Post-stroke fatigue: Assessment, trajectories and associated factors

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS……...7

ABBREVIATIONS……...9

THESIS SUMMARY…….....11

LIST OF PAPERS……...13

1. INTRODUCTION……...14

1.0 Background……14

1.1 Stroke…….15

1.1. The pathophysiology of stroke and the relation to fatigue……....15

1.2 Fatigue…….....16

1.2.1 Fatigue: prevalence and definition …….16

1.2.2 Post-stroke fatigue (PSF): prevalence and definition…….16

1.2.3 Assessment of fatigue……..17

1.2.4 Courses of fatigue development post-stroke…….....19

1.3 Understanding mechanisms of post-stroke fatigue (PSF)……..19

1.3.1 Associations between demographic factors and PSF……...20

1.3.2 Associations between biomedical factors and PSF……..20

1.3.2.1 Cytokines and blood-components……..20

1.3.2.2 Stroke-types, lesion location and size of stroke……..21

1.3.3 Associations between comorbidities and PSF…….22

1.3.4 Associations between physical disabilities, residual neurological deficits

And PSF…….23

1.3.5 Associations between pain, quality of sleep and PSF…….23

1.3.6 Associations between psychosocial factors and PSF……..24

1.3.6.1 Psychological distress and PSF……...24

1.3.6.2 Life-stressors, self-efficacy beliefs, coping-strategies and PSF……25

1.3.7 Associations between cognitive impairments and PSF……..27

1.3.8 Associations between life-style factors and PSF……30

1.4 Models of post-stroke fatigue……...31

1.5 Treatment of post-stroke fatigue……34

2. AIMS……...35

2.1 Paper I……...35

2.2 Paper II……35

2.3 Paper III……35

3. METHODS……36

3.1 Participants and procedures……...36

3.1.1 Participants and procedures in paper I……36

3.1.2 Participants and procedures in paper II and III……..37

3.2 Measures……38

3.2.1 Outcome measures……..38

3.2.2 Demographic variables……40

3.2.3 Medical variables……40

3.2.4 Symptom-related measures……41

3.2.4.1 Measures of physical function, activities of daily living and subjective symptom burden……41

3.2.4.2 Psychological and psychosocial measures……42

3.2.4.3 Neurocognitive measures……43

3.3 Statistical analyses……44

3.3.1 Data analyses in paper I……...44

3.3.2 Data analyses in paper II……..…45

3.3.3 Data analyses in paper III……...46

3.4 Ethical considerations……47

4. SUMMARY OF MAIN RESULTS……....48

4.1 Demographic, clinical and stroke-related characteristics of the sample……48

4.2 Main findings from paper I: Trajectories of fatigue among stroke patients from the acute phase to 18 months post-injury: A latent class analysis……49

4.3 Main findings from paper II: A cross-sectional study exploring overlap in post-stroke fatigue caseness using three fatigue instruments: Fatigue Severity Scale, Fatigue Questionnaire and the Lynch' Clinical interview……..49

4.4 Main findings from paper III: Biopsychosocial factors associated with fatigue from the acute phase to 12 months post stroke…… 50

4.5 Summary of main findings across the papers……51

4.5.1 Prevalence and trajectories of PSF……..51

4.5.2 Factors associated with PSF in paper I, II and III……...52

5. DISCUSSION……..54

5.1 Discussion of main findings…….....54

5.1.1 Courses and trajectories of PSF……...54

5.1.2 Identification of fatigue-caseness using different instruments: Content and prevalence……55

5.1.3 Identification of fatigue-caseness using different instruments: Cut-off……..58

5.1.4 Factors associated with PSF at different time-points……..60

5.1.4.1 Associations between PSF and demographic variables……60

5.1.4.2 Associations between PSF, medical factors and stroke-related impairments……60

5.1.4.3 Associations between comorbidities, pre-stroke fatigue, sleep-quality and PSF……63

5.1.4.4 Associations between psychosocial factors and PSF……63

5.2 Post-stroke fatigue; disease specific or generic?.....65

5.3 Methodological issues; strengths and limitations…….68

5.3.1 Sample characteristics, sample size, and generalizability of study findings…..68

5.3.2 Design characteristics…….70

5.3.3 Use of self-report measures and performance-based methods for assessing cognitive function……70

5.4 Implications for the clinic……..71

5.5 Implications for research……...72

6. CONCLUSIONS…….73

7. REFERENCES……74

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ABBREVIATIONS

ADL: Activities of Daily Living

Barthel ADL/BARTHEL INDEX (BI): Barthel Index for Activities of daily Living

BDI: Becks Depression Inventory

Brief–COPE: Coping Orientation to Problems Experienced

CPSP: Central Post Stroke Pain

D-KEFS: Delis-Kaplan Executive Function System

ICD-10: International Classification of Disease-10th Edition

FAS: Fatigue Assessment Scale

FQ: Chalder Fatigue Scale

FSS: Fatigue Severity Scale

FSMC: Fatigue Scale for Motor and Cognitive Functions

GMM: Growth Mixture Modelling

HSCL-25: Hopkins Symptom Checklist Scale-25

MMSE: Mini Mental Status Exam

MOCA: Montreal Cognitive Assessment

NEL: Negative Life Events scale

NHISS: National Health Institute Stroke Scale

PROM: Patient Reported Outcome Measure

OR: Odds Ratio

PADL: Personal Activities of Daily Living

PSQI: Pittsburgh Sleep Quality Index

PSF: Post-stroke fatigue

ROC-curve: Receiver Operating Characteristic-curve

QOL: Quality of Life

RPQ: Rivermead Post Concussion Scale

SEB: Self-Efficacy Beliefs

TBI: Traumatic Brain Injury

TIA: Transient Ischemic Attack

TMT: Trail Making Test

WAIS IV: Wechsler Abbreviated Scale of Intelligence

THESIS SUMMARY

Fatigue is a frequent and severe symptom in stroke survivors, associated with poorer physical health, reduced quality of life and even increased mortality. Although post-stroke fatigue (PSF) is common and disabling, there is no consensus on definition, evaluation methods or interventions. Furthermore, the underlying mechanisms of PSF and the significance of different biopsychosocial factors in PSF development are not fully elucidated.

The overall aim of this thesis was to increase the knowledge about assessment, trajectories and associated factors of PSF to establish a better knowledge base for developing treatment strategies aiming at ameliorating PSF. The work is based on two longitudinal observational studies. In the first study, displayed in paper I, trajectories of PSF through the first 18 months post-stroke were investigated. The second study yielded the data for paper II and III. In paper II the overlap and differences in prevalence-estimates in fatigue-caseness using the Fatigue Severity Scale, the Fatigue Questionnaire and the Lynch Interview at one time-point in a sample of stroke-patients was explored. In addition, we investigated how PSF measured with these instruments were associated with different predictor-variables. In paper III, the associations of demographic, medical and symptom-related factors with PSF in the acute phase, at three and twelve months post-stroke were explored.

The first aim of the thesis was to explore whether subgroups of stroke survivors with distinct trajectories could be identified using Growth Mixture Modeling and secondly whether these subgroups differed on sociodemographic, medical and symptom-related characteristics. Paper I displays three distinct trajectories of PSF from the acute phase to 18 months post stroke, namely courses displaying low, medium and high fatigue. Belonging to the high fatigue-class was associated with pre-stroke fatigue, multiple comorbidities and not working. Belonging to a low fatigue-class was associated with few symptoms of depression and being more independent in personal activities of daily living.

Paper II displays a vast variance in prevalence of fatigue-cases in the same sample at the same time-point depending on which of three instruments was used to assess fatigue symptoms and cases. There was also a variance in the associations between being a

fatigue-case and the analyzed predictor variables using the different instruments, probably reflecting that they cover slightly different aspects of the PSF-experience. In paper III, the associations of demographic, medical and symptom-related factors with PSF at different time-points were explored. The findings suggest that PSF may be triggered, maintained or worsened by stroke-related impairments, psychological distress and/or maladaptive coping strategies. Furthermore, we found that significant PSF also occur in patients with minor stroke-sequelae.

In summary, this thesis gives insights into different trajectories of fatigue post-stroke. It also expands on current knowledge about which factors may serve as protective against PSF-development and which factors may render stroke survivors vulnerable for developing PSF, hereby suggesting possible targets for development of interventions aimed at ameliorating PSF. A special awareness should be on patients with minor stroke-sequale as they may have unmet need for follow-up, increasing the risk of PSF-development. The results in this thesis also demonstrate how different methodology yields a wide variance in identification of fatigue-cases, underscoring the importance of reaching a consensus on how to measure fatigue. Correct identification of fatigue-cases is crucial for understanding fatigue, its causes and for development of empirically based interventions. Further studies are warranted in larger samples, preferably multicenter studies, to allow for necessary increase in the sample size, to achieve consensus on how to measure fatigue. Methods should include a wide array of measurements, reflecting a biopsychosocial understanding of fatigue.

LIST OF PAPERS

This thesis is based on the following research papers which are referred to in the text by their roman numbers I-III:

Paper I Trajectories of fatigue among stroke patients from the acute phase to 18 months post-injury: A latent class analysis.

Paper II A cross-sectional study exploring overlap in post-stroke fatigue caseness using three fatigue instruments: Fatigue Severity Scale, Fatigue Questionnaire and the Lynch's Clinical Interview.

Paper III Biopsychosocial factors associated with fatigue from the acute phase to 12 months post stroke.

1. INTRODUCTION

To illustrate the experience of fatigue post-stroke, I will start with two excerpts from the Lynch Interview:

"I'm trying to live a normal life, but I cannot bear the slightest of noise. I was sensitive for sounds and light before as well, but it has gotten worse. I get so tired from having visitors over. I get tired every day, and some days are worse than others. I usually gets worse throughout the day, depending on what I am doing. If I go grocery shopping, I get totally exhausted. Doing light housework is enough. My sight hampers me a lot. I now have double vision after my stroke and it gets worse when I get tired. I have also become more anxious."(Woman, 72 years)

I get more easily tired, I get easily irritated, especially in situations with sounds or in situations that demand a high degree of concentration. My head is more tired, it feels like I have a slight dizziness and like I have cotton in my head. I have started working 40%. In my job, there is a lot of impressions and sounds and I have become very sensitive to sounds. The sum of everything makes me very tired by the end of the day". (Male, 53)

(Excerpts from answers on the questions on The Lynch interview)

1.0 Background

Stroke is among our most prevalent and serious diseases, the second most common cause of death and a major reason for disability worldwide [1, 2]. In Norway, about 11 000 patients are admitted to hospital each year with an acute stroke [3]. Globally, the incidence of stroke is increasing. Epidemiological projections estimate that the number of stroke survivors will rise to 77 million globally by 2030 [4]. The incidence of ischemic stroke in young adults is also rising [5]. Outcomes after stroke vary depending on stroke lesion site and severity, and access to acute medical treatment, but include motor handicaps, cognitive impairments, depression, fatigue and risk of early hospitalization or institutionalization [4].

Fatigue is a common and severe symptom following stroke, affecting about 48% (CI 42-53%) of stroke survivors [6]. Post-stroke fatigue is associated with a reduced quality of life and poorer physical health [7], it impacts in rehabilitation outcome [8] and is

even associated with increased mortality 2 years after stroke onset [9]. Due to the lack of knowledge about the underlying factors that may contribute to PSF, there is yet not an established treatment [10]. In a recent study of 731 stroke patients and caregivers at 12-months follow-up, post-stroke fatigue was among the top-priority of research [10], underscoring the need of more knowledge about the subject.

The work presented in this thesis aims to increase knowledge about trajectories of post-stroke fatigue, methodological issues in measuring PSF and which factors are associated with PSF at different time-points. Hopefully, this will contribute to the development of empirically based interventions aiming at ameliorating PSF. In this introduction, the current status of how to measure fatigue and knowledge regarding the underlying factors that contribute to PSF at different time points will be summarized.

1.1 Stroke

1.1. The pathophysiology of stroke and the relation to fatigue

A stroke is caused by impaired supply of blood to the brain preventing brain tissue to get necessary oxygen and nutrients [11]. Stroke is characterized as a neurological deficit of cerebrovascular cause that persists beyond 24 hours [12]. Strokes can be either hemorrhagic, due to bleeding caused by rupture of a blood vessel, or ischemic, due to lack of blood flow. About 98% of strokes are ischemic. In an ischemic stroke, blood supply to a part of the brain is decreased either by a thrombosis, i.e. obstruction of a blood vessel by a blood clot that has formed locally [13], or by an embolism, i.e. obstruction caused by an embolus formed elsewhere in the body [12]. About a quarter of ischemic strokes are cryptogenic [14], i.e. the origin of the stroke is unknown [14]. In addition to lack of oxygen, causing brain cells to die within minutes [5], a cascade of neurodegenerative changes follows an ischemic brain injury such as a stroke. These subsequent events progress even if the blood flow is restored. Changes in the ionic balance of affected regions lead to a variety of pathological events, including a release of glutamate [15].

Changes in the metabolism and/or glucose utilization of an injured hemisphere may persist for days and have severe effects on brain functioning also in otherwise healthy tissue, leading to more severe impairments than what would be expected from brain scans. Reparative processes may begin almost immediately after the cell death. Stem

cells may be stimulated to increase division in the sub-ventricular zone and migrate to the injury. Microglia invade the damaged region via the vascular system to clear away degenerative debris, a process that may take months to complete [16].

1.2 Fatigue

1.2.1 Fatigue: prevalence and definition

Fatigue is a common symptom in the population in general, and even more prevalent in different pathological/medical conditions. The prevalence of fatigue in the Norwegian population in general ranges from 14-23 % [17], whereas reported prevalence rates of fatigue in relation to cancer, multiple sclerosis, fibromyalgia, and other chronic conditions ranges from 40 to 74% [18].

Fatigue differs from normal tiredness in being chronic, persistent and have an impact on activities of daily living [19-21]. It is a multidimensional condition which represents a complex interaction of biological, motor-perceptive, cognitive, emotional, psychosocial and behavioral factors, and is consequently challenging to define [22]. Severely fatigued patients report limitations in physical, mental, social functioning, and often report fatigue to be among their most debilitating symptoms [13].

There is currently no consensus among clinicians or researchers on one definition of fatigue. Different definitions to a varying degree include fatigue-related symptoms and the impact of fatigue. Fatigue is commonly described as subjective lack of physical and/or mental energy that interferes with usual activities and as an early exhaustion and weariness which is usually not ameliorated by rest [23-25].

Fatigue can be classified as objective or subjective. Subjective fatigue is described as a feeling of early exhaustion, while objective fatigue refers to observable and measurable decrement in performance during physical or mental tasks [25]. Depression and fatigue has overlapping symptoms and consequences, but in the recent years, fatigue has been distinguished from depression [26-28].

1.2.2 Post-stroke fatigue (PSF): prevalence and definition

Fatigue is a common symptom in stroke survivors. A systematic review that included 49 studies, reported prevalence rates between 25-85%, the wide prevalence estimate

possibly reflecting a variation in stroke severity between the studies, different methodology for defining stroke-cases and assessment at different time-points post stroke [6]. A recent meta-analyses of 35 studies using Fatigue Severity Scale with a cut off of 4 or more resulted in a prevalence estimate of 48% (95% CI: 42-53%) [6]. Although PSF is frequent and disabling, there is still no consensus on definition [29], standardized evaluation method or treatment [26, 30-33]. The variation in assessment of PSF hinders comparison of results between studies.

The underlying mechanisms of PSF and the significance of different biopsychosocial factors in PSF development are not yet fully understood. Earlier literature has shown associations between PSF and low mood [34-36], female gender [33, 37-39], biological contributors [40, 41], poor sleep-quality [36, 42, 43], stroke-related impairments [44-46] and cognitive dysfunction [44, 47-49]. There is, however, a lack of longitudinal studies of PSF and few theoretical models.

Few of the definitions used in literature on PSF is specific to stroke [26]. Lynch and colleagues [50] created a case-definition of PSF based on interviews with stroke-patients:

"For hospital patients: Since their stroke, the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities (for inpatients this may include therapy and may include the need to terminate an activity early because of fatigue).... For community-dwelling patients: Over the past month, there has been at least a 2 week period when patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. And this fatigue has led to difficulty taking part in everyday activities."[50]·

PSF is considered a primary fatigue, i.e related to changes in function following a stroke. However, several contributing pre- and comorbid contributing factors have been proposed, such as pre-stroke fatigue, pain [51-53], de-conditioning, medication side effects, sleep disorders and depression [52-54].

1.2.3 Assessment of fatigue

Many different self-report fatigue instruments are currently used to assess fatigue. There are about 50 different fatigue scales used in research studies [8]. Patients are often

dichotomized into belonging to a non-fatigue or fatigue group by a cut-off on a scale, and different studies use different cut-off criteria [55].

The Fatigue Severity Scale (FSS) [56] is the most frequently used instrument for measuring fatigue in observational stroke studies [55]. It was originally developed for measuring fatigue in clinical populations such as multiple sclerosis or systemic lupus erythematosus. The FSS has been described as a valid and reliable instrument for measuring fatigue in the stroke population [57, 58]. Other frequently used measures include the Fatigue Impact Scale [59] and the Fatigue Assessment Scale [60]. Some fatigue-scales aim at assessing both mental and physical fatigue. One of these scales is the Chalder Fatigue Questionnaire (FQ) [61], which is a commonly-used fatigue measure across different patient populations. The Multidimensional fatigue Inventory (MFI) and the Fatigue Scale for Motor and Cognitive Functions (FSMCF) [62] are other less used self-report instruments with subscales for mental and physical fatigue [63].
A recent analysis of 11 fatigue instruments yielded 83 unique items covering four different dimensions of the fatigue experience, *characteristics* (quality and diurnal variations, degree and presence of fatigue related symptoms), *the severity and impact dimension* (how much the fatigue bothers the person affected), *the interference-dimension* (activities that are affected) and *the management and coping-dimension* (how the fatigue is dealt with) [64]. The majority of instruments used for measuring PSF covers only the characteristics or interference-dimension, and some, such as the VAS-F or the SF-36 Vitality, only cover the characteristics-dimension [64].
Self-report instruments are convenient for screening and research, however, clinical interviews allow for a deeper exploration of the patient's experience [65]. Lynch et al. [50] created a semi-structured clinical interview that includes operationalized questions about the fatigue experience (Lynch Interview) in order to develop a case definition for post-stroke fatigue.

As mentioned earlier, fatigue can be described as subjective or objective. Objective physical measures may be used to investigate the mechanisms of fatigue following a specific exercise [66]. There are few existing procedures to assess mental fatigue objectively, although eye tracking, electrophysiological indicators such as

electroencephalography or brain connectivity patterns have been used to quantify mental load and fatigue [67, 68].

1.2.4 Courses of fatigue development post-stroke

To date, there are relatively few studies on short and long term courses of fatigue-development post-stroke [69]. It has been proposed that more patients report fatigue in the later stages post-stroke as they start to resume normal activities, but there are conflicting evidence around this [6].

Wu et al [8] have suggested different temporal courses of PSF where some have early fatigue, some recover, others have persistent fatigue while yet others develop late onset fatigue. In line with this, a recent review of prevalence of PSF over time [6] found that two longitudinal studies reported a decrease of fatigue levels [70, 71], one study found an increase [72] and two studies found fluctuation of fatigue-levels over time [73].

The current knowledge base also includes studies using latent class growth mixture modelling, such as Seves et al. [74], who identified distinct trajectories of PSF over the first 18 months post-stroke. The authors found a high, low and recovery-trajectory the first year post-stroke. Comparing results from studies on trajectories is however challenging as they use different methods, have different sample-sizes and designs [6]. Clinically, identifying those at risk for persistent fatigue may be important for tailoring interventions. Factors influencing fatigue the courses of fatigue are complex, and it is likely that different factors may be associated with PSF at different time-points [8]. However, the causes of fatigue at different time points have not been fully elucidated.

1.3 Understanding mechanisms of post-stroke fatigue (PSF)

In a biopsychosocial model illness and health are results of biological, psychological and social factors [75]. PSF probably results from complex interactions between demographic, biological, psychosocial, physical, neurocognitive and behavioral factors [29, 76]. To identify patients at risk of developing PSF, a deeper understanding of the phenomenon and its associated variables at different time-points is warranted.

1.3.1 Associations between demographic factors and PSF

Contradictory findings have been reported on the relationship between age and PSF [77]. In some studies, no relationship is found between age and PSF [50, 78], whereas older age was related to a higher degree of fatigue in a study controlling for gender, depressive symptoms and comorbidity [79]. In another study, a weak U-shaped relationship was found between age and PSF, with the youngest (<60 years) and oldest (>75) groups being most fatigued [77].

Maaijwee et al. [80] found that 40.1% in a sample of stroke survivors ≤50 years suffered from fatigue. They argue that fatigue may be more pronounced in younger stroke survivors as they are in the midst of their working years and active family life. Thus, they may have to cope with higher demands than older stroke survivors do. This is supported in a recent study that found that fatigue was common among person who had returned to work, and that it affected their everyday life [38]. Persistent fatigue is, however, also associated with inability to resume working [81].

There is also conflicting evidence regarding the association between gender and PSF. Although some studies have shown a predominance of PSF in women, [38, 39, 50, 51, 53, 78, 82, 83], other studies have reported no difference in fatigue prevalence between men and women [84-86].

1.3.2 Associations between biomedical factors and PSF

1.3.2.1 Cytokines and blood-components

A handful of studies have explored the relationship between stroke-induced inflammation and PSF [41, 87]. Cytokine-induced sickness behavior may be advantageous after sickness or injury because it results in rest. Prolonged production of inflammatory cytokines, however, seem to be associated with depression and chronic fatigue [88].

Elevated plasma high-sensitivity C-reactive protein-levels in the acute phase were associated with fatigue 6 months post stroke in one study by Liu et al [89], suggesting that these elevations predicted PSF. In a study by Ormstad et al., [40] levels of various cytokines and other blood components present in the acute phase following ischemic stroke was found to predict fatigue 6 and 12 months after stroke. The relationship

between cytokines, blood components and PSF disappeared after 12 months, while mean fatigue scores still persisted in many cases, thus, other factors seemed to contribute to the sustained levels of PSF [40]. In a recent study by Gyawali et al [90], the score on FAS was significantly associated with levels of cytokines and high-sensitivity C-reactive protein. However, this relationship was no longer statistically significant once entered into a multivariate analyses that included cardiovascular covariables. It has also been proposed that as a result of an ischemic event, there is decreased activity of hypothalamic orexin neurons, which is associated with fatigue/lethargy [91]. Furthermore, changes in glutamate transmission may be involved in mental fatigue [92].

1.3.2.2 Stroke-types, lesion location and size of stroke

"Stroke" encompasses different sub-diagnoses; ischemic, hemorrhagic and clinical stroke. Some patients receive revascularization therapy, while other do not, and the size and sites of stroke-lesion differ widely. It is possible that differences in stroke-types and severity may yield different degrees of fatigue. In a recent review of prevalence of stroke, an unexpected outcome was the high difference in proportion of PSF between patients with hemorrhagic stroke (66%) and those with ischemic stroke (36%). There are not yet sufficient data to fully understand this difference [6].

Fatigue symptoms have not been associated with infarct volume [40, 83, 93]. However, several studies indicates that presence of a brain lesion may be important in the etiology of PSF [94]. One population-based study showed that fatigue was more frequent after mild ischemic strokes than transient ischemic attacks (TIAs). Another study found that fatigue was less frequent in those who had their first stroke compared to those who had recurrent strokes [95]. There are, however, also studies that indicate that cognitive impairments and fatigue may be present after TIA or minor infarcts [11, 96-98] and persist after apparent full neurological recovery [99]. Interestingly, one study found fatigue to be more severe in patients with radiologically unconfirmed infarctions. Possibly, an unconfirmed stroke leads to less acknowledgement and less rehabilitation [40, 100].

It is unclear whether receiving acute revascularization therapy (thrombolysis and/or mechanical thrombectomy) is associated with less PSF. In a sample of patients who had received revascularization therapy, fatigue was reported in about a third of the patients [49].

The relationship between lesion location and PSF is uncertain [101]. In a study by Delva et al. [102] neither infarct volume nor or infarct localization were found to be associated with PSF.

