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Fatigue –
perceived, described and assessed

by persons with
systemic lupus erythematosus

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ABSTRACT

Fatigue is an individual and subjective sensation interfering with daily living for patients with several chronic conditions. Systemic lupus erythematosus (SLE) is characterized by inflammation in different organs combined with immunological abnormalities. The complexity of the disease SLE has several consequences for daily living, and fatigue is among one of the most burdensome symptoms of SLE. The impact of fatigue in a person's life is difficult for others to understand. Therefore, to better understand the enigma of fatigue, how fatigue can be measured and patient's descriptions of how fatigue is experienced are necessary.

Aim: The overall aim of this cohort-based project, was to explore patients experiences of symptoms related to SLE with a main focus on fatigue, how it is described and measured.

Subjects: 327 patients from the SLE-cohort at Karolinska University Hospital, Solna, and 311 age- and gender- matched control persons contributed to the data. Both qualitative and quantitative data have been used, with interview material from focus group discussions (study I), free-written answers (study II) and self-assessments measures/questionnaires (study II+III+IV).

Results: In study I, women (n=33) in seven focus group discussions (FGD) described their experience of SLE-related fatigue; how they perceived the feeling of fatigue, impact on life and strategies developed to manage fatigue in daily living. Transcripts from the FGD were analyzed using content analysis. The results were presented as four themes where the "Nature of fatigue" involved the sensation, occurrence and character of fatigue, "Aspects affected by fatigue" described emotions that arose with fatigue as well as aspects of work, family life, social contacts, and leisure activities that were affected by SLE related fatigue; "Striving towards power and control" described a balance of strategies used to manage daily life and were categorized into mental struggle, structure, restrict, and provide; "Factors influencing the perception of fatigue" described understanding from surrounding persons and the pain as strongly influencing the experience and perception of fatigue. The result from the open questions in study II (n=324), showed that fatigue and pain were reported as most troublesome symptoms of SLE, followed by musculoskeletal symptoms. In study III (n=51) in groups of 6-9 patients patents filled in seven questionnaires about fatigue; Numeric rating scale (NRS), Chalder fatigue scale, Vitality from SF-36, Fatigue Severity Scale, Multi-dimensional Assessment of Fatigue, Multidimensional Fatigue Inventory and Functional Assessment of Chronic Illness Therapy – Fatigue. This followed by a dialogue procedure resulting in 260 contrasting assessment. The minimally clinically important difference for the seven measures of fatigue was calculated using the comparative assessment as anchor. All measures of fatigue used in the study seemed to capture differences as experienced by the group of patients themselves, least favorable was however the one question (NRS) this were strengthen by patients free written comments. In study IV (n=305 patients and 311 controls) three clusters of fatigue were

identified. The High fatigue cluster (n = 221) had most symptoms of anxiety/depression, lowest health related quality of life and were dominated by the patients (80%). Participants in the Low fatigue cluster (n = 240, controls 78%) reported more physical exercise and less smoking than the other clusters.

Conclusion: Patients description of SLE related fatigue (study I) provide important knowledge that can be used in educational discussions with patients as well as health care workers. The recommended measures of fatigue, evaluated in this thesis, can detect clinically important differences as perceived by the patients (study III). Not all patients with SLE experienced distress from current illness, 10 % reported that they did not perceive any SLE related symptom (study II) and 17% had low levels of fatigue and healthy behavior (physical exercise, non-smoker)(study IV). With special focus on fatigue, this thesis contributes to the understanding of patients' experience of SLE. Knowledge of the experience of symptoms from the patients' perspective is pivotal in order to support the patient, facilitate assessment and choice of treatment as well as generate a base for appropriate intervention programs.

LIST OF PUBLICATIONS

This thesis is based on the following original papers and manuscripts, which will be referred to in the text by their Roman numerals.

I. **Pettersson, S.,** Möller, S., Svenungsson, E., Gunnarsson, I., Welin Henriksson, E. Women's experience of SLE-related fatigue: a focus group interview study.
Rheumatology (Oxford) 2010;49:1935-42

II. **Pettersson, S**., Lövgren, M., Eriksson, L.E., Moberg, C., Svenungsson, E., Gunnarsson, I., Welin Henriksson, E.
An exploration of patient reported symptoms in systemic lupus erythematosus and the relation to health related quality of life.
Scandinavian Journal of Rheumatology.
(Epub ahead of print May 31, 2012.).

III. **Pettersson, S**., Lundberg, I.E., Liang, M.H., Pouchot, J., Welin Henriksson, E. Determination of the Minimal Clinically Important Difference for Seven Measures of Fatigue in Swedish Patients with Systemic Lupus Erythematosus. (Manuscript)

IV. **Pettersson, S**., Eriksson, K., Boström, C., Svenungsson, E., Gunnarsson, I., Welin Henriksson, E.
Clusters of fatigue - a comparison of persons with systemic lupus erythematosus and age and gender matched controls. (Manuscript)

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1. LIST OF ABBREVATIONS

SLE	Systemic Lupus Erythematosus
CFS	Chalder Fatigue Scale
CNS	Central Nervous System
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FGD	Focus Group Discussions
FSS	Fatigue Severity Scale
HADS	The Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
IQR	Interquartile Range
MAF	Multidimensional Assessment of Fatigue scale
MCID	Minimally Clinically Important Difference
MFI-20	Multidimensional Fatigue Inventory
NRS	Numeric Rating scale
RA	Rheumatoid Arthritis
SF-36	The Medical Outcomes Study 36-item Short Form Health Survey
SLAM	Systemic Lupus Activity Measure
SLAQ	Systemic Lupus Activity Questionnaire
SLE	Systemic Lupus Erythematosus
SLEDAI	SLE disease activity index
SLICC/ACR	Systemic Lupus International Collaboration Clinics/American College of Rheumatology
VT	Vitality (from SF-36)

2. INTRODUCTION

In 1948, the World Health Organization (WHO) cited the definition of health, which describes a basic principle of happiness, harmonious relations and security as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. As a nurse with more than twenty years of experience with patients with long-term rheumatic disorders, I have become more and more interested in perceptions of health and ill health and the influence of personal as well as context-related factors, particularly the self-question “When do I consider myself as not healthy or having a disease?” When dimensions of health are problematised, the concepts of disease, illness and sickness are interesting to consider since they are interdependent [1]. A diagnosis is made from objective criteria that describe the disease, and the personal, subjective perception—a feeling—fulfills the definition of illness. To consider sickness as an identification by others is interesting, and could be compared to the perceptions of illness as socially defined. The main focus of this thesis is on the disease systemic lupus erythematosus (SLE) and the perceptions of illness, symptoms, and patients’ experiences of disease-related fatigue. The subjective sensation of fatigue is often described as “uncommon, abnormal or extreme whole bodily tiredness disproportionate or unrelated to activity or exertion” [2]. Extensive research has sought to understand the meaning of fatigue, but has reached no definition or consensus.

In my work for this thesis, it has been important to remember that we should never regard persons, patients, health professionals or caregivers, as concepts, but we should use concepts to better understand actions, reactions and interpretations. For example, a patient is a person and not a disease or illness but he/she is influenced by his or her own experience. Thus, the expressions of patients, physicians and health professionals are used in this thesis to describe the experiences that these persons have had and how their perspectives and knowledge might influence the data. The aim of this project is to contribute to the understanding of patients’ experience of disease-related fatigue, as well to recommend choices of adequate assessment methods for fatigue in the rheumatic disease SLE.

3. BACKGROUND

3.1. When life changes

When falling ill or receiving a diagnosis life is influenced, even a period with flue and fever impose changes in daily routines. Increased rest and diet change is often necessary but temporary and normally every day schedule is back within a couple of days or weeks. When afflicted with ill health or a disease with chronic or long-term character, life-changes are often imposed for the ill person as well as for the family and friends [3]. Living a life as "normal" as possible and maintaining social roles can be a struggle for persons with chronic conditions, and the adaption to live with a chronic illness is a transition and reformulation of self [4-7]. Rare diseases or diseases with vague symptoms or when symptoms evolve slowly over time, might lead to a long-period of not feeling well. This period is often filled with uncertainty before diagnosis. Even though receiving a diagnosis is a life challenge, the period of self-awareness of an illness, before formal diagnosis is also a struggle. In the rheumatic disease systemic lupus erythematosus (SLE) this period "pre-diagnosis" is described as a luminal state, were the identity as healthy is changed, but a reconstruction not yet possible [8]. In this period before diagnosis symptoms can be dismissed by the ill person as stress related or due to overworking [8]. Receiving a diagnosis often gives the social permission for being ill, authorizing a person to become a patient [9]. According to these thoughts the concept of sickness is related to the social context in which a person exists or relates. Cultural belonging has been shown to affect perceptions of symptoms as e.g. fatigue in everyday life with consequences and alternative management strategies [10]. Exploring ill-health through investigations of patient´s perception of symptoms and of biological, psychological and social perspectives of health can increase our understanding of illness and how it affects patients [11, 12]. These types of studies give a perspective on the possible diversity in the perception of a specific disease or symptom. Psychological reactions to the disease combined with the individual's social context have been of great interest in previous research on SLE-related fatigue [13]. Different components interact differently in each individual person because patient's response to illness is associated with both behavioural and psychosocial factors as well as disease activity [14].

3.2. Systemic lupus erythematosus

This thesis focuses on persons with systemic lupus erythematosus (SLE). SLE is characterized by inflammation of different organs combined with immunological abnormalities. SLE is a rather rare disease with an estimated incidence in Western Europe is 5 to 7/100 000 per year [15-17]. The prevalence varies from 7 to 159/100 000 with the highest number among Afro-Caribbean's in the UK [17]. The pathogenesis of the disease has not in depth been clarified, however autoantibodies and the formation of immune complexes, have an important pathogenic role [18, 19]. The disease affects women more often than men, with a women to men ratio of 9:1 [17]. However there are indications that men with SLE have a more severe disease with e.g. more nephritis and more autoantibodies [20, 21].

In 1982, The American College of Rheumatology (ACR) established classification criteria for SLE. The criteria were revised in 1997 and are primarily used for research [22, 23]. To be classified as having SLE, a person must have four or more of the eleven criteria, present simultaneously or on separate occasions (Table 1). These criteria's have been discussed, and recently been reformulated, by an extended expert panel [24]. The work from the expert panel indicates that the new classification criteria's are more sensitive, than the old ACR criteria's, and also suggested to be more clinically relevant. However these new criteria's have recently been published and were not used in this thesis.

Table 1. Classification criteria for SLE, 4 or more of 1 to 11 [22]

1. Malar rash	Fixed erythema over the malar eminences
2. Discoid rash	Red, scaly patches on skin that cause scarring
3. Photosensitivity	Exposure to ultraviolet light causes rash or flareups
4. Oral ulcers	Oral or nasopharyngeal ulcers
5. Arthritis	Non-erosive arthritis, ≥2 peripheral joints
6. Serositis	Pleuritis or pericarditis
7. Renal disorder	Proteinuria > 0.5 g per day or pathological urine sedimentation, with cellular casts
8. Neurologic disorder	Seizures or psychosis
9. Hematologic disorder	Hemolytic anaemia leuko- lympho- or trombocytopenia
10. Immunologic disorder	Positive anti-ds DNA or anti-Sm antibodies
11. Anti-nuclear antibody (ANA)	Positive ANA

ANA = Anti-nuclear antibody, anti-Sm = anti Smith, ds-DNA = double stranded DNA

SLE is heterogenic since a multitude of combinations concerning organ involvement may occur, which differ from patient to patient. Arthritis and arthralgia have been reported as the most common initial manifestations in SLE [25]. In several cases, the onset of disease can be diffuse and delay diagnosis, in particular if the symptoms are atypical or appear over a long period of time. Cognitive impairment in SLE varies between 22% and 80%, depending on the definition [26-28], but it is suggested to be mild most of the time [28].

Inflammation in a specific organ may come and go, but if prolonged it might cause organ damage, and may result in a permanent dysfunction of an organ. Permanent organ damage established during the first year of disease onset is a negative prognostic factor for survival [29]. Prognosis of the disease has improved, and the survival rates have increased since the 1970s [30]. A survival rate of five years is estimated at more than 95%, but it depends on the degree of organ involvement [31]. A reduction in early deaths seems be a trend during the last decade [31], but the most common cause of death in SLE is still related to cardiovascular disease in later phases of disease [32, 33].

The medical treatment of active SLE is based on the organ involvement and its severity, and it is always a balance between benefit (reducing inflammation and preventing organ damage) and risk (side-effects). Antimalarial drugs have been used for a long time and they are often considered as the initial agent to prevent flares in general, and they are also prescribed to treat skin and joint flares [34]. To reduce inflammation during flares glucocorticoids is another important treatment [35], while non-steroid-anti-inflammatory drugs (NSAIDs) are often used to reduce symptoms in particular arthralgia. More potent immunosuppressive treatments are used to reduce the use of glucocorticoids and protect from organ damage e.g. mycophenolate mofetil and cyclophosphamide are used to treat SLE related nephritis [36]. The new advanced biological treatment e.g. anti-cytokine therapies and B-cell depleting therapies, have recently also been used to treat severe SLE. However this treatment is not indicated for the majority of patients [37].

As previously mentioned, SLE includes inflammatory processes in several organs although the disease is sometimes described as a “medical imitator”. SLE is in the majority of cases characterized by flares with immune activation and accompanying clinical symptoms, which can vary considerably. Flares usually come and go but the number of flares and length of intervening periods with low disease activity vary among patients. However, it is important to remember that some patients can have continuously active disease. Possible multi-organ involvement gives a broad variation in the individual perception of SLE related symptoms. It is important for health-professionals, both clinicians and researchers, to remember that patients with SLE are often disturbed by symptoms of a subjective nature (i.e., not visible or objectively measurable) which are not included in the classification criteria e.g. fatigue, pain, malaise, anorexia [38].

Nevertheless these symptom can from the patients perspective be the most disabling or bothersome consequences of the disease [39]. Living with the disease SLE has been described as a life of uncertainty [6]. The variety of symptoms and the unpredictive nature of flares result in the experience of the body as being unreliable [6].

3.3. Health-related quality of life

In health care research, one aspect of the impact of disease concerns quality of life from the individuals' perspective. Quality of life has garnered increasing interest since the 1960s when new technologies have raised new questions in medicine. Better care and treatment facilities increased survival rates in several conditions, and questions concerning how to live with a medical condition and qualities in life were raised. Today that discussion continues regarding the theme of quality of life, in medicine this is related to the themes of ethics and health economics and attempts to capture quality of life as an outcome measure [40]. Nevertheless, the perception of quality of life is subjective and it is affected by a variety of influences on a person's life, and by what gives or reduces life satisfaction to the individual. In medicine and from a health care perspective, the concept of health-related quality of life (HRQoL) focuses on the influence of illness and its relation to quality of life. There is a distinction between quality of life and HRQoL, where quality of life as a whole include housing, income and perceptions of the environment [41, 42], and HRQoL focus on subjective perceptions of health and illness which is strongly interrelated with personal factors [43, 44]. When wanting to capture HRQoL self-assessments questionnaires that incorporate the physical, psychological and sometimes social consequences of disease are used [45].

Despite better prognosis in SLE during recent years [30] living with is SLE is described as a life of uncertainty [46] and a major challenge is still to improve the HRQoL of these patients [17]. Several studies demonstrate that persons with SLE perceive lower HRQoL than healthy controls and figures are also lower or in parity with other chronic conditions [47-49]. It has also been suggested that measuring HRQoL is more difficult in SLE compared to other rheumatic diseases because of the complexity and variety in disease characteristics [45]. There is furthermore an indication that HRQoL varies between subgroups of SLE in patients with different organ involvement [50, 51].

Fatigue has been described as a core factor negatively influencing SLE patients´ quality of life, often interfering with most routine aspects of family life. There are also implications that fatigue in SLE interferes with HRQoL more than the activity of the disease does [49]. The literature has stated that it is important to measure HRQoL, in rheumatology, since it incorporates dimensions other than traditional disease activity or organ damage [52-54]. For the assessment of HRQoL, in SLE both disease specific and generic questionnaires have been used [55, 56]. One of the most frequently used questionnaires is the generic HRQoL instrument, the Medical Outcomes Study 36-item

Short Form Health Survey (SF-36). The SF-36 is adapted for the general Swedish population [57-59] but the questionnaire is also valid and recommended in SLE and therefore considered suitable in this thesis [48, 60, 61].

3.4. Perception of symptoms

According to the Oxford Dictionary of English, a symptom is defined as "a physical or mental feature which is regarded as indicating a condition of disease, particularly such a feature that is apparent to the patient" [62]. To interpret a bodily sensation as a symptom of a specific disease, a person must first accept having a disease to be able to associate the sensation to it. Both external and internal stimuli affect the subjective perception of symptoms, in which a person's beliefs, experience as well as information from others have important roles [63]. Person perception of symptoms incorporates experiences of frequency, intensity, distress and meaning [64]. One symptom may also act as catalysts for other symptoms and occur in clusters [64]. The concepts of symptom occurrence, distress and experience are interrelated [65] (Figure 1). A more complex model for symptom experience have been described by Armstrong where antecedents that precede the occurrence of symptom experience are defined as characteristics of demographics (social aspects) disease (biological) and individual e.g. health knowledge, values and past experience [64]. A similar description is found in the conceptual model of symptom management revised by Dodd and colleagues [66] where the important domains from nursing science; person, health/illness incorporates the antecedents as described by Armstrong [64]. However in the study by Dodd and colleagues, the environmental domain includes physical, social as well as cultural conditions within the context of symptom management. [66]

The way a person experience a symptom influences individual management strategies. An individual's own management strategies might influence the distress that a symptom creates, and sometimes contribute to the occurrence of the symptom. An example is putting oneself in a situation that increases the risk of the stimulus that triggers a symptom, such as increasing fatigue by not going to bed to sleep. A person's beliefs and perceptions of symptoms have implications for the congruence between patients and personal health, such as regarding what aspects of the disease need present focus, which can result in misunderstanding and dissatisfaction with the outcomes of interventions [67, 68].

Living with SLE often include managing several symptoms, but also to interpret the meaning of these symptoms [6]. Several symptoms which are not included in the classification criteria of SLE are often the most prominent symptoms for the patients, fatigue is one example [39]. Patients have reported increased intensity of subjective symptoms, such as pain, stiffness and fatigue, as signals of flares. Others describe a

flare as something they “just know” or as the opposite—“couldn´t tell” whether or not they had a flare [69]. The course of the disease SLE often fluctuates and is unpredictable. There can be periods, sometimes years, with no symptoms of disease activity. Cognitive and behavioral aspects interact over time with the process of adaption to the progress of the disease. Life transitions might also alter a person’s reaction to and perception of symptoms. Some patients described decreased distress as they gained more knowledge and experience about the disease, but this is not the case in all patients [69].

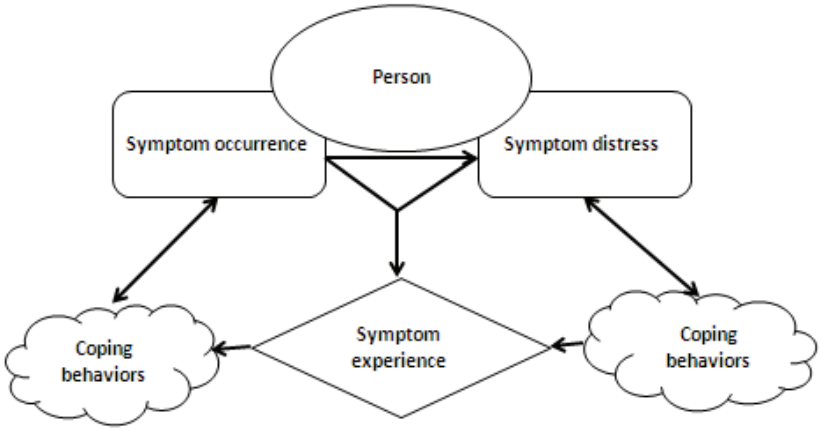

Figure 1. Model of symptom experience, occurrence and distress
(Adapted from Fu, 2007)[65]

3.5. Fatigue

A patient’s experience of disease-related symptoms, such as fatigue, is one example of perceived illness. Fatigue is an often dominant problem for many patients with chronic conditions. Fatigue has been described as an enigma that is hard to grasp and explain [70]. The concept of fatigue has been defined in several ways, including tiredness, which represents something familiar and manageable. By healthy individuals tiredness is generally regarded a temporary sign of needing recovery [71]. It is considered easier to understand than the more unfamiliar fatigue, which is related to illness and regarded as unmanageable [72]. One way to explain the difference between tiredness, fatigue and exhaustion and implications for e.g. sleep quality, emotional state, and social interactions is presented by Olson and collegues (Table 2) [73, 74]. According to Olson

a person experiencing tiredness may continue engagement in social activities, whereas when fatigue is perceived he/she deliberately saves energy for more enjoyable activities, while exhaustion usually leads to total withdrawal from social activities. Further Olson describe adaption as the relation between the three concepts, were e.g. successful adaptation may change fatigue to tiredness or if no adaptation, to exhaustion [73]. This distinction seems categorical because real-life experience of fatigue could be regarded as a continuum ranging from tiredness to exhaustion as described by Ream and Richardson [75]. Perceptions are sometimes more varied and complex, but a description of key domains and adaption to fatigue, as demonstrated by Olson (Table 2), may help the understanding of the consequences of fatigue.

Another important distinction is between sleepiness and fatigue. The concepts are interrelated but the distinction could be important when choosing treatment measures and interventions. Sleepiness is mainly caused by an imbalance in sleeping and waking mechanisms. This imbalance may, but not does not necessarily, also contribute to fatigue [76]. The use of the terms, sleepiness and fatigue, overlap, which may be unavoidable given that they are interrelated [77].

To understand the physiological mechanism of fatigue in chronic conditions, two types with different origins are described: central and peripheral. Peripheral fatigue results from neuromuscular dysfunction and relates to impaired neurotransmission in peripheral nerves and/or defects in muscular contraction. Central fatigue is described as abnormalities in neurotransmitter pathways within the central nervous system (CNS), and often co-exists with psychological complaints, such as depression or anxiety [78]. Central fatigue is sometimes translated as general fatigue and peripheral fatigue as physical [76, 79]. It is suggested that central fatigue is more frequent in patients with chronic disease, but that the contribution of peripheral fatigue to overall fatigue varies among different diseases [80]. It is suggested that most rheumatologic patients with fatigue suffer from both peripheral and central fatigue [78].

Among the suggested mechanisms for central fatigue in chronic disease are the chronic stress, cytokines and immune activation, central neurotransmitter pathways and disorders of mood [80]. Cytokines with direct or indirect contributions to fatigue are e.g. interleukin-1 and interleukin-6 which have been studied in cancer-related fatigue as well as in inflammatory disease [81-83]. These findings about the biological mechanisms behind fatigue are important and could contribute to the development of new drugs, which may help patients with inflammatory disorder. However, since these mechanisms not are the focus of this thesis, they are not further explored here. Having a background knowledge of theoretical mechanisms behind disease related fatigue, and combine these with the experiences of fatigue as described by the patients, new important research questions can be raised.

Table 2. Olsons descriptions of: Key domains of adaptation in relation to tiredness, fatigue and exhaustion. (adapted from Olson et al 2005, Olson, 2007)[73, 74]

Term	Sleep quality	Cognition	Stamina	Emotional role	Control over Body pro-cesses	Social interaction
Tiredness	Normal sleep pattern Feel rested	Forgetful	Gradual loss of energy in propor-tion to energy expended	Impatient	Body and mind work together	Engages in normal social activities
Fatigue	Chronic disrupted sleep patterns Do not feel rested	Inability to concentrate	Gradual loss of energy out of propor-tion to energy expended	Anxious	Mind over body	Saves energy for participa-tion in enjoyable activities
Exhaustion	Erratic sleep patterns, including periods of insomnia and periods of hyper-somn-olence	Confusion	Sudden loss of energy out of propor-tions to energy expended	Emo-tionally numb	Body over mind	Withdraws from all social activities

3.5.1. Fatigue in SLE

In SLE, fatigue has been described as one of the most prominent symptoms [39, 83], with high levels of fatigue reported from a majority of patients and described to diminishing the ability for daily living [14, 84, 85].

Disease activity as a main contributor to fatigue in SLE has been debated, and the relation between disease activity and fatigue is suggested to be weak [13, 85, 86]. Empirical experience has shown that some patients with inactive disease report levels of fatigue with impact on daily life, which suggest disease activity not to be the only explanation for the fatigue patients with SLE may perceive [85]. Possible contributing factors to disease-related fatigue are described in the literature e.g. mood disorder, sleep patterns, and low levels of aerobic fitness [13]. However, the findings of these studies are not consistent and a majority (80%) of patients with SLE reported fatigue as a need, which is not met by the health service [87], indicating that a greater focus on fatigue is required both at the clinic and in research.

Fatigue related to SLE is considered multidimensional and includes a multitude of disease-related and non-disease related symptoms that interact with the experience and perception of fatigue. Many studies have focused on the physiological aspects of fatigue in SLE but other interrelated aspects have been studied and the results indicate that pain, depression and perceived low social support are strongly associated with fatigue in SLE [88]. Others have shown that sleep disturbance and low physical activity contributed to higher physical fatigue scores (Table 3). Using a multiple regression model, Da Costa et al [89] found that depressed mood was the strongest determinant of mental fatigue.

Bio-psychosocial interactions in sleep disturbance and poor sleep were suggested to play a major role in disease-related fatigue [90]. In another study, Da Costa et al. used a multiple regression model to demonstrate that sleep disturbances and low level of physical activity contributed to higher physical fatigue scores and that depressed mood had the strongest impact on mental fatigue [89]. Studies on sleep in SLE are few and conflicting [91]. In patients with SLE 56 to 60% reported poor sleep quality [85, 90]. More sleep disturbances have been reported in patients with SLE compared to controls [92, 93]. At least one study showed that more than 80% of the participating patients with SLE were considered to have severe sleep difficulties [91]. Sleep disruption has been attributed to pain in SLE [85, 94-96] while other studies do not support this association [90].

Fatigue and the effect on fatigue by physical activity have been explored for several decades [97-99]. Several studies indicate physical exercise to reduce fatigue [98, 99], but a supervised controlled study could not demonstrate any difference in fatigue

between the exercise group and the control group [100]. A circular relation between fatigue and physical exercise is suggested where fatigue itself may lead to reduced physical fitness and functional capacity, leading to difficulties to perform physical exercise, and then fatigue may increase [101]. Tench et al. [102] concluded in a patient-control study that patients with SLE were less fit than sedentary controls in exercise capacity, muscle strength, fatigue, and disability. Controversially, Da Costa et al. found in their multivariate analyses that participation in exercise contributed to physical fatigue [89]. Logically high levels of fatigue were associated to low physical activity [14]. Oxidative stress is suggested as a bio-chemical link between aerobic capacity, physical activity and fatigue in SLE [103], with the theory that disease activity induces oxidative stress in autoimmune disorders. Disease activity in SLE has also been suggested to induce depression and problems to sleep, these are then considered to be mediators to SLE related fatigue [104].

Patients with SLE have been reported to be less physically active than people in general [105]. However, lack of physical activity may not be the cause of fatigue in all patient with SLE [106]. More research is needed to understand the complex relationship between fatigue, depression, anxiety and physical activity [38] and a potential true causal relationship between exercise and fatigue can only be demonstrated in prospective studies.

Table 3 Fatigue in SLE, influencing factors derived from the literature

Negative association		**Positive association**
Depressed mood [13, 88, 89, 104, 107]	**FATIGUE**	Physical exercise [98, 99]
Poor sleep [90, 104]		Behavioral intervention (support) [88, 108, 109]
Pain [14, 86, 88]		
Low social support [88]		

[Number in brackets correspond to the reference list]

In a review summarizing non-pharmacological interventions for fatigue in adults, six studies included patients with SLE [110]. Most interventions (24 of 28) referred to in the review either produced significant reductions in fatigue or increased vitality. They identified four main intervention categories: exercise, behavioral strategies, nutritional supplement and physiological approaches [110]. For SLE most the most common type of studies was exercise interventions [110].

3.5.2. Patients' descriptions of fatigue

A number of qualitative studies focusing on fatigue have been in the scientific arena during the last decades [111]. In the database PubMed, in a recent search, 704 hits were found when searching for qualitative studies and fatigue. A majority of these studies were carried out in the area of cancer research, in which fatigue has been approached by different methods, such as phenomenology [112] grounded theory [113], and content analysis [114]. In rheumatology, a qualitative approach has been carried out with patients representing diseases as fibromyalgia [71, 115, 116], ankylosing spondylitis [72], and rheumatoid arthritis [117, 118].

In addition to the qualitative study presented in the present thesis, at least three other qualitative studies have recently analyzed patients' descriptions and experiences of SLE [6, 54, 119]. They had a more general focus on living with SLE and not the main focus on fatigue. However fatigue emerged in all three studies, with different qualitative approaches. One of the three did not clarify their use of qualitative methodology [119] the other two used phenomenology [54] and ethnography with both interviews and narratives [6].

In the study using the phenomenological approach, fatigue was among one of the eleven themes identified in patients' descriptions of their lived experiences of SLE [54]. The study did not present extended descriptions of fatigue but instead summarized the presence of fatigue and its consequences, which often prevented them from joyful activities.

In the study that used an ethnography approach, with the combination of repetitive interviews and patients report of the fluctuation of daily symptoms, fatigue was described as contributing to a life of uncertainty for patients with SLE [6]. Living with SLE were also described as to result in a shifting sense of identity of one-self, imposed by changes in roles, at home and at work [6].

One of the studies had an interest in the psychosocial challenge of living with SLE [119], and revealed physical and emotional fatigue a major challenge for these patients.

Qualitative studies exploring patients' description of SLE are few and more studies focusing on patients perceptions and experiences of SLE related fatigue are needed to better understand how patients experience fatigue related to SLE.

3.5.3. Measuring fatigue

It is important that clinicians and researchers determine which aspects of fatigue they are interested in, that is, the severity as reported by the patient, the impact of fatigue, or other aspects. A simple question can be used to capture a subjective feeling like fatigue, to which the patient responds by describing his or her experiences and perceptions. This is useful in a single meeting and opens a unique dialogue between the patient and the caregiver. When collecting data from a larger population or following symptoms longitudinally, a measurement facilitates comparisons over time and between different groups. The importance of measuring fatigue as an outcome is also motivated by the consequences for several life areas, such as functional activities, work and social activities [120]. Sometimes it is regarded as sufficient to include measures of health-related quality of life or disease activity scores [53]. Questionnaires including only a few items on fatigue as one aspect among others risk yielding a one-dimensional reproduction of fatigue [121].

Considering the non-specific and subjective nature of fatigue, most measurements of fatigue are based on self-reported questionnaires. The information derived from such questionnaires depends on the questions asked, and the answers are based on the respondents' own interpretation. The way the responses are interpreted might confer scales measuring different aspects of fatigue related experiences [122]. Researchers interested in fatigue are challenged to ensure that the chosen questionnaires mirror aspects of fatigue that are in line with the purpose of the study [121]. Three issues to be considered when choosing fatigue scale for research or clinical practice have been suggested [122]:

1) Determine the aspect of fatigue to be assessed and why.
2) Use a one-dimensional or multidimensional scale. One-dimensional scales are often shorter, while multidimensional scales can provide more information.
3) The scale should be suitable for the patient population. A validation for specific populations cannot automatically be extended to other populations.[122]

Additional to these important considerations it is most interesting that the questionnaire of choice is sensitive to change to be able to use when following disease course or evaluating interventions [123].

In rheumatology, the international network Outcome Measures in Rheumatology (OMERACT), which was established in 1992 (http://www.omeract.org) has a special interest in outcome measurements. In 2002, OMERACT 6 incorporated for the first time a patient perspective with the purpose of identifying new outcomes and instruments. Because of this work, fatigue is recommended as a patient-centered outcome for measurement in rheumatoid arthritis (RA) [124]. Some conclusions from the workshop at OMERACT 8 (2006) were that fatigue does provide additional

information for the understanding of the outcome of the disease from a patient perspective. Suggestions were given that fatigue relates to sleep disturbance, psychosocial dysfunction and chronic pain. The majority (89%) agreed to include fatigue as a positive measure in future studies of RA whenever possible [124]. The conference concluded that although measures of fatigue exist and may be used, there is still room for improvement. Further clarifications and research were suggested, such as more detailed studies of the relationship between fatigue and other outcomes.

The scales for measuring fatigue can be divided into one-dimensional or multidimensional [122]. Questionnaires that include only a single question or result in the total score without any sub-scales are considered one-dimensional. Comprehensive questionnaires with subscales that reflect different dimensions of fatigue are considered multi-dimensional. Most instruments used in this thesis to capture fatigue, had the original focus of measuring fatigue. However, the Medical Outcomes Study Short Form-36 is an instrument that was developed to reflect health-related quality of life (HRQoL), and it consists of several subscales. One of these subscales focuses on vitality which is described to mirror fatigue. As mentioned above, a questionnaire that includes only a single question or presents results in a single total score without using sub-scales can be regarded as one-dimensional.

The variety of questionnaires used to assess fatigue call for comparisons between groups of patients or interventions [110]. In SLE studies, many of these questionnaires have been used. One of the questionnaires that is validated in SLE is FSS [125, 126], and it has been recommended because the instrument is widely used, which facilitates comparisons among studies [127].

The most extensive work concerning measures of fatigue in rheumatology has been conducted in the field of RA. In a Delphi study focusing on dimensions of fatigue in RA, twelve aspects of fatigue were suggested to be crucial in questionnaires capturing the occurrence. The twelve aspects were severity, frequency, duration, changes in fatigue, perceived causes of fatigue, energy, sleep/rest, body feeling, cognition/concentration, coping, negative emotions/mood and consequences [128]. These aspects are also of interest for those working with fatigue related to other diseases than RA. Hewlett et al. [129] identified six instruments that demonstrated reasonable validity for measuring RA fatigue: the multidimensional assessment of fatigue scale (MAF)[130], the short form-36 vitality subscale , the functional assessment of chronic illness therapy fatigue scale (FACIT-F)[131], the ordinal scales, the profile of mood states (POMS) and the visual analogue scales (VAS) [132]. Despite extended evaluations, Hewlett et al. recommended further research. Another research team [133] identified seven validated self-administrated instruments used to measure fatigue in RA. The same sample of seven questionnaires have been used and tested in SLE in a North American context but never in a Swedish setting [134]. (see section 7.3.3)

4. THESIS RATIONALE

The complexity of SLE has several consequences for daily living. Previous research has confirmed fatigue as a significant characteristic of SLE, and fatigue has been described as a core factor that negatively affects SLE patients' quality of life and interferes with many aspects of family life. Fatigue is an individual and subjective sensation; thus, its impact on an individual's life can be difficult for others to understand and few studies have explored patients' description of their own experiences of SLE related fatigue.

To understand the burden of symptoms from the patients' perspective facilitates the assessments and generates a base for appropriate intervention programs which can provide support to the patient. Several questionnaires have been used in rheumatology to assess fatigue. When assessing symptoms such as fatigue it is important to be able to detect differences and change over time, to evaluate interventions as well as disease course.

This project was designed to enhance the understanding of the patients' experiences of SLE-related fatigue, as well as to contribute to better recommendations for adequate assessment methods to capture disease-related fatigue in SLE.

5. AIMS OF THE THESIS

The overall aim of this cohort-based, cross-sectional project is to explore patients' experiences of symptoms related to systemic lupus erythematosus (SLE) with the main focus on fatigue and how it is described and measured.
The specific aims of the present thesis are as follows:

I To describe women's experiences of SLE-related fatigue and how they express the feeling of fatigue, the impact of fatigue on daily life, and strategies to manage fatigue in daily living.

II To explore patient-reported SLE symptoms in relation to age and disease duration, and to compare these reports with instrument-assessing disease activity and health-related quality of life.

III To identify the smallest difference in score in the domain of fatigue that patients perceive as beneficial, by estimating the minimally clinically important difference of seven self-administered measures of fatigue in persons with SLE.

IV To identify clusters of fatigue in patients with SLE as well as in age and gender match controls, and with regard to health-related quality of life, anxiety, depression and life-style habits compare these clusters.

6. PATIENTS AND METHODS

6.1. Design

This research-project included both qualitative and quantitative data collections to answer the research questions. A summary of the four studies is presented in Table 4. The data used in studies II and IV were collected at the same time as the participants were included in the research project SLE-2004, which is a cohort project with patients with SLE. Data for study I and III were collected on two additional scheduled visits in separate group sessions using different approaches. The data collected was generated from patients (study 1-IV) and from age- and gender-matched controls (study IV).

Disease characteristics were obtained from the medical assessment performed by physicians working with project SLE-2004. SLE-2004 is an on-going inter-professional cohort project where medical data, patient's characteristics and self-assessments are collected at a single inclusion visit. In the joint database, data concerning different aspects of the disease and its consequences has been recorded. Beside the data regarding fatigue in this thesis, other studies of special interest such as cardiovascular disease and physical activity have been published elsewhere [33, 105, 135, 136].

