The Sahlgrenska Academy

Fibromyalgia and chronic widespread pain

Dimensions of fatigue and effects of physiotherapy

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Ale Tryckteam, Bohus

To my mother

Inga Johansson

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Dimensions of fatigue and effects of physiotherapy

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Abstract

Aims. Fatigue is a severe problem for patients with fibromyalgia (FM) and chronic widespread pain (CWP). The general aims of the thesis were to describe the fatigue experienced by patients with FM and CWP, explore the usefulness of the Multidimensional Fatigue Inventory (MFI-20) in women with FM and investigate the effects of different types of physiotherapy on fatigue and other health related aspects in patients with FM and CWP.

Methods. The patients in the thesis were mainly recruited from primary health care. Two methodological studies were performed to investigate psychometric properties and usefulness of the Multidimensional fatigue inventory (MFI-20). Ratings of fatigue were also compared between different populations. Two randomized-controlled studies were conducted to evaluate effects of physiotherapy in patients with FM and CWP.

Results. I. The study included 166 women and 44 men with FM and CWP (the analyses in men were additional in the thesis). All five subscales of the MFI-20 showed fair to moderate (women) and moderate to good (men) associations with the one-dimensional subscale of fatigue included in the Fibromyalgia Impact Questionnaire (FIQ), indicating sufficient convergent validity. In analyses of 36 women and 26 men with FM and CWP, the MFI-20 was found to possess acceptable test-retest reliability and internal consistency.

II. The study included 133 women with FM. The subscales of the MFI-20 were found to be associated with employment, physical activity and the 6-minute walk test (6MWT) ($p<0.01$), while the FIQ fatigue was not. The MFI-20 and the FIQ fatigue were equally associated with pain, sleep and distress (r $p<0.01$). Women with FM (n=133) rated their fatigue higher ($p<0.001$) than the healthy women (n=158) in all fatigue dimensions.

III. The randomized controlled trial included 166 women with FM or CWP. The FIQ total ($p=0.040$) and the FIQ pain ($p=0.018$) improved in the exercise-education group as compared to the control group which only received education. Patients with at least 60% attendance in exercise sessions improved in the FIQ total, the 6MWT and the FIQ pain compared with controls ($p<0.05$). Analyses within subgroups showed that patients with milder stress, pain or distress improved most by exercise on the FIQ total ($p<0.05$) compared with controls. Patients with more severe symptoms appeared to improve equally regardless of the type of intervention.

IV. The pilot study comprised 44 men with FM and CWP and 28 men with CWP were included in the main analyses of the randomized controlled trial. Resistance training improved isometric force in right arm shoulder abduction ($p=0.010$) and knee flexion (right: $p=0.005$, left: $p=0.002$) as compared to pool exercise. Within-group analyses showed that the resistance training group also improved in general fatigue ($p=0.035$) and right hand grip force (p=0-009) and the pool exercise group improved in MFI-20 reduced motivation ($p=0.008$) and symptoms of anxiety ($p=0.032$).

Conclusions. The MFI-20 was found to possess sufficient test-retest reliability, convergent validity and internal consistency in patients with FM and CWP. Assessment of multiple fatigue dimensions appears to be most useful in relation to aspects of employment and physical function in female patients with FM. Physiotherapy including exercise and education appears to improve health, including some dimensions of fatigue, in patients with FM and CWP.

Keywords: fatigue, fibromyalgia, chronic pain, widespread pain, assessment, physiotherapy, exercise, education

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SAMMANFATTNING PÅ SVENSKA

Syfte: Trötthet är ett stort problem för personer med fibromyalgi (FM) och långvarig generaliserad smärta (CWP). Syftet med avhandlingen var att beskriva trötttheten hos personer med FM och CWP, undersöka tillförlitlighet och användbarhet hos ett frågeformulär avsett att mäta flera dimensioner av trötthet (the Multidimensional Fatigue Inventory (MFI-20)) samt utvärdera effekten av sjukgymnastisk behandling hos personer med FM och CWP.
Metod: 166 kvinnor och 44 män med FM eller CWP rekryterades till studierna, huvudsakligen från primärvården. I två metodstudier undersöktes tillförlitlighet och användbarhet hos MFI-20, för personer med FM och CWP. Jämförelser av trötthet gjordes också mellan olika grupper. I två randomiserade kontrollerade studier studerades också effekten av olika sjukgymnastiska behandlingsmetoder hos personer med FM och CWP.
Resultat: *I.* 166 kvinnor med FM eller CWP deltog i studien. Extra analyser av validitet och reliabilitet hos MFI-20 gjordes i avhandlingen på 44 män med FM eller CWP. MFI-20 visade tillfredsställande och intern konsistens stabilitet över tid. MFI-20 dimensionerna visade signifikant samband med en endimensionell skala för global trötthet som ingår i Fibromyalgia Impact Questionnaire (FIQ fatigue). *II.* 133 kvinnor med FM deltog i analyserna av användbarheten hos MFI-20. MFI-20 visade signifikanta samband med arbetsgrad, fysisk aktivitetsnivå och gångförmåga, medan FIQ fatigue inte gjorde det. Både MFI-20 och FIQ fatigue samvarierade med smärta, sömn, nedstämdhet och ängslan. Kvinnor med FM (n=133) skattade sin trötthet högre än friska kvinnor (n=158) för alla dimensioner av trötthet.
III. Patienter med FM eller CWP som deltog i bassängträning och utbildning (n=81), förbättrades signifikant i allmän hälsostatus och smärta, jämfört med patienter som endast deltog i utbildning (n=85). Patienter med mildare nivåer av stress, smärta och depression förbättrades mest av träningen. Patienter med svårare symtom uppvisade förbättring i hälsostatus oavsett behandling.
IV. 44 män med FM eller CWP rekryterades till pilotstudien, och 28 män med CWP inkluderades i huvudanalysen av den randomiserade kontrollerade studien. Styrketräning förbättrade isometrisk styrka signifikant jämfört med bassängträning. Förbättringar av vissa dimensioner av trötthet kunde ses i analyser inom grupperna.
Konklusion: MFI-20 uppvisade homogenitet och stabilitet över tid. Mätning av flera dimensioner av trötthet verkar vara mest användbart i relation till arbetsgrad, fysisk aktivitet och fysisk funktion. Sjukgymnastik, bestående av träning och/eller utbildning, förefaller förbättra hälsan, och även vissa dimensioner av trötthet, hos patienter med FM och CWP.

LIST OF PAPERS

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

I. Ericsson, A. Mannerkorpi, K. Assessment of fatigue in patients with fibromyalgia and chronic widespread pain. Reliability and validity of the Swedish version of the MFI-20.
Disability and Rehabilitation 2007; 29(22): 1665 – 1670

II. Ericsson, A. Bremell, T. Mannerkorpi, K. Usefulness of multiple dimensions of fatigue in fibromyalgia.
Submitted.

III. Mannerkorpi, K. Nordeman, L. Ericsson, A. Arndorw, M and the GAU study group. Pool exercise for patients with fibromyalgia or chronic widespread pain: a randomized controlled trial and subgroup analyses.
Journal of Rehabilitation Medicine 2009; 41: 751–760.

IV. Ericsson, A. Cider, Å. Bremell, T. Mannerkorpi, K. Pool exercise and resistance training in men with chronic widespread pain. A pilot study.
Manuscript.

CONTENTS

ABBREVIATIONS

6MWT	Six-minute walk test
ACR	American College of Rheumatology
AB	Activity Beliefs
AH	Activity Habits
AR	Activity-related physical Relaxation
AS	Activity-related Symptoms
AUC	Area Under the receiver operating characteristic Curve
AW	Activity-related Well-being
BMI	Body Mass Index
BRPE	Borg scale for Rating Perceived Exertion
CFS	Chronic Fatigue Syndrome
EULAR	European League Against Rheumatism
FIQ	Fibromyalgia Impact Questionnaire
HADS	Hospital Anxiety and Depression Scale
HPA	Hypothalamic-Pituitary-Adrenal
HR	Heart Rate
IASP	International Association for the Study of Pain
ICC	Intra Class Correlation
IISD	Intra-Individual Standard Deviation
LOA	Limits Of Agreement
LTPAI	Leisure Time Physical Activity Instrument

MCS	Mental Component Summary
ME	Myalgic encephalomyelitis
MFI-20	Multidimensional Fatigue Inventory
OMERACT	Outcome Measures in Rheumatology
PCS	Physical Component Summary
RM	Repetition Maximum
SCI-93	Stress and Crisis Inventory
SD	Standard Deviation
SF-36	Short-Form 36
SNRI	Serotonin-nonepinephrine reuptake inhibitors
SS	Symptom Severity Scale
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	TriCyclic Antidepressant
VAS	Visual Analogue Scale
WCPT	World Confederation for Physical Therapy
WPI	Widespread Pain Index

DEFINITIONS IN SHORT

Chronic widespread pain	The presence of pain on the left and right side of the body, above and below the waist and axial skeletal pain, for at least three months (Wolfe et al., 1990)
Exercise	A type of physical activity consisting of planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness (Thomson, 2009)
Fibromyalgia	The presence of chronic widespread pain and pain in at least 11 of 18 predefined tender points on manual palpation with a pressure of ~4 kg (Wolfe, et al., 1990)
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage (Merskey & Bogduk, 1994)
Patient education	Planned organized learning experiences designed to facilitate voluntary adoption of behaviors or beliefs conducive to health (Burckhardt et al., 1994)
Physical activity	Any bodily movement produced by the contraction of skeletal muscles that results in a substantial increase over resting energy expenditure (Thomson, 2009)
Physical function	The capacity of an individual to carry out the physical activities of daily living (Garber et al., 2011)
Reliability	The degree of consistency and accuracy of an instrument (Polit & Tatano Beck, 2004)
Repetition maximum	The heaviest resistance that can be used for one complete repetition of an exercise (Fleck & Kraemer, 2004)

Resistance training	A type of exercise that requires the body´s musculature to move (or attempt to move) against an opposing force, usually presented by some kind of equipment (Fleck & Kraemer, 2004)
Validity	The degree to which an instrument measures the concept it is supposed to measure (Polit & Tatano Beck, 2004)

1 INTRODUCTION

Patients with fibromyalgia (FM) and chronic widespread pain (CWP) are common in primary health care. Their symptoms often have a complex etiology with multiple causes, which makes it challenging to find methods in health care to support these patients and continuous research is needed in the area. Thus, when the opportunity came to our primary care physiotherapy unit to enter a multicenter treatment study for patients with FM or CWP, we were positive and motivated to participate.

This thesis arose from that treatment study (study III in this thesis) in which our research group developed a growing interest in fatigue. In the contacts with patients with FM or CWP, it became clear that fatigue was perceived as a great problem – perhaps equal to pain. Awareness of the importance of fatigue has increased in research on FM and CWP during the last decade. The perspective on the assessment of fatigue has also changed. There is a growing interest in ratings of multiple dimensions of fatigue instead of one global fatigue question, not only in studies of patients with pain but also in other somatic conditions.

The studies in the present thesis describe the multidimensional fatigue experienced by patients with FM and CWP and investigate the usefulness of an instrument aimed to measure multiple dimensions of fatigue, the Multidimensional Fatigue Inventory (MFI-20). Investigation were also made on the effects of different types of physiotherapy treatments on fatigue and other health related aspects in patients with FM.

While FM has been considered in some theories to be a distinct disorder, recent research inclines toward the idea that the conditions of FM and CWP are parts of a severity continuum of pain and distress, along with other chronic pain conditions (J. N. Ablin et al., 2011; Staud, 2009; Wolfe & Michaud, 2009). Inclusion of both FM and CWP can be considered to increase the clinical value of the studies since the results will be able to be generalized to a broader target group. However, inclusion of only FM in studies differentiates a more homogenous group of patients with regard to intensity of symptoms, which facilitates research.

Studies I, II and III in the present thesis included only women. There is a scarcity of studies of physiotherapy treatments for men with widespread pain. A pilot study was therefore initiated as study IV, which investigated the effects of two types of exercise in male patients with CWP.

2 BACKGROUND

2.1 Criteria for chronic widespread pain and fibromyalgia

In 1990, the American College of Rheumatology (ACR) defined criteria for CWP and FM. These were used as inclusion criteria for the study populations in this thesis.

CWP was defined as the presence of pain, as follows, for at least three months: pain on the left side of the body, pain on the right side of the body, pain above the waist, pain below the waist and axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back).
In this definition, left or right shoulder and buttock pain was considered to be pain in each involved side. Low back pain was considered lower segment pain (Wolfe, et al., 1990).

The ACR criteria for FM in 1990 were the presence of the following two conditions:

- CWP (as described above)

- Pain in at least 11 of 18 predefined tender points on manual palpation with a pressure of ~ 4 kg. (Wolfe, et al., 1990) (figure 1).

New criteria for FM were developed in 2010. The new criteria were not meant to replace the 1990 criteria but to represent an alternative method of diagnosis in which the tender point criterion was excluded and all characteristic features of FM were taken into consideration (Wolfe et al., 2010). The 2010 criteria for FM are in short defined as the presence of all of the following three conditions (Wolfe, et al., 2010):

- Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale ≥5 or WPI 3-6 and SS scale score ≥ 9.

- Presence of symptoms at a similar level for at least three months.

- Lack of a disorder that would otherwise explain the pain.

In the 2010 criteria above, WPI consists of a total of 19 predefined body areas and the score represents how many painful areas in which the patient has had pain during the most recent week (score 0-19). In the SS scale (score 0-12) the level of severity over the past week is noted for the following three features: fatigue, waking unrefreshed and cognitive symptoms. The level of severity is rated on a Likert scale from 0 to 3, where 0 is no problem and 3 is severe problem. The extent of somatic symptoms in general is also noted in the SS scale, ranging from 0 to 3 where 0 is no symptoms and 3 is a great number of symptoms (Wolfe, et al., 2010).

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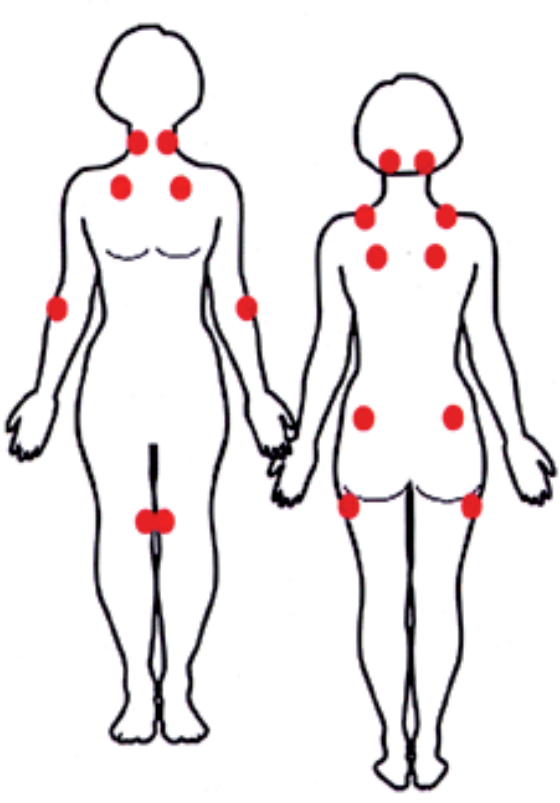

Figure 1. Locations of the tender points included in the 1990 American College of Rheumatology criteria for fibromyalgia. © Karen Lee Richards. Reprint courtesy of Karen Lee Richards.

The 1990 criteria for FM were used in the present thesis as inclusion criteria for the study populations and in all references to FM. The 1990 FM criteria were initially recommended for use in research. Later, the criteria were also applied in clinical practice (ICD-10 diagnosis M79.7) (J. Ablin, Neumann, & Buskila, 2008). The tender point criterion dichotomizes the patients with CWP into two groups: those who fulfill the criteria for FM and those who do not (Wolfe, et al., 2010). The 2010 criteria, on the other hand, make a more diffuse limit between FM and CWP. In physiotherapy, similar treatment strategies are often applied for FM and CWP and, in that context, the 2010 criteria can be adequate for use in health care.

2.2 Characteristics

As mentioned above, FM and CWP are characterized by widespread pain and tenderness. Other important features are fatigue, sleep disturbances, stiffness, symptoms of depression and anxiety and cognitive difficulties (P. Mease et al., 2009; Rohrbeck, Jordan, & Croft, 2007; Wolfe, Ross, Anderson, Russell, & Hebert, 1995; Wolfe, et al., 1990).

CWP has been shown to be associated with older age, being an immigrant, lower socio-economic class, lower educational level and family history of chronic pain (Bergman, 2005). The majority of patients with FM and CWP experience work limitations due to their pain, fatigue and cognitive symptoms (Henriksson, Liedberg, & Gerdle, 2005; White, Speechley, Harth, & Ostbye, 1999). However, with individual adjustments to their work conditions, many patients with FM manage to stay active at work (Henriksson, et al., 2005).

Patients with FM have been shown to have impaired physical function, such as flexibility, strength, walking capacity (Mannerkorpi, Burckhardt, & Bjelle, 1994), balance (Jones, Horak, Winters-Stone, Irvine, & Bennett, 2009) and oxygen uptake (Valim et al., 2002). A previous study investigated explanatory variables of self-reported high physical function in FM and showed that male gender, higher education, younger age, less fatigue and use of aerobic exercise or strength training were some of the explanatory variables of high self-rated physical function in FM (Rutledge, Jones, & Jones, 2007).

2.3 Prevalence

Most FM and CWP population studies have been conducted in Western Europe and North America, for which reason there is a lack of knowledge about the prevalence of these conditions in other regions (Gran, 2003). The prevalence of FM and CWP also varies in different studies depending on definition of widespread pain, methods for recruitment, the country in question and even which part of the country the study is carried out.

Fibromyalgia

The prevalence of FM in the Western world has been estimated to be between 1 % and 3 % of the population and is more prevalent in older ages and among women (Gran, 2003; Wolfe, et al., 1995).

Among men, the prevalence of FM in the Western world has been found to be between 0.2 % and 1.6 % and, among women, between 1.0 % and 4.9 % (Gran, 2003).

Chronic widespread pain

The prevalence of CWP in the Western world has been estimated to be between 7 % and 13 % of the population (Gran, 2003).

Among men, the prevalence of CWP has been found to be between 3 % (Gerdle et al., 2008) and 9 % (Bergman et al., 2001; Gran, 2003) and, among women, between 6.5 % (Gerdle, et al., 2008) and 16 % (Bergman, et al., 2001; Gran, 2003).

Widespread pain coexists in several other conditions. In rheumatic diseases such as rheumatoid arthritis, systemus lupus erythematosus and osteoarthritis, the prevalence of FM has been reported to be between 11 and 16 % and in myalgic encephalomyelitis (ME), the prevalence of FM has been estimated to be 55 % (Yunus, 2012). CWP has also been shown to be present in 28 % of women with chronic low back pain consulting primary health care (Nordeman, Gunnarsson, & Mannerkorpi, 2012).

2.4 Etiology

Pain is always subjective and can also be present when tissue damage is absent. The International Association for the Study of Pain (IASP) has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”(Merskey & Bogduk, 1994).

The pathogenesis of pain in FM is not entirely understood. Environmental factors such as physical trauma, certain infections, auto-immune disorders, emotional stress and other regional pain conditions may play a role in the triggering and maintenance of widespread pain in FM (Clauw, 2007) but there may also be a familial component (Arnold et al., 2004).

