

Fatigue in persons with rheumatoid arthritis

**A person-centered
physical therapy approach**

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ABSTRACT

Fatigue is a prominent symptom in persons with rheumatoid arthritis (RA) with great impact on daily life. Despite the improvement in pharmacological treatment of RA over the last decades, a large number of persons with RA experience consequences from fatigue. From a patient perspective, fatigue is established as one of the most important symptoms to address in rheumatology.

The overall aim of this thesis was to search for deeper knowledge about fatigue in persons with RA of working age and to evaluate a person-centered physical therapy treatment to reduce fatigue and its consequences on daily life.

Specific aims of the studies included in the thesis were:

To describe how persons with RA experience and manage their fatigue in daily life.

To investigate variations in fatigue levels reported by persons with RA at seven different time-points during the four seasons.

To investigate how disease-related aspects contribute to the variation in general fatigue and multiple aspects of fatigue in persons with RA at four time-points during the four seasons.

To examine effects of a person-centered physical therapy intervention, with focus on health-enhancing physical activity and balance in life, on fatigue-related variables in persons with RA.

Methods: Qualitative and quantitative methods were used in this thesis, including one qualitative interview study in focus groups, two quantitative observational longitudinal studies and one randomized controlled trial. Participants, diagnosed with RA and of working age, were recruited from the rheumatology clinic at Sahlgrenska University hospital.

Results: The participants described their fatigue to be associated with negative emotions and an imbalance in daily life due to increased need for rest. They also described difficulties to obtain understanding for their fatigue from significant others and healthcare, forcing the participants to manage their fatigue symptoms

by themselves. A variation in fatigue levels was found over time and season with higher levels of physical fatigue during winter. Pain threshold and depressive mood were the strongest explanatory and predictive factors for variations in fatigue over time. Person-centered physical therapy showed significant and sustained effects in reducing fatigue, as well as improving physical function and health in the intervention group compared to the reference group.

In conclusion: Fatigue causes considerable consequences for persons with RA of working age which draws attention to the importance of developing new modes of treatment to address fatigue in RA. Fatigue, especially the physical aspects, was worse during the winter and pain threshold and depressive mood influenced the variation in fatigue. This highlights the importance of promoting physical activity especially during wintertime to lessen fatigue in persons with RA. Person-centered physical therapy focusing on health-enhancing physical activity and balance in life can be recommended as an intervention for fatigue management in persons with RA.

Keywords: fatigue, rheumatoid arthritis, person-centered, physical therapy, physical activity, qualitative content analysis, focus groups, longitudinal study, randomized controlled trial, outcome measures

SAMMANFATTNING PÅ SVENSKA

Reumatoid artrit (RA) är en autoimmun, systemisk, inflammatorisk ledsjukdom som medför smärta, funktionshinder, och psykisk ohälsa. Trötthet är trots adekvat farmakologisk behandling ett vanligt symtom hos personer med RA som medför betydande konsekvenser i vardagen. Tillsammans med smärta beskrivs tröttheten vara det mest framträdande symtomet vid sjukdomen.

Det övergripande syftet med denna avhandling var att söka fördjupad kunskap om trötthet hos personer med RA i arbetsför ålder och att utveckla en personcentrerad fysioterapeutisk behandlingsmodell för att lindra tröttheten och dess konsekvenser i det dagliga livet.

Avhandlingen består av fyra delarbeten vars specifika syften var att:

Beskriva hur personer med RA upplever och hanterar sin trötthet i vardagen.

Undersöka hur tröttheten hos personer med RA varierar över tid och om det finns en årstidsvariation.

Undersöka hur sjukdomsrelaterade aspekter bidrar till att förklara och predicera trötthetens variation över tid.

Utveckla en personcentrerad fysioterapeutisk intervention med fokus på hälsofrämjande fysisk aktivitet och balans i vardagen och undersöka dess effekter på trötthet och aspekter relaterade till trötthet hos personer med RA.

Det första delarbetet var en kvalitativ intervjustudie i fokusgrupper. Delarbete 2 och 3 var kvantitativa observationsstudier över tid och det fjärde delarbetet var en randomiserad kontrollerad behandlingsstudie. Personer med RA i arbetsför ålder rekryterades från reumatologkliniken på Sahlgrenska Universitetssjukhuset.

Resultat. Deltagarna beskrev att tröttheten orsakade en obalans i vardagen på grund av ett ökat behov av vila och sömn. Tröttheten medförde negativa känslor i form av skuld och skam, samt att det var svårt att få förståelse för tröttheten från omgivningen vilket medförde att deltagarna var tvungna att på egen hand ta ansvar för att hantera sin trötthet. Tröttheten varierade över tid med högre fysisk trötthetsnivå under vintern. Smärtröskel och depressiva symtom var de faktorer som bäst kunde förklara och predicera trötthetens

variation över tid. En personcentrerad fysioterapeutisk behandling visade betydande och kvarstående effekter med minskad trötthet och förbättrad fysisk funktion och hälsa.

Sammanfattningsvis visar avhandlingen att tröttheten medför betydande konsekvenser för personer med RA i arbetsför ålder, vilket uppmärksammar vikten av att utveckla nya behandlingsstrategier riktat mot trötthet. Tröttheten varierade signifikant under ett år. De fysiska aspekterna av trötthet var högst under vintern, vilket kan betyda att fysisk aktivitet för att minska tröttheten, är särskilt viktig under vintern. Smärtröskel och depressiva symptom visade sig ha betydelse för trötthetens variation över tid. Personcentrerad fysioterapi med fokus på hälsofrämjande fysisk aktivitet och balans i vardagen är en behandling som kan rekommenderas för att minska trötthet hos personer med RA.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Feldthusen C, Björk M, Forsblad-d'Elia H, Mannerkorpi K. **Perception, consequences, communication, and strategies for handling fatigue in persons with rheumatoid arthritis of working age - A focus group study.** Clin Rheumatol. 2013. 32(5): p. 557-66
- II. Feldthusen C, Grimby-Ekman A, Forsblad-d'Elia H, Jacobsson L, Mannerkorpi K. **Seasonal variations in fatigue in persons with rheumatoid arthritis: A longitudinal study.** *Submitted Manuscript*
- III. Feldthusen C, Grimby-Ekman A, Forsblad-d'Elia H, Jacobsson L, Mannerkorpi K. **Explanatory factors and predictors of fatigue in persons with rheumatoid arthritis: A longitudinal study.** *Submitted Manuscript*
- IV. Feldthusen C, Dean E, Forsblad-d'Elia H, Mannerkorpi K. **The effects of person-centred physical therapy on fatigue related variables in persons with rheumatoid arthritis: A randomized controlled trial.** *Submitted Manuscript*

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ABBREVIATIONS

6MWT	Six-Minute Walk Test
ACR	American College of Rheumatology
ASES	Arthritis Self-Efficacy Scale
BMI	Body Mass Index
BRAF-MDQ	Bristol Rheumatoid Arthritis Fatigue-Multi-Dimensional Questionnaire
DAS 28	Disease Activity Score
DMARD	Disease Modifying Anti Rheumatic Drug
EULAR	European League Against Rheumatology
ESR	Erythrocyte Sedimentation Rate
EQ	Euro QoL (Quality of Life)
HADS	Hospital Anxiety and Depression Scale
HAQ	Health Assessment Questionnaire
ICD-10	International Classification of Diseases
LTPAI	Leisure Time Physical Activity Index
OMERACT	Outcome Measures in Rheumatology Clinical Trials
RA	Rheumatoid Arthritis
STS	1-minute Sit To Stand test
VAS	Visual Analogue Scale
WCPT	World Confederation for Physical Therapy
WHO	World Health Organization

DEFINITIONS IN SHORT

Fatigue	An overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work (<i>Repping-Wuts, 2009</i>)
Person-centeredness	In a person-centered approach patients are seen as persons with reasons, will, feelings and needs. Person-centeredness focuses on the partnership between patient and healthcare provider and include sharing of information, shared deliberation and shared decision-making (<i>Ekman et al., 2011</i>)
Physical activity	Any bodily movement produced by skeletal muscles resulting in energy expenditure (<i>Caspersen et al., 1985</i>)
Health-enhancing physical activity	Refers to the recommendation for adults from the American College of Sports Medicine and the American Heart Association, i.e., moderately-intense aerobic physical activity for a minimum of 30 min, five days a week, or vigorous aerobic physical activity for a minimum of 20 min, three days a week or some combination of moderately-intense and vigorous activity (<i>Huskell et al., 2007</i>)
Balance in life	The way a person's intentions, resources and environment match their goals in life (<i>Grönblom-Lundström, 1992</i>)
Function	Refers to the International Classification of Functioning, Disability and Health (ICF) and the umbrella term of functioning encompassing body functions and structures, activities and participation (<i>WHO, 2001</i>)

INTRODUCTION

Persons with rheumatoid arthritis (RA) suffer from an autoimmune inflammatory joint disease. The pharmacological treatment of RA has improved substantially over the last decades, contributing to a better control of inflammation, reduced joint damages and better maintenance of function (1). However, despite adequate pharmacological treatment a large number of persons with RA describe that they suffer from fatigue which has been increasingly noticed during the recent years. From a patient perspective, fatigue is established as one of the most important issues in rheumatology (2). It is, beside pain, expressed as the most prominent symptom in RA (3-5), and has been described as having a greater impact on daily life than pain (5). Although fatigue is a common symptom of RA no current treatment for fatigue in RA has been described other than standard pharmacological treatment (6) and only few studies have focused on fatigue management (6, 7). Therefore, little is known about the management of fatigue in persons with RA and both patients and healthcare professionals describe that fatigue mainly is left for the persons with RA to manage on their own (5, 8-10). Fatigue impacts individuals differently due to personal and environmental circumstances, thus the management of fatigue in persons with RA needs to include several perspectives. The concept of person-centeredness is compelling (11-14) and has been shown to augment treatment planning concordance between patient and healthcare provider, improve health outcomes and increase patient satisfaction (11).

Person-centeredness

Person-centeredness emanates from a holistic approach that views each person through a biological, psychological and social perspective (12). In a person-centered approach patients are seen as persons, as a human with reasons, will, feelings and needs (11). In this context the concept of being a person is about identity, *who* you are, being someone unique and irreplaceable while a patient is about *what* you are, a role that can be assumed and replaced. This definition of being a person is based upon theories on personalism (15). The identity of a person, *who* you are, can only be brought about through communication (16, 17). Therefore the patient narrative forms the basis in a person-centered approach (15). However, the identity of the person in a healthcare setting is always communicated through the role of being a patient. Being a person, being

human includes the possession of being capable (16, 18). This implies that persons with chronic conditions are capable of enhancing their health and are active partners in the rehabilitation process (12). However, a capable person is simultaneously always vulnerable. Being vulnerable is part of being human and allows us to be open in relation to others. In this way a person is both capable and vulnerable (15, 16).

