

# Mindfulness-based and acceptance-based interventions and physical activity in the management of fibromyalgia

- evaluation of a multicomponent rehabilitation programme

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“One does not love a person, one does not love a body, one loves a life established in a body.”

— Maurice Merleau-Ponty,  
Institution and Passivity: Course  
Notes from the Collège de France,  
1954-1955

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## Abbreviations

ACR	American College of Rheumatology
ACT	Acceptance and Commitment Therapy
ANCOVA	Analysis of Covariance
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
EQ-5D-5L	EuroQoL 5L - Health-related Quality of Life
EULAR	European League Against Rheumatism
FFMQ	The Five Facet Mindfulness Questionnaire
FM	Fibromyalgia
GHQ	General Health Questionnaire
GP	General Practitioner
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
HLC	Healthy Life Centre
ITT	Intention to Treat
LCGA	Latent Class Growth Analysis
MBCT	Mindfulness-Based Cognitive Therapy
MBSR	Mindfulness-Based Stress Reduction
MeSH	Medical Subject Headings
NRS	Numeric Rating Scale
OMERACT	Outcome Measures in Rheumatology
PDS	Polysymptomatic Distress Scale
PGIC	Patient Global Impression of Change
PICO	Patient, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomised Controlled Trial
ROB	Risk of Systematic Bias
SALSA	SAMhandling, LivsStyrketrening og fysisk Aktivitet (Interaction, Vitality training and physical activity)
SD	Standard Deviation
SMD	Standardised Mean Difference
SR	Systematic Review
SSS	Symptom Severity Scale
TIDieR	Template for Intervention Description and Replication
VTP	Vitality Training Programme
WPAI	Work Productivity and Activity Impairment Questionnaire
WPI	Widespread Pain Index

## List of papers

This thesis is based on the following papers, which will be cited in the subsequent text by their Roman numerals (I–IV).

I. Trond Haugmark, Kåre Birger Hagen, Geir Smedslund, Heidi A. Zangi (2019) Mindfulness- and acceptance-based interventions for patients with fibromyalgia – a systematic review and meta-analyses. *PLoS ONE* 14(9): e0221897. <https://doi.org/10.1371/journal-pone.0221897>

II. Trond Haugmark, Kåre Birger Hagen, Sella Aarrestad Provan, Elisebeth Bærheim, Heidi A. Zangi (2018) Effects of a community-based multicomponent rehabilitation programme for patients with fibromyalgia: protocol for a randomized controlled trial. *BMJ Open* 2018;8:e021004. doi: 10.1136/bmjopen-2017-021004

III. Trond Haugmark, Kåre Birger Hagen, Geir Smedslund, Sella Aarrestad Provan, Heidi A. Zangi. Effects of a mindfulness-based and acceptance-based group programme followed by physical activity for patients with fibromyalgia: a randomised controlled trial. *BMJ Open* 2021;11:e046943. doi:10.1136/bmjopen-2020-046943

IV. Trond Haugmark, Kåre Birger Hagen, Sella Aarrestad Provan, Joseph Sexton, Heidi A. Zangi (2021) Trajectories of change in symptom severity in patients with fibromyalgia: exploratory analyses of a randomised controlled trial. *Rheumatol Int* 41, 691–697 (2021). <https://doi.org/10.1007/s00296-021-04801-x>

## Summary

**Background** Fibromyalgia (FM) is a heterogeneous and complex musculoskeletal pain disorder characterised by multiple symptoms. The often unpredictable remission and recurrence of FM symptoms further impair social and physical function and reduce overall quality of life. No curative treatment is available for FM, and pharmacological treatment is inadequate. In Norway, treatment is usually limited to general practitioner (GP) consultations and physiotherapy. Traditionally, health care services have been based on a biomedical approach focusing on pathogenesis, diagnosis, and treatment of diseases. This approach is less likely to benefit patients with FM who have complex symptoms and no effective treatments to access. This condition calls for a broader perspective on health and more holistic management approaches. For optimal management, the European League Against Rheumatism (EULAR) has developed evidence-based recommendations including prompt diagnosis and patient education as first-line treatment. Furthermore, nonpharmacological treatment, such as physical exercise and psychological interventions, should be initiated with the aim of improving patient quality of life. According to Norwegian health authorities, FM treatment is to be provided at the primary care level. However, the treatment modalities described in the EULAR recommendations are available in Norwegian primary health care only to a limited degree.

**Aims** The main aim of this thesis was to evaluate the effects of a multicomponent rehabilitation programme combining two nonpharmacological treatment modalities for patients with newly diagnosed FM delivered in primary health care. The specific objectives were 1) to analyse the health effects of mindfulness- and acceptance-based interventions for patients with FM, with an exploration of the content and delivery components in the interventions; 2) to design and implement a randomised controlled trial and to evaluate health effects of a Norwegian mindfulness- and acceptance-based intervention followed by physical activity; and 3) to identify groups of patients with different symptom severity trajectories and to explore differences in baseline characteristics among these groups.

**Materials and methods** This thesis comprises a systematic review with meta-analyses, a randomised controlled trial (RCT), and an observational exploratory study. The systematic review included RCTs investigating the effects of mindfulness- and acceptance-based interventions for patients with FM. Furthermore, the Template for Intervention Description and Replication checklist was used to specifically extract, describe, and explore the reported content and delivery components in each study's intervention. In the RCT, eligible patients were invited to a 3-hour FM patient education programme before randomisation. A multicomponent programme, including a 10-session mindfulness- and acceptance-based group programme followed by 12 weeks of physical activity, was evaluated in comparison to a control group that received treatment as usual, i.e., no treatment or any other treatment of their choice. We collected data using patient-reported questionnaires, with the Patient Global Impression of Change (PGIC) as the primary outcome measure. Secondary outcomes evaluated at the 12-month follow-up were pain, fatigue, sleep quality, psychological distress, physical activity, health-related quality of life, motivation for and barriers to physical activity,

mindfulness, and work ability. In the observational exploratory study, to identify groups of patients with different symptom severity trajectories, we evaluated Polysymptomatic Distress Scale (PDS) scores using latent class growth analysis. The study participants were those included in the RCT. We also explored differences in baseline characteristics between groups with different trajectories.