Hyperalgesia and allodynia in FM have been shown to result from an increased sensitivity in central nervous mechanisms referred to as central sensitization (Clauw, 2007; Woolf, 2011). In central sensitization, nociceptive neurons of the dorsal horn become hyperresponsive to nociceptive, and sometimes non-nociceptive, somatic stimuli. This increased responsiveness leads to an increased input of signals to the cerebral cortex (Woolf, 2011). Central sensitivity syndromes or central pain conditions are concepts emerging in research, implying that several overlapping chronic pain conditions, such as FM, ME, irritable bowel syndrome, interstitial cystitis and tension-type headaches, may all be results of central sensitisation (Phillips & Clauw, 2011; Yunus, 2008).

Descending pain inhibiting pathways from the brain stem, utilizing neurotransmitters, have been shown to be deficient in patients with chronic pain. This reduced inhibition of pain in combination with the increased input of pain signals are considered to cause the hyperalgesia found in FM.

Other neurobiological aberrations have been observed in the hypothalamic-pituitary-adrenal (HPA) axis and the noradrenaline-sympathetic system in patients with chronic pain, which are components of the human stress response. These two components have been shown to be hypo-reactive in FM, which is also considered to be a possible part of the pathogenesis of FM (Kadetoff & Kosek, 2010; Price & Staud, 2005).

To conclude, the maintenance of widespread pain in FM is considered to be due to an increase in pain facilitation and a decrease in pain inhibition. These alterations are influenced by cognitions, emotions and behaviors (Nijs & Van Houdenhove, 2009). While the etiology of pain in patients with FM is under continuous study, there is limited knowledge of the cause of their fatigue. However, it has been suggested that the fatigue in FM can also be partly explained by central sensitization (Casale & Rainoldi, 2011; Yunus, 2007).

2.5 Fatigue

Fatigue can be referred to as acute or chronic. The acute fatigue is considered a normal protective mechanism and is often relieved by rest or a change of habits. Chronic fatigue on the other hand is abnormal and non-functional, often with complex or unknown causes (Guymer & Clauw, 2002).

Fatigue is a symptom of substantial importance for patients with FM (Guymer & Clauw, 2002; Yunus, 2007) and appears to be a major limitation both in their social life and for their work ability (Liedberg & Henriksson, 2002; Sallinen, Kukkurainen, Peltokallio, & Mikkelsson, 2011; Wuytack & Miller, 2011). Patients with FM have described their fatigue in terms of sleepless nights, physical weakness, social withdrawal, loss of mental energy and overwhelming exhaustion (Sallinen, et al., 2011).

Previous research indicates that fatigue levels in FM decrease with age (Wolfe, Hawley, & Wilson, 1996). Fatigue in fibromyalgia has been shown to be associated with other health related aspects, such as increased muscular tenderness, depression, poor sleep quality (Kurtze & Svebak, 2001; Nicassio, Moxham, Schuman, & Gevirtz, 2002; Wolfe, et al., 1996) and low level of physical activity and physical function (Kop et al., 2005; Rutledge, et al., 2007), as well as socio-demographic aspects such as female gender, low age, low working capacity and low education. Previous research has indicated that high BMI may be associated with fatigue (Wolfe, et al., 1996), while recent studies show no relationship between BMI and fatigue in FM (Kim, Luedtke, Vincent, Thompson, & Oh, 2012; Okifuji, Bradshaw, & Olson, 2009).

There are many conditions besides FM and CWP where chronic fatigue is a severe problem, such as other rheumatic diseases (Barendregt et al., 1998; Rupp, Boshuizen, Jacobi, Dinant, & van den Bos, 2004; van Tubergen et al., 2002), myalgic encephalomyelitis (Carruthers et al., 2011), cancer (Furst & Ahsberg, 2001), neurological disorders (Catalan et al., 2011; Duncan, Kutlubaev, Dennis, Greig, & Mead, 2012) and psychiatric conditions (Ferentinos et al., 2011).

Myalgic encephalomyelitis (ME), also referred to in the literature as chronic fatigue syndrome (CFS), is a complex condition characterized by an abnormally low threshold of fatigability after minimal physical or mental exertion. The pathophysiology of ME is believed to involve aberrations in the central nervous system, the immune system and the cellular energy metabolism as well as cardiovascular abnormalities (Carruthers, et al., 2011). ME occurs as a co-morbidity in patients with FM, but is also present in other conditions. As mentioned previously, about 55 % of ME patients have been

shown to fulfil the criteria for FM (Yunus, 2012). The patients described in this thesis were not examined for the ME criteria, and this condition will therefore not be further mentioned in this thesis.

2.5.1 Assessment of fatigue

Fatigue is an important domain in FM and recommended to be assessed in all clinical trials involving patients with FM (Choy et al., 2009).

There are currently no accepted definition of fatigue in FM and CWP, which complicates its assessment (Casale & Rainoldi, 2011). The term fatigue often alludes to physical muscle fatigue, such as in healthy individuals where fatigue has been defined as "a condition related to an exercise-induced reduction in the ability to produce force, which determines whether the performance of the task can be sustained" (Barry & Enoka, 2007).

It has been suggested that a distinction can be made between peripheral muscle fatigue and central fatigue in FM and that assessment of fatigue should include both subjective ratings and objective evaluation of local muscle fatigue with surface electromyography (Casale & Rainoldi, 2011). This thesis comprises only subjective ratings of perceived fatigue in patients with FM and CWP. The patients´ subjective experiences of fatigue might have a higher relevance for their well-being than objective measures. However, subjective experiences of fatigue fluctuate and are multidimensional, which complicates the assessment (Guymer & Clauw, 2002; Smets, Garssen, Bonke, & De Haes, 1995; Watt et al., 2000); it is also difficult to compare between two individuals. In research, group comparisons of fatigue are carried out continuously between different populations and conditions. In such comparisons it is important to take into consideration that different conditions bring different experiences of fatigue. The patients´ experiences affect their frames of references for severe fatigue and influence their ratings.

Dimensions of fatigue

The traditional way to subjectively rate fatigue has been to use a one-dimensional visual analogue scale (VAS). When the perspective on assessments of fatigue started to change, instruments intended to measure multiple dimensions of fatigue were developed. The complexity of fatigue favors the use of multiple dimensions. It is possible that different treatments could have an impact on different dimensions of fatigue, which can be studied when ratings of multiple dimensions are used in research. There is no consensus on how many dimensions of fatigue exist. Most fatigue scales

therefore differ in which and how many dimensions of fatigue they comprise, probably due to the group of patients for which they are constructed.

The Multidimensional Fatigue Inventory (MFI-20)

The MFI-20 is a self-administered instrument that comprises five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation.

The MFI-20 was originally developed to assess cancer-related fatigue (Smets, et al., 1995). The construct validity of the instrument was assessed in comparisons between and within populations hypothesized to differ in different dimensions of fatigue, such as cancer patients receiving radiotherapy, patients with CFS/ME, psychology students, medical students, army recruits and junior physicians. The structure of five different fatigue dimensions was investigated using confirmatory factor analyses. The MFI-20 was also investigated for convergent validity by correlation with a VAS for fatigue in cancer patients as well as internal consistency for all populations described above. The results indicated satisfactory reliability and validity for assessment of cancer-related fatigue (Smets, et al., 1995).

The MFI-20 was translated to Swedish in a study of cancer patients receiving radiotherapy. The internal consistency of the subscales of the Swedish version of the MFI-20 was also investigated in the study and was found to be satisfactory for patients with cancer (Furst & Ahsberg, 2001).

At the time when the studies in the present thesis were planned, there was no accepted assessment tool for multidimensional fatigue for use in FM. However, the MFI-20 had been used in several other chronic pain conditions, such as rheumatoid arthritis (Rupp, et al., 2004), primary Sjögren´s syndrome (Barendregt, et al., 1998) and ankylosing spondylitis (van Tubergen, et al., 2002). It was thus chosen to assess multidimensional fatigue in this thesis. The MFI-20 has recently been recommended for use in patients with FM (Choy, et al., 2009) and has also been used in pharmacological studies in FM (Arnold et al., 2010). However, the Swedish version of the MFI-20 had not been validated or tested for reliability in patients with FM, and, for this reason, Study I in the present thesis was initiated.

The MFI-20 is more comprehensive and time-consuming than a one-dimensional scale. The Fibromyalgia Impact Questionnaire (FIQ) is an accepted tool for measuring self-rated symptoms and disabilities in FM, and it includes a one-dimensional VAS for fatigue. For both ethical and practical reasons, patients should not be subjected to unnecessarily extensive

questionnaires. It is therefore of interest to investigate the contexts in which it is indicated to add the more comprehensive MFI-20 to the patient examination and when the one-dimensional FIQ fatigue is sufficient, and this was the reason for initiating Study II in the present thesis.

2.6 Gender differences

FM and CWP are more prevalent among women than men (Bergman, et al., 2001; Gerdle, et al., 2008; Gran, 2003). Female patients with FM have been shown to have more tender points than male patients with FM (Hauser et al., 2011; Yunus, Inanici, Aldag, & Mangold, 2000).

No gender differences have been found in socio-demographic aspects such as age, marital status and education (Hauser, et al., 2011), or in health related aspects such as pain intensity and symptoms of depression and anxiety (Hauser, et al., 2011; Yunus, 2001).

However, there appear to be gender differences in ratings of fatigue in FM, where several studies have shown that women report higher fatigue levels than men (Nicassio, et al., 2002; Wolfe, et al., 1996; Yunus, 2001). There appears to be a gender difference with regard to fatigue in the general population as well (Watt, et al., 2000).

An epidemiological study showed that the strongest explanatory variable for high self-rated physical function in FM was being a man and that 27 % of men with FM were highly functioning compared to only 12 % of the women (Rutledge, et al., 2007).

Most studies of patients with CWP and FM concern female patients only or a mix of men and women where the men are in minority. Since there appear to be gender differences in ratings of fatigue and physical function it might be preferable to study the effects of treatment in men and women separately. This conclusion is supported by a previous study suggesting that men retain positive effects in pain and distress after chronic pain management programmes longer than women (Keogh, McCracken, & Eccleston, 2005)

2.7 Treatment

There is no cure for FM and CWP as yet, and the treatment is mainly symptomatic. The European league against rheumatism (EULAR) has suggested guidelines for treatment in FM (Carville et al., 2008). The most

efficacious treatment of FM requires a multidisciplinary approach combining pharmacological treatment, exercise and cognitive behavioral therapy (Carville, et al., 2008; Kosek & Löfgren, 2009; Sarzi-Puttini et al., 2011). Both pharmacological and non-pharmacological treatments have been shown to have an effect on symptom severity and physical function. The treatments need to be tailored with consideration to pain, fatigue, function and other features associated with FM (Busch, Barber, Overend, Peloso, & Schachter, 2007; Carville, et al., 2008; Mannerkorpi & Henriksson, 2007).

2.7.1 Physiotherapy

The main objective of physiotherapy treatment is to promote health. The physiotherapist should regard the patient as a physical, psychic, social and existential whole (Broberg & Tyni-Lenné, 2009). Physiotherapy 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.”(WCPT, 2007)

The description above illustrates that physiotherapy needs to include many dimensions. According to the WCPT, physiotherapy involves “identifying and maximising quality of life and movement potential within the spheres of promotion, prevention, treatment/intervention, habilitation and rehabilitation“ (WCPT, 2007).

As mentioned, a multidisciplinary approach is recommended for patients with FM and CWP. However, many patients with widespread pain in primary health care may be in need of physiotherapy as their only treatment form (Nijs, Mannerkorpi, Descheemaeker, & Van Houdenhove, 2010). Primary care physical therapy is recommended to include aerobic exercise, strengthening exercise and education. There is less evidence for the use of passive treatments, relaxation and activity management (Nijs, et al., 2010).

Exercise

Exercise has been defined as “a type of physical activity consisting of planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (Caspersen, Powell, & Christenson, 1985; Thomson, 2009), where *physical activity* means “any

bodily movement produced by the contraction of skeletal muscles that results in a substantial increase over resting energy expenditure" (Thomson, 2009). The concept *physical function* is also used in the present thesis, which has been defined as "the capacity of an individual to carry out the physical activities of daily living" (Garber, et al., 2011) and reflects motor function and control, physical fitness, and habitual physical activity (Garber, et al., 2011).

Different types of exercise are being used for FM and CWP in health care, such as aerobic exercise, resistance training, flexibility exercise and body awareness therapy (Busch, et al., 2007). Engagement in exercise has been shown to be a strong explanatory variable of high self-rated physical function in patients with FM (Rutledge, et al., 2007). Aerobic exercise has been shown to improve global outcome measures, physical function and, to some degree, also pain and the number of tender points in FM (Busch, et al., 2007). There is limited evidence for the effect of resistance training and flexibility exercise in FM (Busch, et al., 2007). Only a few exercise studies have included measures of fatigue in FM patients, indicating that exercise can decrease fatigue levels (Jones et al., 2008; Pedersen & Saltin, 2006).

Pool exercise is one type of aerobic exercise that has been recommended for patients with FM (Carville, et al., 2008) and been shown to improve physical function and overall health in FM and CWP (Carville, et al., 2008; Mannerkorpi & Henriksson, 2007).

Pool exercise is commonly performed in temperate water (30-34 ºC) for patients with pain, which appears to reduce pain and stiffness and enhance relaxation. The viscosity of the water provides resistance to the exercises, while the buoyancy facilitates them (Mannerkorpi & Iversen, 2003).
In patients with FM, aerobic exercise has been recommended to be performed two times a week in sessions between 20 to 60 minutes for at least six weeks (Busch, et al., 2007; Hauser et al., 2010). Patients with FM often experience increased pain and fatigue following exercise. However, if they continue to exercise for a few weeks at appropriate intensity, the symptoms most likely decrease again. It is thus important that the patients are informed of this initial increase in symptom severity before starting an exercise programme in order to keep them motivated to continue (Hauser, et al., 2010).

Previous findings show that patients with more severe pain and physical impairments obtain the best effects from operant and cognitive behavioral treatment programmes (Thieme, Turk, & Flor, 2007) while, to the best of our knowledge, there are no studies that report which patients with FM or CWP

benefit most from physical exercise. Study III in the present thesis was initiated to explore this subject in sub-group analyses.

Resistance training has been described as "a type of exercise that requires the body´s musculature to move (or attempt to move) against an opposing force, usually presented by some kind of equipment" (Fleck & Kraemer, 2004).

There is a scarcity of studies concerning resistance training in patients with FM, and there is limited evidence of positive effects on symptom severity and physical function (Busch, et al., 2007). There is even less knowledge about effects of exercise in men with FM or CWP. This was the motivation for Study IV. There are no standardized recommendations for resistance training in patients with FM and CWP, and the resistance training programme in Study IV in the present thesis was therefore based mainly on recommendations for healthy individuals (Ratamess, Alvar, & Evetoch, 2009).

For healthy adults, a resistance training programme has been recommended at a minimum of two times a week in sessions between 20 and 60 minutes for at least six weeks and to include exercises with concentric, excentric and isometric muscle actions. Resistance training has also been recommended to involve both unilateral and bilateral single-joint and multiple-joint exercises for maximizing strength (Ratamess, et al., 2009).

Progression in resistance training has been defined as "the act of moving forward or advancing toward a specific goal over time until the target goal has been achieved" (Kraemer et al., 2002). Progression in resistance training in healthy individuals has been recommended to be dependent on individual goals and guided by a specialist (Ratamess, et al., 2009).

Patient education

Patient education is a common treatment in many chronic conditions (Weingarten et al., 2002) and has been defined as "planned, organized learning experiences designed to facilitate voluntary adoption of behaviors or beliefs conducive to health" (Burckhardt, Lorig, et al., 1994).

Education can be conducted in many forms, usually between physiotherapist and patient and interactions between patients. Different forms of education over the internet have recently become common (Burckhardt, 2005; Lorig et al., 2008).

In FM, education programmes have been recommended to be multidisciplinary and enhance a self-efficacy change in relation to healthy behaviors. Three general assumptions are suggested to guide the treatment of patients with FM: "that patients need skills for managing their symptoms on a day-to-day basis, that they can learn how to manage their fibromyalgia symptoms, and that effective practice of healthy behaviors will lead to positive changes in symptoms and health status" (Burckhardt, 2005). Education including cognitive behavioral techniques is recommended to be combined with exercise in order to be most effective in FM (Burckhardt, 2005; Mannerkorpi, Nyberg, Ahlmen, & Ekdahl, 2000; Rooks et al., 2007)

2.7.2 Pharmacological treatment

Pharmacological treatment has been shown to be effective in some patients with FM, while showing no effect in many patients. Different types of medications are being studied continuously. Medications affecting the central nervous system are considered to be the most effective in pharmacological treatment in FM (Goldenberg, 2007; P. J. Mease, Dundon, & Sarzi-Puttini, 2011).

Serotonin-nonepinephrine reuptake inhibitors (SNRI), such as duloxetine, and anti-epilectic drugs, such as pregabalin and gabapentin, have been recommended for use in FM because of their effect on pain, physical function and general well-being (Carville, et al., 2008; Kosek & Löfgren, 2009; P. J. Mease, et al., 2011). There is limited evidence that selective serotonin reuptake inhibitors (SSRI) have also been shown to have effect on pain, fatigue, mood and function in patients with FM (Goldenberg, 2007).

Low doses of tricyclic antidepressants (TCAs) have also been recommended for patients with FM (Goldenberg, 2007; Kosek & Löfgren, 2009). TCAs have shown a mild improvement in fatigue in patients with FM and moderate improvement in other features such as pain, sleep and general well-being (Goldenberg, 2007). Analgesics are often ineffective in patients with FM, except for tramadol, which has been shown to have a positive effect on pain and function in some patients with FM (Carville, et al., 2008; Kosek & Löfgren, 2009).

Combinations of antidepressants, analgesics and anti-epileptic drugs are frequently used in practice, but such drug combinations have not yet been sufficiently studied (Goldenberg, 2007; P. J. Mease, et al., 2011).

In conclusion, there are various pharmacological treatments that are recommended for use in FM. The EULAR recommends tramadol and

different types of TCAs, SNRI and anti-epileptic drugs (Carville, et al., 2008). However, for many patients, medications have limited or no effect, and thus pharmacological treatment must be combined with exercise and cognitive behavioral therapy (Carville, et al., 2008; Goldenberg, 2007; Kosek & Löfgren, 2009).

2.8 Methodological considerations

2.8.1 Validity

The validity of a study concerns whether the findings of the study are convincing and well-grounded. The design of the study is crucial for the validity of the study results (Polit & Tatano Beck, 2004).

The validity of an instrument or a scale refers to the degree to which it measures the concept it is supposed to measure. There are several aspects that must be considered when the validity of an instrument is established: content and face validity, criterion validity and construct validity (Polit & Tatano Beck, 2004; Streiner & Norman, 2008).

Face validity and content validity are closely related concepts and describe whether the scale seems to be reasonable (Streiner & Norman, 2008). Face validity refers to whether an instrument appears on the surface to assess the concept in question (Polit & Tatano Beck, 2004). Content validity concerns whether the instrument appears to include all the important and necessary aspects of the concept in question (Streiner & Norman, 2008). Criterion validity refers to the instrument's relationship with an external criterion, often a "gold standard"(Streiner & Norman, 2008).