However, significant associations between severity of white matter lesion and risk of PSF have been found [103]. In a study of 334 patients 3 months post stroke, basal ganglia infarct was found to be an independent predictor of PSF. A systematic meta-analysis found no robust relationship between lesion location or laterality and PSF [104]. Recent studies go beyond the lesion-site approach and investigates brain activity and connectivity in relation to PSF. It is hypothesized that striatal-thalamic-frontal cortical networks may be involved in the neuroanatomy of fatigue [45, 76, 98, 105-107]. In a recent study, lesion location located in the right thalamus was found to be an independent predictor of PSF 6 months post-stroke, but not in the acute phase [108]. Furthermore, PSF has been associated with posterior hypoactivity and prefrontal hyperactivity, possibly reflecting a relationship between PSF and impaired executive and/or visual functioning [105].

1.3.3 Associations between comorbidities and PSF

A recent meta-analysis concluded that PSF was largely attributable to having multiple comorbidities [109]. Many stroke survivors also have chronic conditions such as hypertension, diabetes mellitus and heart conditions that may influence fatigue [54, 110, 111]. One study found that while early fatigue might be attributed to stroke severity, chronic fatigue is associated with medical comorbidities and medication use [112]. Comorbid vascular factors may contribute significantly to persistent fatigue, implicating that these should be targeted and treated early following stroke [113]. Other conditions, such as fibromyalgia, multiple sclerosis, lupus and depression are in themselves associated with fatigue [18]. Some stroke-survivors may thus already suffer from fatigue from other medical conditions.

Some of the factors that are commonly associated with fatigue in different conditions are the same. These generic factors, such as sleep-disturbances, depressive symptoms and pain, are also common in the general population and may contribute to fatigue both pre- and post-stroke [18]. Furthermore, several studies show that pre-stroke fatigue itself is a strong predictor of PSF [51, 114-117].

1.3.4 Associations between physical disabilities, residual neurological deficits and PSF

Stroke is associated with functional decline [118], and the severity of fatigue is associated with the severity of disability [33, 44-46, 118, 119]. At least one third of stroke survivors remain impaired in personal activities of daily living (PADL) [120]. Following stroke, motor impairment can negatively affect balance and the ability to ambulate. Contributing factors to impaired mobility and independency in PADL include hemiparesis, hemiplegia, sensory disturbances, ataxia, apraxia, spasticity, cognitive impairments, and visual perceptual deficits. Approximately 35% of survivors with initial leg paralysis do not regain useful function.

Although improvement may continue for a long time post-stroke, disability levels tend to stabilize 6 months post stroke [121]. In a meta-analysis by Wondergem et al. [122], improvement in PADL-function mainly seemed to occur between three and twelve months post stroke. Return of motor capacity can be either through recovery, use of new movement patterns or through substitutes such as assistive devices to replace lost motor function [123]. In individual patients, return of motor capacity may be a combination of compensation and substitution [124]. Fatigue can thus be attributed both to the increased effort that is associated with use of new movement patterns and to coping with impairment in PADL and everyday life [22, 44, 125].

Whereas improving function may be a target for interventions aimed at reducing fatigue [45], the presence of fatigue in stroke patients with little or no motor deficit suggests that fatigue at least in some patients, is most likely attributable to other factors [22]. A study by Lerdal et al. [126] indicates that level of fatigue in the acute phase may also predict PADL-function at 18 months post stoke. A possible explanation for this may be that fatigue-related symptoms impact on motivation for rehabilitation. Fatigue, cognitive dysfunction and depressive symptoms seemed to have a negative impact on PADL even seven years post stoke [127].

1.3.5 Associations between pain, quality of sleep and PSF

Pain affects 20- 45% of stroke patients and is associated with fatigue [128-130], depression and a lower quality of life [52, 131]. Pain is probably underdiagnosed and undertreated, and post-stroke pain problems include central post-stroke pain, spasticity, contractures, headache and shoulder pain [130]. In a study on the associations between stroke and pain by Miller et at [132], 45% of the participants reported pain, and 34%

reported combined fatigue and pain. Both fatigue and pain are associated with less optimal outcomes of rehabilitation [132].

Some patients may suffer from central post-stroke pain (CPSP), some from musculoskeletal pain, and some patients suffer from both types of pain. CPSP was associated with low quality of life in a sample of young stroke patients [133]. Spasticity is common in stroke-patients affecting approximately 40% after first-ever stroke [134, 135]. There seem to be little research on the relationship between spasticity and PSF, however, one study found that fatigue in stroke-patients was related to motor-functions and ability to perform daily activities. Motor function and PADL-function was associated with spasticity and pain [136].

In general, severity of fatigue post stroke seem to worsen with addition of symptoms such as pain, fatigue and depression [52].

Poor sleep quality is an independent predictor of fatigue [42, 43, 137] . A study of sleep-wake patterns in the acute phase after stroke showed that both hypersomnia and insomnia may occur, as well considerable amounts of waking up during the night [138].

1.3.6 Associations between psychosocial factors and PSF

1.3.6.1 Psychological distress and PSF

Depression is common after stroke, affecting approximately 30% of stroke survivors [35, 100, 139, 140]. It has been found that the risk of depression is highest at 3 months post stroke. [141]. Further, depression tends to persist after 6 months among patients with mild to moderate stroke [142]. A strong relationship between depression and PSF has been described, and the association has been extensively studied [33, 34, 54, 69, 99, 143].

Fatigue and depression are often concomitant, and in a review-article by Ponchel et al.,[29] only 3 of 48 studies failed to find an association between depression and PSF [70, 128, 144]. There is, however, not a one–to one relationship, as fatigue is observed in in patients who are not depressed [78, 145, 146] and there are fatigued patients who do not have any depressive symptoms [147].

The temporal relationship between depression and PSF is not well understood [100, 148]. For some, pre-stroke depression might constitute a risk factor for PSF [8, 35, 53]. Depression may also be a maintaining factor for long-lasting fatigue [103].

Furthermore, depression may be a consequence of fatigue if PSF impacts on ability to take part in various aspects of life.

Depression and PSF may share some common risk factors, biologically and psychologically [149]. In a recent study on factors affecting PSF, linear regression analyses showed that degree of depression and degree of inflammation were significantly associated with PSF [143]. There is evidence for inflammation impacting on dopamine, norepinephrine and serotonin neurotransmission. Dysfunction in these monoamine networks may lead to reduced motivation and anhedonia in depression [88], symptoms that may also be present in severe fatigue. Recently, it has been proposed that inflammatory processes may be involved in neuropsychiatric symptoms such as fatigue, depression, and anxiety in long-Covid as well [150].

Questionnaires and interview-guides assessing either depressive symptoms or fatigue often have similar items such as questions about reduced initiative/motivation, tiredness and impaired sleep-quality. In addition, fatigue often constitutes a criteria for depression on many scales [22, 151]. This overlap in symptoms and in items in questionnaires makes the phenomena challenging to distinguish if using cut-off scales alone.

The relationship between anxiety and PSF has been less extensively studied than the one between PSF and depression [29]. However, there are studies that show an association between anxiety and PSF [53, 80, 147, 152].

1.3.6.2 Life stressors, self-efficacy beliefs, coping-strategies and PSF

Depression, anxiety and PSF may share common risk factors such as life stressors, low self-efficacy beliefs and maladaptive coping strategies [8]. For instance, life stressors such as comorbidities, illness or death of loved ones, financial problems or interpersonal stress are among the strongest risk factors for depression [153, 154]. Although psychological stress is a risk factor for depression, and depression is associated with fatigue, to our knowledge there exists little research on how life-stressors are associated with fatigue-severity after stroke. However, in a recent study, patients with severe fatigue were more likely to report stressful life-events in the previous 6 months than those less fatigued [154].

Self-efficacy beliefs (SEB) and coping-strategies are constructs that has received attention in the management of several chronic diseases [155-163]. Having a stroke

represents a potential life stressor, and self-efficacy beliefs and coping strategies may influence to which degree this leads to fatigue or depression post-stroke.

Self-efficacy is described as the belief people hold about their capabilities to exercise influence over their life and events that affect their lives [164]. Low self-efficacy beliefs is shown to be associated with less optimal recovery and lower quality of life [155]. Patients and people in general form expectations about possible future actions. Inability to engage in for instance physical exercise despite potential benefits may be accounted for by poor self-efficacy beliefs [165].

A recent study found that self-efficacy beliefs, resilience and stroke-impact together explained 20.6% of the variance in PSF [166]. However, research on self-efficacy beliefs and stroke is not extensive, and the evidence that exists mostly focuses on the role of self-efficacy on belief in the ability to be independent in PADL and to attain improvements in physical function.

Low self-efficacy beliefs can be associated with PSF either directly or indirectly through more dependency in PADL, less recovery in physical function or depression. A higher belief in one's ability to avoid falling (fall self-efficacy beliefs) was associated with fatigue in one study [125]. Another study found that lack of confidence in controlling one's health was associated with more severe fatigue [79].

The construct of coping strategies is closely related to that of self-efficacy beliefs. Coping strategies are often operationalized as either "avoidant coping" or "approach coping". Avoidant coping strategies include denial, substance use, venting, behavioral disengagement, self-distraction and self-blame. Approach coping strategies include problem solving, positive reframing, planning, acceptance, seeking emotional support and seeking informational support [167]. Avoidant coping is associated with being less effective at managing anxiety and stress than approach coping, and approach coping strategies are considered more adaptive.

Higher levels of PSF has been associated with self-blame and focusing on own emotions [168] and passive coping is also associated with a lower quality of life [169]. Maladaptive coping has also been associated with more symptoms of post-traumatic stress, which indirectly may be associated with more severe PSF [98, 170]. Coping styles were in one study associated with a higher level of subjective cognitive complaints. Subjective cognitive complaints adversely affected quality of life and were associated with more severe PSF [171].

A study on fatigue following traumatic brain injury demonstrates the importance of taking into account protective factors which may serve as a buffer against fatigue. Among these are the ability to perceive the future as manageable and have high self-efficacy [172].

All in all, psychosocial factors may serve as both vulnerabilities and buffers in face of potential life-changes as consequence of a stroke. Identifying which factors put patients at risk and which factors may serve as protective, also have implications for treatment strategies to prevent or alleviate development of PSF.

1.3.7 Associations between cognitive impairments and PSF

As many as 80% of stroke survivors may suffer from cognitive impairments post-stroke [173, 174]. This may include difficulty with psychomotor speed, attention, executive or visuospatial function [175]. While some patients display stable cognitive function over time post-stroke [176], others cognitively improve over the first year [177], while yet others deteriorate [177].

PSF, and fatigue in general, has one mainly physical dimension and one mainly mental dimension, often described as a disability to sustain attention over time [178]. The latter form of fatigue is often associated with sleep disorders, pain, affective and/or cognitive alterations [88]. According to the "coping-hypotheses" suggested by van Zomeren [179] fatigue may be triggered by energy expenditure during mental tasks in patients with cognitive deficits. However, there are relatively few studies exploring how cognitive impairments impact on PSF-courses. Moreover, the results of the existing studies are inconclusive [11, 47-49, 180-182]. The different results may be due to use of different methods to assess cognitive function, different ways of categorizing fatigue, different ways of categorizing data on cognitive function, data collected at different time-points post-stroke and heterogeneous samples. This makes the results difficult to compare, and also hinders a clear understanding of the relation between cognitive impairments and PSF [181].

In some studies, cognitive screening-instruments are used [33, 180, 183], while other studies use more extensive neuropsychological assessment batteries [47, 181, 184]. Mini Mental Status Exam (MMSE) is sometimes used in studies, despite being a screening measure of global cognitive status with ceiling effects [185]. Furthermore, it

does not assess attention, executive function and processing speed [47, 181], and patients may thus be misclassified as not having cognitive impairments. On the other hand, stroke patients may have low scores due to focal impairments as the MMSE has items that require verbal answers, writing and visual attention [186].

The Montreal Cognitive Assessment (MOCA) is a screening instrument that seems to be better than the MMSE at detecting cognitive deficits post stroke [187], and one study did find a significant association between scores on the MOCA and PSF in a sample of ischemic stroke patients who had received acute vascularization therapy at 6 months post stroke [49]. Nevertheless, there are studies using the MOCA in the acute phase [180] and three months post stroke [183] that did not find a significant association between the results and PSF. As screening instruments, it is likely that neither the MMSE nor the MOCA may detect more subtle cognitive deficits. Furthermore, the total score on the MOCA may also be affected by visuomotoric impairments [186].

Up to 60% have visual impairments such as visual field defects, double vision or nystagmus [188].Visual problems may affect daily life through loss in confidence, accidents and fear of falling [189], as well as potentially causing fatigue. A strong association has been found between PSF and binocular visual dysfunction in one study. It may be that dysfunction in frontal-occipital networks may cause visual dysfunction and fatigue [45].

Slow visual tracking and impaired fine-motor control may make both mental and physical tasks more effortful and thus cause fatigue. Previous studies on traumatic brain injury have found that impaired visual tracking is associated with fatigue [190]. It is likely that the same mechanisms would apply for stroke. A recent study found that stroke-survivors with prominent self-reported visual problems were more likely to report fatigue 3-4 years post-stroke. It is suggested that visual rehabilitation may contribute to fatigue-reduction in stroke-survivors with visual impairments [191].

To date, there are few studies on how impairments such as neglect, apraxia and aphasia may be associated with PSF. Some patients with focal cognitive impairments may be excluded from studies as they may have an overall impaired function that hampers data-collection or they are perceived as too fragile for participation.

Neglect, i.e., paying insufficient or no attention to the contralateral side of the stroke, is estimated to affect as many as 30% of stroke survivors [192]. Apraxia is a cognitive-

motor disorder that impacts the performance of learned, skilled movements and is not uncommon after stroke [193]. About 20-30% of stroke patients have aphasia, i.e the loss or impairment of language caused by injuries or pathology in the brain [194]. Patients with aphasia are often excluded from studies as they may not be able to respond to questionnaires or comprehend information about the study. Speech-language pathologists, however, frequently observe signs of fatigue in their clients with aphasia and perceive that client fatigue impedes therapeutic interventions [195].

Some stroke-related cognitive impairments, such as attention, information-processing and executive function, have been more studied in relation to PSF. It has been suggested that attention and information-processing speed is associated with fatigue [48, 80, 182, 196, 197]. Furthermore, impaired working memory, attentional and executive function has shown association with PSF or TBI in some studies [47-49, 196, 198, 199]. In a sample of 142 young stroke-survivors, cognitive dysfunction was found to be an important contributor to long-term work-disability and more fatigue [197]. A recent meta-analysis of the relationship between cognitive impairment and fatigue after acquired brain injury, including studies on patients with TBI, stroke and subarachnoid hemorrhage, found weak associations between fatigue and information processing and attention, with an overall pattern of fatigue being associated with cognitive slowing on tasks on sustained attention. They concluded, however, that there is a need of more focused research on specific cognitive domains to understand the mechanisms of fatigue [200].

A prospective cohort study on young stroke survivors found, a bit surprisingly, that better performance on cognitive assessment predicted more fatigue 10 years after stroke. According to the authors, this indicates a dissociation between fatigue and fatigability among stroke patients [201, 202]. Cognitive tests are often structured and usually lasts for a short amount of time, thus the result may not always capture subtle cognitive impairments or ability to stay focused over time [203, 204]. As many patients report increased fatigue while engaging in a task, mental fatigue may be associated with a vulnerability to sustained effort rather than an impairment in information processing per se [184]. These cognitive alterations may be “invisible symptoms”, i.e cognitive or emotional problems that may be overlooked, leading to too high expectations for performance [205].

Subjective cognitive complaints are associated with reporting a high degree of fatigue one year post stroke. A study of patients with mild stroke by Rijsbergen et al. [206] showed that subjective cognitive complaints remained stable from three to twelve months post stroke although objective cognitive function improved. The study also showed that high levels of psychological distress, including physical, cognitive or emotional changes, was an independent predictor of subjective cognitive complaints [206].

Anosognosia, the lack of awareness of motor, visual or cognitive impairments in patients with neurological diseases, occurs up to 85% of right-hemisphere stroke patients and in up to 17% in patients with left-hemisphere stroke [207]. Anosognosia is associated with poor functional outcome [208]. The association between anosognosia and fatigue is not clear, but a lack of awareness of impairments will likely influence self-report of different symptoms post-stroke [209], possibly also the self-report of fatigue.

All in all, inconsistency in measures of cognitive function and fatigue makes the interpretation and comparison of the results difficult. However, the associations between fatigue and cognitive deficits is of interest in elaborating future interventions and therapeutic strategies such as cognitive rehabilitation aimed at ameliorating fatigue.

1.3.8 Associations between life-style factors and PSF

Life style both pre- and post-stroke may have impact on the degree of fatigue. A low level of activity pre-stroke has been associated with higher levels of PSF in several studies [69, 210, 211], and being physically active is also associated with less fatigue post stroke [211-213].

Sedentary behavior is any waking behavior with low energy expenditure such as sitting, lying or reclining posture and is associated with poorer health outcomes and higher levels of mobility disability. Sedentary behavior may be due to fatigue or pain [214], and stroke survivors have a tendency to be more sedentary than age-matched controls [210]. Fatigue in itself may also lead to sedentary behavior that in turn leads to less optimal rehabilitation and possibly more fatigue and/or pain.

Interventions aimed at increasing function post stroke encourage an increase of activity level [215]. Physical activity is also recommended as it along with other lifestyle

factors, such not smoking and reduced alcohol consumption, is associated with reduced risk of new cardiovascular events, encourages socialization and increases quality of life [74, 210]. A recent review-article concluded that fitness, such as aerobic fitness, muscle endurance, muscle strength and body composition, might protect against PSF and that higher PSF is associated with impaired fitness [216]. In the few studies conducted on interventions aimed at ameliorating PSF, graded physical activity is usually included as a treatment strategy [217, 218]. Graded exercise is also a common intervention in chronic fatigue syndrome. Along with cognitive therapy, graded exercise has been shown to moderately affect fatigue-levels [219].

1.4 Models of post-stroke fatigue

Models of fatigue in general differentiate between pre-disposing, triggering and maintaining factors [8, 18]. Further, the existing models of PSF are biopsychosocial, including biological, psychological and social perspectives on fatigue-development [8, 100]. Longitudinal studies on the factors associated with early and late fatigue are still scarce [69], and there are few conceptual models of PSF.

Based on a review of studies of PSF, its associations and its courses, Wu et al. [8] proposed a theoretical model of fatigue. They identified three fatigue-courses; persistent PSF, recovery and late-onset fatigue. Furthermore, they described that a myriad of biopsychosocial and behavioral factors may affect fatigue, and that it is important to consider which factors may influence fatigue at different time-points (see Fig1). Similar biopsychosocial models have been suggested for understanding fatigue following traumatic brain injury [220]. Some associated factors are demographical, such as age, gender and educational level. Others include personality and behavioral factors such as self-efficacy beliefs and coping strategies. Some factors may be present pre-stroke, such as depression, pre-stroke fatigue, comorbidities and life-style factors, other as co-existing, such as pain and poor quality of sleep. Yet other factors are environmental, such as access to social support, rehabilitation and treatment, while some factors are associated with the stroke itself, such as residual impairments [8]. Hence, factors associated with fatigue may be both generic and disease-specific.

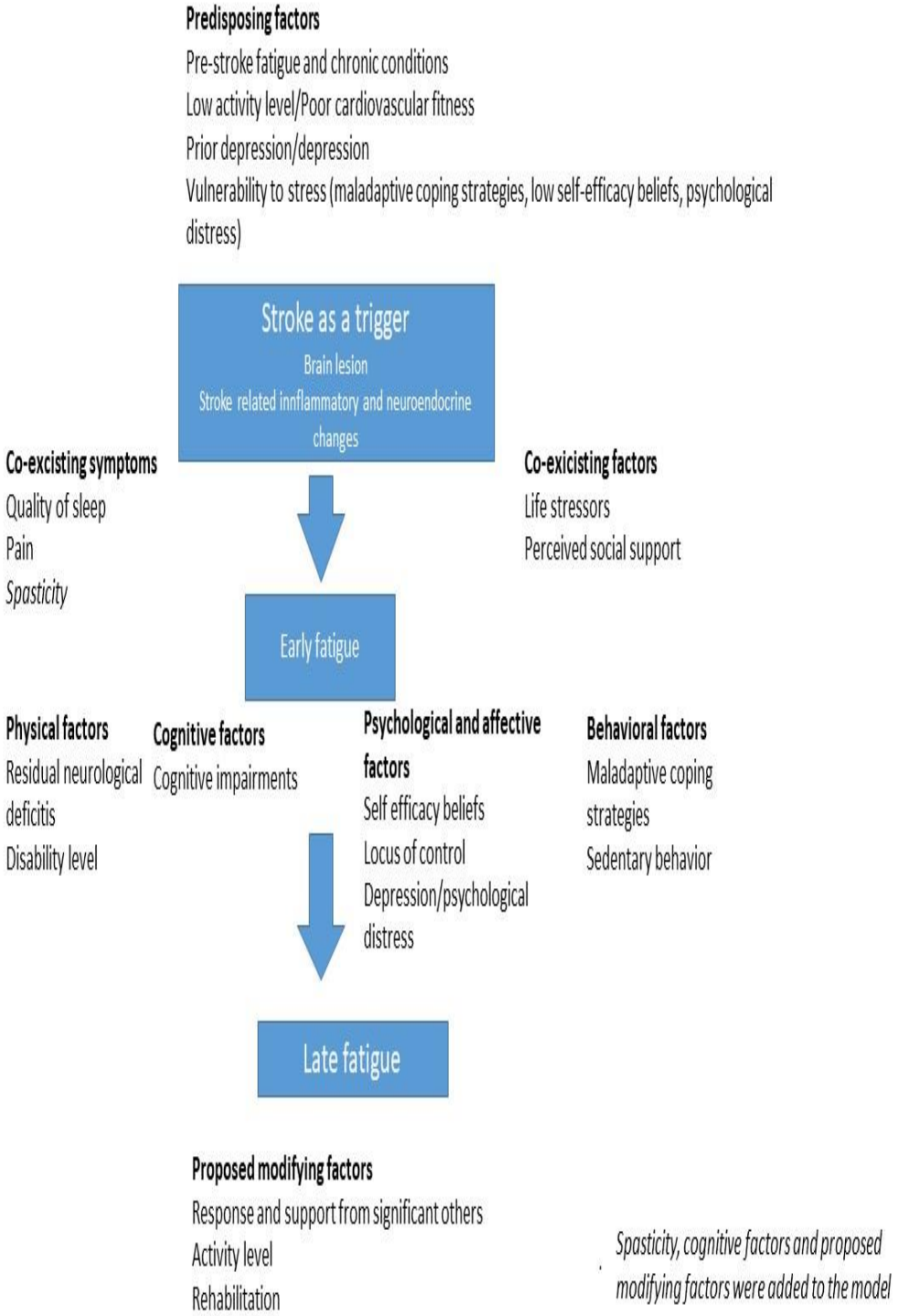
A recent study by Kirchberger et al. [69] on early and late onset fatigue in a stroke cohort of 505 participants, found that prior diagnosis of depression, higher NHISS and

higher scores on a measure of depression post-stroke were significantly associated with higher fatigue levels 3 months post stroke. I the same sample, higher fatigue levels at 12 months post stroke were associated with younger age, a worse rating of general health at baseline and low pre-stroke activity level. The study did not include variables on cognitive or physical function, nor PADL-function.

Seves et al. [74] found that being physically active pre- and post-stroke was associated with a trajectory of having few fatigue-symptoms. In a study on trajectories of health related quality of life in a sample of 1100 people with physical disabilities or chronic conditions, trajectory membership was associated with person-related factors (age and body-mass index), disease-related factors (fatigue, pain and acceptance of the disease) and life-style related factors (alcohol-consumption). The trajectories were disease-overarching, suggesting that patients in general can benefit from interventions aimed at managing pain and fatigue, and acceptance of the disability [210].

As the model proposed in Fig. 1 implies, there are factors that are associated with more severe fatigue, and there are factors that probably modify degree of fatigue. Modifying factors include activity-level [216] perceived social support [8] and rehabilitation.