Table 4. Overview (summary) of the four studies with regard to data collection and analysis

Study	Study outcomes	Number of participants	Method for data collection	Analysis
I	Women's description of SLE related fatigue	N = 33	Focus group discussion	Qualitative content analysis Descriptives
II	Exploration of patients reported symptoms and comparison to health related quality of life	N = 324	Cross-sectional Free-written answers Self-assessments questionnaires	Inductive qualitative analysis of free written answers. Descriptive Comparative: Mann-Whitney U-test, Wilcoxon's signed ranks test.
III	Comparison of seven measures of fatigue. To detect minimal clinically important difference using patients comparative assessment of fatigue	N = 51 (patients-patients)	Self-assessment of fatigue, own fatigue and comparative with other patients. Opportunity to give written comments.	MCID: descriptive and regression approach. Descriptives
IV	Clusters of fatigue, and comparison between clusters and SLE and controls	N = 305+311 (patients, controls)	Cross-sectional Self-assessment of; fatigue, HRQoL, anxiety, depression. life-style factors	Hierarchic cluster analysis Descriptives Comparative: Chi-square Mann-Whitney U-test ANOVA

MCID = minimally clinically important difference, HRQoL = health related quality of life, ANOVA = analysis of variance between groups

6.2. Study subjects

All participants were included in the same cohort study, which explored different aspects of SLE (see design section.) In total, 327 patients participated in the four studies, mean age 47 years ±15, with a low mean dose of glucocorticoids (5 mg, ±6.75). The majority (91%) of the patients were women. A presentation of organ manifestations and ongoing anti-rheumatic medication is presented in Table 5.

Table 5 Organ manifestations (ever) and ongoing anti-rheumatic treatment for the cohort of 327 patients with SLE

Organ manifestation (ever)	
Arthritis	83%
Blood manifestation[a]	72%
Photosensitivity	67%
Malar rash	54%
Nephritis	40%
Pleuritis	36%
Oral ulcers	34%
Discoid rash	19%
Pericarditis	18%
Neurological disorder[b]	11%
Disease-Modifying Anti-Rheumatic Drug (ongoing medication)	
Chloroquine	32%
Azathioprine	19%
Cyclophosphamide	13%
Mycophenolate mofetil	7%
Methotrexate	4%
Cyclosporine	2%
Glucocorticoids	57%

[a] Neurological disorder = psychosis or seizures
[b] Blood manifestation = leucopenia, thrombocytopenia, lymphopenia or haematolytic anaemia.

In study IV each patient had an age- and gender-matched control from the same county (Stockholm area).
Most patients (79%) were included in study II and study IV with an overlap of 98% (Figure 2). Between the two smaller studies (study I & III), the overlap was 20%. Only a few (4%) patients participated in all four studies.

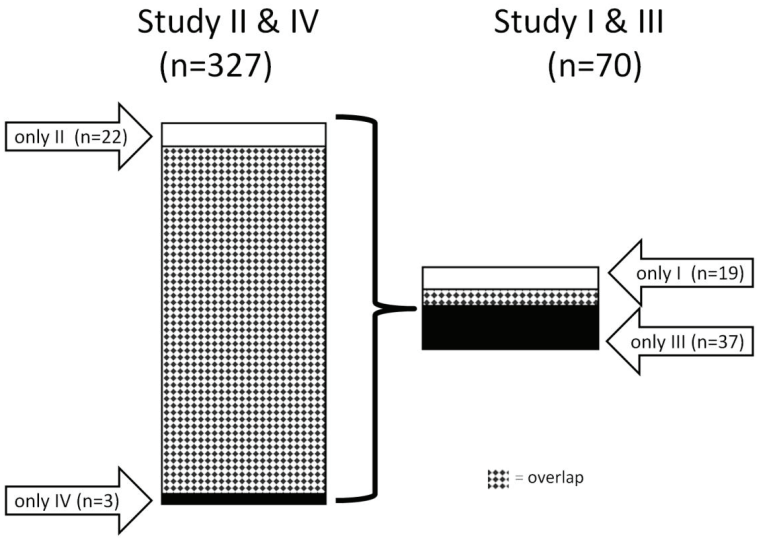

Figure 2. Patient's participation and overlap per study
(Study I n=33, Study II n=324, Study III n=51, Study IV n=305 patients)

Table 6 illustrates the distribution in age and disease duration for patients in the four studies. The oldest and the youngest were not included in the two smallest studies, which involved group attendance. In study I we wanted to include patients with experience of SLE-related fatigue, which is why the shortest disease duration included in that study was two years, thus meaning no newly diagnosed patients were included. The SLE diagnosis was verified by a medical examination and laboratory examinations in all patient [22] (see section systemic lupus erythematosus 3.2.).

Table 6. Patient demographic per study

Study	Number	Age, years, mean	range	Disease duration, years, mean	range
I	33	48 ±12	29-68	18 ±14	2-49
II	324	47 ±15	18-84	15 ±12	0-58
III	51	52 ±12	26-72	19 ±14	0-51
IV	305	47 ±15	18-84	14 ±12	0-58

7. DATA COLLECTION

Data collection was conducted three times. The data for study II and IV were collected simultaneously. There were two additional data-collection settings for studies I and III. The data was both qualitative and quantitative. The qualitative data derived from the interview material (transcribed verbatim) from focus group discussions (study I) and free-written answers (study II). The quantitative data consisted mainly of data from self-assessment measures/questionnaires (study II+III+IV) and assessments collected from physicians' evaluations of patients, such as disease specific measures. In study III patients met in one single group session with 6-9 patients (n=51). After initial presentation they answered seven questionnaires assessing fatigue followed by a procedure of patient's dialogues and individual assessment as illustrated in Figure 3. Each patient had at least five dialogues followed by the individual assessment, resulting in 260 contrasting assessment.

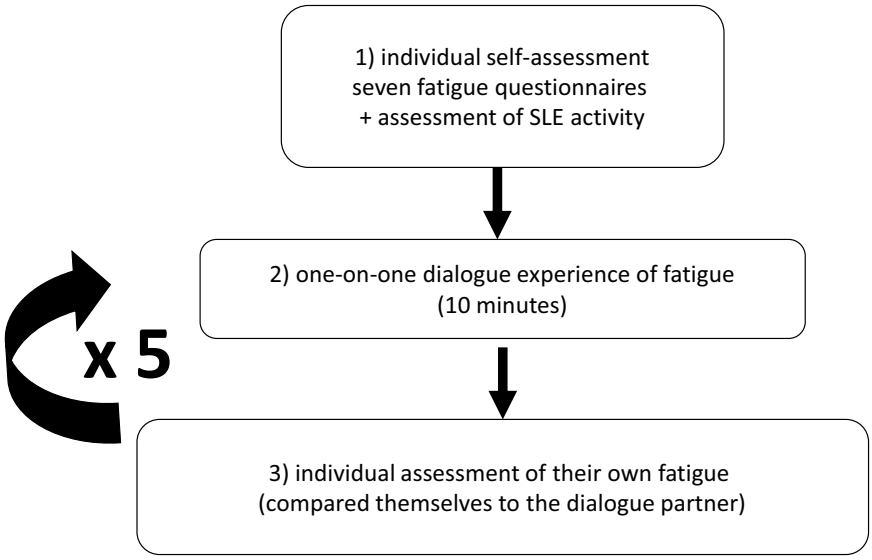

Figure 3 Schematic procedures of fatigue dialogues.
1) Individual assessment of fatigue (see methods section).
2) Respondents' one-on-one dialogues (10 minutes) discussing their experiences of fatigue, **3)** followed by an individual assessment of their own fatigue (compared themselves to the dialogue partner) on a 7-grade scale: (Much More/ Somewhat More/ A Little Bit More/ About the Same/ Little Bit Less/ Somewhat Less/ Much Less). Points 2 and 3 were repeated until each respondent had five unique dialogues, each followed by an individual comparative assessment of their own level of fatigue.

7.1. Focus group discussion

Focus group discussions (FGD) were chosen for study I. This to collect diverse perspectives and to stimulate interactions between patients, which resulted in reflections as well as the generation of ideas [137-139]. Topics and comments derived from the participants were encouraged. To ensure that relevant topics were covered, an interview guide with open-ended questions was used in all seven focus groups (Table 7). At the end of each FGD, the interview leader summarized the session to ensure that all interview topics were covered. The interviewer then allotted time for clarification and further associations. Two researchers were present at all FGDs as interview leader and observer. The interviews were digitally audio taped and transcribed verbatim (names were withdrawn from the transcriptions, which were then assigned a number).

Table 7. Interview guide used in the focus group discussions (study I)

- Can you describe the feeling of fatigue that you associate with SLE
    - The feeling itself
- How does it affect your daily living?
    - Is there anything that you avoid doing?
    - Is there anything that you miss, for example that you can't do?
- How do you manage in daily life when you have this feeling/fatigue?
    - Do you have any tricks or strategies?

7.2. Freely written answers

The patients in study II gave written answers to two open questions: *"What SLE-related symptoms have you experienced as most difficult during your disease?"* and *"What symptoms do you presently perceive as most difficult*?". The written answers consisted of a single word, sentences or longer descriptions up to one page. The data collection of the written answers was inspired from the free-listing methods originally used in anthropology. This method has also been used in oncology to collect data on patient-reported symptoms in persons with lung cancer [140]. The method of using open questions was applied to capture *free* answers from the respondents, without any predefined alternative answers. The questions were given in a questionnaire, which was sent to the patients' home address one week before the hospital appointment. At the hospital appointment the patients met a nurse, handed in the questionnaires and then had a medical examination by physicians. This collection procedure was chosen to ensure

the patients' free report of symptoms without interference from health care professionals.

7.3. Questionnaires

An overview of the questionnaires used in this thesis is presented in Table 8.

Table 8. Overview of questionnaires used in the thesis

Main focus	Name	Study I	Study II	Study III	Study IV
HRQoL	SF-36	x	x		x
Anxiety and depression	HADS		x		x
Fatigue	FSS			x	x
	MAF	x		x	x
	FACIT-F			x	
	CFS			x	
	VT			x	x
	MFI-20			x	
	NRS			x	
Disease activity/organ damage	SLEDAI		x		
	SLAM		x		x
	SLICC/ACR		x		x
	SLAQ			x	

HRQoL= Health Related Quality of Life, SF-36= The Medical Outcomes Study 36-item Short Form Health Survey, HADS= The Hospital Anxiety and Depression Scale, FSS= Fatigue Severity Scale, MAF=Multidimensional Assessment of Fatigue scale, FACIT-F= Functional Assessment of Chronic Illness Therapy – Fatigue, CFS= Chalder Fatigue Scale, VT= Vitality (from SF-36), MFI-20= Multidimensional Fatigue Inventory, NRS= Numeric Rating scale, SLEDAI= SLE disease activity index, SLAM= Systemic Lupus Activity Measure, SLICC/ACR= Systemic Lupus International Collaboration Clinics/American College of Rheumatology, SLAQ=Systemic Lupus Activity Questionnaire

7.3.1. Health related quality of life

The medical outcomes study 36-item short form health survey (SF-36) was used to assess HRQoL [58]. The questionnaire is frequently used in 14 languages in more than 40 countries (www.sf-36.org, August 2012). The SF-36 has been previously used in the general Swedish population [57-59] and national reference values from the general population are available [141]. The questionnaire is also valid and recommended in SLE and therefore considered suitable in this thesis [48, 60, 61]. The SF-36 is comparable to more disease specific questionnaires assessing HRQoL in SLE [142].

The results from the 36 questions are divided into eight different dimensions HRQoL: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Each domain ranges from 0 to 100, and high values represent better HRQoL. The eight dimensions are often used to illustrate the health profile of a person or a group of persons. The dimensions can also be grouped together, which results in two health components subscales, the physical (PCS) and the mental (MCS). The dimensions of physical functioning, role physical, bodily pain and general health indicate physical health and the mental health are reflected by the combination of vitality, social functioning, emotional role, and mental health.

7.3.2. Anxiety and Depression

The questionnaire, hospital anxiety and depression scale (HADS) were used to assess anxiety and depression [143, 144]. It consists of 14 items, each with four alternative answers. Half the items represent anxiety and half indicate signs of depression, which results in two sub-scales. Each item is weighted from 0 to 3, giving a possible sum ranging from 0 to 21 for the two sub-scales. Scores ≥7 in each area indicates symptoms of mental disorder [143].

7.3.3. Fatigue

Seven questionnaires measuring fatigue were used in this thesis (Table 8). The choice of questionnaires were based on the result from an expert panel [127] and the extended work on measuring fatigue in SLE by Goligher et al [134].

The fatigue severity scale (FSS) [125, 126] is one of the most frequently used for SLE. It is a nine-item scale scored from one to seven; the mean value of the answered questions results in the final score (range 1-7). The ad hoc committee on systemic lupus erythematosus suggested that for FSS a reduction in score by 10 to 15% would

represent clinical improvement [127]. The cut-off for fatigue is suggested to be >3 [14]. The questionnaire has been tested in Swedish patients with SLE [126].

The multidimensional assessment of fatigue scale (MAF) is a 16 item scale involving four dimensions of fatigue: severity, distress, interference with daily activities, and timing [130, 145]. A final score ranging from 1 to 50 is calculated. The number 1 indicates no fatigue and high values represent greater fatigue. The first question asks "To what degree have you experienced fatigue in the past week?" If the answer to that question is "1", the final score will be 1. In Swedish the questionnaire has been tested for the rheumatic disease systemic sclerosis [146].

The multidimensional fatigue inventory (MFI-20) [147] is a 20-item questionnaire, resulting in five subscales with four items in each (general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue). Each sub-scale is scored between 4 and 20 and the total score range is 20 to 100 [89, 148]. The Swedish version has been tested in several cancer diagnosis [148, 149], fibromyalgia and widespread pain [150].

The Chalder fatigue scale (CFS) [151] includes eleven items resulting in two dimensions, physical fatigue (7 items) and mental fatigue (4 items). Two different scoring systems are in used previous research with CFS, and in this thesis we adopted the Likert system (0, 1, 2, 3) ranging from 0 to 33, which is in line with Goligher et al.[134]. No publication of the Swedish version has been found.

One of the questionnaires was a single-question scale with numeric answers (scale 0-10) for fatigue: the numeric rating scale (NRS). In cancer related fatigue, the cut-off for moderate fatigue is suggested at 4 and for severe fatigue at 7, when using a 0-10 scale [152].

Two of the self-assessment instruments were constructed with negative scoring, which means that high values indicate less fatigue. These are the vitality subscale with four items from the short form–36 (SF-36) and functional assessment of chronic illness therapy – fatigue (FACIT-F). FACIT-F is a 13-item questionnaire with five response alternatives on a Likert scale. The total score ranges between 0 and 52 (52 = no fatigue) [131, 153, 154], 2011). The Swedish version has been tested on persons with Parkinson´s disease [153].

7.3.4. Disease activity and organ damage

Two instruments were used by the physicians to assess disease activity: the systemic lupus activity measure (SLAM) and the SLE disease activity index (SLEDAI). SLAM contains 30 items, seven of which correspond to laboratory parameters; 23 items capture clinical manifestations during the last month (scale 0-83, high values indicate more activity) [155, 156]. SLEDAI includes 24 items corresponding to nine organ systems (scores 0-105) [157].

There is an indication that SLEDAI is not as effective as SLAM regarding sensitivity to capturing changes in disease activity that are important to the patients [158]. The differences in sensitivity to patients' perceptions of the disease have been explained by the fact that the subjective SLE manifestations, such as fatigue and pain, which are included in SLAM but not in SLEDAI.

To evaluate SLE disease damage, the systemic lupus international collaboration clinics/American College of Rheumatology (SLICC/ACR) damage index, was used to record cumulative organ damage involving 12 organ systems [159, 160] (scores 0-47).

In study III patients assessment of disease activity was used; The systemic lupus activity questionnaire (SLAQ). The SLAQ is based on the instrument SLAM, excluding laboratory parameters, and it is described as a tool to screen for SLE activity and possible flares. In SLAQ, the patients answer 24 questions related to disease activity. The SLAQ scores are calculated using the same scoring system as the SLAM [161]. In addition to the SLAQ score, one question reflects the patient's assessment of the severity of SLE flares (0-3 score) and one asks for the patient's assessment of global disease activity (0-10 scale).

8. DATA ANALYSIS

8.1. Study I

To understand, explore and explain SLE-related fatigue, qualitative content analysis was used to analyse the transcripts from the seven focus group discussions [162]. The first step of the analysis was to identify words, sentences or paragraphs that the patient used to describe experiences of SLE-related fatigue. The descriptions concerned mainly their sensations of fatigue its, influence on their life, and the strategies they used to manage daily life with fatigue. The identified statements were sorted into categories with shared content. Two researchers read and analyzed the transcripts separately and then compared the results. Differences in the separate analyses were discussed until consensus was reached. The categories were then further discussed with a third author. Finally, the analysis linked the categories together into themes.

The demographics from the interview group were described with means and standard deviations. Comparisons with the non-interview group were made using the Mann Whitney U and independent samples tests.

8.2. Study II

To explore patients experiences of SLE related symptoms patients written responses to two questions; *"What SLE related symptoms have you experienced as most difficult during your disease?"* followed by *"What symptoms do you presently perceive as most difficult*?" were analyzed in study II. The approach used to process the written answers from the open questions emanated from an inductive procedure of the mixed methods approach [140]. Using an inductive approach, the answers from the initial 200 respondents (i.e., the number of patients included at the time) were classified by the principal author (SP) according to content similarities. The inductive process and the results of "groups of patient answers" were discussed by two authors, which resulted in a preliminary coding list. This coding list was tested and used by a third author as a pilot to categorize answers, which was followed by suggestions used to adjust and clarify distinctions among the codes. After discussion and clarification, a final coding list was used, and three authors each coded 25% of the statements from the 320 consecutive respondents included in the project. Cohen's kappa was calculated, which showed that the majority of the coding categories had good to very good agreement (from 0.74 to 1.0) [163]. In four symptom categories, agreement was moderate; these were reported by only few patients ($n \leq 6$). Using this final coding list, the first author of the study coded all statements made by the 320 respondents. Regarding the continuing inclusion in the project four later included patients were added, giving the final number of 324 respondents. To further explore the symptom categories,

comparisons were conducted between reporters (patients with a written statement in a specific symptom category) and non-reporters (patients reporting any other symptom but not the specific symptom investigated) within the symptom categories using the Mann-Whitney U test. Quantitative descriptions in this study were made with medians and inter-quartile ranges for numerical data and per cent for frequency data.

8.3. Study III

To estimate the MCID for seven questionnaires measuring fatigue the procedure of study III closely follows the research agenda described in Goligher et al. and Pouchot et al [133, 134]. These studies was based on the statistical structure of Brant et al [164]. Each instrument was computed according to given scorings; however, to enable comparison of the results, all fatigue questionnaires were further normalised into a positive scoring scale of 0–100. The difference in levels of fatigue between each dialogue pair where calculated for each of the seven fatigue measurements. Then the paired differences between the dialogue partners were stratified into seven groups. The grouping into seven levels was based on the patients' self-estimation of the comparative level of fatigue, (7-grade scale) to that of his or her dialogue partner, which was conducted after each fatigue dialogue. As recommended by Pouchot et al. [133], the mean differences were standardised and adjusted by subtracting the mean difference for "about the same". This was done in order to estimate the minimally clinically important difference (MCID) for "a little more" and "a little less" fatigue. The procedure of standardisation was based on the assumption that the mean difference between the dialogue partners in the "about the same" group ought to be null.
Figure 4 shows the method and graphs of the data derived during the data analysis, standardization.

The MCIDs were established using a regression approach wherein the individual fatigue scores were used as predictors in a regression model for each instrument. This method is based on the assumption that the relative degree of difference between the comparative groups was roughly equal [164]. The MCID and its statistical significance were then calculated using the slope of the regression line.

Patients were also given the opportunity to write down free comments concerning the seven questionnaires, how the questions were formulated, and how the questions reflected their kind of fatigue. The frequencies of positive and negative votes were calculated for each questionnaire separately.

Patient's characteristics were described with means and standard deviation or 95% confidence intervals. Pearson's correlation coefficient was used to study the associations between fatigue score and disease activity, fatigue and age.

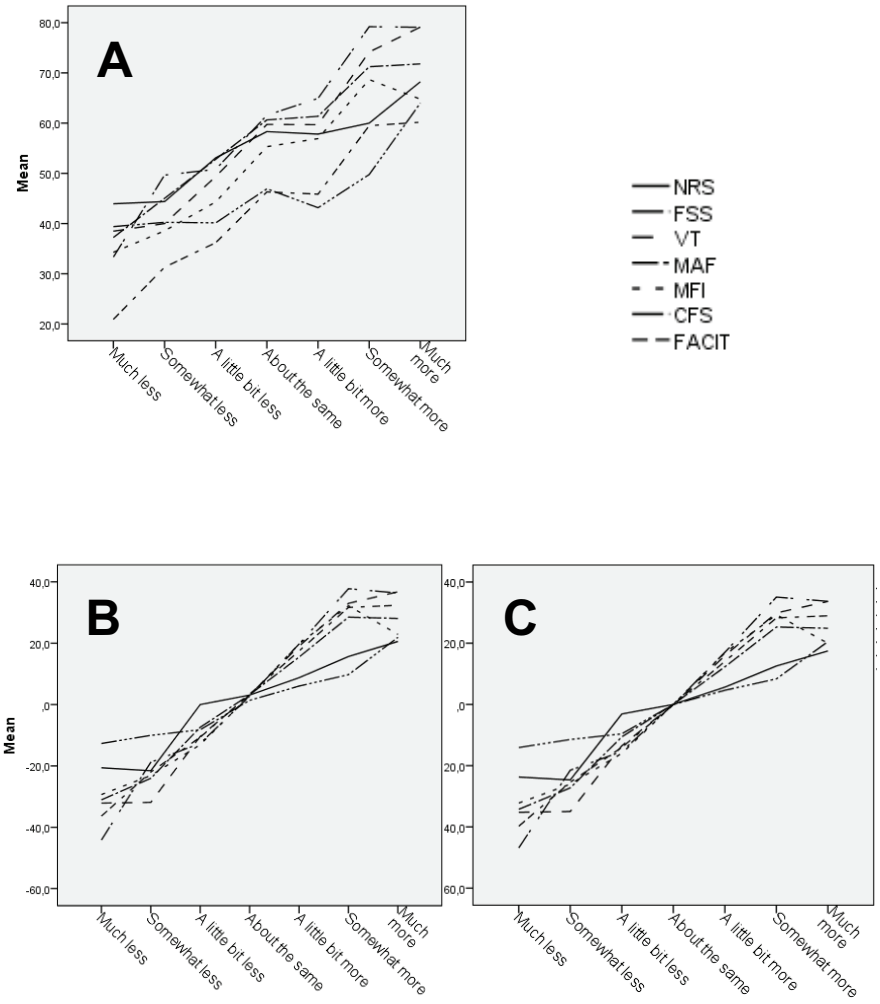

Figure 4. Illustrations of the analyzing procedure in study IV.
The lines represent the seven fatigue questionnaires. Abbreviations see Table 8.

A: The picture demonstrates the mean value of fatigue (after normalization) by contrast group.
B: Illustrates the mean paired difference between dialogue partners
C: The mean-paired difference after standardization with the mean for "About the same".

8.4. Study IV

In study IV, a hierarchical method of cluster analysis was used to form homogeneous groups [165] based on data from the variables measuring fatigue (FSS, VT, MAF). The fatigue measures on which the clusters were based use different scoring. Hence, to avoid one instrument dominating the analysis, the data computed z-scores to standardize the scores.
Clusters were formed stepwise, to simplify that each person is initially considered a cluster. Two clusters were then chosen according to the clustering criteria and were merged into a new cluster. The process continued until all objects belonged to one cluster. The average linkage (within group) was used for clustering, and the combined clusters were based on the model that the average distance between clusters was as small as possible [166]. The number of relevant clusters was three and the relevance of the clusters was compared with other hierarchical methods and then confirmed by the average linkage (between groups), complete linkage (furthest neighbour), which confirmed the choice of number of clusters. The methods of nearest neighbour (single linkage) and median method did not yield the same distinct cluster patterns.

Comparisons were then made between the persons with SLE and the controls and between the emerged clusters of fatigue. Descriptive data were calculated for all variables. A Chi-square test was then used for comparisons regarding the distribution of dichotomized data between groups, and an independent samples test was used for continuous data. For comparison among the three clusters, one-way ANOVA was used for continuous data with additional correction using the Bonferroni post-hoc test. Chi-square tests were used to explore the ordinal data and comparisons between the clusters of fatigue and multiple comparisons were made to detect differences.

9. ETHICAL CONSIDERATIONS

The thesis followed the ethics set down in the Helsinki Declaration. The participants were ensured of confidentiality, and they participated according to their own free will. The participants were given written information before inclusion in any of the four studies. Separate information was given for the three time points of the data collection (study I, II+IV, III). The information included details about the aim and procedure of the study. The patients and controls were informed that their contributions to the studies were voluntary and that if they declined participation it would not interfere with their future contact with the clinic. No economic compensation was offered to the patients or the controls. However, a small breakfast meal—sandwich, tea or coffee—was offered to the participants. It is hoped that the participants considered the aims of the studies compelling enough to be willing to contribute to clarifying the important issues of this research. The controls obtained a free health examination since the procedure also included testing for blood pressure, body mass index, cholesterol, and blood glucose (not analyzed in this thesis). The patients included in the group sessions (studies I and III) also pointed out the benefits of getting the chance to meet other patients and discuss SLE-related fatigue. They expressed that this opportunity was lacking in the regular health care system.

To ensure confidentiality, all data analyses were conducted after removing names and assigning a code-number.

Autonomy – voluntarily participation

Since the present thesis is part of an extended clinical cohort-based study, it was important that the researcher ensured the confidence of the respondents that their quality of care would not change whether they participated in the project or not. It might be considered a dilemma that most patients had a relation to the clinic and met some of the staff (e.g., physicians or nurses) before they were asked to participate [167]. The first 140 patients had previously participated in a baseline study about ten years ago. There was a risk that some of them thought that they ought to participate this time since they accepted ten years ago. It was important to the researchers to ensure that both patients and the controls thoroughly understood the given information.

10. RESULTS

10.1.Study I

Seven semi-structured focus group discussions (FGD) concerning patients' perceptions of SLE-related fatigue were conducted with 33 women with SLE. The women had all documented experience of fatigue at a previous visit (≥7, scale 1-10, question number 1 in MAF). The number of patients in each FGD ranged from three to six.

SLE-related fatigue was portrayed as an overwhelming, unpredictable phenomenon, resulting in the feeling that fatigue dominated and controlled several situations in everyday life. The results were illustrated as the landscape of fatigue, divided into four themes with underlying categories (Figure 5).

The themes were the following:
"Nature of fatigue" involves the sensation, occurrence and character of fatigue. The character was described as controlling and unbeatable. The occurrence was described to be constant but with unpredicted peaks. The sensation of fatigue was experienced in the body but also as a misty feeling more concentrated to the head.
"Aspects affected by fatigue" describes emotions that arose with fatigue. Work, family life, social contacts, and leisure activities that were other aspects that were affected by SLE related fatigue;
"Striving towards power and control" concluded the array of ways used to manage daily life and were categorized into mental struggle, structure, restrict, and provide. The choice of strategies used was described as a balance with implications for how fatigue limited a person's life.
"Factors influencing the perception of fatigue" described understanding from the surroundings and the pain as strongly influencing the experience and perception of fatigue.

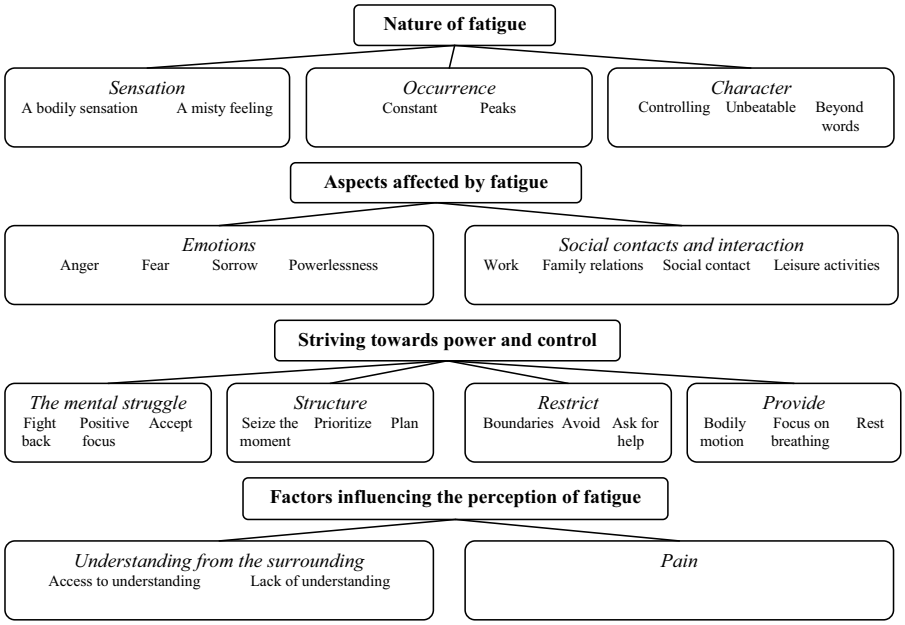

Figure 5. The landscape of fatigue (Pettersson, 2010)[168]

10.2.Study II

In the cross-section data collection 23 symptom categories were identified from the respondents' (n=324) answers to the open questions: *"What SLE related symptoms have you experienced as most difficult during your disease?"* followed by *"What symptoms do you presently perceive as most difficult?"*
The three most frequently reported symptom categories were fatigue, pain and musculoskeletal distress. The median number of reported categories corresponding to the question of ever-present symptoms was three (IQR 2-4). A majority of the patients (n = 255, 78.7%) described at least one of the top three most frequently reported symptom categories (fatigue, pain and musculoskeletal distress) as being an ever-present problem.

Present symptoms were further evaluated by comparing patients who reported a specific symptom with patients who did not report that specific symptom. Patients reporting cognitive distress at inclusion in the study had shorter disease duration (median 4 years, IQR 1-17, p = 0.04) than patients reporting other symptoms (median 12 years, IQR 5-21).

The symptom categories were further analyzed for disease activity, disease duration and organ damage. Higher disease activity measured by SLAM was assessed in reporting patients in the following categories: fatigue, pain musculoskeletal, swelling, psychological/emotional, fever, cognitive distress and sleeping. Only patients reporting reduced physical capacity had more extensive organ damage (SLICC/ACR, median = 3, IQR 0.5-5, $p = 0.008$) than those not reporting the corresponding symptom category (no reduced physical capacity: SLICC/ACR, median = 1, IQR 0-2).

Patients who reported no present symptoms of SLE had lower disease activity (SLAM, median = 3, IQR 2-6, $p < 0.001$) and organ damage (SLICC/ACR, median = 0, IQR 0-1, $p < 0.05$) than patients reporting any kind of symptom (SLAM, median = 7, IQR 4-10; SLICC/ACR, median = 1, IQR 0-2), but no differences in disease duration.

Each category was subsequently compared with results from the anxiety, depression and HRQoL self-assessment questionnaires. Patients with present psychological/emotional distress had the highest anxiety levels (n = 22) (HADS anxiety median = 9.5, IQR 5.75-14) compared with those without psychological/emotional distress (HADS anxiety median = 6, IQR 3-9) ($p = 0.005$).
In comparison with the patients reporting any symptom, the no-symptom patients showed higher HRQoL, less anxiety, and less depression.

The three most frequently reported symptom categories (fatigue, pain and musculoskeletal distress) were associated with reduced HRQoL. Patients with fatigue reported significantly lower scores (meaning worse) in both MCS and PCS and higher scores (meaning worse) on the questionnaires measuring anxiety and depression. Patients reporting pain had lower scores on PCS and more depression but not more anxiety. Patients in the symptom category musculoskeletal distress reported reduced PCS. Fatigue and pain were further analyzed as subgroups, leaving out patients who reported both fatigue and pain. Statistically significant differences between the subgroups were detected in the dimensions of bodily pain and vitality. Respondents reporting fatigue (n = 65) but not pain scored lower on vitality ($p = 0.013$), whereas respondents reporting pain (n = 45) but not fatigue scored lower on bodily pain ($p = 0.003$).

10.3. Study III

Seven sessions with 6-9 patients per session included totally 51 persons. Each patient initially responded to seven fatigue questionnaires in addition to patient assessment of SLE activity. They also had at least five one-on-one dialogues followed by an individual assessment of each patient's own fatigue, compared to that of his or her dialogue partner. The procedure with dialogues addressing fatigue and the following comparative assessment resulted in 260 contrasting assessments. After normalisation of

the seven fatigue measures to a positive score range of 0–100, the mean differences in fatigue between pairs of dialogue partners were calculated for each of the seven fatigue questionnaires. For most instruments, the mean paired difference followed a slope where the contrast groups represented a reasonable and increasing level of fatigue, compared to the neighbouring contrast group. However, for the MFI-20, patients in "much more fatigue" had lower means than patients in "somewhat more fatigue". The mean paired difference for the patients scoring "about the same fatigue" ranged from 1.4 for CFS fatigue scale to 3.4 for FACIT-F.

The standardised mean paired differences in the seven instruments for the "little more fatigue" group varied from 4.6 on the CFS to 17.0 on the FSS. The contrast group "little less fatigue" had adequately negative values, meaning lower levels of fatigue, and ranged from -16.0 for the MFI-20 to -3.1 for the NRS.

The coefficient from the regression model varied from 4.45 for CFS to 10.75 for FSS. The two questionnaires (NRS and CFS) with the lowest coefficient had standardized MCIDs under 0.3, and all others had an MCID of 0.4 or slightly above. The estimates in the regression approach were consistently higher than in the descriptive paired approach, and with the lowest coefficients, NRS and CFS showed the smallest difference between the two models.

In addition to collecting data for the statistical procedures, the researchers encouraged the respondents to provide written comments as positive or negative criticism on whether any of the instruments were better or worse in mirroring their own experience of fatigue. A majority of the participants (76%) gave their opinion on any of the instruments, with either a positive or negative rating. The most favourable responses were given to CFS and to FSS, to which 14 of the 51 respondents (28%) gave positive comments. Interestingly, CFS was also the single instrument with the most negative comments (from six respondents, 12%). Four questionnaires (FACIT-F, FSS, VT, NRS) were given only one negative comment each from four different respondents. Other comments from the respondents were that the questionnaires often included aspects of physical activity but lacked items regarding the effects of pain and sleep.

10.4.Study IV

In study I, women with SLE described that people around them neglected their fatigue and said, "*everybody is a little tired*". We therefore explored and compared patients' assessments of fatigue with assessments made by persons from the general population matched on age and gender.

Three divergent clusters of fatigue were identified in this study (Table 9). The levels of fatigue were significantly different among the three clusters regarding all three questionnaires of fatigue. The difference remained significant after correction with Bonferroni. Cluster one (n = 221) had distinctly more fatigue and was dominated by the patients (80%); cluster number two (n = 240) had the least fatigue and was dominated by the controls (78%). Cluster number three (n = 155) had the most equal distribution with 48% patients and 52 % controls; their levels of fatigue were more moderate. The clusters were denominated by their levels of fatigue: High Fatigue cluster (one), Low Fatigue cluster (two), and Intermediate Fatigue cluster (three). There were no differences in gender distribution or age among the clusters. The results from the questionnaires measuring anxiety, depression, and HRQoL showed the same pattern as fatigue, which indicated that persons in the high fatigue cluster were most affected, and persons in the low fatigue cluster were the least affected.

Table 9. Participants and levels of fatigue per cluster

Cluster (1-3) result of : Average Linkage (Within Group)	Fatigue questionnaire (mean)			Distribution of participants (%)	
	VT	FSS	MAF	SLE n=305	Controls n=311
Cluster one (High fatigue)	26.8	5.7	37.1	58	14
Cluster two (Low fatigue)	78.6	2.4	11.4	17	60
Cluster three (Intermediate)	57.1	4.0	23.5	25	26
All (616)	54.6	4.0	23.7		

VT = Vitality, FSS = Fatigue Severity Scale,
MAF = Multidimensional Assessment of Fatigue scale

In the **High Fatigue Cluster,** regular exercise at least two times a week was less frequent (25%) compared to both the low fatigue cluster (46%, $p < 0.001$) and the intermediate fatigue cluster (36%, $p = 0.015$). The high fatigue cluster had the highest proportion of persons sleeping less than five hours (13%) as well as sleeping more than nine hours (12%). The majority of those sleeping more than nine hours per night (26 of

30 persons) were in the high fatigue cluster. The persons in the high fatigue cluster also had the highest proportion of persons sleeping or resting during the day (Table 10).