Construct validity

Construct validity describes the extent to which the instrument adequately assesses the concept of interest (Polit & Tatano Beck, 2004). When the purpose of an instrument is to assess an abstract concept, such as fatigue, it is important to consider the construct validity of the instrument (Streiner & Norman, 2008). The construct validity of an instrument is often divided into *convergent validity* and *discriminant validity,* which describes the relationship between the instrument and other scales or methods of measurement (Polit & Tatano Beck, 2004; Streiner & Norman, 2008). High convergent validity of an instrument requires a high correlation between the instrument and another measurement assessing the same concept of interest (Streiner & Norman, 2008). High discriminant validity (or divergent validity) of an instrument requires a low correlation between the instrument and

another measurement assumed to be unrelated to the concept of interest (Streiner & Norman, 2008).

Another approach of construct validation is known-groups technique. *Known-group validity* is determined by the degree to which an instrument can demonstrate different scores for groups expected to vary on the variables being measured (Polit & Tatano Beck, 2004).

2.8.2 Reliability

Reliability refers to the accuracy and consistency of the information obtained in a study (Polit & Tatano Beck, 2004). There are several types of reliability of measurement, and the two aspects that will be described below are *test-retest reliability* and *internal consistency*.

Test-retest reliability

The stability of an instrument is often referred to as *test-retest reliability* and is established by investigating whether a self-administered instrument gives the same result on two different occasions. The time between the two occasions is crucial and needs to be chosen with respect to the specific concept of interest to prevent the influence of extraneous variables. High test-retest reliability of an instrument requires a high correlation between the results on the two occasions (Polit & Tatano Beck, 2004).

Internal consistency

Internal consistency concerns the extent to which the items of a scale all measure the same concept (Pallant, 2010). When a scale consists of several subscales that assess different but related concepts, the internal consistency should be assessed separately for the subscales (Polit & Tatano Beck, 2004).

2.8.3 Responsiveness

It is necessary in experimental studies that the instruments used for evaluation of possible effects of the intervention have the ability to detect changes in the outcome variables. The *responsiveness* of an instrument has been described as its ability to detect clinically relevant and meaningful changes in the concept of interest (Streiner & Norman, 2008). Another commonly used term is *sensitivity to change,* which has been described as the instrument's ability to detect any changes at all in the concept of interest, regardless of whether the changes are clinically relevant (Streiner & Norman, 2008).

3 AIM

3.1 General aims

The general aims of this thesis were to describe the multi-dimensional fatigue experienced by patients with FM and CWP, to explore the usefulness of the MFI-20 in women with FM and to investigate the effects of different types of physiotherapy on fatigue and other health related aspects in patients with FM and CWP.

3.2 Specific aims

I. To investigate the convergent construct validity and test-retest reliability of the Swedish version of the MFI-20 for female patients with FM and CWP

II. To explore the context in which ratings of multiple dimensions of fatigue (MFI-20) are useful in women with FM by comparing the MFI-20 and the one-dimensional FIQ fatigue in associations with socio-demographic and health related aspects and analyses of explanatory factors of severe fatigue

To compare multiple dimensions of fatigue between women with FM and age matched healthy women.

III. To investigate the effects of supervised physical exercise on health status and physical function in female patients with FM or CWP, and to analyse whether the level of pain, distress, stress and activity limitations might influence the outcomes

IV. To investigate the effects of pool exercise in temperate water and resistance training in men with CWP on multidimensional fatigue, symptoms of distress and isometric force, pain and health related quality of life.

Additional aims

To investigate the internal consistency of the Swedish version of the MFI-20 in female and male patients with FM and CWP and the convergent construct validity and test-retest reliability in male patients with FM and CWP.

To compare multiple dimensions of fatigue between men and women with CWP.

4 PATIENTS AND METHODS

The present thesis comprises four quantitative studies, The primary methods used are briefly described in Table 1.

Table 1. Methods used in studies I, II, III and IV

Study	I	II	III	IV
Design	Measurement study	Cross-sectional study	RCT	RCT Pilot study
Population	Female, n=166 *Validity:* n=166 (134 FM, 32 CWP) *Reliability:* n=36 (28 FM, 8 CWP)	Female, n=291 *Patient group:* 133 FM *Reference group:* 158 healthy women	Female, n=166 (134 FM, 32 CWP)	Male, n=38 *Randomized trial:* 28 CWP *Reference group:* 10 CWP
Outcomes	MFI-20 FIQ fatigue	MFI-20 FIQ fatigue Socio-demographic and health related variables	*Primary:* FIQ total, 6MWT *Secondary:* FIQ pain, FIQ fatigue,HADS, SF-36, LTPAI	*Primary:* MFI-20 *Secondary:* HADS Isometric force
Data analyses	*Validity:* Spearman´s rho *Reliability:* ICC, LOA, IISD **Internal consistency:* Cronbach´s alpha	Spearman´s rho Multivariate logistic regression *Between group:* Mann-Whitney U-test	*Between-group:* Mann-Whitney U-test, Fisher´s exact test Mantel-Haenszel $\chi 2$ test	*Between-group:* Kruskal Wallis test Mann-Whitney U-test, Fisher´s exact test, Mantel-Haenszel $\chi 2$ test

FM=fibromyalgia, CWP=chronic widespread pain, MFI-20=Multidimensional Fatigue Inventory, FIQ=Fibromyalgia Impact Questionnaire, 6MWT=Six-minute Walk Test, HADS=Hospital Anxiety and Depression Scale, SF-36=Short-Form 36 health survey, LTPAI=Leisure Time Physical Activity Instrument,
ICC=Intra class Correlation Coefficient, LOA=Limits of Agreement, IISD=Intra-Individual Standard Deviation, RCT=Randomized Controlled Trial
*Additional analysis in this thesis, not included in paper I

4.1 Populations

The thesis had two main populations, referred to as the female population and the male population (Figure 2). The female population (n=166) was included as a whole or in parts in Studies I, II and III. A reference group of healthy women (n=158) was also recruited to Study II. The male population (n=44) was included in Study IV, although only the 38 patients with CWP in the male population were included in the main analyses in Study IV. Both populations were also included in additional analyses described below.

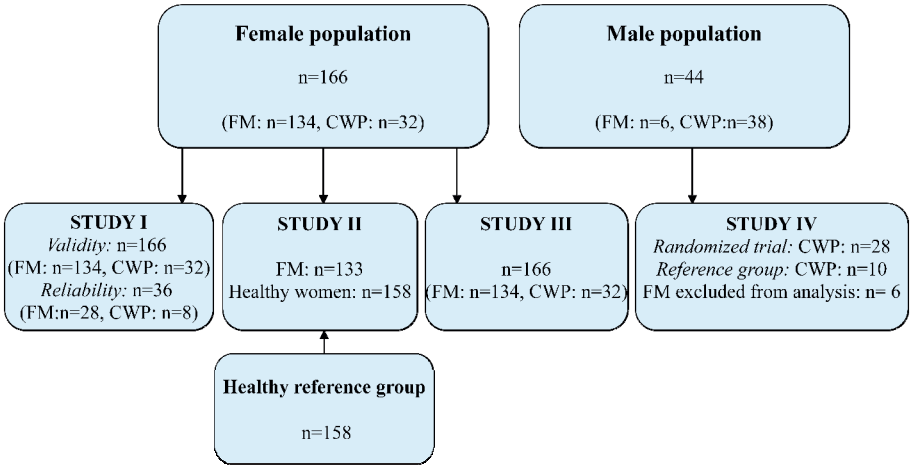

Figure 2. The populations in the present thesis

4.1.1 Female population

The female population was recruited from primary health care centres in Western Sweden by searching patient journals for the diagnoses of FM, CWP and unspecific pain (between 1995 and 2004) and by consecutive recruitment (in 2004 and 2005).

The inclusion criteria were women with FM or CWP according to the ACR 1990 criteria (Wolfe, et al., 1990), in the age range 18–60 years.

The exclusion criteria were other severe somatic or psychiatric disorders, such as cancer, stroke or schizophrenia, inability to understand Swedish,

allergy to chlorine, ongoing exercise therapy supervised by a physical therapist, or plans to start such therapy during the study period.

A systematic search of patient journals identified 818 subjects who had diagnoses related to pain disorder. However, when the journals were scrutinized, 520 individuals did not fulfil the inclusion criteria for FM or CWP or fulfilled exclusion criteria. The remaining 298 potentially eligible individuals were contacted by post (n=55) or telephone (n=243) for further screening. Forty-eight persons could not be contacted, 35 did not meet the inclusion criteria, and 61 declined to participate in the study, while 154 agreed to participate in an examination. Twenty-two of them did not meet the inclusion criteria, 12 were excluded due to treatment in progress (n=3) or severe disorders (n=9) and 18 declined to participate.

In total, 102 patients were referred to the intervention study and one patient was excluded for not fulfilling the inclusion criteria, leaving a total of 101 patients. At the same time, 93 individuals were consecutively recruited to the study. Sixty-five of them fulfilled the criteria and agreed to participate in the study. The study population therefore comprised 166 patients, 134 of whom fulfilled the criteria for FM and 32 for CWP.

Study I

The whole female population (n=166) participated in the validity study and 48 of the 166 patients were recruited to the reliability study. Sixteen per cent (n=7) of the patients in the test-retest reliability study did not complete and return the MFI-20 on the second occasion, and 8% (n=4) were excluded because the time between test 1 and test 2 exceeded two days. The final number of patients participating in the reliability study was 36 (28 FM, 8 CWP).

Study II

Patient group. 133 patients with FM from the female population were included in Study II.

Healthy reference group. A total of 189 healthy women between 21 and 60 years of age were recruited to an age and sex matched reference group from a mammography screening centre (n=83) and from employees in the public sector (n=106). Twenty persons were excluded from the reference group due to exclusion criteria: pregnancy (n=2) and severe psychiatric or somatic disorders (n=18). Eleven persons aged 21-30 years were randomly excluded to achieve adequate age matching with the patient group. The remaining 158 persons constituted the reference group in Study II.

Study III

All patients in the female population (n=166) were recruited to the randomized trial in Study III. The patients were allocated to one of the two treatment programmes using stratified randomization for the disorder, FM or CWP (Pocock & Simon, 1975) (See flow-chart in Figure 3).

The exercise-education group. 81 patients in the female population were allocated to the intervention group that participated in exercise and education.

The education group. 85 patients in the female population were allocated to the control group that participated only in education.

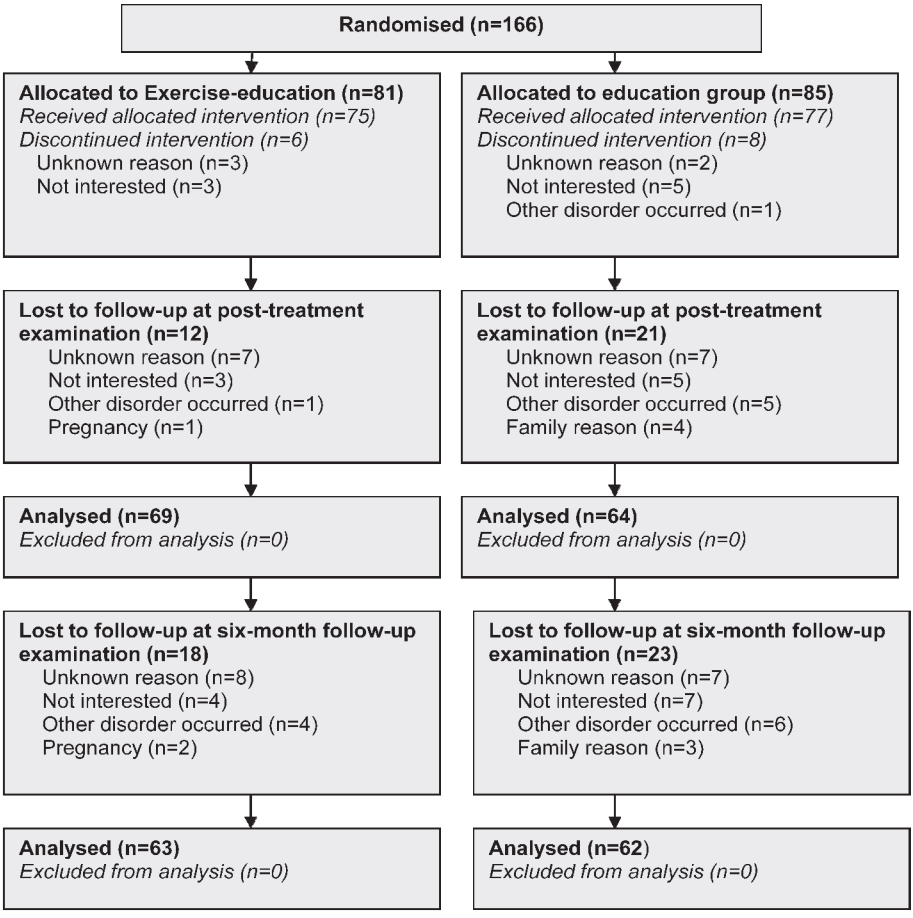

Figure 3. Flow chart for the patient population in Study III

Additional analyses female population

The internal consistency of the Swedish version of the MFI-20 was calculated here for the whole female population (n=166) as a complement to the analyses of convergent validity and test-retest reliability in Study I.

The 32 female patients with CWP were also included in an additional analysis that compared the scores of the MFI-20 and FIQ fatigue between men and women with CWP.

4.1.2 Male population

Study IV

The total male population recruited to the pilot study included 44 men, six with FM and 38 with CWP. The male population comprised two different parts; the patients that were included in the randomized trial and the patients that were included in the reference group.

The inclusion criteria for both parts were male patients, 18 to 60 years of age, with CWP according to the ACR criteria (Wolfe, et al., 1990). The exclusion criteria were inability to understand Swedish, severe psychiatric or somatic disorders, such as other rheumatic diseases, neurologic conditions, cancer, diagnosed depression or panic disorder, or having participated in resistance training or pool exercise at a physical therapy clinic during the preceding six months.

The randomized trial. The patients in the randomized trial were recruited from primary health care centres in Uddevalla in Western Sweden by searching through patient journals for the diagnoses of CWP and FM and unspecific pain (between 2005 and 2007) and consecutive recruitment (in 2008). Thirty-four patients (28 CWP, 6 FM) were allocated to one of the two exercise programmes using stratified randomization for the disorders of CWP or FM (Pocock & Simon, 1975). The recruitment process for the ramdomized trial is shown in the flow chart in Figure 4.

The six men with FM were found to create a small subgroup with greater impairments than the patients with CWP. They tended to report more severe fatigue, pain, stress and distress (paper IV) than the patients with CWP, and isometric force appeared to be lower for the patients with FM than for the patients with CWP at baseline in all performance-based tests. Thus, to achieve a more homogenous study sample, the FM patients were excluded from the data analysis (Figure 1). The final number of patients included in the

randomized trial was 28, 14 in the pool exercise group and 14 in the resistance training group, all classified as CWP (Figure 4).

The reference group. The reference group of male patients with CWP was recruited in parallel from different primary health care centres than the exercise groups in the western part of Sweden by searching patient journals for FM, CWP and unspecific pain diagnoses (between 2005 and 2007) and consecutive recruitment (in 2008). The recruitment process for the reference group is shown in Figure 5). The purpose of the reference group was to obtain information about the natural course of CWP during the study period. The number of patients included in the reference group was ten, all classified as CWP. The reference group did not participate in any intervention.

Additional analyses male population

Convergent construct validity, test-retest reliability and internal consistency were calculated in the present thesis for the Swedish version of the MFI-20 for men with FM or CWP, as a complement to the analyses in Study I that included only female patients.

The whole male population (n=44) participated in the analyses of convergent validity and internal consistency of the MFI-20. Forty of them were recruited to the test-retest reliability study. Sixteen per cent (n=7) of the patients in the test-retest reliability study did not complete and return the MFI-20 on the second occasion and 13% (n=5) were excluded because the time between test 1 and test 2 exceeded two days. The final number of patients participating in the reliability study was 26 (5 FM, 21 CWP).

The 38 male patients with CWP were also included in an additional analysis comparing the scores of the MFI-20 and FIQ fatigue between men and women with CWP.

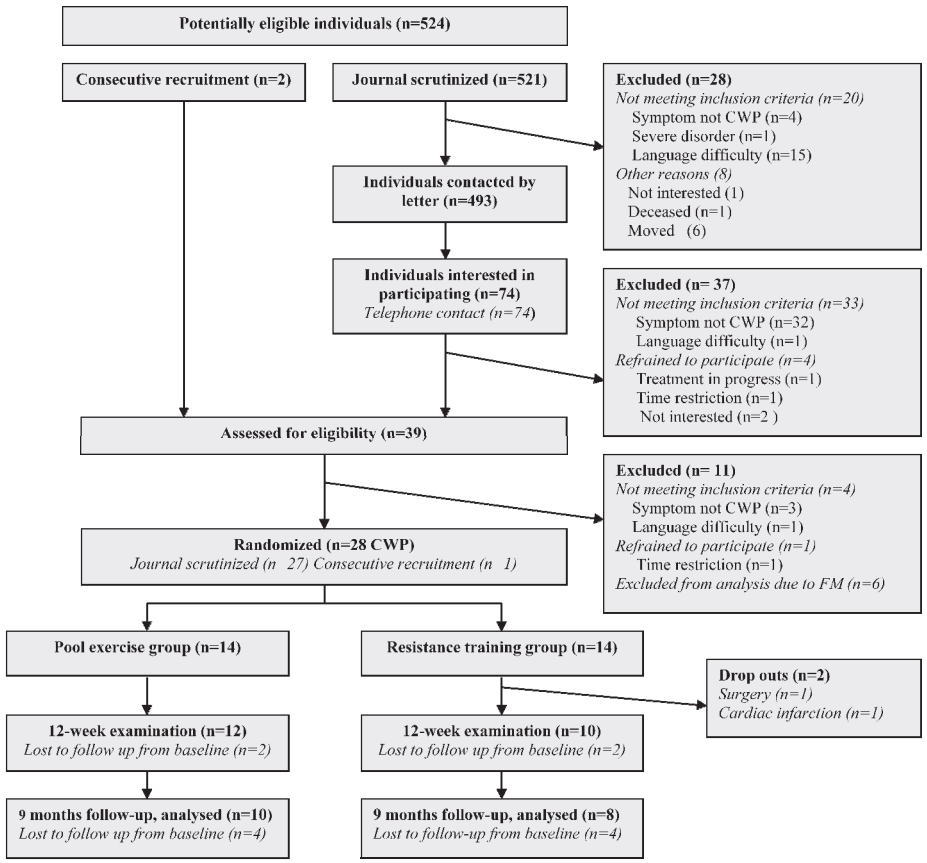

Figure 4. Flow chart for the randomized trial of men with FM and CWP in Study IV.