Figure 1 Factors that may pre-dispose, trigger, maintain and modify PSF (adapted from Wu et al [8]



1.5 Treatment of post-stroke fatigue

There is relatively little systematic research on treatment strategies and interventions aimed at alleviating PSF [55, 221]. One study on graded exercise combined with cognitive therapy, showed a modest effect on PSF [218], however, this study lacked a control-group. In a review-article from 2019, 10 randomized controlled trials (RCTs) of non-pharmacological interventions for post-stroke fatigue were identified [31]. They concluded that cumulative probabilities indicated that the best non-pharmacological intervention for fatigue-reduction was community health management which included education, community activities and psychological care [31].

Mindfulness-training has been applied in an attempt to alleviate fatigue in TBI, MS and other neurological conditions [222]. Mindfulness-based stress-reduction has been associated with health and well-being [223], possibly through improving attentional regulation [224] and reducing rumination. A meta-analysis estimated a total effect size of 0.37 for treatment across studies, showing a potential to relieve fatigue in neurological conditions [222].

Modafenil is a neurostimulant that may improve functionality after stroke, and is also applied to reduce fatigue. However, a meta-analysis concluded that there is need for more robust data to confirm the utility [26, 225].

International guidelines on management of cardiovascular diseases including the subject of PSF, encourages regular physical activity and aerobic exercises to decrease fatigue. In addition, establishing good sleep patterns and avoiding excessive alcohol consumption is proposed [226, 227].

A pilot study on a group-based intervention for participants with acquired brain injury (including TBI or stroke-patients) suggests that a multifaceted intervention has potential to alleviate fatigue. The intervention consisted of metacognitive strategies for improving attention and problem solving, educational fatigue management, the use of cognitive behavioral therapy techniques, and the use of adaptive coping strategies. It is suggested that including treatment addressing self-efficacy and emotional problems may be advantageous [228]. Based on the multidimensional nature of PSF reflected in the model depicted in Fig. 1, a multifaceted approach to treatment seems advisable, with inherent flexibility to make individually tailored interventions.

2. AIMS

The overall objective of this thesis was to establish a better knowledge base for developing treatment strategies aimed at ameliorating PSF. The work is based on two longitudinal observational studies.

2.1 Paper I

The aims of this study were to explore whether subgroups of stroke survivors with distinct trajectories of fatigue in the first 18 months after stroke could be identified, and if so, to determine whether these subgroups differ on sociodemographic, medical and symptom-related characteristics, such as sleep, pre-stroke fatigue and depression.

2.2 Paper II

The main aim of this study was to investigate the overlap and differences in defining fatigue- caseness in stroke patients using the FSS, FQ and Lynch interview at a single point of time. Furthermore, we aimed to explore how the FSS, the FQ and the Lynch interview are differentially or similarly associated with demographic, medical and symptom-related characteristics, such as psychological distress and physical disability three months post-stroke.

2.3 Paper III

In this study, we aimed to explore how factors from different post-stroke domains are associated with PSF at three different time-points; in the acute phase, and at three and twelve months post-stroke.

We included physical and cognitive stroke-related impairments and psychological factors in a broad protocol. A special focus was on the use of different coping-strategies and cognitive function.

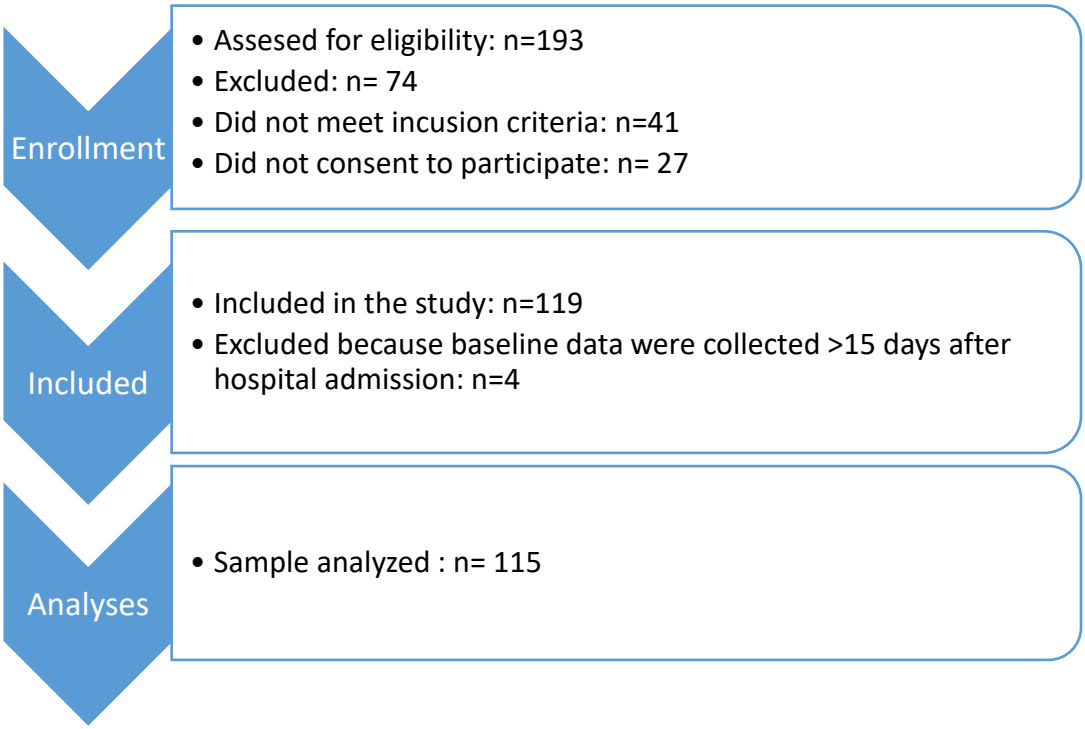
3. METHODS

3.1 Participants and procedures

3.1.1 Participants and procedures in paper I

Paper I is based on the Post-Stroke Fatigue Study, a longitudinal, observational study that recruited stroke patients with first-ever stroke according to the International Classification of Disease (ICD-10 diagnoses I60-I64). The patients were admitted to either of two hospitals in Oslo and Buskerud counties in Norway between March 2007 and September 2008. They had to be fully conscious, have sufficient cognitive function to consent to participate and be oriented to person, place, and time. They were excluded if they were unable to point to response alternatives on a questionnaire. Details of the recruitment and inclusion process are described in Figure 2. Data were collected at four time-points: during the acute phase (within 14 days of the stroke), and at 6, 12 and 18 months after the stroke. The data were collected through structured interviews and standardized questionnaires. Data on stroke type, lesion location and comorbid diseases were collected from the patients' medical records.

Figure 2: The recruitment process for Paper I.



3.1.2 Participants and procedures in paper II and III

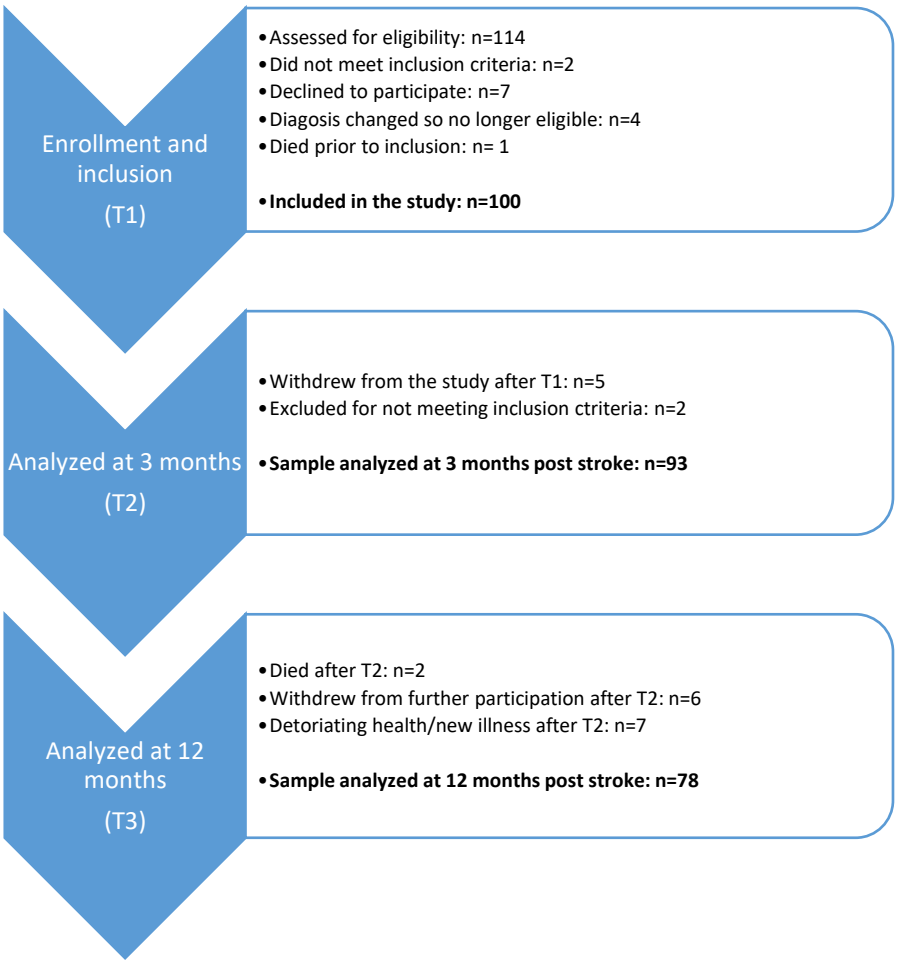
These papers are derived from a longitudinal observational study recruiting stroke patients from one hospital in Innlandet Hospital Trust, Norway, between February 2017 and October 2019.

Patients were eligible for the study if they had ischemic stroke according to the International Classification of Disease (ICD-10 I60 -I64). Trained physicians in the acute hospital confirmed the diagnosis. Exclusion criteria were intracerebral hemorrhagic stroke, other debilitating somatic or psychiatric diseases or severe language or cognitive dysfunction causing potential problems with data collection. If they had sufficient language to understand consent-information, study instructions and answer questionnaires, patients with aphasia were included.

A power analysis conducted prior to the start of data collection indicated that a minimum of 67 patients were needed for the study, assuming 30% prevalence of both fatigue and depression. Seventy-eight patients were included in the analyses of data on all three time-points. Details of the recruitment process are described in Figure 3.

Data were collected using semi-structured interviews, standardized questionnaires, physical and neuropsychological tests. The first author conducted all interviews, scoring of interviews and testing at 3 months (T2) and 12 months (T3) post stroke. The first author also collected data on fatigue severity in the acute phase, defined as within the two first weeks after stroke onset. Data from the acute phase also include demographic and medical variables. Medical data were collected from the patient's medical records.

Figure 3: The recruitment process for Papers II and III



3.2. Measures

A summary of measures included in Paper I, II and III is given in Table 1.

3.2.1 Outcome measures

For assessment of fatigue-severity, Fatigue Severity Scale (FSS) was used in Paper I, II and III. In Paper II, we also used the Chalder Fatigue Questionnaire (FQ) and the Lynch Interview.

The Fatigue Severity Scale (FSS) is the most used self-report instrument for measuring fatigue in stroke-patients [55]. The instrument includes 9 items about fatigue severity and how potential fatigue affects different activities, such as “Exercise brings on my fatigue” and “Fatigue interferes with carrying out certain duties and responsibilities”. Based on experience within the last seven days, responses reflect the degree to which one agrees with each statement on a 1-7 Likert scale [56]. Higher mean scores indicates

more severe fatigue. Validity and reliability is acceptable across different clinical populations, including in the stroke population [58].

We chose the FSS as an outcome measure because it is frequently used to measure fatigue in stroke populations, making the results comparable to other studies, and because the FSS to a larger degree than e.g. FQ measures fatigue impact on everyday life. We chose the nine-item version of FSS as most studies have selected this version [6], making our results more comparable with results of other studies.

Different cut-offs for identifying fatigue-cases are used in different studies using the FSS. In Paper I and II we used a cut-off of 5 because a cut off of 4 would lead to possible overestimation of PSF [17]. In Paper III, we chose to use continuous FSS scores to analyze how degree of self-reported fatigue was associated with the different variables.
In the reporting and the discussion of results, the terms "fatigue-case", "having a high degree of fatigue interference" or having "high fatigue-scores" will be used.

The Chalder Fatigue Questionnaire (FQ) was originally developed to measure fatigue in patients with myalgic encephalopathy/chronic fatigue syndrome and consists of 11 items [61]. The FQ includes items about general fatigue, symptoms of physical and mental fatigue. The scale includes two sub-scales: physical fatigue (items 1-7) and mental fatigue (items 8-11) and has two scoring systems; Likert and bimodal. In the bimodal scoring, each question is scored as either 0 or 1. A score of ≥ 4 is considered a case of fatigue. Both scoring-systems are used in Paper II.

The Lynch interview [50] was developed for the purpose of identifying fatigue-cases based on operationalized questions about aspects of the fatigue experience. The interview includes 7 operationalized questions about aspects of the possible fatigue experience such as "Can you describe what the fatigue feels like, in your own words?" and "Over the last month, how much of the time do you feel fatigued?" A case definition is based on whether there has been at least a two-week period when the patient has experienced fatigue and/or a need to rest every day or nearly every day. In addition, to be a case, the fatigue must have affected the ability to take part in everyday activities.

3.2.2 Demographic variables

Information on age, family relationships, employment status and educational level was obtained by personal interview three months post stroke and from medical records.

3.2.3 Medical variables

Stroke type Computerized tomography was conducted on all patients on hospital admittance. The stroke was categorized as ischemic, haemorrhagic or negative finding based on the radiologist's description. For diagnostic reasons, additional magnetic resonance imaging was performed on some patients some days after stroke onset. Lesion-location was classified as left, right, bilateral or unspecified.

Revascularization therapy Data on whether the patient had received thrombolysis or thrombectomy was collected from medical records.

Stroke impairment The National Institutes of Health Stroke Scale (NHISS) is used to objectively quantify the impairment caused by a stroke [229]. It is scored during the admittance to hospital in the acute phase and score was obtained from medical records.

Comorbidities A sum score was made of the total of relevant comorbidities based on self-report on The Self-Administered Comorbidity Questionnaire [230] and medical record inspection.

Body Mass Index was calculated as the patient's weight in kilograms divided by the square of their heights in meters. Weights and heights were obtained from the patients' medical records.

Pre-stroke fatigue was assessed through questions in a semi-structured interview according to Lerdal [51]. To be defined as pre-stroke fatigue, the fatigue would have to had to affect the ability to perform daily activities and must had lasted for at least 3 months before the stroke.

3.2.4 Symptom-related measures

3.2.4.1 Measures of physical function, activities of daily living and subjective symptom burden

Degree of disability The Modified Rankin Scale (mRS) is a commonly used instrument to measure the degree of disability or dependency in daily living of people who has suffered a stroke. The scale ranges from 0- 6; 0 meaning no disability, 6 meaning dead. A score of 1 indicates ability to carry out all usual activities, despite some symptoms, a score of 5 indicates severe disability [231]. In paper III, the mRS is used mainly to compare our sample's disability level with the disability level in the stroke population in general. In the analyses, the Barthel Index (BI) for ADL, which is more domain-specific and finely grained, is used.
The Barthel Index (BI) for ADL is a 10-item self-report questionnaire used to assess the level of dependency in activities of daily living. The scores are based on patient's self-rating and ranges from zero to 20. Higher scores represent higher levels of independence [232].

Balance was assessed by the Berg balance scale, a test of 14 steps where scores below 45 of a total of 56 indicate a risk of falling [233].

Pain severity To assess degree of pain a Numerical Rating Scale (NRS) was used. The patients were asked to circle the number between 0 and 10 that fits best to their pain intensity during the last week. Zero represents 'no pain at all' whereas ten represents 'the worst pain ever possible'. The NRS has shown good sensitivity in assessing subjective pain [234] .

Sleep disturbance Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI). The 19 items self-report questionnaire assesses sleep quality over a one-month time period. A sum score ranging from 0 to 21 is calculated. Higher scores indicate worse sleep quality, and a score of 5 or higher is associated with sleep-disturbances [235].

Subjective post-stroke symptoms were measured using the Rivermead Post Concussion Symptoms Questionnaire (RPQ). Although the RPQ was developed to measure

symptom severity following concussions, the items are relevant for assessing post-stroke symptoms although the questionnaire originally was developed to measure symptom severity following concussion. Total scores range from 0-64 and includes 16 items assessing self-reported cognitive function, vision, fatigue and physical function, such as poor balance and dizziness. Higher scores indicate worse symptom severity [236].

3.2.4.2 Psychological and psychosocial measures

Psychological distress In paper I, depressive symptoms were measured using the Beck Depression Inventory (BDI), a 21-item questionnaire. BDI scores of 0-9 indicate normal mood, 10-14 mild depression, 15-24 moderate depression and scores of 25 and above indicate severe depression [237]. In paper II and III, psychological distress was measured by the Hopkins Symptom CheckList-25 (HSCL-25), a 25-item screening instrument measuring symptoms of depression and anxiety. Higher scores indicate a higher degree of distress, and a cut off of 1.75 is used to indicate depression and/or anxiety within the clinical range [238].

Coping strategies were assessed by the BRIEF-Cope. The 28-item scale was designed to assess optimistic self-beliefs to cope with difficult demands in life [239]. In this study coping-strategies are operationalized as either "avoidant coping" or "approach coping". "Avoidant coping" is comprised of the scores on the subscales of denial, substance use, venting, behavioral disengagement, self-distraction and self-blame. Higher scores indicate more use of avoidant coping strategies. Higher scores on the approach coping scale indicates more use of of active coping strategies, positive reframing, planning, acceptance, seeking emotional support and seeking informational support [167].

Self Efficacy beliefs were assessed by the General Self Efficacy Scale (GSE) which consists of 10-items. The scale is designed to assess optimistic self-beliefs to cope with difficult demands in life [240]. Higher scores represent a more optimistic belief in coping.

Negative Life Events were assessed by the Negative Life Events Scale. The 12-item scale registers negative life event during the last 12 months, such as serious illness, death of family member or close friend or loss of one's job. Higher scores represents the presence of more negative life events during the last year [241].

3.2.4.3 Neurocognitive measures

The following standardized neuropsychological tests defining different cognitive domains were administered:

Visuo-motor speed: Grooved pegboard test [242] and conditions 1 and 5 from the Trail Making Test [243] were used to assess visuo-motor speed. The Trail Making Test from the Delis-Kaplan Executive Function System consists of five conditions which assesses visual scanning, visual-motor sequencing, and a cognitive set shifting procedure.

Processing speed: Condition 2 and 3 from the Trail Making Test and the conditions Color naming and Word reading from the Color-Word interference Test from Delis-Kaplan Executive Function System [243] was used to assess processing speed.

Executive function and attention: The subtests Inhibition and Inhibition/switching from The Color-Word interference test and condition 4 from the Trail making test from Delis-Kaplan Executive System [243] together with the result on Digit span from WAIS IV [244] were used to assess the ability to inhibit cognitive interference, attentional control and working memory.

Table 1. Measures included in papers I, II and III

	Paper I	**Paper II**	**Paper III**
Participants	**N=115**	**n=93**	**n=78**
Fatigue measures			
Fatigue Severity Scale (FSS)	X	X	X
Chalder Fatigue Questionnaire (FQ)		X	
Lynch interview		X	
Medical variables			
Stroke type	X	X	X
Revascularization therapy			X
The self-administered comorbidity questionnaire	X	X	X
Body Mass Index (BMI)	X		
Functional measures			

National Institute of Health Stroke Scale (NHISS)	X	X	X
The Modified Rankin Scale (mRS)			X
Barthel Index (BI) for ADL	X	X	X
Berg Balance Scale		X	X
Other symptom measures			
Beck's Depression Inventory (BDI)	X		
Hopkins Symptom Checklist-25 (HSCL-25)		X	X
General Self Efficacy Scale (GSE)		X	X
Brief COPE		X	X
Pittsburgh Sleep Quality Index (PSQI)	X	X	X
Numeric Rating Scale of Pain (NRS)	(X)	X	
Rivermead Post Concussion Symptoms (RPQ)		X	
Negative Life Events (NEL)			X
Pre-stroke fatigue	X	X	X
Neuropsychological Tests			
Grooved Pegboard			X
Trail Making Tests 1-5 and Color-Word interference Test from Delis Kaplan Executive System			X
Digit Span from WAIS IV			X

3.3 Statistical analyses

In all three papers, statistical analyses were performed using the SPSS software version 23 (IBM Corp, Armonk, NY, USA). In addition, in paper I, the GLLAMM package in Stata [245] was used to identify latent classes, i.e. subgroups of patients based on their FSS scores at the four time points.

3.3.1 Data analyses in paper I

Growth mixture modelling (GMM) was used to identify different PSF trajectories. GMM estimates growth curves for previously unidentified subgroups that change differently over time [246]. The number of latent classes are identified based on the stability of the estimated classes. In general, mixture models aim to discover substantively meaningful groups of people that are similar in their responses to measured variables or trajectories [247].

The significance level was set at 0.05 for hypothesis testing. Chi-square tests, or Fishers Exact test when expected cell frequencies were <5, were used to evaluate univariate associations between pre-stroke fatigue and comorbidities. Ordinal regression was used for both univariate and multivariate analyses of associations between sociodemographic, medical, and symptom-related characteristics and the latent classes (i.e., fatigue trajectories). Variables included in the multivariable analyses were based on theoretical importance (i.e., gender) or a p-value of ≤ 0.10 in the univariate analyses. Effect sizes for the associations were reported as odds ratios (ORs) with 95% confidence intervals (CI).

3.3.2 Data analyses in paper II

Fatigue caseness, i.e categorical scores, were calculated on basis on the scores on the fatigue-instruments. Categorical scores of the fatigue instruments were then used in analyzing the degree of overlap in fatigue case identification. How demographic, medical and symptom-related characteristics related to level of fatigue were also analyzed using categorical scores. Continuous values were used in the correlational analyses between the three instruments and for descriptive statistics for the FSS and the FQ. Pearson Correlational analyses were used to assess associations between the three fatigue instruments. For the nine-item version of FSS, the Cronbach's alpha was 0.90. The Cronbach's alpha was 0.91 for the 7-item version. For the full FQ, Cronbach's alpha was 0.68. For the for the physical and mental fatigue subscales, the Cronbachs's alpha was 0.60, and 0.73 respectively. Scores of the full FQ and caseness scores based on the bimodal scoring system was used in further analyses.

Cohen's K was employed to assess the degree of measurement agreement, with K >0.75 indicating excellent agreement, 0.40-0.75 fair to good, and <0.40 poor agreement [248]. A Kolgomorov-Smirnov test indicates that the scores on the FSS (D93)= 0.18 and the FQ (D92)= 0.20 follow a normal distribution.

P-values <0.05 were considered statistically significant and two-tailed tests were used in the statistical analyses. Bivariate associations between fatigue caseness and demographic, medical and clinical variables were evaluated using Chi-square tests for categorical variables and one-way analysis of variance for continuous variables. Predictor variables included in multivariate analyses were based on theoretical

importance (e.g., gender) or a p-value ≤0.10 in bivariate analyses. Stepwise entry for medical and clinical predictor variables that showed significant association in the univariate analyses was used in multivariate logistic regression analyses of associations with fatigue-caseness. Effect sizes for the associations are reported as odds ratios (OR, Exp (B) with 95% CI. Model fit is reported as Nagelkerke R^2. A power analysis conducted prior to the start of data collection indicated that a minimum of 67 patients were needed for the study, assuming 30% prevalence of both fatigue and depression.

3.3.3 Data analyses in paper III

One-way ANOVA was used for univariate analyses of how categorical variables such as pre-stroke fatigue were related to fatigue-severity. All neuropsychological test scores were converted to T-scores. A T-score of 35 (<1.5 SD) or below represents performance in the clinical range and a T-score of 50 (SD =10) represents the normative mean.

To test whether predictor-variables significantly predicted self-reported fatigue on the FSS, simple linear regression was used. The level of statistical significance to $p<0.001$ in order reduce the risk of type I error due to multiple testing. Hence, findings of associations between fatigue scores and predictor variables significant at the 0.05 level must be regarded as tendencies.

To predict degree of self-reported fatigue from predictor- variables with a p-value ≤0.001 in univariate analyses, we used multiple regression. For multivariate analyses of variables significantly associated with being more fatigued at three and twelve months post stroke, the data met the assumption of independent errors (Durbin-Watson value = 2.0 at three months and 2.32 at twelve months, values ranging from 1.5 to 2.5 are considered acceptable indicating that there is no first-order autocorrelation).