The proportion of persons working 50% or more were the lowest in the high fatigue cluster (60%), which was significantly lower than both the low fatigue cluster (87%, $p < 0.001$) and the intermediate fatigue cluster (81%, $p < 0.001$). Fewer persons in the high fatigue cluster lived together with a partner (56%) compared to the low fatigue cluster (71%, $p = 0.001$) but there was no difference with regard to the intermediate fatigue cluster (63%).

In the **Low Fatigue Cluster,** all participants' answers on the HADS-D represented zero signs of depression. Fewer persons reported that they were smokers in the low fatigue cluster (13%) compared to both the high fatigue cluster (20%, $p = 0.030$) and the intermediate fatigue cluster (20%, $p = 0.044$). Compared to the intermediate fatigue cluster, the respondents in the low fatigue cluster were less likely to rest during the day. With regard to daytime sleep, there was a trend towards a lower proportion of respondents in the low fatigue cluster who took a daytime nap compared to the intermediate fatigue cluster. The highest percentage (87%), of persons working 50% or more of the time, was found in the low fatigue cluster. Similar results were found for marital status where the low fatigue cluster had the highest proportion of persons living with partner (71%), which was more than the high fatigue cluster (56%, $p = 0.001$), but did not differ from the intermediate fatigue cluster (63%). Of all patients 17% were in the Low fatigue cluster.

The **Intermediate Fatigue Cluster** showed similarities with both the high and the low fatigue cluster. The habits of sleeping and rest were close to the low fatigue cluster, whereas the answers of living with partner and smoking were close to the high fatigue cluster.

There were no significant differences among patients in the three clusters regarding the number of ACR criteria or disease duration. However, the patients in the high fatigue cluster had more disease activity (SLAM) (median 6, IQR 4-10) than in both the low fatigue cluster (median 3, IQR 2-7, $p < 0.001$) and the intermediate fatigue cluster (median 5, IQR 4-7, $p < 0.001$). No difference in disease activity was found between the low fatigue cluster and the intermediate fatigue cluster.

Table 10 Comparison between fatigue cluster groups (n = 616).

	High n=221 %	Low n=240 %	Intermediate n=155 %	p-value[a]
Living with partner	56	71	63	0.004[b]
Work ≥ 20 hours/week [c]	60	87	81	<0.001[d]
Current smoker	20	13	20	0.057[e]
Anxiety (HADS) >7	51	10	28	<0.001[f]
Depression (HADS) >7	34	0	8	<0.001[f]
Exercise (≥2/week)	25	46	36	<0.001[g]
Sleep (hours/night) <5/5-9/>9	13/74/12	2/97/1	6/93/2	<0.001[h]
Daytime sleep (≥2/week)[j]	26	3	7	<0.001[k]
Daytime rest (≥2/week)[j]	39	5	10	<0.001[l]

[a] Chi-square
[b] Sub analysis: statistical difference only between high and low, p = 0.001
[c] Separate analysis on persons with age < 65 years
[d] Sub analysis: p < 0.001 remains for high vs. low, high vs. intermediate clusters
[e] Sub analysis: high vs. low p = 0.030, low vs. intermediate p = 0.044
[f] Sub analysis: p < 0.001 for all combinations,
[g] Sub analysis: high vs. low p<0.001, high vs. intermediate p=0.015,
low vs. intermediate p=0.054
[h] Sub analysis: high vs. intermediate p= 0.073, other combinations p<0.001
[j] Daytime rest/sleep ≥ 30 minutes
[k] Sub analysis: low vs. intermediate p=0.054, other combinations p<0.001
[l] Sub analysis: low vs. intermediate p=0.029, other combinations p<0.001

11. DISCUSSION

The overall aim of this thesis was to explore patients' experiences of symptoms related to the disease SLE by focusing on fatigue and how it is described and measured. Furthermore, the thesis explored clusters of fatigue comparing patients with SLE and age- and gender-matched controls. The results revealed that fatigue is among the most troublesome symptoms for patients with SLE. The patients described the character of SLE related fatigue as controlling, unbeatable and beyond words. However, it is noteworthy that in the fatigue clustering analyses, where both patients with SLE and age- and gender-matched controls were included, 17% of the patients had very low levels of fatigue and were in the group with a healthier life-style. Among the seven questionnaires measuring fatigue, evaluated for the ability to detect differences as assessed by the patients themselves, the single question questionnaires showed the least favorable results. In accordance this questionnaire was not favored by the free comments from the patients.

11.1. Experiences and perceptions of SLE related fatigue

In study I, the respondents portrayed SLE-related fatigue as overwhelming with an unpredictable character, which resulted in the feeling that fatigue dominated and controlled most situations in life. The descriptions of fatigue were similar to those of patients with e.g. multiple sclerosis and RA [118, 169]. The unpredictive nature of fatigue has previously been described by women with chronic illness [170].

In study I the women described emotions that rise as a consequence of fatigue, similar reactions have been described FGDs, as mood disturbance in patients with post cancer fatigue [171]. Frustration is one emotion previously described by patients, to be a negative consequence of SLE related fatigue [172].

In conditions like multiple sclerosis environmental factors as the weather are described to increase fatigue, this is not mentioned by our respondents [169]. Strategies to manage fatigue found in study I are comparable to some of the strategies previously described by women when exploring their perception of SLE in general [69] and for fatigue in other conditions such as MS, fibromyalgia, RA [169] [71, 118]. The misty feeling, as described by the women in study I, are confirmed by the study by Gallop et al were patients with SLE described an inability to think that the patients them self related to fatigue [172].

The thesis demonstrates that women with SLE use physical activity as a strategy to balance life despite SLE-related fatigue. This is most certainly not the strategy used by all patients and is not even experienced as beneficial by all patients. In study IV the

persons in the cluster with lowest fatigue performed physical activities more often than the others. Previous studies have shown that physical activity may reduce fatigue [98, 99, 110], but other show that fatigue limited physical activities [172]. However, the persons in the FGDs expressed physical activity as a way to gain strength to manage fatigue, rather than reducing fatigue itself.

The descriptions by the participants in study I showed resemblance to the term exhaustion as framed by Olson [73]. However, as shown in study IV not all patients suffer from the overwhelming and life controlling aspect of high degrees of fatigue. Moreover, no comparisons were made regarding the use of the concepts of tiredness, fatigue or exhaustion in this thesis. A frame based on the classifications suggested by Olson could be used to analyse qualitative data, providing that the interviews aimed to cover the themes. This could generate important knowledge, since the conceptualization by Olsen is based on cancer-related fatigue, and a possibility to further explore differences and similarities between fatigue in relation to different diagnosis. This kind of qualitative study could be combined with questionnaires assessing sleep quality, cognition, stamina, emotional role, control over body processes and social interaction.

11.2. Patients report of symptoms – fatigue and others

In study II, fatigue and pain were freely reported as the most troublesome symptoms of SLE, collected by written reports from the patients. A recent study using an oral interview approach allowed patients to report freely the experience of SLE-related symptoms as well as how fatigue affected daily life [172]. They also reported pain and fatigue at the top, sorted by frequency. In study II about 50% of the patients reported that fatigue and/or pain were one of the most troublesome symptoms. Compared to our study, they did not explore how troublesome the symptoms were, but they reported how much the symptoms interfered with daily life. They demonstrated that most participants (86%) felt that their fatigue had cognitive impact. Study II does not explore how the symptoms per se affected the patients' day-to-day activities. Instead, the more general effect on HRQoL were explored and the symptoms that possibly affect a person's life. It could also be the other way around; patients experiencing reduced quality of life perceive a symptom as more troublesome.
In a conceptual model of HRQoL, for patients with SLE, Gallop et al. revealed patient reported triggers to SLE symptoms [172]. These triggers were perceived to trigger symptoms of SLE including pain and fatigue. The influencing factors as described in study I have similarities to Gallops´ so called triggers, but in study I, the women also described them to possibly reduce the impact of fatigue.

In study II, fatigue and pain were definitely at the top of troublesome SLE symptoms. One remaining question is whether the patients reporting pain had received appropriate pain- relieving medication. In a study on patients with RA the majority pointed out pain

as an important health aspect needing improvement, one-third of the patients did not report use of relevant pain relieving medication [173]. More studies are needed to explore the agreement between perceived symptoms and medical treatment e.g. the concordance between patients, physician assessments, and specific treatments of pain.

11.3. Measuring fatigue

The question is no longer whether to include measures of fatigue into the agenda of SLE assessments or not, but how should this important aspect of SLE be incorporated? Our results indicated that NRS is the least suitable for the regression model although the distance between responses from patients who perceived their fatigue lower than that of their dialogue partners tended to vary more than those of respondents who reported their fatigue as the same as or higher than that of their dialogue partners. This might be due to the number of respondents. It may also be because a single question can elicit more individual variations in the interpretation of the impact of fatigue than questionnaires with more specified questions [174]. The use of a generally worded question has been found to cause difficulties when interpreting score differences [174]. Interestingly, in study III the only questionnaire without any positive vote was NRS, which has only a single item, and could thus be considered simple and easy to answer. However, it should be considered that all patients in that study were selected because they were persons with a special experience or interest in fatigue. Otherwise, they would probably not have agreed to participate in a group session where they had to talk about fatigue. This could have biased the patients to favour questionnaires that gave more attention to fatigue. To follow the course of fatigue, identify change over time and to evaluate the effect of interventions, a questionnaire that is sensitive to differences is important. In study III, five (FSS, MAF, FACIT-F, VT, MFI-20) of the seven questionnaires demonstrated almost equal sensitivity to change, tested with the regression model. Other aspects have to be considered when choosing any of the five [121, 122].

11.4. Everyone is not "a little tired"

In study I, some patients told of comments by ignorant health workers and relatives, which expressed that a person with SLE should not complain of fatigue because “everyone is a little tired or fatigued. However it is important to remember and that even if fatigue is a very common and disabling problem for many patients with SLE, some patients do not perceive elevated levels of fatigue, and it is not the worst symptom for all patients. This argument is supported by the result from study IV where 17% of the patients were in the Low fatigue cluster. However, fatigue is sufficiently widespread to justify screening to detect those needing more attention. Moreover a majority of the controls were in the low fatigue cluster and only 14% of the controls were in the high

fatigue cluster, this result is supported by findings which demonstrates that fatigue scores may be skewed towards the absence of fatigue in the general population [175].

In the general population optimal sleep duration, to maintain god health, is suggested to be 7–8 hours per night [176]. In this thesis the range for "normal" sleep was 5-9 hours per night. A majority of participants in the cluster study (study IV) reported that they usually slept a normal number of hours per night. This result was true even in the high fatigue cluster which also represented persons with the fewest hours of sleep (< 5 hours per night) as well as the persons with the most hours of sleep (> 9 hours per night). The participants in this cluster were consistent with previous research indicating that persons with suboptimal sleep to be less active and more often smokers than persons with "normal" sleep duration [176]. Habitual sleep duration less than 5 hours or more than 9 hours have previously indicated associations of increased mobility e.g. cardiovascular disease and diabetes mellitus [177-179].

The low fatigue cluster had the "healthiest" behavior, with most persons reporting a normal number of hours of sleep per night. Most were non-smokers, and they reported more regular exercise. In a previous study, patients with SLE, reported that they avoided physical activity if they believed it would worsen SLE in the short term [180]. However, the same study report that the majority of patients believed in the benefits of physical activity in the long term. Considering the association between cardiovascular disease and SLE, it is most important for health personal to promote patients physical activity and exercise habits, however the effect of exercise programs to reduce SLE related fatigue need further studies [101], and previous studies indicate that physical exercise do not seem to worsen the disease [98, 99].
To capture the relation between life-style behaviour and fatigue prospective studies are of interest since behavior most certainly could influence fatigue and vice versa.

SLE is a heterogeneous disease with a spectrum of symptoms, organ involvement and autoantibody patterns. Recently clusters of autoantibodies have been suggested as one way to possibly identify subgroups in the panorama of SLE [19]. It would be interesting to explore the clusters of fatigue presented in this thesis in combination with autoantibody profiles.

12. METHODOLOGICAL CONSIDERATIONS

In this thesis, both qualitative and quantitative data were collected to answer the research questions. Because several methods were used, a number of methodological considerations ought to be discussed.

By using focus group discussion for the data collection in study I, we hoped to reveal aspects deeply incorporated in the daily lives of the patients. Things that one is very used to are often difficult to explain. In a group of persons with similar experiences, the wording of others might help one to express, confirm or deny descriptions. In this way, the picture of combined experiences might clarify the image under consideration. However, if individual interviews were used instead, it might have facilitated deeper, personal descriptions, especially concerning individual consequences, which could be very personal and possibly inhibited by the presence of other patients.

In the focus group study, we chose to include women only, based on the knowledge that only about 10% of SLE patients are male [17]. Moreover, we considered that there might be a risk that a minority of male patients would have been reluctant to discuss their experiences. If individual interviews had been chosen, the impact of being a minority in a group would have not been an issue. To explore gender differences concerning patients' own experiences of SLE-related fatigue a multi-center study would probably be best. Since we do not know enough about male fatigue in SLE, this would be a most interesting project and it would add new knowledge to the field.

Content analyses were used to analyse the data in study I. This method is frequently used when processing material from FGD [181]. Compared to basic statistical calculations, qualitative analyses depend very much on the researcher/analyzer and their experiences and skills. The findings were discussed in the research group and were compared to other studies on fatigue. The results seem relevant however a re-analysis of the transcripts might reveal more than our findings, but the content would be the same.

One limitation of this project is its linguistic limitation to the Swedish language. When asking patients about fatigue, we had to use the word tiredness, since an accurate translation of the word into everyday Swedish would be disease related tiredness (study I). This is important to remember when comparing results from different contexts. Although an instrument shows excellent psychometric figures in the validation, the limitations of cultural difference and language translation do always interact in the personal interpretation of a participant answering a written or spoken question. Another limitation is that most self-reported fatigue questionnaires were developed and validated in English speaking countries. Different perceptions of fatigue related to cultural context have been discussed in other studies [117, 182]. This indicates that questionnaires

require tailoring to both language and cultural aspects, not only translation. A cross-cultural adaptation of fatigue measures per se may also include the need to replicate studies in different settings. For research, outcome measures should have optimal psychometric properties [123, 183-186] but for them to reflect patient concerns, their ability to detect a clinically meaningful difference is essential, thus making work on defining the MCID important. In research on fatigue the MCID should not assumed to be fixed property between groups of patients and provides the reasoning underlying our study, since it was conducted in another cultural setting than previous studies [133, 134].

One dilemma was the wording and the use of the word fatigue (even in studies with English speaking participants the use of fatigue is described as used both in normal fatigue and illness-related fatigue) [187]. Even though medical personal have an opinion of fatigue, few patients in Sweden use that word. They often use the word “tired” when they talk about fatigue, but seem to address the expression “disease related fatigue”—in this context “SLE related fatigue”—when they talk about fatigue beyond “normal” every-day tiredness.

Moreover, the coding list used in study II could be further tested in a longitudinal study following patients’ reports of symptom and HRQoL over time. This could be used to validate whether some categories of symptom distress are more stable over time as well to explore the extent to which patients change their subjective distress over time. Longitudinal reports of the most distressing SLE symptoms could also explore differences in perceived symptom distress between newly diagnosed and established diseases.

In study IV, we collected data on sleeping as few ordinal variables, unfortunately the items were overlapping, when asking for hours of sleep two alternatives were 5-7 and 7-9 hours per night. It would have been more appropriate to ask for number of hours slept, 0-24. However, we could detect those who reported that they slept very few hours per night (<5 hours per night) and those sleeping more than 9 hours per night.
Sleep is as multidimensional as fatigue and most probably cannot be assessed by a single question. This limitation of the project could most certainly be countered in future parts of the cohort work.

In this thesis, we did not explore possible confounding factors relating to fatigue, such as psychological disorders (other than symptoms of anxiety or depression), hyperthyroidism, electrolyte imbalance, anaemia, renal failure or diabetes. These omissions might be regarded as a weakness, but these factors were not our main focus.

With the exception of the data from the matched controls, the data in this study were all collected from patients with SLE followed at a university hospital. The first contact was

made by a referral from the clinic. Hence, general practitioners or other specialists must have first suspected or diagnosed SLE. Thus, patients having a mild disease or unclear symptoms of SLE would not have been asked to participate in this study. The aspects of context that might have influenced our patients reduced the generalizability of our results even though the cohort was large (n = 324). One other methodological consideration is that the patients in the cohort were all affiliated with a university hospital. These patients presented with disease that was more severe than that of other cohorts, which might be reflected in the patients' reports of their symptoms.

13. CLINICAL IMPLICATIONS

In the clinical care it is important that healthcare professionals take a more active role to empower persons with SLE to find their own balance as a way to achieve a feeling of being in control. Different behavioral strategies are suggested by previous research to be a beneficial approach for patients with SLE related fatigue [14]. Parallel to this it is also important that patient's feel respected and understood when talking about disease related fatigue. In the focus group study (study I) the patient's described that when health care professionals did not acknowledge the fatigue, the burden became heavier. This has been mentioned before when patients with different chronic illness describe a fear of not being properly understood when mentioning fatigue [170].

As mentioned in the discussion the question is not whether to include measures of fatigue into the agenda of SLE assessments or not, but rather how we should incorporate this important aspect. One suggestion is to screen all patients with SLE for fatigue using the same cut-off as suggested in clinical practice. Even if the one question assessment of fatigue did not have the best support in this thesis it as the advantage of being easy to use in clinical practice, and a follow up of fatigue could then be done in patients with a fatigue score of four and above (scale 0-10). Most effort and research has to be done in patients with high degree of fatigue (>7), but we shouldn´t neglect patients with moderate fatigue (4-7), thus regard our work and interventions as preventive care antagonist to periods of high degree fatigue. Using this method, patients with moderate to severe fatigue could be identified and then be followed by a more complex assessment of fatigue. Any of the seven measures used in study III can be used to detect differences and then most certainly to detect change in levels of fatigue.

In the network of the European League Against Rheumatism (EULAR) recommendations for the role of rheumatology nurses role in the care of patients with chronic inflammatory arthritis, were recently identified [188]. The rheumatology nurse is identified as access for education and knowledge to the patients. Patient education should also aim to improve coping strategies and increase self-care. Hopefully the results from the FGD in study I can be used as a base in an educational discussion of fatigue, the sensation, consequences and individual benefits with chosen strategies. When nurses or other health professionals promote self-management for e.g. fatigue the sense of being in control hopefully rises despite the unpredictable nature of fatigue.

It is also important that health personnel continue to discuss what we, and our patients, mean when we talk about fatigue, tiredness or disease-related fatigue. One way to continue the discussion is to examine how health personnel regard fatigue, do they separate fatigue as a sickness, illness or disease? Or are these different perspectives incorporated when talking about fatigue.

14. SUMMARY AND CONCLUSIONS

The overall aim of this thesis was to explore patients experience of symptoms related to the disease SLE with main focus of fatigue, how it is described and measured. The character of SLE related fatigue was described by the patients as controlling, unbeatable and beyond word. The respondent described emotions that arose with fatigue as well as aspects of work, family life, social contacts, and leisure activities that were affected by SLE related fatigue.

Several ways used to manage daily life with fatigue were described by the patients as a striving for balance and control. Some of the strategies they used were described as: mental struggle, structure, restrict, and provide. The choice of strategies was described as a balance with implications for how fatigue limited a person's life. Two main factors influencing the experience and perception of fatigue were described as the understanding from the surroundings and the pain.

The result from written answers, from open questions, revealed fatigue and pain as the most troublesome symptoms of SLE followed by musculoskeletal symptoms. A majority of the patients reported any of these three symptoms as being an ever-present problem. However twenty-three different symptom descriptions were reported, some from only a few persons. Thus if only standard are used assessments with no open alternatives when asking for symptom distress there is a risk that not so common problems not will be identified. Patient's description of SLE related fatigue and report of most troublesome symptoms (study I and II) provide important knowledge that can be used in education and in discussions with patients and health care workers
Seven well known measures of fatigue were evaluated considering sensitivity to differences identified by the patients. All measures of fatigue used in the study seemed to capture differences as experienced by the group of patients themselves; least favorable was however the one question assessment. This study comparing questionnaires was smaller than previous studies; on the other hand patient free comments did not support the single questionnaire either. Recommended measures of fatigue can detect differences as determined as clinically important (study III).
Using a method of hierarchic clustering analysis three clusters of fatigue was identified. In this study both persons with SLE and age and gender matched controls were includes. The high fatigue cluster (n = 221) was dominated by the patients (80%). In this clusters the participants had beside high levels of fatigue, low levels of HRQoL, and more symptoms of anxiety and depression. Participants in the Low fatigue cluster (n = 240, controls 78%) reported more physical exercise and less smoking than the other clusters. When meeting persons with SLE it is important to remember that not all patients with the diagnosis perceive present illness or high levels of fatigue (study II and IV).

This thesis is a contribution to the understanding of patients' experience of SLE and disease related fatigue. To understand the meaning of symptoms, from the patients' perspective, facilitates the assessment and choice of treatment, and generate a base for appropriate intervention programs and to support the patient.

15. SUGGESTIONS FOR FUTURE RESEARCH

The result from this thesis generates interesting and new questions to be answered. Although increasing data have emerged considering SLE related symptom and symptom experiences, there is much to explore. The multi-factorial phenomenon, fatigue, would best be investigated in collaboration with different specialties, to increase the knowledge and put the pieces of the puzzle of fatigue into place. One important aspect to consider when planning for future research is the collaboration with the patient organizations and patient research partners. Such an approach will help researchers focus and select research questions which are important to those that it concerns the most.

Some interesting areas for future research in the area of fatigue and SLE is the exploration of possible subgroups in this multifaceted syndrome. One example of a subgroup is the male patients with SLE, which are underrepresented in the literature. Thus the perspective of male SLE is an important area of future research on fatigue. To identify other subgroups cluster analysis can be used, as in this thesis. This method could include other disease variables to explore possible subgroups and their relation to fatigue. The contribution of the social and cultural context to the experience of SLE-related fatigue is not elucidated in this study, but believed to influences the individual's attitude towards fatigue and it warrants further research.
Suggestions for future research are the following:

- Perceptions and experiences of SLE-related fatigue from the perspective of the male patient.

- Prospective research exploring fatigue longitudinally and compare with management strategies and disease fluctuations

- Using groups of fatigue, identified by cluster analysis, and explore disease variables, such as antibodies, which could be a possible method for identifying subgroups with different disease characteristics.

- Health personnel's´ attitudes towards fatigue and the strategies they use in patient education and other work patients with SLE related fatigue.

16. SVENSK SAMMANFATTNING

Bakgrund

Att bli sjuk påverkar livet och när sjukdomen blir långvarig eller kronisk som t ex vid en reumatisk sjukdom är det många aspekter av livet som berörs. Upplevelser och känslor som tidigare varit lätta att förstå och förklara kan t.ex. få en annan innebörd. Trötthet är en sådan upplevelse som när man är frisk kan förklaras av att man arbetat intensivt eller sovit för lite, och genom att ta det lugnt och vila så kan trötthetен försvinna och vardagen återgå till det normala. I samband med ett flertal långvariga sjukdomstillstånd är trötthet däremot beskrivet som mycket besvärande och inte lika lätt att förstå eller bli av med som den mera normala trötthetен. Denna avhandling fokuserar på trötthet (fatigue) relaterat till den reumatiska sjukdomen systemisk lupus erytematosus (SLE). SLE är en relativt ovanlig sjukdom och i Sverige insjuknar ungefär 400 personer varje år. I samband med SLE kan olika delar (organ) i kroppen påverkas av inflammation. Vilka organ som påverkas varierar från person till person men symptom från leder, muskler och huden är bland det vanligaste. Andra delar av kroppen som kan påverkas är hjärtsäcken, lungsäckarna, nervsystemet, blodceller och njurar. Mera allmänna symptom som nedsatt aptit, smärta och trötthet förekommer också. I forskning kring sjukdomar och hur dessa påverkar livet, lyfts ofta frågan kring hälsorelaterad livskvalitet. Vad som är livskvalitet varierar, då människor upplever och värdesätter olika saker i livet. Vad som är viktigt kan skifta och påverkas av situationer som förändrar livet, t.ex. sjukdom. När fokus är att studera livskvalitet i relation till sjukdom, benämns detta ibland som hälsorelaterad livskvalitet.

Trötthet beskrivs i litteraturen som ett stort bekymmer i samband med många sjukdomar, trötthet och hälsorelaterad livskvalitet påverkar varandra. I tidigare studier kring SLE är trötthet beskrivet som ett av de symptom där patienter saknar stöd och åtgärder. Upplevelsen av SLE relaterad trötthet påverkas av flera faktorer, både inre och yttre. De inre faktorerna består bland annat av olika sjukdomsprocesser där den inflammatoriska sjukdomsaktiviteten är en del. På vilket sätt sjukdomen orsakar trötthet är inte klarlagt. Personer med en SLE sjukdom som inte är så aktiv kan uppleva hög grad av trötthet. Tidigare studier har även försökt att förklara sambandet mellan trötthet och faktorer som nedstämdhet, oro, sömn och träning men resultaten från studierna är inte entydiga. I några studier har det påvisats att fysisk träning kan minska upplevelsen av trötthet, men inte heller här är mekanismen klarlagd. Yttre faktorer som den miljö som en person befinner sig i kan också påverka den enskilda individens upplevelse av SLE relaterad trötthet.

Syfte

Syftet med avhandlingen var att utforska patienters erfarenheter av symptom, relaterade till sjukdomen systemisk lupus erytematosus (SLE), med huvudfokus på trötthet, hur den upplevs, beskrivs samt hur bra de frågeformulär som används för att bedöma trötthet fungerar.

Avhandlingen består av fyra delarbeten. Beskrivningar av trötthet har inhämtats muntligt i gruppintervjuer (studie I), samt med hjälp av frågeformulär (studie II, III, IV). Svar på frågor om symptom generellt (studie II) och trötthet specifikt (IV) har relaterats till andra faktorer såsom hälsorelaterad livskvalitet, symptom på oro och nedstämdhet samt livsstilsfaktorer.
Utvärdering av olika frågeformulär kring trötthet gjordes i studie III.

Deltagare

De personer som har bidragit med material till denna avhandling har ingått i ett stort forskningsprojekt under namnet SLE 2004. I SLE 2004 undersöks flera olika aspekter av sjukdomen SLE och denna avhandling kan ses som en del i ett större sammanhang.

Totalt deltog 327 patienter med SLE i de fyra delarbeten som ingår i denna avhandling. I den fjärde studien deltog även 311 kontrollpersoner (personer från Stockholmsregionen utan SLE).
Material till delarbete II och IV samlades in parallellt, i samband med ett forskningsbesök där deltagarna dessutom träffade en läkare för en medicinsk bedömning.
I delarbete I och III har ett mindre antal patienter träffas i olika gruppkonstellationer. De patienter som bidragit i delstudie I och III har samtliga även ingått i delstudie II och/eller IV.

Metod och Resultat

Delarbete I var en fokusgrupps studie där sju grupper med tre till sex kvinnor med SLE i varje grupp (totalt 33 stycken personer) träffades och diskuterade sina erfarenheter av SLE relaterad trötthet (fatigue). De besvarade frågor som; hur tröttheten känns i kroppen, hur den påverkar vardagen och hur de hanterar vardagen med den SLE relaterade tröttheten. Den kroppsliga känslan av trötthet beskrevs av deltagarna både i ”kroppen och knoppen”. I kroppen kunde den beskrivas som en tyngdkänsla medan känslan i knoppen (huvudet) beskrevs som en avskärmande känsla, som att befinna sig i en glaskupa. Tröttheten beskrevs av många som något som var ständigt närvarande, men som hos andra kunde komma med plötsliga oförutsägbara toppar av stark trötthet. Det beskrevs som om tröttheten ofta ”tog kommandot”, och kraften att bekämpa tröttheten inte räckte till. Deltagarna beskrev även andra känslor som uppstod i samband

med den SLE relaterade trötttheten, dessa känslor kunde vara ilska, rädsla, sorg och hjälplöshet. De framkom även påverkan på sociala kontakter, relationer, arbete och fritidsaktiviteter.
De strategier som deltagarna beskrev att de använde var olika sätt för att försöka få kraft att orka med trötttheten, att sträva efter kontroll över livet. Att upprätthålla denna balans beskrevs som en mental kamp, där det kunde hjälpa att strukturera upp vardagen, prioritera och planera. Samtligt beskrevs erfarenheter av att fånga de stunder där trötttheten inte var lika förlamande. Tydliggöra gränser både för sig själv, och andra, eller be om hjälp när trötttheten blev för övermäktig var andra strategier som användes. För att tillföra kraft att klara av trötttheten beskrevs både vila och olika typer av fysisk aktivitet som att röra på kroppen trots att den kändes tung. Fokusering på andningen under yoga eller vistelse i skogen beskrevs som andra sätt att tillföra kraft.

I delarbete II har deltagarna besvarat två öppna frågor; ”Vilka SLE symptom har du upplevt som svårast under din sjukdom?” följt av frågan ”Vilka symptom upplever du som svårast just nu?”, vidare besvarades formulär med frågor kring symptom på oro och nedstämdhet (HADS) och hälsorelaterad livskvalitet (SF-36). Svaren på de öppna frågorna sorterades så att synonyma svar grupperades tillsammans t.ex. smärta och ont i samma grupp. Analysen av svaren resulterade i 23 olika grupper, men de tre symptom-grupper som rapporterades av flest personer var trötthet, smärta och besvär från muskel/skelett. De 23 symptom-grupperna jämfördes också med svaren för livskvalitet samt symptom på oro och nedstämdhet. En tiodel av patienterna rapporterade att de inte upplevde några aktuella symptom från SLE sjukdomen i dagsläget. Dessa patienter rapportade också bättre livskvalitet, färre symptom på oro respektive depression och hade även mindre sjukdomsaktivitet. Endast de patienter som rapporterade trötthet som ett aktuellt symptom hade statistiskt lägre värden på både mentala och fysiska aspekter av livskvalitet.

Delarbete III utgick från en amerikansk/kanadensisk studie där sju frågeformulär som bedömer trötthet jämfördes. Studien genomfördes för att undersöka vilket av dessa frågeformulär som är mest känsliga för den skillnad i trötthet som patienterna själva beskriver. Sju grupper med sex till nio personer i varje grupp arrangerades (totalt 51 personer). När en grupp träffades så fyllde deltagarna först i de sju frågeformulären som reflekterar trötthet den senaste veckan (Chalder Fatigue Scale (CFS), Fatigue Severity Scale (FSS), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), Multidimensional Assessment of Fatigue scale (MAF), Multidimensional Fatigue Inventory (MFI-20), Numeric Rating scale (NRS), Vitality (VT)). Deltagarna uppmanades dessutom att kommentera skriftligt om något eller några instrument var bra eller dåligt på att reflektera den trötthet som de själva upplevt under sin sjukdomstid. Därefter påbörjades en procedur där deltagarna fick sitta avskilt och under tio minuter beskriva och diskutera sin egen trötthet för varandra. När tio minuter hade gått gjorde var och en, en bedömning av sin egen trötthet i relation till sin samtalspartner på en

sjugradig skala (Mycket mer trött/ Mer trött/ Lite mer trött/ Ungefär samma trötthet/ Lite mindre trött/ Mindre trött/ Mycket mindre trött). Därpå följde en ny tio minuters sejour där personerna diskuterade sin trötthet med en ny person, med efterföljande självbedömning av trötthet. Denna procedur fortsatte tills samtliga deltagare samtalat med minst fem olika personer och gjort den efterföljande självbedömningen av sin egen trötthet. Resultatet analyserades enligt två metoder (en beskrivande modell och en regressions modell) där skillnader i trötthet mellan dialogpersonerna beräknades. Frågeformulären CFS och NRS visade på lägst känslighet för skillnad i trötthet. Detta resultat bekräftades även av de kommentarer som patienterna gav, där CFS fick flest negativa kommentarer och NRS var det enda instrument som inte fick några positiva kommentarer alls.

I delarbete IV deltog både patienter med SLE (305 personer) och kontrollpersoner utan SLE (311 personer). Patienter och kontrollpersoner hade samma ålder, könsfördelning och var bosatta i samma stad. Samtliga besvarade tre frågeformulär som reflekterar trötthet (FSS, MAF, VT). Dessa analyserades enligt en clustermetod där svar som liknar varandra så mycket som möjligt grupperas tillsammans statistiskt. Resultatet blev grupper; ”Hög-”, ”Låg-”, och ”Mellan-” grad av trötthet. Gruppen hög grad av trötthet, dominerades av patienter med SLE (80%) och gruppen låg grad av trötthet dominerades av kontrollpersoner (78%).
Deltagarna besvarade även frågor som reflekterade symptom på oro och nedstämdhet (HADS), hälsorelaterad livskvalitet (SF-36)samt frågor kring levnadsvanor som rökning, träning, sömn och vila, dessa svar jämfördes mellan de tre trötthetsgrupperna (”Hög”, ”Låg”, ”Mellan”). Svaren på frågor om livskvalitet och symptom på oro och nedstämdhet följde samma mönster som svaren på trötthet, så att gruppen som hade hög grad av trötthet hade högsta värden när det gäller symptom på oro och nedstämdhet och lägsta värden när det gällde hälsorelaterad livskvalitet. Gruppen hög grad av trötthet urskiljde sig när det gällde sömnvanor, där fler personer rapporterade att de sov mycket (>9 timmar/natt) eller lite (<5 timmar/natt) vilket var ovanligt i de andra trötthetsgrupperna. Patienterna som hade hög grad av trötthet hade mer sjukdomsaktivitet än patienterna i de andra grupperna. De skiljde sig däremot inte när det gällde hur länge de haft sin sjukdom. Personerna i den grupp som hade låg grad av trötthet var det flest antal personer som rapporterade att de tränade två gånger i veckan eller mer, i denna grupp var det också färre personer som rökte, 13% jämfört med 20% i de andra grupperna. Även om gruppen låg grad av trötthet dominerades av kontrollpersoner så var 17% av alla patienter i denna grupp, som rapporterade värden vilka tyder på att de mår relativt bra (när det gäller trötthet, hälsorelaterad livskvalitet och symptom på oro och nedstämdhet) och har friskfaktorer som färre rökare och mer fysisk aktivitet.

Slutsats

Av de sju trötthetsformulär som utvärderas i avhandlingen visade fem likvärdiga resultat d.v.s. samtliga kan fånga upp skillnader i trötthetsnivåer. Andra egenskaper hos formuläret såsom vilka aspekter av trötthet som mäts, kan därför få avgöra hur trötthetsformulär väljs för att fånga trötthet i klinisk verksamhet eller forskning.

I mötet med patienter med SLE är det viktigt att beakta att alla personer med SLE, inte alltid är trötta. 17% av patienterna i studie IV hamnade i gruppen med låg grad av trötthet. Dessa mådde också bättre och hade fler positiva livsstilsfaktorer. 10% av patienterna som deltog i studie II hade inga aktuella SLE symptom. De rapporterade också bättre hälsorelaterad livskvalitet jämfört med de som rapporterar att de upplevde något eller några aktuella symptom av sin sjukdom. De hade även hade lägre sjukdomsaktivitet.

Personer med SLE beskriver i denna avhandling SLE relaterad trötthet, dess konsekvenser och ger exempel på hur de hanterar trötttheten i vardagen. Resultatet kan användas i undervisning för sjukvårdspersonal som träffar denna patientgrupp och på så sätt bidra till ökad förståelse för patientguppens upplevelse. I samtal med patienter kan resultatet användas som en utgångs punkt kring sjukdomsrelaterad trötthet.