**Results** The systematic review included nine RCTs and 750 patients with FM. The meta-analyses, giving standardised mean differences (SMDs) with 95% confidence intervals (CIs), showed small to moderate effects in favour of mindfulness- and acceptance-based interventions at the end of treatment for pain (SMD -0.46 [95% CI -0.75, -0.17]), depression (SMD -0.49 [95% CI -0.85, -0.12]), anxiety (SMD -0.37 [95% CI -0.71, -0.02]), sleep quality (SMD -0.33 [95% CI -0.70, 0.04]), health-related quality of life (SMD -0.74 [95% CI -2.02, 0.54]), and mindfulness (SMD -0.40 [95% CI -0.69, -0.11]). At follow-up, all effect sizes decreased except for anxiety, for which there was a small increase in effect size. We graded the certainty of evidence as very low to moderate. The included studies reported and assessed adherence and fidelity differently. In the RCT, 170 patients were randomised, 85 to the intervention group and 85 to the control group. Our main analysis was the dichotomised PGIC, and we found no statistically significant differences between the intervention and control groups at the 3- and 12-month follow-ups. Additional analyses of the distribution of PGIC showed statistically significant differences between groups in favour of the intervention group at the 3-month follow-up ( $p=0.01$ ) but not at the 12-month follow-up ( $p=0.06$ ). For secondary outcomes, we found no statistically significant differences between the groups at the 12-month follow-up, except for a tendency to be mindful ( $p=0.016$ ) and perception of the benefits of exercise ( $p=0.033$ ) in favour of the intervention group. We intended to capture patients with FM at an early stage of their disease, but the included patients reported a median symptom duration of 8 years. In the observational study, we identified two distinct groups of PDS trajectories: one group defined by having no improvement and another defined by having some improvement. The analyses showed no statistically significant differences in baseline characteristics between these two groups.

**Conclusion** In the systematic review, we found overall small to moderate uncertain effects of mindfulness- and acceptance-based interventions for patients with FM. The RCT demonstrated no enhanced benefit over treatment as usual with the addition of a multicomponent rehabilitation programme that added a mindfulness- and acceptance-based intervention followed by physical activity to patient education. In the observational exploratory study, analyses identified two groups of FM trajectories, one group that improved slightly and one group that experienced no improvements, but the two groups did not differ in baseline characteristics.



Summary in Norwegian

**Bakgrunn** Fibromyalgi (FM) er en diagnose med et sammensatt sykdomsbilde. Utbredte muskelsmerter, utmattelse og dårlig søvnkvalitet er vanlige symptomer. Symptomene kan være uforutsigbare, svekke pasientenes fysiske og sosiale funksjon og redusere generell livskvalitet. Dagens medisinske behandling er kun symptomlindrende, og medikamentell behandling er som regel utilstrekkelig. Tradisjonell biomedisinsk tilnærming med fokus på patogenese, diagnoser og behandling av sykdommer er mindre hensiktsmessig for denne pasientgruppen. FM krever et videre perspektiv på helse og en mer helhetlig tilnærming. European League Against Rheumatism (EULAR) har utviklet evidensbaserte anbefalinger med diagnostisering og pasientopplæring som førstelinjebehandling. Videre anbefales ikke-medikamentell behandling som fysisk trening og kognitive tilnærminger. Den overordnede hensikten er å bedre pasientens helserelaterte livskvalitet. Helsedirektoratets prioriteringsveileder slår fast at pasienter med FM skal behandles i primærhelsetjenesten. Behandlingsmetodene som er anbefalt av EULAR, er imidlertid i begrenset grad tilgjengelige i primærhelsetjenesten i Norge.

**Mål** Avhandlingens overordnede mål var å evaluere effekten av et sammensatt rehabiliteringsprogram for pasienter med FM i norsk primærhelsetjeneste. Mer spesifikt var hensiktene: 1) å analysere helseeffektene av mindfulness- og akseptbaserte intervensjoner for pasienter med FM, samt utforske hvordan intervensjonene ble gjennomført og hvilke komponenter intervensjonene besto av; 2) designe og gjennomføre en randomisert kontrollert studie for å evaluere helseeffekter av en norsk mindfulness- og akseptbasert intervensjon, etterfulgt av fysisk trening; 3) å identifisere grupper med ulike symptomforløp og utforske forskjeller i pasientkarakteristika mellom disse gruppene.

**Metoder** Avhandlingen består av en systematisk litteraturoversikt med metaanalyser, en randomisert kontrollert studie (RCT) og en eksplorativ observasjonsstudie. Den systematiske oversikten inkluderte RCTer som undersøkte effekten av mindfulness- og akseptbaserte intervensjoner for pasienter med FM. Sjekklisten 'Template for Intervention Description and Replication' (TIDieR) ble brukt til å utforske og beskrive hvordan intervensjonene ble gjennomført i de inkluderte studiene og hvilke komponenter intervensjonene besto av. I RCTen ble pasienter først invitert til et 3-timers pasientopplæringskurs før de ble randomisert til et mindfulness- og akseptasjonsbasert gruppeprogram etterfulgt av fysisk trening på en Frisklivssentral eller til en kontrollgruppe som fulgte behandling etter eget ønske. Pasientene ble fulgt over ett år. Effekten ble målt som forskjeller mellom intervensjon- og kontrollgruppen ved hjelp av selvrapporterte spørreskjema etter 12 måneder. Det primære utfallsmålet var pasientens egen opplevelse av endring i helsetilstand. I tillegg ble det målt effekter på utfallsmål som smerte, utmattelse, søvnkvalitet, emosjonell helse, helserelatert livskvalitet, fysisk aktivitet, barrierer og mestring av fysisk aktivitet, mindfulness og arbeidsevne. Vår hensikt var å inkludere pasienter på et tidlig stadium av sykdommen, men de inkluderte pasientene rapporterte en median symptomvarighet på åtte år. I den eksplorative observasjonsstudien ble pasientene fra RCTen analysert med 'Polysymptomatisk distress skala' (PDS) for å identifisere

pasientgrupper med ulike symptomforløp. I tillegg ble forskjeller i pasientkarakteristika mellom gruppene med ulikt forløp utforsket.