As well as highlighting the uniqueness and autonomy of each person (12), person-centeredness embraces interpersonal relationships and interactions with others (13). Person-centeredness focuses on the partnership between patient and healthcare provider in which the patient's individual wishes, needs and resources forms the basis for shared decision-making (11, 14). Acknowledging that both the patient and the healthcare provider are persons, makes them equal in the rehabilitation process but with different knowledge and competences. The patient contributes knowledge about her/his body, access to resources, preferences and life situation and the healthcare provider contributes professional knowledge. The partnership, sharing of information and shared deliberation leads to a common understanding and the opportunity to shared decision-making (15).

However, a definition of and consensus about the elements of person-centeredness has not been established (14), and a need exists for elucidation and elaboration of the concept across clinical settings (13). In this thesis, person-centeredness is defined, based on the standards outlined in a position paper by the Swedish center for person-centered care (University of Gothenburg Centre for Person-Centered Care, GPCC) (11). Consistent with these standards, person-centered care starts with partnership building based on the persons narrative and includes sharing of information, shared deliberation and shared decision-making and documentation (11).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic, inflammatory, autoimmune disorder characterized by synovial inflammation and associated damage to articular cartilage and underlying bone (1, 19). The predominant symptoms are pain, stiffness, and swelling of peripheral joints but the clinical features also include extra-articular involvement (e.g., vasculitis), comorbidities (e.g., coronary heart disease and infections) and patient-related factors (e.g., symptoms of weakness, fatigue, weight loss, and depression). The clinical course is variable, ranging from mild arthritis to progressive multisystem inflammation (1, 19, 20).

The etiology is unclear but the risk of developing RA is attributed to genetic factors as well as environmental factors. The dominant environmental risk factor is smoking which doubles the risk of developing RA (1, 19, 21). The prevalence of rheumatoid arthritis in developed countries is about 0.5–1.0% in an adult population (1, 22). The disease is three times more frequent in women than men and the prevalence rises with age and is highest in women older than 65 years (1, 21). In Sweden, the prevalence is about 0.7% (23, 24).

Table 1. The American College of Rheumatology (ACR) 1987 revised criteria and the ACR and European League Against Rheumatism (EULAR) 2010 new classification criteria for early arthritis.

ACR 1987 criteria	ACR/EULAR 2010 criteria
<ol style="list-style-type: none"> 1. Morning stiffness (at least 1h) 2. Arthritis of three or more joint areas 3. Arthritis of hand joints (≥ 1 swollen joint) 4. Symmetrical arthritis 5. Rheumatoid nodules 6. Serum rheumatoid factor 7. Radiographic changes (erosion) 	<ol style="list-style-type: none"> 1. Joint involvement (0–5) <ul style="list-style-type: none"> • One medium-to-large joint (0) • Two to ten medium-to-large joints (1) • One to three small joints (large joints not counted) (2) • Four to ten small joints (large joints not counted) (3) • More than ten joints (at least one small joint) (5) 2. Serology (0–3) <ul style="list-style-type: none"> • Negative RF and negative ACPA (0) • Low positive RF or low positive ACPA (2) • High positive RF or high positive ACPA (3) 3. Acute-phase reactants (0–1) <ul style="list-style-type: none"> • Normal CRP and normal ESR (0) • Abnormal CRP or abnormal ESR (1) 4. Duration of symptoms (0–1) <ul style="list-style-type: none"> • Less than 6 weeks (0) • 6 weeks or more (1)
<p>Four of these seven criteria must be present to fulfill the diagnosis of RA. Criteria 1–4 must have been present for at least 6 weeks.</p>	<p>Points are shown in parentheses. Cut-point for rheumatoid arthritis 6 points or more. Patients can also be classified as having rheumatoid arthritis if they have: (a) typical erosions; (b) long-standing disease previously satisfying the classification criteria.</p>

RF=Rheumatoid Factor, ACPA=Anti-Citrullinated Protein Antibodies, CRP=C-Reactive Protein, ESR=Erythrocyte Sedimentation Rate.

Classification criteria

The American College of Rheumatology (ACR) 1987 classification criteria for RA (25), were defined to identify persons with established RA. However, the criteria are limited by poor sensitivity and specificity and fail to identify individuals with very early arthritis who subsequently develop RA (26). New classification criteria have been developed by the ACR and European League Against Rheumatism (EULAR) 2010 for classifying persons in early disease (26). The classification criteria from 1987 and 2010 are presented in Table 1.

In this thesis, persons with RA, diagnostic codes M05 (Seropositive rheumatoid arthritis) and M06 (Other rheumatoid arthritis) according to the International Classification of Diseases, Tenth revision (ICD-10) (27), were recruited. This means that before 2010 patients were classified according to the 1987 criteria and after 2010 patients have been able to be classified according to the 1987 and the 2010 criteria.

Treatment of persons with RA

The research in RA is making major progress in understanding the pathogenesis of the disease and in developing new efficient treatment approaches. The key treatment goal in RA is remission with no active joint inflammation and no erosive or functional deterioration. It is estimated that 10–50% of patients with early RA achieve remission (1, 19). Other important goals are reduced disease activity (if not remission can be achieved), reduced pain, maintenance of function, and preservation of work and recreational activities (1, 19). The 2013 update of the EULAR RA management recommendations on pharmacological treatment brings the patient into focus stating, in the first overarching principle, that “treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist” (28).

Pharmacological treatment. The key component in treatment of RA is early and aggressive treatment with synthetic and/or biological Disease Modifying Anti Rheumatic Drugs (DMARDs) (29), to reduce inflammation and joint damage (19). Pharmacological treatment of RA also include treatment of symptoms such as pain and stiffness using analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), treatment of comorbidities such as osteoporosis, cardiac disease and depression and treatment of systemic complications such as lung disease and vasculitis (1).

Non-pharmacological treatment. In addition, in persons with RA non-pharmacological treatments play an active role in the management of the disease and are important to maintain and improve health, function and to reduce risk-

factors of comorbidities (1, 30). Also, to support the persons with RA in coping with consequences of the disease are important in the management of RA (30). Non-pharmacological treatments include physical activity/exercise, self-management, joint protection, foot care and psychological support (1, 30) and are given by a multidisciplinary team of e.g. rheumatologists, nurses, physical therapists, occupational therapists and psychologists (1). Strongest evidence, among non-pharmacological treatments, has been found for physical activity/exercise and self-management programs (30). Patients' education delivered by a multidisciplinary team, is also of major importance in the treatment of RA (1).

Fatigue

Fatigue is a common symptom in many chronic conditions as well as in the general population (31). In fact, in a large population-based study, fatigue was found to be the second most common symptom after neck- and back pain (32). There is no definition of consensus for fatigue. However, fatigue is often defined as "an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work" (6). A distinction between normal non-pathological fatigue and pathological fatigue associated with chronic illness has been described, suggesting that non-pathological fatigue relates to brief periods of fatigue that lasts less than three months and has an identifiable cause, whereas pathological fatigue relates to prolonged (1-5 months) or chronic (>6 months) fatigue with the precise cause unclear but likely multidetermined (31). Chronic fatigue may be constant or recurrent, it is not dispelled easily by sleep or rest and it can have a profound negative impact on the person's quality of life (6). Chronic fatigue in the general population seems to be associated with psychological factors such as depression, anxiety or emotional stress. Physical inactivity also seems to be a risk-factor for chronic fatigue (33).

Fatigue in persons with RA

Persons with RA describe their fatigue as multidimensional including both physical and mental aspects (5, 9). It is described as overwhelming and uncontrollable with consequences impacting on every sphere of life including work life, family life and social life thereby causing an imbalance in life (5, 9). The fatigue has been found to affect health-related quality of life as different aspects of fatigue explained several dimensions of health-related quality of life (34). In persons with RA, the physical aspects of fatigue explained function, pain, vitality, physical role limitations and general health while mental aspects of fatigue explained mental health and emotional role limitations (34).

The prevalence of fatigue varies from 42%-80% (3, 4, 35, 36), the wide range being due to different definitions of fatigue and different methods of measuring fatigue in different studies. Severe fatigue has been reported in about 40-50% of persons with RA (35, 36). There are inconsistent results about causes and consequences of fatigue (37). The fatigue in RA is suggested to be caused by proinflammatory cytokines (19). However, despite improvement of pharmacological treatment of inflammation, a large number of persons with RA describe that they suffer from fatigue and the effect of biological DMARDs on fatigue is regarded as small (38). Strongest evidence is found for associations between fatigue in RA, and pain (3, 35, 37, 39-42), disability/physical function (3, 36, 37, 39, 43) and depression/depressive mood (3, 35, 37, 39, 44, 45).

There are individual differences in the experience, impact and management of fatigue (46) and persons with RA experience that their fatigue varies over time concerning duration and frequency (9). Younger women with multiple daily roles describe the most negative impact of fatigue (47). A conceptual model for fatigue in RA suggests fatigue as being dependent on the interactions between the disease process, thoughts, feelings, behaviors and personal life issues (48), Figure 1.

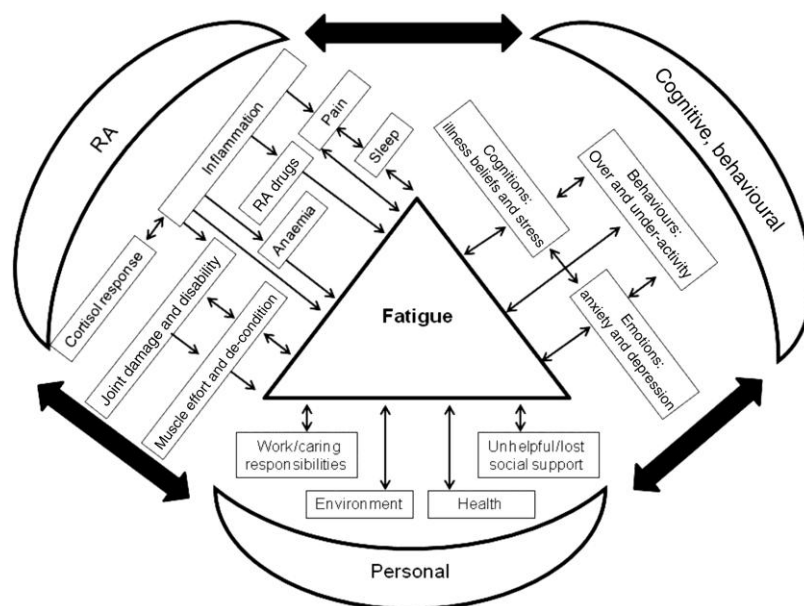


Figure 1. Conceptual model of RA fatigue. © Hewlett et.al 2011

Measuring fatigue in persons with RA

The assessment and quantification of fatigue makes it possible to study fatigue (6). To evaluate and quantify fatigue, patient reported outcome measures are used (49). Outcome Measures in Rheumatology Clinical Trials, (OMERACT), is an international network of professionals in rheumatology initiated in 1992 aiming at improving outcome measurement in rheumatology. An executive committee prepares and updates recommendations which include core sets of measurements for most of the major rheumatologic conditions. The core set for RA include outcome measures of pain, tender joints, swollen joints, patients overall opinion, clinicians overall opinion, function and radiographs (50). Since 2002 patients have been actively engaged in the process (51). As fatigue has a negative impact on daily life in persons with RA, the OMERACT group now recommends that measurements of fatigue also should be included in RA clinical trials (2).