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18. REFERENCES

1. Twaddle, A. and L. Nordenfelt, *Disease, illness and sickness : three central concepts in theory of health : a dialogue / between Andrew Twaddle and Lennart Nordenfelt*. 1993, Linlöping: Tema Univ.
2. Piper, B.F., *Fatigue*, in *Pathophysiological Phenomena in Nursing: Human Responses to Illness*, V. Carrieri-Kohlman, A.M. Lindsey, and C.M. West, Editors. 1993, WB Saunders: Philadelphia. p. pp 279-302.
3. Ek, K., et al., *Shifting life rhythms: Couples' stories about living together when one spouse has advanced chronic obstructive pulmonary disease.* J Palliat Care, 2011. **27**(3): p. 189-97.
4. Townsend, A., S. Wyke, and K. Hunt, *Self-managing and managing self: practical and moral dilemmas in accounts of living with chronic illness.* Chronic Illn, 2006. **2**(3): p. 185-94.
5. Kralik, D., *The quest for ordinariness: transition experienced by midlife women living with chronic illness.* J Adv Nurs, 2002. **39**(2): p. 146-54.
6. Mendelson, C., *Managing a medically and socially complex life: women living with lupus.* Qual Health Res, 2006. **16**(7): p. 982-97.
7. Ohman, M., S. Soderberg, and B. Lundman, *Hovering between suffering and enduring: the meaning of living with serious chronic illness.* Qual Health Res, 2003. **13**(4): p. 528-42.
8. Mendelson, C., *Diagnosis: a liminal state for women living with lupus.* Health Care Women Int, 2009. **30**(5): p. 390-407.
9. Jutel, A., *Sociology of diagnosis: a preliminary review.* Sociol Health Illn, 2009. **31**(2): p. 278-99.
10. Karasz, A. and P.S. McKinley, *Cultural differences in conceptual models of everyday fatigue: a vignette study.* J Health Psychol, 2007. **12**(4): p. 613-26.
11. Borrell-Carrio, F., A.L. Suchman, and R.M. Epstein, *The biopsychosocial model 25 years later: principles, practice, and scientific inquiry.* Ann Fam Med, 2004. **2**(6): p. 576-82.
12. Engel, G.L., *The need for a new medical model: a challenge for biomedicine.* Science, 1977. **196**(4286): p. 129-36.
13. Omdal, R., et al., *Fatigue in patients with systemic lupus erythematosus: the psychosocial aspects.* J Rheumatol, 2003. **30**(2): p. 283-7.
14. Zonana-Nacach, A., et al., *Systemic lupus erythematosus in three ethnic groups. VI: Factors associated with fatigue within 5 years of criteria diagnosis. LUMINA Study Group. LUpus in MInority populations: NAture vs Nurture.* Lupus, 2000. **9**(2): p. 101-9.
15. Stahl-Hallengren, C., et al., *Incidence studies of systemic lupus erythematosus in Southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis.* J Rheumatol, 2000. **27**(3): p. 685-91.
16. Somers, E.C., et al., *Incidence of systemic lupus erythematosus in the United Kingdom, 1990-1999.* Arthritis Rheum, 2007. **57**(4): p. 612-8.
17. D'Cruz, D.P., M.A. Khamashta, and G.R. Hughes, *Systemic lupus erythematosus.* Lancet, 2007. **369**(9561): p. 587-96.

18. Papp, K., et al., *Immune Complex Signatures of Patients with Active and Inactive SLE Revealed by Multiplex Protein Binding Analysis on Antigen Microarrays.* PLoS One, 2012. **7**(9): p. e44824.
19. Ching, K.H., et al., *Two major autoantibody clusters in systemic lupus erythematosus.* PLoS One, 2012. **7**(2): p. e32001.
20. Ding, Y., et al., *Gender differences are associated with the clinical features of systemic lupus erythematosus.* Chin Med J (Engl), 2012. **125**(14): p. 2477-81.
21. Schwartzman-Morris, J. and C. Putterman, *Gender differences in the pathogenesis and outcome of lupus and of lupus nephritis.* Clin Dev Immunol, 2012. **2012**: p. 604892.
22. Tan, E.M., et al., *The 1982 revised criteria for the classification of systemic lupus erythematosus.* Arthritis Rheum, 1982. **25**(11): p. 1271-7.
23. Hochberg, M.C., *Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus.* Arthritis Rheum, 1997. **40**(9): p. 1725.
24. Petri, M., et al., *Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus.* Arthritis Rheum, 2012. **64**(8): p. 2677-86.
25. Ozbek, S., et al., *Delay in the diagnosis of SLE: the importance of arthritis/arthralgia as the initial symptom.* Acta Med Okayama, 2003. **57**(4): p. 187-90.
26. Hanly, J.G., et al., *A prospective analysis of cognitive function and anticardiolipin antibodies in systemic lupus erythematosus.* Arthritis Rheum, 1999. **42**(4): p. 728-34.
27. Ainiala, H., et al., *The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus.* Neurology, 2001. **57**(3): p. 496-500.
28. Nowicka-Sauer, K., et al., *Neuropsychological assessment in systemic lupus erythematosus patients: clinical usefulness of first-choice diagnostic tests in detecting cognitive impairment and preliminary diagnosis of neuropsychiatric lupus.* Clin Exp Rheumatol, 2011.
29. Rahman, P., et al., *Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus.* Lupus, 2001. **10**(2): p. 93-6.
30. Urowitz, M.B., et al., *Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus.* J Rheumatol, 2008. **35**(11): p. 2152-8.
31. Trager, J. and M.M. Ward, *Mortality and causes of death in systemic lupus erythematosus.* Curr Opin Rheumatol, 2001. **13**(5): p. 345-51.
32. Bjornadal, L., et al., *Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95.* J Rheumatol, 2004. **31**(4): p. 713-9.
33. Gustafsson, J., et al., *Risk factors for cardiovascular mortality in patients with systemic lupus erythematosus, a prospective cohort study.* Arthritis Res Ther, 2012. **14**(2): p. R46.
34. Wallace, D.J., et al., *New insights into mechanisms of therapeutic effects of antimalarial agents in SLE.* Nat Rev Rheumatol, 2012. **8**(9): p. 522-33.
35. Ruiz-Irastorza, G., A. Danza, and M. Khamashta, *Glucocorticoid use and abuse in SLE.* Rheumatology (Oxford), 2012. **51**(7): p. 1145-53.

36. Arends, S., et al., *Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus cyclophosphamide in patients with proliferative lupus nephritis.* Ann Rheum Dis, 2012. **71**(6): p. 966-73.
37. Gunnarsson, I. and R.F. van Vollenhoven, *Biologicals for the treatment of systemic lupus erythematosus?* Ann Med, 2011.
38. Ramsey-Goldman, R. and N. Rothrock, *Fatigue in systemic lupus erythematosus and rheumatoid arthritis.* PM R, 2010. **2**(5): p. 384-92.
39. Grootscholten, C., et al., *Health-related quality of life in patients with systemic lupus erythematosus: development and validation of a lupus specific symptom checklist.* Qual Life Res, 2003. **12**(6): p. 635-44.
40. Chen, T.-h., L. Li, and M.M. Kochen, *A systematic review: How to choose appropriate health-related quality of life (HRQOL) measures in routine general practice?* Journal of Zhejiang University SCIENCE, 2005. **6B**(9): p. 936-940.
41. Bowling, A., *Measuring disease : a review of disease-specific quality of life measurement scales*. 2nd ed. 2001, Buckingham ; Phildelphia: Open University Press. xx, 395 p.
42. Guyatt, G.H., D.H. Feeny, and D.L. Patrick, *Measuring health-related quality of life.* Ann Intern Med, 1993. **118**(8): p. 622-9.
43. Muldoon, M.F., et al., *What are quality of life measurements measuring?* BMJ, 1998. **316**(7130): p. 542-5.
44. Wilson, I.B. and P.D. Cleary, *Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes.* JAMA, 1995. **273**(1): p. 59-65.
45. Yazdany, J. and E. Yelin, *Health-related quality of life and employment among persons with systemic lupus erythematosus.* Rheum Dis Clin North Am, 2010. **36**(1): p. 15-32, vii.
46. Cleanthous, S., et al., *What constitutes uncertainty in systemic lupus erythematosus and rheumatoid arthritis?* Psychol Health, 2012.
47. Gilboe, I.M., T.K. Kvien, and G. Husby, *Health status in systemic lupus erythematosus compared to rheumatoid arthritis and healthy controls.* J Rheumatol, 1999. **26**(8): p. 1694-700.
48. Jolly, M., *How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses?* J Rheumatol, 2005. **32**(9): p. 1706-8.
49. Choi, S.T., et al., *Subscale analysis of quality of life in patients with systemic lupus erythematosus: association with depression, fatigue, disease activity and damage.* Clin Exp Rheumatol, 2012.
50. Kulczycka, L., A. Sysa-Jedrzejowska, and E. Robak, *Quality of life and satisfaction with life in SLE patients-the importance of clinical manifestations.* Clin Rheumatol, 2010. **29**(9): p. 991-7.
51. Zhu, T.Y., et al., *Relationship between flare and health-related quality of life in patients with systemic lupus erythematosus.* J Rheumatol, 2010. **37**(3): p. 568-73.
52. Strand, V., et al., *Outcome measures to be used in clinical trials in systemic lupus erythematosus.* J Rheumatol, 1999. **26**(2): p. 490-7.
53. Strand, V., et al., *Endpoints: consensus recommendations from OMERACT IV. Outcome Measures in Rheumatology.* Lupus, 2000. **9**(5): p. 322-7.

54. McElhone, K., et al., *Patient perspective of systemic lupus erythematosus in relation to health-related quality of life concepts: a qualitative study.* Lupus, 2010. **19**(14): p. 1640-7.
55. Panopalis, P. and A.E. Clarke, *Quality of life in systemic lupus erythematosus.* Clin Dev Immunol, 2006. **13**(2-4): p. 321-4.
56. Yazdany, J., *Health-related quality of life measurement in adult systemic lupus erythematosus: Lupus Quality of Life (LupusQoL), Systemic Lupus Erythematosus-Specific Quality of Life Questionnaire (SLEQOL), and Systemic Lupus Erythematosus Quality of Life Questionnaire (L-QoL).* Arthritis Care Res (Hoboken), 2011. **63 Suppl 11**: p. S413-9.
57. Sullivan, M., J. Karlsson, and J.E. Ware, Jr., *The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden.* Soc Sci Med, 1995. **41**(10): p. 1349-58.
58. Persson, L.O., et al., *The Swedish SF-36 Health Survey II. Evaluation of clinical validity: results from population studies of elderly and women in Gothenborg.* J Clin Epidemiol, 1998. **51**(11): p. 1095-103.
59. Sullivan, M. and J. Karlsson, *The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population.* J Clin Epidemiol, 1998. **51**(11): p. 1105-13.
60. Gladman, D., et al., *Systemic Lupus International Collaborating Clinics conference on assessment of lupus flare and quality of life measures in SLE. Systemic Lupus International Collaborating Clinics Group.* J Rheumatol, 1996. **23**(11): p. 1953-5.
61. Gladman, D.D., et al., *A comparison of five health status instruments in patients with systemic lupus erythematosus (SLE).* Lupus, 1996. **5**(3): p. 190-5.
62. Stevenson, A., *Oxford dictionary of English*. 3rd ed. 2010, New York, NY: Oxford University Press. xxii, 2069 p.
63. Leventhal, H., M. Diefenbach, and E.A. Leventhal, *Illness Cognition - Using Common-Sense to Understand Treatment Adherence and Affect Cognition Interactions.* Cognitive Therapy and Research, 1992. **16**(2): p. 143-163.
64. Armstrong, T.S., *Symptoms experience: a concept analysis.* Oncol Nurs Forum, 2003. **30**(4): p. 601-6.
65. Fu, M.R., R.W. McDaniel, and V.A. Rhodes, *Measuring symptom occurrence and symptom distress: development of the symptom experience index.* J Adv Nurs, 2007. **59**(6): p. 623-34.
66. Dodd, M., et al., *Advancing the science of symptom management.* J Adv Nurs, 2001. **33**(5): p. 668-76.
67. Pimm, T.J. and J. Weinman, *Applying Leventhal's self regulation model to adaptation and intervention in rheumatic disease.* Clinical Psychology & Psychotherapy, 1998. **5**(2): p. 62-75.
68. Yen, J.C., et al., *Determinants of discordance between patients and physicians in their assessment of lupus disease activity.* J Rheumatol, 2003. **30**(9): p. 1967-76.
69. Goodman, D., et al., *Illness representations of systemic lupus erythematosus.* Qual Health Res, 2005. **15**(5): p. 606-19.
70. Rasker, J.J., *The enigma of fatigue.* J Rheumatol, 2009. **36**(12): p. 2630-2.

71. Soderberg, S., B. Lundman, and A. Norberg, *The meaning of fatigue and tiredness as narrated by women with fibromyalgia and healthy women.* J Clin Nurs, 2002. **11**(2): p. 247-55.
72. Mengshoel, A.M., *Life strain-related tiredness and illness-related fatigue in individuals with ankylosing spondylitis.* Arthritis Care Res (Hoboken), 2010. **62**(9): p. 1272-7.
73. Olson, K., *A new way of thinking about fatigue: a reconceptualization.* Oncol Nurs Forum, 2007. **34**(1): p. 93-9.
74. Olson, K. and J.M. Morse, *Delineating the concept of fatigue using a pragmatic utility approach*, in *The essential concepts of nursing : building blocks for practice*, J.R. Cutcliffe and H.P. McKenna, Editors. 2005, Elsevier Churchill Livingstone: Edinburgh. p. 141-157.
75. Ream, E. and A. Richardson, *Fatigue: a concept analysis.* Int J Nurs Stud, 1996. **33**(5): p. 519-29.
76. Shen, J., J. Barbera, and C.M. Shapiro, *Distinguishing sleepiness and fatigue: focus on definition and measurement.* Sleep Med Rev, 2006. **10**(1): p. 63-76.
77. Pigeon, W.R., M.J. Sateia, and R.J. Ferguson, *Distinguishing between excessive daytime sleepiness and fatigue: toward improved detection and treatment.* J Psychosom Res, 2003. **54**(1): p. 61-9.
78. Staud, R., *Peripheral and Central Mechanisms of Fatigue in Inflammatory and Noninflammatory Rheumatic Diseases.* Curr Rheumatol Rep, 2012.
79. Norheim, K.B., G. Jonsson, and R. Omdal, *Biological mechanisms of chronic fatigue.* Rheumatology (Oxford), 2011. **50**(6): p. 1009-18.
80. Swain, M.G., *Fatigue in chronic disease.* Clin Sci (Lond), 2000. **99**(1): p. 1-8.
81. Ahlberg, K., T. Ekman, and F. Gaston-Johansson, *Levels of fatigue compared to levels of cytokines and hemoglobin during pelvic radiotherapy: a pilot study.* Biol Res Nurs, 2004. **5**(3): p. 203-10.
82. Lampa, J., et al., *Peripheral inflammatory disease associated with centrally activated IL-1 system in humans and mice.* Proc Natl Acad Sci U S A, 2012. **109**(31): p. 12728-33.
83. Omdal, R., et al., *Fatigue in patients with systemic lupus erythematosus: lack of associations to serum cytokines, antiphospholipid antibodies, or other disease characteristics.* J Rheumatol, 2002. **29**(3): p. 482-6.
84. Krupp, L.B., et al., *A study of fatigue in systemic lupus erythematosus.* J Rheumatol, 1990. **17**(11): p. 1450-2.
85. Tench, C.M., et al., *The prevalence and associations of fatigue in systemic lupus erythematosus.* Rheumatology (Oxford), 2000. **39**(11): p. 1249-54.
86. Burgos, P.I., et al., *Disease activity and damage are not associated with increased levels of fatigue in systemic lupus erythematosus patients from a multiethnic cohort: LXVII.* Arthritis Rheum, 2009. **61**(9): p. 1179-86.
87. Moses, N., et al., *Prevalence and correlates of perceived unmet needs of people with systemic lupus erythematosus.* Patient Educ Couns, 2005. **57**(1): p. 30-8.
88. Jump, R.L., et al., *Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support.* J Rheumatol, 2005. **32**(9): p. 1699-705.
89. Da Costa, D., et al., *Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioral and psychosocial factors.* J Rheumatol, 2006. **33**(7): p. 1282-8.

90. Costa, D.D., et al., *Determinants of sleep quality in women with systemic lupus erythematosus.* Arthritis Rheum, 2005. **53**(2): p. 272-8.
91. Greenwood, K.M., L. Lederman, and H.D. Lindner, *Self-reported sleep in systemic lupus erythematosus.* Clin Rheumatol, 2008. **27**(9): p. 1147-51.
92. Valencia-Flores, M., et al., *Objective and subjective sleep disturbances in patients with systemic lupus erythematosus.* Arthritis Rheum, 1999. **42**(10): p. 2189-93.
93. Iaboni, A., et al., *Fatigue in systemic lupus erythematosus: contributions of disordered sleep, sleepiness, and depression.* J Rheumatol, 2006. **33**(12): p. 2453-7.
94. Abad, V.C., P.S. Sarinas, and C. Guilleminault, *Sleep and rheumatologic disorders.* Sleep Med Rev, 2008. **12**(3): p. 211-28.
95. Gudbjornsson, B. and J. Hetta, *Sleep disturbances in patients with systemic lupus erythematosus: a questionnaire-based study.* Clin Exp Rheumatol, 2001. **19**(5): p. 509-14.
96. Milette, K., et al., *Clinical correlates of sleep problems in systemic sclerosis: the prominent role of pain.* Rheumatology (Oxford), 2011. **50**(5): p. 921-5.
97. Robb-Nicholson, L.C., et al., *Effects of aerobic conditioning in lupus fatigue: a pilot study.* Br J Rheumatol, 1989. **28**(6): p. 500-5.
98. Ramsey-Goldman, R., et al., *A pilot study on the effects of exercise in patients with systemic lupus erythematosus.* Arthritis Care Res, 2000. **13**(5): p. 262-9.
99. Tench, C.M., et al., *Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise.* Rheumatology (Oxford), 2003. **42**(9): p. 1050-4.
100. Carvalho, M.R., et al., *Effects of supervised cardiovascular training program on exercise tolerance, aerobic capacity, and quality of life in patients with systemic lupus erythematosus.* Arthritis Rheum, 2005. **53**(6): p. 838-44.
101. Balsamo, S. and L.D. Santos-Neto, *Fatigue in systemic lupus erythematosus: An association with reduced physical fitness.* Autoimmun Rev, 2011.
102. Tench, C., et al., *Aerobic fitness, fatigue, and physical disability in systemic lupus erythematosus.* J Rheumatol, 2002. **29**(3): p. 474-81.
103. Segal, B., et al., *Oxidative stress and fatigue in systemic lupus erythematosus.* Lupus, 2012. **21**(9): p. 984-92.
104. McKinley, P.S., S.C. Ouellette, and G.H. Winkel, *The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus. A proposed model.* Arthritis Rheum, 1995. **38**(6): p. 826-34.
105. Eriksson, K., et al., *Physical activity in patients with systemic lupus erythematosus and matched controls.* Scand J Rheumatol, 2012. **41**(4): p. 290-7.
106. Ayan, C. and V. Martin, *Systemic lupus erythematosus and exercise.* Lupus, 2007. **16**(1): p. 5-9.
107. Wang, B., D.D. Gladman, and M.B. Urowitz, *Fatigue in lupus is not correlated with disease activity.* J Rheumatol, 1998. **25**(5): p. 892-5.
108. Austin, J.S., et al., *Health outcome improvements in patients with systemic lupus erythematosus using two telephone counseling interventions.* Arthritis Care Res, 1996. **9**(5): p. 391-9.
109. Karlson, E.W., et al., *A randomized clinical trial of a psychoeducational intervention to improve outcomes in systemic lupus erythematosus.* Arthritis Rheum, 2004. **50**(6): p. 1832-41.

110. Neill, J., I. Belan, and K. Ried, *Effectiveness of non-pharmacological interventions for fatigue in adults with multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus: a systematic review.* J Adv Nurs, 2006. **56**(6): p. 617-35.
111. Paterson, B., et al., *Embedded assumptions in qualitative studies of fatigue.* West J Nurs Res, 2003. **25**(2): p. 119-33.
112. Wu, H.S. and M. McSweeney, *Cancer-related fatigue: "It's so much more than just being tired".* Eur J Oncol Nurs, 2007. **11**(2): p. 117-25.
113. Spichiger, E., et al., *Fatigue in patients undergoing chemotherapy, their self-care and the role of health professionals: a qualitative study.* Eur J Oncol Nurs, 2012. **16**(2): p. 165-71.
114. Porock, D. and J.A. Juenger, *Just go with the flow: a qualitative study of fatigue in biotherapy.* Eur J Cancer Care (Engl), 2004. **13**(4): p. 356-61.
115. Lofgren, M., J. Ekholm, and A. Ohman, *'A constant struggle': successful strategies of women in work despite fibromyalgia.* Disabil Rehabil, 2006. **28**(7): p. 447-55.
116. Humphrey, L., et al., *Fatigue in fibromyalgia: a conceptual model informed by patient interviews.* BMC Musculoskelet Disord, 2010. **11**: p. 216.
117. Repping-Wuts, H., et al., *Fatigue as experienced by patients with rheumatoid arthritis (RA): a qualitative study.* Int J Nurs Stud, 2008. **45**(7): p. 995-1002.
118. Nikolaus, S., et al., *New insights into the experience of fatigue among patients with rheumatoid arthritis: a qualitative study.* Ann Rheum Dis, 2010. **69**(5): p. 895-7.
119. Beckerman, N.L., *Living with lupus: a qualitative report.* Soc Work Health Care, 2011. **50**(4): p. 330-43.
120. Carr, A., et al., *Rheumatology outcomes: the patient's perspective.* J Rheumatol, 2003. **30**(4): p. 880-3.
121. Cleanthous, S., et al., *What do we know about self-reported fatigue in systemic lupus erythematosus?* Lupus, 2012. **21**(5): p. 465-476.
122. Dittner, A.J., S.C. Wessely, and R.G. Brown, *The assessment of fatigue: a practical guide for clinicians and researchers.* J Psychosom Res, 2004. **56**(2): p. 157-70.
123. Liang, M.H., et al., *Measuring clinically important changes with patient-oriented questionnaires.* Med Care, 2002. **40**(4 Suppl): p. II45-51.
124. Kirwan, J.R., et al., *Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis.* J Rheumatol, 2007. **34**(5): p. 1174-7.
125. Krupp, L.B., et al., *The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus.* Arch Neurol, 1989. **46**(10): p. 1121-3.
126. Mattsson, M., et al., *Reliability and validity of the Fatigue Severity Scale in Swedish for patients with systemic lupus erythematosus.* Scand J Rheumatol, 2008. **37**(4): p. 269-77.
127. Avina-Zubeieta A, A.G., Bischoff Ferrari HA, Fischer R, Gall V, Illei G, Liang MH, Mikdashi J, Petri M, Phillips C, Pouchot J, Schneider M, Schur P, St Clair W. (Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue), *Measurement of fatigue in systemic lupus erythematosus: a systematic review.* Arthritis Rheum, 2007. **57**(8): p. 1348-57.

128. Nikolaus, S., et al., *Which Dimensions of Fatigue Should be Measured in Patients with Rheumatoid Arthritis? A Delphi Study.* Musculoskeletal Care, 2011.
129. Hewlett, S., M. Hehir, and J.R. Kirwan, *Measuring fatigue in rheumatoid arthritis: a systematic review of scales in use.* Arthritis Rheum, 2007. **57**(3): p. 429-39.
130. Belza, B.L., *Comparison of self-reported fatigue in rheumatoid arthritis and controls.* J Rheumatol, 1995. **22**(4): p. 639-43.
131. Cella, D., et al., *Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis.* J Rheumatol, 2005. **32**(5): p. 811-9.
132. Wolfe, F., *Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients.* J Rheumatol, 2004. **31**(10): p. 1896-902.
133. Pouchot, J., et al., *Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis.* J Clin Epidemiol, 2008. **61**(7): p. 705-13.
134. Goligher, E.C., et al., *Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus.* J Rheumatol, 2008. **35**(4): p. 635-42.
135. Gustafsson, J., et al., *Predictors of the first cardiovascular event in patients with systemic lupus erythematosus - a prospective cohort study.* Arthritis Res Ther, 2009. **11**(6): p. R186.
136. Svenungsson, E., et al., *A STAT4 risk allele is associated with ischaemic cerebrovascular events and anti-phospholipid antibodies in systemic lupus erythematosus.* Ann Rheum Dis, 2010. **69**(5): p. 834-40.
137. Kidd, P.S. and M.B. Parshall, *Getting the focus and the group: enhancing analytical rigor in focus group research.* Qual Health Res, 2000. **10**(3): p. 293-308.
138. Krueger, R.A. and M.A. Casey, *Focus groups : a practical guide for applied research* 3 rd ed. 2000, Thousand Oaks, Calif: Sage publications.
139. Marshall, N.J., et al., *Patients' perceptions of treatment with anti-TNF therapy for rheumatoid arthritis: a qualitative study.* Rheumatology (Oxford), 2004. **43**(8): p. 1034-8.
140. Tishelman, C., et al., *Are the Most Distressing Concerns of Patients With Inoperable Lung Cancer Adequately Assessed? A Mixed-Methods Analysis.* J Clin Oncol, 2010. **28**(11): p. 1942-9.
141. Sullivan, M., J. Karlsson, and C. Taft, *SF-36 Hälsoenkät: Svensk Manual och Tolkningsguide (Swedish Manual and Interpretation Guide)*. 2 ed. 2002, Gothenburg: Sahlgrenska University Hostpital.
142. Touma, Z., et al., *Is there an advantage over SF-36 with a quality of life measure that is specific to systemic lupus erythematosus?* J Rheumatol, 2011. **38**(9): p. 1898-905.
143. Bjelland, I., et al., *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res, 2002. **52**(2): p. 69-77.
144. Lisspers, J., A. Nygren, and E. Soderman, *Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample.* Acta Psychiatr Scand, 1997. **96**(4): p. 281-6.

145. Sohng, K.Y., *Effects of a self-management course for patients with systemic lupus erythematosus.* J Adv Nurs, 2003. **42**(5): p. 479-86.
146. Sandqvist, G., et al., *The Swedish version of the Multidimensional Assessment of Fatigue (MAF) in systemic sclerosis: reproducibility and correlations to other fatigue instruments.* Scand J Rheumatol, 2011. **40**(6): p. 493-4.
147. Smets, E.M., et al., *The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue.* J Psychosom Res, 1995. **39**(3): p. 315-25.
148. Furst, C.J. and E. Ahsberg, *Dimensions of fatigue during radiotherapy. An application of the Multidimensional Fatigue Inventory.* Support Care Cancer, 2001. **9**(5): p. 355-60.
149. Hagelin, C.L., et al., *The psychometric properties of the Swedish Multidimensional Fatigue Inventory MFI-20 in four different populations.* Acta Oncol, 2007. **46**(1): p. 97-104.
150. Ericsson, A. and K. Mannerkorpi, *Assessment of fatigue in patients with fibromyalgia and chronic widespread pain. Reliability and validity of the Swedish version of the MFI-20.* Disabil Rehabil, 2007. **29**(22): p. 1665-70.
151. Chalder, T., et al., *Development of a fatigue scale.* J Psychosom Res, 1993. **37**(2): p. 147-53.
152. Mock, V., et al., *NCCN Practice Guidelines for Cancer-Related Fatigue.* Oncology (Williston Park), 2000. **14**(11A): p. 151-61.
153. Hagell, P., et al., *Measuring fatigue in Parkinson's disease: a psychometric study of two brief generic fatigue questionnaires.* J Pain Symptom Manage, 2006. **32**(5): p. 420-32.
154. Lai, J.S., et al., *Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial.* J Rheumatol, 2011. **38**(4): p. 672-9.
155. Liang, M.H., et al., *Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus.* Arthritis Rheum, 1989. **32**(9): p. 1107-18.
156. Bae, S.C., et al., *Reliability and validity of systemic lupus activity measure-revised (SLAM-R) for measuring clinical disease activity in systemic lupus erythematosus.* Lupus, 2001. **10**(6): p. 405-9.
157. Bombardier, C., et al., *Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE.* Arthritis Rheum, 1992. **35**(6): p. 630-40.
158. Chang, E., et al., *Comparison of the responsiveness of lupus disease activity measures to changes in systemic lupus erythematosus activity relevant to patients and physicians.* J Clin Epidemiol, 2002. **55**(5): p. 488-97.
159. Gladman, D., et al., *The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus.* Arthritis Rheum, 1996. **39**(3): p. 363-9.
160. Gladman, D.D., et al., *The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus.* Arthritis Rheum, 1997. **40**(5): p. 809-13.

161. Karlson, E.W., et al., *Validation of a Systemic Lupus Activity Questionnaire (SLAQ) for population studies.* Lupus, 2003. **12**(4): p. 280-6.
162. Graneheim, U.H. and B. Lundman, *Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness.* Nurse Educ Today, 2004. **24**(2): p. 105-12.
163. Brennan, P. and A. Silman, *Statistical methods for assessing observer variability in clinical measures.* BMJ, 1992. **304**(6840): p. 1491-4.
164. Brant, R., L. Sutherland, and R. Hilsden, *Examining the minimum important difference.* Stat Med, 1999. **18**(19): p. 2593-603.
165. Sharma, S., *Cluster Analysis*, in *Applied multivariate techniques*. 1996, J. Wiley: New York. p. xviii, 493 p.
166. IBM, *IBM SPSS Statistics Base 19*. 2010, SPSS Inc 1989,: New York, USA.
167. Loue, S., *Textbook of research ethics : theory and practice*. 2000, New York: Kluwer Academic/Plenum Pub. xvii, 255 p.
168. Pettersson, S., et al., *Women's experience of SLE-related fatigue: a focus group interview study.* Rheumatology (Oxford), 2010. **49**(10): p. 1935-42.
169. Stuifbergen, A.K. and S. Rogers, *The experience of fatigue and strategies of self-care among persons with multiple sclerosis.* Appl Nurs Res, 1997. **10**(1): p. 2-10.
170. Kralik, D., et al., *Women's experiences of fatigue in chronic illness.* J Adv Nurs, 2005. **52**(4): p. 372-80.
171. Bennett, B., et al., *The experience of cancer-related fatigue and chronic fatigue syndrome: a qualitative and comparative study.* J Pain Symptom Manage, 2007. **34**(2): p. 126-35.
172. Gallop, K., et al., *Development of a conceptual model of health-related quality of life for systemic lupus erythematosus from the patient's perspective.* Lupus, 2012. **21**(9): p. 934-43.
173. Heiberg, T. and T.K. Kvien, *Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority.* Arthritis Rheum, 2002. **47**(4): p. 391-7.
174. Atkinson, M.J. and R.D. Lennox, *Extending basic principles of measurement models to the design and validation of Patient Reported Outcomes.* Health Qual Life Outcomes, 2006. **4**: p. 65.
175. Watt, T., et al., *Fatigue in the Danish general population. Influence of sociodemographic factors and disease.* J Epidemiol Community Health, 2000. **54**(11): p. 827-33.
176. Bixler, E., *Sleep and society: an epidemiological perspective.* Sleep Med, 2009. **10 Suppl 1**: p. S3-6.
177. Chen, J.C., et al., *Sleep duration and risk of ischemic stroke in postmenopausal women.* Stroke, 2008. **39**(12): p. 3185-92.
178. Gangwisch, J.E., et al., *Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey.* Hypertension, 2006. **47**(5): p. 833-9.
179. Gangwisch, J.E., et al., *Sleep duration as a risk factor for diabetes incidence in a large U.S. sample.* Sleep, 2007. **30**(12): p. 1667-73.
180. Mancuso, C.A., et al., *Perceptions and measurements of physical activity in patients with systemic lupus erythematosus.* Lupus, 2011. **20**(3): p. 231-42.

181. Webb, C. and J. Kevern, *Focus groups as a research method: a critique of some aspects of their use in nursing research.* J Adv Nurs, 2001. **33**(6): p. 798-805.
182. Hewlett, S., et al., *Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored.* Arthritis Rheum, 2005. **53**(5): p. 697-702.
183. Lehman, A. and M. Liang, *Health Status Measurement, assessing meaningful change*, in *Encyclopedia of medical decision making*, M.W. Kattan and M.E. Cowen, Editors. 2009, SAGE Publications: Thousand Oaks, Calif. p. 556-560.
184. Liang, M.H., *Longitudinal construct validity: establishment of clinical meaning in patient evaluative instruments.* Med Care, 2000. **38**(9 Suppl): p. II84-90.
185. Boers, M., et al., *The OMERACT filter for Outcome Measures in Rheumatology.* J Rheumatol, 1998. **25**(2): p. 198-9.
186. Tugwell, P., et al., *OMERACT: an international initiative to improve outcome measurement in rheumatology.* Trials, 2007. **8**: p. 38.
187. Power, J.D., et al., *Fatigue in osteoarthritis: a qualitative study.* BMC Musculoskelet Disord, 2008. **9**: p. 63.
188. van Eijk-Hustings, Y., et al., *EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis.* Ann Rheum Dis, 2012. **71**(1): p. 13-9.

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Original article

Women's experience of SLE-related fatigue: a focus group interview study

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Abstract

Objective. The aim of this study was to describe women's experience of SLE-related fatigue, how they express the feeling of fatigue, impact on life and strategies developed to manage fatigue in daily living.

Method. Seven, semi-structured focus group discussions with 33 women were audio-taped, transcribed verbatim and analysed according to qualitative content analysis.

Results. Perceptions of SLE-related fatigue were sorted into four themes. Nature of Fatigue, involved the sensation, occurrence and character. Aspects Affected by Fatigue described emotions that arose together with fatigue as well as aspects of work, family life, social contacts and leisure activities that were affected by fatigue. Striving Towards Power and Control concluded the array of ways used to manage daily life and were categorized into the mental struggle, structure, restrict and provide. Factors Influencing the Perception of Fatigue described understanding from their surroundings and pain as strongly influencing the experience and perception of fatigue.

Conclusion. SLE-related fatigue was portrayed as an overwhelming phenomenon with an unpredictable character, resulting in the feeling that fatigue dominates and controls most situations in life. The choice of strategies was described as a balance with implications for how fatigue limited a person's life. Health care professionals are advised to take a more active role to empower people with SLE to find their own balance as a way to achieve a feeling of being in control.

Key words: Systemic lupus erythematosus, Fatigue, Qualitative research, Focus groups.

Introduction

To be diagnosed with SLE can be a harsh blow to a person, and life after diagnosis has been described as an existence filled with uncertainty [1] of how the disease will affect life in both the short and long run. Studies have shown that patients with SLE perceive lower health-related quality of life (HRQoL) than healthy controls [2, 3] and patients with other chronic conditions [4]. Previous research has confirmed fatigue as a significant characteristic of SLE, and fatigue has been described as a core factor that negatively affects SLE patients' quality of life [5, 6] and interferes with many aspects of family life [1]. The pathophysiological mechanisms of SLE-related fatigue are unclear. Several studies claim that disease activity alone cannot fully explain the fatigue [7–9] and that psychosocial factors might play a major role [8, 10]. Fatigue is an individual and subjective sensation; thus its impact on a person's life can be difficult for others to understand [11], which may provide one explanation for the finding that 81% of SLE patients indicated that the health care service did not support them enough in the management of SLE-related fatigue [12].

The complexity of fatigue has been explored in healthy individuals [13], in qualitative research from the perspective of patients diagnosed with cancer [14, 15], and in patients living with chronic conditions such as multiple sclerosis (MS) [16] and RA [17–19]. Further research has sought to understand the meaning of fatigue, but no consensus definition has been reached. Piper [20] emphasizes its subjective nature, defining fatigue as 'an uncommon, abnormal or extreme whole bodily

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tiredness disproportionate or unrelated to activity or exertion' ([21], p. 279). Piper's widely used definition is applied in this study.

The purpose of this study was to explore women's experiences of SLE-related fatigue. In a qualitative interview-based approach, women described their sensations of fatigue, its influence on their life and the strategies they used to manage daily life with fatigue.

Materials and methods

From January 2004 to October 2006, 237 persons (217 women, 20 men) with SLE were recruited to a cross-sectional cohort study at a rheumatology clinic at a university hospital in an urban part of Sweden. All participants fulfilled at least four of the ACR criteria for SLE [22]. Based on the low number of men in the cohort, this study chose to focus on women's perceptions. From the cohort all 75 women (aged 25–70 years) diagnosed with SLE at least 2 years earlier and who had previously self-reported high levels of fatigue ($\geqslant$7, scale 1–10) were asked to participate in focus group discussions (FGDs). The cut-off points were used to assure that the respondents at one point had had experience of severe fatigue. An information letter was sent by post along with a pre-paid consent form, and 45 women (60%) agreed to participate by sending back a written consent [23]. No significant differences were found between the 45 women who agreed to participate and the 30 women who did not, using the parameters age, disease duration, disease activity SLAM [24], SLEDAI [25], SLE disease damage according to SLICC/ACR [26], corticosteroid dose or self-assessment of fatigue (scale 1–10). Data for each patient were collected at inclusion to the cohort.

Seven FGDs were constructed based on the patient's preference for timepoint. None of the women who agreed to participate withdrew, but 12 were unable to attend the scheduled group sessions due to illness or personal reasons. Fatigue was significantly higher and more patients in the interview group were treated with chloroquine. No other differences were found between the final participants (n = 33) and the other women in the cohort (Table 1). The cohort study, including the FGDs, was approved by the local ethics committee at the Karolinska Institutet.

Data collection

This study used descriptive qualitative methodology. The use of FGDs was chosen to facilitate collection of diverse perspectives [27] and stimulate interaction between patients through generation of ideas as well as verbal reflections [28, 29]. S.P. and E.W.H. were present at all FGDs as interview leader and -observer, respectively. Suggestions and comments from the participants themselves were encouraged, to supplement the researcher-generated interview guide containing open-ended questions (Table 2). At the end of each FGD, the interview leader concluded the discussion and gave the respondents time for clarifications and further associations. This conclusion also ensured that all areas in the interview guide were covered. To reassess fatigue and HRQoL, the participants were asked to complete two self-assessment questionnaires: Short Form-36 (SF-36; eight domains, each ranging from 0 to 100) [30] and Multidimensional Assessment of Fatigue (MAF) scale (range 1–50) [31].