**Resultater** Den systematiske oversikten inkluderte ni RCTer og 750 pasienter med FM. Metaanalysene viste små til moderate samlede effekter til fordel for mindfulness- og akseptbaserte intervensjoner kort tid etter intervensjonens slutt for smerte (SMD -0,46 [95% CI -0,75, -0,17]), depresjon (SMD -0,49 [95% CI -0,85, -0,12]), angst (SMD -0,37 [95% CI -0,71, -0,02]), søvnkvalitet (SMD -0,33 [95% CI -0,70, 0,04]), helse relatert livskvalitet (SMD -0,74 [95% CI -2,02, 0,54]) og mindfulness (SMD -0,40 [95% CI -0,69, -0,11]). Ved senere oppfølging viste alle utfallsmålene noe redusert effekt bortsett fra angst som viste en liten økning i effektstørrelse. Påliteligheten av effektestimatene ble gradert fra svært lav til moderat. Sjekklisten TIDieR viste ulik rapportering av hvorvidt pasienten fulgte opp behandlingen og hvorvidt instruktørene etterlevde manualen for intervensjonen. I RCTen ble 85 pasienter randomisert til intervensjonsgruppen og 85 til kontrollgruppen. Det var ingen signifikant forskjell mellom gruppene i primært utfallsmål ved oppfølgingene da dette ble dikotomisert. Da vi analyserte PGIC som ordinal variabel hadde intervensjonsgruppen en statistisk signifikant større bedring i opplevet helsetilstand enn kontrollgruppen ved tre måneders oppfølging ( $p=0,01$ ), men ikke ved 12 måneders oppfølging ( $p=0,06$ ). Det var ingen forskjeller i de sekundære utfallsmålene mellom gruppene ved 12-måneders oppfølging, bortsett fra 'pasientene i intervensjonsgruppen opplevde større fordeler med fysisk aktivitet' ( $p=0,033$ ) og 'økt evne til oppmerksomt nærvær' ( $p=0,016$ ). I den eksplorative observasjonsstudien identifiserte vi to grupper med ulike symptomforløp, en gruppe med "ingen bedring" og en gruppe med "noe bedring". Det var ingen signifikante forskjeller i pasientkarakteristika mellom de to gruppene.

**Konklusjon** Metaanalysen i den systematiske oversiktsartikkelen fant små til moderate effekter av mindfulness- og akseptasjonsbaserte intervensjoner for pasienter med FM. Det var ingen forskjeller mellom studier som rapporterte strategier for å øke sannsynligheten for at pasientene fulgte behandlingsmanualen og studier som ikke rapporterte slike strategier. I RCTen fant vi ingen statistisk signifikante forskjeller mellom intervensjons- og kontrollgruppen i noen av utfallsmålene. Den eksplorative observasjonsstudien viste ingen forskjeller i pasientkarakteristika mellom pasientene med noe bedring i løpet av studieperioden og pasientene uten noen bedring.

TIDieR-sjekkliste var et velegnet supplement til CONSORT-sjekklisten for å forbedre rapporteringen av RCTer. Polysymptomatisk distress skala var nyttig for å kvantifisere symptombyrden av FM. Det anbefales å utforske strategier for å forbedre etterlevelse av intervensjoner for fysisk aktivitet, samt fokusere på hvordan man kan tilpasse og skreddersy fysisk aktivitet for den enkelte pasient i primærhelsetjenesten. Fremtidig forskning bør ta sikte på å inkludere FM pasienter på et tidlig stadium av sykdommen og utforske effekten av tidlig diagnostisering og pasientopplæring.

## 1 Introduction

As a nurse in occupational health care, I have worked for a company that employed personnel for cleaning and cafeteria jobs. Women traditionally occupy these jobs, which can be physically stressful with a strict schedule and high work strain. Many employees reported musculoskeletal pain, often with an unexplained medical cause. The employee, employer, and I cooperated in supporting employees on the job so that they could stay healthy. Some were already on sick leave and their general practitioners (GPs) frequently referred them traditional treatment, such as physiotherapy. The recovery was often short term, resulting in frequent, extended, or long-term periods of sick leave.

During that time, I learned about the Vitality Training Programme (VTP), a Norwegian mindfulness- and acceptance-based group programme for patients on long-term sick leave because of chronic musculoskeletal pain (1). A colleague and I were trained as VTP facilitators. Later, we introduced and offered the VTP for employees in the company during several periods so that they could avoid sick leave or extended sick leave. It appeared successful and inspired me to write my master thesis in Mental Health Work on one of the completed programmes.

In 2016, the Norwegian National Advisory Unit on Rehabilitation in Rheumatology, Division of Rheumatology and Research, at Diakonhjemmet Hospital initiated a PhD project comprising the VTP for patients with fibromyalgia (FM), and I had the good fortune to be enrolled. Management of FM varies throughout Norway, and most patients are not offered any targeted treatment in primary health care. Moreover, research involving patients with FM remains scarce.

During the initial period of the project, patients were recruited and attended an education programme where they could share their experiences living with pain and ask questions about the study. I still remember a woman who said: "I called a doctor's office yesterday, and when I told the person on the phone that I had fibromyalgia, I was lectured that I could throw this diagnosis in the litter. It's like nobody wants us ... I have nowhere else to go, and I've tried everything ...". Such stories illustrate the importance of this project.

FM is not a new condition. FM-like symptoms, such as disabling pain, unrefreshing sleep, and physical exhaustion associated with stress and depression, are described in the Old Testament (2). In modern times, Dr. P.K. Hensch introduced the term 'fibromyalgia' in 1976. Soft tissue pain was described as the primary clinical feature (3, 4). The word 'fibromyalgia' consists of the Latin syllable *fibro-*, meaning fibrous tissues, and the Greek syllables *myo* (muscle) and *algos* (pain), meaning "muscle and fibrous connective tissue pain" (5). FM constitutes a significant health challenge for individuals and health care systems and is a common cause of sick leave as well as disability benefits claims (6-9). FM can affect daily life and function, ability to work and engage in everyday activities, and a patient's relationships with family, friends, and employers (10).

The Norwegian Coordination Reform was intended to ensure better and accessible health care, preferably in the local community (11). According to the Norwegian Directorate of Health, patients with FM are to be treated in primary health care (12), and GPs most commonly diagnose patients with FM in Norway. The treatment offered is usually limited to GP consultations and physiotherapy. Some patients may be referred to specialist rehabilitation centres, but waitlists are long, and many patients are refused. For these reasons, patients "shop around" for various alternative treatments in the hope of finding something that helps (13).