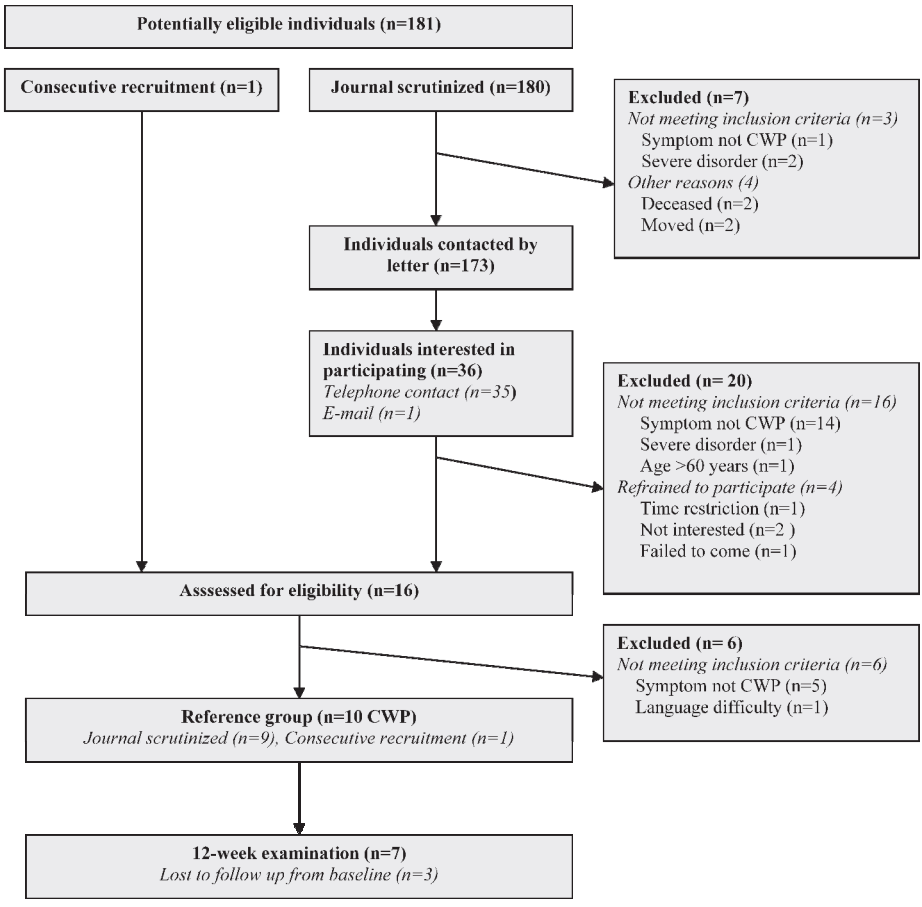

Figure 5. Flow chart for the reference group of men with CWP in Study IV

4.2 Measurements

In 2009, the international research group for Outcome measures in rheumatology (OMERACT) suggested key domains for FM, including recommendations for which domains should be assessed in clinical trials (P. Mease, et al., 2009). A hierarchy for the assessment of different domains in FM was suggested (Figure 6) (P. Mease, et al., 2009).

According to this hierarchy, pain, tenderness, fatigue, patient global, multidimensional function and sleep disturbance are recommended to be assessed in all clinical trials (P. Mease, et al., 2009). Study III and Study IV

in this thesis appear to have embraced all these aspects as well as symptoms of depression, which are recommended to be included in some FM trials, and anxiety, which according to the hierarchy may or may not be included.

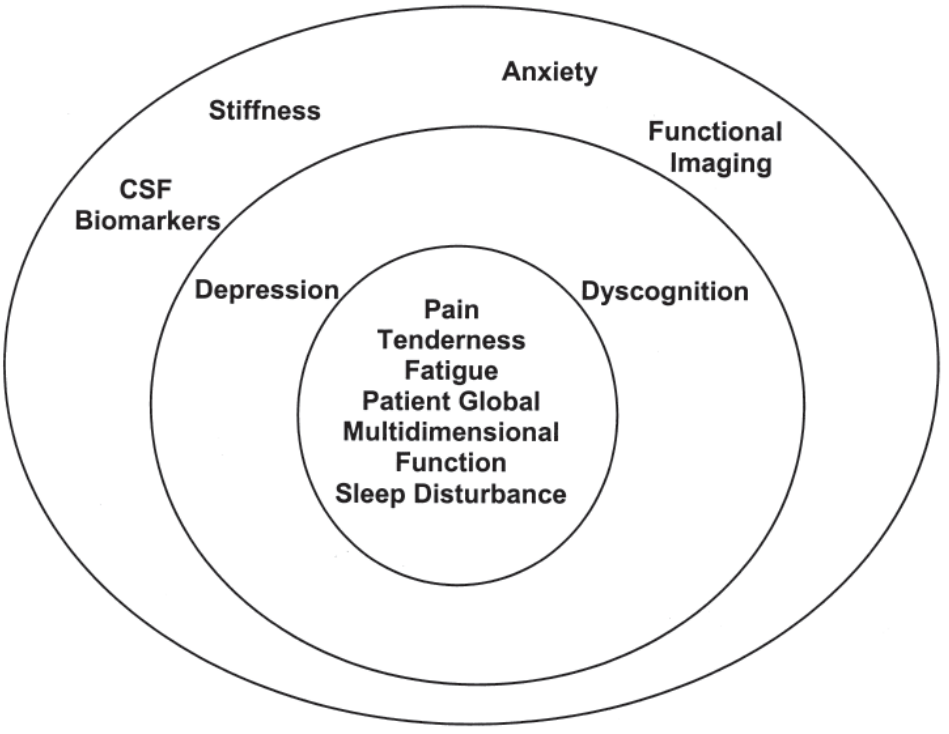

Figure 6. Hierarchy of domains for fibromyalgia. The inner circle includes the core set of domains to be assessed in all clinical trials of FM. The second concentric circle includes the outer core set of domains to be assessed in some but not all FM trials. The outermost circle includes the domains on the research agenda that may or may not be included in FM trials. (Mease, P et al.. published in J Rheumatol 36(10): 2318-2329) © Journal of Rheumatology. Reprint courtesy of Journal of Rheumatology.

The measurements used in the thesis are listed in Table 2 and presented in detail below

Table 2. Overview of measurements in the thesis.

Measurements	Study I	Study II	Study III	Study IV
Self-administered questionnaires				
MFI-20 [5 subscales à 4-20]	X	X	X	X
FIQ total [0-100]			X	
FIQ fatigue [0-100]	X	X		X
FIQ pain [0-100]		X	X	X
Pain localizations [0-18]		X	X	X
HADS-Anxiety [0-21]		X	X	X
HADS-Depression [0-21]		X	X	X
SF-36 [0-100]		X	X	X
LTPAI [hours]		X	X	
SCI-93 [0-140]			X	
Experience of physical activity [0-7]			X	
Sleep quantity [1-4]		X		
Sleep quality [1-4]		X		
BRPE [6-20]			X	X
Examinations				
Tender points [0-18]	X	X	X	X
Pain pressure treshold [kPa/sec]			X	
Body mass index (BMI) [kg/m^2]	X	X	X	X
Performance-based tests				
Six-minute walk test (6MWT) [m]		X	X	
Isobex, shoulder abduction [N]				X
Steve Strong, knee extension [N]				X
Steve Strong, knee flexion [N]				X
Grippit [N]		X		X

HADS= The Hospital Anxiety and Depression Scale, SF-36=Short Form 36 health survey, LTPAI= Leisure Time Physical Activity Instrument, SCI-93=Stress and Crisis Inventory, BRPE= Borg scale for rating perceived exertion

Background data

The background data on the patients were collected in the same way in all four studies of the thesis.

Information about socio-demographics, duration of widespread pain and pharmacological treatment was gathered in a standardized interview.

Marital status was divided into two categories referring to whether the patient lived with another adult.

Employment was divided into four categories referring to the percentage of full time work, which is defined as 40 hours per week.

Sick leave and *disability pension* were categorised as none, part time or full time sick leave/disability pension, based on 40 hours of work per week.

Medications. Use of analgesics/NSAID and psychotropics (meaning antidepressants and sedatives) was registered as positive when use was regular or as needed.

Self-administered questionnaires

The MFI-20. The instrument assesses five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. It contains 20 statements on a five-point Likert scale that refer to aspects of fatigue experienced during the most recent days. The sum scores range from 4 to 20 for each subscale, and higher scores indicate a higher degree of fatigue (Furst & Ahsberg, 2001; Smets, et al., 1995).

Fibromyalgia Impact Questionnaire (FIQ). The FIQ comprises ten subscales of disabilities and symptoms, ranging from 0 to 100 (Burckhardt, Clark, & Bennett, 1991), and it is validated for a Swedish FM population (Hedin, Hamne, Burckhardt, & Engstrom-Laurent, 1995). A higher score indicates lower health status. The total score, being the mean of the ten subscales, and the subscales for pain and fatigue were applied in the thesis. The patients estimated their pain intensity/how tired they had been during the previous week on a VAS, ranging from 0 to 100 mm (Burckhardt, et al., 1991).

Pain localizations. The localization and distribution of pain were reported in a self-administered pain drawing with 18 predefined body regions, ranging from 0 to 18, referring to the number of body regions in pain (Bergman, 2005).

The Hospital Anxiety and Depression Scale (HADS). The HADS contains 14 statements, with a rating from 0 to 3, in which a higher score indicates a higher degree of distress. The scores build two subscales, for anxiety (HADS-A) and depression (HADS-D), ranging from 0 to 21 (Zigmond & Snaith, 1983). The cut-off score of eight is suggested to indicate possible anxiety and depression (Herrmann, 1997).

Short Form-36 (SF-36). The SF-36 is a generic instrument assessing health related quality of life, comprising eight subscales. The subscales of physical functioning, role physical, bodily pain and vitality range from 0 to 100 and were used in study III in the present thesis. The eight subscales build two composite scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), ranging from 0 to 100. The PCS and the MCS were used in studies III and IV in the present thesis. A higher score indicates better health related quality of life (Ware & Sherbourne, 1992).

Leisure Time Physical Activity Instrument (LTPAI). This instrument assesses the amount of physical activity during a typical week, divided into light and moderate and vigorous. The sum of hours of moderate exercise was used in study III in the present thesis. The total score is the sum of hours for the activities and it was used in studies II and III in the present thesis (Mannerkorpi & Hernelid, 2005).

Stress and Crisis Inventory (SCI-93). The SCI-93 comprises 35 items, assessing clinical manifestations of stress on a scale ranging from 0 "not at all" to 4 "very much". The questions include physical and mental sensations. The total score ranges from 0 to 140 and a higher score indicates more stress (Krafft & Nystrom, 2002).

Experience of physical activity. This scale consists of 22 items that comprise five subscales about aspects related to physical activity: activity-related physical relaxation (AR), activity-related well-being (AW), activity beliefs (AB), activity-related symptoms (AS) and activity habits (AH). The subscales range from 0 to 7 and a higher score indicates more dissatisfaction (Mannerkorpi, Rivano-Fischer, Ericsson, Nordeman, & Gard, 2008).

Sleep quantity and quality. Two questions about the patients´ quantity and quality of sleep (Akerstedt et al., 2002) were used; "Do you think you get enough sleep?" and "On the whole, how do you think you sleep?" The scores range from 1 to 4 and a higher score indicates poorer sleep.

*Borg scale for rating perceived exertion (BRPE).*The BRPE range from 6 to 20 and was used to record exertion during pool exercise in Study III and Study IV (Borg, 1982).

Manual examinations

Tender points. Tender points were examined by manual palpation by trained physiotherapists (Wolfe, et al., 1990).

Pain pressure threshold. Muscle tenderness was examined using a Somedic algometer (Somedic Production AB, Sollentuna, Sweden) (Kosek, Ekholm, & Hansson, 1996).

Body Mass Index (BMI). The BMI was calculated as the patient's body weight divided by the square of his or her height.

Performance-based tests

Six-minute walk test (6MWT). The patient was instructed to walk as quickly as he or she could without running and the distance in metres covered in six minutes was used as a measure of walking capacity. The test has shown satisfactory test-retest reliability in a Swedish FM population (Mannerkorpi, Svantesson, Carlsson, & Ekdahl, 1999).

Isobex, shoulder abduction force. The isometric force of shoulder abduction was measured in Newton in Study III with Isobex 3.0 (Medical Device Solution AG, Burgdorf, Switzerland) in the plane of scapula at 45° and shoulder elevation at 90°, in a standardized position. Subjects were seated on a chair with their feet supported by the floor. The dynamometer was placed on the floor and the band from the dynamometer was placed just proximally to the styloid process of the ulna (Leggin, Neuman, Iannotti, Williams, & Thompson, 1996)

Steve Strong, Knee extension and flexion force. Isometric force in the knee extensors and flexors was measured in Study III. The patients were seated with the back supported, a seat belt around the waist, with both legs hanging freely. The knee angle was 90°. A non-elastic strap was placed around the ankle and attached to a pressure transducer with an amplifier (Steve Strong, Stig Starke HB, Gothenburg, Sweden). The subjects were instructed to pull the ankle strap maximally for three seconds in either knee extension or flexion. The best of three efforts was reported as the maximal isometric quadriceps/hamstrings force in Newton (Schaufelberger et al., 2001).

The Grippit, hand grip force. Hand grip force was measured as the sustained maximum voluntary contraction during ten seconds, measured in Newton using an electronic instrument, the Grippit (Nordenskiold & Grimby, 1993).

4.3 Procedures

4.3.1 Study I

All 166 patients in the female population completed the FIQ fatigue and the MFI-20 and the correlations between the two instruments were calculated to investigate the convergent construct validity of the Swedish version of the MFI-20.

The patients were also asked to complete the MFI-20 on two occasions, one day apart, so the test – retest reliability of the Swedish version of the MFI-20 could be investigated. The data for the test-retest reliability study were collected six months after the validity study.

Additional analyses Study I

The Swedish version of the MFI-20 was analysed for convergent construct validity (n=44) and test-retest reliability (n=26) also in the male population, following the same procedure as described above for the female population.

The internal consistency of the Swedish version of the MFI-20 was calculated separately for the female population (n=166) and the male population (n=44).

4.3.2 Study II

The data of the female population collected at baseline in Study III were used to investigate the usefulness of multiple fatigue dimensions in patients with FM. The subscales of the MFI-20 and the FIQ fatigue were compared by correlating the two fatigue instruments with socio-demographic and health related aspects as well as explanatory factors for severe fatigue. Variables shown to be associated with fatigue in previous research were chosen to be included in the analyses of correlations and explanatory factors (Kop, et al., 2005; Kurtze & Svebak, 2001; Nicassio, et al., 2002; Rutledge, et al., 2007; Wolfe, et al., 1996).

4.3.3 Study III

Outcomes

Primary outcomes in study III were the FIQ total and the 6MWT. *Secondary outcomes* were the FIQ Pain, the FIQ fatigue, the SF-36, the HADS and the LTPAI. *Exploratory outcomes* were the SCI-93, the MFI-20 and Experience of physical activity.

Examinations

The trained examiners were blinded to the patients' group assignments. The examination for the ACR criteria for FM and CWP (Wolfe, et al., 1990) included a pain localization sheet (Bergman, 2005), a standardized interview and an examination of tender points (Wolfe, et al., 1990). The patients completed a battery of questionnaires and performed the 6MWT. The FIQ, the SF36, the HADS, the LTPAI and the SCI-93 were completed at baseline, post-test (20 weeks after baseline) and follow-up (11-12 months after baseline). The MFI-20 and the Experience of Physical Activity scale were completed at baseline and post-test. The patients were instructed to continue their baseline medical treatment with no change throughout the 20-week study period, and their medical treatment was monitored at post-test.

Interventions

The education programme, which was designed to introduce strategies to cope with the FM symptoms, consisted of six one-hour sessions, conducted once a week for six weeks. The programme was led by a physiotherapist. The pedagogical approach was based on the active participation of the patients through discussions and practical exercises. The topics were theories for long-lasting pain, pain alleviation, physical activity, stress, relaxation and modifications of lifestyle to enhance health. At each session, the patients drew up a plan (a contract) for physical activity for the next week and performed a short relaxation exercise. The control group received the same education programme. Details of the programme are shown in paper III, Appendix I.

The exercise programme comprised 20 sessions of 45-min pool exercise once a week for 20 weeks in temperate (33°C) water, supervised by a physiotherapist. The exercise was planned to permit individual progress, aiming to improve overall function and to motivate regular physical activity. The median value for exertion (6–20), measured by the BRPE (Borg, 1982), ranged from 9 ("very light") to 11 ("fairly light") during flexibility, co-ordination and stretching exercises, while it was 13 ("somewhat hard") during aerobic exercise (Garber, et al., 2011). Heart rate (HR) was monitored

with a Polar S610i HR monitor (Kempele, Finland) and expressed in values for age-adjusted maximum HR, 220 minus age (HRmax). The mean value for HR during the programme ranged from 48% to 65% HRmax, which corresponds to very light to moderate intensity (Garber, et al., 2011). Details of the programme are shown in paper III, Appendix II.

Outcomes in Study III were evaluated using both an intention to treat (ITT) and a per-protocol design, which was defined as attendance at least 60 % of the sessions.

4.3.4 Study IV

Primary outcomes in study IV were the MFI-20. *Secondary outcomes* were the HADS, isometric force in shoulder abduction (Isobex), isometric force in knee extension and flexion (Steve Strong) and hand grip force (Grippit). *Exploratory outcomes* were the FIQ Pain, number of pain localizations, the SF-36 PCS and the SF-36 MCS.

Examinations

The trained examiners were blinded to the patients´ group assignments in the randomized trial. The examination for the ACR criteria for CWP and FM (Wolfe, et al., 1990) included the pain localization sheet (Bergman, 2005), a standardized interview and an examination of tender points (Wolfe, et al., 1990). The patients in the randomized trial and in the reference group completed a battery of questionnaires and the performance-based tests (Table 2) at baseline and 12 weeks after baseline. The patients in the randomized trial also performed the tests nine months after baseline. All patients were instructed not to change their baseline medical treatment throughout the 12-week study period, and their medical treatment was monitored at the 12-week examination.

Interventions

The pool exercise programme comprised 50-minute sessions in groups of six to eight patients twice a week for a period of 12 weeks in temperate (33°C) water, supervised by a physical therapist. The session included aerobic exercise for endurance, strength, flexibility, coordination and relaxation. The patients were instructed to exercise at their own rhythm and to modify the exercises individually with respect to thresholds of pain and fatigue. During the 12-week study period, they were encouraged to increase intensity and resistance with or without water equipment. The intensity during the pool exercise session was assessed with rate of perceived exertion on the BRPE (Borg, 1982) on two occasions in weeks 8 and 11.

The resistance training programme was followed twice a week for 12 weeks with free weights and resistance machines in groups of about eight to ten patients, supervised by a physical therapist. The session lasted for about one hour and included exercise for all four extremities, back and trunk, using dynamic exercises with excentric, concentric and isometric muscle actions (Ratamess, et al., 2009). A standardized protocol for resistance progress was applied (Hakkinen, Hakkinen, Hannonen, & Alen, 2001; Ratamess, et al., 2009; Valkeinen et al., 2005). During the 12-week study period, the load was planned to be increased individually from approximately 40 % to 80 % of one repetition maximum (RM) established at baseline. One RM is defined as "the heaviest resistance that can be used for one complete repetition of an exercise"(Fleck & Kraemer, 2004). At week 1, the patients performed three sets with 15-20 repetitions of each exercise. When the load increased, they still performed three sets but with fewer repetitions. All sessions started with ten minutes of warm-up on an ergometer bicycle.

4.4 Statistical analyses

An overview of the statistical tests used in the thesis is shown in Table 3. All the tests were two-tailed and conducted at the 5% significance level

Descriptive statistics are presented as mean, standard deviation (SD) and range for continuous variables and as number and percent for categorical variables.

The Spearman's correlation coefficient was used in Study I to calculate convergent construct validity and in Study II to calculate correlations between fatigue and other variables. The following classification was used to interpret the correlation values: correlations from 0 to 0.25 indicate little or no relationship, those from 0.25 to 0.50 indicate a fair degree of relationship, those from 0.50 to 0.75 a moderate to good relationship, while a correlation above 0.75 indicates a very good to excellent relationship (Colton, 1974).