Numerous questionnaires to assess fatigue have been developed, assessing fatigue in general and/or multiple aspects of fatigue. Although consensus has been reached to include measurements of fatigue in RA clinical trials (2) there is no gold standard measuring fatigue in RA and many different questionnaires are used, all with different benefits and drawbacks (52, 53). Traditionally fatigue is measured by single-item measures assessing general fatigue, e.g., a one-dimensional visual analogue scale (VAS). In addition, due to the multidimensional nature of fatigue, measurements that measure multiple aspects of fatigue including consequences and impacts are recommended (37, 54, 55). Such fatigue measures provides sub-scores that incorporate e.g. physical and mental aspects of fatigue and measures severity of fatigue as well as consequences due to fatigue (52). It appears that measures of general fatigue or multiple aspects of fatigue are useful in different contexts (54, 56). Both single-item measures of general fatigue and multidimensional measures of fatigue seem to assess mainly fatigue severity, but they differ in their measurement precision. If precise assessment is required, for instance in longitudinal settings, multidimensional fatigue measures appear to be a better choice (54).

Treatment of fatigue in persons with RA

Although fatigue is a common symptom in RA, few studies have focused on fatigue management (7). Pharmacological treatment with biological DMARDs is regarded to have positive effects on fatigue in persons with RA (19, 38). However, the overall effect size of all biological therapies vs. placebo, in reducing fatigue, is considered as small (38). In addition to pharmacological treatment, non-pharmacological strategies are considered important for fatigue management.

Non-pharmacological interventions include rest, relaxation, physical activity/exercise, education, counseling, rehabilitation and energy conservation (57). General fatigue and the physical aspects of fatigue have been found to be the most prominent aspects of fatigue among persons with RA (34) and therefore treatments focusing on these aspects of fatigue would be of special importance. Physical activity/exercise has been found to be the non-pharmacological intervention with the strongest evidence to reduce fatigue (7) and to improve sleep quality in persons with RA (58). Especially the physical aspects of fatigue have been found to benefit from physical activity/exercise (34). Cognitive behavioral therapy also shows evidence to reduce fatigue in RA (59, 60). However, as fatigue influences life on personal, environmental and social levels, the treatment of fatigue in persons with RA needs to assume a holistic perspective taking each person's individual circumstances into account.

Physical Therapy

Physical therapy was described in 2007 by The World Confederation for Physical Therapy (WCPT) as follows: "Physical therapy provides services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan. This includes providing services in circumstances where movement and function are threatened by ageing, injury, disease or environmental factors. Functional movement is central to what it means to be healthy" (61).

The aim of physical therapy is to promote health, to prevent illness and to relieve and cure illness and injury as well as to achieve, maintain or restore optimal function to be able to participate in daily life activities and work life (62). From a physical therapy perspective, a patient is regarded as a physical, mental, social and existential whole (62).

Physical therapy in persons with RA

The main goal of physical therapy in RA is to restore or maintain optimal physical function (63). Physical therapy in persons with RA focus in particular on monitoring a patient's physical function and performance, to educate the patient regarding the optimal management of daily tasks and to encourage healthy physical activity behavior in everyday life (63, 64).

Recommendations concerning physical therapy treatment include physical exercise and education on physical activity whereas passive interventions such as: heat and cold, mechanical, electric and electromagnetic energy, massage and

passive mobilization/manipulation can neither be recommended nor discharged due to conflicting evidence or lack of evidence (64). There is a growing body of evidence demonstrating the benefit of physical activity and physical exercise on functional limitation, disability, comorbidities, and quality of life in persons with RA (63-67). However, in the physical therapy treatment of persons with RA several points of attention need to be considered including: extent of damage to cartilage, bone, surrounding tendons and articular capsule; deformities and instability of joints; presence of rheumatoid nodules; high level of disease activity and radiographic damage; presence of joint prostheses; and presence of complications of RA or co-morbidity (64).

Physical activity in persons with RA

Physical activity is defined as “any bodily movement produced by skeletal muscles resulting in energy expenditure”, and includes all kinds of movements or tasks a person performs (68).

Physical exercise a subcomponent of physical activity defined as “physical activity that is planned, structured, and repetitive and has a final or an intermediate objective: the improvement or maintenance of physical fitness” (68).

Physical fitness is defined as “a subset of attributes that people have or achieve that relates to the ability to perform physical activity” (68).

Physical activity/exercise, supervised or incorporated into daily life, is found to have specific health benefits in people with RA and is an important component of RA management. Physical activity/exercise has been shown to improve overall function in persons with RA and to promote health without exacerbating disease activity and pain (65, 69). Thus, all persons with RA should be encouraged to include some form of physical activity/exercise as part of their routine care (65, 69). The recommendations of physical activity/exercise in persons with RA conform to the recommendations for healthy adults developed by the American College of Sport Medicine and the American Heart Association (65, 70). These recommendations state that to promote and maintain health, all healthy adults between 18-65 y need moderately-intense aerobic (endurance) physical activity/exercise for a minimum of 30 min, five days a week, or vigorous aerobic physical activity for a minimum of 20 min, three days a week or some combination of moderately-intense and vigorous activity. Along with aerobic physical activity/exercise, persons with RA are recommended to include strengthening and flexibility exercises to reduce pain and improve function (65, 71).

Despite evidence of substantial benefits of physical activity/exercise, persons with RA are less physically active than a general healthy population (72). Fatigue

has been found to contribute to the reduced physical activity in persons with RA (73). Therefore incorporating physical activity into the routine of daily life is considered important to enhance constancy over time. A coaching program for healthy physical activity in persons with RA, led by physical therapists, was found to improve perceived health status (74). The persons more severely affected by their disease seemed to benefit most from this structured coaching program (75) indicating the diversity of needs among persons with RA and the importance of including the patients, all with specific resources and life situations, in the treatment planning.

Summary

Fatigue in persons with RA is a complex concept in which biological, physiological, psychological and social mechanisms interact (6). Greatest negative impact of fatigue has been described in younger persons with multiple daily roles (47). Therefore, in this thesis we chose to include only persons of working age who are likely to have multiple daily roles and high demands in life and thereby are vulnerable to several factors affecting fatigue. The knowledge about the impact of fatigue in persons with RA, of working age, with multiple daily roles and high demands in life is limited.

As the impact of fatigue differs among persons with RA, the treatment of fatigue needs to consider each person's circumstances. However, interventions can best be designed and tested if the causal pathway of fatigue in RA is understood (76). To date, there are inconsistent conclusions about causes and consequences of fatigue (37). Also, little is known about fluctuations in fatigue over time and season. As most studies investigating associations with fatigue are cross-sectional, longitudinal studies that measure fatigue regularly over time are necessary to gain more knowledge about fatigue (36).

Among persons with RA, general and physical aspects of fatigue have been found to be the most prominent aspects of fatigue (34) and therefore, treatments for fatigue that improves these aspects are of importance. Physical activity/exercise programs are suggested to be especially beneficial in the treatment of physical fatigue (34). At the same time, fatigue has been found to be a contributor to reduced physical activity in persons with RA (73) and having RA has been found to have an extensive impact on activity pattern causing an imbalance in life (77). Therefore, to optimize and incorporate physical activity in everyday life and to enhance balance in life, a program comprising a person-centered approach (11) was used for the management of fatigue in this thesis.

AIM

The overall aim of this thesis was to search for deeper knowledge about fatigue in persons with RA of working age and to design and evaluate a person-centered physical therapy treatment to reduce fatigue and its consequences on daily life.

Specific aims

Specific aims of the studies included in the thesis were:

Study I

To describe how persons with RA experience and manage their fatigue in everyday life.

Study II

To investigate variations in fatigue levels reported by persons with RA at seven different time-points during the four seasons.

Study III

To investigate how disease-related aspects contribute to the variation in general fatigue and multiple aspects of fatigue in persons with RA at four time-points during the four seasons.

Study IV

To examine effects of a person-centered physical therapy intervention, with focus on health-enhancing physical activity and balance in life, on fatigue-related variables in persons with RA.

METHODS

This thesis comprises four studies using both qualitative and quantitative research designs. Qualitative research methodology is used when the aim is to understand and describe qualities and characteristics of a phenomenon (78). Qualitative interviews were in this thesis chosen to describe experiences of fatigue in daily life (Study I). The aim of the quantitative research methodology was to, in a longitudinal study design, explain and predict variations in fatigue (Study II) and disease-related factors associated with this variation (Study III). Quantitative research methodology was also used in a randomized controlled trial examining effects of a person-centered physical therapy intervention on fatigue-related variables (Study IV).

All studies were conducted at the Sahlgrenska University hospital, Gothenburg, Sweden, and all participants were current patients at the rheumatology clinic and of working age. An overview of the research designs are presented in Table 2.

Table 2. Research design overview

	Study		
	I	II & III	IV
Study design	Qualitative interview study	Observational longitudinal study	Randomized controlled trial
Recruitment	The administrative register at the rheumatology clinic, Sahlgrenska University hospital	The administrative register at the rheumatology clinic, Sahlgrenska University hospital	The Swedish Rheumatology Quality register(SRQ) at Sahlgrenska University hospital
Study population	Persons with RA of working age	Persons with RA of working age	Persons with RA of working age
Number of participants	n=25	n=65	n=70 Intervention group (n=36) Reference group (n=34)
Data collection	Short questionnaire on demographics Focus group interview	Standardized interview on demographics Self-reported questionnaires Clinical examination Performance-based test	Standardized interview on demographics Self-reported questionnaires Clinical examination Performance-based test
Analysis	Qualitative content analysis	Multiple linear regression models	Non-parametric within- and between- group comparisons

Study participants

In Study I, II and III all the participants were diagnosed before 2010 according to the 1987 criteria. In Study IV, 65 participants were diagnosed before 2010 according to the 1987 criteria and five participants were diagnosed 2010 or later according to the 1987 or the 2010 criteria.

Study I

A total of 25 participants, 19 women and six men, were included in this focus group interview study.

Inclusion criteria: Diagnosis of RA, diagnosis codes M05 and M06, according to ICD-10 (26), being of working age (20–60 years) and a fatigue level >3 on a verbal 0-10 scale from “no fatigue” to “worst imaginable fatigue”.

Exclusion criteria: Other primary physical or mental illness or inability to understand and speak Swedish.

Initially 49 persons were interested in participating of whom 25 participated in a focus group discussion. Of the 24 persons not participating, 15 cancelled for personal reasons and nine did not show up.

Study II & III

Sixty-five participants were included in this observational longitudinal study.

Inclusion criteria: Diagnosis of RA, diagnosis codes M05 and M06 according to ICD-10 (26), being of working age (20–65 years), disease duration >3 years, and stable pharmacological treatment with DMARDs, including synthetic DMARDs, biological DMARDs and glucocorticosteroids, for >3 months prior to entry into the study.

Exclusion criteria: Other primary physical or mental illness or inability to understand and speak Swedish.