The Norwegian medical community has ranked FM as one of four diagnoses with the lowest prestige (14). Some physicians question FM as a diagnostic label or if the diagnosis will benefit the patient (15). Consequently, patients might experience a considerable delay in getting the FM diagnosis. Some patients hesitate to present their symptoms to the doctor, believing that the symptoms might resolve because their severity often fluctuates throughout the day. In addition, FM symptoms such as pain, sleep problems, fatigue, cognitive difficulties, and physical exhaustion can be challenging for patients to communicate, and doctors can find it difficult to differentiate between FM and other diagnoses (6). This complexity often leaves physicians frustrated and patients dissatisfied and still experiencing chronic, unremitting symptoms (16).

Traditionally, Norwegian health care services have been based on a biomedical approach focusing on pathogenesis, diagnosis, and treatment of diseases and prevention of

comorbidities and late complications (11). This approach has been beneficial for disorders with a clear diagnosis and evidence-based treatments. However, it is less likely to benefit patients with chronic health conditions, such as FM, that involve complex symptoms and no available curative treatment. This situation calls for a broader perspective on health and a more holistic treatment (17). Contrary to the biomedical perspective, a phenomenological approach asks how people experience and interpret phenomena, such as disease and symptoms (18, 19).

Over recent decades, the salutogenic model of health has gained increased attention within health care. Pathogenesis is the study of disease origins and causes, but salutogenesis is the study of how to promote health (20). The latter explores how to enhance, create, and improve people's health-promoting resources and physical, mental, and social wellbeing. A person's ability to mobilise resources to manage stressors is strongly related to their sense of coherence, the degree to which a person experiences life as understandable, manageable, and meaningful. A salutogenic approach focuses on how people remain healthy despite stress (21).

The VTP is a Norwegian mindfulness- and acceptance-based group intervention that was originally developed for patients on long-term sick leave because of chronic musculoskeletal pain (1). The VTP is based on a salutogenic approach with the goal of understanding patients from a phenomenological perspective. Participants are invited to nonjudgmentally explore the relationship among their feelings, thoughts, and body sensations to better understand the meaning of their experiences (22, 23).

The main aim of this thesis was to evaluate for patients with newly diagnosed FM the effects of a multicomponent rehabilitation programme delivered in primary health care. The rehabilitation programme comprised the VTP followed by physical activity counselling at a healthy life centre (HLC). We named the study SALSA, an acronym for "SAMhandling, LivsStyrketrening og fysisk Aktivitet" (Interaction, Vitality Training and physical activity) for patients with FM. The SALSA study was designed to strengthen primary and secondary health care interaction to improve FM management in Norway. Another aim of this thesis was a review of the current literature to examine the health effects of mindfulness- and acceptance-based interventions for patients with FM. Furthermore, Polysymptomatic

Distress Scale (PDS) scores collected during the RCT were analysed to identify potential groups of PDS trajectories and explore differences in baseline characteristics between the groups.

The thesis consists of four papers. **Paper I** is a systematic review (SR) with a meta-analysis of studies reporting mindfulness- and acceptance-based interventions for patients with FM. **Paper II** is a study protocol for a randomised controlled trial (RCT). **Paper III** reports the results from an RCT that evaluated the effects of a multicomponent rehabilitation programme compared to a control group that followed treatment as usual. **Paper IV** reports exploratory analyses to identify groups of symptom trajectories and differences in baseline characteristics between the groups.

## 2 Background

### 2.1 Fibromyalgia

FM is a heterogeneous and complex musculoskeletal pain disorder characterised by multiple symptoms such as sleep problems, fatigue, cognitive difficulties, and physical exhaustion (24, 25). Additional symptoms such as irritable bowel syndrome, anxiety, and depressive disorders are reported (24, 25). The symptomatology may vary in terms of expression and intensity and synergistically creates a greater severity than individual symptoms alone (24, 26-28). Patients have reported that the symptoms often present in an unpredictable remitting-relapsing cycle that further impairs social and physical function and reduces the overall quality of life (29, 30). The FM diagnosis is based on symptoms and symptom severity in the absence of objective biomarkers (24).

#### 2.1.1 Diagnostic classification criteria

The understanding of FM has evolved during the last 40 years. In the 1980s, a series of FM diagnostic criteria were developed that eventually culminated into the American College of Rheumatology (ACR) classification criteria for FM in 1990 (31). FM was then recognised and classified as a discrete disorder, primarily based on the doctor's examination of widespread pain and tender point count (Wolfe 1990). In 2010, the 1990 criteria were revised. The ACR 2010 FM diagnostic criteria were based on the Widespread Pain Index (WPI), which assesses the number of painful body regions, and the Symptom Severity Scale (SSS), which measures symptom severity. The WPI includes a 19-region body map, on which the patient marks painful regions, and an FM questionnaire mapping the symptoms and the degree of severity. The ACR 2010 criteria provided a tool for evaluating and measuring symptom severity. However, one of the items of the SSS required grading of somatic symptoms, as assessed by a physician. In 2011, the ACR 2010 criteria were modified into a self-report questionnaire, the Fibromyalgia Survey Questionnaire, for use in research. The 2011 criteria also introduced the PDS, correspondingly termed the 'fibromyalgianess score', which measures the magnitude and severity of FM symptoms. PDS combines the WPI and SSS into a FM severity score, with a range of 0 to 31 points (32-34). This scale also can be used with the 2010 criteria because the WPI and SSS are part of both criteria sets. Patient self-report alone is not considered valid for individual diagnosis, which requires an interview by a physician who

considers or excludes other diagnostic possibilities. Another requirement is that the symptoms are present at a similar level for at least 3 months, with the absence of another disorder that could sufficiently explain the pain (32, 35). Based on the PDS, FM can be differentiated into mild, moderate, and severe forms depending on the number and severity of symptoms and the degree of dysfunction (25, 36). The development of the ACR diagnostic criteria is displayed in table 1.