Intra Class Correlation, Limits of Agreement and Intra-individual standard deviation (SD). The test-retest reliability of the MFI-20 was calculated in Study I using the intraclass correlation coefficient (ICC) with 95% confidence intervals (Shrout & Fleiss, 1979) as well as the mean, SD and range of the differences between the readings (test 2 - test 1), the limits of agreement (J. M. Bland & Altman, 1986) and the intra-individual SD (J.M. Bland & Altman, 1996). The limits of agreement provide a range within which 95% of all the differences between test 2 and test 1 are found (J. M.

Bland & Altman, 1986). Wilcoxon's Signed rank test was used to analyse systematic differences in the variables between test 1 and test 2.

The following classification was used to interpret the ICC values in Study I: correlation values below 0.40 represent poor reliability, values from 0.40 to 0.75 indicate fair to good reliability and values above 0.75 may be taken to represent excellent reliability (Fleiss, 1986).

Cronbach´s alpha As an additional analysis to Study I in the present thesis, Cronbach´s alpha was calculated for the five subscales of the MFI-20 to investigate internal consistency. Cronbach´s alpha coefficients above 0.7 are considered acceptable but values above 0.8 are preferable (Pallant, 2010).

Logistic regression. Explanatory factors of severe fatigue in Study II were analysed using logistic regression (Altman, 1999). As there is no known cut-off score for any of the five continuous MFI-20 subscales or for FIQ fatigue indicating more or less severe fatigue in an FM population, the cut off value for severe fatigue was defined as the median value of the patients´ scorings. The variables that showed a statistically significant association with MFI-20 and/or FIQ fatigue in the Spearman´s correlation analyses were included in the univariate logistic regression. The statistically significant explanatory factors ($p<0.05$) of the dichotomised subscales of the MFI-20 and FIQ fatigue in the univariate logistic regression analysis were included in the stepwise multivariate procedure, where a set of independent predictors of explanatory factors was selected for each of the six outcome variables. Odds ratios (OR) with 95% confidence intervals and p-value are presented.

The AUC values (the area under the Receiver Operating Characteristic (ROC) curve) were calculated in Study II for description of goodness of explanatory factors (Hanley & McNeil, 1982). $0.7 \leq AUC < 0.8$ indicates that the explanatory variables are acceptable, $0.8 \leq AUC < 0.9$ indicates that they are excellent and $AUC \geq 0.9$ indicates that they are outstanding (Hosmer & Lemeshow, 2000).

In Study II and the additional analyses of between-group differences in fatigue, logistic regression with group as dependent variable and the FIQ fatigue, the MFI-20 subscales and the covariates as independent variables was used to analyse differences in fatigue scales between the two groups adjusted for the covariates.

Between-group comparisons. For comparisons between two groups in Study II, III and IV and in the additional analyses, the *Mann Whitney U-test* was

used for continuous variables, *Fisher´s exact test* for dichotomous variables and *Mantel- Haenszel chi-square test* for ordinal categorical variables.

Within-group comparisons. For comparisons within groups in Study IV, p-values for change over time were calculated. *McNemar´s test* was used for change over time in dichotomous variables and *Wilcoxon´s Signed rank test* was used for change over time in continuous variables.

Effect size was calculated in study III for variables showing a significant change. Effect size for between-group analyses was calculated by dividing the mean difference between the post-test score and baseline score in the exercise-education group and in the education group by the pooled SD. Effect size for the 11–12 months follow-up was calculated as the mean difference between the follow-up score and baseline score divided by the SD at baseline. Effect sizes from 0.20 to < 0.50 were regarded as small, while effect sizes from 0.50 to < 0.80 were regarded as moderate (Fayers & Machin, 2001).

Upper limit of expected number of false significances. To control Type I errors, the upper limit of expected number of false significances for the secondary and exploratory variables was calculated in Study III and IV by the following formula: $\alpha/1-\alpha \times$ number of tests – number of significant tests on the significance level α).

Sub-group analysis. Pre-specified subgroups were created in study III by dichotomized values for the SCI-93, the FIQ Pain, the HADS-D and the SF-36 physical functioning. The SCI-93, the FIQ Pain and the SF-36 physical functioning were dichotomized by the median value, as there are no known cut-off points for these variables indicating more or less pathology in a pain population, while the HADS-D was dichotomized by a score of 8, which indicates possible depression (Herrmann, 1997). The heterogeneity, an interaction between the independent variable, group membership and the change score for the primary outcome measure (the FIQ total and the 6MWT), was analysed using a generalized linear model for subgroup analyses. A significant heterogeneity implies different effects of the intervention for 2 subgroups. Differences in the change scores were analysed by *Fisher's non-parametric permutation test*, and mean differences with 95% confidence intervals within each subgroup are presented in the graph (Figure 7).

Table 3. Overview of statistical tests in the thesis

Statistical test	Study I	Study II	Study III	Study IV
Descriptive statistics	X	X	X	X
Spearman´s correlation coefficent	X	X		
Intra Class Correlation coefficient	X			
Intra-Individual standard deviation	X			
Limits of agreement	X			
Wilcoxon´s Signed rank test	X		X	X
Cronbach´s alpha*	X			
Mann-Whitney U-test.		X	X	X
Fisher's exact test .		X	X	X
Mantel Haenszel Chi-2 test		X	X	X
McNemar´s test			X	X
Logistic regression		X		
Effect size			X	
Fisher's non-parametric permutation test			X	
Upper limit of expected number of false significances			X	X

*Additional analysis in the present thesis, not included in paper I.

4.5 Ethical considerations

Ethical approval was granted for all four studies in the present thesis by the Regional Ethical Review Board in Gothenburg, Sweden. Written informed consent was obtained from all patients.

5 RESULTS

The present thesis will be available electronically. Papers II and IV have not yet been published. To avoid compromising future publications, the results of Studies II and IV will only be presented briefly in the following results section.

5.1 Group characteristics

Group characteristics are given in Table 4 for the female population and Table 5 for the male population. The age for the whole female population ranged from 22 to 60 years, mean 45.6 (SD 8.8). The age for the whole male population ranged from 26 to 59 years, mean 49 (SD 8.7).

The patients with FM had significantly more tender points and self-rated pain localizations and worked significantly less hours per week than the patients with CWP, in both the female and the male population.

Table 4. Socio-demographic data of the female population (n=166: 134 FM, 32 CWP).

	FM&CWP n=166 Mean(SD)	FM n=134 Mean(SD)	CWP n=32 Mean(SD)	FM vs CWP p-value
Age [years]	45.6 (8.8)	45.6 (8.6)	45.5 (9.8)	0.905
Symptom duration [years]	10.5 (7.1)	10.7 (7.2)	9.5 (7.0)	0.340
Tender points [*n*]	13.5 (3.5)	14.8 (2.4)	8.1 (2.1)	**<0.001**
Pain localization [0-18]	12.9 (3.4)	13.4 (3.3)	10.9 (3.2)	**<0.001**
	n (%)	*n* (%)	*n* (%)	
Living with an adult	123 (74)	104 (78)	19 (59)	**0.044**
Born outside Sweden	27 (16)	22 (16)	5 (16)	1.000
Education				
≤9 years	38 (23)	30 (22)	8 (25)	
10-12 years	89 (54)	71 (53)	18 (56)	0.563
>12 years	38 (23)	32 (24)	6 (19)	
Employment				
0 %	98 (59)	83 (62)	15 (47)	
1-49 %	14 (9)	13 (10)	1 (3)	**0.044**
50-79 %	37 (22)	26 (19)	11 (34)	
80-100 %	17 (10)	12 (9)	5 (16)	
Sick leave				
None	87 (52)	68 (51)	18 (56)	0.546
Part time	31 (19)	26 (19)	6 (19)	
Full time	48 (29)	40 (30)	8 (25)	
Disability pension				
None	100 (60)	78 (58)	22 (69)	0.451
Part time	29 (18)	26 (19)	3 (9)	
Full time	37 (22)	30 (22)	7 (22)	
Pharmacological treatment				
Analgesics	118 (29)	93 (69)	25 (78)	0.391
Psychotropic drugs*	74 (45)	59 (44)	15 (47)	0.844

*Antidepressants, sedatives
SD = Standard deviation

Table 5. Socio-demographic data of the male population (n=44: 6 FM, 38 CWP).

	FM&CWP n=44 Mean(SD)	FM n=6 Mean(SD	CWP n=38 Mean(SD	FM vs CWP p-value
Age [years]	49.3 (8.7)	53.7 (4.0)	48.6 (9.0)	0.288
Symptom duration [years]	6.1 (4.2)	6.8 (2.9)	6.0 (4.5)	0.269
Tender points [*n*]	6.7 (4.1)	14 (2.4)	5.6 (3.0)	**<0.001**
Pain localization [0-18]	9.5 (3.4)	13.8 (3.7)	8.8 (2.9)	**0.004**
	n (%)	*n* (%)	n (%)	
Living with an adult	35 (80)	3 (50)	32 (84)	0.089
Born outside Sweden	8 (18)	1 (17)	7 (18)	1.000
Education				
≤9 years	17 (39)	4 (67)	13 (34)	0.079
10-12 years	16 (36)	2 (33)	14 (37)	
>12 years	11 (25)	0 (0)	11 (29)	
Employment				
0 %	9 (20)	3 (50)	6 (16)	**0.029**
1-49 %	2 (5)	0 (0)	2 (5)	
50-79 %	5 (11)	2 (33)	3 (8)	
80-100 %	28 (64)	1 (17)	27 (71)	
Sick leave				
None	41 (93)	5 (83)	36 (94)	0.581
Part time	2 (5)	1 (17)	1 (3)	
Full time	1 (2)	0 (0)	1 (3)	
Disability pension				
None	33 (75)	2 (33)	31 (82)	**0.025**
Part time	5 (11)	2 (33)	3 (8)	
Full time	6 (14)	2 (33)	4 (10)	
Pharmacological treatment				
Analgesics	25 (57)	4 (67)	21 (55)	0.058
Psychotropic drugs*	10 (23)	3 (50)	7 (18)	

*Antidepressants, sedatives
SD = Standard deviation

5.2 Validity and reliability of the Swedish version of the MFI-20

5.2.1 Convergent construct validity

Female population

Spearman's correlation coefficient revealed a significant association between all five subscales of the MFI-20 and the FIQ fatigue in the female population. The correlation values ranged from 0.32 for MFI reduced motivation to 0.62 for MFI general fatigue (Table 6).

Male population

Additional analyses (not included in papers I to IV) of convergent construct validity were made for the male population (n=44). Significant associations were found between all five subscales of the MFI-20 and the FIQ fatigue in the male population. The correlation values ranged from 0.55 for MFI reduced motivation to 0.78 for MFI general fatigue (Table 6).

Table 6. Spearman's correlation coefficients (r_s) between the five subscales of the Multidimensional Fatigue Inventory (MFI-20) and FIQ fatigue for the female population (n=165) and the male population (n=44).

	FIQ fatigue			
	Female population		Male population	
	r_s	p-value	r_s	p-value
General Fatigue	0.62	**<0.001**	0.78	**< 0.001**
Physical Fatigue	0.36	**<0.001**	0.58	**< 0.001**
Mental Fatigue	0.37	**<0.001**	0.57	**< 0.001**
Reduced Motivation	0.32	**<0.001**	0.55	**< 0.001**
Reduced Activity	0.36	**<0.001**	0.58	**< 0.001**

FIQ=Fibromyalgia Impact Questionnaire

5.2.2 Test-retest reliability

Female population

The scores of the 36 women on the MFI-20 at test 1 and test 2 are presented in Table 7. The mean interval between test 1 and test 2 of the MFI-20 was 1.06 days (SD 0.3).

The ICC values for the MFI-20 in the 36 women are given in Table 8. All five subscales showed relatively high ICC values, ranging from 0.75 for MFI physical fatigue to 0.92 for MFI mental fatigue. The mean, SD and range of the differences, the limits of agreement and the intra-individual SD in the 36 women are presented in Table 9. All the subscales had low means of the differences, around zero.

A systematic difference was found for MFI mental fatigue (p=0.03), showing that the patients' levels of mental fatigue were slightly lower at the second occasion (test 2). Figure 3 in paper I shows how the differences between test 1 and test 2 vary over the range of measurement (J. M. Bland & Altman, 1986).

Table 7. The scores of the Multidimensional Fatigue Inventory at test 1 and test 2, in 36 women with FM or CWP.

	Test 1		Test 2	
	mean (SD)	range	mean (SD)	range
General Fatigue	16.0 (3.2)	6 – 20	15.9 (3.8)	4 – 20
Physical Fatigue	15.9 (3.6)	5 – 20	15.3 (3.7)	6 – 20
Mental Fatigue	14.4 (4.3)	4 – 20	13.8 (4.1)	4 – 20
Reduced Motivation	9.9 (3.8)	4 – 20	9.7 (4.0)	4 – 20
Reduced Activity	14.1 (3.8)	7 – 20	14.3 (3.8)	7 – 20

SD=Standard deviation

Table 8. The Multidimensional Fatigue Inventory. The Intra class Correlation Coefficients (ICC) and 95 % confidence intervals (CI) for the ICC in 36 women with FM or CWP.

	ICC	95 % C.I.
General Fatigue	0.88	0.78 - 0.94
Physical Fatigue	0.75	0.56 - 0.86
Mental Fatigue	0.92	0.85 - 0.96
Reduced Motivation	0.86	0.75 - 0.93
Reduced Activity	0.89	0.79 - 0.94

Table 9. The Multidimensional Fatigue Inventory. The mean, standard deviation (SD) and range of the differences (test 2 – test 1), the limits of agreement (LOA) and the intra-individual standard deviations (IISD) in 36 women with FM or CWP.

	Difference mean (SD)	Difference min-max	LOA	IISD
General Fatigue	-0.1 (1.7)	-5.0 – 3.0	-3.5 – 3.3	1.2
Physical Fatigue	-0.6 (2.6)	-8.0 – 6.0	-5,7 – 4,5	1.9
Mental Fatigue	-0.7 (1.7)	-7.0 – 1.0	-4,0 – 2,7	1.3
Reduced Motivation	-0.2 (2.0)	-7.0 – 3.0	-4.2 – 3,9	1.4
Reduced Activity	0.1 (1.8)	-5.0 – 5.0	-3,4 – 3,6	1.3

Male population

Additional analyses (not included in papers I to IV) of test-retest reliability of the Swedish version of the MFI-20 were made for 26 patients in the male population. The scorings of the 26 men on the MFI-20 at test 1 and test 2 are presented in Table 10. The mean interval between test 1 and test 2 of the MFI-20 was 1.12 days (SD 0.4).

The ICC values for the MFI-20 in the 26 men are given in Table 11. All five subscales showed high ICC values, ranging from 0.83 for MFI reduced motivation to 0.94 for MFI physical fatigue. The mean and standard deviation (SD) of the differences, the limits of agreement and the intra-individual SD in the 26 men are presented in Table 12. All the subscales had low means of the differences, around zero.

No systematic differences were found between test 1 and test 2 for any of the fatigue measures.

Table 10. The scores of the Multidimensional Fatigue Inventory test 1 and test 2, in 26 men with FM or CWP.

	Test 1		Test 2	
	mean (SD)	Range	mean (SD)	Range
General Fatigue	14.1 (3.9)	5 – 20	14.1 (4.9)	4 – 20
Physical Fatigue	13.7 (4.3)	5 – 20	13.4 (4.7)	4 – 20
Mental Fatigue	10.4 (3.8)	4 – 17	10.2 (3.9)	4 – 16
Reduced Motivation	8.6 (3.2)	4 – 16	9.2 (3.2)	4 – 15
Reduced Activity	12.1 (4.3)	4 – 20	12.1 (4.2)	4 – 20

SD=Standard deviation

Table 11. The Multidimensional Fatigue Inventory. The Intra class Correlation Coefficients (ICC) and 95 % confidence intervals (CI) for the ICC in 26 men with FM or CWP.

	ICC	95 % C.I.
General Fatigue	0.91	0.80-0.96
Physical Fatigue	0.94	0.87-0.97
Mental Fatigue	0.84	0.66-0.93
Reduced Motivation	0.83	0.63-0.92
Reduced Activity	0.88	0.74-0.94

Table 12. The Multidimensional Fatigue Inventory. The mean, standard deviation (SD) and range of the differences (test 2 – test 1), the limits of agreement (LOA) and the intra-individual standard deviation (IISD) in 26 men with FM or CWP.

	Difference mean (SD)	Difference min-max	LOA	IISD
General Fatigue	-0.1 (1.9)	-4.0 – 5.0	-3.9 – 3.6	1.3
Physical Fatigue	-0.2 (1.6)	-4.0 – 3.0	-3.3 – 2.8	1.1
Mental Fatigue	-0.3 (2.2)	-7.0 – 4.0	-4.6 – 4.0	1.5
Reduced Motivation	0.3 (2.0)	-3.0 – 4.0	-3.6 – 4.3	1.4
Reduced Activity	-0.1 (2.0)	-4.0 – 4.0	-3.9 – 3.8	1.4

5.2.3 Internal consistency

Additional analyses (not included in papers I to IV) were made in the present thesis to investigate the internal consistency of the Swedish version of the MFI-20. Cronbach´s alpha values for the five subscales of the MFI-20 are given in Table 13, for both the female and the male population.

In the female population, the Cronbach´s alpha values ranged from 0.65 for MFI reduced motivation to 0.82 for MFI mental fatigue and MFI reduced activity. In the male population, the Cronbach´s alpha values ranged from 0.65 for MFI reduced motivation to 0.89 for MFI reduced activity.

Table 13. Cronbach´s alpha for the five subscales of the Swedish version of the Multidimensional Fatigue Inventory in the female population (n=166) and the male population (n=44).

	Cronbach´s alpha	
	Female population	Male population
General Fatigue	0.68	0.81
Physical Fatigue	0.78	0.86
Mental Fatigue	0.82	0.83
Reduced Motivation	0.65	0.65
Reduced Activity	0.82	0.89

5.3 Usefulness of the MFI-20

133 patients with FM (mean age 46 years, SD: 8.6, range: 22-60) from the female population participated in the study of the contexts in which MFI-20 is useful in FM. The socio-demographic data of the female patients with FM are shown in Table 4 and descriptive statistics of the health related aspects for the patient group are given in paper II, Table 2.

5.3.1 Associations with fatigue in FM

Socio-demographic aspects

Age and education showed no association with fatigue. Employment showed a fairly negative correlation to MFI physical fatigue and MFI reduced activity, indicating that these two fatigue dimensions were associated with fewer work hours per week. Employment was not associated with FIQ fatigue (paper II, Table 4).

In the analyses of differences in fatigue between the two groups of marital status, no statistically significant differences were found for the MFI-20, but FM patients living with another adult reported less FIQ fatigue than those who did not cohabit (p=0.01). No statistically significant differences were found between smoking and non-smoking patients with FM for the MFI-20 or FIQ fatigue scores.

Health related aspects

FIQ fatigue and nearly all dimensions of the MFI-20 showed fair to moderate correlations with depression (HADS-D) and anxiety (HADS-A). MFI general fatigue and FIQ fatigue also showed a fair correlation to sleep quantity and sleep quality. FIQ pain showed a fair correlation to MFI general fatigue, MFI physical fatigue and FIQ fatigue. Number of tender points, pain localizations and BMI were not associated with any of the fatigue measures (paper II, Table 4).