Initially, 1627 persons were identified from the clinic administrative register as having a diagnosis code of RA and fulfilling the age criterion. Out of these, 250 persons were randomly selected, using a computerized randomization list, and checked against the inclusion and exclusion criteria by review of the medical records. A letter of invitation was sent to 140 eligible persons of whom 72 were interested in participating and 65 were included in the study. Seven declined to

participate, citing health problems (n=3), a lack of time (n=2), family reasons (n=1) or the study required too much effort (n=1).

Study IV

In total, 70 participants were included in this randomized controlled trial.

Inclusion criteria: Diagnosis of RA, diagnosis codes M05 and M06 according to ICD-10 (26, 27), being of working age (20-65 years), disease activity score DAS-28 <3.8, fatigue rating ≥ 50 on a VAS (0-100), disease duration >3 years and stable pharmacological treatment with DMARDs, including synthetic DMARDs, biological DMARDs and glucocorticosteroids, for >6 months prior to entry into the study.

Exclusion criteria: Other primary physical or mental illness that would prevent participation or inability to understand and speak Swedish.

Participants were recruited from the Swedish Rheumatology Quality register (SRQ). Due to difficulties in recruiting participants several recruitment strategies were performed. A flowchart of the study process is presented in Figure 2. At the first recruitment from the register, a letter of invitation was sent to eligible persons (n=141) based on data from the register and on the review of medical journals. Fifty-five persons met the criteria for the study and agreed to participate. The second recruitment from the register did not include the DAS-28 restriction resulting in letter of invitation to eligible persons (n=34). Twelve persons met the criteria for the study and agreed to participate. In addition, participants were recruited through recruitment notices accessed in the waiting room of the rheumatology clinic. Three persons met the criteria for the study, with exception of the DAS-28 restriction and agreed to participate.

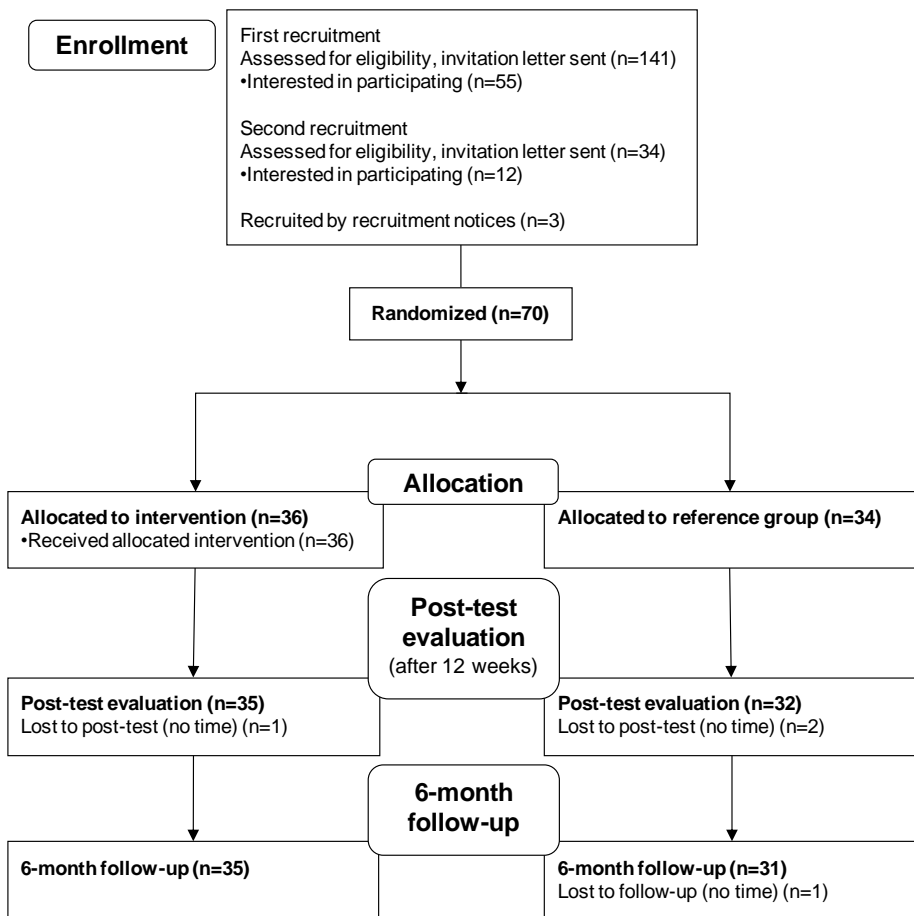


Figure 2. Consort flowchart of the study process in Study IV.

Data collection

Data was collected using qualitative interviews and quantitative outcome measures. The quantitative outcome measures are listed in Table 3 and included demographic data, self-reported questionnaires, clinical assessments and performance-based tests.

Demographic data

Demographic data were recorded in a standardized manner using medical records, a questionnaire in Study I and standardized interview in Study II-IV and included age (years), sex (female/male), disease duration, medication, work status and body mass index (BMI). Disease duration was presented as years since diagnosis according to the medical records. Medication included use of synthetic and biological DMARDs, glucocorticosteroids and analgetics. Work status was divided into categories and presented as: working or studying (full-time or part-time), unemployed, retired, disability benefits (full-time or part-time) and parent's allowance. BMI was calculated as the weight in kilograms divided by the height in square meters (kg/m^2).

Qualitative interviews

In this thesis qualitative interviews in focus groups were used to search for deeper understanding about experiences and management of fatigue in everyday life.

Qualitative research designs are used to understand aspects that are not quantifiable. The strength is to provide open questions without predefined response options and thereby deepen the understanding of a complex phenomenon such as fatigue (78). The researcher is regarded an active part in the construct of new knowledge (78). Even if the aim is to reflect the participants' experiences and opinions, the research process from creating research questions to interpreting and analyzing the data is influenced by the researchers pre-understanding, including previous experience, hypothesis, and professional perspectives (78).

In focus group methodology the social interaction is central for the development of new knowledge (79). This provides opportunities to express individual thoughts and experiences and to share reflections on a common subject. The participants' discussions and questions to each other are anticipated to reveal multiple understandings and meanings and to provide the researcher with a number of different perspectives. In addition, the participants learn from each other and re-evaluate their own understanding (79). Group interactions

that encourage open conversation about complex subjects facilitate the expression of ideas and experiences to reach a deeper understanding. Therefore focus group methodology was chosen in this thesis to be suited to capture the complex phenomenon of fatigue.

Self-reported questionnaires

Fatigue was assessed in this thesis using measures of both general fatigue and multiple aspects of fatigue.

VAS fatigue, a single-item fatigue measure, was used to assess general fatigue (0–100 mm) during the previous week with anchors “no fatigue” and “worst imaginable fatigue”. The VAS fatigue has been found to have good test-retest reliability, construct validity and sensitivity to change in persons with RA (52, 80, 81).

The Bristol Rheumatoid Arthritis Fatigue – Multi-Dimensional Questionnaire (BRAFM-DQ) (Swedish version) (53, 82), was used to measure multiple aspects of RA-specific fatigue during the previous week. The BRAF-MDQ consists of a main score (summa-score) and four sub-scores. The main score “*Total*” measures general fatigue (0–70) and the four sub-scores are “*Physical*” (0–22) a measure quantifying the intensity and duration of physical fatigue, “*Living*” (0–21) describing sequelae on activities in daily living due to the unpredictability of fatigue, “*Cognition*” (0–15) describing the cognitive effects of fatigue, such as errors and/or a lack of concentration, and “*Emotion*” (0–12) describing the effects of fatigue on emotions and mood. A higher score denotes more severe fatigue. The BRAF-MDQ has shown good internal consistency, test–retest reliability, construct validity and sensitivity to change in persons with RA (82). In this thesis, the sub-scores *Physical* and *Living* are considered to represent physical aspects of fatigue and the sub-scores *Cognition* and *Emotion* are considered to represent mental aspects of fatigue.

VAS pain was used to assess general pain intensity. Pain experienced over the previous week was rated on a VAS (0–100 mm), with anchors “no pain” and “worst imaginable pain”. The VAS pain has shown good internal consistency and test–retest reliability in persons with RA (81, 83).

VAS stress was used to assess the general level of stress. Stress experienced over the previous week was rated on a VAS (0–100 mm), with anchors “no stress” and “worst imaginable stress”. VASs of fatigue and pain have been shown to be valid measures with good test-retest reliability in persons with RA (52, 81, 83).

Health Assessment Questionnaire (HAQ) (Swedish version) was used to assess general activity limitations. The HAQ is a RA specific questionnaire containing eight aspects of activity limitations during previous week ranging from 0 to 3 where a score of ≤ 1.0 indicates little activity limitations. The questionnaire has shown satisfactory reliability, validity and sensitivity to change in persons with RA (84-86).

Leisure Time Physical Activity Index (LTPAI) was used to assess physical activity (87). The amount of physical activity in hours over the previous week was rated as light, moderate or vigorous physical activity. The number of hours engaged in moderate and vigorous physical activity was recorded in this thesis. The instrument has shown satisfactory reliability and validity in persons with fibromyalgia (87).

Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression. The HADS contains 14 statements with the items scored on a 4-point Likert scale range 0-3. The scores build two subscales, seven items for anxiety (HADS-A) (0-21) and seven items for depression (HADS-D) (0-21). Higher scores denote more anxiety and depressive symptoms, respectively. A cut-off score of eight has been suggested to indicate possible anxiety or depression (88). The instrument has shown satisfactory validity, reliability and good sensitivity to change in physically ill persons including persons with RA (89).

EuroQoL single index value for health status (EQVAS) was used to assess self-rated health state. Perceived health state was rated on a 20-cm vertical line with anchors being 100 at the top “best imaginable health state” and 0 at the bottom “worst imaginable health state” (90). The instrument has shown satisfactory reliability and validity in persons with RA (91, 92)

Arthritis Self-efficacy Scale-Swedish version (ASES) was used to assess disease-specific self-efficacy. In this thesis the other symptoms sub-scale was used. This sub-scale concerns personal beliefs in the ability to control symptoms of RA and includes perceived ability to control fatigue. Perceived ability to control symptoms was rated on a six-item questionnaire with score range 10–100 with anchors “very uncertain” and “very certain”. A higher score denotes greater self-efficacy. The instrument has shown satisfactory reliability and validity in persons with chronic arthritis (93, 94).

Clinical assessments

Disease Activity Score (DAS-28), was used to assess disease activity and includes examination of tenderness and swelling in 28 joints, self-reported global health rated on a VAS (0–100 mm) and erythrocyte sedimentation rate (ESR) (mm). The DAS-28 is scored from 0 to 10 with scores <3.2 indicating low and >5 high disease activity, with moderate activity in between (95). The instrument has shown to be valid to assess disease activity in RA (96, 97).

A pressure Algometer (Somedic Sales AB, Hörby, Sweden) was used to assess pain pressure threshold. Pain thresholds were measured in kPa and examined bilaterally in the upper and lower limb (thumb nail base; m. trapezius; m. supraspinatus; knee m. vastus medialis; and m. gluteus) with a 1cm² probe area and a pressure increase of approximately 50kPa/s (98). A mean value of the ten locations assessed was calculated. The pain threshold examination with the Somedic algometer has shown satisfactory reliability in healthy women (99).