**Table 1. Differences among the ACR 1990 (37), revised ACR 2010 criteria (32), and modified ACR 2010 criteria (ACR 2011) for FM (33).**

1990 criteria	<ul style="list-style-type: none"> <li>• Included the patient’s history of widespread pain</li> <li>• Widespread pain was defined as axial pain, left- and right-side pain, and upper and lower segment and multiple soft tissue pain</li> <li>• Pain ≥3 months in duration</li> <li>• Based on examination by physician</li> <li>• Pain or tenderness in 11 or more of 18 possible “tender points” (37)</li> </ul>
2010 criteria	<ul style="list-style-type: none"> <li>• No specific physical examination required, but recommended</li> <li>• A clinical interview by a physician</li> <li>• Tender point examination eliminated; widespread pain replaced by the WPI</li> <li>• WPI ≥ 7 and SSS ≥ 5 OR WPI 3–6 and SSS ≥ 9</li> <li>• Symptoms present at similar level for ≥3 months</li> <li>• No other disorder that the patient has that would explain the pain</li> <li>• The number of areas in which the patient has had pain over the last week (six lower extremities, six upper extremities, seven axial skeleton)</li> <li>• The sum of severity of fatigue, waking unrefreshed, and cognitive symptoms present over the past week, plus the severity of general somatic symptoms</li> <li>• Each symptom is rated on a scale of 0–3, where 0=no symptoms/problem and 3=severe symptoms/problems</li> <li>• Final score: 0 and 12 (32)</li> </ul>
2011 criteria	<ul style="list-style-type: none"> <li>• 2010 ACR criteria modified to allow self-report of FM severity in clinical research (33)</li> <li>• A valid clinical diagnosis combined physician based and self-reported questionnaires (35)</li> </ul>
ACR, American College of Rheumatology; FM, fibromyalgia; SSS, Symptom Severity Scale; WPI, Widespread Pain Index	

### 2.1.2 Epidemiology

The worldwide prevalence of FM is about 2%, with women predominantly affected (25, 38). The prevalence differs among countries, and in Norway, FM affects about 6% of women and 3% of men (39). FM can appear at any age, including during childhood (25).



### 2.1.3 Pathogenesis

The pathophysiology of FM has been poorly understood. Most recently, pain centralisation represents the dominant hypothesis (25, 28). Centralisation implies that the central nervous system takes the leading role in increasing or decreasing pain, like a 'volume control' for pain. This central sensitisation hypothesis could explain the heterogeneous clinical aspects of FM and several of the associated symptoms. Patients with FM may experience increased sensitivity, such as pain with an input that people without FM perceive only as touch. Many patients may develop other comorbid FM symptoms such as sleep disturbance, fatigue, and depressed mood (28). The mechanism behind this development is that the same neurotransmitters that control pain and sensory sensitivity also control sleep, mood, memory, and alertness (25, 40, 41).

### 2.1.4 Aetiology

The aetiology of FM is currently unknown. Studies have identified risk and vulnerability factors that include genetics, female sex, psychosocial stress, or untreated painful conditions such as acute pain that would typically last for a few weeks (28, 42). Additional potential risk factors include physical inactivity, sleep disturbances, and overweight or obesity, indicating that FM may be triggered or aggravated by multiple stressors (43-45). Consequently, patients may have comorbidities that need to be treated accordingly (46).

### 2.1.5 Living with FM

Living with long-lasting pain of unknown origin can be stressful. For some patients with FM, pain and exhaustion might be overwhelming and devastating (47). Qualitative studies show that many patients struggle with unpredictable and fluctuating FM symptoms that restrict participation in social life (48-52).

Patients also have reported ambivalence about telling others about their diagnosis because of the stigma associated with FM (49). Some patients have reported avoiding social interaction because of the stigma, consequently risking loneliness (48).

One qualitative study reported experiences from patients who participated in Acceptance- and Commitment Therapy (ACT), which promoted pain acceptance, pursued valued goals, and activities despite experiencing pain. The participants seemed to cope better when they

gave up on their attempts to fight their limitations and were willing to experience pain sensations and clarify what was important and meaningful in their lives. They needed to find alternative ways of doing things, working with their pain rather than against it and dealing with painful thoughts and feelings (53). According to another qualitative study, patients with FM report recovering from their illness by taking an active part in the rehabilitation processes (54). Therefore, patients may need to make adaptations to their lives, social roles, and work to self-manage their condition (47, 55).

## 2.2 EULAR recommendations for the management of FM

No curative treatment is available for FM, and the effects of pharmacological treatment alone are inadequate (56). The European League Against Rheumatism (EULAR) has developed evidence-based recommendations for optimal FM management. Table 2 displays a selection of the recommendations (24).

**Table 2. Treatment flow with nonpharmacological treatment options for FM based on EULAR recommendations for the management of FM (24).**

History and physical examination		
Prompt diagnosis		
Patient education and information		
Management/treatment	Strength of recommendation	Comment
Aerobic and strengthening exercise either on land or in water that works and strengthens muscles of the body	Strong for	Can reduce pain and increase physical function. Although it may increase pain at the very beginning, resistance training with weights may be beneficial also.
Cognitive-behavioural therapy	Weak for	Cognitive-behavioural therapy (also called CBT) is a talk therapy that challenging negative ideas. It may help change the way the recipient thinks and behaves and could help with management of FM, including ways of coping
Multicomponent therapies	Weak for	Multicomponent therapies may include different combinations of exercise, education, relaxation, or some other specific treatments such as tai chi or massage. This approach can help yield short-term improvements in pain and fatigue.
Acupuncture or hydrotherapy	Weak for	Traditional or electric acupuncture can help to improve pain when added to other treatments. Hydrotherapy or spa therapy sessions can deliver improvements that last for up to 14 weeks.
Meditative movement therapies and mindfulness-based stress reduction	Weak for	Meditative movement techniques such as qigong, yoga or tai chi or the practice of mindfulness and stress-reduction can help to improve sleep and fatigue.

The recommendations include prompt diagnosis and that patients initially should receive education about the condition. Furthermore, management should rely on a graduated approach based on assessment of individual needs. Nonpharmacological modalities aiming to improve health-related quality of life are recommended as first-line treatment. Physical exercise should be recommended to all patients. Psychological treatment is recommended for patients with mood disorders or unhelpful coping strategies (24). In this thesis, physical exercise has been combined with a mindfulness- and acceptance-based cognitive-behavioural intervention in a multicomponent rehabilitation programme.

### 2.2.1 Prompt diagnosis

A diagnosis is the classification tool in biomedicine, organising the clinical picture, guiding intervention, and providing a patient education framework (57). A definitive diagnosis for patients confers legitimacy on the condition and mirrors the medical understanding of the disease, illness, and health (50, 58). A diagnosis may furthermore provide reassurance, so that patients with FM may be better able to cope with their health status (59).

### 2.2.2 Patient education

Patient education as defined by Ramos-Remus et al. as follows: *“An information-giving process, designed to encourage positive changes in behaviours and beliefs conducive to health”* (60).

Patient education is included in the EULAR recommendations for the management of FM, with the aim of limiting disability in FM and improving quality of life (24). Patient education plays an essential role in FM management (61). Furthermore, in general, receiving support from others is beneficial to mental and physical health (62, 63).