Table 1 Characteristics of women with SLE, data collected at inclusion to the cohort study (not interviewed compared with the interview group)

	Not interviewed (n = 184) Mean (S.D.)	Interview group (n = 33) Mean (S.D.)	P-value[a]
Age, years	48.8 (15.1)	46.1 (11.5)	0.327[b]
	Median (interquartile range)	Median (interquartile range)	
Disease duration, years	14 (8–23)	12 (5.5–26.5)	0.480
SLAM	6 (4–9)	7 (4.5–11)	0.113
SLEDAI	2 (0–6)	3 (1–8)	0.160
SLICC	1 (0–2)	1 (0–2)	0.413
Fatigue (scale 1–10)	7 (5–9)	8 (8–9)	<0.001
Corticosteroids, mg	2.5 (0–5.6)	2.5 (0–6.2)	0.961
Lupus manifestation, %			
Malar rash	53	54.5	0.874
Discoid rash	23	24	0.893
Photosensitivity	72	67	0.689
Oral ulcers	35	30	0.588
Arthritis	87	91	0.601
Pleuritis	34	30	0.615
Pericarditis	16	24	0.285
Nephritis	36	39	0.703
Neurology[c]	12	6	0.300
Blood manifestation[d]	70	79	0.335
DMARD, %			
AZA	19	9	0.159
Chloroquine	28	48	0.043
Ciclosporin	1	3	0.557
Cyclophosphamide[e]	14	6	0.283
MTX	5	9	0.288
Mycophenolate mofetil	6	6	0.913

[a]P-value calculated with Mann–Whitney U-test if not indicated otherwise. [b]Independent Samples Test. [c]Neurology: psychosis or seizures. [d]Leucopenia, thrombocytopenia, lymphopenia or haematolytic anaemia. [e]p.o. or i.v.

Table 2 Interview guide used in FGDs

- Can you describe the feeling of fatigue that you associate with SLE?
  - The feeling itself.
- How does it affect your daily living?
  - Is there anything that you avoid doing?
  - Is there anything that you miss, for example that you can't do?
- How do you manage in daily life when you have this feeling/fatigue?
  - Do you have any trick or strategies?

To avoid statements from the instruments directly influencing the discussion, the reassessment was conducted after each FGD. The interviews were digitally audio-taped and transcribed verbatim, and the names were replaced with a number during transcription. The accuracy of the transcripts was checked by re-reading while the tape was played.

Data analysis

To understand, explore and explain the SLE-related fatigue phenomenon, qualitative content analysis was used to analyse the transcripts [32]. The first critical step in the analysis was to identify words, sentences or paragraphs and mark them with codes. Categories were generated based on codes with shared content. S.P. and E.W.H. read and analysed the transcripts separately and then compared the results. Differences from the separate analyses were discussed until consensus was reached. The categories were further discussed with S.M., an experienced rheumatology nurse. Finally, the analysis linked the categories together into themes. The quantitative data from the questionnaires were calculated with Statistical Package for the Social Sciences (SPSS; Chicago, IL, USA) version 15.

Results

The result from the questionnaires (Table 3) showed that the interviewed group scored lower on all dimensions of SF-36 than women of the same age in a normal Swedish population [33]. The lowest score in the eight domains of the SF-36 was for vitality (VT), and the interviewees' fatigue scores (MAF) ranged from 13.4 to 46.9, with a mean (S.D.) of 34.2 (7.9), on a scale of 1–50, where 1 represents no fatigue.

Four themes emerged through analysis of respondents' experiences of SLE-related fatigue: Nature of Fatigue; Aspects Affected by Fatigue; Striving Towards Power and Control; and Factors Influencing the Perception of Fatigue (Fig. 1). The themes included two to four categories each. Nature of Fatigue gave a picture of the sensation, occurrence and character of fatigue. Aspects Affected by Fatigue included the emotions that fatigue aroused, and the category social contacts and interactions concerned disruption of work, family life, social contacts and leisure activities. Striving Towards Power and Control involved the repertoire of strategies that patients employed to manage daily life despite fatigue. Factors Influencing the Perception of Fatigue described understanding and pain as modulators of fatigue. The themes were supported by quotes. Abbreviations after each quote referred first to the interview session in numerical order and the second number denoted the person in that session.

Nature of Fatigue

The Nature of Fatigue was divided into three categories based on descriptions of sensation, occurrence and character. The category sensation was based on perceptions of SLE-related fatigue as a bodily sensation and a misty feeling. The bodily sensation was a perception that parts of the body were heavy or paralysed, which made them difficult, but not impossible, to move. Descriptions related to the misty feeling included foggy-headedness or the sense of a screen or glass ball around the head. This shield made it hard to concentrate, listen, speak or sort impressions. It also interfered with the women's ability to focus and concentrate on work tasks and social interactions. 'Well I'd say my fatigue has gone so far that I feel like my head is just empty, there's not much that works inside my head anymore' (5:3).

TABLE 3 Comparison of group-mean for the eight dimensions[a] of HRQoL from the SF-36

	Interview group Mean (S.D.)	Normal[b] Mean (S.D.)	*P*-value[c]
Physical function	68.1 (25.6)	84.9 (6.3)	0.001
Role: physical	40.9 (38.4)	80.9 (6.0)	0.000
Bodily pain	55.7 (21.9)	70.7 (4.0)	0.001
General health	36.3 (19.9)	73.5 (4.8)	0.000
Vitality	33.2 (20.1)	67.0 (1.6)	0.000
Social function	59.1 (22.8)	87.4 (0.9)	0.000
Role: emotional	67.7 (41.2)	84.5 (2.2)	0.102
Mental health	69.8 (21.0)	79.8 (0.8)	0.061

[a]Range 0–100, high scores reflect better perceived health state than lower. [b]Normal-based values, mean value is calculated on gender and age match in range of 5 years, for each individual. [c]Wilcoxon signed ranks test.

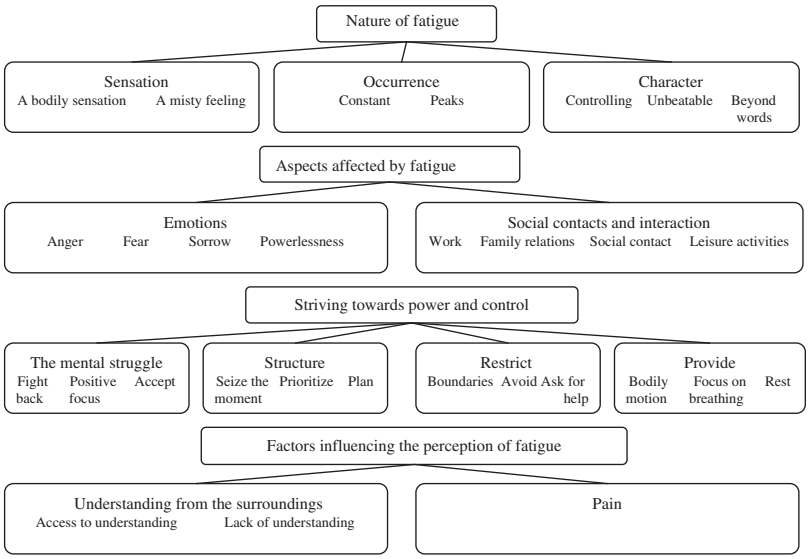
The category occurrence involved disparate descriptions: constant and peaks. Many patients depicted fatigue as something constantly present, 'I carry it with me, something in my backpack' (3:3). Yet at the same time there was an unpredictable variability in the occurrence, with sudden attacking peaks. 'It's like the tide going in and out, like suddenly you're full of energy and then suddenly you're not full of energy anymore' (5:3).

The character of fatigue was described as controlling, unbeatable and beyond words. Controlling included descriptions that fatigue takes control of a person's life. Unbeatable involved statements that showed fatigue as being impossible to resist or combat. Beyond words portrayed the fatigue as something more than normal fatigue, something not comprehensible if not experienced.

> 2: No, you can't do anything about it of your own free will. If it comes it comes and all you can do is resign yourself to it,
> 1: Exactly, it just takes over. It takes over and there's not one thing you can do about it, it doesn't matter, uh, what you do, even if you sleep for twenty hours or a night you can still be tired the next day. (FGD 6)

In this discussion, the respondents sometimes found it difficult to find words adequately expressing their feeling of SLE-related fatigue. In summary, they described it

Fig. 1 The landscape of SLE-related fatigue. Result of content analysis of transcripts from FGDs with women (n = 33) with SLE. Themes, categories and codes.



as something beyond previously experienced normal fatigue, which resulted in a feeling of being dominated by SLE-related fatigue.

Aspects Affected by Fatigue

The respondents' perception of the Nature of Fatigue is reflected in their description of the impact that fatigue has on daily life. The theme Aspects Affected by Fatigue included emotions and social contacts and interactions. The category emotions depicted feelings that arose as a result of fatigue, and included anger, fear, sorrow and powerlessness. 'You get tired from being tired, and it's like, because you don't have the strength to do anything, nothing, and you get scared every single time' (4:4).

In the category social contacts and interaction, respondents described how fatigue impacted interpersonal relations in various contexts: work, including perceived performance and work capacity; family relations, social contacts and leisure activities. Leisure activities differed from person to person according to their habits and interests, and were hampered as a result of fatigue.

> 5: I think it affects my marital relations too, that I don't have, I just want to stay at home, I don't have the energy to get out and around, all the fun that others have, oh so shall we go there and there, and do this and that, and eat out. Can't we just stay at home?
> 6: But that's exactly what I've felt too, like say this thing of going out with your coworkers after work, or a friend or someone, and ohhhh it's such a challenge, it's like, . . .
> 1: It's so hard to book anything, because you never know how you'll feel that day, it's almost impossible not to let people down all the time. (FGD 4)

The respondents regarded these risen emotions and consequences on interactions and social contacts as an area that would not have been influenced in this way if they were liberated from SLE-related fatigue.

Striving Towards Power and Control

The act of handling fatigue was described in Striving Towards Power and Control, and included four categories: the mental struggle, structure, restrict and provide. The patients described that when they found their personal way of balancing life affected by fatigue, the fatigue did not have the same controlling effect.

The category mental struggle involved three descriptive groups: fight back, positive focus and accept. Fight back was articulated as an active way of ignoring the fatigue and forcing oneself to do all the tasks one wanted. 'I don't think I've ever lost out on anything because I've decided that despite being tired I'm going to see things through, I must say that, and so I think I have actually done that and I mean to keep doing it until I'm not around anymore, No, that's what I've decided, this fatigue isn't going to get me' (3:3). The category also involved an optimistic attitude with attention on things that the respondents were able to do, activities less affected by fatigue, described as

positive focus. Accept was a more passive approach but involved a reassessment of daily life.

The category structure expressed pacing daily life as a way to plan or prioritize the everyday existence, but also establishing a strategy to seize the moment and be prepared to make use of moments of strength.

> 4: Yeah, but you can't always pull things off, even if you've planned carefully, so it's important that you...
> 3: That's also how I feel, that all these visitors and all the things you're supposed to do, to do all the planning I think all that's really important. (FGD 3)

In the category restrict, the respondents described ways to establish boundaries. This included restrictions both on inner demands and demands from one's surroundings. The respondents stated the importance of declaring what to do or not to others as well as to themselves. To avoid was based on strategies focused on staying away from things that consumed too much power or strength. One action described as difficult, but often essential, was to ask for help when needed. '...but I tell my family and the people I spend time with, my friends, that, that I'm not feeling so good today, and I'm down in the dumps, and I'm really tired because of my disease, and I need to be left alone a bit more and so on, because I need to be alone more, and take it easy, I can't rush around like other people, and they accept it much better, I think, now that I'm being more explicit' (4:4).

In addition to the mental struggle, structure and restrict, the respondents described a selection of actions to provide strength to deal with the fatigue. The women emphasized that the actions did not eliminate fatigue, but gave more power to accomplish things. Ways to provide strength were described as rest, focus on breathing and bodily motion. The concept focus on breathing was expressed as essential to the women. To focus on intentional breathing, indoors as well as outdoors, was described as something that eased the burden of fatigue. One important way to find air indoors was yoga, with its focus on breathing; for outdoors, just standing or strolling around with the intention of breathing fresh air. 'if you're out and about, you keep yourself going, you can breathe, so you can stay at a higher energy level' (7:4).

Actions given the code bodily motions included physical activities as diverse in character as walking, gym exercises or just the gentle movement of the body. Although described as sometimes difficult, for many of the women such actions were a crucial way to provide strength. 'The only time I feel really energetic, that's when I've been working out, and it's like it's then I get some kind of recuperation, Sleep isn't what helps me recuperate' (6:2).

In this context, strategies used to provide did not fully erase the SLE-related fatigue. The reason why the strategies were still used was that the respondents described that the dimension of more normal fatigue was reduced, which otherwise was cumulated on top of the SLE-related fatigue. Actions to provide strength also gave power to more efficient coping with the SLE-related fatigue.

Factors Influencing the Perception of Fatigue

Factors described as influencing the experience of fatigue were divided into two categories: pain, and understanding from their surroundings. The respondents described pain as a disease-related symptom that influenced and compounded fatigue. Their comments showed that perceived pain was clearly associated with a deepened perception of fatigue.

> 4: because pain also saps your energy
> 3: exactly
> 6: It consumes a whole lot of energy. (FGD 3)

Lack of understanding from the surroundings, i.e. family, health care and society, made the burden of fatigue more difficult to handle and was described as a factor that exacerbated fatigue. The respondents pointed out a problem they face: fatigue cannot be seen and is a common topic in everyday conversation. They saw for a fact that people around them regarded fatigue as a normal state, a product of today's society. This led the focus group to discuss the question 'What is normal fatigue?' Society norms were viewed as a possible basis for the lack of understanding, which could be compounded by the lack of words that distinguish disease-related fatigue from more natural or normal fatigue.

> The moment anyone asks 'How are you?' That I'm tired, and in the end it doesn't count for anything, 'tired, yeah, but isn't everybody a bit tired'. (4:5)

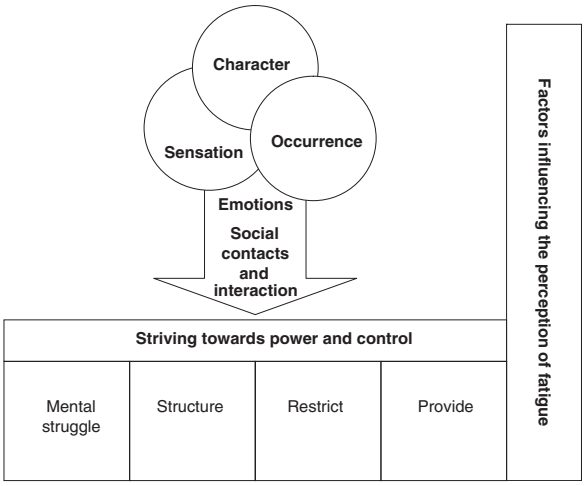
In contrast, support and understanding from significant others and from the surrounding society, including the health care system, worked as factors that reduced the burden of fatigue for patients with SLE. One aspect important for the perception of support was that significant others acknowledged the fatigue as being true and not just something fabricated by the patient.

Discussion

The result reflects the complex meaning of fatigue and outlines the landscape of SLE-related fatigue. The themes identified included Nature of Fatigue, with categories sensation, occurrence and character of SLE-related fatigue; Aspects Affected by Fatigue, including the emotional and social consequences of fatigue; Striving Towards Power and Control, comprising strategies used to handle daily life with fatigue; and Factors Influencing the Perception of Fatigue, with factors that compound or alleviate perceived SLE-related fatigue (Figs 1 and 2).

A phenomenon like fatigue, which thoroughly permeates a person's daily life, can be difficult to describe and explain without reflection. Data collection with FGD was constructive since it gave the respondents opportunities to recall and confirm aspects together with others who had the same experience. The advantage of revealing unreflected aspects of the phenomenon could otherwise have been missed if the women had been interviewed individually. To reduce the risk that respondents refrained from describing atypical experiences or voicing differing

FIG. 2 A model based on patients' description of SLE-related fatigue. The perception of fatigue involves: the sensation, a bodily sensation together with a misty feeling in the head; the character is described as controlling, unbeatable and beyond words; and occurrence depicts fatigue as constantly present, yet at the same with unpredictable attacking peaks. Aspects Affected by Fatigue include emotions that arise together with fatigue and social contacts and interactions at work, family life, social contacts and leisure activities. All these influence the perception of fatigue and Striving Towards Power and Control describes the array of strategies that may be chosen to manage daily life. Factors Influencing the Perception of Fatigue describes understanding and pain as strongly influencing the experience and perception of fatigue at all levels.



opinions, the interview leader had an active and important role. This included paying attention to body language to recognize respondents who had something to say as well as allowing moments of silence during the sessions to give all participants ample opportunity to speak up. Dependability is explained as part of the trustworthiness in qualitative content analysis [32]. The dependability of this study was ensured by the interview guide and the analysis process.

To our knowledge, this is the first published qualitative study of fatigue related to SLE. The results show similarities with the meaning of fatigue as experienced by women with MS [16, 34] or RA [19]. However, in this study, the experience of fatigue included an impression that one's body was very heavy, and that all or parts of it were impossible to move. A similar experience is shown in a study of persons with MS where fatigue is described as a paralysing force [16]. The simile of fatigue as having something in the backpack is interestingly also expressed in a British study where patients described fatigue related to RA [17]. A misty feeling in the head affecting one's capacity to interact was seen as one of the reasons why fatigue had an impact on social interactions, and feelings of isolation as a psychosocial consequence of fatigue were reported.

The emotions that fatigue arouses are thus complex and may intensify the perception of fatigue. These aspects of fatigue have, as far as we know, not previously been described for SLE. Previously reported emotions that are associated with fatigue in other conditions, e.g. anger [19] and anxiety [15]. Emotions can influence both reactions to fatigue and the actions chosen to manage fatigue. To our knowledge neither powerlessness nor sorrow have been previously described in relation to disease-related fatigue, and further explorative research with focus on emotional reactions related to fatigue in chronic conditions is needed.

Paterson *et al*. [35] reports that individuals with an invisible chronic illness felt that they were met with scepticism by others, even by health care professionals. Family support has been shown to be associated with improved mental health for persons with SLE [36]. Notably, the perception of fatigue is not an isolated problem, but it is probably the combined result of factors relating directly to the disease and indirectly to the psychosocial support and the complex response to a chronic condition [37]. Interestingly, Thumboo and Strand [6] found spontaneous improvement in HRQoL in control groups where symptoms were monitored without specific interventions, suggesting that simply paying attention to certain aspects of the patient's life, such as fatigue, may improve HRQoL. In Striving Towards Power and Control, individuals find their own tools to handle both inner and outer demands. The choice of strategies would most

certainly have an effect on how fatigue limits a person's life. The strategy tools coded as restrict and provide are reminiscent of the discussion about handling secondary fatigue in Stuifbergen and Rogers [16], where sleep, healthy eating habits and physical activity are mentioned. The respondents of our study said that even if sleep did not reduce the fatigue, it was essential and provided strength that made it possible to balance life with fatigue. This theme of the Landscape of Fatigue is almost certainly most strongly influenced by individual experience. A meta-study on qualitative studies of fatigue describe the choice of strategies as based on understanding of fatigue as well as personal experience of previous successful strategies [35]. Lack of explanation of the mechanism underlying SLE-related fatigue together with its unpredictable nature could make the balance even more difficult.

To what extent finding an individual management strategy can improve HRQoL and what strategies are the most successful needs further exploration. One well-known model for how to cope with fatigue is the Fatigue Care Wheel, used as a tool to help patients identify factors that bring on or decrease fatigue [38]. Our model can be seen as a complement to other models to help health professionals and patients understand and address the complex nature of SLE-related fatigue (Fig. 2). All the respondents perceived an obvious difference between SLE-related fatigue and the tiredness they related to as normal or natural and explainable. Even so, they had trouble finding words adequately articulating the sensation. There are probably several dimensions of SLE potentially influencing the experience of fatigue either directly (e.g. disease activity) or indirectly (e.g. pharmacotherapy). In this qualitative study, the aim was not to explain the cause of SLE-related fatigue, but to focus on patient perceptions. To accurately compare the perception of fatigue a quantitative study with questions based on descriptions from qualitative studies conducted within a large multi-centre sample is suggested.

Insufficient knowledge of fatigue could be a hindrance in the development and implementation of interventions [16]. Hopefully, this study will contribute by highlighting patients' experiences, show the complexity of SLE-related fatigue and inspire further development of interventions for the patient's benefit. We advise health professionals to take a more active role in supporting patients to manage fatigue in chronic conditions [16, 17], to empower individuals with SLE to find their own way of Striving Towards Power and Control, to strengthen individuals' ability to deal with SLE-related fatigue and to attain a feeling of being in control.

Rheumatology key messages

- Women with SLE perceived fatigue as unpredictable, dominating and controlling.
- Individuals with SLE need advice, support and guidance to managing strategies of fatigue.

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References

1 Mendelson C. Managing a medically and socially complex life: women living with lupus. Qual Health Res 2006;16:982–97.

2 McElhone K, Abbott J, Teh LS. A review of health related quality of life in systemic lupus erythematosus. Lupus 2006;15:633–43.

3 Johnson SR, Glaman DD, Schentag CT, Lee P. Quality of life and functional status in systemic sclerosis compared to other rheumatic diseases. J Rheumatol 2006;33:1117–22.

4 Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? J Rheumatol 2005;32:1706–8.

5 McElhone K, Abbott J, Shelmerdine J *et al*. Development and validation of a disease-specific health-related quality of life measure, the lupusqol, for adults with systemic lupus erythematosus. Arthritis Rheum 2007;57:972–9.

6 Thumboo J, Strand V. Health-related quality of life in patients with systemic lupus erythematosus: an update. Ann Acad Med Singapore 2007;36:115–22.

7 Bruce IN, Mak VC, Hallett DC, Gladman DD, Urowitz MB. Factors associated with fatigue in patients with systemic lupus erythematosus. Ann Rheum Dis 1999;58:379–81.

8 Omdal R, Mellgren SI, Koldingsnes W, Jacobsen EA, Husby G. Fatigue in patients with systemic lupus erythematosus: lack of associations to serum cytokines, antiphospholipid antibodies, or other disease characteristics. J Rheumatol 2002;29:482–6.

9 Wang B, Gladman DD, Urowitz MB. Fatigue in lupus is not correlated with disease activity. J Rheumatol 1998;25:892–5.

10 Jump RL, Robinson ME, Armstrong AE, Barnes EV, Kilbourn KM, Richards HB. Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. J Rheumatol 2005;32:1699–705.

11 Flensner G, Ek AC, Soderhamn O. Lived experience of ms-related fatigue—a phenomenological interview study. Int J Nurs Stud 2003;40:707–17.

12 Moses N, Wiggers J, Nicholas C, Cockburn J. Prevalence and correlates of perceived unmet needs of person with systemic lupus erythematosus. Patient Educ Couns 2005;57:30–8.

13 Dzurec LC. Relationships as an inherent component in healthy women's fatigue. West J Nurs Res 2002;24:441–53.

14 Holley S. Cancer-related fatigue. Suffering a different fatigue. Cancer Pract 2000;8:87–95.
15 Bennett B, Goldstein D, Friedlander M, Hickie I, Lloyd A. The experience of cancer-related fatigue and chronic fatigue syndrome: a qualitative and comparative study. J Pain Symptom Manage 2007;34:126–35.
16 Stuifbergen AK, Rogers S. The experience of fatigue and strategies of self-care among persons with multiple sclerosis. Appl Nurs Res 1997;10:2–10.
17 Hewlett S, Cockshott Z, Byron M *et al*. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis Rheum 2005;53:697–702.
18 Tack BB. Fatigue in rheumatoid arthritis. Conditions, strategies, and consequences. Arthritis Care Res 1990;3: 65–70.
19 Repping-Wuts H, Uitterhoeve R, van Riel P, van Achterberg T. Fatigue as experienced by patients with rheumatoid arthritis (RA): a qualitative study. Int J Nurs Stud 2008;45:995–1002.
20 Piper BF. Instruments for clinical health-care research. In: Frank-Stromborg M, Olsen SJ, eds. Measuring fatigue. Sudbury: Jones and Bartlett, 2004.
21 Piper BF. Pathophysiological phenomena in nursing: human responses to illness. In: Carrieri-Kohlman V, Lindsey AM, West CM, eds. Fatigue. Philadelphia: WB Saunders, 1993:279–302.
22 Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
23 Vollmann J, Winau R. Informed consent in human experimentation before the Nuremberg code. Br Med J 1996;313:1445–9.
24 Liang MH, Socher SA, Larson MG, Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 1989;32:1107–18.
25 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. Arthritis Rheum 1992;35: 630–40.
26 Gladman D, Ginzler E, Goldsmith C *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
27 Kidd PS, Parshall MB. Getting the focus and the group: enhancing analytical rigor in focus group research. Qual Health Res 2000;10:293–308.
28 Krueger RA, Casey MA. Focus groups: a practical guide for applied research. 3rd edition. Thousand Oaks, CA: Sage, 2000.
29 Marshall NJ, Wilson G, Lapworth K, Kay LJ. Patients' perceptions of treatment with anti-TNF therapy for rheumatoid arthritis: a qualitative study. Rheumatology 2004;43:1034–8.
30 Persson LO, Karlsson J, Bengtsson C, Steen B, Sullivan M. The Swedish SF-36 health survey II. Evaluation of clinical validity: results from population studies of elderly and women in Gothenborg. J Clin Epidemiol 1998; 51:1095–103.
31 Belza BL, Henke CJ, Yelin EH, Epstein WV, Gilliss CL. Correlates of fatigue in older adults with rheumatoid arthritis. Nurs Res 1993;42:93–9.
32 Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today 2004;24: 105–12.
33 Sullivan M, Karlsson J, Taft C. SF-36 Hälsoenkät: svensk manual och tolkningsguide (Swedish manual and interpretation guide). 2nd edition. Gothenburg: Sahlgrenska University Hostpital, 2002.
34 Olsson M, Lexell J, Soderberg S. The meaning of fatigue for women with multiple sclerosis. J Adv Nurs 2005;49:7–15.
35 Paterson B, Canam C, Joachim G, Thorne S. Embedded assumptions in qualitative studies of fatigue. West J Nurs Res 2003;25:119–33.
36 Thumboo J, Fong KY, Chan SP *et al*. A prospective study of factors affecting quality of life in systemic lupus erythematosus. J Rheumatol 2000;27:1414–20.
37 Omdal R, Waterloo K, Koldingsnes W, Husby G, Mellgren SI. Fatigue in patients with systemic lupus erythematosus: the psychosocial aspects. J Rheumatol 2003;30:283–7.
38 Belza B. Clinical care in the rheumatic diseases. In: Bartlett SJ, Bringham CO, Maricic MJ, Iversen MD, Ruffing V, eds. Fatigue. Atlanta: Association of Rheumatolgy Health Professionals, 2006.

II

An exploration of patient-reported symptoms in systemic lupus erythematosus and the relationship to health-related quality of life

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Objective: The aim of this study was to explore the most distressing symptoms of systemic lupus erythematosus (SLE) and determine how these relate to health-related quality of life (HRQoL), anxiety/depression, patient demographics, and disease characteristics (duration, activity, organ damage).

Methods: In a cross-sectional study, patients with SLE (n = 324, age 18–84 years) gave written responses regarding which SLE-related symptoms they experienced as most difficult. Their responses were categorized. Within each category, patients reporting a specific symptom were compared with non-reporters and analysed for patient demographics, disease duration, and results from the following questionnaires: the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), the Hospital Anxiety and Depression Scale (HADS), the Systemic Lupus Activity Measure (SLAM), the SLE Disease Activity Index (SLEDAI), and the Systemic Lupus International Collaboration Clinics/American College of Rheumatology (SLICC/ACR) damage index.

Results: Twenty-three symptom categories were identified. Fatigue (51%), pain (50%), and musculoskeletal distress (46%) were most frequently reported. Compared with non-reporters, only patients reporting fatigue showed a statistically significant impact on both mental and physical components of HRQoL. Patients with no present symptoms (10%) had higher HRQoL ($p < 0.001$) and lower levels of depression ($p < 0.001$), anxiety ($p < 0.01$), and disease activity (SLAM) ($p < 0.001$).

Conclusion: Fatigue, pain, or musculoskeletal distress dominated the reported symptoms in approximately half of the patients. Only patients reporting fatigue scored lower on both mental and physical aspects of HRQoL. Our results emphasize the need for further support and interventions to ease the symptom load and improve HRQoL in patients with SLE. Our findings further indicate that this need is particularly urgent for patients with symptoms of pain or fatigue.

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with individual variation of organ involvement (e.g. skin, joints, kidneys, nervous system, and serous membranes) (1). Disease activity often varies over time and subjective symptoms are described as being prominent (2, 3). Both clinical care and research assessments are traditionally focused on predefined aspects of SLE (e.g. selected symptoms or aspects of disease impact) in which patients are asked to rate or assess different parameters according to chosen standards. When SLE disease activity and manifestation are assessed, the focus is often on objective signs and symptoms traditionally observed by physicians. There are, however, indications that several concepts of importance to patients (e.g. subjective symptoms) are not adequately captured by recommended measures of disease activity and health status (4, 5). This insight has contributed to today's recommendation to incorporate patient-reported outcomes in research (6) in an attempt to cover disease activity and impact more fully. In recent years a number of studies have sought to gain a better understanding of the aspects of living with SLE by involving the patient's perspective and thus identify variations in the experience of SLE and disease-related symptoms. One example of this approach is the development of a SLE Specific Symptom Checklist (7–9), in addition to other procedures used to identify disease-driven health issues identified by patients (10).

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To understand the consequences of patient-reported symptoms on disease impact, data from health-related quality of life (HRQoL) questionnaires can be used. HRQoL includes several dimensions, physical as well as psychological, and represents a broad perspective of the overall impact of disease. HRQoL is an important complement to measures of disease activity and damage (11–13). For instance, comparative studies have shown that patients with SLE perceive reduced HRQoL compared with controls and in parity with several other diseases (14–19).

How the broad spectrum of SLE symptoms affects patients' experience of HRQoL is not yet well understood. Different methods, such as focus groups and Delphi studies, have been used to capture aspects of SLE that are important to the patient (4, 20). Stamm et al (4) looked at whether important concepts of daily functioning per se are represented in the HRQoL and Bauernfeind et al (20) examined how important concepts could be identified by the International Classification of Function, Disability and Health (ICF). However, these studies did not explore whether these concepts represent differences in self-reported HRQoL.

To contribute to the understanding of patients' experience of SLE we aimed to explore the spontaneously most distressing symptoms of SLE and to determine how these symptoms relate to HRQoL, anxiety/depression, patient characteristics (age, partner status), and disease characteristics (duration, activity, and organ damage).

Patients and methods

The present study is part of an ongoing cohort project started in 2004 at Karolinska University Hospital Solna, where all patients with SLE have consecutively received an information letter and have been given the opportunity to participate. The patients gave their written consent in a reply-paid envelope. Patients included in the cohort study from January 2004 to March 2010 were consecutively and continuously included in the present study. All patients were aged $\geq$ 18 years, Swedish speaking and writing, and fulfilled the American College of Rheumatology (ACR) 1982 revised criteria for SLE ($\geq$ 4 ACR criteria) (21). Exclusion criteria were difficulties to read and write Swedish. The study was approved by the regional ethical review board.

At the study inclusion, the participants gave written answers to two open questions: 'What SLE-related symptoms have you experienced as most difficult during your disease?' and 'What symptoms do you presently perceive as most difficult?' The patients also completed self-assessment measures of HRQoL, anxiety, and depression. These self-assessments were followed by a physical examination, and an assessment of disease manifestations, activity, and organ damage, all of which were performed by a rheumatologist.

Self-assessment measures

The study used the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), a self-assessment questionnaire, to measure HRQoL (22). The 36 items of the SF-36 are divided into eight dimensions: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Each dimension is rated on a scale from 0 to 100, with high values representing better HRQoL. The eight domains can be divided into two summary scales, the mental component summary scale (MCS) and the physical component summary scale (PCS). The MCS is represented by VT, SF, RE, and MH and the PCS by PF, RP, BP, and GH. The SF-36 standard version representing health status for the past 4 weeks was used.

The Hospital Anxiety and Depression Scale (HADS) (23, 24) consists of 14 items, divided equally into two scales, an anxiety scale and a depression scale. The range for each scale is 0–21 and the cut-off for normal values is 7. According to the standard protocol, the respondents were asked to answer each item based on their feelings during the past week.

Disease-specific measures

At the inclusion visit the physicians performed all of the disease-specific assessments. Two frequently used instruments were used to assess disease activity: the Systemic Lupus Activity Measure (SLAM) (25, 26) and the SLE Disease Activity Index (SLEDAI) (27). The SLAM covers clinical symptoms during the past month, including laboratory parameters, organ manifestations, and some subjective symptoms such as fatigue and headache. It is divided into nine areas (score range 0–86, with high values representing a higher level of activity). The SLEDAI includes 24 items corresponding to nine organ systems (score range 0–105). We chose to use both of these instruments because of indications that the SLAM is more sensitive to changes important to patients (28) although the SLEDAI is more frequently used. To assess cumulative organ damage the Systemic Lupus International Collaboration Clinics/American College of Rheumatology (SLICC/ACR) damage index was used. This index includes 12 organ systems with scores ranging from 0 to 47 (29, 30).

Data analysis

The study used a mixed method approach involving data from free written answers and from the standardized questionnaires. The data collection of the written answers was inspired by the free-listing methods originally used in anthropology and also used and described in oncology in the collection of patient-reported symptoms from persons

with, for example, lung cancer (31). The method of using an open question was applied to capture spontaneous answers from the respondent.

The approach to processing the written answers from the open questions arose from an inductive procedure of the mixed method (31) and was conducted as follows. To increase the study's validity, independent researchers (LEE, ML, CM) with experience in qualitative methods in fields other than rheumatology were involved in the process of categorizing the patients' symptom descriptions. Using an inductive approach, the answers from the initial 200 respondents (i.e. the number of included patients at the time) were classified by the principal author (SP) according to content similarities. The inductive process and the result of 'groups of patient answers' were discussed between SP and the last author (EWH), resulting in a preliminary coding list. This list was tested and used by another author (LEE) as a pilot to categorize answers from the 300 first responders, followed by suggestions used to adjust and clarify distinctions between the codes. The adjusted coding list was discussed and revised by three of the authors (SP, ML, and EWH). Finally, SP, ML, and CM each coded 25% of the statements from the 320 consecutive respondents included in the project. Cohen's kappa was calculated and the majority of the coding categories had good to very good agreement (0.74–1.0). In four symptom categories agreement was moderate; these were all reported by only a few patients ($n \leq 6$) (32). Using the final coding list, SP coded all statements from the 320 respondents and four later included patients, giving a final number of 324 respondents.

The second of the two open questions referred to present time ('What symptoms do you presently perceive as most difficult?'). Because several parameters could possibly change over time, statements from this question were used when comparing the symptom categories with the patients' answers from the questionnaires. Two categories were excluded from the comparative analysis: allergy (not reported by any respondents as present at time of inclusion in the study) and discomfort (reported by one respondent as a current problem at inclusion). Wilcoxon's signed ranks test was applied to compare individual responses within each symptom category between the first and second open questions (symptom ever vs. present symptom).

To explore the symptom categories comparisons were conducted between reporters (patients with a written statement in a specific symptom category) and non-reporters (patients reporting any other symptom but not the specific symptom investigated) within the symptom categories using the Mann–Whitney U-test.

The collected quantitative data were mostly categorical, nominal, or ordinal and therefore non-parametric tests were used. Medians with interquartile ranges (IQRs) are presented for numerical data and percentage is used for frequency data. The quantitative data from the questionnaires were analysed using SPSS version 15 (SPSS Inc, Chicago IL, USA).

Results

Participants

This study included a total of 324 patients with SLE: median age 48 years (IQR 35–58), median disease duration 12 years (IQR 5–22), and median number of fulfilled SLE criteria 6 (IQR 5–7). Demographic variables are presented in Table 1 and the results from the self-assessments of HRQoL, anxiety, and depression are summarized in Table 2.

Patients' report of symptom distress

Twenty-three symptom categories were identified from the respondents' answers to the open questions (Table 3).

Table 1. Characteristics of patients with SLE (n = 324).