An additional analysis of a possible curvilinear association between age and fatigue-level was performed using a hierarchical multiple regression of age and FSS-scores. In addition, categorical scores were made based on the following age groups; ≤60 years, 61-74 years and >75. One-way ANOVA was used to analyze how age-categories was related to fatigue.

3.4 Ethical considerations

Paper I: The study was approved by the Regional Medical Research Ethics Committee of Health for the South East of Norway (Ref #2.2007.90) and by the Data Protection Officer at Oslo University Hospital.

Paper II and III: the Regional Ethics Committee for Medical and Health Research Ethics in South-Eastern Norway (Ref. 2016/589 /REK Sør-Øst C) approved the study.

Written informed consent was obtained from the participants before inclusion in the study. If health-related information in need of treatment was discovered, we were ethically committed to refer to the adequate health-service. Two participants were in need of psychological treatment and were referred, one was referred to physiotherapy and one to multidisciplinary vocational rehabilitation.

4. SUMMARY OF MAIN RESULTS

4.1 Demographic, clinical and stroke-related characteristics of the samples

The demographic, clinical and stroke-related characteristics of the samples in the three papers in this thesis are summarized in Table 2.

Table 2. Demographic, clinical and stroke-related characteristics of the samples for paper I (n=115) and paper II (n=93) and III (n=78)

	Sample paper I (n= 115)	**Sample paper II (n=93)**	**Sample paper III (n=78)**
Sociodemographic			
Gender, n (%)			
Male	68 (59%)	57 (61%)	50 (64.1)
Female	47 (41%)	36 (39%)	28 (35.9)
Age (mean (SD)	68.3 (13.3)	66.7 (10.7)	66.5 (9.4)
Cohabitation n (%)	72 (63%)	67 (72%)	62 (79.5)
Education			
Education >= High school n (%)	32 (30%)	28 (30.1)	23 (29.5)
Education < High school	83 (70%)	65 (69.9)	55 (70.5)
Employment n (%)			
Working at T1	28 (24%)	39 (41.9)	36 (46.2)
		22 (23.9)	20 (25.6)
Working at 18 and 12 months post-stroke	15 (13%) (18 months post-stroke	-	23 (29.9 %) twelve months post-stroke
Medical variables			
Side of stroke lesion			
Right	31 (27%)	36 (39%)	31 (40.6)
Left	29 (25%)	35 (38%)	28 (36.4)
Bilateral	20 (17%)	4 (4%)	3 (3.9)
Unknown	35 (31%)	18 (20%)	15 (19.5)
Thrombolysis n (%)	No data	27 (30%)	25 (32.3)
Comorbidities n (%)		1.9 (1.9)	1.9 (1.4)
Pre-stroke fatigue n (%)	34 (30%)	23 (30%)	20 (25.6)
Symptom-related variables			
NHISS score at admittance mean (SD)	No data	3.5 (4.1)*	3.5 (4.1)
Barthel ADL at three months post stroke, mean (SD)	19.3 (1.8)	19.5 (1.6)	19.5 (1.4)

* In this sample, the median NHISS-score was 2, and 54 % had a NHISS from 0-2. In this sample, a majority had minor strokes as classified by the NHISS (scores 0-4), 7.7% had moderate stroke (NHISS 5-15) and 2.6 had moderate to severe strokes (NHISS>15). Further, in this sample, 92% had a mRS 0-2 at three months post-stroke, meaning that a large majority of the patients in the sample were independent in PADL. The data from the Norwegian registry show that 73% had a mRS 0-2 at three months post-stroke.

4. 2 Main findings from paper I: Trajectories of fatigue among stroke patients from the acute phase to 18 months post-injury: A latent class analysis

Paper I investigates whether subgroups of stroke survivors with distinct trajectories of fatigue in the first 18 months post stroke could be identified using Growth Mixture Modelling (GMM). Furthermore, we analyzed whether these subgroups differ regarding sociodemographic, medical and/or symptom-related characteristics.
Three main findings are reported:

1) Based on the scores on the FSS, three distinct classes of trajectories of fatigue following stroke from the acute phase to 18 months post stroke was identified characterized by differing levels of fatigue, namely classes of low, medium and high fatigue. The mean FSS-scores remained relatively stable across the four time-points on a class-level.
2) Belonging to a higher fatigue-trajectory was associated with age >75 years, pre-stroke fatigue, multiple comorbidities, some ADL-impairment, disturbed sleep and depressive symptoms in the univariate analyses. Pre-stroke fatigue (OR 4.92, 95% CI 1-84-13.2), multiple comorbidities (OR4.52, 95% CI1.85-11.1) and not working (OR4.61, 95% CI 1.36-15.7) predicted belonging to a higher fatigue trajectory in the multivariate analyses.
3) Fatigue in the acute phase predicted long-lasting fatigue.

4.3 Main finding from paper II: A cross-sectional study exploring overlap in post-stroke fatigue caseness using three fatigue instruments: Fatigue Severity Scale, Fatigue Questionnaire and the Lynch's Clinical Interview.

Paper II investigates the overlap and differences in defining fatigue caseness using three different fatigue measures in a sample of patients at three months post stroke.

Furthermore, the instrument's associations with demographic and clinical characteristics were explored. Four main findings are reported:

1) The proportion of fatigue cases varied from 24 to 62% depending on which instrument was used. The FQ yielded the highest proportion of cases (62%), followed by the Lynch interview (52%), while only 20.5% were classified as cases based on a cut-off of 5 on the FSS.
2) While the FQ is sensitive in measuring fatigue-related symptoms, the FSS and the Lynch interview to a larger degree reflect fatigue impact.
3) Exploring the associations between fatigue-caseness and predictor-variables, we found a variance between the instruments. In bivariate analyses, PSF measured by all the three instruments was significantly associated with having pre-stroke fatigue, high symptom burden as measured by the RPQ, sleep disturbances, being more dependent in PADL, poor balance and pain. Being a fatigue-case using the FSS or the Lynch interview was also significantly associated with having psychological distress symptoms in the clinical range. This possibly reflects that the different instruments cover slightly different aspects of the fatigue experience.
4) The FQ possibly overestimates fatigue cases in patients with stroke. This is because some of the items meant to measure fatigue symptoms may reflect the presence of subjective stroke-related impairments.

4.4 Main findings from paper III: Biopsychosocial factors associated with fatigue from the acute phase to 12 months post stroke

Paper III investigates how stroke-related impairments and psychological factors are associated with degree of fatigue at three and twelve months post-stroke. The association between degree of self-reported fatigue and self-efficacy beliefs, coping strategies and cognitive impairments were of special interest because they seem understudied in the stroke-population.

Three main findings are reported:

1) We found that that poor balance, psychological distress-symptoms and using maladaptive coping strategies was associated with more severe fatigue at three and twelve months post stroke. The model explained 55% of the variance.

2) In line with previous research, early post-stoke fatigue was found to be a strong predictor of persistent fatigue. The fatigue-score at 3 months post stroke was strongly associated with the fatigue-score at 12 months post stroke. A model of FSS-scores at 3 months and high scores on the HSCL-25 explained 51% of the variance.

3) PSF may be present in patients with minor stroke-sequeale, a special awareness should thus be on these patients as they may have unmet needs for follow-up.

4.5. Summary of main findings across the papers

4.5.1 Prevalence and trajectories of PSF

In paper I, 35% of the sample had a trajectory of high fatigue based on the GMM analyses of FSS-scores. In paper II, 20.5% of the sample were fatigue-cases based on a cut-off of 5 on the FSS. However, using the bimodal scoring on the FQ, 62% were fatigue-cases. In paper III, the prevalence of fatigue-caseness was not a core-question as we used continuous FSS-scores. However, most of the patients had scores below 5, reflecting that a majority did not report severe fatigue.

In paper I, we identified three distinct classes of trajectories of fatigue following stroke, namely classes of low, medium and high fatigue. Also in paper III, the mean FSS scores differed little over the three time-points. In both the acute phase and at three months post-stroke, 20.5% had a score above 5. At twelve months post-stroke 17.5 % had a score above 5. The mean FSS-score was lower at 12 months post stroke (3.6, SD 1.5) than at three months post stroke (3.8, SD 1.3), most likely a clinically non-significant difference.

Inspecting individual scores across the three time-points in Paper III, there were however variations in change in fatigue-scores. From the acute phase to three months post stroke, there was a median increase of 1 point in this sample. From three months to 12 months, there was a median reduction of 2 points. There were individual differences in at which time-point the patients had the highest score, some had the highest FSS-scores in the acute phase, some at three months and others at twelve months post-stroke.

4.5.2 Factors associated with PSF in paper I, II and III

Pre-stroke fatigue was significantly associated with post-stroke fatigue across all three papers. Of those reporting pre-stroke fatigue in paper I, only one patient did not report post-stroke fatigue. In paper II, 15 of those 22 (68%) who were fatigue-cases on the FSS also reported pre-stroke fatigue. Of those who were cases on the FQ, 20 of 58 reported pre-stroke fatigue (34%). Being a fatigue-case on the Lynch-interview, 20 of 48 (42%) also reported pre-stroke fatigue. In paper III, those who reported pre-stroke fatigue tended to have higher scores on the FSS than those who did not report pre-stroke fatigue. The mean scores on the FSS was 3.31 (SD 1.2) in the acute phase, 3.5 (SD 1.2) at three months post stroke and 3.7 (SD 1.6) at twelve months post stroke among those who did not report pre-stroke fatigue. Among those who reported pre-stroke fatigue, the mean scores were 4.5 (SD 1.5) in the acute phase, 4.8 (SD 1.2) at three months post stroke and 4.3 (SD 1.6) at twelve months post stroke.

In paper II and III, in the univariate analyses, being a fatigue case or having a higher fatigue-score was significantly associated with NHISS score at three months post-stroke, indicating that having neurological deficits and focal impairments are associated with more fatigue. In line with this, severity of disability measured by the mRS was also strongly associated with fatigue in paper III, suggesting that more severe disability is associated with more fatigue-symptoms.

Psychological distress symptoms were associated with post-stroke fatigue across all three papers. A strong association was found between psychological distress-symptoms and high fatigue-scores at both three and twelve months post-stroke in paper III. In paper II, having symptoms of psychological distress was significantly associated with fatigue-caseness on all the fatigue measures in univariate analyses at three months post stroke. 10-12% of those considered cases on the three fatigue measures reported symptoms equivalent to being in the clinical range on depression/anxiety on the HSCL-25. However, the majority of fatigue-cases did not report symptoms in what is considered to be within the clinical range of potential depression/anxiety disorder regardless of which instrument was used (HSCL-25 $\geq$ 1.75). In paper I, 49% of the patients belonging to the high fatigue class scored within the clinical range on the BDI.

In paper III, in simple linear regression higher scores on avoidant coping and lower scores on the General Self Efficacy scale were associated with higher scores on the FSS

at three and twelve months. Reporting using avoidant coping-strategies at three months post-stroke, was also associated with higher FSS-scores at twelve months post-stroke. In multivariate analyses, fatigue-score in the acute phase, avoidant coping and impaired balance explained 55% of the variance of fatigue at three months post stroke.

In paper I, scoring within the range of disturbed sleep (PSQI >5) was associated with a three times higher risk of having a high fatigue-trajectory (OR 3.1). In paper II, fatigue-cases scored in the clinical range of disturbed sleep on a group-level. In paper III, lower quality of sleep was associated with higher fatigue scores in univariate analyses at three and twelve months after stroke.

In paper I, having multiple comorbidities yielded an OR of 4.42 in the multivariate analyses, indicating a clearly higher risk of fatigue associated with added numbers of medical conditions. The association between comorbidities and PSF was significant in the univariate analyses in paper II (on the FSS and Lynch interview, not on the FQ). Examining the results, on a group level, those classified as being fatigue cases had almost 1.5 to twice as many other medical conditions besides the stroke than the no-fatigue cases. In paper III, a higher fatigue score was associated with a higher number of comorbidities at twelve months post stroke.

In paper I, age > 75 years was significantly associated with being in the high fatigue class in the univariate regression analyses. In paper II and III, no significant association was found between increasing age and being a fatigue case. There was no significant association between age-categories and fatigue level nor a curvilinear relationship between age and fatigue in this sample, and the mean fatigue level was quite similar in all three age-categories. The level of education was quite similar in all groups and no significant associations were found between level of education and severity of fatigue.

A majority of the participants was cohabiting in both samples. In paper II, those cohabiting reported more fatigue-related symptoms on the FQ.

5. DISCUSSION

5.1 Discussion of main findings

5.1.1 Courses and trajectories of PSF

In this thesis**,** three distinct classes of fatigue-trajectories from the acute phase to 18 months post stroke were identified using GMM; namely a low, a moderate and a high fatigue class. A similar stable pattern was found looking at FSS scores over three time-points, although there were individual variations.

Follow-up beyond 12 months was not possible within the time-frame of the studies in paper II and III, and there is no data on how the degree and presence of fatigue changed or stayed stable after this. The length of this follow-up period makes the extrapolation to long-term courses of PSF uncertain. However, the results of the study in paper I indicates that PSF-courses tend to be stable, also beyond 12 months post stroke. Although improvement in function can occur over a long time, a meta-analysis suggests that disability levels tend to stabilize 6 months post stroke [122]. At what time PSF-trajectories tend to stabilize, might be dependent on whether, and to which degree, the associated factors remain stable or change. For instance, it has been found that e.g. depressive symptoms tend to persist after 6 months post stroke [100]. Individual trajectories can be expected as the combinations of stroke-related impairments, personal and external factors will vary at any given time.

The trajectories identified by GMM seemed fairly stable through the first 18 months post stroke. However, regardless of the method used, there will be individual courses or trajectories within the main groups with different degrees of variation. For instance, although on a group-level, fatigue in the acute phase was associated with a high level of later post-stroke fatigue, some reported very little fatigue in the acute phase, and substantially more 3 or 12 months post stroke. One possible explanation of this was found in the clinical interview, where some stated that in the acute phase they had little experience of the impact of the stroke, and having survived without having visible sequela made them very thankful and optimistic, leading them to report very few symptoms.

In paper II, we found a large variability of fatigue-caseness depending on which instrument was used. For further research, it could be interesting to explore whether

courses of fatigue is displayed similarly or differently depending on which instrument is used, and whether the degree of overlap between the instruments is stable over time/at different time-points. As the FQ primarily seems to reflect presence of fatigue- and impairment-related symptoms, it is possible that courses measured by the FQ might be different than courses measured by the FSS, primarily measuring the impact or interference of fatigue on daily life.

5.1.2 Identification of fatigue-caseness using different instruments: Content and prevalence

A major point in the literature on prevalence of PSF is how the methodology used for identifying cases yield vastly different results [249]. This is in accordance with our findings in paper II, where the large difference in the estimated prevalence of PSF seems to reflect the different content and cut-offs of the instruments used. Thus, depending on choice of assessment, post-stroke fatigue may be under- or over-diagnosed. This is in line with a recent study evaluating content validity of patient-reported outcome measures (PROMS), showing that currently used instruments omit specific aspects of PSF, lack content overlap and fail to take into account the multidimensional nature of PSF [64].

In clinical populations, especially in populations with conditions affecting the central nervous system, identification of mental fatigue is of particular interest. Mental and physical fatigue may be regarded as subscales on the "characteristics-dimension". For clinical purposes, differentiating between these two dimensions may have implications for treatment-strategies. The FSS have no items that specifically addresses mental fatigue. In the Lynch Interview, one question is "Would you describe your fatigue as mainly physical or mental?" The FQ contains two subscales, namely of physical and mental fatigue. The four items intended to measure mental fatigue,- a grading of whether one experiences trouble finding words, impaired memory, concentration and "slip-of the tongue", might reflect self-report of cognitive deficits more than mental fatigue per se, especially among stroke patients and in other clinical populations with central-nervous affection [181]. Used in clinical populations with neurological diseases, the answers on these items need not reflect mental fatigue but rather the experience of objective cognitive impairments [181], or both.

Subjective cognitive complaints is a common characteristic of fatigue. In general, as patients with fatigue often report mental fatigueability expressed as lack of focus and forgetfulness, questions about i.e subjectively impaired memory or attentional function may be valid as items covering the mental-fatigue -characteristic-dimension of fatigue-measurements in many patient groups and in the general population. Patients with chronic fatigue often report impaired concentration and memory, although they objectively may perform within normal range on formal neuropsychological assessment [250, 251].

Furthermore, in our experience, patients often describe mental fatigue as "After a while of working I just can't concentrate anymore", which implies that mental fatigue may be an expression of fatigability, i.e. an impaired ability to sustain effort. This is in line with a recent study by Ulrichsen et al [184] demonstrating that mental fatigue is associated with an increased vulnerability for sustained effort. Thus, instruments designed more specifically to consider cognitive aspects of fatigue, with items such as "During episodes of fatigue, I am noticeably more forgetful", may be appropriate at identifying mental fatigability.

The points in the last paragraphs may be exemplified by a case in this study. He had no cognitive impairments on the neuropsychological tests or problems with memory or word-finding per se. However, he described an increased sensitivity to light, sound and impressions, making him very tired after a period of work that demanded sustained effort. Neither the FSS nor the FQ identified him as a fatigue-case, but the Lynch Interview did. This also serves to illustrate how the use of semi-structured interviews may be helpful when addressing fatigue-symptoms in the clinic. An interview may identify characteristics of individual fatigue-experiences, avoid false negatives and also give hints to the process of finding individualized interventions.

Post-stroke fatigue was also somewhat differently associated with the analyzed predictor-variables depending on which instrument was used possibly also reflecting different content of the scales. The FSS and the Lynch interview mainly measure the impact and interference of fatigue, while the FQ to a larger degree measure the presence of fatigue-related symptoms. Some people may be more easily tired than they were pre-stroke and experience more fatigue-related symptoms. However, not all will perceive this as having a significant impact on their lives. They may adjust their lifestyle to being

more easily tired. Different life-circumstances will yield different expectations and demands of participation. This is in line with findings in studies showing that fatigue is more pronounced among persons that are in the midst of their working and active family life. Higher fatigue-interference on everyday life and activities might lead to higher degree of psychological distress-symptoms as well as a higher fatigue impact [77, 80].

The Cronbachs alpha of the FQ was lower in this sample than expected when compared to other studies [252]. This possibly reflects a higher proportion of respondents with cognitive impairments in this sample than in samples drawn from other clinical populations that do not necessarily have central-nervous affection. The content validity and utility of the FQ might thus be questioned when used in populations with neurological diseases.

In the future, when designing fatigue instruments, a complete measurement of fatigue should cover all the four possible dimensions of fatigue-experience, namely fatigue characteristics, fatigue impact, fatigue interference and coping-strategies for fatigue. Further, instruments should contain items that cover aspects of fatigability, i.e differentiate between symptoms being present “never”, “all the time” or “at certain times” or “after sustained effort”. Furthermore, there is a need of a clarification of the concept of mental fatigue and how to measure it.

It may also be that physical or cognitive testing could be helpful in identifying objective fatigue through measuring decreasing performance over time due to reduced ability for sustained effort. While the inconsistency in prevalence rates for PSF may be affected by the subjective nature of fatigue, performance measures may offer more objective and reliable way of identifying fatigue and/or fatigability [253].

All in all, there is still a need of consensus on how to measure fatigue. When choosing a fatigue-instrument, the aspects covered by the measure should be considered. In discussing the findings, which aspects of the fatigue-experience is covered by the measurements should be addressed.

5.1.3 Identification of fatigue-caseness using different instruments: Cut-off

The large variability of estimates of PSF prevalence in different studies does not only reflect different content of the measures used. It also reflects different cut-offs used to identify fatigue-cases.

FSS is one of the most frequently used instruments to measure fatigue. However, some studies use a cut-off of 4 [40, 103], others use a cut off of 5 [51]. A cut-off of 5 was chosen in paper II, as it has been argued that using a cut-off of 4 may lead to an overestimation of the burden of PSF [17]. Furthermore, in a Norwegian study, the mean score of the general population was 3.9 and 4.7 in people with different chronic illness [17]. Based on a ROC-curve, Poulsen et al [254] found a cut-off of 4.9 to be the best compromise between specificity and sensitivity when considering a case in the stroke population.

The prevalence of fatigue-cases would have been higher in paper II and III if a cut-off of 4 had been used. In paper II, the overlap of caseness using the FQ and the FSS would also have been higher using a cut-off of 4 on the FSS. However, in the high fatigue-class in paper I, the mean score was above 5 at all four time-points. This may support using a cut-off of 5 to identify severe fatigue.

As being a fatigue-case on the FQ is based on a bimodal score of 4 or above, one might in this instrument be considered a fatigue-case based on report of subjective cognitive complaints alone. This may explain why the FQ identified almost twice as many fatigue-cases as the FSS in paper II, as many stroke-survivors suffer from cognitive impairments because of their stroke [190]. This also illustrates how both content and cut-off on different instruments impacts on prevalence of fatigue-cases.

The use of cut-offs by using the mean score on an instrument to identify cases is debatable. Clinically, it might not be meaningful to distinguish between i. e. a score of 4.9 and 5.1 as these scores may reflect more similarity in fatigue-burden than scores of i.e 2.3 and 4.9. In paper III, we chose to analyze the associations between FSS and the predictor-variables using FSS as a continuous variable. The background for this is two-folded. The first reason is the lack of consensus on a cut-off to identify cases on the FSS. Secondly, treating the data as continuous instead of categorical there is less risk of losing meaningful associations due to being close to a cut-off within a dichotomic

category. As such, using continuous data may yield more differentiated and accurate results.

Related to the challenge of defining a cut-off for identifying a fatigue-case vs a non-case, is the question regarding how large a change in a score has to be to constitute a clinically meaningful difference. The minimal clinically important difference (MCID) is defined as the smallest difference in score in any domain or outcome of interest that patients can perceive as beneficial [255]. The MCID is of special relevance when assessing potential benefit from an intervention [256]. In this study, the MCID is relevant in exploring change of reporting fatigue-related symptoms from one point of time to another, i.e the trajectories of change and for discriminate a case from a non-case. At an individual level, the MCID of FSS has been proposed to be 0.6 [257] or 1 [258].

In paper I, as GMM is used as a method of discovering trajectories, there is not a need to define which difference in scores that constitutes a change in category from being a non-case from being a case. GMM has the benefit of identifying subgroups of people in the sample that are similar in their responses on a variable, i.e on FSS.

Both clinically and scientifically, a mean score may be misleading. This is exemplified by a case described in paper II. The participant had a mean score of 3.3 on the FSS, supposedly reflecting a low degree of fatigue. However, the participant indicated total agreement with the statements “Fatigue is among my three most disabling symptoms” and “Fatigue interferes with my work, family and social life”. He strongly disagreed on the items “Physical exercise makes me tired. In the Lynch interview, he elaborated that physical exercise was one of the things that alleviated fatigue in his experience. However, he likely had clinically significant fatigue affecting his everyday life, more specifically mental fatigue that had impact on his ability to work. This example also reflects the lack of items that separate mental and physical fatigue on the FSS, as discussed above.

The proportion of fatigue-cases estimated by using the FSS in our studies is in the lower end of occurrence of PSF compared to many earlier studies. In a recent review, Alghamdi et al. estimated a prevalence of PSF of 48% (CI of 42-53%) [6]. Our use of a cut-off of 5 instead of 4 is one probable reason for this. Further, the samples in our studies consisted of patients with ischemic stroke, the proportion of PSF might have been higher if patients with hemorrhagic strokes had been included [6]. A review-article

found a stark difference between proportion of PSF between patients who suffered haemorraghic stroke (66%) and ischemic stroke (36%). The difference in prevalence between ischemic and haemorraghic stroke has not yet been sufficiently investigated to make firm inferences about the associations [6]. Further, the majority of patients in our studies were fairly independent in PADL, and the prevalence of PSF might have been higher if the disability level had been higher. However, the prevalence of substantial fatigue measured by the FAS was 65.2 % (CI of 54.6% -74.8%) in a study of patients with TIA and minor stroke [183].

5.1.4 Factors associated with PSF at different time-points

5.1.4.1 Associations between PSF and demographic variables

No significant associations were found between PSF and gender, whereas our findings regarding the relationship between age and PSF are diverging. Severe fatigue was more frequent in the group aged > 75 in paper I. No curvilinear association was found between age and fatigue level in an additional analyses performed on the sample in paper III. It may be that the relationship between age and fatigue is mediated by other factors such as number of comorbidities, family obligations or work-status. These possible relationships are not explored in this thesis, mainly because there were not enough participants to perform relevant subgroup analyses. In another study, the oldest (>75 years) and the youngest (<60 years) were the most fatigued [77].