Physical activity (LTPAI) showed a fairly negative correlation with MFI reduced activity. Walking capacity (6MWT) showed fairly negative correlations to MFI physical fatigue and MFI reduced activity. FIQ fatigue was not associated with physical activity or walking capacity (paper II, Table 4).

5.3.2 Explanatory factors of severe fatigue in FM

Cut-off values. The following cut-off values between fatigue and severe fatigue were based on the median of the patients´ scorings: MFI general fatigue >18 vs ≤18, MFI physical fatigue >18 vs ≤18, MFI mental fatigue >15 vs ≤15,MFI reduced motivation >10 vs ≤10, MFI reduced activity >16 vs ≤16 and FIQ fatigue >85 vs ≤85. Independent explanatory factors for MFI-20 and FIQ fatigue from univariate analyses are given in paper II, Table 5, and multivariate analyses in paper II, Table 6.

MFI general fatigue. The multivariate stepwise logistic regression showed that depression (HADS-D) ($p<0.001$) and sleep quality ($p<0.001$) contributed to the strongest model for explanatory factors for severe general fatigue (AUC=0.77) (paper II, Table 6)

MFI physical fatigue. FIQ pain ($p<0.001$) alone contributed to the strongest model for explanatory factors of severe physical fatigue (AUC=0.70). An alternative model could be created with the same AUC value (0.70), in which the variables of employment ($p=0.020$) and depression (HADS-D) ($p=0.009$) explained severe physical fatigue (paper II, Table 6).

MFI mental fatigue. Depression (HADS-D) ($p=0.005$) and anxiety (HADS-A) ($p=0.019$) contributed to the strongest model for explanatory factors for severe mental fatigue (AUC=0.78) (paper II, Table 6).

MFI reduced motivation. Depression (HADS-D) ($p<0.001$) alone contributed to the strongest model for explanatory factors for severely reduced motivation (AUC=0.80) (paper II, Table 6).

MFI reduced activity. Age (p=0.003), employment (p=0.028), depression (HADS-D) (p<0.0001) and physical activity (LTPAI) (p=0.005) contributed to the strongest model when predicting severely reduced activity (AUC=0.82) (paper II, Table 6).

FIQ fatigue. FIQ pain (p=0.027), sleep quality (p=0.043) and depression (HADS-D) (0.003) contributed to the strongest model for explanatory factors for severe FIQ fatigue (AUC=0.77). An alternative model was able to be created with the same AUC value (0.77), in which anxiety (HADS-A) (p= 0.003) together with FIQ pain (p=0.010) and sleep quality (p=0.024) explained severe FIQ fatigue (paper II, Table 6).

5.4 Dimensions of fatigue in FM and CWP

Female population

The scores of the MFI-20 and the FIQ fatigue for the whole female population (n=166) as well as separately for FM and CWP are given in Table 14. There were no significant differences in scores on MFI-20 and FIQ fatigue between the women with FM (n=134) and the women with CWP.

Table 14. The female population (n=166). Mean, standard deviation (SD) and range for the five subscales of the Multidimensional Fatigue Inventory (MFI-20) and the subscale for fatigue included in the Fibromyalgia Impact Questionnaire (FIQ), as well as p-values for the difference between FM and CWP.

	FM & CWP n=166 mean(SD) range	FM n=134 mean(SD) range	CWP n=32 mean(SD) range	FM vs CWP p-value
GF	17.4 (2.7) 9-20	17.5 (2.7) 9-20	16.8 (2.7) 12-20	0.123
PF	17.1 (2.8) 9-20	17.2 (2.8) 9-20	16.6 (2.7) 10-20	0.137
MF	14.3 (4.0) 4-20	14.5 (4.0) 4-20	13.3 (4.1) 4-20	0.136
RM	10.5 (3.8) 4-20	10.4 (3.9) 4-20	11.0 (3.6) 4-18	0.409
RA	15.5 (3.4) 7-20	15.7 (3.5) 7-20	14.6 (3.1) 7-20	0.092
FIQ fat	79.1 (20) 15-100	80.0 (20) 15-100	74.1 (20) 42-100	0.076

GF= general fatigue, PF= physical fatigue, MF=mental fatigue, RM= reduced motivation, RA=reduced activity, FIQ fat= FIQ fatigue

The scorings of 133 women with FM were compared with the scorings of the reference group of 158 healthy women. The socio-demographic data of the patients (n=133) and the reference group (n=158) are given in paper II, Table 1. There were no significant differences between the patient group and the reference group in age, marital status, smoking or being born outside Sweden. There were significant differences between the groups ($p<0.001$) in education, employment, sick leave, disability pension and use of medication.

The mean scores in the MFI-20 in the healthy reference group ranged from 7.8 (SD 3.0) for MFI reduced motivation to 10.7 (SD 4.1) for MFI general fatigue. The female patients with FM showed statistically significantly ($p<0.001$) higher fatigue levels than the healthy women in all five dimensions of the MFI-20 and FIQ fatigue. Logistic regression showed that the differences in fatigue between the groups were also significant when adjusted for education, employment, sick leave and disability pension (paper II, Table 3).

Male population

The scores of the MFI-20 and the FIQ fatigue in the whole male population (n=44) as well as separately for FM and CWP are given in Table 15. Significant differences were found between men with FM (n=6) and men with CWP (n=38) for MFI general fatigue and FIQ fatigue.

Table 15. The male population (n=44). Mean, standard deviation (SD) and range for the five subscales of the Multidimensional Fatigue Inventory (MFI-20) and the subscale for fatigue included in the Fibromyalgia Impact Questionnaire (FIQ) and p-values for the difference between FM and CWP.

	FM & CWP n=44 mean(SD) range	FM n=6 mean(SD) range	CWP n=38 mean(SD) range	FM vs CWP p-value
GF	15.2 (3.6) 8-20	18.5 (2.3) 14-20	14.6 (3.5) 8-20	**0.013**
PF	14.3 (4.2) 5-20	17.3 (3.9) 10-20	13.9 (4.1) 5-20	0.052
MF	11.4 (4.3) 4-20	13.7 (5.5) 7-20	11.1 (4.1) 4-19	0.236
RM	9.4 (3.6) 4-17	11.8 (3.5) 7-16	9.0 (3.5) 4-17	0.096
RA	12.6 (4.6) 4-20	15.8 (4.0) 10-20	12.1 (4.6) 4-20	0.075
FIQ fat	60.0 (29) 0-100	87.3 (12) 71-100	55.7 (28) 0-99	**0.008**

GF= general fatigue, PF= physical fatigue, MF=mental fatigue, RM= reduced motivation, RA=reduced activity, FIQ fat=FIQ fatigue

Gender differences

Socio-demographic data are given in Table 4 for the women with CWP and in Table 5 for men with CWP. There were no statistically significant differences between genders in age, employment, being born outside Sweden, disability pension and use of analgesics in the patients with CWP. The women with CWP reported a longer duration of widespread pain ($p=0.023$), had more tender points ($p<0.001$) and pain localizations ($p=0.004$) and a higher sick leave ($p<0.001$) than the men with CWP. There were also a higher usage of psychotropic drugs among the women than among the men with CWP ($p=0.035$). A significant difference was also found between the genders in education ($p=0.006$) and whether the patients lived with another adult ($p=0.030$), 84 % of the men with CWP lived with another adult, compared with 59 % of the women with CWP (Table 5, Table 6).

Women with CWP (n=32) scored higher on all five subscales of the MFI-20 and the FIQ fatigue than men with CWP (n=38) (Tables 14, Table 15), p-value was 0.013 for MFI general fatigue, 0.004 for MFI physical fatigue, 0.035 for MFI mental fatigue, 0.026 for MFI reduced motivation, 0.012 for MFI reduced activity and 0.008 for FIQ fatigue (the p-values are not shown in the tables).

Logistic regression showed that the differences in fatigue between women and men with CWP no longer were significant when adjusted for duration, tender points, education, localizations, living with adult, sick leave and use of psychotropic drugs.

Possible differences in fatigue between men and women with FM were not analysed due to the low number of men with FM.

5.5 Effects of physiotherapy in women with FM and CWP

No significant baseline differences in socio-demographic data were found between the patients (n=166) randomized to either the exercise-education group (n=81) or the control group only receiving education (n=85) (paper I, Table I).

No significant change in pharmacological treatment over time was found for either of the two groups.

5.5.1 20 - week examination

Intention-to-treat population

The results of the intention-to-treat analysis including all patients who completed the baseline and 20-week examination are presented in Table 16.

Primary outcomes. Significant improvement (p=0.040) was found for change in the FIQ total in the exercise-education group (–4.8, SD 13.2) compared with change in the education group (–0.7, SD 12.2) after the 20-week study period.

The effect size of the FIQ total for the exercise-education group compared with the education group was 0.32. The change in the 6MWT in the exercise-education group (7.5, SD 53.5) was not statistically significant (p=0.067) compared with the change in the education group (–2.0, SD 63.2) after the 20-week study period.

Secondary outcomes. Significant improvement (p=0.018) was found for change in the FIQ pain in the exercise-education group (–7.8, SD 22.6) compared with change in the education group (1.7, SD 19.5) after the 20-week treatment.

The effect size of the FIQ pain was 0.45 for the exercise-education group compared with the education group.

Exploratory outcomes. The change in the MFI reduced motivation in the exercise-education group (–0.8, SD 3.3) was a significant improvement (p=0.046) compared with change in the education group (0.3, SD 3.2). Change in the activity related relaxation in the exercise education group (–0.4, SD 1.2) was also significantly improved (p=0.017) compared with change in the education group (0.2, SD 1.4).

The effect size of the MFI-20 reduced motivation was 0.34, while the effect size of the activity related relaxation was 0.45 for the exercise-education group compared with the education group.

Type I error. The secondary and exploratory between-group analyses comprised a total of 23 statistical analyses, and the upper limit of expected number of false significances was 1.05, which indicates that one of the significances found might be false.

Per-protocol population

Forty-seven of 81 patients (58%) randomized to the exercise-education group and 56 (66%) of 85 patients randomized to the education group were defined as active participants with attendance at at least 60 % of the sessions. The results of the per-protocol analyses are presented in Table 16.

Primary outcomes. Significant improvement (p=0.013) was found for the change in the FIQ total in the exercise-education group (–6.3, SD 14.4) compared with change in the education group (–0.6, SD 12.5) at the 20-week post-test.

The effect size of the FIQ total for the exercise-education group compared with the education group was 0.44. Significant improvement (p=0.013) was found for the change in the 6MWT in the exercise-education group (14.5, SD 35.8) compared with the change in the education group (–6.4, SD 58.3) after 20 weeks. The effect size of the 6MWT for the exercise-education group compared with the education group was 0.43.

Secondary outcomes. Significant improvement (p=0.002) was found for change in the FIQ pain (–10.0, SD 18.8) in the exercise-education group compared with change in the education group (3.0, SD 18.9).

The effect size of the FIQ pain for the exercise-education group compared with the education group was 0.69.

The change in the LTPAI total activity (1.0, SD 3.7) was significantly increased (p=0.026) in the exercise-education group compared with the change in the education group (–0.1, SD 5.06). The greater part of the increase was at a moderate level, shown by a significant (p=0.048) change in the LTPAI moderate activity (1.3, SD 2.7) in the exercise-education group compared with change in the education group (0.2, SD 2.9).

The effect size of the LTPAI total activity was 0.25, while the effect size of the LTPAI moderate activity was 0.39 in the exercise-education group compared with the education group.

Exploratory outcomes. Significant improvement (p=0.005) was found for change in the MFI reduced motivation in the exercise-education group (–1.1, SD 3.1), compared with the education group (–0.7, SD 3.0), the effect size being 0.13.

A significant improvement (p=0.002) was also found for change in the activity related physical relaxation in the exercise-education group (–0.6, SD 1.2), compared with the education group (0.4, SD 1.5), as well as for the activity related well-being (p=0.021) in the exercise-education group (–0.7, SD 1.4) compared with the education group (–0.1, SD 1.4).

The effect size of activity related relaxation was 0.72, while the effect size of activity related well-being was 0.43 in a comparison of the exercise-education group with the education group.

Type I error. A total of 23 between-group analyses were made, and the upper limit of expected number of false significances was 0.89, which indicates that one of the significances found might be false.

5.5.2 11 to 12 - month follow-up

Intention-to-treat population

A total of 125 patients (75%) randomized to the study completed the follow-up at the 11–12-month examination. In the exercise-education group, significant improvement was found for change in the 6MWT (14.1, SD 57.6, p=0.013), as well as for change in the SF-36 PCS (2.86, SD 8.6, p= 0.006), the SF-36 role physical (12.1, SD 40.7, p=0.035) and the SCI-93 (–3.9, SD 13.2, p=0.011).

The effect size of the 6MWT was 0.18. The effect size of the SF36 physical component was 0.35 and of the SF36 role physical 0.38. The effect size of the SCI-93 was 0.17. In the education group, change in the FIQ total (–4.5, SD 14.3) significantly improved (p=0.024) over time, the effect size being 0.29 (Table 16).

Type I error. A total of 15 analyses were made, and the upper limit of expected number of false significances was calculated to be 0.78, which indicates that one of the significances found might be false.

Per-protocol population

The follow-up outcomes were analysed separately for the PP population. Significant improvements over time were found in the exercise-education group for: the 6MWT (21.5, SD 48.2; p=0.007), the FIQ pain (–9.1, SD 20.9; p=0.019); the SF-36 PCS (3.0, SD 6.7; p=0.002); the SF-36 physical functioning (4.2, SD11.1; p=0.024); the SF-36 bodily pain (8.3, SD 32.5;

p=0.014); the LTPAI moderate activity (0.8, SD 2.7; p=0.045); and the SCI-93 (4.5, SD 10.2; p=0.010).

The effect size was 0.29 for the 6MWT, 0.54 for the FIQ pain, 0.35 for the SF36 PCS, 0.43 for SF-36 bodily pain, 0.12 for SF-36 vitality, 0.41 for the LTPAI moderate activity, and 0.18 for the SCI-93.

No significant improvements over time were found in the education group (Table 17).

Type I error. A total of 15 analyses were made, and the upper limit of expected number of false significances was 0.42, which indicates that 0–1 significances found might be false.

Table 16. Intention-to-treat analysis in study III. Baseline values, change from baseline in outcome variables, within-group and between-group differences for the exercise education group and the education group.

	Exercise Education group					Education group					Ex-Edu vs Edu
	Baseline n=81 mean (SD)	Δ20 w n=69 mean (SD	p	Δ11-12 mo n=63 mean (SD)	p	Baseline n=85 mean (SD)	Δ20 w n=64 mean (SD)	p	Δ11-12 mo n=62 mean (SD)	p	20 w p
Primary outcomes											
FIQ Total	61.6 (16.42)	-4.8 (13.19)	**0.006**	-3.9 (15.45)	0.077	66.6 (15.30)	-0.7 (12.22)	0.952	-4.5 (14.32)	**0.024**	**0.040**
6MWT	511 (79.7)	7.5 (53.51)	**0.047**	14.1 (57.59)	**0.013**	517 (77.2)	-2.0 (63.18)	0.591	3.9 (66.27)	0.800	0.067
Secondary outcomes											
FIQ Pain	67.7 (16.79)	-7.8 (22.57)	**0.007**	-6.5 (23.68)	0.119	70.4 (20.05)	1.7 (19.47)	0.674	-2.5 (19.85)	0.252	**0.018**
FIQ Fatigue	76.3 (22.49)	-5.0 (25.50)	0.103	-2.7 (24.35)	0.486	81.7 (17.64)	-3.8 (19.05)	0.035	-5.5 (21.88)	0.134	0.980
SF36 PCS	30.8 (8.09)	3.1 (7.70)	**0.006**	2.86 (8.64)	**0.006**	29.4 (8.03)	0.6 (8.32)	0.776	1.3 (7.93)	0.234	0.129
SF36 MCS	40.9 (13.77)	0.4 (10.64)	0.864	0.51 (13.93)	0.561	36.6 (12.29)	2.2 (12.02)	**0.040**	1.3 (11.26)	0.197	0.146
SF36 PF	56.6 (19.00)	0.7 (11.98)	0.614	2.19 (14.46)	0.252	50.9 (18.30)	0.7 (16.79)	0.839	1.3 (16.93)	0.761	0.702
SF36 RP	22.8 (32.16)	14.8 (44.26)	**0.008**	12.1 (40.68)	0.035	15.2 (26.04)	7.6 (33.34)	0.099	9.3 (43.62)	0.056	0.719
SF36 BP	28.6 (14.32)	5.1 (16.72)	**0.014**	5.0 (21.13)	0.084	25.7 (16.09)	0.4 (17.07)	0.650	3.6 (18.22)	0.129	0.236
SF36 VT	28.4 (21.09)	6.6 (20.67)	**0.009**	4.2 (23.03)	0.130	24.2 (16.72)	3.9 (21.57)	0.132	2.3 (21.02)	0.713	0.377
HADS Anxiety	8.1 (5.53)	-0.7 (3.01)	0.117	-0.7 (3.30)	0.112	9.1 (4.82)	0.4 (3.39)	0.429	0.4 (3.79)	0.369	0.148
HADS Depression	6.4 (4.01)	-0.2 (2.98)	0.508	-0.4 (3.26)	0.555	7.8 (3.64)	-0.1 (2.77)	0.748	0.0 (3.15)	0.673	0.993
LTPAI, total	5.4 (4.06)	1.0 (4.26)	**0.036**	-0.6 (4.09)	0.309	5.0 (4.23)	0.3 (4.64)	0.861	-0.4 (5.72)	0.811	0.117
LTPAI, mod	2.0 (2.14)	1.2 (2.91)	**0.000**	0.2 (2.85)	0.677	2.1 (2.72)	0.3 (2.69)	0.413	-0.5 (3.68)	0.530	0.068
Exploratory outcomes											
SCI-93	73.3 (23.43)	-2.8 (11.97)	0.094	-3.9 (13.23)	**0.011**	79.4 (26.09)	-0.8 (12.14)	0.650	-2.6 (12.36)	0.339	0.436
MFI GF	16.9 (2.65)	-0.4 (2.75)	0.394			17.8 (2.30)	-0.8 (3.07)	**0.037**			0.368
MFI PF	16.6 (3.06)	-0.6 (2.89)	0.083			17.6 (2.42)	-1.0 (3.80)	0.010			0.544
MFI RA	15.0 (3.38)	-0.6 (3.09)	0.075			16.0 (3.46)	-1.1 (3.25)	0.008			0.436
MFI RM	10.2 (3.89)	-0.8 (3.26)	**0.040**			10.8 (3.75)	0.3 (3.22)	0.451			**0.046**
MFI MF	14.4 (4.15)	-0.2 (3.34)	0.585			14.2 (3.86)	0.3 (2.79)	0.408			0.390
A-Relaxation	4.6 (1.50)	-0.4 (1.22)	**0.008**			4.6 (1.24)	0.2 (1.44)	0.439			**0.017**
A-Wellbeing	2.8 (1.46)	-0.4 (1.41)	**0.023**			2.9 (1.31)	-0.0 (1.41)	0.486			0.284
A-Beliefs	2.3 (1.35)	0.1 (1.39)	0.870			2.2 (1.25)	-0.2 (1.02)	0.838			0.983
A-Symptoms	3.4 (1.23)	-0.1 (1.42)	0.472			3.2 (1.23)	-0.1 (1.59)	0.518			0.993
A-Habits	3.4 (1.59)	0.2 (1.58)	0.500			4.0 (1.55)	-0.1 (1.85)	0.768			0.437

Significant values are shown in bold. FIQ=Fibromyalgia Impact Questionnaire. 6MWT=Six-minute walk test, SF-36=36-item short form health survey, PCS=Physical Component Summary, MCS=Mental Component Summary, PF=physical functioning, RP=role-physical, BP=bodily pain, VT=vitality, HADS=Hospital Anxiety and Depression Scale, LTPAI= Leisure Time Physical Activity Instrument, SCI-93=Stress and Crisis Inventory, MFI=Multidimensional Fatigue Inventory, GF=General fatigue, PF=Physical fatigue, RA=Reduced activity, RM=Reduced motivation, MF=Mental fatigue, A=Activity.