	%	Median	(IQR)	Range
Age (years)		48	(35–58)	18–84
Women	91			
Living with partner	57			
Disease duration (years)		12	(5–22)	0–58
SLE criteria		6	(5–7)	4–10
SLAM		6	(4–10)	0–27
SLEDAI		2	(0–6)	0–26
SLICC		1	(0–2)	0–10
Lupus manifestation				
Malar rash	54			
Discoid rash	19			
Photosensitivity	67			
Oral ulcers	34			
Arthritis	83			
Pleuritis	36			
Pericarditis	18			
Nephritis	40			
Neurology*	11			
Blood manifestation†	69			
Ongoing medication‡				
Chloroquine	32			
Cyclophosphamide p.o.	2			
Cyclophosphamide i.v.	11			
Azathioprine	19			
Methotrexate	4			
Mycofenolatmofetil	7			
Cyclosporin	2			
Rituximab (ever)	8			
Steroid dose (mg)		3.4	(0–7.5)	

SLAM, Systemic Lupus Activity Measure; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR, Systemic Lupus International Collaboration Clinics/American College of Rheumatology damage index; IQR, interquartile range.
*Psychosis or seizures.
†Leucopaenia, thrombocytopaenia, lymphopaenia, or haemolytic anaemia.
‡Ongoing treatment with disease-modifying anti-rheumatic drugs (DMARDs).

Table 2. Patients' self-assessment of health-related quality of life (HRQoL)*, anxiety, and depression (n = 324).

	Median	IQR
Physical Functioning (PF)*	75	50–90
Role Physical (RP)*	50	0–100
Bodily Pain (BP)*	52	41–84
General Health (GH)*	42	25–62
Vitality (VT)*	40	25–60
Social Functioning (SF)*	75	50–100
Role Emotional (RE)*	100	0–100
Mental Health (MH)*	72	52–84
Mental Component Summary (MCS)*	44	33–53
Physical Component Summary (PCS)*	39	29–50
HADS Depression	4	2–7
HADS Anxiety	6	3–9

HADS, Hospital Anxiety and Depression Scale (range 0–21, cut-off $\geq$ 7); IQR, interquartile range.
*Dimension and summary component from the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), scale 0–100.
MCS is represented by VT, SF, RE, and MH. PCS is represented by PF, RP, BP, and GH.

The three most frequently reported symptom categories were fatigue, pain, and musculoskeletal distress (Table 3). The median number of reported categories corresponding to the question of ever-present symptoms was 3 (IQR 2–4). The patients reported fewer ($p < 0.001$) symptom categories as being present at the time of study inclusion (median 2, IQR 1–3) compared with symptom categories reported as ever-present. A majority of the patients (n = 255, 78.7%) described at least one of the top three most frequently reported symptom categories (fatigue, pain, and musculoskeletal distress) as being an ever-present problem.

We investigated whether patients reported the same symptoms as present at the time of study inclusion and compared this with symptoms ever experienced (Table 3). In half of the symptom categories the respondents did not change their answer. In six categories (fatigue, pain, psychological/emotional, cognitive, reproduction, and sleeping disorder) > 45% of the respondents described the complaint as an ever-present distress and as one of the presently most distressing symptoms.

One-tenth of the patients stated that they perceived no present symptom at time of inclusion in the study.

Symptom distress compared with demographic data

Present symptoms were further evaluated by comparing patients who reported a specific symptom with patients who did not report a specific symptom. The reporters in

Table 3. Categories of patient-reported symptoms* related to SLE (n = 324). Symptoms reported as most difficult ever and compared with most difficult at the present time.

	Ever		Present		p-value†	
Category	n	(%)‡	n	(%)‡		% §
Missing/no answer	16	(4.9)	53	(16.4)		
Fatigue	165	(50.9)	124	(38.3)	0.058	64
Pain	162	(50.0)	104	(32.1)	< 0.001	49
Musculoskeletal	148	(45.7)	102	(31.5)	0.017	40
Skin, hair, or nails	77	(23.8)	39	(12.0)	0.001	33
Lungs	47	(14.5)	26	(8.0)	0.016	28
Eyes or mouth	38	(11.7)	23	(7.1)	0.074	40
Heart or circulation	34	(10.5)	18	(5.6)	0.194	15
Neurological distress	33	(10.2)	21	(6.5)	0.289	43
Kidney function	32	(9.9)	6	(1.9)	< 0.001	16
Swelling	28	(8.6)	10	(3.1)	0.001	25
Reduced physical capacity	28	(8.6)	16	(4.9)	0.008	29
Blood (cells/vessels)	24	(7.4)	5	(1.5)	< 0.001	17
Psychological/emotional distress	24	(7.4)	22	(6.8)	0.808	46
Fever	19	(5.9)	9	(2.8)	0.012	26
Infections	16	(4.9)	4	(1.2)	0.002	19
Cognitive distress	15	(4.6)	17	(5.2)	0.705	80
Treatment/examination	11	(3.4)	7	(2.2)	0.317	0
Gastrointestinal distress	11	(3.4)	6	(1.9)	0.527	9
Forced adaptation or dependence	9	(2.8)	8	(2.5)	0.317	11
Discomfort	8	(2.5)	1	(0.3)	1.000	13
Reproduction	5	(1.5)	3	(0.9)	0.157	60
Allergy	2	(0.6)	0	–	–	0
Sleeping disorder	2	(0.6)	5	(1.8)	1.000	50

*Analysis of answers from the two questions: ever: 'What SLE-related symptoms have you experienced as most difficult during your disease? present: 'What symptoms do you presently perceive as most difficult?'
†Wilcoxon's signed ranks test for change in answer.
‡Percentage of all patients.
§Percentage of patients reporting symptom distress as ever distressing as well as present distress.

Table 4. Present symptoms reported by patients with SLE (n = 324) and compared with patients' self-assessment of depression (HADS), anxiety (HADS), physicians' assessment of SLE activity (SLAM and SLEDAI), and organ damage (SLICC/ACR).

Category	HADS Depression	HADS Anxiety	SLAM	SLEDAI	SLICC/ACR
No present symptom†	**1.5*****	**4****	**3*****	2	**0***
Fatigue	**5*****	**6.5***	**7****	2	1
Pain	**5****	6	**7*****	**4****	1
Musculoskeletal	4	6	**7****	3	1
Neurological	**5***	7	6	2	1
Swelling	4.5	8	**8.5***	**7***	1
Reduced capacity	3.5	**1***	7	3	**3****
Blood (cells or vessels)	**1***	4	10.5	3.5	0
Psychological/emotional	**6.5****	**9.5****	**9****	2	1
Fever	5	5	**14*****	**6***	1
Cognitive	**7****	6	**10****	4	2
Sleeping	**13.0***	**10****	**15****	**9***	0

SLAM, Systemic Lupus Activity Measure; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR, Systemic Lupus International Collaboration Clinics/American College of Rheumatology damage index.
Median values from patient reporting a symptom compared with non-reporters of that symptom category. Only categories with statistically significant differences are shown. Significant differences between non-reporters and reporters within the category are shown in bold.
*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, Mann–Whitney U-test.
†Patients given a clear description of no SLE-related symptom at inclusion compared with patients reporting any symptom.

each symptom category were also compared in relation to age, disease duration, and partner status. Patients reporting cognitive distress at inclusion in the study had shorter disease duration (median 4 years, IQR 1–17, $p = 0.04$) than patients reporting other symptoms (median 12 years, IQR 5–21). Only three patients reported present problems with reproductive distress, all with a disease duration of < 1 year. The question of present symptoms was not answered (i.e. left blank) by 16.3% of the patients and was therefore analysed separately. Patients who did not answer the question regarding present SLE-related symptoms (n = 53) at inclusion had a longer disease duration (median 18 years, IQR 7.5–25.5) than patients reporting any SLE-related symptom (median 11 years, IQR 4.5–21, $p = 0.009$). There were no statistically significant differences in age or partner status within any of the symptom categories (data not shown).

Symptom distress compared with disease characteristics

The symptom categories were further analysed for disease activity, disease duration, and organ damage (Table 4). When comparing reporting patients with non-reporting patients within each symptom category (see data analysis), reporting patients in the categories fatigue, pain musculoskeletal, swelling, psychological/emotional, fever, cognitive distress, and sleeping had higher disease activity as measured by the SLAM. Only patients reporting reduced physical capacity had more extensive organ damage (SLICC/ACR, median = 3, IQR 0.5–5, $p = 0.008$) than those not reporting the corresponding symptom category (no reduced physical capacity: SLICC/ACR, median = 1, IQR 0–2). Patients who reported no present symptoms of SLE had lower disease activity (SLAM, median = 3, IQR 2–6, $p < 0.001$) and organ damage (SLICC/ACR, median = 0, IQR 0–1, $p < 0.05$) than patients reporting any kind of symptom (SLAM, median = 7, IQR 4–10; SLICC/ACR, median = 1, IQR 0–2), but no differences in disease duration.

Symptom distress compared with measurements of anxiety, depression, and HRQoL

Each category was subsequently compared with results from the anxiety, depression (Table 4), and HRQoL self-assessment questionnaires (Table 5 and supplementary data). Patients with present psychological/emotional distress had the highest anxiety levels (n = 22) (HADS anxiety median = 9.5, IQR 5.75–14) compared with those without psychological/emotional distress (HADS anxiety median = 6, IQR 3–9) ($p = 0.005$). In comparison with the patients reporting any symptom, the no-symptom patients showed higher HRQoL, less anxiety and less depression (Tables 4 and 5). The groups did not differ in age.

The three most frequently reported symptom categories (fatigue, pain, and musculoskeletal distress) were associated with reduced HRQoL (Table 5). Patients with fatigue reported significantly lower scores (meaning worse) in both MCS and PCS and higher scores (meaning worse) on the questionnaires measuring anxiety and depression. Patients reporting pain had lower scores on the PCS and more depression but not more anxiety. Patients in the symptom category musculoskeletal distress reported reduced PCS. Because fatigue and pain were symptoms that might interact, they were further analysed as subgroups, leaving out those patients who reported both fatigue and pain. The statistically significant differences between the subgroups were detected in the dimensions of bodily pain and vitality (supplementary

Table 5. Distress reported from patients with SLE at inclusion of study grouped by symptom category and compared with self-assessment of quality of life* (n = 324).

	MCS Median (IQR)	p-value†	PCS Median (IQR)	p-value†
No symptom‡	52 (46–56)	< **0.001**	54 (51–57)	< **0.001**
Fatigue	40 (25–48)	< **0.001**	37 (29–46)	**0.002**
Pain	43 (27–52)	0.187	34 (25–41)	< **0.001**
Musculoskeletal	43 (30–54)	0.850	34 (26–42)	< **0.001**
Skin/hair/nails	45 (32–51)	0.504	43 (31–52)	0.384
Lungs	47 (30–56)	0.547	33 (24–48)	**0.040**
Eyes/mouth	45 (31–55)	0.583	44 (32–52)	0.334
Heart or circulation	36 (26–47)	0.106	33 (27–43)	0.065
Neurological	33 (24–49)	**0.049**	36 (29–41)	0.139
Kidney	54§ (50–60)	**0.036**	36 (19–49)	0.561
Swelling	27 (23–51)	0.214	35 (26–41)	0.098
Reduced physical capacity	49 (28–60)	0.219	25 (15–36)	< **0.001**
Blood	52 (45–57)	0.103	46 (26–52)	0.821
Psychological/emotional	37 (24–43)	**0.005**	33 (30–49)	0.427
Fever	40 (34–48)	0.404	26 (18–32)	**0.001**
Infections	39 (14–51)	0.429	35 (20–43)	0.281
Cognitive	39 (25–44)	**0.033**	34 (30–42)	0.156
Treatment/examination	44 (30–55)	0.872	23 (15–27)	**0.009**
Gastrointestinal	41 (27–52)	0.716	38 (22–50)	0.695
Forced adaptation or dependence	31 (25–58)	0.733	36 (15–46)	0.244
Sleep	33 (18–38)	0.074	25 (14–44)	0.094

*Subscales of the SF-36: the Mental Component Scale (MCS) and the Physical Component Scale (PCS).
†Mann–Whitney U-test.
‡Patients given a clear description of no SLE-related symptoms at inclusion of the study compared with patients reporting any symptom. Symptom groups excluded from this table: discomfort (only one person), allergy (reported by none), and reproduction (only three respondents).
§Better HRQoL than non-reporters (other categories with statistically significant difference represent worse HRQoL than non-reporters).
Significant differences between non-reporters and reporters within the category are shown in bold. For numbers of patients reporting in each symptom category see the column 'Present' in Table 3.

data). Respondents reporting fatigue (n = 65) but not pain scored lower on vitality (p = 0.013) whereas respondents reporting pain (n = 45) but not fatigue scored lower on bodily pain (p = 0.003). Notable here is that lower levels on these domains indicate more or worse impact, meaning that the results from the questionnaires were congruent with the symptoms spontaneously reported by the patients.

Discussion

In the responses to the open-ended questions, more than 75% (n = 255) of the SLE patients reported fatigue, pain, or musculoskeletal distress as the most difficult symptoms. Only patients reporting fatigue scored lower on both mental and physical aspects of HRQoL. Other symptom categories showed a statistically significant impact on either the mental or the physical components of HRQoL. Of note, 10% of the patients reported that they perceived no SLE symptom at the time of study inclusion. This latter finding is consistent with the finding that these patients also had lower disease activity and higher HRQoL. In recent years there have been several improvements in the treatment of patients with SLE (33, 34), but the new therapies do not seem to have changed the fact that fatigue and pain are still perceived as the most distressing symptoms. Our results emphasize the need for further support and interventions to recognize and ease symptom load and thus improve the HRQoL of patients with SLE. Furthermore, the results indicate that the need is particularly urgent for patients with symptoms of pain or fatigue.

To the best of our knowledge this is the largest cohort study, to date, focusing on patients' self-report of SLE-related symptoms and providing us with data representing the heterogeneous variation of patient-reported distress. The results are based on data from only one cohort, which suggests caution concerning generalizability. However, the results from our study are strengthened by similarities to the symptoms identified in other studies (7, 20). In the study of Grootscholten et al, 89% of the patients reported fatigue, 61% painful joints, and 54% painful muscles (7). Their symptom category 'loss of concentration' (reported by 54%) has similarities to our category of cognitive distress (reported by 5%). Their results presented the highest scores for perceived burden of single symptoms related to fatigue but also to sensitivity to sunlight and disturbed memory. At least six of our categories were not clearly described in the lupus specific symptom checklist (7) (kidney function, reduced physical capacity, fever, infections, treatment/examination, forced adaptation, or

dependence). Stamm et al (4) used the World Health Organization (WHO) ICF as a framework to sort 'concepts of importance' collected from persons with SLE. The authors pointed out that environmental factors are not covered by standard measures suggested for SLE (35) and specifically mentioned medication to be an environmental factor. Our symptom category distress related to treatment/examination could be considered as such an environmental factor reported by patients as having a distressing impact. In future studies it would be informative to compare patients' reports of symptoms with nursing diagnostic terms (e.g. the North American Nursing Diagnosis Association, NANDA; www.nanda.org).

Patients reporting fatigue and pain in the present study scored lower than non-reporting patients on self-assessments of HRQoL. This finding is consistent with previous studies showing that pain and fatigue influenced HRQoL in patients with SLE (3, 36). Fatigue and pain are thus well-known symptoms that need more attention if we want to improve the care of patients with SLE. It is possible that we would have obtained similar results using SLE-specific instruments such as the SLEQOL or LupusQoL to assess HRQoL (37, 38) but at the time of data collection they were not available in Swedish. In addition, an approach using predefined answers would not have allowed us to explore spontaneous answers from the informants.

In clinical care as well as in research, attention must be paid to how questions are posed to patients. It was previously demonstrated that physicians only detect 62% of the most important health outcomes in SLE as reported by individual patients (39). Our approach with open questions without fixed answer alternatives reflects the patient's experiences of symptoms. This approach makes it possible to enlighten and detect problem areas neglected by physicians but crucial to the individual patient. A potential limitation of our study is that the results are dependent on how the respondents interpret the questions. Interpretations are based on the patients' knowledge, individual perception, and personal thoughts of their disease-related distress. A previous study has shown a discrepancy between patients' and physicians' selection of important health and symptom outcomes (39). This discrepancy has also been illustrated by the fact that even when physicians incorporate aspects of what patients tell them, a discrepancy is found between patients' and physicians' assessment of disease activity (40). When evaluating disease activity, patients are influenced by their psychological and physical well-being. Physicians, however, score disease activity based on the clinical and physical signs and symptoms of lupus (41, 42). It is important to note that some patient-reported symptoms are manifestations of active disease, and are therefore not surprisingly significantly associated with disease activity measures. To further explore patients' experience of symptom distress, physicians could be given the same possibility to answer an open question of the patients' most distressing symptom and compare this with the perceptions of the patients. In future studies it would also be valuable to follow symptom reports over time, using the procedure with an open question to allow detection of symptom change and distress over time, as well as to increase the possibility of uncovering symptoms reported by only a few patients.

To conclude, patients with SLE reported a multitude of distressing symptoms, many of which are not covered by present measures of disease activity. The three most frequently reported symptom categories (i.e. fatigue, pain, and musculoskeletal distress) were associated with lower HRQoL, but only patients reporting fatigue showed an impact on both mental and physical components of HRQoL. Notably, one-tenth of the patients reported that they did not perceive having present symptoms of SLE, and this group also had less disease activity and better HRQoL. We suggest that open questions should be used as a complement to standard measures of disease activity to facilitate communication and capture the patient's perspective of disease-related distress.

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References

1. Swaak AJG. Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. Rheumatology 1999;10:953–8.
2. Tench CM, McCurdie I, White PD, D'Cruz DP. The prevalence and associations of fatigue in systemic lupus erythematosus. Rheumatology (Oxford) 2000;11:1249–54.
3. McElhone K, Abbott J, Gray J, Williams A, Teh LS. Patient perspective of systemic lupus erythematosus in relation to health-related quality of life concepts: a qualitative study. Lupus 2010;14:1640–7.
4. Stamm TA, Bauernfeind B, Coenen M, Feierl E, Mathis M, Stucki G, et al. Concepts important to persons with systemic lupus erythematosus and their coverage by standard measures of disease activity and health status. Arthritis Rheum 2007;7:1287–95.
5. Haq I, Isenberg DA. How does one assess and monitor patients with systemic lupus erythematosus in daily clinical practice? Best Pract Res Clin Rheumatol 2002;2:181–94.
6. Kirwan JR, Newman S, Tugwell PS, Wells GA. Patient perspective on outcomes in rheumatology – a position paper for OMERACT 9. J Rheumatol 2009;9:2067–70.
7. Grootscholten C, Ligtenberg G, Derksen RH, Schreurs KM, de Glas-Vos JW, Hagen EC, et al. Health-related quality of life in patients with systemic lupus erythematosus: development and validation of a lupus specific symptom checklist. Qual Life Res 2003;6:635–44.
8. Freire EA, Guimaraes E, Maia I, Ciconelli RM. Systemic lupus erythematosus symptom checklist cross-cultural adaptation to Brazilian Portuguese language and reliability evaluation. Acta Reumatol Port 2007;4:341–4.

9. Grootscholten C, Snoek FJ, Bijl M, van Houwelingen HC, Derksen RH, Berden JH. Health-related quality of life and treatment burden in patients with proliferative lupus nephritis treated with cyclophosphamide or azathioprine/methylprednisolone in a randomized controlled trial. J Rheumatol 2007;8:1699–707.
10. Robinson D Jr, Aguilar D, Schoenwetter M, Dubois R, Russak S, Ramsey-Goldman R, et al. Impact of systemic lupus erythematosus on health, family, and work: the patient perspective. Arthritis Care Res (Hoboken) 2010;2:266–73.
11. Aggarwal R, Wilke CT, Pickard AS, Vats V, Mikolaitis R, Fogg L, et al. Psychometric properties of the EuroQol-5D and Short Form-6D in patients with systemic lupus erythematosus. J Rheumatol 2009;6:1209–16.
12. Kiani AN, Petri M. Quality-of-life measurements versus disease activity in systemic lupus erythematosus. Curr Rheumatol Rep 2010;4:250–8.
13. Yee CS, McElhone K, Teh LS, Gordon C. Assessment of disease activity and quality of life in systemic lupus erythematosus – new aspects. Best Pract Res Clin Rheumatol 2009;4:457–67.
14. McElhone K, Abbott J, Teh LS. A review of health related quality of life in systemic lupus erythematosus. Lupus 2006;10:633–43.
15. Wolfe F, Michaud K, Li T, Katz RS. EQ-5D and SF-36 quality of life measures in systemic lupus erythematosus: comparisons with rheumatoid arthritis, noninflammatory rheumatic disorders, and fibromyalgia. J Rheumatol 2010;2:296–304.
16. Da Costa D, Dobkin PL, Fitzcharles MA, Fortin PR, Beaulieu A, Zummer M, et al. Determinants of health status in fibromyalgia: a comparative study with systemic lupus erythematosus. J Rheumatol 2000;2:365–72.
17. Gilboe IM, Kvien TK, Husby G. Health status in systemic lupus erythematosus compared to rheumatoid arthritis and healthy controls. J Rheumatol 1999;8:1694–700.
18. Almehed K, Carlsten H, Forsblad-d'Elia H. Health-related quality of life in systemic lupus erythematosus and its association with disease and work disability. Scand J Rheumatol 2010;1:58–62.
19. Mok CC, Ho LY, Cheung MY, Yu KL, To CH. Effect of disease activity and damage on quality of life in patients with systemic lupus erythematosus: a 2-year prospective study. Scand J Rheumatol 2009;2:121–7.
20. Bauernfeind B, Aringer M, Prodinger B, Kirchberger I, Machold K, Smolen J, et al. Identification of relevant concepts of functioning in daily life in people with systemic lupus erythematosus: a patient Delphi exercise. Arthritis Rheum 2009;1:21–8.
21. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;11:1271–7.
22. Persson LO, Karlsson J, Bengtsson C, Steen B, Sullivan M. The Swedish SF-36 Health Survey II. Evaluation of clinical validity: results from population studies of elderly and women in Gothenborg. J Clin Epidemiol 1998;11:1095–103.
23. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;2:69–77.
24. Lisspers J, Nygren A, Soderman E. Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample. Acta Psychiatr Scand 1997;4:281–6.
25. Liang MH, Socher SA, Roberts WN, Esdaile JM. Measurement of systemic lupus erythematosus activity in clinical research. Arthritis Rheum 1988;7:817–25.
26. Liang MH, Socher SA, Larson MG, Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 1989;9:1107–18.
27. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;6:630–40.
28. Chang E, Abrahamowicz M, Ferland D, Fortin PR. Comparison of the responsiveness of lupus disease activity measures to changes in systemic lupus erythematosus activity relevant to patients and physicians. J Clin Epidemiol 2002;5:488–97.
29. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;3:363–9.
30. Gladman DD, Urowitz MB, Goldsmith CH, Fortin P, Ginzler E, Gordon C, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997;5:809–13.
31. Tishelman C, Lovgren M, Broberger E, Hamberg K, Sprangers MA. Are the most distressing concerns of patients with inoperable lung cancer adequately assessed? A mixed-methods analysis. J Clin Oncol 2010;11:1942–9.
32. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. Br Med J 1992;6840:1491–4.
33. Gunnarsson I, van Vollenhoven RF. Biologicals for the treatment of systemic lupus erythematosus? Ann Med. Published online 15 April 2011. doi:10.3109/07853890.2011.561362.
34. Kalunian K, Joan TM. New directions in the treatment of systemic lupus erythematosus. Curr Med Res Opin 2009;6:1501–14.
35. Strand V, Gladman D, Isenberg D, Petri M, Smolen J, Tugwell P. Endpoints: consensus recommendations from OMERACT IV. Outcome Measures in Rheumatology. Lupus 2000;5: 322–7.
36. Thumboo J, Strand V. Health-related quality of life in patients with systemic lupus erythematosus: an update. Ann Acad Med Singapore 2007;2:115–22.
37. Leong KP, Kong KO, Thong BY, Koh ET, Lian TY, Teh CL, et al. Development and preliminary validation of a systemic lupus erythematosus-specific quality-of-life instrument (SLEQOL). Rheumatology (Oxford) 2005;10:1267–76.
38. McElhone K, Abbott J, Shelmerdine J, Bruce IN, Ahmad Y, Gordon C, et al. Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus. Arthritis Rheum 2007;6:972–9.
39. Kwoh CK, Ibrahim SA. Rheumatology patient and physician concordance with respect to important health and symptom status outcomes. Arthritis Rheum 2001;4:372–7.
40. Leong KP, Chong EY, Kong KO, Chan SP, Thong BY, Lian TY, et al. Discordant assessment of lupus activity between patients and their physicians: the Singapore experience. Lupus 2010;1:100–6.
41. Yen JC, Abrahamowicz M, Dobkin PL, Clarke AE, Battista RN, Fortin PR. Determinants of discordance between patients and physicians in their assessment of lupus disease activity. J Rheumatol 2003;9:1967–76.
42. Neville C, Clarke AE, Joseph L, Belisle P, Ferland D, Fortin PR. Learning from discordance in patient and physician global assessments of systemic lupus erythematosus disease activity. J Rheumatol 2000;3:675–9.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table

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Supplementary material: Distress reported from patients with SLE at inclusion of study grouped by symptom category and compared with self-assessment of quality of life† (n = 324).

Category	PF	RP	BP	GH	VT	SF	RE	MH
No symptom‡	**95*****	**100*****	**100*****	**77*****	**70*****	**100*****	**100*****	**84*****
No answer§	65	50	51	40	40	62.5	100	72
Fatigue	**70****	**25*****	**47****	**37*****	**30*****	**50*****	**50*****	**64*****
Pain	**65*****	**25*****	**41*****	**34*****	**35*****	**63*****	67	**64***
Musculoskeletal	**65*****	**25*****	**41*****	**35****	40	**63***	66.7	68
Skin/hair/nails	80	50	52	45	45	75	100	72
Lungs	58	25	41	**33***	40	56	67	72
Eyes or mouth	85	87.5	62	45	50	75	100	72
Heart/circulation	70	**0***	**41***	**30***	30	**38****	33	60
Neurological	70	**12.5***	**41***	37	40	**50****	**0***	60
Kidney	80	33	74	17	45	88	100	84
Swelling	70	25	**41***	30	40	**4***	0	56
Reduced physical capacity	**35*****	**0***	**31****	**30***	20	50	100	52
Blood cells or vessels	85	50	84	67	60	100	100	***92**
Psychological or emotional distress	65	13	51	37	33	**38****	**33***	**50****
Fever	**60***	**0****	**31****	**27***	**15****	**25****	67	60
Infection	63	13	48	28	35	**25***	50	76
Cognitive distress	65	13	41	40	**25****	50	**33***	**60***
Distress related to treatment or examination	**25****	0	31	25	40	62.5	100	64
Gastrointestinal distress	**60***	0	36.5	42	33	38	0	78
Forced adaptation or dependence	60	25	**22***	42	**23***	63	67	42
Sleeping disorder	35	12.5	0	15	10	13	**0***	**40***

†Dimensions of SF-36: PF = Physical functioning, RP = Role Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Functioning, RE = Role Emotional, MH = Mental Health. Reported as median value per symptom group.
‡Patients given a clear description of no SLE-related symptom at inclusion of the study compared with patients reporting any symptom.
§Patients did not answer the question of SLE-related symptom distress compared with patients reporting any symptom distress.
Significant differences between non-reporters and reporters within the category are shown in bold.
*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, Mann–Whitney U-test.
Symptom groups excluded from this table: discomfort (only one person), allergy (reported by none), and reproduction (only three respondents).

III

Determination of the Minimal Clinically Important Difference for Seven Measures of Fatigue in Swedish Patients with Systemic Lupus Erythematosus

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ABSTRACT

Objective. The objective of this study was to estimate the minimal clinically important difference (MCID) of seven self-administered measures assessing fatigue in persons with systemic lupus erythematosus (SLE).

Methods. The respondents (n=51, women 98%, age 52.8 ± 12.1 years, disease duration 18.7 ± 13.6 years) met in group sessions of six to nine participants each. After initial self-assessment with the seven fatigue questionnaires (Chalder Fatigue Scale, Vitality scale from SF-36, Fatigue Severity Scale, Multidimensional Assessment of Fatigue, Multidimensional Fatigue Inventory, Functional Assessment of Chronic Illness Therapy – Fatigue, and a single numeric rating scale), each respondent had a minimum of five face-to-face discussions, all followed by an individual comparative assessment of his or her own level of fatigue (7-grade scale). This method resulted in 260 contrasting assessments; MCIDs were first calculated using the paired differences and then established by a regression approach. Patients were offered the opportunity to provide additional free comments regarding the questionnaires.

Results. The paired approach (using "little more fatigue" as an anchor for MCID during the face-to-face comparative assessments) provided estimates of 4.6–17.0; the regression approach provided estimates of 4.25–10.75. Estimates using the regression approach were consistently lower than those using the paired model. The MCID estimates were least favourable for the single numeric rating scale. Fewer respondents supported the use of the single-question measure compared to the other self-reported questionnaires.

Conclusions. Based on our results, we determined that all seven instruments detect clinically important differences of fatigue in Swedish patients with SLE. However, the single-question measure was not supported by the MCID estimates or by comments from the respondents.

Keywords: systemic lupus erythematosus, fatigue, self-assessment, MCID

INTRODUCTION

Fatigue is a major and disabling symptom of many diseases, and over the past two decades, there has been a major interest in the patients' experiences, as well as how to measure and manage fatigue in various systemic rheumatic conditions [1-3]. Fatigue is an individual and subjective sensation; therefore, its impact on an individual's life can be difficult for others to understand [2, 4]. Using psychometrically standardised questionnaires to quantify fatigue and to capture its qualities as they apply to each individual advances its study [5]. As fatigue is an important outcome, it is crucial that the measure be able to detect changes in the state ("sensitivity"), and that these changes are clinically important differences ("responsive") [6-8]. A clinically important difference is described as a change that would be considered meaningful by a patient, and a minimal clinically important difference (MCID) is the smallest change that is important to patients' outcomes [9, 10]. One approach used to calculate MCID is anchor-based, where a global assessment is applied as the anchor, and a "within-patient" score or a "between-patients" score is computed [10].

An international expert panel of clinicians and trials methodologists reviewed 34 studies and the 15 published instruments with documented psychometric properties in the assessment of fatigue in patients with systemic lupus erythematosus (SLE) [1]. The panel noted that responsiveness to change in fatigue had not been well established and needed further study, and that the Fatigue Severity Scale (FSS) should be used in future studies of fatigue in SLE, based on the frequency of use and other considerations.

The majority of studies on fatigue and its measurement are performed in English-speaking countries, which led us to explore whether the results reflect patients' experience with fatigue in Scandinavia. The aim of our study was to identify the smallest difference in score in the domain of fatigue that patients perceive as beneficial, by estimating the MCID of seven self-administered measures of fatigue in persons with SLE.

PATIENTS AND METHODS

The participants were recruited from an ongoing SLE cohort project in the rheumatology clinic at Karolinska University Hospital, with adults fulfilling ≥4 American College of Rheumatology criteria for SLE [11] (n=290). Exclusion criteria were non-Swedish-speaking persons, age >75 years, having moved from the county, and currently hospitalized, leaving 186 persons. An information letter and invitation to participate were mailed to the patients, along with a pre-paid, self-addressed consent letter. The response rate was 73%, of which half accepted the offer to participate (n=68). The study was approved by the regional ethics committee (Ethical approval, Dr 03-556 + 2008/887-32).

The design closely follows a study of US and Canadian subjects [12]. A total of 51 persons had the opportunity to attend any of the seven group sessions, each with six to nine participants. Each of the groups met once, and after an initial presentation of the study objective, the respondents completed self-assessments, using the seven fatigue questionnaires, as well as a patient self-assessment of SLE activity during the previous week, using the Systemic Lupus Activity Questionnaire (SLAQ) [13, 14]. Then, the respondents paired with another person in separate rooms, where they had a ten-minute, one-on-one discussion on their experiences with fatigue. This dialogue was followed by an individual assessment of each patient's own fatigue, compared on a 7-grade scale to that of his or her dialogue partner. This procedure continued until each respondent had at least five separate one-on-one discussions, each followed by an individual comparative assessment of his or her own level of fatigue (Figure 1).

Self-assessment of fatigue

This study uses the seven fatigue assessment questionnaires recommended by an expert committee [12]. To compare the instruments, the participants were asked to consider fatigue and its consequences during the previous week when responding to all questionnaires. The Short Form-36 (SF-36) includes 36 items that explore eight different dimensions of quality of life, each with a sub-scale score of 0–100 (negative scoring): physical functioning (PF), role physical (RP), bodily pain (BP), general health

(GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH) [15-17]. The VT subscale represents fatigue, and it is based on four of the 36 items. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) is a 13-item questionnaire with five Likert-type response choices for each question; the total score range is 0–52 (negative scoring) [18-20]. The remaining five self-assessments used in this study have positive scoring (i.e. high values indicate high degree of fatigue). The numeric rating scale (NRS) for fatigue is one single question with numeric answers (scale 0–10). The Fatigue Severity Scale (FSS) [21, 22] is a nine-item scale, with each item scored on a 1–7 scale and a total score range of 7–63. The Multidimensional Fatigue Inventory (MFI-20) [23] is a 20-item questionnaire with five subscales, for a total score range of 20–100 [24, 25]. The Chalder Fatigue Scale (CFS) [26] includes 11 items that assess physical fatigue (seven items) and mental fatigue (four items). In this study, we adopted a Likert system (0, 1, 2, 3) for the CFS, giving a total score range of 0–33. The Multidimensional Assessment of Fatigue scale (MAF) is a 16-item scale [27-29] with a total score range of 1–50.

Disease activity

All patients in this study had previously been medically assessed by a rheumatologist, who verified the SLE diagnosis, and they were included in a hospital-based cohort registry; disease duration for each patient was obtained from this registry.

The SLAQ, based on the Systemic Lupus Activity Measure (SLAM) [30, 31] and developed as a tool to screen for possible disease flares, has been shown to detect clinically significant disease activity [13, 14]. The SLAQ includes 24 questions related to disease activity, one question on patient global assessment of severity of lupus flares (0–3 range), and one numerical rating scale for patient assessment of global disease activity (0–10 range). The SLAQ has been used in several studies [32-34] and was completed by the patients in this study.

Data analysis

The procedures used in this study closely followed the research protocols used by Goligher et al and Pouchot et al [12, 35], based on sample size requirements from Brant

et al. [36]. Each instrument was scored according to its original instructions; however, the fatigue scores were normalised to a scale of 0–100, with 100 being the most severe fatigue. The paired differences between the dialogue partners' scores were stratified into seven groups, based on the patients' self-estimation after each dialogue; in the Results section, these are called "contrasting groups". As recommended by Pouchot et al. [35], the mean differences were standardised and adjusted by subtracting the mean difference for "about the same" in order to estimate the MCID for "a little more" and "a little less" fatigue. The standardisation was based on the assumption that the mean difference between the dialogue partners in the group "about the same" ought to be null. The MCIDs were established using a regression approach wherein the individual fatigue scores were used as predictors in a regression model for each instrument. This method is based on the assumption that relative degree of difference between the comparative groups was roughly equal [36]. The MCID and its statistical significance were then calculated using the slope of the regression line.

A t-test was used to compare our data with data from Goligher et al. [12]. Pearson's correlation coefficient was used to study the association among each of the seven fatigue scores, global assessment of disease activity, and SLAQ score. The descriptive statistical analyses and the paired approach were calculated using the Statistical Package for the Social Sciences version 15 (SPSS, Chicago, IL, USA) and 19 (IBM Corporation, Somers, NY, USA). PROC MIXED in SAS 9.2 (SAS Institute Inc., Cary, NC, USA) were used for the estimates in the regression model.

RESULTS

Participants

The seven sessions included 51participants; all except one were women, the age range was 52.8 ± 12.1 years, and the disease duration range was 18.7 ± 13.6 years. Patient characteristics and raw scores of fatigue for the seven instruments are presented in Table 1. Correlations between the raw fatigue scores for the seven questionnaires and the patients' global assessment of disease activity varied between 0.42 ($p<0.01$) and 0.64 ($p<0.001$) and were considered fair to moderate [37]. The self-reported disease

activity (SLAQ) and fatigue correlations of the patients varied between 0.50 and 0.56 ($p<0.001$ for all) (data not shown). No correlations were found between fatigue and age ($r = -0.13–0.06$) or disease duration ($r = -0.11–0.01$).

Patient pairs comparison of fatigue

The above exercise resulted in 260 contrasting assessments (Table 1 and Figure 1). After normalisation of the results of the seven measures to a score of 0–100, the mean differences in fatigue between pairs of dialogue partners were calculated for each of the seven questionnaires. The results from the contrast groups are displayed in Table 2. For most instruments, the mean paired difference followed a slope of increasing fatigue compared to the neighbouring contrast group. However, for the MFI-20, patients scoring "much more fatigue" had lower means than patients scoring "somewhat more fatigue", as illustrated in Figure 2. The mean paired difference for the patients scoring "about the same fatigue" ranged from 1.4 for the CFS fatigue scale to 3.4 for the FACIT-F (Table 2).

As described in the Methods section, the means for the "about the same" groups were used to standardise the estimates. Except for the CFS, the estimates for the MCID relative to ''little *less* fatigue'' tended to be smaller than those for ''little *more* fatigue''. The standardised mean paired differences in the seven instruments for the "little more fatigue" group varied from 4.6 for the CFS to 17.0 for the FSS. The contrast group "little less fatigue" had adequately negative values, meaning lower levels of fatigue, and ranged from -16.0 for the MFI-20 to -3.1 for the NRS (Table 3).