The reason for cohabiting being more associated with fatigue-symptom measured by the FQ in paper II is not clear, and there were not significant associations between being a fatigue-case and cohabiting when using the FSS or the Lynch-interview.

5.1.4.2 Associations between PSF, medical factors and stroke-related impairments

The samples included in the papers in this thesis were probably not large enough to detect potential associations between side of stroke-lesion or revascularization therapy and PSF. It may be that as a higher proportion of stroke sufferers receive revascularization therapy, less cases of fatigue due to stroke-related impairments and disabilities can be expected. Studies in larger samples are needed to explore this possible association. There are several studies showing an association between degree

of stroke-related impairments and fatigue [33, 46, 259, 260]. Indirectly, this may imply that revascularization reduces proportion of severe fatigue cases.

In line with previous research [119, 122], significant associations were found between PADL-dependency and fatigue-caseness/having a high fatigue score in all three papers. There was also a strong association between impaired balance and fatigue-caseness/having a high fatigue score. This supports an association between residual neurological impairment and PSF. Impaired balance is associated with increased dependency in PADL, and it is likely that also minor impairments in balance might lead to more energy expenditure in performing everyday activities, causing more fatigue. Improving balance and physical function might thus be a treatment-option when aiming to reduce PSF.

Both the stroke itself and residual neurological impairments may cause pain, e.g. related to spasticity, shoulder subluxation and central pain [112]. In line with previous findings [112], being a fatigue-case was significantly associated with degree of pain using all the three measures. Reducing pain and spasticity may thus be targets for interventions aimed at alleviating fatigue. Further research is needed for in depth exploration of these associations and treatment options.

Exploring the associations between fatigue-caseness and several cognitive domains, we found significant associations between PSF and visuo-motor function and processing speed in the univariate analyses at twelve months post stroke. The finding might be in line with previous studies on TBI that found that impaired visual tracking leads to fatigue [190]. The results also support the finding in a recent study where stroke-survivors with prominent self-reported visual problems experience more fatigue [191]. Impaired fine-motor control and slow visual tracking may make mental and physical tasks more effortful and thus cause fatigue. Hence, rehabilitation of visual problems may reduce fatigue in stroke-survivors with visual impairments.

Some studies have found an association between impaired working memory, attention or executive function and fatigue [47, 48]. In this study no significant associations were found between PSF and the domain of attention/ executive functions. It may be that as a whole, the sample did not include a high enough proportion of patients with cognitive impairments to significantly identify possible associations between PSF and this cognitive domain.

There is a need for further research on how cognitive impairments and fatigue are associated as the results from earlier studies are difficult to compare due to use of different tests, methodology and operationalization to measure cognitive function [181]. Further, how mental fatigue is related to cognitive function needs exploration in future research. Tests that measure sustained attention should be included in protocols in studies on PSF in general and on mental fatigue specifically. The reason for this is that mental fatigue may be more associated to the vulnerability for sustained effort than to cognitive impairments per se [184]. Including both measures of ability of sustained effort and tests of different cognitive domains may thus shed light on how these different aspects of cognitive function affect the degree of mental fatigue. The samples in earlier studies are also different in regard to severity of stroke, and more studies are needed on how impairments such as aphasia, neglect or visual field defects affect level of fatigue post stroke. Including a selection of validated neuropsychological tests measuring cognitive function within several cognitive domains, instead of screening-tests or self-report, is a strength of this study.

In everyday life, other factors may mediate how minor and major cognitive impairments cause fatigue. Possible mediating factors include work status, family-situation and other environmental factors that put demands on ability to concentrate, remember and plan. It is possible that subtle cognitive impairments may affect degree of fatigue more as life returns to normal and demands for participation is higher. In line with this, a strong association was found between self-report on the RPQ of symptoms such as visual problems, dizziness and impaired cognitive function and being a fatigue case in paper II. Those who were cases on the FSS reported the most problematic symptoms, i.e self-report of problematic stroke-related symptoms was strongly associated with having a high fatigue-impact. The symptom-burden of experienced stroke-related impairments may increase with situational factors that put demands on the individual. Hence, in line with the results in the study by Rijsbergen et al [206] some patients may experience less optimal quality of life, more fatigue and other adverse symptoms over time, even though their objective function may improve. Similar findings are reported in a study by Morsund et al [72]. The study described a general improvement in cognitive function within the first year post-stroke. However, there was still a high prevalence of minor cognitive impairments, with an increasing prevalence of depressive symptoms and a persisting high prevalence of fatigue.

If these symptoms are subtle, they may not be discovered in patients that are independent in PADL and/or has little visible disability. This implicates that the patient's description of symptom-burden post-stroke is of importance when assessing PSF and considering treatment options. Clinically, it may be that interventions targeted at reducing perceived stress have a therapeutic potential to reduce subjective symptom burden in these patients, including reduced degree of fatigue

5.1.4.3 Associations between comorbidities, pre-stroke fatigue, sleep-quality and PSF

In line with previous studies [51, 54, 145], a strong association was found between pre-stroke fatigue and PSF in all three papers.

It may be that there are common factors underlying both pre- and post-stroke fatigue, such as psychological distress, life-stressors and/or comorbid medical conditions [54]. In line with this, we found that having pre-stroke fatigue was associated with having multiple pre-existing co-morbidities, particularly a mental health comorbidity. Furthermore, having multiple existing comorbidities were associated with being a fatigue case or belonging to the high fatigue trajectory class.

Our findings are in line with earlier research that identifying and treating sleep-disturbances is clinically important to reduce fatigue and improve quality of life [261]. In all three papers, fatigue was associated with poorer sleep-quality.

5.1.4.4 Associations between psychosocial factors and PSF

Psychological distress-symptoms were associated with higher fatigue scores in all three of our papers.

In paper I, an association was found between depressive symptoms and belonging to the high-fatigue trajectory. These findings are in line with a recent study by Sibbritt et al [54] that found that increases in depression-scores were associated with increase in fatigue-scores. In general, the association between depression and fatigue is well established [29, 34, 69, 143].

However, in our samples, there also were patients defined as fatigue-cases that were not clinically depressed. Hence, although the degree of symptoms of psychological distress

often is associated with high fatigue-scores, there is not a one-to-one relationship between fatigue and depression [94].

We found that avoidant coping and poorer self-efficacy beliefs were associated with high fatigue-scores. This is in line with previous research that has found that having low self-efficacy beliefs, using maladaptive coping-strategies and life-stressors may contribute to both depression and fatigue [262]. According to Wu et al [8], vulnerability to stress may be a pre-disposing factor that leads to both pre-and post-stroke fatigue. Using avoidant coping-strategies and having poor self-efficacy may render people vulnerable to stress. In general, resilience, or robustness, plays an important role in adjusting to life after stroke and/or coping with adversities in life [263-268], it is likely that this also includes adjusting to PSF.

We did not find a significant association between number of life-stressors and symptoms of PSF. One possible explanation for this, is that the NEL does not grade the impact of different life-stressors, hence you may get 1 point for "loss of child or family-member" and also 1 point for "having a valuable item stolen". A more fine-grained assessment that differentiates more between type of life-stressors may have yielded a stronger association between life-stressors and fatigue. It is also possible that the presence of substantial life stressors increases vulnerability for fatigue in combination with using maladaptive coping strategies and/or having low self-efficacy beliefs, and that the latter factors mask the effect of the life stressors per se. These possible associations between life-stressors and PSF needs further exploration in larger samples.

There might be sub-groups of those who experience more severe fatigue post-stroke; one group where the main reason for the fatigue is the residual impairments after their stroke, and another group where psychosocial factors are the main reason for the fatigue. These factors may also coexist and interact. For some, psychological factors such as depression or low self-efficacy beliefs may also impact on rehabilitation and motivation for rehabilitation [269], thus also affecting the patients' physical stroke sequelae. In general, through multidisciplinary rehabilitation, enabling stroke-patients to perceive the future as more manageable may not only decrease PSF, but also increase function and quality of life.

Our findings suggest that enhancing psychological robustness through interventions aimed at increasing adaptive coping strategies and bolstering self-efficacy may decrease

fatigue symptoms as well as psychological distress. Furthermore, the results in this study indicate that rehabilitation aimed at improving function, increase independence in PADL and how to cope with residual impairments, may indirectly also reduce severity of fatigue through increasing function and QOL.

Finally, it is also worth noting that the majority of patients in our samples did not suffer from post-stroke depression nor post- stroke fatigue, indicating that on a group level, many patients are psychologically robust and cope well with having suffered a stroke.

5.2 Post- stroke fatigue; disease specific or generic?

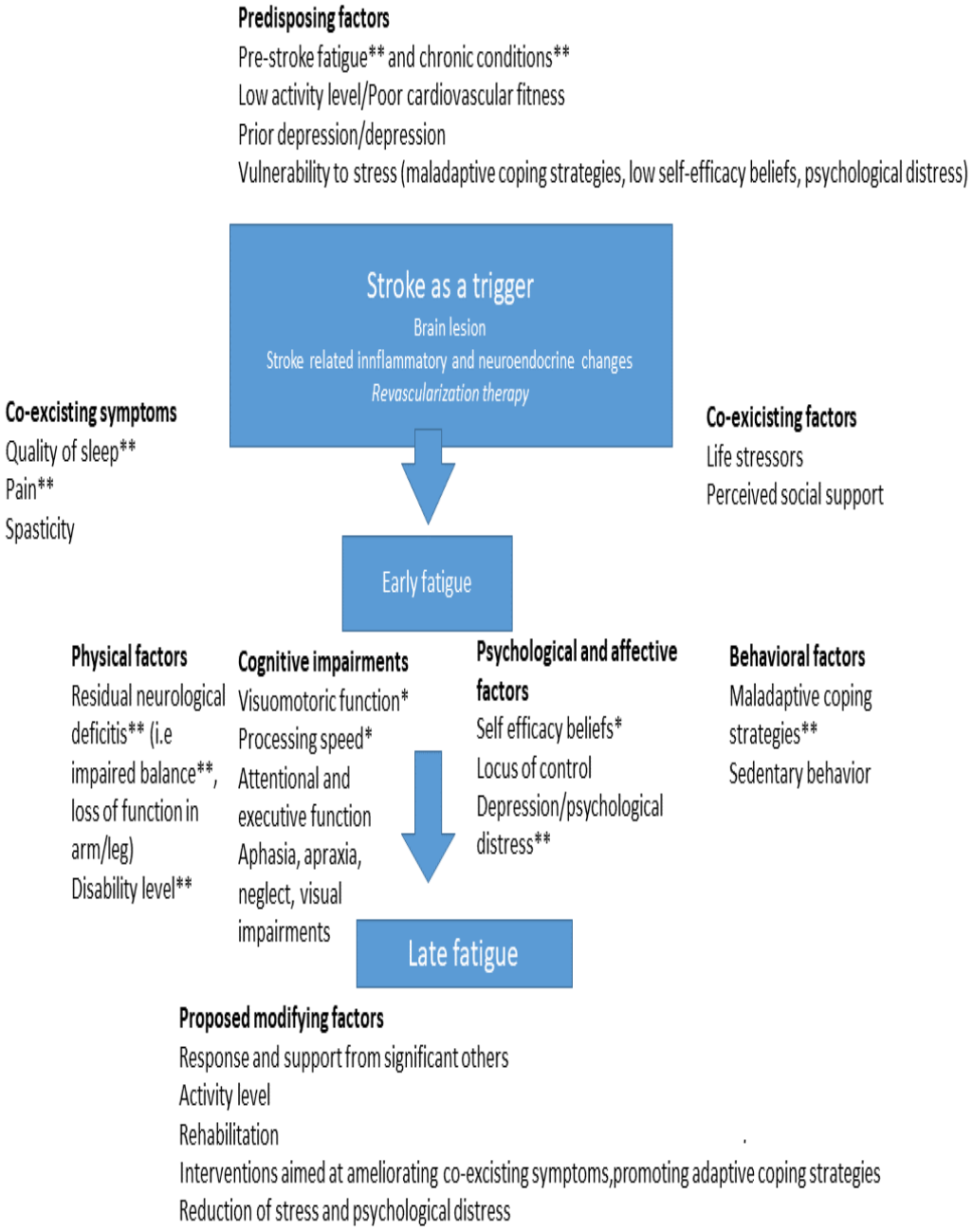
Studies of fatigue often explore the relationship between fatigue and specific diseases, and the terms used to describe fatigue in chronic disorders are often disease-specific, such as “multiple sclerosis fatigue”, “cancer fatigue”, “rheumatoid arthritis fatigue”, “post-stroke fatigue” and so on [26]. Yet, the relationship between fatigue and the somatic processes associated with the different conditions is often weak, and it is possible that factors associated with fatigue are generic and similar across diagnoses. Thus, development of treatments could be transdiagnostic. A study by Menting et al [18] reanalyzed data of patients suffering from 15 common chronic diseases that cause disability. The purpose was to explore to what extent fatigue severity can be explained by the specific disease and to what extent non-disease specific factors were related to fatigue. Non-disease-specific factors found to be associated with fatigue included demographic variables, aspects of daily functioning, health-related factors, pain, lower levels of physical activity, more disturbed sleep and lower self-efficacy scores. Depressive symptoms were significantly related to fatigue in half of the studies. There was also some evidence for fatigue being related to younger age, possibly reflecting that younger people face more challenges in their daily life in regard to work and family obligations [18].

Currently, fatigue in the general population is actualized through long-Covid, i.e.adverse symptoms persisting for months after the acute illness. In a review article [270] on prevalence and associations of long-Covid, symptoms of fatigue was reported in 13-33% of patients. It was found that the severity of the acute illness, psychological status at baseline and the cognitive and behavioral responses to the illness predicted post-infective fatigue states. The authors of the review article proposed that in general,

assessment of fatigue following diseases may incorporate the following factors; predisposing factors such as psychosocial vulnerability, the severity of the disease and residual impairments, and maintaining factors such as pain, sleep disturbances, mood disorders and behavioral factors such as activity patterns [270]. This is in line with the proposed model of PSF presented in this thesis (see fig.4).

PSF may be diagnosis specific in the sense that for many patients the stroke was the trigger for the fatigue and that fatigue may be maintained by stroke-related impairments such as impaired balance, impaired visuo-motor function and dependency in PADL. In sum, however, some factors are likely to be common to fatigue in general (psychological distress, maladaptive coping strategies, low self-efficacy beliefs, impaired quality of sleep, comorbidities and pain), while other factors may be common to medical conditions that affects the central nervous system (dependency in PADL, impaired balance, cognitive dysfunctions). Thus, the notion that interventions aimed at ameliorating fatigue to a large degree may be transdiagnostic, is supported.

Fig.4 Proposed model of PSF



* p<0.05 in univariate analyses, ** p< 0.05 in multivariate analyses

5.3 Methodological issues; strengths and limitations

5.3.1 Sample characteristics, sample size, and generalizability of study findings

A power analysis conducted prior to the start of data collection indicated that a minimum of 67 patients were needed for the study, assuming 30% prevalence of both fatigue and depression. In paper I, 115 responders completed all four data-collection time-points. Of the 112 included in the study in paper II and III, the sample consisted of 93 for follow up at 3 months, i.e a percentage of 83. Of these, 78 (83.9%) completed the follow up at 12 months. Although the sample size in all papers exceeded the calculated minimum of included patients, the sample is small in regards to conducting subgroup-analyses. This may also have affected our possibility to find significant associations between post-stroke fatigue and associated factors such as number of life-stressors, attention and executive functions.

In both studies, the samples were representative of the stroke population in Norway regarding the gender distribution (men > women). The distribution of age was slightly skewed in the direction of our samples being younger than the average population of stroke-survivors in Norway. According to "Norsk hjerneslagregister" (the Norwegian registry of stroke patients), a database containing data on prevalence, demographics, medical factors and treatment of stroke in Norway, the distribution of age of patients who suffered a stroke in Norway during 2020 shows that the group older than 75 years is the largest. In our sample in paper II and III, the group <65 years is the largest. The age-distribution probably also reflect who were eligible for participation, and that the older patients in the acute hospital tended to be more frail and have more severe comorbidities. There was also a higher drop-out between three and twelve months among the older participants in paper III due to deteriorating health, new illnesses and death.

Although the sample contains some patients with hemiparesis and focal impairments, the study samples mainly consisted of patients with mild stroke. In this regard, they differ from the Norwegian stroke population. In the Norwegian registry of stroke patients, 45% of the stroke-patients had a NHISS-score of 0-2, indicating a minor stroke. Before thrombolytic treatment, the median NHISS-score was 5. A majority of the patients in this sample had minor strokes as classified by the NHISS, and a majority were independent in PADL (mRS 0-2). There were some patients that had moderate

stroke, and a few had moderate to severe stroke (for details, see table 1). Patients with severe aphasia were excluded, as this would impair their ability to respond to the questionnaires and complete neuropsychological assessment. Thus, the most severely impaired stroke patients in whom the prevalence of fatigue might be highest may have been lost. This makes generalizability of the findings to the stroke population as a whole restricted.

Further, most of the patients scored within the normal range on tests of cognitive function. It is possible that patients with more severe cognitive impairments either declined participation or were not included. One patient was also excluded after inclusion due to not having comprehended the consent-information due to cognitive impairments. Hence, the proportion of patients with disabilities and/or cognitive impairments may be too small for associations to be significant in the statistical analyses. In addition, the neuropsychological tests used in this study, may not capture impairments in sustained attention and effort which may be more evident in real life situations.

In sum, inclusion bias may have rendered our samples most representative of relatively younger stroke-patients with relatively few physical and cognitive residual impairments.

There are some possibly confounding factors in regards to internal validity. It is estimated that about 5-7% of those aged ≥60 suffers from dementia [271] and it may be that there are participants with undiagnosed dementia in the sample. This would make the association between stroke-related cognitive impairments and PSF less clear.

Patients with previous stroke were also included in the studies in paper II and III. Although this may have implications for internal validity regarding the relationship between cognitive impairments or site of stroke lesion and PSF, it may also be a strength regarding external validity, making the sample more representative for the stroke population in general.

There is a risk of Type I-error due to multiple testing. Findings of associations between fatigue and predictor-variables at significance level of $p<0.05$ are described, however, the findings have to be regarded with caution. In order to reduce this risk, in paper III we reduced the level of significance from $p<0.05$ to $p<0.001$.

5.3.2 Design characteristics

A study with data-collection at different time-points allows for both cross-sectional and longitudinal exploration of data. This is a notable strength of the studies included in this thesis, and an important addition to previous research.

This thesis also has a strength in using a broad biopsychosocial protocol that includes demographic, medical, physical, psychological, cognitive and environmental factors. There are, however, no data on blood components or genetic markers that may make stroke-patients vulnerable for fatigue-development. Ideally, if these variables also were included in the protocol and the sample was larger, an even more complex and complete in depth exploration of associates of PSF would have been possible.

5.3.3 Use of self-report measures and performance- based methods for assessing cognitive function

In this thesis, self-report measures for symptom-related factors and PSF were used in all three papers. This methodological approach has several possible weaknesses.

Reliability, the ability to reproduce a result consistently in time, is among the main desired property of measurement instruments [272]. Self-report, either through interviews (i.e Lynch interview) or questionnaires (i.e FSS and FQ), tend to be biased by the current state of the participant [273]. In general, fatigue is a symptom that may fluctuate over time [217, 218], possibly affecting the reliability of self-report measures used to estimate the prevalence of these symptoms at different time-points.

The accuracy of self-report measures may be influenced by several factors. Symptoms may be over- or underreported. Further, upon consenting to participate in the study, the participants were informed about the rationale of the study. Anticipating findings, participants may be prone to demand characteristics [274]. Questions may be miscomprehended due to cognitive impairments/dysfunction or affected by lack of insight into one´s symptoms. Furthermore, retrospective assessment of symptoms, such as pre-stroke fatigue, may be affected by recall-bias [275] These issues may threaten the accuracy and validity of the information obtained.

Neuropsychological tests were used to assess cognitive function in paper III. Standardized tests often deviate from real-world activities; they are often short,

executed within a laboratory-like environment and with structured instructions. The validity of the tests in regard to higher level functioning and sustained attention is thus limited [204]. However, using validated neuropsychological tests, and not relying solely on self-report, is a strength of this study. Finally, there are some missing data on some of the tests as some patients had focal impairments making the test unsuitable. Choosing tests for a sample of stroke patients will always be a compromise between sensitivity, allowing for identification of subtle cognitive dysfunction, and suitability, with risk of missing data.

5.4 Implications for the clinic

This thesis contributes to the current knowledge by providing a holistic, biopsychosocial model of PSF and in describing development of PSF over time. Our findings provide insights into which factors may contribute to different courses of fatigue and which factors may predict PSF at different time-points. To date, this is a field of research where there has been little knowledge.

The findings presented in this thesis have important clinical implications, providing valuable insight into factors associated with long-lasting post-stroke fatigue and factors that may be used to identify patients at risk for fatigue development. A need for early assessment and identification of fatigue is confirmed. As the factors associated with fatigue are biopsychosocial, such assessment should be multidisciplinary.
Clinicians should be aware of factors associated with vulnerability for fatigue development, such as pre-stroke fatigue, early fatigue post stroke, comorbidities, using maladaptive coping strategies, psychological distress-symptoms and stroke-related physical impairments. Clinicians should also be aware that severe fatigue may occur in patients with some degree of residual impairment post-stroke, but who are fairly independent in everyday life. These may suffer from so-called invisible handicaps such as subtle cognitive impairments or psychological distress. If such symptoms are left unattended, the patients may experience an increase in symptom-burden over time.

As there may be individual clusters associated with fatigue, the interventions should be tailored according to individual needs. Furthermore, as factors associated with PSF to a large degree are transdiagnostic, treatment programs and interventions may be applicable for patients with different medical diagnoses and conditions.

5.5 Implications for research

This thesis also provides insight into factors that should be the target for further research.

First, we have shown that the use of different instruments to assess fatigue leads to variability in estimated prevalence. From both a clinical and a scientific point of view, it is important that severe fatigue is correctly identified. The causes of fatigue will remain unclear without correct identification, further delaying development of interventions. The variability of fatigue estimates also highlights the need for consensus on how to measure fatigue.

Longitudinal studies on how different measures similarly or differently measure changes in fatigue-related symptoms over time is also of importance when understanding prevalence of fatigue measured at different time-points.

As the instruments differ in content and associations with other factors, knowing which aspects of fatigue measured is essential. A mixed method approach, using a combination of questionnaires and clinical interviews might add in-depth assessment and understanding of the fatigue experience. Using a semi-structured interview with open-ended questions that adds insight into the phenomenology may be a source for development of new instruments with better content validity.

In line with a biopsychosocial model of PSF, using a broad protocol that assesses both physical, psychological and neurocognitive function and coexisting and modifying symptoms is advisable. It is also advisable to use a longitudinal design as a cross-sectional design is not suited to study different courses of fatigue.

Furthermore, the sample-sizes should be large enough for subgroup-analyses. The samples should also have a certain proportion of participants with stroke-related impairments allowing for development of complex models of PSF. In order to attain a large sample size, multi-center studies are called for. This would also facilitate collaboration between researchers who are interested expanding the knowledge base on post-stroke fatigue and relevant interventions. Research where several diagnoses are included in the samples could also be of interest to shed light on the generic and disease-specific aspects of fatigue.

6. CONCLUSIONS

Our findings suggest that PSF has three different courses over time, the most common being stable courses of low or medium fatigue. There are, however, also those who display a stable course of high fatigue. Within these courses, there were individual trajectories where some recover from fatigue, while others show a course of increasing fatigue and symptom burden.

Furthermore, our findings suggest that fatigue may be triggered, maintained or worsened by stroke-related physical impairments and/or psychological factors such as using avoidant coping strategies, experiencing psychological distress, and having impaired balance. Psychological robustness, including having positive self-efficacy beliefs and using adaptive coping strategies, may be protective against PSF and should be emphasized in stroke rehabilitation.