Performance-based tests

Six-minute walk test (6MWT) was used to assess physical capacity. The 6MWT measures total walking distance (m) covered during a period of six minutes. The standardized instructions are to walk as fast as possible without running (100). The test has shown satisfactory reliability in a Swedish Fibromyalgia population (100).

One-minute sit-to-stand (STS) test was used to assess leg strength/endurance. The maximum number of complete rises from a standard chair (without armrests and 45 cm high), with arms crossed over the chest and feet kept on the floor, during one minute was recorded (100, 101). The test has shown satisfactory reliability in a Swedish Fibromyalgia population (100).

Table 3. Outcome measurements used in Study I-IV.

Outcomes	Measures	Study			
		I	II	III	IV
Demographic data					
Age		x	x	x	x
Sex		x	x	x	x
Disease duration		x	x	x	x
Medication			x	x	x
Work status		x	x	x	x
BMI				x	
Season			x	x	
Self-reported questionnaires					
Fatigue	VAS Fatigue	x	x	x	x
	BRAF-MDQ		x	x	x
Pain	VAS Pain	x	x	x	x
Stress	VAS Stress				x
Activity limitations	HAQ	x	x	x	x
Physical activity	LTPAI				x
Depressive symptoms	HADS-Anxiety				x
	HADS-Depression			x	x
Self-rated health state	EQVAS				x
Self-efficacy	ASES				x
Clinical assessment					
Disease activity	DAS-28		x	x	x
Inflammation	ESR			x	
Pain threshold	Algometer			x	
Performance-based tests					
Physical capacity	6MWT			x	
Leg strength/endurance	STS-test				x

BMI=Body Mass Index, VAS=Visual Analogue Scale, BRAF-MDQ=Bristol Rheumatoid Arthritis Fatigue-Multi-Dimensional Questionnaire, HAQ=Health Assessment Questionnaire, LTPAI=Leisure Time Physical Activity Index, HADS=Hospital Anxiety and Depression Scale, EQVAS=EuroQoL single index value, ASES=Arthritis Self-Efficacy Scale, DAS-28=Disease Activity Score, ESR=Erythrocyte Sedimentation Rate, 6MWT=6-Minute Walk Test, STS=1-min Sit To Stand.

Procedures

Study I

An interview schedule for the focus group discussions was developed in cooperation with a research partner with personal experience of rheumatic disease and fatigue, and with specific education from the Swedish Rheumatism Association. A pilot focus group discussion was performed with participants recruited from the rheumatology clinic, which resulted in minor revisions of the interview schedule. The focus group discussions were led by a moderator and an assistant. Both were healthcare professionals, one physical therapist mainly working as a clinician and one occupational therapist mainly working as a researcher. The moderator guided the discussion and encouraged each participant to talk freely, and the assistant presented a brief summary at the end of the discussions and invited the participants to confirm or clarify it. Each focus group discussion was initiated with the question "How would you describe your fatigue in RA" followed by questions of how the fatigue was managed, experienced in relation to others, and when the fatigue became a hindrance. The focus group discussions lasted approximately 90 min and were digitally recorded and transcribed verbatim after all interviews were conducted.

Study II & III

The participants were invited to attend four separate clinical examinations, every three months, during the course of the study in order to capture the variations in fatigue levels across the four seasons. At these examinations, demographic data were collected, clinical assessment of disease activity, inflammation parameters and pain thresholds were assessed, a performance-based test of physical capacity was performed and self-reported questionnaires aimed at assessing the level of fatigue and other health aspects in RA were administered, Table 3. Fatigue assessment questionnaires were also sent to participants by mail between the clinical examinations in order to obtain a nuanced picture of the variations in fatigue levels over time and to ensure that information was recorded during all four seasons. A flowchart of the data collection is presented in Figure 3.

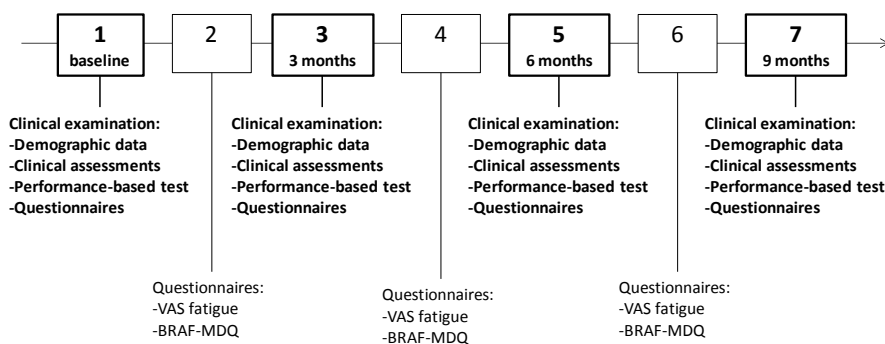


Figure 3. Flowchart of the data collection in the longitudinal studies, Study II-III.

Study IV

The participants in this randomized controlled trial were randomized to an intervention group that was assigned to a 12-week person-centered physical therapy intervention or a non-intervention reference group. All participants continued to receive usual care consisting of on-going medical attention and standard rehabilitation as prescribed. Thus, the two groups only differed with respect to the intervention group's receiving person-centered physical therapy. Three testing periods were built into the design, Figure 2: baseline, post-test evaluation after the 12-week intervention period, and follow-up six-months after baseline testing over which time participants in the intervention group continued their self-care programs independently. After the baseline examination, the participants were randomized to the intervention group or the non-intervention reference group by an independent individual not involved in the study using a computer-generated sequence (www.randomization.com).

At each testing occasion, assessments of demographics were collected, clinical assessment of disease activity and inflammation parameters were assessed, a performance-based test of leg strength/endurance was performed and self-reported questionnaires of fatigue and health status were administered, Table 3. Two specially trained nurses, blind to each participant's group, performed the clinical assessments, performance-based test and administered the questionnaires in a standardized manner. All participants were invited to attend all three testing occasions.

Person-centered physical therapy intervention. The goal of the intervention was to, through partnership (between the participant and the physical therapist), devise a mutually-agreed self-care plan that guided the participant in alleviating and managing her/his fatigue, and to effectively do so over time.

The self-care plan focused on health-enhancing physical activity and balance in daily life. Health-enhancing physical activity refers to the recommendations for healthy adults, i.e., moderately-intense aerobic physical activity for a minimum of 30 min, five days a week, or vigorous aerobic physical activity for a minimum of 20 min, three days a week or some combination of moderately-intense and vigorous activity (70) and the self-care plan was inspired by these recommendations. When adequate, strengthening and flexibility exercises were also included in the self-care plan (65, 71). Balance in daily life refers to the way a person's intentions, resources and environment match their life goals (102) including factors such as sleep, stress, work life, family life, social life and well-being, which was discussed during the sessions.

The intervention was initiated with an individual person-centered meeting based on a semi-structured dialogue between the participant and the physical therapist. The participant contributed knowledge about her/his body, access to resources, preferences and life situation. The physical therapist contributed professional knowledge about general-, disease-specific-, personal- and environmental aspects associated with fatigue as well as about evidence-based treatments and strategies to manage fatigue and its consequences in daily life. Also, the physical therapist contributed with clinical expertise on how to modify and adjust physical activity as well as specific exercises included in the self-care plan according to disease-specific-, personal- and environmental aspects. The main role of the physical therapist was to support and coach each participant according to her/his resources, context, will and needs.

The self-care plan was signed by the participant and the physical therapist to ensure that the intervention was person-centered and mutually agreed as well as regarded to be both feasible and expected to have an alleviating effect on fatigue. The participants were asked to keep a daily journal about their fatigue management strategies and reflections. This information guided the person-centered process, and facilitated the interactions and discussions for on-going refinement of the self-care plan. Follow-up meetings and phone contacts were scheduled according to each person's preferences.

Analysis

Qualitative analysis

The transcribed interviews were analyzed according to qualitative content analysis (103). Content analysis is used to methodically describe the content of communication (104). The systematic procedure ensures that all units of analysis receive the same attention thereby increasing trustworthiness and credibility.

After conducting all interviews, the interviews were digitally recorded and transcribed verbatim. The transcribed interviews were analyzed separately and together, by the two first authors (CF and MB in Study I), according to the process described by Graneheim and Lundman (103), Figure 4. First the transcripts were read several times to get a sense of the whole. The unit of analysis consisted of whole interviews, and no parts were excluded from the analysis. After reading the transcripts, meaning units adequate for answering the research question of the study i.e., describing fatigue in everyday life, were derived from the texts. The meaning units were condensed, a process where the unit is shortened while the core is preserved, and abstracted, meaning that the condensed units are interpreted and lifted to a higher logical level, and finally coded. From the codes, subcategories and categories that shared communality were formed. The analysis moved continuously back and forth between the whole and the parts of the text.

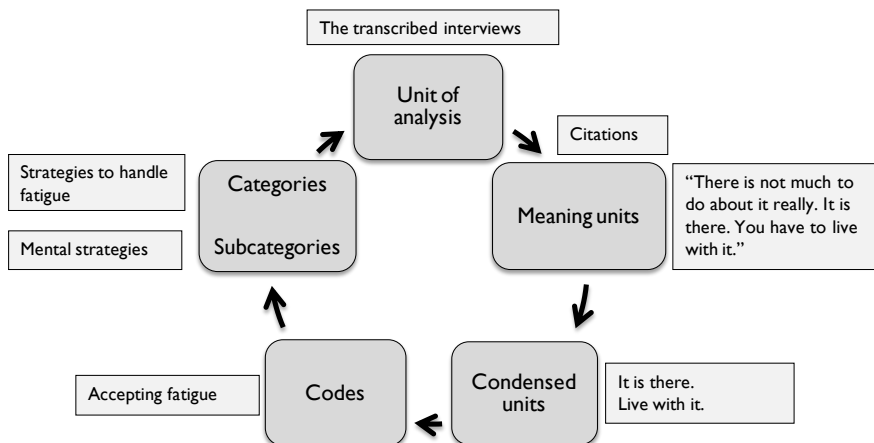


Figure 4. The process of the content analysis starting from Unit of analysis.

The coding was made separately by the two first authors, and the subcategories and categories were formed together and discussed until consensus was met. To further enhance the credibility of the analysis, the results were finally confirmed by an expert on qualitative methods (last author KM in Study I) and a research partner.

Statistical analysis

Statistical analyses were performed using the Statistical Package Software for the Social Sciences, SPSS version 15.0, (SPSS Inc., IBM, Chicago USA). In Study II the Statistical Analysis Software, SAS version 9.3 (SAS Institute Inc. North Carolina USA) PROC MIXED was used for the multiple regression analysis, mixed models. The significance level was set at $p < 0.05$. In Study II-IV all measured values were included in the analyses. An overview of the statistical tests used in the thesis is presented in Table 4.

Descriptive statistics. Descriptive data are presented as the mean \pm standard deviation (SD) and/or median (min;max) for continuous variables and as numbers (n) and percentages (%) for categorical variables.