The results from estimates for MCID using the regression model are presented in Table 4. The coefficient from the regression model varied from 4.25 for the CFS to 10.75 for the FSS. The two questionnaires (NRS and CFS) with the lowest coefficient had standardized MCIDs under 0.3, and all others had MCIDs of 0.4 or slightly above. The estimates in the regression approach were consistently lower than in the descriptive paired approach, and NRS and CFS, having the lowest coefficients, showed the smallest difference between models.

Free comments from the respondents

Participants were encouraged to provide written comments regarding their experience with the exercise and whether any of the instruments were better or worse in mirroring their own experiences with fatigue. Most of the participants (76%) provided their opinions (Supplementary Data). The only questionnaire with no favourable comments was NRS. The most favourable responses were given to CFS and to FSS, to which 14 of the 51 respondents (28%) gave positive comments. Interestingly, CFS was also the single instrument with the most negative comments (from six respondents, 12%). Four questionnaires (FACIT-F, FSS, VT, and NRS) were given only one negative comment each, from four different respondents. The participants also pointed out that although the questionnaires often included aspects of physical activity, they lacked questions regarding the impact of sleep, which they felt was important and related to fatigue.

DISCUSSION

The central importance of inpatient-oriented fatigue outcome research and patient care, as well as involving patients in operationalising the definition of clinically important changes, has been long recognised in inflammatory rheumatic conditions [38, 39]. For research purposes, outcome measures should have optimal psychometric properties [6-8, 40, 41]. However, in order to reflect patient concerns, their ability to detect a clinically meaningful difference is essential, thus making work on defining the MCID important for translational research. In research on fatigue, the MCID should not be assumed to be a fixed property between groups of patients; this concept provides the reasoning underlying our study.

This study resulted in 260 contrasting assessments, utilising the anchor-based approach for estimates of MCID. The anchor is either a “within-patient” score or “between-patients” score [10]; in this study, a between-patients perspective was used to estimate MCID [12, 35]. Critics of the approach [42] point out that the threshold for a significant group change could be different from the threshold for change in the individual patient’s score. The levels of fatigue in the present study were comparable to or lower than previously indicated in other studies involving patients with SLE [4, 20, 25, 43-45]; the comparisons in this study were fairly analogous to the results reported by Goligher et al.

[12]. However, our Swedish patients were older, had their disease longer, and experienced lower disease activity. In addition, the fatigue scores were significantly lower on two of the seven questionnaires—FSS (our study: mean 4.5 ±1.6; Goligher et al.: mean 5.3 ± 1.5, p=0.001) and FACIT-F (our study: mean 30.1 ±11.9; Goligher et al.: mean 25.7 ±12.0, p=0.011). In our study, the correlations between disease activity and fatigue were fair to moderate. We confirmed no associations between fatigue and age or disease duration [12]. In our paired approach, the scales showed a positive slope, with increasing values for higher degree of fatigue. It is worth mentioning that some peripheral values had a tendency to be "out of order" (e.g. the contrast group representing "much more fatigue" seemed to be lower than the group "somewhat more" for the MFI-20 questionnaire, and the group "somewhat less fatigue" seemed to be lower than "much less fatigue" for the NRS). To conclude the comparison, our results were consistent with previous results [12].

The open-ended comments from our respondents regarding the questionnaires were meant as a probe for future work in the area and for assessing whether the current recommended questionnaires truly capture patients' experiences with fatigue. One new insight emerged: while the effect of fatigue on physical activity was elicited, its effect on pain or sleep was not.

When estimating MCID, several aspects might influence the result. The information derived from questionnaires is ultimately dependent on the questions asked, and the answers will reflect the respondents' interpretation of the intent of the questions, their experiences with fatigue, and their opinion of what fatigue is [46]. There are no standard or ideal techniques for establishing MCID, and the paired technique approach used in this study has inherent methodological limitations, such as lack of statistical independence between data points and self-reference bias [12](9). However, the results are also a benchmark that can be used to estimate effects in clinical trials and benefits for clinical interventions [10, 12].

The standardised MCID is useful for comparing sensitivity of questionnaires [12]. Most of our questionnaires showed similar properties; the data indicate that NRS and CFS

might be the two questionnaires with the least advantageous MCID for assessing fatigue in SLE. The use of a single question, such as NRS, is easy to use and has previously been shown to be sensitive to change and comparable to longer questionnaires [47]. A single question is practical when screening or monitoring large populations; however, our results do not support the use of a single question by MCID estimates or by the open-ended comments from the participants.

Conclusion

The question is no longer whether or not to include measures of fatigue into the agenda of SLE assessments, but how we should incorporate this important aspect. How to interpret the results is not yet conclusive. Our results indicated that the instruments perform similarly in Swedish patients and that the NRS is the least suitable for the regression model, although the distance between responses from patients who perceived their fatigue lower than their dialogue partners tended to vary more than those of respondents who reported their fatigue as the same as or higher than their dialogue partners. This might be due to the number of respondents and because a single question might result in greater individual variation in the interpretation of the impact of fatigue than questionnaires with more specified questions [48]. The patients' free comments regarding the ability of the questionnaires to capture their experiences with fatigue did not seem to support the use of NRS.

Key message

The seven fatigue questionnaires had similar results, and all seemed able to detect differences in Swedish persons with SLE.
The use of a single-question measure showed the fewest advantages for estimates of MCID for fatigue.
Patients' free comments did not support the use of a single-question measure to assess fatigue.

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REFEFERENCES

1. Avina-Zubeieta A, A.G., Bischoff Ferrari HA, Fischer R, Gall V, Illei G, Liang MH, Mikdashi J, Petri M, Phillips C, Pouchot J, Schneider M, Schur P, St Clair W. (Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue), *Measurement of fatigue in systemic lupus erythematosus: a systematic review.* Arthritis Rheum, 2007. **57**(8): p. 1348-57.
2. Pettersson, S., et al., *Women's experience of SLE-related fatigue: a focus group interview study.* Rheumatology (Oxford), 2010. **49**(10): p. 1935-42.
3. Pettersson, S., et al., *An exploration of patient-reported symptoms in systemic lupus erythematosus and the relationship to health-related quality of life.* Scand J Rheumatol, 2012.
4. Jump, R.L., et al., *Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support.* J Rheumatol, 2005. **32**(9): p. 1699-705.
5. Rasker, J.J., *The enigma of fatigue.* J Rheumatol, 2009. **36**(12): p. 2630-2.
6. Liang, M.H., *Longitudinal construct validity: establishment of clinical meaning in patient evaluative instruments.* Med Care, 2000. **38**(9 Suppl): p. II84-90.
7. Liang, M.H., et al., *Measuring clinically important changes with patient-oriented questionnaires.* Med Care, 2002. **40**(4 Suppl): p. II45-51.
8. Lehman, A. and M. Liang, *Health Status Measurement, assessing meaningful change*, in *Encyclopedia of medical decision making*, M.W. Kattan and M.E. Cowen, Editors. 2009, SAGE Publications: Thousand Oaks, Calif. p. 556-560.
9. Jaeschke, R., J. Singer, and G.H. Guyatt, *Measurement of health status. Ascertaining the minimal clinically important difference.* Control Clin Trials, 1989. **10**(4): p. 407-15.
10. Copay, A.G., et al., *Understanding the minimum clinically important difference: a review of concepts and methods.* Spine J, 2007. **7**(5): p. 541-6.
11. Tan, E.M., et al., *The 1982 revised criteria for the classification of systemic lupus erythematosus.* Arthritis Rheum, 1982. **25**(11): p. 1271-7.
12. Goligher, E.C., et al., *Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus.* J Rheumatol, 2008. **35**(4): p. 635-42.
13. Karlson, E.W., et al., *Validation of a Systemic Lupus Activity Questionnaire (SLAQ) for population studies.* Lupus, 2003. **12**(4): p. 280-6.
14. Yazdany, J., et al., *Validation of the systemic lupus erythematosus activity questionnaire in a large observational cohort.* Arthritis Rheum, 2008. **59**(1): p. 136-43.
15. Sullivan, M., J. Karlsson, and J.E. Ware, Jr., *The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden.* Soc Sci Med, 1995. **41**(10): p. 1349-58.
16. Persson, L.O., et al., *The Swedish SF-36 Health Survey II. Evaluation of clinical validity: results from population studies of elderly and women in Gothenborg.* J Clin Epidemiol, 1998. **51**(11): p. 1095-103.
17. Sullivan, M. and J. Karlsson, *The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population.* J Clin Epidemiol, 1998. **51**(11): p. 1105-13.

18. Cella, D., et al., *Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis.* J Rheumatol, 2005. **32**(5): p. 811-9.
19. Hagell, P., et al., *Measuring fatigue in Parkinson's disease: a psychometric study of two brief generic fatigue questionnaires.* J Pain Symptom Manage, 2006. **32**(5): p. 420-32.
20. Lai, J.S., et al., *Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial.* J Rheumatol, 2011. **38**(4): p. 672-9.
21. Krupp, L.B., et al., *The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus.* Arch Neurol, 1989. **46**(10): p. 1121-3.
22. Mattsson, M., et al., *Reliability and validity of the Fatigue Severity Scale in Swedish for patients with systemic lupus erythematosus.* Scand J Rheumatol, 2008. **37**(4): p. 269-77.
23. Smets, E.M., et al., *The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue.* J Psychosom Res, 1995. **39**(3): p. 315-25.
24. Furst, C.J. and E. Ahsberg, *Dimensions of fatigue during radiotherapy. An application of the Multidimensional Fatigue Inventory.* Support Care Cancer, 2001. **9**(5): p. 355-60.
25. Da Costa, D., et al., *Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioral and psychosocial factors.* J Rheumatol, 2006. **33**(7): p. 1282-8.
26. Chalder, T., et al., *Development of a fatigue scale.* J Psychosom Res, 1993. **37**(2): p. 147-53.
27. Belza, B.L., *Comparison of self-reported fatigue in rheumatoid arthritis and controls.* J Rheumatol, 1995. **22**(4): p. 639-43.
28. Sohng, K.Y., *Effects of a self-management course for patients with systemic lupus erythematosus.* J Adv Nurs, 2003. **42**(5): p. 479-86.
29. Sandqvist, G., et al., *The Swedish version of the Multidimensional Assessment of Fatigue (MAF) in systemic sclerosis: reproducibility and correlations to other fatigue instruments.* Scand J Rheumatol, 2011. **40**(6): p. 493-4.
30. Liang, M.H., et al., *Measurement of systemic lupus erythematosus activity in clinical research.* Arthritis Rheum, 1988. **31**(7): p. 817-25.
31. Liang, M.H., et al., *Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus.* Arthritis Rheum, 1989. **32**(9): p. 1107-18.
32. Costenbader, K.H., et al., *Barriers to a trial of atherosclerosis prevention in systemic lupus erythematosus.* Arthritis Rheum, 2005. **53**(5): p. 718-23.
33. Lee, C., et al., *Disease damage and low bone mineral density: an analysis of women with systemic lupus erythematosus ever and never receiving corticosteroids.* Rheumatology (Oxford), 2006. **45**(1): p. 53-60.
34. Trupin, L., et al., *The role of neighborhood and individual socioeconomic status in outcomes of systemic lupus erythematosus.* J Rheumatol, 2008. **35**(9): p. 1782-8.

35. Pouchot, J., et al., *Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis.* J Clin Epidemiol, 2008. **61**(7): p. 705-13.
36. Brant, R., L. Sutherland, and R. Hilsden, *Examining the minimum important difference.* Stat Med, 1999. **18**(19): p. 2593-603.
37. Colton, T., *Statistics in medicine*. 1st ed. 1974, Boston: Little, Brown. xii, 372 p.
38. Kirwan, J., et al., *Outcomes from the Patient Perspective Workshop at OMERACT 6.* J Rheumatol, 2003. **30**(4): p. 868-72.
39. Kirwan, J.R., et al., *Patient perspective on outcomes in rheumatology -- a position paper for OMERACT 9.* J Rheumatol, 2009. **36**(9): p. 2067-70.
40. Boers, M., et al., *The OMERACT filter for Outcome Measures in Rheumatology.* J Rheumatol, 1998. **25**(2): p. 198-9.
41. Tugwell, P., et al., *OMERACT: an international initiative to improve outcome measurement in rheumatology.* Trials, 2007. **8**: p. 38.
42. Wyrwich, K.W. and F.D. Wolinsky, *Identifying meaningful intra-individual change standards for health-related quality of life measures.* J Eval Clin Pract, 2000. **6**(1): p. 39-49.
43. Bruce, I.N., et al., *Factors associated with fatigue in patients with systemic lupus erythematosus.* Ann Rheum Dis, 1999. **58**(6): p. 379-81.
44. Omdal, R., et al., *Fatigue in patients with systemic lupus erythematosus: lack of associations to serum cytokines, antiphospholipid antibodies, or other disease characteristics.* J Rheumatol, 2002. **29**(3): p. 482-6.
45. Tench, C., et al., *Aerobic fitness, fatigue, and physical disability in systemic lupus erythematosus.* J Rheumatol, 2002. **29**(3): p. 474-81.
46. Brealey, S., *Measuring patient health status in rheumatoid arthritis -- what is a minimal clinically important difference?* J Rheumatol, 2004. **31**(6): p. 1026-8.
47. Wolfe, F., *Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients.* J Rheumatol, 2004. **31**(10): p. 1896-902.
48. Atkinson, M.J. and R.D. Lennox, *Extending basic principles of measurement models to the design and validation of Patient Reported Outcomes.* Health Qual Life Outcomes, 2006. **4**: p. 65.

Table 1. Clinical characteristics of the 51 participants with SLE

	Mean (SD)	Range
Age (years)	52.1 (12.1)	26–72
Women/men	50/1	
Disease duration, (year)	18.7 (13.6)	0.2–51
Disease activity	4.2 (2.7)[a]	0–9
SLAQ score	14.5 (8.5)	0–40
Fatigue raw scores	**Mean**	**SD**
FSS	4.5	1.6
VT	44.2	25.1
MAF	29.2	10.2
CFS	15.0	5.2
FACIT-F	30.1	11.9
MFI	61.0	18.1
NRS	5.5	2.1
Fatigue contrast groups [b]	**n**	**%**
Much More	17	7
Somewhat More	30	12
A Little Bit More	32	12
About the Same	77	30
Little Bit Less	39	15
Somewhat Less	32	12
Much Less	33	13

Disease activity= patients' global assessment, score 0–10, 0=no activity; [a] missing data from three persons; SLAQ score (Systemic Lupus Activity Questionnaire): 0–47, 0= no activity; Fatigue questionnaires: FSS= Fatigue Severity Scale; MAF= Multidimensional Assessment of Fatigue Scale; MFI= Multidimensional Fatigue Inventory-20; CFS= Chalder Fatigue Scale; VT=Vitality subscale from Short Form-36; FACIT-F= Functional Assessment of Chronic Illness Therapy Fatigue Scale; NRS= Numeric rating scale; [b] n=260.

A contrast was defined as the subjective comparison rating obtained at the end of a one-on-one conversation between the two participants in a pair (one conversation providing two contrasts).

Table 2. Mean paired difference (CI) for seven questionnaires [a] regarding fatigue after normalisation (scale 0–100)

Group[b]	FSS	MAF	MFI-20	CFS	VT	FACIT-F	NRS
3 (n=17)	36.4	28.1	22.9	21.9	36.8	32.4	20.6
	(24.5, 48.2)	(17.8, 38.4)	(9.0, 36.7)	(11.5, 32.4)	(26.4, 47.2)	(19.3, 45.4)	(11.4, 29.8)
2 (n=30)	37.8	28.5	32.2	9.8	33.0	31.7	15.7
	(25.9, 49.7)	(21.7, 35.3)	(26.1, 38.3)	(2.5, 17.1)	(25.9, 40.1)	(23.5, 39.9)	(5.1, 26.3)
1 (n=32)	19.7	15.5	19.8	6.0	19.1	17.5	8.8
	(9.7, 29.7)	(8.3, 22.6)	(11.6, 27.9)	(-0.4, 12.5)	(11.1, 27.0)	(8.9, 26.1)	(-0.4, 17.9)
0 (n=77)	2.7	3.2	2.9	1.4	3.1	3.4	3.1
	(-3.3, 8.8)	(-2.7, 9.1)	(-2.8, 8.6)	(-3.5, 6.2)	(-3.8, 10.1)	(-2.0, 8.8)	(-3.0, 9.2)
-1 (n=39)	-12.6	-7.4	-13.0	-8.2	-10.4	-10.6	0.0
	(-22.5, -2.8)	(-16.6, 1.9)	(-22.5, -3.6)	(-14.0, -2.4)	(-20.1, -0.7)	(-19.7, -1.6)	(-9.6, 9.6)
-2 (n=32)	-18.8	-24.0	-23.1	-10.0	-31.9	-22.0	-21.6
	(-30.7, -6.8)	(-32.7, -15.4)	(-30.7, -15.5)	(-17.5, -2.6)	(-39.5, -24.2)	(-32.5, -11.5)	(-30.2, 1-3.0)
-3 (n=33)	-44.2	-31.0	-29.3	-12.7	-32.1	-36.4	-20.6
	(-52.9, -35.5)	(-37.2, -24.9)	(-36.7, -21.9)	(-19.2, -6.1)	(-39.4, -24.8)	(-43.4, -29.3)	(-27.1, -14.1)

[a] Abbrevations as in Table 1. [b] Fatigue by contrast group. A contrast was defined as the subjective comparison rating obtained at the end of a one-on-one conversation between the two participants in a pair (each conversation providing two contrasts). Contrast group: 3= Much More; 2= Somewhat More; 1=Little More; 0=About the Same; -1=Little Less; -2= Some; -3=Much Less.

Table 3. Estimates for MCID for fatigue[a] by contrast groups[b] "A little more fatigue" and "A little less fatigue"

Fatigue Instrument[a]	Standardisation value[c]	A little more[d] mean (CI).	A little less[d] mean (CI).	p-value[e]
FSS	2.7	17.0 (7.0. 27.0)	-15.3 (-25.2. -5.5)	<0.001
VT	3.1	16.0 (8.1. 23.9)	-13.5 (-23.2. -3.8)	<0.001
MAF	3.2	12.3 (5.1. 1-.5)	-10.6 (-19.8. -1.3)	<0.001
CFS	1.4	4.6 (-1.8. 11.1)	-9.6 (-15.4. -3.8)	0.001
FACIT-F	3.4	14.1 (5.4. 22.7)	-14.0 (-23.1.-5.0)	<0.001
MFI	2.9	16.9 (8.7. 25.0)	-16.0 (-25.4. -6.5)	<0.001
NRS	1.4	5.6 (-3.4. 14.7)	-3.1 (-12.7. 6.5)	0.191

[a] Abbrevations as in Table 1. [b] Fatigue in contrast rating. A contrast was defined as the subjective comparison rating obtained at the end of a one-on-one conversation between the two participants in a pair (each conversation providing two contrasts). [c] Mean difference score from the group "About the same" used for standardisation of the values of the contrasting groups. [d] Results were adjusted by subtracting the "About the same" value from the raw mean paired difference for the fatigue contrast rating category. [e] Independent sample t-test.

Table 4. MCID estimates obtained from the regression modelling for the seven questionnaires regarding fatigue, and 95% confidence interval

		95% confidence interval			
Questionnaires[a]	Coefficient	Lower	Higher	Standardised	Raw scaling
NRS	5.35	3.63	7.08	0.26	0.54
FSS	10.75	8.72	12.79	0.40	0.58
VT	10.06	8.18	11.94	0.41	-10.06
MAF	8.55	7.01	10.09	0.42	4.22
MFI	8.67	6.94	10.40	0.39	6.94
CFS	4.25	2.98	5.52	0.28	1.42
FACIT-F	9.42	7.71	11.13	0.42	-4.90

[a] Abbrevations as in Table 1.

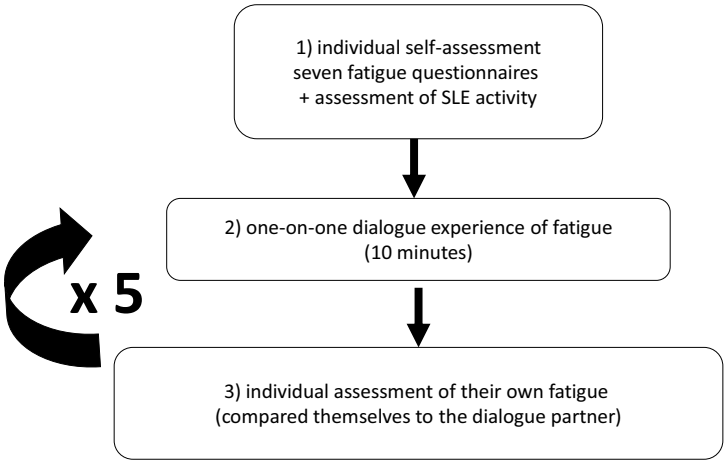
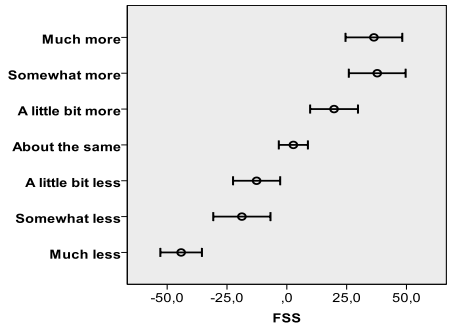
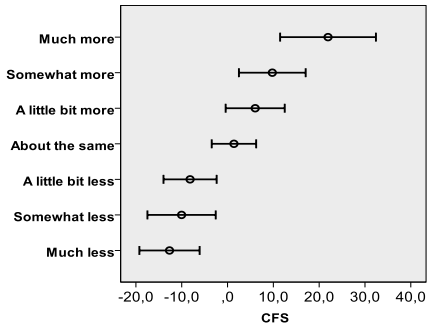
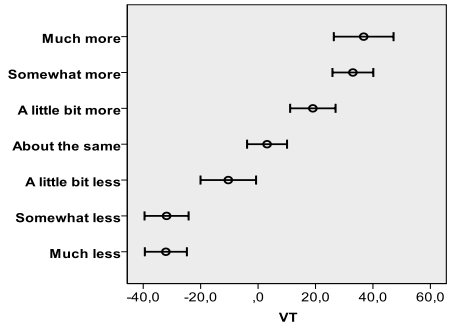


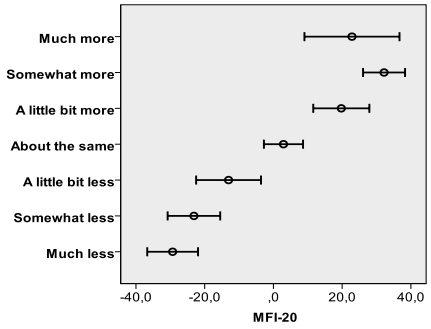
Figure 1. Schematic procedure of fatigue dialogues

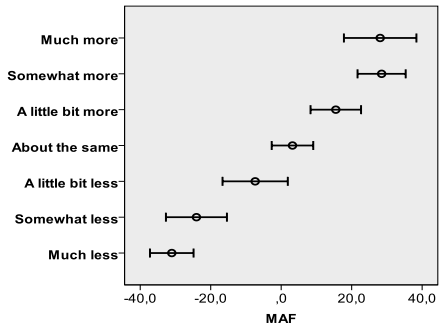
1) Individual assessment of fatigue (see Methods section). 2) Respondents' one-on-one dialogues (10 minutes) discussing their experiences with fatigue, 3) followed by an individual assessment of their own fatigue (comparing themselves to their dialogue partner) on a 7-grade scale. Points 2 and 3 were repeated until each respondent had five unique dialogues, each followed by an individual comparative assessment of his or her own level of fatigue.

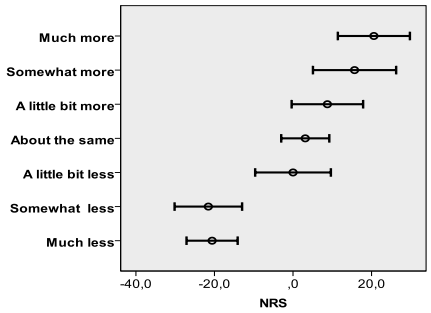

Much more
Somewhat more
A little bit more
About the same
A little bit less
Somewhat less
Much less
-50,0 -25,0 ,0 25,0 50,0
FSS


Much more
Somewhat more
A little bit more
About the same
A little bit less
Somewhat less
Much less
-20,0 -10,0 ,0 10,0 20,0 30,0 40,0
CFS


Much more
Somewhat more
A little bit more
About the same
A little bit less
Somewhat less
Much less
-40,0 -20,0 ,0 20,0 40,0 60,0
VT


Much more
Somewhat more
A little bit more
About the same
A little bit less
Somewhat less
Much less
-40,0 -20,0 ,0 20,0 40,0
MFI-20


Much more
Somewhat more
A little bit more
About the same
A little bit less
Somewhat less
Much less
-40,0 -20,0 ,0 20,0 40,0
MAF


Much more
Somewhat more
A little bit more
About the same
A little bit less
Somewhat less
Much less
-40,0 -20,0 ,0 20,0
NRS

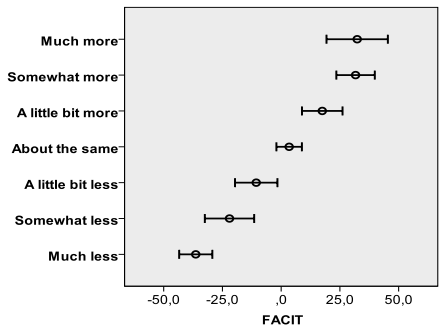

Much more
Somewhat more
A little bit more
About the same
A little bit less
Somewhat less
Much less
-50,0 -25,0 ,0 25,0 50,0
FACIT

Figure 2. Mean paired difference for seven fatigue instruments[a] per contrast group (260 assessments/51 patients). The figure illustrates error bars for mean and 95% confidence intervals, before adjustment for the mean of "About the same".

[a] Abbrevations as in Table 1.

Supplementary Data

Number of positive and negative comments from the respondents (n=39 of 51)

Questionnaire [a]	**Positive comments**	**Negative comments**
CFS	14 (27%)	6 (12%)
FACIT-F	11 (22%)	1 (2%)
FSS	14 (27%)	1 (2%)
MAF	4 (8%)	3 (6%)
MFI	7 (14%)	4 (8%)
VT	8 (16%)	1 (2%)
NRS	0%	1 (2%)

[a] Abbrevations as in Table 1

%= percentage of all 51 participants

IV

Clusters of fatigue - a comparison of persons with systemic lupus erythematosus and age and gender matched controls

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Abstract

Objective: To identify clusters of fatigue in patients with systemic lupus erythematosus (SLE) and controls, and compare the clusters according to health-related quality of life (HRQoL), anxiety, depression and lifestyle habits.

Method: Patients with SLE and age- and gender-matched controls (n=616; 305 patients, 311 controls; age: mean 47 years ±14.6) answered questionnaires about fatigue using the Fatigue severity scale (FSS), Vitality (VT) subscale from the medical short from-36 (SF-36) and Multidimensional Assessment of Fatigue scale (MAF). Health related quality of life (HRQoL) was assessed by the eight domains of SF-36, anxiety/depression by Hospital anxiety and depression scale (HADS) (cut-off >7) and lifestyle habits by self-reported questions.

Results: Hierarchic cluster analysis identified three groups of fatigue. The cluster exhibiting the highest levels of fatigue (VT 26.8, FSS 5.7, MAF 37.1) included persons (80% patients, 20% controls) with the most symptoms of depression (51%), anxiety (34%), the lowest HRQoL ($p<0.001$ in all dimensions), the lowest proportion (60%) of persons working at least 20 hours per week and the lowest proportion living with a partner (56%). The cluster with the lowest levels of fatigue (VT 78.6, FSS 2.4, MAF 11.4) included persons (22% patients, 78% controls) with the highest perceived HRQoL ($p<0.001$ for all dimensions), the lowest distribution of anxiety symptoms (10%), no detected depression, the lowest proportion of smokers (13%) and the highest proportion of those exercising more than twice per week (46%). The controls dominated this cluster, but 17% of *all* patients were found to be in this cluster. The intermediate fatigue cluster had 48% patients and 52% controls. No differences in gender distribution, age or sedentary behaviour were found between the three clusters.

Conclusion: In this study, a high number of patients with SLE were affected by fatigue, but non-SLE persons also reported elevated levels of fatigue. It is notable that even if a majority of the patients were in the high fatigue cluster, 17% had low levels of fatigue with high levels of wellbeing and healthier lifestyle habits. The results evidence that not all patients with SLE should be considered 'fatigued'; rather, there is a need for guidelines to help identify those with fatigue and support beneficial strategies.

INTRODUCTION

Fatigue is a prevalent problem for many patients with inflammatory disorders [1-5]; it is enigmatic, however, in that 'Everyone seems to know what it is, but a detailed definition is hard to provide. Like water, it slips away and cannot be grasped' [6]. This study focuses on one inflammatory disease—systemic lupus erythematosus (SLE)—where fatigue is often identified as one of the most prominent symptoms [1, 7-9].

SLE is a heterogenic disease with possible multi-organ involvement, resulting in broad variation for the individual perception of SLE-related symptoms. The symptom of fatigue is described as prevalent in more than 80% of patients [1, 10], and is thought to be influenced by several biological factors caused by the disease, such as inflammation [11], and enhanced by combinations of psychological reactions and social context [12]. It has also been proposed that disease activity is a main contributor to fatigue, although this notion has been debated [1, 12]. Furthermore, empirical findings show that patients with inactive disease may still report disabling fatigue [1]. Other symptoms such as pain, depressive symptoms and sleep disturbance have been correlated with fatigue, and are sometimes described as confounding factors [11, 13].

In patients with SLE, 56% to 80% report poor sleep quality or sleeping difficulties [1, 14, 15]. Today, fatigue is known as a dominant problem in SLE. Nevertheless, a previous study showed that women with SLE sometimes encountered ignorance of their condition in the surrounding society, including amongst health care professionals, and that comments about their fatigue to the effect that 'everyone is a little tired' showed a lack of understanding of their condition [16].

Several possible contributing factors to SLE-related fatigue have been described in the literature, specifically disease activity, mood disorder, sleep patterns and low levels of aerobic fitness. More sleep disturbances have been reported in patients with SLE compared to controls [17, 18], and 80% of patients with SLE have been considered to have sleep difficulties [15]. Sleep disturbance and low physical activity were shown to contribute to higher physical fatigue scores, and it was determined that depressed mood had the strongest impact on mental fatigue [19]. There have been indications that

physical exercise reduces SLE-related fatigue [20, 21], but it has also been stated that the relation between physical fitness and fatigue in SLE is still unclear [22].

Gender and age differences have been shown in the general Danish population in cases of fatigue [23]; the age correlation is suggested to derive from an increased disease burden. A recent study on a general population in the United States confirmed the gender difference that women perceived more fatigue; there was also a trend found for the association between age and fatigue in which persons aged 30 to 44 years reported the highest levels of fatigue [24].

To statistically identify subgroups in a sample or cohort, methods of clustering can be used to construct groups with similarities and to explore heterogenic variables or events [25]. Different clustering methods have previously been used to statistically identify subgroups of SLE, regarding organ manifestations, using K-means cluster analysis [26] and autoantibody profiles, using both hierarchical analysis and K-means clustering [27]. The method of K-means clustering need a predefined numbers of cluster were the K represent the chosen numbers of cluster, the number of clusters may be predefined by clinical relevance of by an initial hierarchical cluster analysis [28].

Objectives

The aims of this study were to identify clusters of fatigue in patients with SLE as well as in age and gender match controls, and with regard to health-related quality of life (HRQoL), anxiety, depression and life-style habits compare these clusters.

PATIENTS AND METHODS

Patients over 18 years of age with SLE (score ≥ 4 on the American College of Rheumatology [ACR] criteria)[29] were included after their informed and written consent was obtained. The exclusion criterion was non-Swedish-speaking/writing. Upon inclusion, a medical assessment was conducted by a physician, including disease activity and disease damage, and demographic data were collected. The participants responded to questionnaires assessing HRQoL, fatigue, depression and anxiety parallel to lifestyle questions about sleep, exercise and smoking. After the inclusion of a patient,

a paired population control was matched for sex, age (+-12 months) and region of residence. Controls were recruited from the population registry, and living in the same county as the patients. They were solicited and included after their written informed consent was obtained, according to the same protocol as the patients. This study is a part of a cohort study approved by the local research ethics committee (Karolinska Institutet ethical approval Dr 03-556 SLE).

Assessment of fatigue

The respondents answered three questionnaires to provide information about fatigue:
1) The Fatigue severity scale (FSS) is a nine-item questionnaire reflecting the consequences of fatigue in which the mean value gives the final single score (range 0–7), and a final score of 4 is described as the cut-off for clinical fatigue [30]. The FSS is recommended to evaluate fatigue in SLE and translated validated in Swedish [31, 32].
2) The Multidimensional Assessment of Fatigue Scale (MAF) has 16 items and includes four dimensions of fatigue: severity, distress, timing interference with daily activities [33, 34]. A total score is calculated on a global fatigue index ranging from 1 to 50. A Swedish validation has been published for systemic sclerosis [35].
3) The vitality domain from the Medical Short Form-36 (SF-36; see below) questionnaire is considered to reflect fatigue and is based on 4 of the 36 items, which are transformed into a single domain score.

Assessment of health-related quality of life, anxiety and depression

The 36 items on the questionnaire SF-36 were used to collect data on HRQoL [36-38]. The results from the SF-36 were divided into eight different dimensions (Physical Functioning = PF, Role-Physical = RP, Bodily Pain = BP, General Health = GH, Vitality = VT, Social Functioning = SF, Role-Emotional = RE, Mental Health = MH). Each domain of the SF-36 ranges from 0 to 100, where high values represent better HRQoL.

The Hospital Anxiety and Depression Scale (HADS) [39, 40] has 14 items divided into two subscales: anxiety (HADS-A) and depression (HADS-D). The items have four alternative answers, each weighted from 0 to 3, resulting in a possible score of 0 to 21.

On the respective subscales, a total score higher than 7 is regarded as an indication of symptoms of anxiety/depression [39].

Lifestyle habits and characteristics

The questions about physical exercise have been used in previous studies to explore physical activity and exercise in the general population and compared to persons with SLE [41, 42], but in this study we focused on two questions:

1) "How much did you exercise during the past year? Exercise is counted as intentional physical training such as sports and fitness training that lasts at least 30 minutes per occasion and makes you breathless and sweaty" (irregular/1 time per week/2 times per week/3 or more times per week/never).

2) "How much of your day do you spend sitting down? Choose one answer to show your average during the past six months" (sitting down almost the whole day/about half the day/less than half the day/hardly ever spend time sitting down).

The participants also answered three questions concerning sleep and rest which asked about

1) their usual length of sleep per night (< 5 h, 5–7 h, 7–9 h, > 9 h);

2) frequency of daytime sleep (never, occasionally, sometime per week, 2–3 times per week, 3–6 times per week/daily);

3) daytime rest > 30 min (never, occasionally, sometime per week, 2–3 times per week, 3–6 times per week/daily).

Since the questions about sleep and rest had overlapping answers, the answers were merged in the analysis stage to facilitate comparisons between groups. The answers for sleeping for 5–7 hours and 7–9 hours categories were collapsed into one.

For daytime sleep and rest, never, occasionally and sometimes per week were collapsed into one item, and 2–3 times per week, 3–6 times per week were collapsed into one item as well.

Nurses measured height and weight at inclusion to obtain adequate and up-to-date information. Body mass index (BMI) was calculated as weight (kg) divided by the square of length (m^2).

Disease-specific measures

The systemic lupus activity measure (SLAM) was used to assess disease activity. The SLAM cover clinical symptoms during the last month, including both laboratory parameters and evaluations of nine organ systems (high values indicate more activity) [43, 44]. To estimate SLE disease damage, the Systemic Lupus International Collaboration Clinics/American College of Rheumatology (SLICC)/ACR damage index was used. The SLICC/ACR assesses cumulative organ damage and co-morbidity involving 12 organ systems [45, 46] (score range: 0–47).

Data analysis and statistical considerations

In this study, a hierarchical method of cluster analysis was used to form homogeneous groups [25] with respect to the variables measuring fatigue (FSS, VT, MAF). Since the fatigue measures employed to form clusters used different scoring, the data-computed z-scores were adapted for standardisation of the scores to avoid domination by one instrument in the analysis. Clusters were formed stepwise, that is, each person was initially considered a cluster. Two clusters were then chosen according to the clustering criteria and merged in a new cluster. The data analysing process continued until all objects belonged to one cluster. The average linkage (within group) was used for clustering and clusters were combined based on a model in which the average distance between clusters was as small as possible [28]. The number of relevant clusters was three, and the relevance of the clusters was compared with other hierarchical methods and confirmed by the average linkage (between groups) and the complete linkage (furthest neighbour), which confirmed the choice of number of clusters. The nearest neighbour (single linkage) method and the median method did not yield the same distinct cluster patterns.