In line with previous research, we found that suffering from fatigue pre-stroke is strongly associated with PSF. Furthermore, early fatigue was strongly associated with persistent fatigue in our samples. This emphasizes the need of early assessment of fatigue symptoms. The finding of PSF also in patients with little stroke sequelae is of clinical importance as people with minor stroke often have limited follow-up after they are discharged from the hospital. These patients may thus have unmet needs of information and care for residual impairments, also to prevent fatigue-development. Implementing early assessment of fatigue and associated factors might contribute to preventing late-onset fatigue, also in patients with minor to moderate residual post stroke impairments.

The biopsychosocial model of factors associated with PSF underlines the need of an interdisciplinary approach in the assessments and in interventions aimed at ameliorating post-stoke fatigue.

The complexity of PSF is also demonstrated in how different instruments measuring fatigue provide diverging identification of fatigue-cases. For both clinical and research purposes a consensus on the definition and measurement of fatigue is warranted. Without correct identification of fatigue, the understanding of the phenomenon and its associated factors will remain unclear. This will further delay the development of empirically based interventions.

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RESEARCH ARTICLE

Trajectories of fatigue among stroke patients from the acute phase to 18 months post-injury: A latent class analysis

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Abstract

Introduction

Post-stroke fatigue (PSF) is a common symptom affecting 23–75% of stroke survivors. It is associated with increased risk of institutionalization and death, and it is of many patients considered among the worst symptoms to cope with after stroke. Longitudinal studies focusing on trajectories of fatigue may contribute to understanding patients' experience of fatigue over time and its associated factors, yet only a few have been conducted to date.

Objectives

To explore whether subgroups of stroke survivors with distinct trajectories of fatigue in the first 18 months post stroke could be identified and whether these subgroups differ regarding sociodemographic, medical and/or symptom-related characteristics.

Materials and methods

115 patients with first-ever stroke admitted to Oslo University Hospital or Buskerud Hospital were recruited and data was collected prospectively during the acute phase and at 6, 12 and 18 months post stroke. Data on fatigue (both pre- and post-stroke), sociodemographic, medical and symptom-related characteristics were collected through structured interviews, standardized questionnaires and from the patients' medical records.

Growth mixture modeling (GMM) was used to identify latent classes, i.e., subgroups of patients, based on their Fatigue Severity Scales (FSS) scores at the four time points. Differences in sociodemographic, medical, and symptom-related characteristics between the latent classes were evaluated using univariate and multivariable ordinal regression analyses.

be used for, who is responsible for storage and how it is stored. For example, data can be used in meta-analyses. It will be the Data Protection Officer, and the Regional Committees for Medical and Health Research Ethics, who can give final approval.

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Results and their significance

Using GMM, three latent classes of fatigue trajectories over 18 months were identified, characterized by differing levels of fatigue: low, moderate and high. The mean FSS score for each class remained relatively stable across all four time points. In the univariate analyses, age <75, pre-stroke fatigue, multiple comorbidities, current depression, disturbed sleep and some ADL impairment were associated with higher fatigue trajectories. In the multivariable analyses, pre-stroke fatigue (OR 4.92, 95% CI 1.84–13.2), multiple comorbidities (OR 4,52,95% CI 1.85–11.1) and not working (OR 4.61, 95% CI 1.36–15,7) were the strongest predictor of higher fatigue trajectories The findings of this study may be helpful for clinicians in identifying patients at risk of developing chronic fatigue after stroke.

Introduction

Post-stroke fatigue (PSF) is a common symptom affecting 23–75% of stroke survivors [1]. For many stroke survivors, it is considered among the worst symptoms to cope with following a stroke [2]. Fatigue has been described as a state of weariness unrelated to previous exertion levels, which is usually not ameliorated by rest, and as a chronic and subjective feeling of lack of energy, weariness and aversion to effort [3]. PSF is associated with higher risk of institutionalization and death and impedes patients' rehabilitation [4] and quality of life [5]. Although fatigue in the acute phase is often considered a normal and temporary feature following stroke, Lerdal et al. [6] identified fatigue in the acute phase as an independent predictor of poorer physical health 36 months after stroke. Increased knowledge about the onset and different trajectories of PSF and which factors predict these trajectories may enable us to develop empirically-based interventions that ameliorate PSF and its debilitating sequelae.

Longitudinal studies shed light on trajectories of fatigue and are critical to understanding patients' experience of fatigue over time and its associated factors. Longitudinal studies have the advantage of reporting individual changes over time, in addition to the proportion of patients who have the symptom at particular time points obtainable in cross-sectional studies. A systematic review of longitudinal studies on PSF by Duncan et al. [7] found only nine that assessed fatigue at multiple time points after stroke. Fatigue declined across time points in seven of the studies and increased in two studies. Of these studies, five assessed fatigue at two time points, three at three time points and one at four separate time points, and only two of the studies assessed fatigue within the two first weeks after stroke. More recently, Duncan et al. [8] conducted a longitudinal study, which assessed fatigue within the first month and at 6 and 12 months after stroke and found that a low level of physical activity at 6 and 12 months was associated with a higher degree of fatigue.

From a clinical point of view, it is important to determine whether fatigue in the acute phase following stroke can predict chronic PSF, and if so, what clinical characteristics are associated with the different fatigue trajectories. This is a critical step to the early identification of patients vulnerable to developing PSF and the development of more tailored treatment programs like those in use for patients with cognitive and physical deficits. Findings related to early mobilization indicate that the acute phase following stroke may be a critical period for maximizing recovery [9]. There are, however, few studies that explore fatigue in the acute phase after stroke and whether it is related to chronic fatigue problems. A cross-sectional study by Mutai et al. [10] reported the prevalence of PSF within 2 weeks post-stroke to be 56.4%

using the Multidimensional Fatigue Inventory, and multivariable stepwise regression analyses showed that anxiety, right hemisphere lesion sites and thalamus lesions were associated with general fatigue. The study did not, however, include a follow-up.

PSF is considered a complex symptom influenced by different factors and the interactions between them [11]. Wu et al. has proposed a model for understanding PSF, which states that it is plausible that different factors contribute to PSF at different times. Three longitudinal studies found significant associations between fatigue and mood at the same time point [7]. PSF has been associated with depressive symptoms even among patients who do not meet diagnostic criteria for depression [12]. While early fatigue might be associated with neuroendocrine systems and damage to brain structures responsible for maintaining wakefulness and attention, psychosocial and behavioral factors might be important for both triggering and maintaining fatigue. Vulnerability to stress might be a predisposing factor and lead to both pre- and post-stroke fatigue, and psychological factors such as self-efficacy beliefs and coping style might influence the course of fatigue [11]. In accordance with this, retrospective self-reports of fatigue lasting longer than 3 months prior to stroke were found to be associated with PSF in a group of 115 patients [6]. Choi-Kwon et al. found that pre-stroke fatigue was the strongest predictor of PSF an average of 15 months after stroke in a sample of 220 outpatients [13]. Stroke patients often suffer from other medical conditions, such as diabetes, high blood pressure, and heart conditions [14], and these comorbidities could also lead to both pre- and post-stroke fatigue.

All in all, there seem to be gaps in current knowledge about trajectories of fatigue following stroke, specifically those that include the acute phase, and about which factors might be predictive of PSF from an early phase.

Aims

The aims of this study were to explore whether subgroups of stroke survivors with distinct trajectories of fatigue in the first 18 months after stroke could be identified, and if so, to determine whether these subgroups differ on sociodemographic, medical and symptom-related characteristics, such as sleep, fatigue and depression.

Materials and methods

Patients and procedures

The Post-Stroke Fatigue Study is a longitudinal, observational study that recruited stroke patients admitted to either of two hospitals in Oslo and Buskerud counties between March 2007 and September 2008. The main inclusion criterion was first-ever stroke according to the International Classification of Disease (ICD-10 diagnoses I60-I64). Patients also had sufficient cognitive function to consent to participate, be fully conscious, and be oriented to person, place, and time. If unable to point to response alternatives on a questionnaire, they were excluded. Of the 193 patients with a diagnosis of first-ever stroke admitted to these two hospitals, 119 were included in the study. Four were subsequently excluded because baseline data was collected more than 15 days after hospital admission. Thus, the sample for analyses includes 115 patients. Details of the recruitment and inclusion process are described in Fig 1.

Data were collected at four time points (T1-T4): during the acute phase (within 14 days of the stroke), and at 6, 12 and 18 months after the stroke. The data were collected through structured interviews and by use of standardized questionnaires. Data on stroke type, lesion location and comorbid conditions were collected from the patients' medical records.

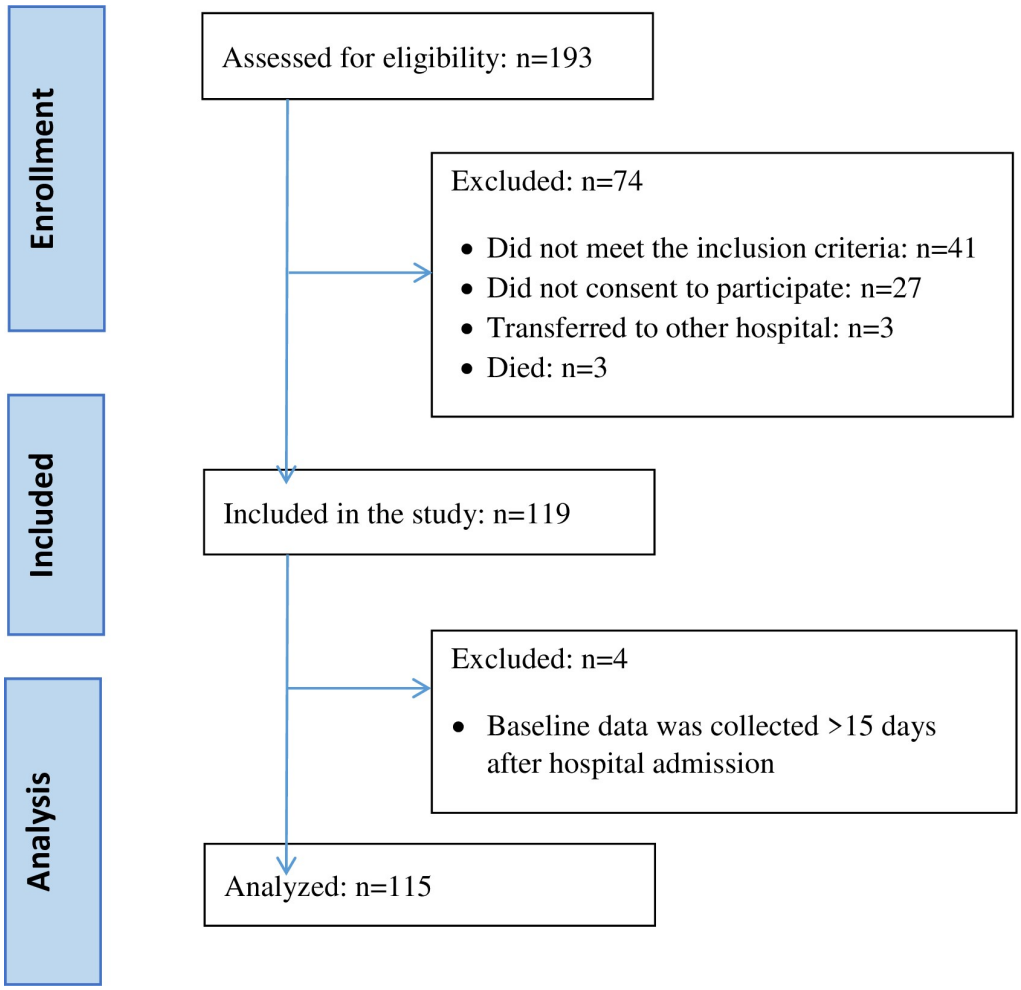

Fig 1. Flow chart showing the recruitment and inclusion of patients in the study.

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Measurements

Sociodemographic variables. Data on sex, age, use of medications, and time since hospital admission were collected from the patients' medical records. Data on cohabitation status (i.e., living alone or with others), level of education, employment status and physical functioning were collected through a structured interview.

Medical characteristics. Stroke type and lesion location: Computed tomography (CT) scans were taken of all patients upon admittance to hospital. Based on the radiologists' descriptions, the stroke was categorized into one of the following three types: ischemic infarct, hemorrhage and negative findings/clinical stroke. The location of the lesion was categorized as left, right or bilateral. Some lesions from previous undiagnosed strokes showed up on CT scans and were included in the classification of stroke type and location.

Comorbidities included present or past conditions. This analysis focused on conditions considered relevant to fatigue, specifically those affecting circulatory, respiratory, endocrine, nervous, mental, or muscular systems.

Body mass index (BMI) was calculated as the patient's weight in kilograms divided by the square of their height in meters. Weights and heights were obtained from the patients' medical records.

Symptom-related measures. Fatigue was measured with the Fatigue Severity Scale (FSS). The FSS is a 9-item instrument where higher mean scores indicate higher degrees of fatigue [15]. The FSS has been shown to be both valid and reliable in different clinical groups [16]. In a study by Nadarajah et al., the FSS had a Cronbach's alpha of >0.90 in samples of stroke patients and healthy controls. The FSS was also strongly correlated with visual analog scales of fatigue (r = 0.60) [16].

Pre-stroke fatigue was assessed through a clinical semi-structured interview. Patients were asked whether they had experienced substantial fatigue, defined as affecting their ability to perform daily activities, before the stroke, and if they had, whether this had lasted less than 3 months, 3–6 months or for more than 6 months. Patients who reported substantial fatigue lasting at least 3 months before the stroke were defined as having pre-stroke fatigue [6].

Depression was measured with the Beck Depression Inventory (BDI), a 21-item self-report questionnaire. BDI scores of 0–9 indicate normal mood, 10–14 mild depression, 15–24 moderate depression and 25 and above severe depression [17] Studies on psychometric properties of the inventory has showed good internal consistency, concurrent validity and a good ability to discriminate subtypes of depression [18]. In this sample the BDI-items had a Cronbach's alpha of 0.855.

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI), a self-report questionnaire consisting of 19 items that assess sleep quality over a one-month time period. A PSQI sum score is calculated and ranges from 0 to 21, where higher scores indicate worse sleep quality. A score higher than 5 is indicative of sleep disturbance. An assessment of the index' psychometric properties showed acceptable internal homogeneity, reliability and validity [19].

Activities of Daily Living (ADL) with regard to the patient's level of dependency- independency were assessed with the Barthel Index (BI) for ADL, a scale of 10 items where higher scores represent higher levels of independence [20]. The BI score was based on the patients' self-rating on the questionnaire or patient interviews. The instrument has been shown to be a reliable and valid measure of basic ADL function in patients with stroke. As we did not have a direct measure of the severity of stroke, such as the National Institute of Health Stroke Scale (NIHSS), a tool used by healthcare providers to objectively quantify the impairment caused by stroke, the BI score served as a measure of severity of function loss following stroke.

Data analysis

Statistical analyses were performed using SPSS software version 23 (IBM Corp, Armonk, NY, USA) and Stata software version 13 (Stata Corp, College Station, TX, USA).

Growth mixture modelling (GMM) in the GLLAMM package in Stata [21] was used to identify latent classes, i.e. subgroups of patients based on their FSS scores at the four time points. GMM allows for the estimation of more than one growth curve, for previously unidentified subgroups that change differently over time. GMM has benefits over alternative methods, as it can allow for variations between individuals and subgroups, not only between individuals and population averages. GMM employs a model-based approach to calculate the probability of membership in each class, and also quantifies uncertainty in class membership [22]. The number of latent classes identified was based on likelihood values and stability of the estimated classes. In general, mixture models aim to uncover unobserved heterogeneity in a population and to find substantively meaningful groups of people that are similar in their responses to measured variables or trajectories [23].

SPSS was used to calculate descriptive statistics and perform hypothesis testing about group differences and associations between variables. For hypothesis testing, the significance level was set at 0.05.Univariate associations between pre-stroke fatigue and comorbidities were evaluated using Chi-square tests, or Fishers Exact test when expected cell frequencies were <5. Associations between sociodemographic, medical, and symptom-related characteristics and the latent classes (i.e., fatigue trajectories) were evaluated by using ordinal regression for both univariate and multivariable analyses. Variables included in the multivariable analyses were based on theoretical importance (i.e., gender) or a p-value of ≤ 0.10 in the univariate analyses. Effect sizes for the associations are reported as odds ratios (ORs) with 95% confidence intervals (CI).

Ethics

This study was approved by the Regional Medical Research Ethics Committee of Health for the South East of Norway (Ref #2.2007.90) and by the Data Protection Officer at Oslo University Hospital. All patients provided written informed consent prior to participation.

Results

One hundred and fifteen patients were included in the analyses (see Fig 1 for details). Most participants were male (n = 68, 59%), lived with a partner or at least one other person (n = 72, 63%) and the mean age was 68.3 (SD 13.3) years. Sociodemographic, medical and symptom-related characteristics of the sample are shown in Table 1. Because the vast majority of patients (77%) had at least one comorbidity relevant to fatigue and only four patients reported more than three, subsequent analyses compared patients with at least two comorbidities to those with less than two.

Using GMM, three latent classes of fatigue trajectories over 18 months were identified. As shown in Fig 2 and Table 2, the mean FSS scores stayed relatively stable across all four time points in all three groups, but each group differed in the degree of fatigue reported across time. Therefore, the three classes were labeled low (n = 23, 20%), moderate (n = 52, 45%) and high fatigue (n = 40, 35%).

While the sample's mean depression level (mean BDI score 9.6, SD 7.6) during the acute phase was below the cutoff score of 14, the BDI scores of the high (mean 13.0, SD 8.1) and moderate (mean 9.0, SD 6.9) fatigue groups were significantly higher ($p < .001$ and $p = .027$, respectively) than in the low group (mean 5.0, SD 5.6). Whereas 13% of those in the low fatigue group suffered from mild to severe depression based on BDI scores, 49% suffered from mild to severe depression in the high fatigue group.

In the univariate ordinal regression analyses, the baseline patient characteristics that were significantly associated with having a higher fatigue trajectory were being over 75 years of age and having pre-stroke fatigue, having at least two comorbidities relevant to fatigue, mild-severe depression, disturbed sleep, or at least some ADL impairment (see Table 3). Living alone and not working at T1 and T4, were not significantly related to a patient's fatigue trajectory, but because their p-values were <0.10, these variables were included in the multivariable analysis. The patient's gender, education, stroke type and location, and BMI were unrelated to their fatigue trajectory, but patient gender was included in the multivariable model based on prior findings of gender differences in fatigue.

In the multivariable ordinal regression analysis, the only baseline patient characteristics associated with having a higher fatigue trajectory were not working, having multiple comorbidities and having pre-stroke fatigue (see Table 3). Although neither depression nor sleep disturbance were associated with fatigue trajectory when controlling for other relevant factors,

Table 1. Demographic, clinical, and stroke-related characteristics of the sample (N = 115).

Characteristic	Total sample (N = 115)	Class 1	Class 2	Class 3
		Low fatigue (n = 23)	Moderate fatigue (n = 52)	High fatigue (n = 40)
Sociodemographics				
Sex, n (%)				
Male	68 (59%)	14 (60%)	34 (61%)	20 (50%)
Female	47 (41%)	9 (40%)	18 (39%)	20 (50%)
Age, mean (SD)	68.3 (13.3)	67.1 (9.2)	67.3 (14.2)	70.3 (14.1)
Cohabitation, n (%)				
Living with others	72 (63%)	18 (78%)	32 (62%)	22 (55%)
Living alone	43 (37%)	5 (22%)	20 (38%)	18 (45%)
Education, n (%)				
Low (<high school)	83 (70%)	15 (65%)	37 (67%)	31 (78%)
High (≥high school)	32 (30%)	8 (35%)	15 (33%)	9 (22%)
Employment, n (%)				
Working at T1[a]	28 (24%)	8 (35%)	14 (27%)	6 (15%)
Working at T4[b]	15 (13%)	4 (17%)	8 (15%)	3 (8%)
Medical variables				
Stroke type				
schemic	90 (78%)	19 (83%)	38 (73%)	33 (82%)
Haemorrhage	7 (6%)	1 (4%)	3 (6%)	3 (8%)
Negative findings/clinical stroke	18 (16%)	3 (13%)	11 (21%)	4 (10%)
Side of stroke lesion				
Right	31 (27%)	10 (43%)	12 (23%)	9 (22%)
Left	29 (25%)	2 (9%)	16 (31%)	11 (28%)
Bilateral	20 (17%)	5 (22%)	7 (13%)	8 (20%)
Unknown	35 (31%)	6 (26%)	17 (33%)	12 (30%)
Comorbidities [c] n (%)				
None	27 (23%)	8 (35%)	14 (27%)	5 (12%)
1	49 (43%)	11 (48%)	26 (50%)	12 (30%)
2 or more	39 (34%)	4 (17%)	12 (23%)	23 (58%)
BMI, mean (SD)	26.2 (5.1)	25.6 (5.5)	26.0 (4.7)	26.7 (5.5)
Symptom-related variables				
Pre-stroke fatigue, n (%)	34 (30%)	1 (4%)	13 (25%)	20 (50%)
BDI, mean (SD)	9.6 (7.6)	5.0 (5.6)	9.0 (6.9)	13.0 (8.1)
PSQI, mean (SD)	6.9 (3.6)	5.2 (3.6)	6.9 (3.6)	7.9 (3.3)
Barthel Index, mean (SD)	17.7 (4.1)	18.0 (5.0)	18.2 (3.5)	16.9 (4.1)

Abbreviations: Barthel Index = measure of independence with activities of daily living; BDI = Beck Depression Inventory II; BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index.

[a] T: At the time of the stroke

[b] T4: Within 18 months after the stroke

[c] Comorbidities relevant to fatigue included chronic conditions affecting the circulatory, respiratory, endocrine, nervous, mental, or muscular systems.

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when either one of these factors was omitted from the model, the other became significant (depression OR = 2.69, 95% CI 1.06, 6.88; sleep OR = 283, 95% CI 1.17, 6.84), suggesting that their associations in the multivariable model were affected by multicollinearity. Nonetheless, having pre-stroke fatigue was the strongest predictor of a worse fatigue trajectory, with patients reporting persistent fatigue (>6 months) prior to their stroke having nearly 5 times higher

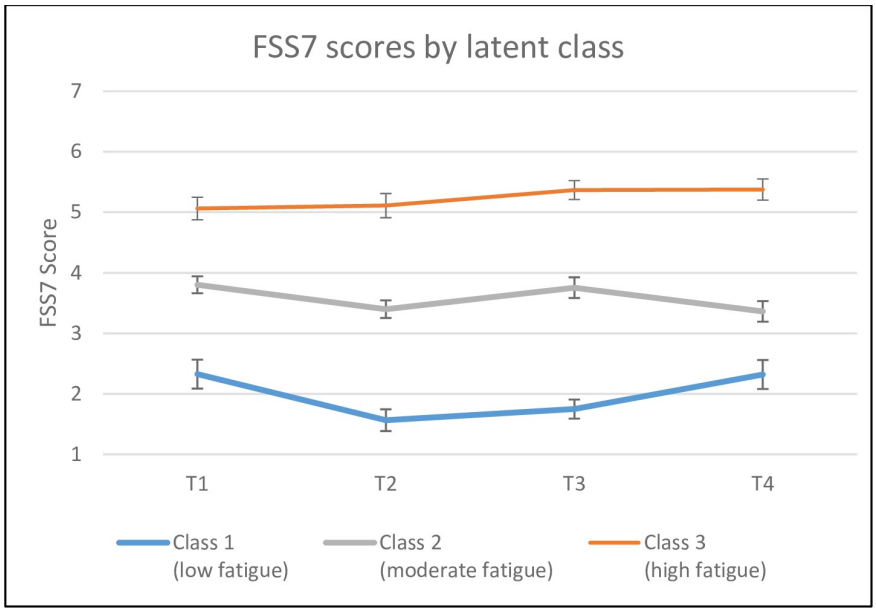

Fig 2. FSS7 scores by latent class.