### 2.2.3 Pharmacological treatment

Pharmacological treatment is recommended for patients with severe pain or sleep disturbances (24). For optimal pharmacological management, a tailored selection of drugs is recommended, selected according to key symptoms beyond pain and sleep problems such as fatigue and depressive or anxiety disorder. Pharmacological treatment as the sole strategy in the management of FM should be discouraged. The physician is advised to monitor the treatment’s efficacy, tolerability, and side effects because the therapy could entail adverse effects (64). The best treatment approach integrates pharmacological and nonpharmacological treatments while engaging the patient as an active participant in the rehabilitation process (24). This thesis does not address pharmacological treatment.

### 2.2.4 Nonpharmacological treatment

The aim with nonpharmacological interventions is to reduce symptom severity and improve quality of life for patients with FM by addressing dysfunction such as high stress, low activity, poor sleep, obesity, and maladaptive illness behaviours (24, 28, 44, 56). Although the evidence remains insufficient, cognitive-behavioural therapy, mindfulness-based stress reduction, meditative movement, and hydrotherapy have yielded small to moderate effects for these patients (24).

Studies on multicomponent treatments combining psychological treatment and exercise therapy have identified beneficial but small synergetic effects on chronic pain and FM

symptoms. The aims of multicomponent treatments have been to enhance psychological self-management and motivation for life-long physical exercise (24, 65).

### 2.3 Multicomponent rehabilitation

Rehabilitation is a set of processes relying on interventions that are planned and limited in time. The interventions involve coordinated efforts of multiple health care professions using various treatment modalities, assisting the patient in an effort to achieve the best possible functioning and coping capabilities and promoting independence and participation in society. Rehabilitation may reduce the consequences of the disease, maximise physical and psychosocial functioning and health, confer autonomy, and support a patient in fulfilling meaningful life roles and maximising wellbeing (66-68).

In this thesis, we combined two EULAR-recommended interventions — physical exercise and a mindfulness- and acceptance-based intervention, the Norwegian VTP — into a multicomponent rehabilitation programme.

#### 2.3.1 Mindfulness

Mindfulness was historically a Buddhist practice to alleviate suffering and cultivate compassion. A U.S. medical doctor, John Kabat-Zinn, adapted mindfulness practice within psychology and medicine in the late 1970s without any requirement for a religious or cultural belief system. Mindfulness is a moment-by-moment awareness and involves observing thoughts and feelings as passing events in the mind, without judging them as good or bad. When patients cultivate mindfulness in this way, the result can be a shift in perspective by observing thoughts, emotions, and sensations as passing experiences and not as *the* truth (69). Through mindfulness practice, the patient may develop a greater sense of emotional balance and wellbeing by disengaging from a strong attachment to beliefs, thoughts, or emotions (70). Mindfulness promotes self-observation, acceptance, and thoughtful responses to thoughts, emotions, and sensations such as pain, and emphasises one's relation to pain experiences rather than the content of the pain. In line with this theory, there is a decrease in the struggle to control what might not be controllable when acceptance increases (71). For pain patients, mindfulness practice may be associated with

better treatment outcomes (72). Pain acceptance involves a willingness to experience pain sensations and pursue valued goals and activities despite being in pain (53).

### 2.3.2 Mindfulness- and acceptance-based interventions

Mindfulness- and acceptance-based interventions for patients with chronic pain and FM include Mindfulness Based Stress Reduction (MBSR) (69), Mindfulness Based Cognitive Therapy (MBCT) (73), and Acceptance and Commitment Therapy (ACT) (74). Systematic reviews have shown beneficial effects in these patient groups, with improved pain, anxiety, depression, and health-related quality of life, especially in the long term (75, 76).

MBSR and MBCT incorporate practical and formal meditation training, such as body scan, sitting and walking meditation, mindful yoga movements, and individual practice between sessions. Participants spend up to 45 minutes on formal meditation practice each day (69). ACT relies on a wide variety of shorter exercises. The focus is on other cognitive skills such as participants' ability to define and clarify values in different life domains, identify achievable goals that embody those values, and plan the future based on identified life goals (74, 77). Mindfulness- and acceptance-based interventions for chronic pain management typically involve five key aspects (72):

- The importance of attentional processes, learning, and memory in the experience of pain and pain management
- The influence of emotion and emotional regulation in pain management through exposure techniques such as mindful yoga
- An emphasis on the intentional and value clarification components
- The cultivation of cognitive, emotional, and behavioural flexibility
- Group factors, such as unity, social learning, and therapeutic alliance

### 2.3.3 The Vitality Training Programme (VTP)

The VTP is a Norwegian mindfulness- and acceptance-based group intervention led by two facilitators trained and certified at VID Specialized University in Oslo. The facilitators are trained not to give advice and do not focus on diagnosis and pain. They provide opportunities to enhance awareness of a patient's health-promoting resources and

strengthen the patient's inner authority and ability to make choices in accordance with their values (1).

The VTP integrates mindfulness practice and emphasises non-judgmental attention to feelings, thoughts, and body sensations without attempting to change or avoid them (1, 23).

The VTP aims:

- to enhance people's health-promoting resources and their capacity to engage in a meaningful and valuable everyday life;
- to strengthen a patient's ability to make more conscious choices about responding to external and internal experiences; and
- to provide opportunities for the group participants to find and develop meaningful ways of coping with and adjusting to their symptoms and life situation through experience-based knowledge (1).

The group aspect, including sharing and listening to each other, is essential for patients by providing a sense of community and not being alone (78). The facilitators invite the patients to explore specific life topics related to living with long-lasting challenges: *If my body could talk/ Who am I?/ Values – what is important to me?/ What do I need?/ Strengths & limitations/ Bad conscience/ Anger/ Joy/ Resources, potentials and choices/ The way ahead.* These topics are explored through various experience-based, interactive, and creative methods. The VTP is based on four theoretical columns: phenomenology, salutogenesis, mindfulness, and gestalt psychology. The methods are derived from mindfulness and confluent education.

As explained in the introduction, health promotion, a salutogenic approach, and a phenomenological perspective are consistent with and incorporated into the VTP throughout the programme (1, 22).

The existential approach of gestalt psychology focuses on the present moment comprising *what is*, as opposed to the past or the future. In contrast to dealing with symptoms or character structures, it describes the entire existence. Gestalt psychology enhances awareness of personal resources and possibilities. Furthermore, the theory is concerned with completing unfinished situations from the past that could be obstacles for present health promotion (79).