Comparisons were made between persons with SLE and the controls concerning HRQoL, anxiety, depression and lifestyle habits, as well as between the emerged clusters related to fatigue. Descriptive data were calculated for all variables. Chi-square tests were then used for comparisons regarding distribution of dichotomised data between groups, and an independent samples test was used for continuous data. For comparison among the three clusters, one-way analysis of variance (ANOVA) was used

for continuous data with additional correction using the Bonferroni post hoc test. When exploring the ordinal data and making comparisons among the fatigue clusters, the Chi-square and Mann-Whitney U tests were used, with repeated sub analysis to detect differences.

The Statistical Package for the Social Sciences (SPSS) version 19 (IBM Corporation, Somers, NY, USA) was used for all statistical analyses. Statistical significance was identified at 0.05, and absolute p-values were reported when appropriate.

RESULTS

Initially 636 participants that were paired together as patients with SLE and corresponding controls and matched according to age and gender were included to the study. The mean age of the participants was 47.1 years (± 14.7; range 18–84), and 92% were women. Those who did not complete all three fatigue questionnaires—MAF, FSS and VT (see Patients and Methods section)—were excluded in the process of clustering (13 patients and 7 controls). Thus, 616 persons were included, with a mean age of 47 years (± 14.6; range 18–84). After the removal of an unequal number of patients and controls, there were still no differences in age or gender between the two groups (Table 1).

Lifestyle and disease characteristics

The demographic variables are presented in Table 1. The comparison of social parameters showed that 59% of the patients and 68% of the controls lived with a partner ($p = 0.015$). The patients had fewer children (mean 1.2 ± 1.2) than the controls (mean 1.4 ± 1.2, $p = 0.047$). Seventy-five per cent of the controls were full-time workers compared to 39% of the patients. More controls (88%) than patients (64%) worked at least 50% of the time ($p = <0.001$). Although the BMI did not differ between patients and controls, the BMI range in absolute values was larger for patients (14.2-59.1) than for controls (18.2-42.2).

There were several differences in lifestyle parameters between the patients with SLE and the controls. The comparison of regular exercise in patients and controls showed

that more controls exercised at least once a week or more (patients 48%; controls 60%; p = 0.002); there were no differences between the groups that exercised at least twice a week (patients 33%, controls 40%; p = 0.066). More controls reported sedentary behaviour with regard to spending the whole day sitting down (patients 18%; controls 27%: p = 0.007). However, in a comparison of the groups that spent less than half the day sitting compared to half day or more, the distribution was about the same (patients 54%, controls 55%; p = 0.887). Only a few controls (n = 12) reported sleeping during the day at least twice a week, while five times more patients reported this behaviour (patients 19%, controls 4%; p < 0.001). The same pattern was exhibited regarding daytime rest at least twice per week (patients 30%, controls 7%; p <0.001). Regarding hours of night sleep, 10% of the patients slept less than five hours and another 9% slept more than nine hours. The vast majority (96%) of the controls slept between five and nine hours per night, the remaining 4% slept less than five hours, none of the controls reported that they slept more than nine hours. No difference in the proportion of smokers was found between the patients and controls (Table 1).

The duration of the disease in the patients ranged from 0–58 years (median 12, IQR 5–22), disease activity ranged from 0 to 27 (SLAM: median 6, IQR 4–10) and SLICC/ACR ranged from 0 to 10 (median 1, IQR 0–2).

Self-assessment of fatigue, health related quality of life, anxiety and depression

Compared to the controls, patients with SLE had higher levels of fatigue on all three fatigue questionnaires. The same pattern was found for all dimensions of HRQoL measured by SF-36 (Table 1). The mean level of self-assessed anxiety was higher among patients (6.8 ±4.8 patients vs. 4.5 ± 3.9 controls; p < 0.001) as well as depression (4.9 ± 3.8 patients vs. 2.6 ± 3.1 controls; p <0.001).

Clusters of fatigue

The three homogenous clusters of fatigue that were identified are presented in Table 2. The levels of fatigue were significantly different among the three clusters regarding all three fatigue questionnaires, and the differences remained after Bonferroni correction. Cluster one (n = 221) had distinctly more fatigue and was dominated by patients (80%).

Cluster two (n = 240) had the least fatigue and was dominated by the controls (78%). Cluster three (n = 155) had the most equal distribution, at 48% patients and 52% controls, and these individuals' levels of fatigue were more moderate than those in the other two clusters. The clusters were named according to levels of fatigue as the 'high fatigue cluster' (one), 'low fatigue cluster' (two) and the 'intermediate fatigue cluster' (three). There were no differences in gender distribution or age between the clusters. In the results from the questionnaires measuring fatigue, the patterns were the same for anxiety, depression and HRQoL, indicating that the high fatigue cluster was the most affected, and the low fatigue cluster was the least affected (Table 2).

In the high fatigue cluster, regular exercise at least two times a week was less frequent (25%) compared to the low fatigue (46%, $p < 0.001$) and intermediate fatigue cluster (36%, $p = 0.015$) (Table 3). Concerning night-sleep patterns, three quarters (74%) of those in the high fatigue cluster slept 5 to 9 hours per night compared to 97% in the low fatigue and 93% in the intermediate fatigue cluster. The high fatigue cluster had the highest proportion of persons sleeping less than five hours (13%) as well as sleeping more than nine hours (12%). Of those that slept more than nine hours per night (30 persons), 26 were in the high fatigue cluster, and the other four were equally distributed between the other two clusters. Daytime rest two or more times per week was represented by 39% of the persons in the high fatigue cluster. This result was higher than in the low fatigue cluster (5%, $p = <0.001$) and the intermediate fatigue cluster (10%, $p<0.001$). A quarter (25.5%) of those in the high fatigue cluster slept during the day two times or more times per week, which was 10 times the proportion of those in the low fatigue cluster (2.5%, $p < 0.001$) and 4 times that of individuals in the intermediate fatigue cluster (6.4%, $p < 0.001$). The proportion of persons working 50% (fulltime is stated to 40 hours per week) or more was the lowest in the high fatigue cluster (60%), compared to both the low fatigue cluster (87%, $p < 0.001$) and the intermediate fatigue cluster (81%, $p < 0.001$). Fewer persons in the high fatigue cluster lived with a partner (56%) compared to those in the low fatigue cluster (71%, $p = 0.001$), but there was no difference compared to the intermediate fatigue cluster (Table 2).

In the low fatigue cluster, the respondents had the lowest figures for self-assessed anxiety (10%, HADS-A >7), and they all reported zero signs of depression (Table 2). When comparing lifestyle habits across the three clusters, fewer persons reported that they were smokers in the low fatigue cluster (13%) compared to both the high fatigue cluster (20%, $p = 0.030$) and the intermediate fatigue cluster (20%, $p = 0.044$). Most individuals (97%) in the low fatigue cluster reported that they normally slept 5 to 9 hours per night, which was not statistically significantly different from the intermediate cluster. However, compared to the intermediate fatigue cluster, the respondents in the low fatigue cluster were less likely to rest during the day (Table 3).

The analysis of daytime sleep showed the trend that a lower proportion of respondents in the low fatigue cluster slept during the day compared to the intermediate fatigue cluster (daytime sleep twice more per week: 2% vs. 6%; $p = 0.054$) (Table 3). The highest proportion of persons working 50% or more was found in the low fatigue cluster (87%; Table 2). However, the difference was statistically significant only in comparison to the high fatigue cluster (60%, $p < 0.001$). Similar results were found for marital status: the low fatigue cluster had the highest proportion of persons living with a partner (71%), which was more than the 'high fatigue cluster' (56%, $p = 0.001$) but similar to the intermediate fatigue cluster (63%). The intermediate fatigue cluster had similarities with both the high and low fatigue clusters (Tables 2 and 3). No differences were detected in age or sedentary behaviour (sitting down during the day) among the three clusters.

Comparison of disease characteristics

The median disease duration of the SLE patients (n=305) was 12 years (range 0–58). The median number of fulfilled ACR criteria was 6, with a range from 4 to 10. Disease activity measured by SLAM was spread from 0 to 27 (median 6, IQR 4-10). Comparison of the clusters using ANOVA with Bonferroni correction showed no significant differences among patients in the three clusters regarding the number of ACR criteria or disease duration. Organ damage (SLICC/ACR) was analysed between all combinations of clusters using the Mann-Whitney U test, but no difference was found. However, patients in the high fatigue cluster exhibited more disease activity

(SLAM) (median 6, IQR 4–10) than both the low fatigue cluster (median 3, IQR 2–7, $p < 0.001$) and the intermediate fatigue cluster (median 5, IQR 4–7, $p < 0.001$), but also a difference between low and intermediate fatigue cluster was found with lowest disease activity in the low fatigue cluster ($p=0.01$, Mann Whitney U).

DISCUSSION

Previous studies exploring fatigue have demonstrated higher levels of fatigue in patients with SLE than controls [47-49]. In the present study, patients with SLE and non-SLE controls were not initially separated before the clustering analysis. This assumption revealed a result that could identify a subgroup of patients with low levels of fatigue, similar to the majority of non-SLE controls.

The cluster analysis in this study resulted in three divergent clusters, which were denominated as the high, low and intermediate fatigue clusters through their representative levels of fatigue. The high fatigue cluster represented persons with the highest levels of fatigue. The individuals in this cluster were the most affected by symptoms of depression and anxiety and represented the lowest levels of HRQoL. This group also lived without a partner more often, and fewer people of working age had a present working status of more than 50%. The cluster was dominated by patients who had higher disease activity than in the other clusters. The low fatigue cluster was the least affected by fatigue, exhibiting the highest perceived HRQoL and the lowest levels of symptoms of anxiety; no symptoms of depression were detected. This group represented the lowest proportion of smokers. In fact, the proportion of smokers in this cluster (13%) was lower than the proportion of smokers in the same county, which is about 15% [50], and in parity with the population controls in this study. The low fatigue cluster was dominated by the controls, and the results indicate subjective signs of better health.

The intermediate fatigue cluster had moderate levels of fatigue, anxiety, depression and HRQoL. The levels of fatigue in the intermediate fatigue cluster could be regarded as ‘borderline’ fatigue if a cut-off for FSS levels above 4 is considered elevated fatigue [30]. A Norwegian study set the cut-off for FSS at 5 in the general population [51].

Thus, both the low fatigue cluster and the intermediate fatigue cluster could be regarded as nonfatigued, since their confidence intervals are below that limit.

The levels of symptoms of anxiety shown in our study were similar to those in other studies conducted in Singapore [52] and Canada [53]. However, the proportion of patients with signs of depression was higher in our study than in a Swiss sample [54]; on the other hand, depression levels (HADS) were higher than those in the Canadian study [53]. It should be noted, however, that the mentioned studies [52-54] used smaller samples (n = 53–60) than ours. Although, in our study, the mean levels of self-assessed anxiety and depression were higher among the patients than the controls, a majority of both patients' and controls' levels of anxiety and depression were below the cut-off for HADS. This is interesting, since the previous studies concluded that patients with SLE suffer from anxiety or depression more often [52-54] . Even if psychological disturbances are more prominent among persons with SLE, most are in the range of 'normal' symptoms, that is, not in the range for mental disorders as measured by HADS [52].

There was a difference in exercise but not sedentary behaviour between the three clusters, where the low fatigue cluster represented more physical exercise. This is congruent with previous studies where low physical activity and depressed mood were found to contribute to fatigue [19]. The three clusters were diverted not only by fatigue, but also regarding anxiety, depression and HRQoL, which followed the same pattern. The associations between fatigue, depression, anxiety and physical activity have been previously identified, but it has been suggested that these are complex and require further exploration [8].

The incongruent association between disease activity and fatigue has been discussed in previous studies [55]. It is possible that assessments including subjective items in the measure such as fatigue yield this association when SLAM is used [19]. This supports our result that the high fatigue cluster had higher SLAM. Remarkably, one-fifth of the persons in the high fatigue cluster were in the control group, which comprised persons from the general population. However, besides the absence of SLE, no other medical

explanations causing fatigue were explored in this study because the controls represented persons from the general population and were not assessed as completely healthy. Our study confirms that a high degree of fatigue is associated with reduced HRQoL and that symptoms of anxiety and depression are more common. However, we do not know what comes first. The result also suggests that this interaction is probably not disease specific, since the same pattern is described for the controls as for the patients.

In our study, we used three different questionnaires measuring fatigue, which reduced the vulnerability of single-item questionnaires were respondent that might misunderstand the only question and responses could be misclassified. However, one limitation of the study was that the fatigue questionnaires were one-dimensional [56] in that they resulted in only one final score. Therefore, we cannot determine whether the fatigue in each cluster represents differences, such as mental or physical fatigue [19].

The present study, to the best of our knowledge, was the first attempt to use cluster analysis to compare levels of fatigue with lifestyle habits. Other studies using a similar method have used cluster analysis to distinguish or categorise patients into clinically relevant groups that could be used to prioritise management strategies [57]. The distribution of lifestyle habits with a possible positive effect in our study, e.g. more exercise and less smoking, confirms the result from studies of the association between physical activity and fatigue [58]; however, little is known concerning the association between smoking and fatigue. In fibromyalgia, smoking is suggested to induce pain [59] and in lung cancer, there is a suggestion that persistent smoking and pain are associated [60]. It is evident that positive lifestyle habits cluster together, i.e. a physically active person may strive for a healthy lifestyle and avoid habits like cigarette smoking, but the result of the present study calls for more research exploring possible fatigue-smoking relations in SLE.

To continue to investigate clustering in SLE, it would be interesting to include other variables in a cluster analysis focusing on fatigue, such as autoantibodies, to determine

whether the cluster follows the same or another pattern. It would also be interesting to conduct a multicentre study of fatigue, since existing studies—including the present one—are single centre studies and therefore call for caution, considering the generalisability of the results.

The results of this study confirmed that a high number of patients with SLE were affected by fatigue but that non-SLE persons also reported elevated levels of fatigue [1, 30]. Persons with high fatigue levels perceived lower HRQoL and higher degrees of anxiety and depression. The persons in the high fatigue cluster indicated less frequent physical exercise. Notably, in this cross-sectional data collection, a subgroup of patients with SLE reported low levels of fatigue, high levels of wellbeing and healthier lifestyle habits. This support the notion that health professionals require guidelines that help in the identifications of those with fatigue and that they should not consider all patients with SLE as being 'fatigued'.

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REFERENCES

1. Tench, C.M., et al., *The prevalence and associations of fatigue in systemic lupus erythematosus.* Rheumatology (Oxford), 2000. **39**(11): p. 1249-54.
2. Da Costa, D., M. Zummer, and M.A. Fitzcharles, *Biopsychosocial determinants of physical and mental fatigue in patients with spondyloarthropathy.* Rheumatol Int, 2011. **31**(4): p. 473-80.
3. Sandusky, S.B., et al., *Fatigue: an overlooked determinant of physical function in scleroderma.* Rheumatology (Oxford), 2009. **48**(2): p. 165-9.
4. Stuifbergen, A.K. and S. Rogers, *The experience of fatigue and strategies of self-care among persons with multiple sclerosis.* Appl Nurs Res, 1997. **10**(1): p. 2-10.
5. Thombs, B.D., et al., *A systematic comparison of fatigue levels in systemic sclerosis with general population, cancer and rheumatic disease samples.* Rheumatology (Oxford), 2008. **47**(10): p. 1559-63.
6. Rasker, J.J., *The enigma of fatigue.* J Rheumatol, 2009. **36**(12): p. 2630-2.
7. Moses, N., et al., *Prevalence and correlates of perceived unmet needs of people with systemic lupus erythematosus.* Patient Educ Couns, 2005. **57**(1): p. 30-8.
8. Ramsey-Goldman, R. and N. Rothrock, *Fatigue in systemic lupus erythematosus and rheumatoid arthritis.* PM R, 2010. **2**(5): p. 384-92.
9. Pettersson, S., et al., *An exploration of patient-reported symptoms in systemic lupus erythematosus and the relationship to health-related quality of life.* Scand J Rheumatol, 2012.
10. Krupp, L.B., et al., *A study of fatigue in systemic lupus erythematosus.* J Rheumatol, 1990. **17**(11): p. 1450-2.
11. Norheim, K.B., G. Jonsson, and R. Omdal, *Biological mechanisms of chronic fatigue.* Rheumatology (Oxford), 2011. **50**(6): p. 1009-18.
12. Omdal, R., et al., *Fatigue in patients with systemic lupus erythematosus: the psychosocial aspects.* J Rheumatol, 2003. **30**(2): p. 283-7.
13. Wolfe, F., D.J. Hawley, and K. Wilson, *The prevalence and meaning of fatigue in rheumatic disease.* J Rheumatol, 1996. **23**(8): p. 1407-17.
14. Costa, D.D., et al., *Determinants of sleep quality in women with systemic lupus erythematosus.* Arthritis Rheum, 2005. **53**(2): p. 272-8.
15. Greenwood, K.M., L. Lederman, and H.D. Lindner, *Self-reported sleep in systemic lupus erythematosus.* Clin Rheumatol, 2008. **27**(9): p. 1147-51.
16. Pettersson, S., et al., *Women's experience of SLE-related fatigue: a focus group interview study.* Rheumatology (Oxford), 2010. **49**(10): p. 1935-42.
17. Valencia-Flores, M., et al., *Objective and subjective sleep disturbances in patients with systemic lupus erythematosus.* Arthritis Rheum, 1999. **42**(10): p. 2189-93.
18. Iaboni, A., et al., *Fatigue in systemic lupus erythematosus: contributions of disordered sleep, sleepiness, and depression.* J Rheumatol, 2006. **33**(12): p. 2453-7.
19. Da Costa, D., et al., *Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioral and psychosocial factors.* J Rheumatol, 2006. **33**(7): p. 1282-8.
20. Tench, C.M., et al., *Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise.* Rheumatology (Oxford), 2003. **42**(9): p. 1050-4.

21. Ramsey-Goldman, R., et al., *A pilot study on the effects of exercise in patients with systemic lupus erythematosus.* Arthritis Care Res, 2000. **13**(5): p. 262-9.
22. Barnado, A., et al., *Quality of life in patients with systemic lupus erythematosus (SLE) compared with related controls within a unique African American population.* Lupus, 2012. **21**(5): p. 563-9.
23. Watt, T., et al., *Fatigue in the Danish general population. Influence of sociodemographic factors and disease.* J Epidemiol Community Health, 2000. **54**(11): p. 827-33.
24. Junghaenel, D.U., et al., *Demographic correlates of fatigue in the US general population: results from the patient-reported outcomes measurement information system (PROMIS) initiative.* J Psychosom Res, 2011. **71**(3): p. 117-23.
25. Sharma, S., *Cluster Analysis*, in *Applied multivariate techniques*. 1996, J. Wiley: New York. p. xviii, 493 p.
26. Jacobsen, S., et al., *A multicentre study of 513 Danish patients with systemic lupus erythematosus. I. Disease manifestations and analyses of clinical subsets.* Clin Rheumatol, 1998. **17**(6): p. 468-77.
27. Jurencak, R., et al., *Autoantibodies in pediatric systemic lupus erythematosus: ethnic grouping, cluster analysis, and clinical correlations.* J Rheumatol, 2009. **36**(2): p. 416-21.
28. IBM, *IBM SPSS Statistics Base 19*. 2010, SPSS Inc 1989,: New York, USA.
29. Tan, E.M., et al., *The 1982 revised criteria for the classification of systemic lupus erythematosus.* Arthritis Rheum, 1982. **25**(11): p. 1271-7.
30. Krupp, L.B., et al., *The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus.* Arch Neurol, 1989. **46**(10): p. 1121-3.
31. Avina-Zubeieta A, A.G., Bischoff Ferrari HA, Fischer R, Gall V, Illei G, Liang MH, Mikdashi J, Petri M, Phillips C, Pouchot J, Schneider M, Schur P, St Clair W. (Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue), *Measurement of fatigue in systemic lupus erythematosus: a systematic review.* Arthritis Rheum, 2007. **57**(8): p. 1348-57.
32. Mattsson, M., et al., *Reliability and validity of the Fatigue Severity Scale in Swedish for patients with systemic lupus erythematosus.* Scand J Rheumatol, 2008. **37**(4): p. 269-77.
33. Belza, B.L., *Comparison of self-reported fatigue in rheumatoid arthritis and controls.* J Rheumatol, 1995. **22**(4): p. 639-43.
34. Sohng, K.Y., *Effects of a self-management course for patients with systemic lupus erythematosus.* J Adv Nurs, 2003. **42**(5): p. 479-86.
35. Sandqvist, G., et al., *The Swedish version of the Multidimensional Assessment of Fatigue (MAF) in systemic sclerosis: reproducibility and correlations to other fatigue instruments.* Scand J Rheumatol, 2011. **40**(6): p. 493-4.
36. Persson, L.O., et al., *The Swedish SF-36 Health Survey II. Evaluation of clinical validity: results from population studies of elderly and women in Gothenborg.* J Clin Epidemiol, 1998. **51**(11): p. 1095-103.
37. Sullivan, M., J. Karlsson, and J.E. Ware, Jr., *The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden.* Soc Sci Med, 1995. **41**(10): p. 1349-58.

38. Sullivan, M. and J. Karlsson, *The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population.* J Clin Epidemiol, 1998. **51**(11): p. 1105-13.
39. Bjelland, I., et al., *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res, 2002. **52**(2): p. 69-77.
40. Lisspers, J., A. Nygren, and E. Soderman, *Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample.* Acta Psychiatr Scand, 1997. **96**(4): p. 281-6.
41. Ekblom, B., L.M. Engstrom, and O. Ekblom, *Secular trends of physical fitness in Swedish adults.* Scand J Med Sci Sports, 2007. **17**(3): p. 267-73.
42. Eriksson, K., et al., *Physical activity in patients with systemic lupus erythematosus and matched controls.* Scand J Rheumatol, 2012. **41**(4): p. 290-7.
43. Liang, M.H., et al., *Measurement of systemic lupus erythematosus activity in clinical research.* Arthritis Rheum, 1988. **31**(7): p. 817-25.
44. Liang, M.H., et al., *Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus.* Arthritis Rheum, 1989. **32**(9): p. 1107-18.
45. Gladman, D., et al., *The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus.* Arthritis Rheum, 1996. **39**(3): p. 363-9.
46. Gladman, D.D., et al., *The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus.* Arthritis Rheum, 1997. **40**(5): p. 809-13.
47. Tench, C., et al., *Aerobic fitness, fatigue, and physical disability in systemic lupus erythematosus.* J Rheumatol, 2002. **29**(3): p. 474-81.
48. Choi, S.T., et al., *Subscale analysis of quality of life in patients with systemic lupus erythematosus: association with depression, fatigue, disease activity and damage.* Clin Exp Rheumatol, 2012.
49. Stockton, K.A., et al., *Fatigue, muscle strength and vitamin D status in women with systemic lupus erythematosus compared with healthy controls.* Lupus, 2012. **21**(3): p. 271-8.
50. Stockholms läns landsting (SLL)., *Folkhälsan i Stockholms län 2007 (Folkhälsorapport 2007)*. 2007, Centrum för folkhälsa. p. 134.
51. Lerdal, A., et al., *Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale.* Scand J Public Health, 2005. **33**(2): p. 123-30.
52. Mak, A., et al., *Damage accrual, cumulative glucocorticoid dose and depression predict anxiety in patients with systemic lupus erythematosus.* Clin Rheumatol, 2011. **30**(6): p. 795-803.
53. Hanly, J.G., et al., *Neuropsychiatric syndromes in patients with systemic lupus erythematosus and rheumatoid arthritis.* J Rheumatol, 2005. **32**(8): p. 1459-6.
54. Stoll, T., et al., *Prediction of depression in systemic lupus erythematosus patients using SF-36 Mental Health scores.* Rheumatology (Oxford), 2001. **40**(6): p. 695-8.

55. Jump, R.L., et al., *Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support.* J Rheumatol, 2005. **32**(9): p. 1699-705.
56. Cleanthous, S., et al., *What do we know about self-reported fatigue in systemic lupus erythematosus?* Lupus, 2012. **21**(5): p. 465-476.
57. Newcomer, S.R., J.F. Steiner, and E.A. Bayliss, *Identifying subgroups of complex patients with cluster analysis.* Am J Manag Care, 2011. **17**(8): p. e324-32.
58. Zonana-Nacach, A., et al., *Systemic lupus erythematosus in three ethnic groups. VI: Factors associated with fatigue within 5 years of criteria diagnosis. LUMINA Study Group. LUpus in MInority populations: NAture vs Nurture.* Lupus, 2000. **9**(2): p. 101-9.
59. Lee, S.S., et al., *Smoking habits influence pain and functional and psychiatric features in fibromyalgia.* Joint Bone Spine, 2011. **78**(3): p. 259-65.
60. Daniel, M., et al., *Persistent smoking after a diagnosis of lung cancer is associated with higher reported pain levels.* J Pain, 2009. **10**(3): p. 323-8.

Table 1. Comparison between patients (n=305) with SLE and age- and gender-matched controls (n=311; demographics, fatigue, anxiety, depression and health-related quality of life).

	SLE		Controls		p-value
	Mean	(95% CI[a])	Mean	(95% CI[a])	
Age (yrs.) mean	47.0	(44.6–48.0)	47.3	(45.7–49.0)	0.636[b]
Women	92%		92%		0.938[c]
Living with partner	59%		68%		0.015[c]
Number of children [d]	1.2	(1.0–1.3)	1.4	(1.2–1.5)	0.047[b]
Working ≥50% [de]	63%		88%		<0.001[c]
Current smoker	19%		15%		0.133[c]
Body mass index[f]	24.6	(24.0–25.2)	25.1	(24.6–25.6)	0.187[b]
VT [g]	41.9	(39.6–45.5)	67.1	(65.1–69.7)	<0.001[b]
FSS [h]	4.8	(4.6–4.9)	3.2	(3.0–3.3)	<0.001[b]
MAF [j]	29.3	(28.3–31.0)	17.5	(16.2–18.5)	<0.001[b]
HADS[k]					
Anxiety	6.8	(6.1–7.2)	4.5	(4.0–4.9)	<0.001[b]
>7	38%		20%		<0.001[c]
Depression	4.9	(4.3–5.2)	2.6	(2.2–2.9)	<0.001[b]
>7	21%		8%		<0.001[c]
PF [l]	69.3	(66.8–73.2)	91.0	(89.8–93.0)	<0.001[b]
RP [l]	48.8	(44.8–54.8)	88.8	(86.0–92.0)	<0.001[b]
BP [l]	57.0	(54.8–61.3)	78.5	(76.2–81.4)	<0.001[b]
GH [l]	45.2	(43.0–48.7)	77.3	(75.3–79.9)	<0.001[b]
SF [l]	66.9	(64.9–71.7)	89.5	(87.7–92.0)	<0.001[b]
RE [l]	63.2	(59.0–69.0)	86.1	(82.7–89.4)	<0.001[b]
MH [l]	66.0	(64.2–69.6)	79.6	(77.9–81.8)	<0.001[b]
Exercise					<0.001[c]
Never	24%		12%		
Irregularly	29%		28%		
1 time/week	15%		20%		
2 times/week	16%		21%		
≥3 times/week	17%		19%		

Sitting down/day			0.009[c]
Not at all	14%	18%	
< half the day	32%	28%	
Half the day	36%	28%	
All day	18%	27%	
Sleep (hrs/night)			<0.001[c]
<5	10%	4%	
5–9	81%	96%	
>9	9%	0%	
Daytime sleep			<0.001[c]
Never	38%	54%	
Occasionally	25%	33%	
Sometime/week	17%	9%	
2–3 times/week	8%	3%	
3–6 times/week	6%	1%	
Daily	6%	0%	
Daytime rest (≥ 30 min)			<0.001[c]
Never	30	49	
Occasionally	28	35	
Sometime every week	12	9	
2–3 times/week	7	4	
3–6 times/week	7	1	
Daily	16	2	

[a] Confidence Interval
[b] Independent Samples Test.
[c] Chi-square.
[d] Number of biological children.
[e] age 18-64, n = 280, 50%= 20 hours per week.
[f] Body mass index was calculated as weight (kg) divided by the square of length (m^2).
[g] Vitality
[h] Fatigue severity scale
[j] Multi assessment of fatigue
[k] Hospital Anxiety and Depression scale
[l] Domains from SF-36 (descriptions in the Patients and Methods section).

Table 2. Comparison between fatigue cluster groups (n = 616).

Cluster of fatigue	High		Low		Intermediate		
	n=221		n=240		n=155		
	Mean	95% CI	Mean	95% CI	Mean	95% CI	p-value
VT	26.8	24.7–28.8	78.6	77.1–80.1	57.1	55.1–59.0	<0.001[a]
FSS	5.7	5.6–5.8	2.4	2.3–2.5	4.0	3.8–4.1	<0.001[a]
MAF	37.1	36.2–37.9	11.4	10.7–12.1	23.5	22.6–24.4	<0.001[a]
Patients/controls (%)	80/20		22/78		48/52		<0.001[b]
Women %	92.3		92.1		91.6		0.970[b]
Age	47.2	45.2–49.2	47.0	45.1–48.8	47.0	44.7–49.2	0.986[a]
Living with partner	56%		71%		63%		0.004[b,c]
Work ≥ 50%[d]	60%		87%		81%		<0.001[b,e]
Anxiety (HADS)	8.0	7.3–8.7	3.3	3.0–3.7	5.8	5.2–6.5	<0.001[a]
Depression (HADS)	6.4	5.9–6.9	1.5	1.3–1.8	3.3	2.9–3.7	<0.001[a]
Anxiety (HADS) >7	51%		10%		28%		<0.001[b,f]
Depression (HADS) >7	34%		0%		8%		<0.001[b,f]
PF[g]	62.7	59.1–66.2	93.1[h]	91.3–94.8	85.3[h]	82.5–88.2	<0.001[h]
RP[g]	34.7	29.5–39.8	95.1	92.8–97.4	76.4	71.0–81.8	<0.001[a]
BP[g]	46.5	43.2–49.8	84.2	81.9–86.6	72.8	69.1–76.4	<0.001[a]
GH[g]	36.8	34.1–39.5	82.3	80.1–84.5	63.8	60.5–67.1	<0.001[a]
SF[g]	55.1	51.3–58.8	95.8	94.3–97.2	84.4	81.3–87.4	<0.001[a]
RE[g]	47.4	41.5–53.3	97.2	95.7–98.8	77.7	72.1–83.3	<0.001[a]
MH[g]	56.9	54.0–59.8	86.8	85.2–88.4	74.0	71.3–76.6	<0.001[a]
PF[g]	62.7	59.1–66.2	93.1[h]	91.3–94.8	85.3[h]	82.5–88.2	<0.001[h]
RP[g]	34.7	29.5–39.8	95.1	92.8–97.4	76.4	71.0–81.8	<0.001[a]

Abbreviations see Table 1

[a] One-Way ANOVA, $p < 0.001$ remained after correction with Bonferroni.

[b] Chi-square.

[c] Pair wise sub analysis: statistically difference only between high and low, $p = 0.001$.
[d] Separate analysis on persons with age < 65 yrs.
[e] Sub analysis: $p < 0.001$ remains between high and low and high and intermediate clusters.
[f] Sub analysis: $p < 0.001$ for all combinations.
[g] Domains from SF-36, description in the method section..
[h] One-way ANOVA, correction with Bonferroni $p = 0.001$ between low and intermediate fatigue clusters.

Table 3. Distribution (%) of exercise habits, sedentary behaviour, sleep, rest and smoking divided and compared by clusters of fatigue

Cluster of fatigue	High n=221	Low n=240	Intermediate n=155	p-value[a]
Exercise (/week)				<0.001[b]
Never	29	8	17	
Irregularly	32	24	27	
1 time	12	21	17	
2 times	13	22	21	
3 times	12	24	15	
Sitting down (/day)				0.281[c]
Not at all	14	17	17	
Less than half the day	28	32	30	
About half the day	38	26	32	
All day	20	25	21	
Sleep (hours/night)				<0.001[d]
<5	13	2	6	
5–9	74	97	93	
>9	12	1	2	
Daytime sleep				<0.001[e]
Occasionally	74	97	94	
≥ 2 times/week	26	3	6	
Daytime rest (≥30 min)				<0.001[f]
Occasionally	60	95	90	
≥ 2 times/week	39	5	10	
Current smoker	20	13	20	0.057[g]

[a] Chi-square
[b] High vs. low $p < 0.001$, high vs. intermediate $p = 0.012$, low vs. intermediate $p = 0.014$
[c] High vs. low $p = 0.063$, high vs. intermediate $p = 0.647$, low vs. intermediate $p = 0.667$
[d] High vs. low $p < 0.001$, high vs. intermediate $p < 0.001$, low vs. intermediate $p = 0.073$
[e] High vs. low $p < 0.001$, high vs. intermediate $p < 0.001$, low vs. intermediate $p = 0.054$
[f] High vs. low $p < 0.001$, high vs. intermediate $p < 0.001$, low vs. intermediate $p = 0.029$
[g] High vs. low $p = 0.030$, high vs. intermediate $p = 0.983$, low vs. intermediate $p = 0.044$

Department of Neurobiology, Care Sciences and Society
Division of Nursing

Fatigue – perceived, described and assessed by persons with systemic lupus erythematosus

AKADEMISK AVHANDLING
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Abstract

Fatigue is an individual and subjective sensation interfering with daily living for patients with several chronic conditions. Systemic lupus erythematosus (SLE) is characterized by inflammation in different organs combined with immunological abnormalities. The complexity of the disease SLE has several consequences for daily living, and fatigue is among one of the most burdensome symptoms of SLE. The impact of fatigue in a person's life is difficult for others to understand. Therefore, to better understand the enigma of fatigue, how fatigue can be measured and patient's descriptions of how fatigue is experienced are necessary.

Aim: The overall aim of this cohort-based project, was to explore patients experiences of symptoms related to SLE with a main focus on fatigue, how it is described and measured.

Subjects: 327 patients from the SLE-cohort at Karolinska University Hospital, Solna, and 311 age- and gender- matched control persons contributed to the data. Both qualitative and quantitative data have been used, with interview material from focus group discussions (study I), free-written answers (study II) and self-assessments measures/questionnaires (study II+III+IV).

Results: In study I, women (n=33) in seven focus group discussions (FGD) described their experience of SLE-related fatigue; how they perceived the feeling of fatigue, impact on life and strategies developed to manage fatigue in daily living. Transcripts from the FGD were analyzed using content analysis. The results were presented as four themes where the "Nature of fatigue" involved the sensation, occurrence and character of fatigue, "Aspects affected by fatigue" described emotions that arose with fatigue as well as aspects of work, family life, social contacts, and leisure activities that were affected by SLE related fatigue; "Striving towards power and control" described a balance of strategies used to manage daily life and were categorized into mental struggle, structure, restrict, and provide; "Factors influencing the perception of fatigue" described understanding from surrounding persons and the pain as strongly influencing the experience and perception of fatigue. The result from the open questions in study II (n=324), showed that fatigue and pain were reported as most troublesome symptoms of SLE, followed by musculoskeletal symptoms. In study III (n=51) in groups of 6-9 patients patents filled in seven questionnaires about fatigue; Numeric rating scale (NRS), Chalder fatigue scale, Vitality from SF-36, Fatigue Severity Scale, Multi-dimensional Assessment of Fatigue, Multidimensional Fatigue Inventory and Functional Assessment of Chronic Illness Therapy – Fatigue. This followed by a dialogue procedure resulting in 260 contrasting assessment. The minimally clinically important difference for the seven measures of fatigue was calculated using the comparative assessment as anchor. All measures of fatigue used in the study seemed to capture differences as experienced by the group of patients themselves, least favorable was however the one question (NRS) this were strengthen by patients free written comments. In study IV (n=305 patients and 311 controls) three clusters of fatigue were identified. The High fatigue cluster (n = 221) had most symptoms of anxiety/depression, lowest health related quality of life and were dominated by the patients (80%). Participants in the Low fatigue cluster (n = 240, controls 78%) reported more physical exercise and less smoking than the other clusters.

Conclusion: Patients description of SLE related fatigue (study I) provide important knowledge that can be used in educational discussions with patients as well as health care workers. The recommended measures of fatigue, evaluated in this thesis, can detect clinically important differences as perceived by the patients (study III). Not all patients with SLE experienced distress from current illness, 10 % reported that they did not perceive any SLE related symptom (study II) and 17% had low levels of fatigue and healthy behavior (physical exercise, non-smoker)(study IV). With special focus on fatigue, this thesis contributes to the understanding of patients' experience of SLE. Knowledge of the experience of symptoms from the patients' perspective is pivotal in order to support the patient, facilitate assessment and choice of treatment as well as generate a base for appropriate intervention programs.

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