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odds of a higher post-stroke fatigue trajectory than patients without pre-stroke fatigue (OR = 5.92, 95% CI1,84, 15.5). A univariate analyses showed no significant relationships between pre-stroke fatigue and pre-stroke comorbidities in regards to specific conditions which might be associated with fatigue, such as those affecting the circulatory, endocrine, neurological or muscular systems. Pre-stroke fatigue was not only associated with fatigue class, but was also associated with having multiple pre-existing comorbidities (p = .0180), particularly a mental health comorbidity (p = .002). However, pre-stroke fatigue was not specifically associated with comorbid conditions affecting the circulatory, respiratory, endocrine, neurological or muscular systems. Of the 34 patients reporting pre-stroke fatigue, most (59%) had a high fatigue trajectory in the year after stroke, whereas only one of these patients (3%) had a low fatigue trajectory. In contrast, of the 81 patients without pre-stroke fatigue, only 25% had a high fatigue trajectory, and a similar proportion (27%) had a low fatigue trajectory.

Discussion

To our knowledge, this is the first study that has explored a sample of first-ever stroke patients' trajectories of fatigue from the acute phase through the first 18 months post-stroke. Firstly, in this sample, the GMM analyses identified three classes with distinct trajectories of fatigue during the first 18 months post stroke. Our study adds to the current body of knowledge by

Table 2. Mean (SD) FSS scores at each time point, overall and by fatigue class.

Time	Total sample (N = 115)	Class 1	Class 2	Class 3
		Low fatigue (n = 23)	Moderate fatigue (n = 52)	High fatigue (n = 40)
T1: acute phase	3.95 (1.47)	2.33 (1.15)	3.80 (1.01)	5.06 (1.18)
T2: 6 months	3.62 (1.63)	1.56 (0.80)	3.40 (1.01)	5.11 (1.18)
T3: 12 months	3.86 (1.64)	1.74 (0.72)	3.75 (1.17)	5.37 (0.89)
T4: 18 months	3.76 (1.58)	2.32 (1.10)	3.36 (1.15)	5.38 (0.96)

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Table 3. Univariate and multivariable ordinal regression analyses of fatigue class.

Independent variables	Fatigue class, n (%)			Ordinal regression	
	Low (n = 23)	Medium (n = 52)	High (n = 40)	Univariate OR (CI)	Multivariable OR (CI)
Sociodemographics					
Sex					
Female	9 (39%)	18 (35%)	20 (50%)	1.50 (0.75, 3.03)	1.13 (0.50, 2.56)
Male	14 (61%)	34 (65%)	20 (50%)	reference	reference
Age					
<60 years	3 (13%)	12 (23%)	8 (20%)	1.72 (0.68, 4.34)	3.17 (0.87, 11.46)
60–75 years	14 (61%)	24 (46%)	14 (35%)	reference	reference
>75 years	6 (26%)	16 (31%)	18 (45%)	**2.23 (1.02, 4.90)**	1.90 (0.60, 3.74)
Cohabitation					
Living with others	18 (78%)	32 (62%)	22 (55%)	reference	reference
Living alone	5 (22%)	20 (38%)	18 (45%)	**1.86 (0.91, 3.82)**	1.79 (0.71, 4,53)
Education					NI
High	8 (35%)	15 (29%)	9 (22%)	reference	
Low	15 (65%)	37 (71%)	31 (78%)	1.52 (0.71, 3.26)	
Employment at T1					
Working	8 (35%)	14 (27%)	6 (15%)	reference	reference
Not working	15 (65%)	38 (73%)	34 (85%)	**2.13 (0.95, 4.77)**	**4,61 (1,36,15,70)**
Medical variables					
Stroke type					NI
Infarct	19 (83%)	38 (73%)	33 (82%)	1.32 (0.51, 3.40)	
Hemorrhage	1 (4%)	3 (6%)	3 (8%)	1.84 (0.35, 9.54)	
No signs	3 (13%)	11 (21%)	4 (10%)	reference	
Stroke side (n = 80)					NI
Left	2 (12%)	16 (46%)	11 (39%)	0.61 (0.21, 1.75)	
Right	10 (59%)	12 (34%)	9 (32%)	1.38 (0.47, 4.01)	
Bilateral	5 (29%)	7 (20%)	8 (29%)	reference	
Comorbidities[a]					
No comorbidities	7 (30%)	16 (31%)	5 (12%)	reference	reference
Comorbidities	16 (70%)	36 (69%)	35 (88%)	**4,42 (2,024.78)**	4,52(1,8511,10)
BMI (n = 108)					NI
≤25	11 (48%)	19 (39%)	15 (42%)	reference	
>25	12 (52%)	30 (61%)	21 (58%)	0.88 (0.43, 1.80)	
Symptom-related variables					
Pre-stroke fatigue					
Yes	1 (4%)	13 (25%)	20 (50%)	**4.97 (2.18, 11.3)**	**4,92 (1,84,13,20)**
No	22 (96%)	39 (75%)	20 (50%)	reference	reference
Depression (n = 112)					
None, BDI 0–13	20 (87%)	39 (78%)	20 (51%)	reference	reference
Mild-severe, BDI ≥14	3 (13%)	11 (22%)	19 (49%)	**3.87 (1.71, 8.73)**	2.20 (0.85, 5.75)
Sleep Quality (n = 113)					
Normal, PSQI = <5	11 (48%)	16 (32%)	6 (15%)	reference	reference
Disturbed, PSQI>5	12 (52%)	34 (68%)	34 85%)	**3.06 (1.39, 6.73)**	2.41 (0.97, 5.98)
ADL Independence (n = 114)					
Impaired (BI<20)	4 (17%)	19 (36%)	20 (51%)	**2.66 (1.27, 5.54)**	1,99 (0854,65

(*Continued*)

Table 3. (Continued)

Independent variables	Fatigue class, n (%)			Ordinal regression	
	Low (n = 23)	Medium (n = 52)	High (n = 40)	Univariate OR (CI)	Multivariable OR (CI)
Not impaired (BI = 20)	19 (83%)	33 (64%)	19 (49%)	reference	reference

Bold odds ratios and CIs have $p<0.10$ for univariate analyses and $p<0.05$ for multivariable analyses.

Abbreviations: ADL = activity of daily living; BDI = Beck Depression Inventory II; BI = Barthel Index; BMI = body mass index; CI = 95% confidence interval; NI = not included in the multivariable model because the variable was not associated ($p<0.10$) with fatigue class in univariate analysis; OR = odds ratio; PSQI = Pittsburgh Sleep Quality Index.

[a] Comorbidities relevant to fatigue included chronic conditions affecting the circulatory, respiratory, endocrine, nervous, mental, or muscular systems.

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indicating that it might be possible to identify many of those at risk for PSF at an early stage following a first-ever stroke.

A notable finding was that the severity of fatigue symptoms within each of the three classes was quite stable across the four time points. Thus, those who were fatigued at an early stage generally remained fatigued 18 months later, and those who experienced a low degree of fatigue at an early stage continued to experience a low degree of fatigue 18 months after stroke. Our findings thus suggest that distinct trajectories of fatigue intensity following stroke were present in the sample and that the potential onset of the symptom occurs as early as the acute phase. A common belief about fatigue in the acute phase after stroke is that it is a normal consequence of acute injury and will resolve as the patient recuperates. However, as none of the trajectories identified in this study reflect this pattern of fatigue resolution, our findings do not provide empirical evidence to support this belief.

The multivariable analyses identified pre-stroke fatigue as significantly associated with post-stroke fatigue trajectory. Those in the high fatigue class were the most likely to report pre-stroke fatigue, which is consistent with previous literature [6]. There might be factors that underlie both pre- and post-stroke fatigue, such as pre-existing cardiovascular disease and other chronic medical conditions, poor health, lifestyle factors, vulnerability to stress or mental health conditions, such as anxiety and/or depression.

In the univariate analyses, we found an association between higher fatigue trajectories and depressive symptoms and sleep quality, respectively. In the multivariable analyses, however, we did not find a significant association between either of these variables and fatigue class. Regarding depression and fatigue, there may be an overlap in symptoms that makes a clear distinction between these two diagnoses difficult using standardized measures. It might be that some of the symptoms that correlate with fatigue most strongly are also those that overlap the most, such as sleep disturbance, lack of energy and lack of initiative. In line with this, patients with the high fatigue trajectory reported significantly worse sleep quality than those with lower fatigue trajectories, although the mean PSQI score was within the clinical range for all three fatigue classes. This finding is also in line with previous research [24]. PSF and post-stroke depression also share common risk factors, such as premorbid psychiatric illness, social isolation and functional impairments [25]. Even though fatigue and depression might be related, fatigue can also occur without depression [26]. In our study, 51% of the patients in the high fatigue class had BDI scores in the "no depression" range.

There might be clusters of symptoms that are associated with fatigue, including depression and sleep disturbance. These symptoms, along with fatigue, might be part of a self-perpetuating cycle. Such interactions need to be explored in further research.

Although there is no data on cognitive function in this sample, the symptom-related characteristics of the three classes indicate that more symptom burden, such as more depressive

symptoms, more severe sleep disturbance, more dependency in ADL and a higher degree of comorbidity, is related to a higher degree of fatigue over time, although the possible interactions between these factors or possible common predisposing factor(s) remain unclear. Thus, it could be that there are subgroups within the classes as well. For instance, there may be distinct subgroups within the high fatigue class, both in relation to causes of fatigue and trajectories. It might be that some stroke patients suffer from fatigue due to physical impairments, such as hemiparesis, reduced balance or gait, or visual disturbances, while others might suffer from fatigue due to psychological stress, life stressors or inadequate coping styles. In others, cognitive impairments, such as reduced attention or vigilance, might be the driving force for fatigue.

The large variability in estimates of PSF's prevalence across studies reflects differences in definitions and inclusion criteria, assessment at different time points after stroke onset, and use of different fatigue measures and different cut-offs on fatigue scales. This variability also makes comparison between studies challenging [24]. For instance, the 9-item Fatigue Severity Scale (FSS) is the most widely used instrument to measure PSF, but some studies have used a cut-off score of 4 to define fatigue [27, 28], while others have categorized FSS scores into three groups; <4 indicates no/mild fatigue, 4–4.9 indicates moderate fatigue, and > = 5 indicates severe fatigue [6]. It has been argued that using a cut-off of 4 leads to an overestimation of caseness, as 46.7% of a sample of 1893 randomly-selected Norwegians scored in this range. Therefore, using a cut-off of 5 to identify severe fatigue has been proposed [29]. Our findings support a cut-off of 5 to identify severe fatigue cases, given that the high fatigue group had mean FSS scores above 5 at all time points. In comparison, the moderate fatigue group on average scored between 3 and 4.

In our sample, 35% of patients were in the high fatigue class, exceeding the number of those in the general population with FSS scores within the range for fatigue (14–23%). Nevertheless, fatigue is common in many different diagnoses [28], as well as in the population in general [29], so it might be that fatigue is a generic symptom in many medical chronic conditions. If fatigue severity can be explained by transdiagnostic factors, then patients with different diagnoses may be able to benefit from the same interventions [30].

Study strengths and limitations

This is, to our knowledge, the first study identifying distinct classes of fatigue trajectories, including a measure of fatigue in the acute phase and using a statistical approach that allowed us to identify subgroups with distinct trajectories of fatigue. The longitudinal design with four time points over 18 months is another strength of this study, as it allows for identification of trajectories over time. The advantages of GMM compared to more traditional statistical analyses are that it can identify multiple unobserved sub-populations and allows for differences between the identified groups to be examined. Using the classes high, moderate and low fatigue circumvents the challenge of which cut-off score to use for defining PSF cases, as described above.

This study also has limitations. First, the results may be influenced by selection/inclusion bias. We excluded patients unable to respond to the questionnaire. This group may have a significant prevalence of disability-related fatigue. Among those included, there was a tendency for those in the high fatigue group to be older and more dependent in ADL. As a whole, however, the sample is characterized by being fairly independent in ADL. As we have no information on clinical characteristics of eligible patients who did not consent to participate, we do not know what their ADL function was or whether the final sample is representative of the larger population from which it was drawn. Also, it is a limitation that we do not have data from a

direct measure of stroke severity, such as the NIHSS score. Furthermore, limiting the inclusion to first-ever stroke patients makes the sample less representative of the stroke population as a whole. Previous strokes are prevalent and may render patients more vulnerable to fatigue, as well as to a higher degree of other symptoms and/or medical conditions.

Moreover, the sample may have been too small to find significant differences in fatigue across stroke diagnoses, and between those who have a positive finding on MR/CT and those who have clinical strokes. It remains uncertain whether the presence of a lesion or lesion site is of importance in the development of chronic fatigue after stroke. While BMIs were higher in the high fatigue class, the study might have been underpowered to detect statistically significant differences between the three classes on this measure.

The measurement of pre-stroke fatigue was based on retrospective self-report, which renders the measure vulnerable to recall bias, and we have no information on its psychometric properties. Furthermore, the measurement of pre-stroke fatigue was not based on an FSS score, as was the measurement of post-stroke fatigue, and thus, we cannot determine whether the degree of fatigue changed, such that those who were already fatigued became even more fatigued, or whether the degree of fatigue remained stable after stroke.

As PSF is a complex phenomenon, future research on post-stroke fatigue trajectories should include a wide variety of measures in addition to those included in this study, such as objective measures of physical function, pain, cognitive function and life stressors. In addition, psychological factors should be explored, such as coping skills, self-efficacy and personality traits as mediating factors for both the perception and implications of fatigue. Some of these factors will be included in a currently ongoing study that aims to identify predictors and subgroups of post-stroke fatigue.

To address the complexity a larger study with a larger sample in the high fatigue class is needed in order to have sufficient heterogeneity in regards to age, physical, cognitive and psychological factors to find possible clusters. If fatigue severity can be explained by generic factors, interventions aimed at ameliorating fatigue do not have to be diagnosis-specific.

Conclusion

This study identified three distinct classes of trajectories of fatigue following stroke, with stable FSS scores from the acute phase through 18 months post-stroke. Furthermore, the study identified pre-stroke fatigue, multiple comorbidity, and not working as predictors of a higher fatigue class. Fatigue in the acute phase also seems to be predictive of long-lasting fatigue. This knowledge may be useful for identifying patients at risk of developing chronic fatigue, and for developing individually tailored treatment programs for stroke patients. If fatigue severity can be explained by transdiagnostic factors, it might also be possible for patients with different diagnoses to be included in similar intervention programs.

Further research on PSF in a representative sample is needed to verify our findings and to clarify the role of depression, sleep quality and other factors such as cognitive function, life stressors, and both psychological and physical functioning. The implication of potentially different PSF subgroups with different underlying causes would be that assessment should be broad and that interventions should be tailored to the patient as much as possible.

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A cross-sectional study exploring overlap in post-stroke fatigue caseness using three fatigue instruments: Fatigue Severity Scale, Fatigue Questionnaire and the Lynch's Clinical Interview

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ABSTRACT

Objective: Post stroke fatigue (PSF) is a frequent symptom affecting 25–73% of stroke survivors. The variability in estimates of prevalence found across studies reflects differences in fatigue measures and use of different cut-offs for defining clinically significant fatigue. The main aim of this study is to explore the frequency and overlap in caseness of fatigue using three different fatigue measures in a sample of patients at 3 months post stroke. Furthermore, we wanted to explore the instrument's associations with demographic and clinical characteristics.
Methods: The sample consists of 93 patients with new onset stroke. This cross-sectional study includes three measurements of fatigue, The Fatigue Severity Scale (FSS), The Chalder Fatigue Questionnaire (FQ) and the Lynch Interview. Medical, physical, psychological data and estimates of pre-stroke fatigue were collected 3 months post stroke.
Results: The FQ using the bimodal scoring yielded about 2.5 more fatigue cases ($n = 57$) than the FSS with a cut-off mean score of 5 ($n = 22$). The Lynch interview identified 48 patients as fatigue cases. Conducting multivariate analyses, the three instruments were differently associated with predictor variables such as prestroke fatigue, reduced balance and burden of symptoms reported post stroke.
Conclusion: The use of different instruments leads to a large variability in identifying fatigue cases in a sample of stroke patients. Scientifically and clinically a clarification and consensus on how to measure fatigue is warranted. Without correct identification of PSF-cases, knowledge about the causes of fatigue and development of tailored and interdisciplinary interventions are further delayed.

1. Introduction

Post-Stroke Fatigue (PSF) is a frequent and severe symptom, affecting 25–73% of stroke patients [1]. It is associated with reduced quality of life (QoL) [2], impacts rehabilitation outcome [3] and is associated with increased mortality 2 years post-stroke [4]. Although there is agreement that PSF is frequent and disabling, there is still no consensus on a standardized evaluation method. Variations in the assessment of PSF hinders comparisons of results between studies. The large variability in estimates of PSF prevalence across studies reflects differences in the criteria used to define a PSF case, the time points at which fatigue is assessed [5], and the specific content of the fatigue measures used [6].

Fatigue has been described as an experience of tiredness unrelated to previous exertion levels, which is usually not ameliorated by rest [7], and as a state of reduced capacity for work following a period of mental or physical activity [8]. Fatigue is also prevalent in the general population. A Norwegian general population study, including people with somatic and psychiatric diagnoses, reported that 23% scored in a clinical range defined as ≥5 on the Fatigue Severity Scale (FSS) [9].

Many different self-reported fatigue instruments are currently used. The one-dimensional Fatigue Severity Scale (FSS) [10] is most frequently used in stroke studies. The Chalder Fatigue Questionnaire (FQ) [11] assesses both mental and physical fatigue and is a commonly-

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used fatigue measure across different patient populations. Both the FSS and the FQ have cut-off scores to identify fatigue cases, but to our knowledge, neither has to date been validated in a stroke population. Although self-report instruments are convenient for screening and research, clinical interviews are considered the gold standard for diagnostication [12], as they allow for a deeper exploration of the patient's experience. Thus, Lynch et al. [13] developed a semi-structured clinical interview (Lynch Interview) for the purpose of developing a case definition for post-stroke fatigue.

To our knowledge, no studies have examined how these different measures vary in their ability to identify fatigue cases in a stroke sample, to what degree they overlap, or to what degree they differ in their sensitivity in identifying PSF cases. There is also a gap in the literature as to how different fatigue measures might be similarly or differently associated with demographic, medical and clinical variables such as age, comorbidities, psychological distress or disabilities in patients following stroke.

1.1. Aims of the study

The main aim of this study was to investigate the frequency and overlap in caseness of fatigue in a sample of stroke patients using the FSS, FQ and Lynch interview at a single point in time. Furthermore, we aimed to explore how The FSS, the FQ and the Lynch interview are associated with demographic, medical and clinical characteristics, such as psychological distress and physical disability 3 months post-stroke.

2. Materials and methods

2.1. Study sample and procedures

This is the first article from the POSFAT-study (Post-Stroke Fatigue, predictors and subgroups), a longitudinal observational study that recruited stroke patients in the acute phase from one hospital of the Innlandet Hospital Trust, Norway, between February 2017 and October 2019. The present cross-sectional study includes measures of fatigue, psychological distress and physical function 3 months post-stroke, and demographic and medical variables both pre- and post-stroke.

Patients were eligible for the study if they had a new onset ischemic stroke according to the International Classification of Disease (ICD-10 diagnoses I63.0-I63.9, I64). The diagnosis and function was determined by trained physicians in the acute hospital. Exclusion criteria were intracerebral hemorrhage, other debilitating somatic or psychiatric disease impairing the ability to give the information called for in the study, and severe cognitive or language dysfunction that would compromise consent and/or data collection. Patients with aphasia were included if they had sufficient language function to answer questionnaires and understand consent- information and study instructions.

From a sample of 114 consecutive patients, 100 were included in the study, 7 of which were later excluded, leaving a final sample of 93 patients for analysis. Details of the recruitment process are described in Fig. 1.

Data were collected using standardized questionnaires, physical tests and a semi-structured interview. All interviews, scoring of interviews and physical testing were conducted by the first author. Data on stroke classification, lesion location, National Institutes of Health Stroke Scale (NIHSS) score [14], and comorbid conditions were collected from the patients' medical records.

2.2. Fatigue measures

Fatigue severity was assessed with three different instruments: Fatigue Severity Scale (FSS), Chalder Fatigue Questionnaire (FQ) and Lynch et al.'s semi-structured clinical interview (Lynch Interview) [13].

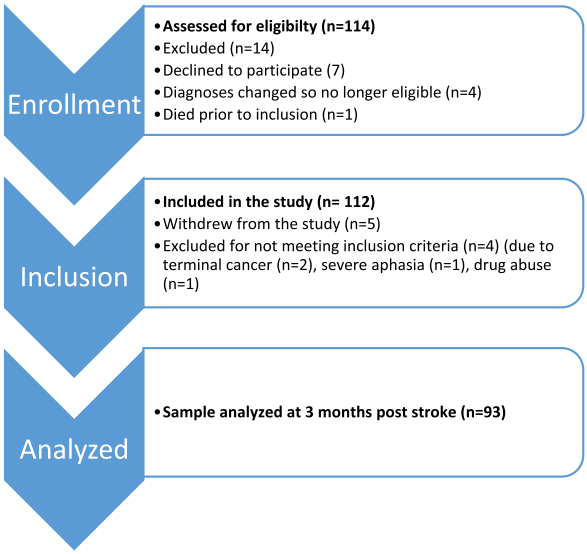

Fig. 1. Flowchart showing the patient recruitment and inclusion process.

2.2.1. Fatigue Severity Scale (FSS)

FSS is a 9-item self-report instrument originally developed for measuring fatigue in patients with multiple sclerosis or systemic lupus erythematosus [10]. The FSS includes items such as "Exercise brings on my fatigue", "Fatigue interferes with carrying out certain duties and responsibilities", and "Fatigue is among my three most disabling symptoms". Responses reflect the degree to which one agrees with each statement on a Likert scale of 1–7 based on experiences within the last 7 days. A mean item score is calculated, with higher scores indicating more severe fatigue [10]. Lerdal et al. [9] evaluated the psychometric properties of the FSS and associations between fatigue and sociodemographic variables in the general population in Norway. Women and respondents with chronic illness were most prone to fatigue, and an inverse correlation was found between fatigue and education level [9]. The FSS has acceptable validity and reliability across different clinical populations. In a study by Nadarajah et al. [15], the FSS had a Cronbach's alpha of >0.93 in samples of stroke patients and healthy controls and was strongly correlated with visual analog scales of fatigue (r = 0.60). While some studies have used a mean score of 4 as a cut-off for identifying clinically significant fatigue [16,17], others have categorized the score into three groups: FSS <4.0 indicates no fatigue, FSS 4–4.9 moderate fatigue and FFS ≥5 severe fatigue [18]. Based on a ROC-curve, Poulsen et al. [19] found a cut off on the FSS at 4.9 to be the best compromise between sensitivity and specificity when considering a case definition, and that a cut-off of 4 would lead to possible overestimation of the burden of post stroke fatigue.

We have used a cut-off of 5 in this study for comparison with other studies. A 7-item version of FSS has been suggested used in stroke populations, as the first two items in a Rasch-analysis did not seem to be crucial in capturing post stroke fatigue symptoms [18]. To make our results more comparable with other studies on fatigue, we used the original version of the FSS. The second item, "Exercise brings on my fatigue", is also of interest when studying fatigue. We did, however, calculate caseness for both versions and found a relatively small difference; while the 7-item version yielded 24 cases (26%), the 9-item version yielded 22 cases (24%).

2.2.2. Chalder Fatigue Questionnaire (FQ)

FQ is an 11-item self-report questionnaire, originally developed to measure fatigue in patients with Myalgic encephalopathy/chronic fatigue syndrome [11]. The FQ includes items about: general fatigue, such as "Do you need to rest more?"; physical fatigue symptoms, such as "Do

you have less strength in your muscles?"; and mental fatigue, such as "Do you have difficulties concentrating?" The 11-item scale includes two subscales: physical fatigue (items 1–7) and mental fatigue (items 8–11) [11].The FQ has two scoring systems: Likert and bimodal. In the Likert scoring system, respondents indicate their experiences within the last month on a scale ranging from 0 ("less than usual") to 3 ("much more than usual"). In the bimodal scoring, each question is scored as either 0 ("less than usual" or "no more than usual") or 1 ("more than usual" or "much more than usual"). A score $\geq$ 4 in the bimodal scoring is considered a case of fatigue, generally and in this study.

The FQ has shown good internal consistency with Cronbach's alpha ranging from 0.86 to 0.92 [11]. De Vries [20], among others, found good convergent validity, as evidenced by strong correlations with other fatigue questionnaires. In a random sample of 3500 Norwegians who completed the FQ, women were more fatigued than men, and 11.4% reported substantial fatigue lasting 6 months or longer [21].