Confluent education is inspired by the principles of gestalt psychology. These principles involve cognitive, emotional, and behavioural learning processes to enhance awareness of the relationship between inner experiences and interpretation of these experiences and behavioural patterns (80).

Awareness is attending to what is happening moment by moment instead of “thinking about” things. It relates to the possibility of shifting perspective on and an individuals’ discoveries of meaningful experiences. This perspective shift may initiate the process of reconstructing potentially unproductive or unhealthy habitual patterns and placing them in new dimensions of understanding (1).

The VTP has many common features with the mindfulness- and acceptance-based interventions described in section 2.3.2. One common assumption is that increased awareness of the present moment can enable patients to reduce their automatic behavioural responses (23).

#### *2.3.3.1 Evidence of the effects of VTP*

The VTP has been evaluated in two RCTs. One trial included patients with chronic musculoskeletal pain, including FM, and resulted in statistically significant improvements in pain and pain coping in favour of the intervention group at the 12-month follow-up (22). Another RCT in patients with inflammatory rheumatic joint disease showed significant improvements in psychological distress, self-efficacy, and fatigue in the intervention compared to the control group at 12-month follow-up (81). A longitudinal pre–post-test study that included patients with inflammatory arthritis and FM showed improvements in the arthritis group but not in the FM group (82). The reasons for this outcome are not clear, but the authors hypothesised that the lack of effect in patients with FM might have been related to living with distressing symptoms over time without receiving any diagnosis or targeted treatment (82).

#### 2.3.4 Physical exercise

Caspersen et al. have defined physical exercise as planned, structured, and repetitive body movements to improve or maintain physical fitness components. Physical exercise is a subset of physical activity, but the latter implies less structured and planned bodily movement (83). Studies have demonstrated that FM patients are less physically active



compared to healthy controls because of a high symptom burden, low self-reported quality of life, and disability. Inactivity has been found to reduce physical functioning in patients with FM (24, 84-87). Several studies have shown that physical exercise, including land or water-based strength training and aerobic exercise, can increase physical functioning for these patients. Exercise maintained for a more extended period can reduce symptoms and improve quality of life (24, 88-91). Physical exercise has generally exhibited larger effect sizes on global wellbeing than pharmacological treatment (92, 93). Thus, physical exercise is one of the cornerstones in FM management (24, 87). Moreover, regular physical activity participation in community settings has yielded additional social benefits, such as peer support (24, 94).

#### 2.3.5 Healthy life centres

Community-based HLCs have been part of the Norwegian primary health care system since 2004. They are established in most communities around the country and provide low-threshold, affordable, and easily accessible individual and group-based physical exercise. The ambitions are to promote good health through strengthening each person's sense of achievement, capacity, function, and ability to cope with everyday life (95). A 12-week HLC period starts with discussing individual goals for follow-up based on the user's objectives, health problems, and functional level. The discussion is based on motivational interviewing, and the user and counsellor jointly create a plan and assess goals and plans after 12 weeks (96). If necessary, the HLC offers further follow-up to maintain changes and continue the activity after the period has ended (95).

#### 2.4 The rationale for this thesis

The treatment modalities described in the EULAR recommendations for FM management are available only to a limited degree in Norwegian primary health care (13, 24). We designed the SALSA study to improve the management of FM in Norway. First, we provided an opportunity for referral to secondary health care, with rapid access and prompt diagnosis by a rheumatologist, followed by basic patient education. Second, we conducted an RCT to test a multicomponent rehabilitation programme in primary health care. In addition, to investigate effects of interventions that were comparable to the VTP, we performed a SR and meta-analysis on mindfulness- and acceptance-based intervention for patients with FM.

Thus, this thesis adds to the knowledge base regarding mindfulness- and acceptance-based intervention for patients with FM. The VTP has previously shown beneficial effects on psychological distress, pain, pain coping, and fatigue in other rheumatic diseases. Patients with FM frequently report symptoms related to these outcomes. A further rationale for this thesis was to strengthen the evidence base for nonpharmacological treatments in patients with FM and knowledge about symptom severity for these patients.

### 3 Aims and objectives

The main aim of this thesis was to evaluate the effects of a multicomponent rehabilitation programme delivered in primary health care for patients with newly diagnosed FM. The rehabilitation programme comprised the VTP plus 12 weeks of physical activity counselling at an HLC.

The specific objectives were to:

- analyse the health effects of mindfulness- and acceptance-based interventions for patients with FM and to explore content and delivery components in the interventions (paper I);
- design and implement a randomised controlled trial (paper II) and to evaluate health effects of a Norwegian mindfulness- and acceptance-based intervention followed by physical activity for patients with FM (paper III); and
- to identify groups of patients with different symptom severity trajectories and to explore differences in baseline characteristics between these groups (paper IV).

#### 4 Materials and methods

SRs and meta-analysis of well-conducted RCTs have the potential to present the best sources of evidence. If the quality of evidence were considered a pyramid, these methods would be placed at the top of a hierarchy, as illustrated in figure 1 (97).

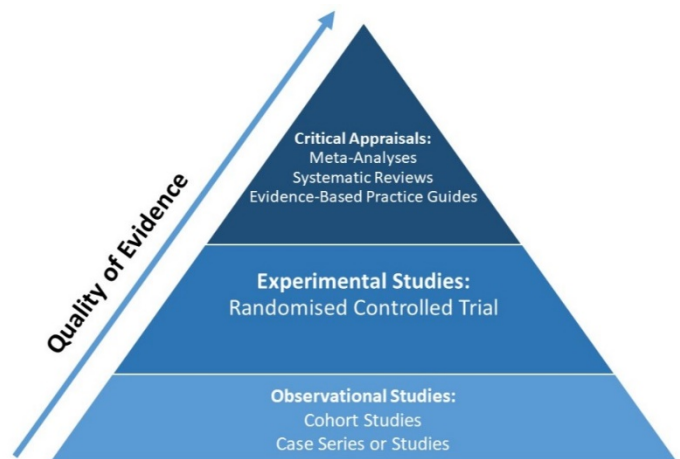
SRs are suitable for summarising empirical evidence in areas where knowledge about treatment effects is uncertain and clinical practice varies. The methods are intended to minimise bias and make the findings more accessible to health care providers, consumers, researchers, and policymakers instead of requiring reading and interpreting of many primary studies. Thus, clinicians extensively use SRs with robust and reliable findings to keep up to date within their field or as a starting point for developing clinical practice guidelines (98, 99).