Table 17. Per-protocol analysis in study III. Baseline values, change from baseline in outcome variables, within-group and between group differences for the active participants in the exercise education group and the education group.

	Exercise Education group					Education group					Ex-Edu vs Edu
	Baseline *n=47* mean (SD)	Δ20 w *n=46* mean (SD	p	Δ11-12 mo *n=42* mean (SD)	p	Baseline *n=56* mean (SD)	Δ20 w *n=50* mean (SD)	p	Δ11-12 mo *n=40* mean (SD)	p	20 w p
Primary outcomes											
FIQ Total	61.2 (17.73)	-6.3 (14.41)	**0.003**	-4.7 (13.45)	0.063	65.9 (15.98)	-0.6 (12.47)	0.881	-4.4 (15.53)	0.121	**0.013**
6MWT	507 (75.05)	14.5 (35.79)	**0.024**	21.5 (48.18)	**0.007**	511 (71.07)	-6.4 (58.34)	0.287	3.7 (59.53)	0.856	**0.013**
Secondary outcomes											
FIQ Pain	68.8 (16.73)	-10.0 (18.83)	**0.002**	-9.1 (20.89)	**0.019**	68.3 (19.87)	3.0 (18.92)	0.512	-2.3 (19.69)	0.595	**0.002**
FIQ Fatigue	75.1 (23.74)	-7.6 (27.12)	0.063	-4.0 (25.31)	0.473	82.3 (17.76)	-4.7 (19.59)	**0.042**	-5.6 (21.33)	0.534	0.732
SF36 PCS	30.4 (8.65)	2.9 (6.28)	**0.007**	3.0 (6.69)	**0.002**	29.3 (8.24)	-0.3 (8.73)	0.942	1.4 (8.44)	0.412	0.104
SF36 MCS	41.9 (14.17)	0.1 (10.21)	0.562	0.0 (11.94)	0.856	36.2 (12.80)	3.8 (12.38)	**0.008**	1.8 (12.39)	0.162	0.085
SF36 PF	53.6 (19.64)	1.5 (11.22)	0.346	4.2 (11.08)	**0.024**	50.6 (16.90)	0.2 (16.42)	0.856	1.3 (17.31)	0.724	0.583
SF36 RP	26.2 (33.95)	11.4 (40.15)	0.074	8.3 (32.51)	0.134	15.2 (26.83)	9.9 (36.24)	0.079	10.2 (37.06)	0.067	0.697
SF36 BP	27.9 (15.44)	6.1 (15.07)	**0.006**	6.7 (15.76)	**0.014**	25.1 (14.83)	0.7 (16.01)	0.782	4.1 (19.28)	0.207	0.183
SF36 VT	30.3 (22.15)	6.1 (15.07)	**0.021**	2.6 (17.47)	0.192	23.0 (16.20)	4.9 (21.09)	0.154	3.3 (22.20)	0.659	0.329
HADS Anx	8.16 (5.48)	-0.9 (2.74)	0.055	-0.8 (2.76)	0.071	9.15 (5.03)	0.4 (3.38)	0.471	-0.4 (3.87)	0.352	0.099
HADS Dep	6.21 (4.18)	-0.2 (2.77)	0.327-	0.5 (2.56)	0.418	7.82 (3.41)	-0.3 (2.78)	0.472	-0.0 (3.18)	0.611	0.865
LTPAI, total	5.6 (4.43)	1.0 (3.68)	0.017	0.0 (3.37)	0.823	5.3 (4.15)	-0.1 (5.06)	0.678	-0.2 (4.99)	0.420	**0.026**
LTPAI, mod	1.9 (1.96)	1.3 (2.74)	**0.001**	**0.8 (2.67)**	**0.045**	2.1 (2.90)	0.2 (2.90)	0.654	-0.5 (3.93)	0.802	**0.048**
Exploratory outcomes											
SCI-93	72.3 (24.56)	-3.1 (9.53)	0.053	-4.5 (10.19)	**0.010**	81.4 (25.24)	-1.1 (9.83)	0.512	-3.2 (12.13)	0.168	0.382
MFI GF	17.0 (2.76)	-0.5 (2.68)	0.238				18.0 (2.73)		-0.6 (2.93)	0.217	0.819
MFI PF	16.7 (2.76)	-0.9 (2.71)	**0.036**				18.0 (2.11)		-0.7 (2.60)	0.074	0.738
MFI RA	15.3 (3.47)	-1.1 (2.78)	**0.010**				16.3 (3.02)		-1.0 (3.30)	**0.034**	0.868
MFI RM	10.0 (4.05)	-1.1 (3.13)	**0.031**				10.8 (3.68)		-0.7 (3.02)	0.089	**0.005**
MFI MF	14.6 (4.56)	0.1 (3.09)	0.978				14.3 (3.87)		0.5 (2.75)	0.101	0.379
A-Relaxation	4.8 (1.49)	-0.6 (1.21)	**0.001**				4.6 (1.31)		0.4 (1.54)	0.198	**0.002**
A-Wellbeing	3.0 (1.57)	-0.7 (1.36)	**0.001**				2.9 (1.35)		-0.1 (1.44)	0.943	**0.021**
A-Beliefs	2.5 (1.31)	-0.3 (1.14)	0.102				2.2 (1.36)		0.0 (1.00)	0.984	0.262
A-Symptoms	3.0 (1.08)	0.3 (1.16)	0.070				3.2 (1.27)		-0.0 (1.62)	0.723	0.294
A-Habits	3.4 (1.58)	-0.0 (1.66)	0.624				4.0 (1.63)		-0.2 (1.85)	0.603	0.960

Significant values are shown in bold. FIQ=Fibromyalgia Impact Questionnaire. 6MWT=Six-minute walk test, SF-36=36-item short form health survey, PCS=Physical Component Summary, MCS=Mental Component Summary, PF=physical functioning, RP=role-physical, BP=bodily pain, VT=vitality, HADS=Hospital Anxiety and Depression Scale, LTPAI= Leisure Time Physical Activity Instrument, SCI-93=Stress and Crisis Inventory, MFI=Multidimensional Fatigue Inventory, GF=General fatigue, PF=Physical fatigue, RA=Reduced activity, RM=Reduced motivation, MF=Mental fatigue, A=Activity.

5.5.3 Subgroup analysis

The results of the sub-group analysis are illustrated in Figure 7.

FIQ Total

No significant heterogeneity was found for the subgroups created by level of pain, distress, stress and activity limitations, implying that these aspects did not have any significant influence on change in the FIQ total score. However, a non-significant tendency towards heterogeneity (p=0.073) was found for the subgroup created by the SCI-93 (<78/≥78), implying that the improvement in the FIQ total tended to be influenced by stress, in favor of those with lower stress scores.

Analysis within the subgroup characterized by the lower degree of stress (<78 on the SCI-93) revealed a significant (p=0.013) improvement in the FIQ total in the exercise-education group (–6.0, SD 15.2) compared with change in the control group only receiving education (2.9, SD 11.4), the effect size for the exercise-education group compared with the control group being 0.64.

A significant improvement (p=0.042) was also found for change in the FIQ total (–4.7, SD 15.1) in the exercise-education group characterized by lower ratings on the FIQ pain (< 70), compared with change in the education group (2.8, SD 12.2), the effect size for the exercise-education group compared with the education group being 0.54.

A significant improvement (p=0.025) was also found for change in the FIQ total (–5.0, SD 13.8) in the patients in the exercise-education group reporting a lower level of distress (< 8 on the HADS-D), compared with change in the education group (2.2, SD 13.3), the effect size for the exercise-education group compared with the education group being 0.53.

No significant change in the FIQ total was found in the analyses comparing patients with more severe scores, randomized either to exercise-education or education only, in scores on the SCI-93 (p=0.723), the FIQ pain (p=0.530) or HADS-D (p=0.911).

6MWT

No significant heterogeneity was found for the subgroups created by the level of pain, distress, stress and activity limitations implying their influence on the change score of the 6MWT.

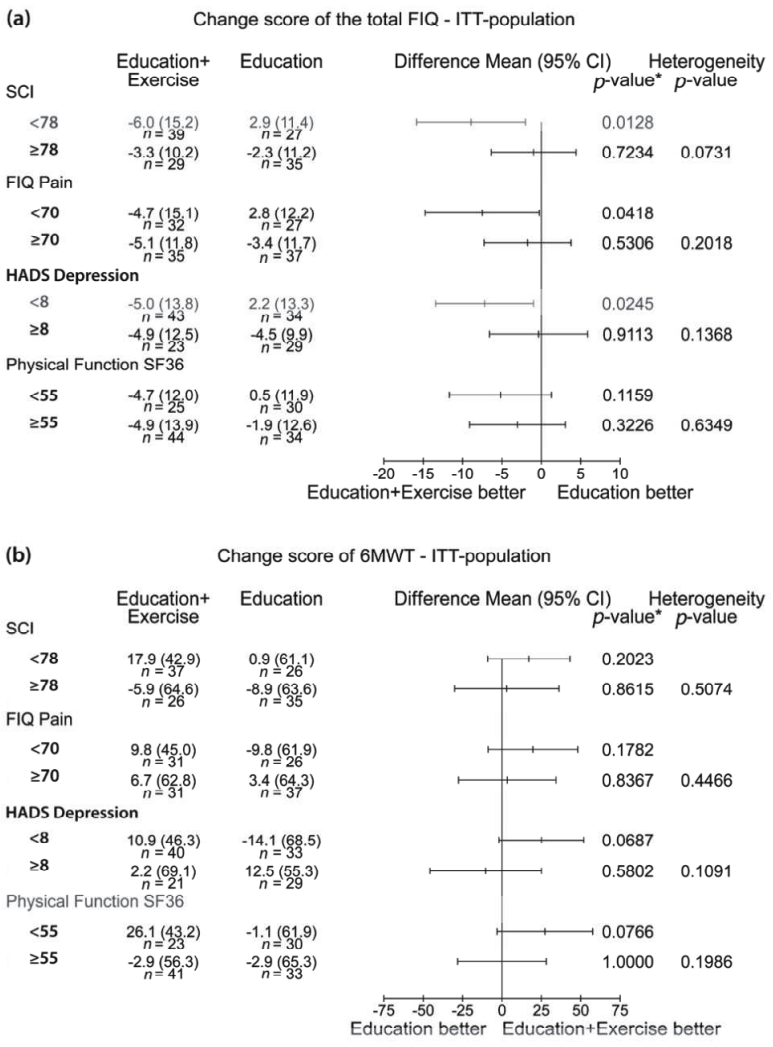

*Figure 7. Subgroup influences on change in the primary outcomes in study III. (a) Fibromyalgia Impact Questionnaire (FIQ) total. (b) Six-minute walk test (6MWT). The subgroups were created by dichotomized values of the Stress and Crisis Inventory (SCI), the FIQ pain, the Hospital Anxiety and Depression Scale (HADS), and the 36-item Short-Form Health Survey (SF36) physical functioning. Mean differences for the change score and 95% confidence intervals (CI) are presented in the graphs, followed by p-value, separately for each subgroup. The p-value for heterogeneity (interaction between the randomized group and the change score of the primary outcome) is given in the right-hand column. ITT: intention-to-treat.*Fisher's Non-Parametric Permutation test.*

5.6 Effects of physiotherapy in men with CWP

The socio-demographic data of the pool exercise group, the resistance training group and the reference group in the male population are given in paper IV, Table 1. Baseline values, change from baseline in outcome variables, within-group and between-group differences for the pool exercise group and the resistance training group are given in paper IV, Table 3.

No significant baseline differences in socio-demographic data or outcome variables were found between the pool exercise group (n=14) and the resistance training group (n=14).

5.6.1 12 - week examination in the randomized trial

The mean attendance at the sessions for the patients completing the 12-week examination was 80 % (SD 17) in the pool exercise group (n=12) and 89 % (SD 6) in the resistance training group (n=10).

In the resistance training group, the initial load at week 1 was 40-50 % of 1 RM, with three sets of 15-20 repetitions. The mean increase in load from week 1 to week 12 was found to be between 37 % and 53 % for the different exercises.

Between-group comparisons

Primary outcomes. No statistically significant differences were found for change in the MFI-20 at the 12-week examination between the pool exercise group and the resistance training group.

Secondary outcomes. A significantly higher improvement was found at the 12-week examination for change in isometric force of the right arm shoulder abduction (p=0.010) and knee flexion in both legs (right: p=0.005, left: p=0.002) in the resistance training group, as compared to the change over time in the pool exercise group.

Exploratory outcomes. No statistically significant differences were found for change in FIQ pain, pain localizations or SF-36 at the 12-week examination between the pool exercise group and the resistance training group.

Type 1 error. The secondary and exploratory outcomes in the between-group analyses at the 12-week examination comprised a total of 14 statistical analyses, and the upper limit of expected number of false significances was 0.58, which indicates that one of the significances found might be false.

Changes over time within the two exercise groups

Pool exercise group. MFI reduced motivation (p=0.008), HADS-A (p=0.032) and the SF-36 PCS (p=0.010) were significantly improved over baseline at the 12-week examination in the pool exercise group.

Resistance training group. MFI general fatigue (p=0.035) as well as isometric force of the right arm shoulder abduction (p=0.008), knee flexion (right leg: p=0.017, left leg: p=0.005) and right hand grip (p=0.009) and number of pain localizations (p=0.014) were significantly improved over baseline at the 12-week examination in the resistance training group.

Type 1 error. The secondary and exploratory within-group analyses at the 12-week examination for the two exercise groups comprised a total of 28 statistical analyses, and the upper limit of expected number of false significances was 1.11, which indicates that one of the significances found might be false.

5.6.2 9 - month follow-up in the randomized trial

Between-group comparisons

Primary outcomes. No statistically significant differences were found for change in MFI-20 at the nine-month follow-up between the pool exercise group and the resistance training group.

Secondary outcomes. A significantly greater improvement was found at the nine-month follow-up for change in isometric force of the right arm shoulder abduction (p=0.043) in the resistance training group, as compared to the change over time in the pool exercise group.

Exploratory outcomes. No statistically significant differences were found for change in pain intensity, pain localization or SF-36 at the nine-month follow-up between the pool exercise group and the resistance training group.

Type 1 error. The secondary and exploratory between-group analyses at the nine-month follow-up comprised a total of 14 statistical analyses, and the upper limit of expected number of false significances was 0.68, which indicates that one of the significances found might be false.

Changes over time within the two exercise groups

Pool exercise group. Significant improvement was found in the pool exercise group at the nine-month follow-up for change in HADS-A (p=0.019), SF-36

PCS (p=0.017) and number of pain localizations (p=0.012), as compared to baseline.

Resistance training group. Significant improvement was found in the resistance training group at the nine-month follow-up for change in MFI general fatigue (p=0.034) and MFI physical fatigue (p=0.034), as compared to baseline. Significant improvements were also found in the resistance training group for right arm shoulder abduction (p=0.021) and the number of pain localizations (p=0.027) at the nine-month follow-up, as compared to baseline.

Type 1 error. The secondary and exploratory within-group analyses at the nine-month follow-up comprised a total of 28 statistical analyses, and the upper limit of expected number of false significances was 1.21, which indicates that one of the significances found might be false.

5.6.3 Reference group

No statistically significant differences were found at baseline in socio-demographic data or MFI-20 subscales when the reference group (n=10) was compared to the pool exercise group (n=14) and the resistance training group (n=14). Three patients in the reference group were lost to follow-up at the 12-week examination (Figure 2). No statistically significant change in outcome variables was found for the reference group at the 12-week examination, as compared to baseline.

6 DISCUSSION

6.1 The MFI-20

6.1.1 Validity

The convergent construct validity of the Swedish version of the MFI-20 was investigated by comparing the five subscales of the MFI-20 with the one-dimensional FIQ fatigue. All five subscales of the MFI-20 showed a statistically significant association with the FIQ fatigue for both female and male patients with FM or CWP. Correlation values with FIQ fatigue were lowest for MFI reduced motivation and highest for MFI general fatigue in both populations, with values ranging from 0.32 to 0.62 in the female population and 0.55 to 0.78 in the male population.

The relatively low correlation values indicate that the subscales of the MFI-20 assess different aspects of fatigue than does the FIQ fatigue. MFI general fatigue showed the highest correlation value with FIQ fatigue in both the female and the male populations, which was expected since both ratings could be considered to comprehend a more global aspect of fatigue. These results are consistent with findings in female patients with primary Sjögren´s syndrome, where the correlation values with the VAS for global fatigue ranged from 0.31 for MFI reduced motivation to 0.70 for MFI general fatigue (d'Elia et al., 2008). Similar results have also been found in studies of patients with rheumatoid arthritis (Rupp, et al., 2004) and patients with cancer (Smets, et al., 1995), in which MFI general fatigue showed the highest association with a VAS for global fatigue.

The Swedish version of the MFI-20 appears to possess acceptable convergent construct validity, when compared to a one-dimensional scale. Unfortunately, there was no established multidimensional rating of fatigue to use in comparisons with the MFI-20, which would have given more valuable information about the accuracy of the different subscales. Another approach to investigating the convergent validity of the MFI-20 has been applied in a study in a general population, in which the subscales of the MFI-20 were correlated with variables previously shown to be associated with fatigue, such as depression, anxiety and health related quality of life (Lin et al., 2009).

There are further aspects that need to be considered when establishing the validity of an instrument. When the MFI-20 was originally developed, the construct validity of the subscales was investigated by comparing the results

of different populations expected to differ in the subscales of fatigue, such as patients with cancer, patients with ME, army recruits, psychology students and medical students. Factor analyses of the MFI-20 were also conducted in all populations, which supported the five subscales of the MFI-20 (Smets, et al., 1995).

6.1.2 Reliability

The test-retest reliability of the Swedish version of the MFI-20 was investigated in female and male patients with FM and CWP. The ICC values for the five subscales of the MFI-20 ranged from 0.75 to 0.92 in the female population and from 0.83 to 0.94 in the male population. According to the interpretation of the ICC values (Fleiss, 1986), the subscales possessed excellent test-retest reliability for the female and the male patients with FM and CWP. The 95 % confidence intervals of the ICC values were above the limit of 0.4, indicating satisfactory reliability for all five subscales of the MFI-20 in both populations..

In a study of women with primary Sjögren´s syndrome that investigated the test-retest reliability of the MFI-20 with a mean of two weeks between the test occasions, the ICC values ranged from 0.65 to 0.80 for the five subscales (d'Elia, et al., 2008). In a similar study in patients with ankylosing spondylitis, with six weeks between the two tests, the ICC values ranged from 0.57 to 0.75 (van Tubergen, et al., 2002). In the present study of FM and CWP, an interval of one to two days between test and retest was accepted. It appears that a longer interval results in lower ICC values, probably due to the fluctuating nature of fatigue.