Analysis of fatigue, explanatory factors and predictors over time were conducted in Study II and in Study III. Multivariable regression analysis, the linear mixed effects model, was used to analyze the outcome fatigue. The regression model was specified to have a random intercept to manage the repeated measurements over time.

To analyze the variation in fatigue over time (Study II) two models were analyzed, one with *month* as time variable and one with *season*, defined as winter (December, January, February), spring (March, April, May), summer (June, July, August) and autumn (September, October, November), as time variable. Sex and age (subdivided into age groups) were included in the models as confounders.

Table 4. Overview of the statistical tests used in the studies.

Statistical tests	Study			
	I	II	III	IV
Descriptive statistics				
Mean±SD		x	x	x
Median (max;min)	x	x	x	x
Number (n) and percent (%)	x	x	x	x
Analysis of fatigue, explanatory factors and predictors over time				
Multivariable regression analysis, linear mixed effects models		x	x	
Test of co-linearity				
Pearson correlation coefficient			x	
Between-group comparisons				
t-test		x		
ANOVA		x		
Fisher's exact test				x
Mann Whitney U-test				x
Within-group comparisons for change over time				
Wilcoxon signed rank test				x
Estimate of magnitude of change between two groups				
Effect size				x
Sample size determination				
Power analysis				x

SD=Standard Deviation, ANOVA=Analysis of Variation

To analyze explanatory factors and predictors of fatigue over time (Study III), a multivariable model building procedure was performed (105). First, correlation analyses using Pearson correlation coefficient were made for the independent variables to test for risk of co-linearity ($r>0.7$). Then, univariate analyses were performed with each independent variable one by one in order to determine which variables to be included in the multivariable regression model. Variables with $p<0.25$ using F-test were included in the full model of the multivariable regression analysis. In the multivariable analysis, variables with $p>0.25$ using t-test were excluded from the full model. The remaining reduced model was compared to the full model. The excluded variables from the full model and the variables with high p-values in the univariate regression analysis were reinserted into the reduced model and once again tested.

Two different analysis approaches were tested, Figure 5:

- I) Explanatory factors for fatigue with variables and outcome recorded at the same time-point, to study the variation in fatigue over time and the association with the explanatory variables at the same time-point.
- II) Predictors of fatigue with variables recorded at the time-point prior to the outcome (approximately three months) to study predictors for fatigue and the association with the predictors approximately three months prior to outcome.

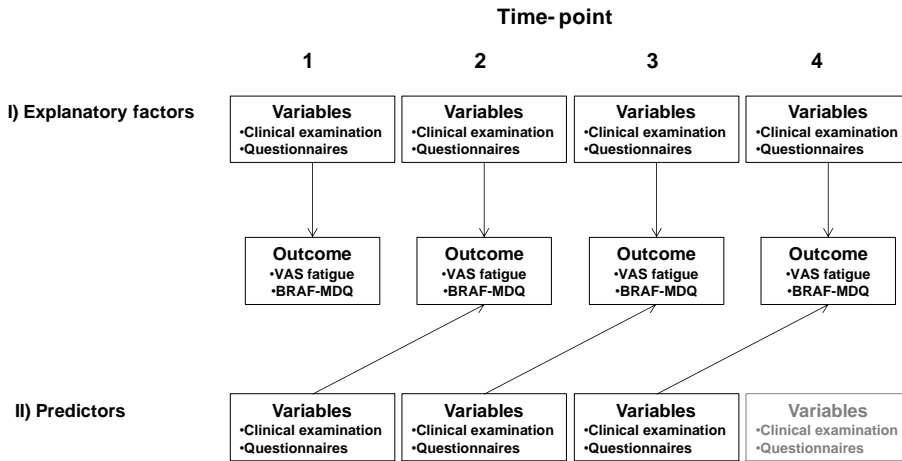


Figure 5. Illustration of the two analyses approaches used in Study III

Between-group comparisons were conducted in Study II and Study IV.

In Study II, the t-test was used to analyze differences in fatigue levels between women and men, and ANOVA was used to analyze differences in fatigue levels between age groups.

In Study IV, between-group differences at baseline were analyzed with Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Between-group differences over time were analyzed with Mann-Whitney U test.

Within-group comparisons were conducted in Study IV. Within-group changes over time were analyzed for each group using Wilcoxon's signed rank test.

Effect size was calculated in Study IV for variables showing a significant difference between groups to estimate the magnitude of change. Effect sizes were calculated by dividing the mean difference between the post-test score and baseline score or follow-up score, and baseline score in the intervention group and in the reference group, by the pooled SD for difference. Effect sizes from 0.20 to 0.49 were regarded as small, from 0.50 to 0.79 were regarded as moderate, and effect sizes over 0.80 were regarded as large (106).

Sample size determination was calculated in Study IV. Determination of sample size was based on the baseline characteristics in Study II and III. To detect a difference of 20 in VAS fatigue (0-100) between the groups with an estimated SD of 26, 80% power and at 5% significance level, 27 participants in each group were needed. With consideration for potential drop-outs, 70 participants were recruited to the study.

Research partner

Research partners from the Swedish Rheumatism Association were invited to participate in the research process. A research partner is a person with personal experience of rheumatic disease and fatigue, and specific education from the Swedish Rheumatism Association. The research partners were involved in Study I in the design and development of the interview schedule and in the interpretation of the analysis and in Study IV in designing the intervention.

Ethical considerations

All studies in this thesis were approved by the Regional Ethical Review Board in Gothenburg, Sweden. Written and oral information about the studies were given to the participants and informed written consent was obtained from all participants prior to their participation. The participants were allowed to withdraw from the studies at any point without giving a reason.

RESULTS

A summary of the main findings from the studies are presented in the following section. Study II-IV have not yet been published, therefore, to avoid compromising future publication, the results of Study II-IV are presented briefly.

The clinical baseline characteristics of the participants in Study I-IV are presented in Table 5.

Table 5. Clinical baseline characteristics of the participants in Study I-IV.

	Study			
	I	II + III	IV	
			Intervention group	Reference group
Subjects, n	25	65	36	34
Age, years	45±12.7 46 (20;60)	54±9.9 56 (23;66)	54±8.5 56 (35;65)	53±10.9 55 (25;65)
Female, n (%)	19 (76%)	48 (74%)	32 (89%)	30 (88 %)
Disease duration, years	10±6.4 8 (1;27)	15±9.6 12 (4;45)	14±11.1 10 (4;54)	12±7.7 10 (3;42)
DAS 28, score		3.7±1.4 3.8 (0.8;6.9)	3.5±1.1 3.5 (1.2;6.6)	3.2±1.1 3.2 (1.6;5.2)
HAQ, (0-3)	0.8±0.7 0.8 (0;2.1)	0.6±0.6 0.6 (0;2.4)	0.9 ±0.6 0.8 (0;2.5)	0.7±0.5 0.6 (0;1.9)
Pain, (VAS 0-100)	42±25.3 43 (0;85)	38±25.5 34 (0;100)	39±22.0 41 (0;94)	41±20.9 41 (1;79)
Fatigue, (VAS 0-100)	49±21.5 50 (8;89)	47±27.1 49 (0;100)	70±17.1 69 (32;99)	67±14.3 70 (40;94)
Working or studying (full- or part-time), n (%)	14 (56%)	41 (63%)	26 (72%)	24 (71%)

Data is presented as mean±SD, median (max; min) or number (n) and percent (%). DAS= Disease Activity Score, HAQ=Health Assessment Questionnaire, VAS=Visual Analogue Scale.

Study I

Perception, consequences, communication, and strategies for handling fatigue in persons with rheumatoid arthritis of working age – a focus group study

Six focus group discussions were conducted with 3 to 5 participants in each group. A total of 25 persons with RA (19 women, 6 men), aged 20–60 years were included in the study. More than one third had children living at home and the majority were working or studying.

The analyses resulted in four categories with related sub-categories presented in Table 6:

Perception of fatigue: Fatigue was experienced as being different from normal tiredness, unpredictable, and overwhelming. It was perceived to be related to disease activity and pain, but also that fatigue in itself created more fatigue. The fatigue was also associated with negative emotions, changed self-image, and fears and feelings of frustration and shame were central when the persons were forced to omit valued life activities.

"It feels like you are stuck in the mud, you have to strive so much for everything you do... of course you get tired of it."

Consequences due to fatigue: The fatigue caused changes in cognitive ability, ability to act, and overall activity pattern where the increased need for rest and sleep caused an imbalance in daily life. The participants struggled not to let the fatigue interfere with work. Therefore, main restrictions due to the fatigue were related to leisure time and included both things of importance to the participants and things that were anticipated to make them feel better. The fatigue also brought negative consequences for their significant others.

"Many times when you shall do stuff with friends, many times I have to call and cancel and say I cannot cope."

Communicating fatigue: Fatigue was difficult to gain understanding for, and the participants adjusted their communication accordingly; it was important to keep up appearances. During medical consultation, fatigue was perceived as a factor not given much consideration, and the participants expressed taking responsibility for managing their fatigue symptoms on their own.

"Close friends who know about the situation, then you can tell them straight. If it's people you don't know so well then you rephrase, or rather lie."

Strategies to manage fatigue: Strategies comprised conscious self-care and the importance of taking care of one-self. Also, mental strategies like distracting the fatigue and keep a positive attitude were described, but most important was planning and prioritizing.

"Shall I do something today, then I must plan to take the consequences tomorrow."

Table 6. Description of fatigue presented in categories and subcategories.

Categories	Subcategories
Perception of fatigue in RA	Character (Not normal, unpredictable, overwhelming, physical, mental)
	Related factors (Disease activity, pain, stress, fatigue creates fatigue)
	Emotions (Frustration, hopelessness, shame, irritability, fear)
	Cognitive consequences (Loss of concentration, being one step behind, hard to learn)
Consequences due to fatigue	Changed activity pattern (Lack of initiative and spontaneity, imbalance in life, rest and sleep)
	Consequences for others (Demands on family and friends, tolerant family and friends)
	Being understood (Invisible nature, common experience)
Communicating fatigue	Conscious communication (Expected reactions, keep up appearances)
	Communication with health professionals (Lack of commitment, nothing to do about it)
	Conscious self-care (Feel good, adjust, exercise, rest, being social, ask for help)
Strategies to handle fatigue	Mental strategies (Mentally distract, positive attitude, acceptance)
	Plan and prioritize (Manage projects, conscious choices, struggle and take the consequences)

Study II & III

–Monthly and seasonal variations in fatigue in persons with rheumatoid arthritis: A longitudinal study

–Explanatory factors and predictors for the variation in fatigue in persons with rheumatoid arthritis: A longitudinal study

The mean value of fatigue indicated substantial fatigue in the study population. The fatigue levels displayed a large variation ranging from no fatigue to maximal fatigue, Table 7.

