. Further study of the relationship between fatigue and vitality is needed in order to interpret the sex differences in fatigue and vitality and to clarify the concepts of fatigue and vitality.

Our findings indicate that poststroke fatigue has different trajectories over time, depending on the patient's level of physical functioning, level of depressive symptoms, and particularly his/her history of chronic fatigue prior to the stroke. In studies exploring the aetiology and possible antecedents of poststroke fatigue, these factors need to be considered. For example, the aetiology of chronic fatigue might be different from fatigue that develops after stroke, and would require a different intervention approach. Fatigue needs to be studied more intensely in homogeneous groups during poststroke recovery.

Strengths of this study include the low attrition over 18 months and perhaps because of the large number of participants who were interviewed, there were no missing responses on any of the questionnaire items. One limitation with the study is that prestroke fatigue was measured retrospectively. Furthermore, the sample was recruited from only two hospitals in Norway. Although only patients with first-ever clinical presentation of stroke were included in the sample, and none of the participants had a history of clinical stroke, the CT findings showed that nine had signs of previous stroke. People who are interviewed face to face may have a tendency to give more socially acceptable responses than those who respond by means of a questionnaire [47]. A possible consequence of this may be under-reporting of depressive symptoms among those who were interviewed. However, at baseline, fatigue scores did not differ by interviewer.

A systematic review of empirical studies of poststroke fatigue [9] concluded that the fatigue experience should be conceptualized and studied as a multidimensional phenomenon including fatigue intensity, quality, timing, fluctuation, and long-term trajectory. In this study, fatigue was measured using the FSS-7 [30], an abbreviated version of the FSS scale [24]. As mentioned by Dittner et al. [48] and others, FSS is predominantly a measure of fatigue interference with daytime function. Thus, other dimensions of fatigue, such as severity or frequency, may have a different trajectory than the fatigue described in this study.

5. Conclusion

Because patients with and without prestroke fatigue experience a different but stable trajectory of poststroke fatigue, future studies need to control for prestroke fatigue experience to develop knowledge about the aetiology of poststroke

fatigue. Intervention studies should either control for pre-stroke fatigue experience or consider excluding patients with prestroke fatigue when studying the effect of interventions for poststroke fatigue. A more critical approach would be to partition out, both conceptually and in measurement, the components of fatigue that are generic and the components that are stroke related. It is possible that the presence of prestroke fatigue exacerbates the fatigue response after experiencing a stroke.

Acknowledgments

The Research Council of Norway (Grant no. 176503) and Buskerud University College, Drammen, Norway, funded this paper. This study is a product stemming from the Research Project: *Poststroke Fatigue* for which Dr. Hesook Suzie Kim is the project director and Drs. Grethe Eilertsen, Anners Lerdal, and Heidi Ormstad are the principal researchers. This paper was funded by the Research Council of Norway and Buskerud University College from 2006 to 2010. The authors acknowledge the support and assistance provided by research assistant Gunn Pedersen and various staff members of Buskerud Hospital Trust in Drammen and Oslo University Hospital, Aker in Oslo, Norway, in carrying out this research project. AL has received funding from the RCN (Leif Eriksson Scholarship Grant number 19256), the Norwegian Nurses Organization and the U.S., Norway Fulbright Foundation.

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