2.2.3. Lynch Interview

Lynch et al. [13] developed a semi-structured clinical interview for the purpose of developing a case definition for post-stroke fatigue. The interview includes operationalized questions about aspects of the fatigue experience following stroke, such as "Can you describe what your fatigue feels like, in your own words?" and "Do you feel that fatigue is a problem for you?" The interview has good inter-rater reliability, with a kappa of 0.82 [13] and good concurrent validity with other fatigue scales, for instance the Fatigue Assessment Scale [13]. The post stroke case definition in community patients is based on "over the past month, there has been at least, a 2 week period when the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or at least nearly every day. The fatigue has lead to difficulty to take part in everyday activities." [13]. As the interview was designed to assess post stroke fatigue, it is primarily used in stroke populations.

2.3. Medical variables

2.3.1. Stroke type

Computerized tomography was conducted on all patients upon hospital admission. Based on the radiologist's description, stroke was categorized as ischemic, haemorrhagic or negative finding (i.e., clinical stroke). Additional magnetic resonance imaging was performed on some patients for diagnostic reasons. Lesion location was classified as left, right, bilateral or unspecified.

2.3.2. Comorbidities

Relevant pre- and co-morbid medical conditions were assessed with the Self-Administered Comorbidity Questionnaire [22] and through medical record review. Comorbidity burden was quantified as the total number of comorbidities reported.

2.4. Demographic variables

Information on age, marital status, living arrangement, employment status, education level and social benefits was obtained from medical records and by personal interview 3 months post-stroke.

2.5. Functional measures

2.5.1. Stroke impairment

Stroke impairment was measured using the National Institutes of Health Stroke Scale (NIHSS), an instrument used clinically to objectively quantify different dimensions of impairment caused by an acute stroke, including consciousness, and motor and language deficits [14]. The NIHSS is scored during the acute phase hospital admission and the NIHSS score was obtained from medical records.

2.5.2. Balance

Balance was assessed at 3 months post stroke with the 14-item Berg Balance Scale [23]. The scale is a performance test where the total scores range 0–56, with higher scores indicating better balance. Scores $<$45 indicate greater risk of falling [23].

2.5.3. Activities of daily living (ADL)

The level of dependency with ADL was assessed with the Barthel Index (BI) for ADL, a 10-item scale with higher scores representing higher levels of independence [24]. The BI score was based on the patients' self-rating on the questionnaire.

2.6. Other symptom measures

2.6.1. Psychological distress

Psychological distress was measured using the Hopkins Symptom Checklist-25 (HSCL-25). The HSCL-25 is a 25-item screening instrument that assesses symptoms of depression (15 items) and anxiety (10 items) as indicators of psychological distress. The severity of each symptom is scored on a scale of 1 (Not at all) to 4 (Extremely). Mean scores range 1–4, with higher scores indicating greater distress. A cut-off score of 1.75 is used to indicate clinically significant psychological distress [25].

2.6.2. Post-stroke symptoms

Psychological distress were measured using the Rivermead Post Concussion Symptoms Questionnaire (RPQ). Although the RPQ was developed to measure symptom severity following concussions, the items are also relevant for assessing post-stroke symptoms. The RPQ includes 16 items assessing self-reported cognitive function, vision, fatigue and physical function, such as poor balance and dizziness [26]. The RCQ includes three symptom domains; physical, cognitive and behavioral. Respondents are asked to rate their symptom severity in the last 24 h on an ordinal scale ranging from 0 (no problems) to 4 (a severe problem). Total scores range 0–64, with higher scores indicating worse symptom severity [26].

2.6.3. Sleep disturbance

Sleep disturbance was assessed with the Pittsburgh Sleep Quality Index (PSQI), a 19-item self-report questionnaire that assesses sleep quality over the prior month. PSQI sum scores range 0–21, with higher scores indicating poorer sleep quality. A score $\geq$ 5 is indicative of clinically significant sleep disturbance [27].

2.6.4. Pain severity

Pain severity was assessed using a Numeric Rating Scale. Patients were asked to circle the number between 0 (no pain at all) and 10 (worst pain ever possible) that best described their pain intensity over the last week. The Numeric Rating Scale has shown good sensitivity and ability to generate data that can be statistically analyzed [28].

2.6.5. Pre-stroke fatigue

Pre-stroke fatigue was assessed through semi-structured questions in the clinical interview. Patients were asked whether they had experienced substantial fatigue lasting for at least 3 months before the stroke. Fatigue was defined as substantial if it affected their ability to perform daily activities. Pre-stroke fatigue was defined as substantial fatigue lasting for at least 3 months before the stroke. For a similar approach see Lerdal et al. [29].

2.7. Data analysis

Statistical analyses were performed using SPSS software version 23 (IBM Corp, Armonk, NY, USA) In analyzing the degree of overlap in fatigue case identification and for analyzing demographic, medical and symptom-related characteristics related to level of fatigue and fatigue caseness, categorical scores were used. Continuous values were used in

the correlational analyses between the three instruments and for descriptive statistics for the FSS and the FQ. Pearson Correlational analyses were used to assess associations between the three fatigue instruments.

For the nine-item version of FSS, the Cronbach's alpha was 0.90. For the 7 item version of FSS, the Cronbach's alpha was 0.91. For the full FQ, Cronbach's alpha was 0.68, and 0.60, and 0.73 for the for the physical and mental fatigue subscales, respectively. In further analyses, scores of the full FQ and caseness scores based on the bimodal scoring system was used.

Cohen's K was employed to assess the degree of measurement agreement, with K > 0.75 indicating excellent agreement, 0.40–0.75 fair to good, and <0.40 poor agreement [30]. A Kolgomorov-Smirnov test indicates that the scores on the FSS (D93) = 0.18 and the FQ (D92) = 0.20 follow a normal distribution.

In the statistical analyses, two-tailed tests were used, and *p*-values <0.05 were considered statistically significant. Bivariate associations between fatigue caseness and demographic, medical and clinical variables were evaluated using Chi-square tests for categorical variables and one-way analysis of variance for continuous variables. Predictor variables included in multivariate analyses were based on theoretical importance (e.g., gender) or a *p*-value ≤0.10 in bivariate analyses. Multivariate analyses of different fatigue caseness definitions were performed using separate logistic regression analyses with stepwise entry for medical and clinical predictor variables that showed significant association in the univariate analyses. Multivariate analyses were performed using logistic regression and effect sizes for the associations are reported as odds ratios (OR, Exp (B) with 95% CI. Model fit is reported as Nagelkerke R^2. A power analysis conducted prior to the start of data collection indicated that a minimum of 67 patients were needed for the study, assuming 30% prevalence of both fatigue and depression.

2.8. Ethics

Before inclusion, all participants signed an informed consent. The study was approved by the Regional Ethics Committee for Medical and Health Research Ethics in South-Eastern Norway (Ref. 2016/589 /REK Sør-Øst C).

3. Results

3.1. Demographics and prevalence of fatigue

A total of 100 patients were included in the study and 93 completed the assessment 3 months after stroke onset. Most participants were male (*n* = 57, 61%), mean age was 66.7 (SD = 10.9) years and most were cohabitating (*n* = 67, 73%). Demographic, clinical and medical characteristics are presented in Tables 1 and 2.

Mean scores were 3.9 on the FSS, and 16.1 on the FQ. The FQ's bimodal scoring yielded the highest proportion of fatigue caseness (*n* = 57, 62%), followed by the Lynch Interview (*n* = 48, 52%). In contrast, using the FSS cut-off score of 5, only 24% of patients were identified as having a high level of fatigue (Tables 3a and 3b).

Cohen's K showed good agreement between FSS caseness and the Lynch Interview (0.45, $p < 0.001$), better agreement between the Lynch Interview and FQ caseness (0.63, $p < 0.001$), and poor agreement between FSS and FQ caseness (0.25, $p = 0.001$). Correlations between the FSS, FQ and Lynch Interview were highly significant, ranging from $r = 0.64$ ($p < 0.001$) between the Lynch Interview and FQ, through $r = 0.54$ ($p < 0.001$) between the Lynch Interview and FSS, to $r = 0.34$ ($p < 0.001$) between FSS and FQ scores, indicating acceptable to good convergent validity.

3.2. Associations between fatigue measures and demographic, medical and clinical variables

In bivariate analyses, all fatigue scores were significantly associated with pre-stroke fatigue, pain, poor sleep quality, impaired balance, reduced ADL independence, and greater symptom severity on the RPQ. In regards to psychological distress, fatigue caseness defined by the FSS and the Lynch Interview was significantly associated with depression and/or anxiety symptoms in the clinical range on the HSCL-25, while FQ caseness was not (Table 2).

In logistic regression analyses (Table 4), fatigue caseness on the FSS was significantly associated with the following predictor variables: pre-stroke fatigue and reduced balance. Fatigue caseness on the Lynch Interview were significantly associated with pre-stroke fatigue and higher symptom scores on the RPQ. None of the predictor variables

Table 1
Demographic and medical characteristics related to level of fatigue and fatigue caseness.

Characteristic	Total sample (*n* = 93)	FSS[1] Non-case	FSS[1] Case	FQ[2] Non-case	FQ[2] Case	Lynch-interview non-case	Lynch-interview case
Total cases, *n* (%)	93 (100%)	71 (76%)	22 (24%)	35 (38%)	58 (62%)	45 (48%)	48 (52%)
Sociodemographic variables							
Male, *n* (%)	57 (61%)	46 (49%)	11 (12%)	26 (28%)	31 (34%)	31 (33%)	26 (28%)
Female, *n* (%)	36 (39%)	25 (27%)	11 (12%)	9 (10%)	26 (28%)	14 (15%)	22 (24%)
Age in years, mean (SD)	66.7 (10.7)	66.9 (10.8)	67.1 (10.3)	65.8 (10.6)	67.2 (10.5)	67.5 (10.0)	66.4 (11.1)
Married/cohabitating, *n* (%)	67 (72%)	54 (76%)	13 (59%)	19 (54%)	37 (65%)*	14 (30%)	33 (70%)
Education in years, mean (SD)	11.4 (3.1)	11.6 (3.2)	10.5 (2.9)	11.2 (2.9)	11.5 (3.3)	11.0 (2.8)	11.6 (3.4)
Working at 3 months post stroke, *n* (%)	22 (24%)	19 (21%)	3 (3%)	9 (10%)	13 (14%)	11 (12%)	11 (12%)
Medical variables							
Right-side ischemic stroke, *n* (%)	36 (39%)	27 (29%)	9 (10%)	13 (14%)	23 (25%)	17 (18%)	19 (20%)
Left-side ischemic stroke, *n* (%)	35 (38%)	28 (30%)	7 (8%)	17 (19%)	17(19%)	20 (22%)	15 (16%)
Bilateral ischemic stroke, *n* (%)	4 (4%)	4 (4%)	0 (0%)	2 (2%)	2 (2%)	3 (3%)	0 (0%)
Negative finding/clinical stroke, *n* (%)	18 (20%)	12 (13%)	6 (7%)	3 (3%)	15 (16%)	5 (6%)	13 (14%)
Thrombolysis, *n* (%)	27 (30)	22 (25%)	5 (6%)	11 (12%)	16 (18%)	13 (14%)	14 (16%)
NIHSS score at admission, mean (SD)	3.45 (4.1)	3.16 (3.9)	4.36 (4.4)	2.57 (3.1)	3.98 (4.5)	2.58 (3.2)	4.19 (4.6)*
Comorbidities, mean (SD)[3]	1.9 (1.9)	1.7 (1.3)	2.5 (1.4)*	1.6 (1.2)	2.1 (1.4)[2]	1.6 (1.3)	2.3 (1.4)*
Pre-stroke fatigue, *n* (%)	23 (30%)	8 (9%)	15 (16.5%) **	3 (3%)	20 (22%) **	3 (3%)	20 (22%)**

*$p < 0.05$; **$p \leq 0.001$.
[1] Fatigue Severity Scale, low fatigue is defined as a score < 5 and high fatigue as a score ≥ 5.
[2] Chalder Fatigue Questionnaire, a case is defined as having a bimodal score ≥ 4.
[3] Among the diagnoses included are high blood pressure, heart disease, diabetes, lung diseases, musculoskeletal conditions, depression and arthritis.

Table 2
Symptoms related to level of fatigue and fatigue caseness 3 months post-stroke.

Characteristic	Total sample (n = 93)	FSS[a] Non case	FSS[a] Case	FQ[b] Non-case	FQ[b] Case	Lynch-interview non-case	Lynch-interview case
Symptom-related variables							
HSCL-25[c], mean (SD)	1.4 (0.3)	1.3 (0.3)	1.7 (0.4)**	1.2 (0.23)	1.4 (0.3)**	1.2 (0.2)	1.5 (0.3)**
HSCL-25 $\geq$ 1.75[f] n (%)	14 (15%)	5 (5%)	9 (10%)	3 (3%)	11 (12%)	3 (3%)	11 (12%)
HSCL-25 < 1.75 n (%)	78 (85%)	65 (71%)	13 (14%)**	31 (34%)	46 (51%)	41 (44%)	37 (40%)
RPQ[d], mean (SD)	12.2 (15.8)	12.2 (9.1)	27.3 (13.5)**	8.6 (8.7)	20.2 (12.1)**	8.6 (7.3)	22.3 (12.1)**
PSQI[e], mean (SD)	4.6 (3.7)	3.9 (2.9)	6.6 (4.9)*	3.0 (2.3)	5.5 (3.9)*	3.3 (2.7)	5.8 (3.9)**
Pain Numeric Rating Scale, mean (SD)	2.3 (2.3)	1.9 (2.1)	2.5 (3.5)*	1.4 (1.9)	2.8 (2.4)*	1.6 (2.0)	2.9 (2.4)*
Barthel Index for ADL, mean (SD)	19.5 (1.6)	16.7 (1.2)	18.7 (2.3)*	20.0 (1.2)	19.4 (2.0)*	19.8 (2.9)	19.1 (2.0)*
Berg Balance Scale, mean (SD)	51.1 (9.1)	53.9 (5.1)**	45.2 (14.4)**	54.9 (2.5)	49.8 (11.0)*	54.4 (5.3)	49.3 (11.1)*

* = $p < 0.05$, ** = $p \leq 0.001$.
[a] Fatigue Severity Scale.
[b] Chalder Fatigue Questionnaire.
[c] Hopkins Symptom Checklist.
[d] Rivermead Post Concussion Questionnaire.
[e] Pittsburgh Sleep Quality Index.
[f] Scores $\geq$ 1,75 is considered within the clinical range for psychological distress.

Table 3a
Descriptive statistics and caseness on Fatigue Severity Scale (FSS), Chalder Fatigue Questionnaire (FQ), and Lynch Interview.

	Mean (SD)	Median (IQR)	Caseness (%)
FSS (n = 93)	3.9 (1.4)	4.0 (2.0)	22 (24%)[a]
FQ (n = 93)	16.1 (5.1)	16.0 (2.1)	57 (62%)[b]
Lynch Interview (n = 93)			48 (52%)

[a] FSS score 5–7.
[b] FQ bimodal score of 4–11.

Table 3b
Overlap of caseness on Fatigue Severity Scale (FSS), Chalder Fatigue Questionnaire (FQ), and Lynch Interview.

	FSS non-case	FSS case	FQ non-case	FQ case
FQ non-case	34 (36%)	2 (2%)	–	–
FQ case	37 (40%)	20 (22%)	–	–
Lynch Interview non-case	45 (48%)	0 (0%)	31 (34%)	13 (14%)
Lynch Interview case	26 (28%)	22 (24%)	4 (4%)	44 (48%)

remained significantly associated with the FQ. However, neither psychological distress, sleep disturbances nor pain remained significantly associated with fatigue caseness using any of the three fatigue measures when controlling for other relevant factors. Omitting two of these three factors from the model at a time did not suggest that the lack of significant associations in the multivariable model was due to multicollinearity.

4. Discussion

To our knowledge, this is the first study to explore the degree of overlap in fatigue caseness between three different fatigue instruments in one sample of patients at the same point in time. This allows for direct comparison between the scales. Our results demonstrate how the use of different instruments leads to variability in the estimated prevalence of fatigue following stroke. From both a scientific and clinical point of view, it is important that fatigue associated with a clinical diagnosis is correctly identified. The variation of fatigue prevalence estimates from different instruments may hinder comparisons of results between studies. Without correct identification of fatigue the understanding of fatigue and what causes it will remain unclear, further delaying the development of interventions. For clinicians, it is essential to know how different instruments identifies cases, the content of the instruments and their strengths and limitations.

Furthermore, this study shows that the three instruments have differing patterns of association with other stroke-related, medical and clinical variables.

4.1. Prevalence and caseness

We found that the FQ, using bimodal scoring, yielded about 2.5 times more fatigue cases than the FSS using a mean score of 5 as the cut-off. Furthermore, 28% of those who were defined as cases using the Lynch Interview were not cases based on the FSS case criterion. This vast variability in caseness indicates that fatigue might be either overestimated or underestimated depending on what fatigue measure is used. Further, the value of the Cohen's K between the FSS and FQ was

Table 4
Logistic regression analyses demonstrating medical and clinical factors most strongly related to fatigue caseness 3 months post-stroke.

	Predictor variables[a,b,c,d]	B	SE	Sig	OR (Exp (B)	95% CI	Nagelkerke R^2
Fatigue severity scale	Pre-stroke fatigue	−2.57	1.12	0.022	0.8	(0.01–0.69)	0.76
	Berg's balance scale	−0.37	0.18	0.040	0.7	(0.49–0.98)	
Lynch Interview	Pre-stroke fatigue	−1.98	0.84	0.019	1.14	(0.03–0.72)	0.56
	RPQ	0.14	0.06	0.01	1.15	(1.04–1.28)	

[a] The multivariate analyses were performed for the FSS, the FQ and the Lynch interview separately.
[b] The following predictor variables were entered into the analyses based on theoretical importance and significant association with the FSS, the FQ and the Lynch interview: Sex, age, pre-stroke fatigue, NHISS score, comorbidities, Barthel ADL-score, RPQ-score, HSCL-25-score, PSQI-score, Pain numeric scale –score Pain numeric scale –score and the Berg test of balance."
[c] None of the predictor-variables remained significantly associated with being a case on the FQ in the multivariate analyses.
[d] No demographic factors were significantly related to the fatigue outcome variables in the multivariable analyses.

fairly low, indicating a less than optimal measurement agreement in identifying fatigue caseness. Since several of the items in the FQ not only represents characteristics of fatigue, but also possible sequelae after stroke, it is possible that FQ contributes to overestimation of fatigue cases.

One might argue that using a mean score of 4 as cut-off on the FSS might have yielded quite similar results as the FQ and the Lynch Interview. However, it has been argued that using a cut-off of 4 will lead to an overestimation of caseness. Therefore, using a cut-off of 5 to identify severe fatigue has been proposed [9].

4.2. Validity and content

There are several points to discuss regarding the identification of fatigue cases using these three different instruments. Firstly, although the Cronbach's alpha is high across studies on fatigue-related patient-reported outcome measures, a mean score on a questionnaire might be misleading for understanding the nature and range of fatigue. As an example, one of the respondents in this study had a mean score of 3.3 on the FSS, supposedly reflecting a low degree of fatigue. However, examining the answers on different items, the patient indicated total agreement with the statements "Fatigue is among my three most disabling symptoms" and "Fatigue interferes with my work, family and social life", while he completely disagreed with statements such as "Physical exercise makes me tired". In fact, physical exercise was something that alleviated fatigue in his experience, but that does not negate the fact that he likely has a debilitating and clinically significant level of fatigue.

The FQ might better detect and differentiate individual differences between physical and mental fatigue, as it consist of these two subscales. However, the internal consistency values were lower in our study sample than in original the Chalder et al. study [11]. One possible reason for this may be that the four items intended to measure mental fatigue might reflect self-report of subjective cognitive deficits more than mental fatigue. Using the bimodal scoring, a fatigue case might be identified based on the four questions about reduced cognitive capacity alone. According to Sun [32], as many as 80% of stroke survivors suffers from cognitive impairments following stroke. For this reason, the content validity of the FQ can be questioned when used in populations with conditions that might affect cognitive function, particularly in neurological diseases.

Regarding the criterion validity of the FQ, one might question whether the experience of being "more easily tired" represents clinical fatigue. As in the case definition operationalized by Lynch et al. [13], clinical fatigue should also include the degree to which tiredness is experienced as having a negative impact on one's quality of life or ability to participate in daily activities. The FSS specifically asks about interference of fatigue in everyday life, and this might be one reason why there are more than twice as many cases identified by the FQ than by the FSS. Some people may be more tired than they were pre-stroke, but they don't necessarily perceive this to have a significant impact on their lives.

4.3. Associations between the fatigue instruments and predictor variables

The three fatigue measures included in this study were similar in regards to their associations with other variables. For all three measures, fatigue caseness was, in line with previous research, significantly associated in bivariate analyses with having pre-stroke fatigue, high symptom burden as measured by the RPQ, sleep disturbance, less ADL independence, poor balance and pain [29,33–35]. Hence, both psychological and physical factors may contribute to PSF.

Reporting clinically significant levels of psychological distress was significantly associated with fatigue caseness on both the FSS and Lynch Interview, but not the FQ. This might be related to the difference in content of the three instruments regarding the impact of fatigue on everyday life. Reduced capacity for participating in activities might lead to psychological distress. In line with previous research, fatigue can also occur without depression or psychological distress [36] as there are patients that score within the clinical range on the HSCL-25 who are not in the high fatigue group and vice versa.

PSF and post-stroke depression and psychological distress might also overlap due to that they share common risk factors, such as premorbid psychiatric illness, social isolation and functional impairments [37].

In the multivariate analyses, however, pre-stroke fatigue and a high symptom burden as measured by the RPQ remained significantly associated with fatigue on the Lynch interview, and pre-stroke fatigue and reduced balance with the FSS, accounting for 76% of the variance. None of the predictor variables were significantly associated with the FQ in the multivariate analyses.

There may also be subgroups within this sample and in the stroke population with differing factors most related to their fatigue. For some, psychological factors may be a contributing cause, while for others, physical disabilities may lead to fatigue. Knowing which factors are associated with PSF at an individual level will be helpful for tailoring clinical interventions.

4.4. Strengths and limitations

This study has strengths and limitations. The ability to compare three fatigue instruments administered at the same point in time post-stroke onset is a notable strength. The sample's heterogeneity with regard to age, comorbidities and functional loss is also a strength and increases its generalizability to the larger stroke population The sample size of 93 might be underpowered for detecting statistically significant associations between fatigue and relevant variables. Some of the predictor variables, as well as the fatigue measures, are based on self-report. Self-report measures may have several sources of errors, such as lack of self-awareness or miscomprehension of questions due to cognitive impairment. In addition, pre-stroke fatigue was assessed retrospectively, which renders the measure vulnerable to recall bias.

4.5. Implications for clinic and research

The FQ and FSS differ in content and have different strengths and limitations. When using a questionnaire to assess fatigue, it is essential to know which aspects of fatigue the questionnaire is designed to assess. While FSS to a large degree measure the impact of fatigue in daily life, the FQ assess the presence and degree of fatigue related symptoms. Clinicians should also be aware that the mean score on a questionnaire might not reflect the degree of the patient's fatigue. In the clinic, a questionnaire might be supported by a supplementary clinical interview for more in-depth symptom assessment.

An interview is usually more time-consuming than a questionnaire and less convenient for research with large samples of patients. In clinical research, however, a semi-structured interview with open questions might yield new insights into the phenomenology and experience and fatigue symptoms and hence be a source for the development of new instruments that have better content validity.

4.6. Conclusions

In summary, this study used three different instruments to identify fatigue caseness in a single sample of patients 3 months post-stroke and found that the proportion of fatigue cases varied from 24 to 62% depending on which instrument was used. Exploring the association between fatigue caseness and relevant predictor variables, we found a variance between the three instruments, possibly reflecting that they cover slightly different aspects of the fatigue experience, and that FQ may overestimate fatigue cases in patients with stroke. All in all, our results might indicate that while the FQ is sensitive in measuring presence of fatigue related symptoms, the FSS and the Lynch interview to a

larger degree reflect fatigue impact. Research with larger samples are needed to clarify this further. The variability in fatigue estimates highlights the need for consensus on how to measure fatigue, whether it be after stroke or in other populations.

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Competing interest statement

The authors have no competing interests to report.

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III