The means of differences between the two test occasions were also low, around zero. However, there were patients fluctuating up to eight points between test and retest. Patients with FM have described fluctuations in fatigue on a day-to-day basis (Sallinen, et al., 2011), which complicates test-retest reliability analyses

The risk of recall bias was considered to be small in the present test-retest reliability study. The patients completed a great number of questionnaires, including the MFI-20, at the first test occasion and were not informed about which instrument they would complete the day after.

A systematic difference was found in the female population for the subscale of physical fatigue, indicating that the female patients were more physically fatigued at the second occasion. This increase in physical fatigue might be

due to the physical tests the patients performed directly after the first test occasion.

Additional analyses not included in papers I to IV were made in the present thesis to investigate the internal consistency of the Swedish version of the MFI-20 in patients with FM and CWP. The Cronbach´s alpha ranged from 0.65 to 0.82 in the female population and from 0.65 to 0.89 in the male population, for the five subscales of the MFI-20. MFI reduced motivation showed the lowest Cronbach´s alpha value in both populations, being close to 0.7, which is considered an acceptable limit.

6.1.3 Usefulness

The FIQ is a well-accepted and frequently used instrument for assessing disabilities and symptoms in FM. The subscale of fatigue included in the FIQ assesses only one global dimension of fatigue, for which reason it would be preferable to add the MFI-20 as a complement to obtain a deeper and more variegated picture of the patients´ fatigue. However, since the MFI-20 is a more comprehensive and time consuming instrument, it is of interest to investigate the context in which the examination would benefit from inclusion of the MFI-20 and where the more global assessment FIQ fatigue would be sufficient.

There is a lack of similar studies comparing two instruments with regard to the field of application. We chose to compare the MFI-20 and the FIQ fatigue by correlating the two instruments with socio-demographic data and health related variables previously shown to be associated with fatigue, as well as investigating explanatory variables of severe fatigue.

The present study found that the MFI-20, and especially its subscales of physical fatigue and reduced activity, appears to contribute valuable aspects of fatigue associated with employment, physical activity and walking capacity, which the FIQ fatigue does not. However, the FIQ fatigue and the MFI-20 possessed an equivalent ability to assess associations with pain, sleep and symptoms of depression and anxiety. Thus, the FIQ fatigue may be sufficient in studies of fatigue in relation to these aspects.

In the analyses of explanatory variables of severe fatigue, the MFI reduced activity differed the most from the FIQ fatigue. Higher age, less work hours per week, more symptoms of depression and less physical activity explained severely reduced activity, while severe FIQ fatigue was explained by high pain intensity, disturbed sleep quality and more symptoms of depression.

These results emphasize the recommendation to use the MFI-20 in relation to aspects of employment and physical function.

6.2 Dimensions of fatigue in FM and CWP

Fatigue is a symptom of substantial importance for patients with FM (Guymer & Clauw, 2002; Yunus, 2007), affecting their daily life negatively (Liedberg & Henriksson, 2002; Wuytack & Miller, 2011). Fatigue has been reported as the third most distressing symptom in women with FM who are over 50 years of age, following fear of symptoms worsening and difficulty staying asleep (Shillam, Dupree Jones, & Miller, 2011).

In the present thesis, the fatigue in patients with FM and CWP was investigated and described in multiple dimensions assessed with the MFI-20. The mean scores of the MFI-20 ranged from 10.5 to 17.4 in the women with FM and CWP and from 9.4 to 15.2 in the men with FM and CWP in the present thesis. Both the female and the male population scored lowest on MFI reduced motivation and highest on MFI general fatigue. The fatigue scores in the female population are similar to findings in women with primary Sjögren´s syndrome, where the mean scores of the MFI-20 subscales ranged from 12.0 for MFI reduced motivation to 17.9 for MFI general fatigue.

In other rheumatic diseases, the mean MFI-20 scores have been shown to range between 8.2 for MFI mental fatigue and 13.4 for MFI general fatigue in patients with rheumatoid arthritis (Rupp, et al., 2004) and between 10.1 for MFI mental fatigue and 15.5 for MFI general fatigue in patients with ankylosing spondylitis (van Tubergen, et al., 2002). However, those studies included both men and women (Rupp, et al., 2004; van Tubergen, et al., 2002).

In the present thesis, women with FM scored significantly higher on all five subscales of the MFI-20, as well as the FIQ fatigue, than the reference group of healthy women did. The mean scores of the healthy reference group ranged from 7.8 for MFI reduced motivation to 10.7 for MFI general fatigue, which is consistent with the results in another healthy female population (d'Elia, et al., 2008). The ability of MFI-20 to demonstrate significantly different scores between the patients with FM and the healthy reference group could be regarded as a measure of known group validity of the instrument, since women with FM are expected to be more fatigued than healthy women.

Female patients with FM and CWP showed high ratings of perceived fatigue, especially on the dimensions of MFI general fatigue and MFI physical fatigue. There is little knowledge about the etiology of their fatigue, but it has been suggested that it can be partly explained by central sensitization (Casale & Rainoldi, 2011; Yunus, 2007). Patients with FM have also been found to have a hypoactive sympatho-adrenal system, a hypo-reactive hypothalamic-pituitary axis during static exercise (Kadetoff & Kosek, 2010) and reduced muscle blood flow during static exercise and after dynamic exercise (Elvin, Siosteen, Nilsson, & Kosek, 2006). This muscle ischemia has been suggested to contribute to the pain experienced by patients with FM during and after exercise (Elvin, et al., 2006). There is a possibility that the muscle ischemia also contributes to physical fatigue in FM. Physical fatigue was explained by pain intensity alone in women with FM in the present thesis.

6.2.1 Gender differences

Additional analyses not included in papers I to IV were made in comparisons of multidimensional fatigue between men and women with CWP. The women with CWP rated their fatigue significantly higher than the men with CWP for all MFI-20 subscales and the FIQ fatigue. However, when the results were adjusted for socio-demographic data that differed between the two groups of genders, the difference in fatigue were no longer statistically significant for the MFI-20 or the FIQ fatigue. Previous findings have shown that women rate their fatigue higher than men in patients with FM (Nicassio, et al., 2002; Yunus, 2001) as well as in the general population (Watt, et al., 2000).

Gender has been found to play a role in how patients with chronic pain manage their symptoms. Women with chronic pain rate their physical function lower (Rutledge, et al., 2007) and have greater difficulty retaining positive effects of pain management programmes than men (Keogh, et al., 2005). Pain also results in disability pension for women to a greater extent than men (Gjesdal, Bratberg, & Maeland, 2011).

The cause of gender differences in FM and CWP in symptoms and effects of treatments is probably complex and multi-factorial, with both biological and psychological explanations, such as socialization, cognitive factors and affective factors (Myers, Riley, & Robinson, 2003). The role of gender in coping strategies has been studied in patients with pain, and women reported significantly greater use of palliative behaviors, positive self-statements, and problem solving and appeared to seek social support more often than men did (Unruh, Ritchie, & Merskey, 1999). Findings in healthy adults also indicate

that men and women hold different gender specific expectations on pain coping strategies (Keogh & Denford, 2009).

6.3 Effects of physiotherapy

Effects of different types of treatment are continuously studied in FM and CWP. A previous study investigated treatment effects in patients with FM and showed that improvements in pain, fatigue, depression, anxiety, physical function and impact of daily living were associated with a subjective impression of improvement (Hudson et al., 2009). Physiotherapy in the forms of exercise and education has been shown to have positive effects on several aspects mentioned above (Busch, et al., 2007; Mannerkorpi, et al., 2000). In addition, exercise is commonly known to enhance general health, which facilitates coping with pain, fatigue and other symptoms in FM (Mannerkorpi & Gard, 2003). Contrary to many pharmacological treatments, physiotherapy generally gives no side effects, except for exercise induced pain in some patients. However, the pain most often decreases if the exercise is continued at an appropriate intensity for a few weeks (Hauser, et al., 2010).

MFI general fatigue and MFI physical fatigue appear to be the most prominent fatigue dimensions regardless of condition and gender (d'Elia, et al., 2008; Rupp, et al., 2004; van Tubergen, et al., 2002). Treatment of fatigue would therefore benefit by being developed to improve these two fatigue dimensions. An improvement in general and physical fatigue could also have a positive impact on other dimensions of the MFI-20.

In the present thesis, fatigue was shown to be associated with distress, and symptoms of depression were shown to be the most consistent explanatory variable of severe fatigue in the women FM, in line with previous findings (Nicassio, et al., 2002). Exercise has been shown to decrease symptoms of depression in female patients with FM (Sanudo et al., 2010), and it could be assumed to have a positive impact on their fatigue as well. Fatigue in FM and CWP might be aggravated as a side effect of some pharmacological treatment, which favors physiotherapy as the primary choice when planning treatment of fatigue in FM and CWP.

In the present thesis, the effects of pool exercise combined with education were investigated in a randomized controlled study in women with FM and CWP. A pilot study was also conducted to explore the effects of pool exercise and resistance training in men with CWP. The results of the studies imply that exercise can improve some dimensions of fatigue. This is discussed further below.

6.3.1 Pool exercise and education in women with FM and CWP

The randomized controlled trial in Study III showed that a 20-week programme combining pool exercise in temperate water with patient education improved health status measured with the FIQ in female patients with FM and CWP, which is consistent with previous studies of exercise and education (Burckhardt, Mannerkorpi, Hedenberg, & Bjelle, 1994; Cedraschi et al., 2004; Gowans, deHueck, Voss, & Richardson, 1999; King, Wessel, Bhambhani, Sholter, & Maksymowych, 2002; Mannerkorpi, et al., 2000; Rooks, et al., 2007). The effect size of the FIQ total was considered to be small (0.31) in the ITT population, but it increased to 0.45 among the active participants (PP population). These results are comparable to effect sizes found in previous studies of patients with FM in primary health care (Garcia-Campayo et al., 2008).

In between-group analyses of active participants attending at least 60 % of the sessions (PP population), the exercise education group also improved in walking capacity measured with the 6MWT, as compared to the control group only participating in education. Compliance appears to be important for gaining positive effects on physical function. The change in 6MWT was smaller than expected, possibly due to the fairly high walking capacity in the patients at baseline.

The improvement in the FIQ total in the exercise education group was supported by improvements in several other health related components in the ITT population. FIQ pain and activity related relaxation showed significant improvement in the exercise education group, as compared to the education only group, which might have contributed to the improved health status. The improvements are in line with previous findings of exercise in FM (Gowans et al., 2001). The pool exercise programme comprised one session a week for 20 weeks. The recommended exercise frequency in FM is two times a week (Busch, et al., 2007; Hauser, et al., 2010), which might have given greater improvements in the exercise education group.

Multiple dimensions of fatigue assessed with the MFI-20 were included as explorative outcomes in the present study. The exercise education group improved in the MFI reduced motivation as compared to the education only group. This result is in line with findings in a study investigating the effects of Nordic Walking in FM, in which the MFI reduced motivation was improved in the Nordic Walking group as compared to a control group with low-intensive walking (Mannerkorpi, Nordeman, Cider, & Jonsson, 2010).

Motivation has been shown to be a predictor of change in health related quality of life and working ability when patients with musculoskeletal pain participated in rehabilitation programme combining education, exercise, body awareness therapy and social activities (Grahn, Ekdahl, & Borgquist, 2000). Thus, the improvement in the MFI reduced motivation in the present study has probably interacted with the improvement in FIQ total and FIQ pain and the within-group improvements in health related quality of life among the exercisers.

The other fatigue dimensions showed conflicting results, as some of them improved in the exercise-education group and others improved in the education group. Within-group analyses among the active participants (PP population) showed that MFI physical fatigue, MFI reduced activity and MFI reduced motivation improved in the exercise education group and MFI reduced activity improved in the education only group. The education programme included a physical contract aiming to motivate the patients to increase their level of physical activity, which could explain the within-group improvement in MFI reduced activity in both groups.

The fatigue results in the present study indicated that the MFI-20 is sensitive to change in patients with FM and CWP. However, the minimal clinically important difference in fatigue dimensions of the MFI-20 needs to be studied further in order to establish the responsiveness of the instrument.

Subgroup analyses were also made in the present thesis to investigate the influence of stress, pain, activity limitations and distress on changes in primary outcomes in female patients with FM and CWP. The patients were divided into two subgroups by using the median value for SCI-93 (<78>), FIQ pain (<70>) and the SF-36 physical functioning (<55>). The patients were also divided into two subgroups regarding distress, assessed with the subscale for depression in the HADS and using the cut-off point of possible depression (<8>) (Herrmann, 1997). No significant heterogeneity was found in the subgroup analyses, but stress tended ($p=0.07$) to influence the change in the FIQ total, indicating that patients with lower scores for stress might improve more in health status as a consequence of the exercise than those with higher scores.

Separate within-group analyses of patients rating lower levels of stress, pain and distress revealed a significant improvement in the FIQ total ($p<0.05$) among the exercisers, compared with the control group. No significant differences between the exercisers and the control group were found for the patients that rated high levels of stress, pain and distress. However, the

patients with more severe symptoms appeared to improve equally regardless of the type of intervention.

No significant heterogeneity was found for change in the 6MWT, which may be related to the small improvement in the exercise-education group discussed earlier. Subgroups based on symptom severity and physical impairments among patients with FM have been described in other studies (Calandre et al., 2011; Giesecke et al., 2003; Thieme, et al., 2007). To the best of our knowledge, the present study is the first to demonstrate subgroup differences in outcomes of exercise in patients with FM, suggesting that patients with milder symptoms gain the best effects of exercise.

A limitation of the study was the choice of the control group that participated in education, a recommended treatment for patients with FM. The education programme consisted of six sessions, once a week, and was based on self-efficacy principles requiring the active participation of the patients. The aim of the education was to introduce strategies to cope with fibromyalgia symptoms and to encourage regular physical activity. It would have been preferable for the control group not to have received any intervention at all. However, there were only few within-group improvements in the control group, which might owe to their long duration of pain. Many of the patients reported previous participation in patient education.

6.3.2 Pool exercise and resistance training in men with FM and CWP

The randomized trial in the pilot study showed that a 12-week supervised resistance training programme improved isometric force in right arm shoulder abduction and knee flexion in both legs in men with CWP when compared to a 12-week supervised pool exercise programme.

The mean values of isometric force of the right arm shoulder abduction and knee flexion in both legs increased from baseline to 12-week examination by between 23 % and 30 % in the resistance training group. This is in line with studies of women with FM who increased their isometric knee extension force by 27-36 % after a 21-week period of resistance training (Hakkinen, et al., 2001; Valkeinen, et al., 2005). The increase in strength in the present study is also consistent with the expected improvement of resistance training in untrained and moderately trained healthy individuals (Kraemer, et al., 2002).

There were no differences between the two exercise groups in change in fatigue at the 12-week examination. However, within-group analyses showed that MFI general fatigue decreased significantly over time in the resistance training group, and a tendency toward improvement in MFI general fatigue was also found in the pool exercise group (p=0.053). At the nine-month follow-up, the decrease in MFI general fatigue was statistically significant in both exercise groups as compared to baseline.

The MFI reduced motivation was significantly improved over time in the pool exercise group, which is in line with the results of pool exercise in Study III in the present thesis as well as a previous study of aerobic exercise (Mannerkorpi, et al., 2010). Within-group improvements were also found in the pool exercise group for anxiety, which agrees with a previous study (Jentoft, Kvalvik, & Mengshoel, 2001), and for the physical component summary of SF-36, with a mean increase of 4.3 (SD 6.1), suggested to be a clinically relevant increase in chronic diseases (Angst, Aeschlimann, & Stucki, 2001; Coteur, Feagan, Keininger, & Kosinski, 2009).

No change in pain intensity was found during the 12-week study period, but the lesser number of pain localizations in the resistance training group after 12 weeks of exercise indicates an improvement in the distribution of pain in this group. Both groups reported a lower number of pain localizations at the nine-month follow-up.

There is a scarcity of studies investigating the effects of exercise in men with CWP, which was the reason for initiating the present pilot study. In women with FM and CWP, pool exercise has been shown to improve symptoms and physical function, while there is limited evidence of the effects of resistance training (Busch, et al., 2007). The two types of exercise were therefore chosen for the present study.

The six men with FM constituted a small subgroup of CWP reporting more severe symptoms, especially in level of fatigue, stress and distress, and only four of them completed the 12-week examination. To achieve a more homogenous sample, the FM patients were excluded from the main analyses. However, when the men with FM were included in the sample in tudy IV, the between-group analysis showed significant improvement in isometric force of right arm shoulder abduction (p=0.010) and right leg knee flexion (p=0.004) in the resistance training group as compared to the pool exercise group. When the men with FM were included in the within-group analyses in study IV, improvements were found in MFI physical fatigue, MFI reduced

motivation, HADS anxiety and SF-36 physical component summary in the pool exercise group ($p<0.05$) and in right arm shoulder abduction, knee flexion in both legs and MFI general fatigue ($p<0.05$) (data not shown in the results section).

The main limitation of the study was the small populations in the two exercise groups. There are also limitations when both groups in a randomized trial receive active treatments. Both treatments could have similar effects, complicating between-group analyses. A reference group was therefore recruited to study the natural course of CWP, which could confirm possible within-group changes in outcome variables. As the outcome variables did not change over time in the reference group, the within-group improvements in the exercise groups can be assumed to have occurred by way of exercise. However, the reference group might be too small to make this conclusion certain.

Despite the small sample size, significant differences were found in performance based tests among patients engaging in resistance exercise when compared to pool exercise, implying that men with CWP can improve muscle strength by resistance training.

7 CONCLUSION

The subscales of the Swedish version of the MFI-20 were found to possess sufficient test-retest reliability and internal consistency in patients with FM and CWP. When the convergent construct validity was investigated, the associations between the subscales of the MFI-20 and the one-dimensional FIQ fatigue were fair to moderate in the female population and moderate to good in the male population, implying that the MFI-20 assesses different aspects of fatigue than the FIQ fatigue does in patients with FM. The MFI-20 was found to be most useful in relation to aspects of employment and physical function in female patients with FM.

Female patients with FM rated their fatigue higher than healthy women. General fatigue and physical fatigue appear to be the most prominent fatigue dimensions regardless of condition and gender.

The randomized controlled trial in female patients with FM and CWP showed that patients participating in an exercise-education programme improved in overall health and pain as compared to patients only participating in education. Patients with milder symptoms of stress, distress and pain improved more in overall health by exercise combined with education than by education only. However, the patients with more severe symptoms appeared to improve equally regardless of the type of intervention.

In the pilot study exploring the effects of exercise in men with CWP, a resistance training programme improved isometric strength as compared to a pool exercise programme. The results imply that men with CWP can increase muscle strength in a way similar to that in healthy individuals by resistance training. Resistance training could be recommended when the preference is to increase muscle strength, while pool exercise might be preferable when the subjective perception of health is of priority. However, larger patient samples are needed to be able to make these conclusions certain.

8 FUTURE PERSPECTIVES

Fatigue is a symptom of substantial importance for patients with FM and CWP and needs to be considered when planning treatments for these patients. Treatments for fatigue should attempt to improve the dimensions of general fatigue and physical fatigue, since they appear to be severe in FM and CWP, as well as the dimension of reduced motivation, since motivation has previously been shown to be a predictor of change in health related aspects (Grahn, et al., 2000) and of importance for subjective impressions of improvement (Hudson, et al., 2009). It is also possible that treatment of distress might have a positive influence on fatigue as well in FM and CWP. Physiotherapy including exercise and education appears to contribute to improvements in fatigue. However, further studies of effects of physiotherapy on multidimensional fatigue are required in both female and male patients with FM and CWP.

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