Table 7. Descriptive data of fatigue at baseline in 65 persons with rheumatoid arthritis

Fatigue		Mean±SD	Median (Min;Max)
Single item			
VAS fatigue	(0-100)	47.1±27.1	49 (0;100)
Multiple aspects			
BRAF-MDQ			
Total	(0-70)	29.0±14.8	29 (0;65)
Physical	(0-22)	13.9±5.1	15 (0;21)
Living	(0-21)	6.1±4.5	6 (0;21)
Cognition	(0-15)	5.3±4.0	5 (0;15)
Emotion	(0-12)	3.6±3.1	3 (0;12)

SD=Standard Deviation, n=number, VAS=Visual Analogue Scale, BRAF-MDQ=Bristol Rheumatoid Arthritis Fatigue-Multi-Dimensional Questionnaire

Analysis of *monthly variations* in fatigue (Study II) showed statistically significant variations in fatigue ratings over time ($p<0.05$) concerning general fatigue as well as all aspects of fatigue with the exception of emotional fatigue ($p=0.088$). Greatest variations were seen from January to September with higher fatigue ratings in January. The changes in VAS fatigue scores over time were >10 and therefore considered to be of clinical importance (107, 108).

Analysis of *seasonal variations* in fatigue (Study II) revealed a statistically significant seasonal variation in fatigue levels over the four seasons with higher fatigue values during the winter for general fatigue ($p < 0.01$) and the physical aspects of fatigue ($p > 0.01$). Greatest variations were found between winter and autumn and between winter and summer.

No significant differences in fatigue levels was found between women and men or in participants of different ages neither in the analysis of monthly nor seasonal variations in fatigue (Study II).

In Study III, disease-related factors were analyzed as *explanatory factors* and *predictors* of variations in fatigue over time, Figure 5. The disease-related factors analyzed were disease activity, physical capacity, pain intensity, pain thresholds, depressive mood, age, sex, BMI and season. Pain threshold and depressive mood were the strongest factors to explain the variation in fatigue over time, both when analyzed as *explanatory factors* of fatigue with the outcome measure of fatigue and the explanatory factors measured at the same time-point and also when analyzed as *predictors* of fatigue with the outcome measure of fatigue measured at the following time-point approximately three months after the predictors. This was seen for general fatigue as well as for physical and mental aspects of fatigue measured with the BRAF-MDQ. Pain intensity was found to explain the variation of general fatigue and the physical aspects of fatigue.

Study IV

The effect of person-centered physical therapy on fatigue-related variables in persons with rheumatoid arthritis: A randomized controlled trial

Seventy participants were included in the study. Thirty-six participants were randomized to the intervention group and 34 participants were randomized to the non-intervention reference group. One person in the intervention group and two persons in the reference group dropped out before post-test evaluation (12 weeks after baseline evaluation) and one person in the reference group dropped out before follow-up (six month after baseline evaluation), Figure 2. The number of contacts with the physical therapist during the 12-week intervention ranged from 3 to 6 (mean 4.1 ± 0.7). Participants preferred personal meetings with the physical therapist compared with phone contacts (mean 3.2 ± 1.2 , range 1-6 and mean 1.0 ± 0.7 , range 0-4, respectively). The personal meetings with the physical therapist lasted 30 min to 1 hour each and the phone contacts with the physical therapist lasted 10 min to 30 min.

With respect to rehabilitation as prescribed, four persons in the intervention group and five persons in the reference group received standard physical therapy during the study period. No differences were found between the intervention group and the reference group at baseline in demographic data, presented in Table 5, or in primary and secondary outcomes presented in Table 8.

Post-test. Within both groups, general fatigue as well as aspects of fatigue were improved ($p < 0.05$) at post-test as well as at follow-up, except for emotional fatigue at post-test in the reference group ($p = 0.066$). According to the result from Study II, showing highest fatigue ratings during the winter, this improvement in fatigue was expected as the study started in the winter and ended after the summer. However, compared with the reference group, the intervention group improved significantly more at post-test ($p < 0.05$) in general fatigue as well as aspects of fatigue, except for Cognition ($p = 0.519$). Also, the intervention group showed greater leg strength/endurance ($p = 0.024$), less anxiety ($p = 0.010$), and spent more time in physical activity ($p = 0.023$) compared to the reference group.

Follow-up. At follow-up the improvements in the intervention group compared with the reference group remained for physical ($p = 0.041$) and living-related aspects ($p = 0.031$) of fatigue. Also, improvements in the intervention group remained for leg strength/endurance ($p = 0.001$), physical activity ($p = 0.019$) and anxiety ($p = 0.015$) and was also found for self-rated health state ($p = 0.010$) and self-efficacy ($p = 0.046$).

The person-centered physical therapy intervention with focus on health-enhancing physical activity and balance in daily life showed significant and sustained effects on fatigue, physical function, general health and mental health over at least a six-month follow-up period.

Table 8. Primary and secondary outcomes at baseline of the participants in Study IV (n=70).

	Intervention group (n=36)	Reference group (n=34)	p-value
Primary outcomes			
VAS fatigue, 0–100	69.5±17.1 69 (32;99)	66.9±14.3 70 (40;94)	0.60
BRAF-MDQ			
Total, 0–70	37.7±11.4 36 (11;61)	39.8±10.6 38 (24;65)	0.51
Physical, 0–22	16.8±3.1 17 (10;22)	16.8±2.4 17 (12;22)	0.86
Living, 0–21	8.5±4.2 8 (0;19)	9.6±4.3 10 (1;18)	0.30
Cognition, 0–15	7.3±3.2 8 (1;13)	7.7±3.5 7 (3;15)	0.92
Emotion, 0–12	5.1±2.9 5 (0;12)	5.8±2.5 6 (1;11)	0.23
Secondary outcomes			
DAS 28, score *	3.5±1.1 3.5 (1.2;6.6)	3.2±1.1 3.2 (1.6;5.2)	0.39
STS test, n †	26.7±11.6 25 (4;53)	25.2±6.7 24 (13;43)	0.57
LTPAI hours	2.7±2.5 2 (0;10)	3.0±2.5 2 (0;11)	0.52
VAS pain, 0–100	38.7±22.0 41 (0;94)	40.9±20.9 41 (1;79)	0.59
VAS stress, 0–100	39.4±26.0 42 (0;93)	39.6±28.1 29 (2;95)	0.91
HADS-A, 0–21	5.9±3.4 6 (2;16)	7.0±4.4 7 (0;16)	0.33
HADS-D, 0–21	5.7±3.2 6 (1;11)	6.3±3.7 6 (0;15)	0.52
EQVAS, 0–100	52.3±21.6 55 (10;89)	55.2±20.1 60 (20;92)	0.65
ASES, 10–100	61.4±13.1 61 (35;86)	58.2±15.9 58 (26;90)	0.35

Values are the mean±SD and median (min;max). * n=27 (intervention and reference group), † n=33 (intervention and reference group). BMI=Body Mass Index, HAQ=Health Assessment Questionnaire, VAS=Visual Analogue Scale, BRAF-MDQ=Bristol Rheumatoid Arthritis Fatigue-Multi-Dimensional Questionnaire, DAS 28=Disease Activity Score, STS=1-minute sit to stand, LTPAI=Leisure Time Physical Activity Index, HADS=Hospital Anxiety and Depression Scale, EQVAS=Euro QoL single index value, ASES=Arthritis Self-Efficacy Scale.

DISCUSSION

The discussion section consists of two parts. In the first part methodological concerns in the thesis are discussed and in the second part the main results of the four studies are discussed.

Methodological concerns

Several study designs and various research methods were used in order to address the specific aims of the included studies.

Qualitative method

A qualitative interview study using focus group methodology (109) was in Study I found to be suitable to gain new knowledge about experiences of fatigue. By listening to others experiences of fatigue, participants opened themselves to personal reflections and new perspectives. The data collection and the data analysis were maintained to increase trustworthiness and credibility (103). As expected in a qualitative study the findings are limited to the small group of participants. A focus group interview study gives a description of the complexity of fatigue based on the interviews and offer perspectives to understand more about the fatigue. Due to loss of participants because of different reasons, some groups might be regarded on the verge of being too small to provide creative discussions (79). However, we found no negative impact on interactions in the small groups. This has also previously been discussed in literature, describing small groups to be comfortable, especially when participants have comprehensive experience to share and the topic is complex (109). The data revealed that the concordance between the groups in this study was high. The groups were formed homogeneously and heterogeneously to get an opportunity for the respondents with similar experiences to share their experiences, and to cover diversity in the topic (79). However, we did not find that the experiences of fatigue among participants in the homogeneously or heterogeneously selected groups differed.

The data in this study was analyzed with qualitative content analysis according to Graneheim and Lundman (103). This is a well established method that allows for various depths of the interpretation of the data. To increase trustworthiness

and credibility the data was analyzed by two authors separately and together, and finally validated with the research partner and an expert.

Measurements of fatigue

To quantify fatigue, patient reported outcome measures, mainly in terms of self-reported questionnaires, are used (49). In this thesis, VAS fatigue was chosen to assess general fatigue. In clinical trials across countries, this is one of the most frequently used measurements of fatigue which enables comparison across studies. Also, the patients are familiar with this way of rating their symptoms (52). However, there is no standardized VAS fatigue for use in RA populations resulting in researchers often creating their own VASs (52). In this thesis, the VAS fatigue from the Swedish rheumatology quality register (SRQ) was used. This VAS fatigue is consistent with other versions described in the literature (80). To get a nuanced picture of the multiple nature of fatigue we also wanted to assess multiple aspects of fatigue. There are numerous generic questionnaires used to measure multiple aspects of fatigue in RA, making comparisons across studies difficult (52). A relatively new fatigue questionnaire was used in this thesis, the Bristol Rheumatoid Arthritis Fatigue–Multi-Dimensional Questionnaire (BRAFF-MDQ) (82, 110). The BRAFF-MDQ is the only RA-specific multidimensional fatigue questionnaire and it was developed in collaboration with persons with RA to assess disease specific fatigue. This scale is suggested to identify multiple aspects of fatigue as well as general fatigue in persons with RA (52).

Statistical analyses

To fully make use of all the information we gathered through the longitudinal design in Study II and Study III we chose to use multivariable analysis with repeated measures (mixed models). This study design required use of parametric statistics and it enabled us to draw conclusions about possible explanatory factors and predictors of fatigue and to take covariation with other factors into account. However, the use of parametric methods with ordinal data limits the possibility to draw conclusions about the magnitude of the estimates and also, when performing a model building process instead of a confirmatory regression analysis there is a larger risk of false-positive results (111). Therefore, the results of the analyzed models need to be interpreted with caution. The studies would also benefit from a larger sample size to increase the reliability of the results and a healthy control group to be able to compare the result to fatigue variability and aspects related to fatigue in a healthy population.

In Study IV non-parametric statistics were used. This was due to that many of the outcome measures that were included consist of ordinal data.

Discussion of the results

The main result of this thesis was that the person-centered physical therapy intervention with focus on health-enhancing physical activity and balance in life showed significant and sustained effects in reducing fatigue, as well as improving function and health in persons with RA.

The design of this intervention was inspired by the result of Study I showing that the fatigue caused an imbalance in daily life. Therefore, a person-centered approach was assumed to be a proper way to address the fatigue and to improve balance in life.

In addition, in Study II, a variation in fatigue levels was found over time and season with higher levels of physical fatigue during the winter. Physical activity has been found to be inversely associated with fatigue (112) and the level of physical activity has been found to be lowest in the winter (113). This further supports the need of a person-centered approach to enhance and incorporate physical activity in daily life.

In Study III, pain threshold and depressive mood were the strongest explanatory and predictive factors for variations in fatigue over time. Physical activity is assumed to result in positive effects also on pain and depressive mood (114) thereby the result of Study III further supports the positive effects of physical activity in the management of fatigue.

Experiences of fatigue

The description of fatigue by the participants in Study I showed that the character of fatigue, being more intense, unpredictable, and not restored by sleep, were in line with the description of fatigue in other qualitative studies. Also, the description of factors perceived to be related to the fatigue in RA such as disease activity, pain, and stress have earlier been described (5, 9, 46, 115). A new finding was the indication that the fatigue itself took energy and that being tired was in itself exhausting (116). This notion that fatigue itself is associated with subsequent fatigue was supported in the longitudinal study of predictors of fatigue (Study III).

The participants perceived to be able to distinguish between their previous normal tiredness and fatigue due to RA. An interesting notion was that the participants described having a new frame of reference of being totally exhausted after having experienced the fatigue due to RA. Individuals with severe fatigue might experience states that are different from what a healthy individual experiences when fatigued (31). Therefore, there are concerns when

comparing fatigue in different populations and instruments need to be validated to differentiate illness-related fatigue from normal fatigue (31). This new frame of reference experienced by persons with RA may explain why some participants rated their fatigue quite low on the VAS but still reported considerable consequences from their fatigue on everyday life.

The fatigue was expressed to be associated with negative emotions, which have earlier been described in the literature (9, 46, 115). Feelings of hopelessness and frustration, irritability and anger, and shame when not being able to fulfill valued social roles, appeared to contribute to increased fatigue.

The environment, social interactions and relationships were found to influence the fatigue. The participants expressed struggling to live as normal a life as possible, which is in line with an earlier study of RA (117). An increased amount of time required for rest and sleep resulted in less time available to accomplish what the participants wanted to, resulting in a feeling of imbalance in life. Balance in life complies with the notion of balance, being dependent on the way a person's intentions, resources and environment matches their goals in life (102). To reduce this imbalance, the participants prioritized vital social roles and expectations, such as work and parenting. The participants experienced a difficulty for others to understand and accept the fatigue. Therefore, they stressed the importance of keeping up appearances and avoid being interpreted as boring, whining or lazy and described being careful when communicating about their fatigue. In turn the lack of communication contributed to the difficulty for others to understand the fatigue. This difficulty, concerning communication, also comprised healthcare, therefore the acknowledgement of fatigue by healthcare professionals is suggested to improve the participants' communication about fatigue with others.

Fatigue and the variation over time

In Study II, the fatigue was found to vary over time and season. Most severe fatigue was seen in the winter regarding general fatigue and physical aspects of fatigue. Interestingly, the mental aspects of fatigue did not display seasonal differences. This information is important for both healthcare professionals in rheumatology and patients. Knowledge about how time and season may affect given aspects of fatigue in persons with RA may be helpful when it comes to developing strategies to manage the fatigue e.g. promoting physical activity during wintertime.

Many factors may influence the variation in fatigue. In Sweden, the great difference in temperature and hours of daylight between winter and summer

plays an important role in daily living and several factors such as outdoor activities and enjoying nature might influence the fatigue level. In addition, the majority of the study participants were either working or studying and therefore likely to take a summer vacation, an aspect likely to contribute to the lower fatigue scores recorded during the summer and early autumn (Study II).

As physical activity has been found to be inversely associated with fatigue (112) and the level of physical activity has been found to be highest in spring and summer (113) this may be one explanation to why the physical aspects of fatigue decreased during summer but not the mental aspects (Study II). According to the result of Study III, there does not seem to be a causal relationship between physical capacity measured with 6MWT and the variation in fatigue. However, many factors may influence physical capacity and the performance on 6MWT. It is possible that the fatigue may influence the performance on 6MWT and not the other way around. The level or amount of physical activity may be relevant to study as a possible predictor for fatigue as a complement to assessments of physical capacity.

In Study III, pain threshold and depressive mood were found to be the most important factors to explain and to predict the variation in fatigue. In previous studies, depression has been found to be one factor with strong association to fatigue in RA (37) and decreased pain thresholds have been found to be more common in persons with RA when compared to a healthy control group (118). In addition, sleep problems are common in persons with RA and have been found to be associated with fatigue (119-121) as well as both low pain threshold (122, 123) and depression (119, 121). This implies that the relationship between decreased pain thresholds, depression and fatigue may be mediated by poor sleep. In addition, pain intensity was found to explain the physical aspects of fatigue, suggesting that pain intensity influences the energy and the ability to cope, physically and socially. In that sense, pain intensity appears to be important to discuss when a patient reports physical fatigue.

Physical activity in the management of fatigue

General and physical aspects of fatigue have been found to be the most prominent aspects of fatigue among persons with RA (34) and therefore treatment of fatigue improving these aspects are of importance. According to the results of this thesis, physical activity seems to be beneficial in the management of these aspects of fatigue. This is in line with an epidemiological study suggesting treatments using physical exercise programs to be especially beneficial for physical fatigue (34). The results of physical exercise interventions in persons with RA display positive effects on fatigue (114) as well as on pain

(114, 124), depression (114) and sleep quality (58). In cross sectional studies, physical activity has been found to be inversely associated with fatigue in RA (73, 112) and a large international study in persons with RA found significantly higher fatigue levels among physically inactive persons compared to those physically active (125). These results imply that interventions focusing on physical activity/exercise may be particularly useful when planning interventions to diminish fatigue, as it influence in particular physical aspects of fatigue. Fatigue, in particular physical fatigue, was in Study II found to fluctuate over time and season with most severe fatigue during the winter months. Therefore, engagement in physical activity may be of special benefit during the winter months, a time when the level of physical activity has been found to be lowest (113). Furthermore, physical activity is assumed to result in positive effects also on pain and depressed mood (114), factors found to be of importance for fatigue (37). Whether physical activity influences the fatigue in itself and/or factors associated with fatigue warrants further elucidation.

RA with or without fatigue has been found to have a major impact on activities in daily life and contribute to an imbalance in life (77, 116). Therefore, enhancing balance in life was assumed to be an essential complement to be able to increase physical activity. In this thesis we adopted a person-centered approach to enhance balance in life and to optimize and incorporate physical activity in everyday life. To enhance balance in life, the participants' narratives (11) concerning daily life and factors of importance were central. Factors that compromised as well as augmented each participant's life balance were discussed. In the context of working with enhancing balance in life, physical activity was discussed and structured according to each participant's preferences, current physical activity level, and life-situation, so that self-management goals and strategies thought best to alleviate her/his fatigue could be identified. An example of a strategy included in a self-care plan was taking a brisk walk after dinner instead of falling asleep on the couch to increase the physical activity and to improve night sleep quality. Another example was to increase the intensity of the daily walk and twice a week perform vigorous Nordic walking thereby the intensity of physical activity was increased and easily incorporated into daily life. Time spent participating in moderate and vigorous physical activity increased significantly more in the intervention group compared with the reference group, at post-test examination and follow-up, indicating that the intervention was effective in increasing physical activity, an increase that was sustained over time.

Clinical implications

The results of this thesis confirm previous knowledge of fatigue causing considerable consequences in daily life in persons with RA. As fatigue, according to the result of Study I, was perceived as a problem not given much consideration during medical consultation, the participants expressed taking responsibility for managing their fatigue symptoms by themselves. This draws attention to the importance of healthcare professionals taking time to address the fatigue and to develop new modes of treatment for the management of fatigue in persons with RA.

Fatigue was found to fluctuate over time and season which is valuable knowledge for patients and healthcare professionals when it comes to developing strategies to manage fatigue. Especially the physical aspects of fatigue were worse during the winter and according to the results of Study IV in this thesis physical activity seems to be of importance in particular to influence the physical aspects of fatigue. This highlights the importance of promoting physical activity/exercise in persons with RA especially during the winter months to first and foremost diminish the physical aspects of fatigue.

In this thesis, pain threshold and depressive mood were found to be the most important factors to explain the variation in fatigue and to predict subsequent fatigue in a longitudinal study. The result of physical exercise interventions in persons with RA show positive effects on both pain (114, 124), and depression (114). This further highlights that physical activity/exercise are useful tools when planning interventions to diminish fatigue.

The person-centered physical therapy intervention with focus on health-enhancing physical activity and balance in life showed significant and sustained effects to reduce fatigue, improve physical function as well as general- and mental aspects of health. As fatigue contributes to reduced physical activity in persons with RA (73), incorporating physical activity in daily life is considered to be important to enhance constancy over time. A person-centered approach was used in this thesis, in which the participant and physical therapist in partnership, discussed and structured how to optimize and incorporate health-enhancing physical activity in everyday life, according to each participant's preferences, function and life-situation. The results indicated that the person-centered approach strengthened the ability of being physically active despite fatigue and was effective in increasing the level of physical activity, an increase that was sustained over time. Person-centered physical therapy with focus on health-enhancing physical activity and balance in life can be recommended as a strategy in the management of fatigue in persons with RA.

CONCLUSION

The results of this thesis confirm the notion that fatigue is a symptom of importance for persons with RA including those who are working, living an active life, and reporting low levels of disability.

The fatigue appears to be of dynamic nature rather than stable over time with higher fatigue levels during the winter. This dynamic nature seems to relate especially to general fatigue and the physical aspects of fatigue.

Different disease-related aspects may influence different aspects of fatigue. As pain threshold and depressive mood appear to be factors of importance for overall fatigue, including general fatigue as well as physical and mental aspects of fatigue, pain intensity appears to be important to assess in patients reporting physical fatigue.

Person-centered physical therapy that focuses on health-enhancing physical activity and balance in daily life showed significant and sustained effects in reducing fatigue and improve physical and mental aspects of health and is recommended as a treatment model in the management of fatigue in persons with RA.

FUTURE PERSPECTIVES

Fatigue is a symptom of importance in persons with RA and hence, there is a need for the fatigue to be considered in the treatment. The person-centered physical therapy intervention in this thesis showed promise in the management of fatigue in persons with RA, and implementation of the concept into clinical practice is warranted. The intervention consisted of several components why further studies are needed to establish whether one component was more effective than the other, for which persons with RA and under which conditions.

As physical capacity measured with 6MWT failed to explain or predict fatigue, other measures, such as the level or amount of physical activity would be interesting for future longitudinal studies investigating aspects of importance for fatigue.

Sleep problems are common in persons with RA and have beside fatigue (119) been found to be associated with increased pain sensitivity (122, 123) as well as depressed mood (119). The hypothesis that the relationship between decreased pain thresholds, depression, and fatigue may be mediated by poor sleep would be an interesting aspect to investigate in a longitudinal approach.

Studies have so far failed to detect a profound relationship between fatigue and inflammation measured as ESR or CRP, which was further supported by the results of this thesis. However, other inflammatory biomarkers might be associated with fatigue (126).

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