Among experimental studies, well-designed and properly executed RCTs provide the most reliable evidence of the efficacy of a health care intervention (100). The practice of medicine depends on the transparent reporting of clinical trials, and a study protocol is an important document that details the background, methods, ethical considerations, and administration of an RCT (101).

An RCT is unlikely to answer all questions about an intervention. Some clinical questions may require other research methods to provide valid evidence for evaluation (102).

Observational and explorative studies can contribute to clinically relevant information that is not necessarily provided by RCTs. These studies can complement and build on the evidence base established by RCTs (103).

Several researchers have emphasised the need for clinical trials that are more generalisable to actual clinical practice, i.e., real-world conditions. The terms “explanatory” and “pragmatic” were coined in 1967 to differentiate trials (104-106). Explanatory trials are performed under ideal conditions, and interventions are evaluated in ideal and controlled settings. In a pragmatic clinical trial, researchers test the effectiveness of interventions in a



**Figure 1. The pyramid of the quality of evidence**

broad patient population, imposing fewer inclusion/exclusion criteria and choosing clinically relevant outcome measures to understand the real-world benefit of an intervention better. Thus, an intervention's real-world effectiveness will usually not be identical to that found in an explanatory trial. Most trials have both explanatory and pragmatic aspects and are placed somewhere on a continuum rather than representing a dichotomy (105, 107). The SALSA study used a pragmatic design to test the real-world effectiveness of the included interventions. Methods used in the current thesis and papers will be elaborated in this chapter.

#### 4.1 The systematic review (Paper I)

##### 4.1.1 Design

Paper I was a systematic literature review with meta-analyses of RCTs assessing mindfulness- and acceptance-based interventions for patients with FM. We used methods recommended by the Cochrane Handbook of Systematic Reviews of Interventions and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (98). A protocol was prepared and published in advance in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018081119) with specified inclusion criteria, methods, and analyses according to the PRISMA-Protocol (PRISMA-P) guidelines (108, 109).

##### 4.1.2 Data collection

The research team comprised two professionals with experience in mindfulness- and acceptance-based interventions and two methodologists. We included RCTs and quasi-RCTs on mindfulness- and acceptance-based interventions for patients with FM. A medical librarian at Diakonhjemmet developed a search strategy following the PICO structure in cooperation and consultation with the researchers, displayed in Table 3.

**Table 3. PICO for inclusion.**

PICO element	Our criteria
<b>(P) Population</b>	
<i>Included</i>	Patients diagnosed with FM according to ACR 1990 or ACR 2010 criteria, age $\geq 18$ years
<b>(I) Interventions</b>	
<i>Included</i>	Mindfulness- and acceptance-based interventions for 6 to 12 sessions of either MBSR, MBCT, or ACT; group-based or online mindfulness meditation for at least 6 weeks
<b>(C) Comparison</b>	
<i>Included</i>	No intervention, wait-list control, treatment as usual, or active interventions
<b>(O) Outcome (s)</b>	
<i>Included</i>	Pain, fatigue, sleep quality, psychological distress, depression, anxiety, mindfulness, health-related quality of life or work ability; effects categorised as end-of-treatment and follow-up scores (2 to 6 months)

#### 4.1.3 Databases

We searched MEDLINE, PsychINFO, CINAHL, EMBASE, Cochrane Central, and AMED. The search strategy was amended for each electronic database for optimal results before the search. We searched the Medical Subject Headings (i.e., MeSH terms) to find appropriate, refined, and validated search terms (Supplementary file S1 Text in paper I). We reviewed and searched the reference lists of the studies that were ultimately included and relevant reviews for additional potential eligible studies.

#### 4.1.4 Searching and selecting studies

Two researchers independently screened all titles and abstracts from the search according to the inclusion and exclusion criteria. To be eligible, the articles had to be full-text publications in peer-reviewed journals, published from the year 1990 to January 25, 2019, and written in English, Swedish, Danish, Norwegian, German, French, Spanish, or Portuguese. We obtained a full-text copy of possibly eligible articles if the abstract was deemed eligible by at least one review author and examined independently by the same reviewers. We resolved discrepancies and achieved a consensus by discussion before the final selection. When needed, we contacted authors of potential studies regarding study clarification. One reminder was sent to non-responders.

#### 4.1.5 Data synthesis and analysis

We used a structured form customised to this review to extract data from eligible studies, including general information, population, setting, methods, outcomes, and follow-up with results (Supplementary file 2 Table in paper I). One reviewer extracted the data, with quality assurance performed by a second reviewer.

We conducted meta-analyses using the Cochrane collaboration Review Manager software (110) for studies that were comparable regarding participants, interventions, comparisons, and outcomes. For this purpose, we performed and reported random-effects meta-analyses to account for the clinical and methodological heterogeneity in the studies. We used tau-squared and I-squared statistics to assess heterogeneity (111), evaluating heterogeneity according to recommendations from the Cochrane Handbook, so that 25% indicated low, 50% moderate, and 75% high heterogeneity (112, 113). The standardised mean differences (SMDs) were computed with 95% confidence intervals (CIs) for all relevant outcomes because the scales used to measure outcomes differed between the included studies. We presented the results graphically for each comparison using a forest plot based on random effects meta-analysis. The level of statistical significance was set at 5%.

#### 4.1.6 Template for Intervention Description and Replication (TIDieR)

Nonpharmacological interventions are often complex, and details are not always adequately described in trials. For this reason, clinicians may find it challenging to replicate trials and implement interventions in clinical practice (114). One aim of the SR was to explore how well the trials reported the components of the interventions, including strategies to improve or maintain intervention fidelity and adherence. Hoffmann et al. developed the TIDieR checklist as an extension of item 5 in the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement (115). We used this checklist to specifically extract and describe the reported content and delivery components in each study (Supplementary file S1 Table in paper I).

#### 4.1.7 Quality assessment

We used the Cochrane methodology for Risk of Systematic Bias (ROB) to assess the information reported in each article and the methodological quality of each study (112). To

avoid biased publications, we used ROB to assess the relevant domains, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.

Two reviewers rated each domain individually as having a low, high, or unclear risk of bias and discussed these ratings until consensus was reached (Supplementary file S1 Fig. in paper I). To make the reporting transparent, we used the Review Manager to systematise the risk of scores and inserted quotes from the articles referring to the specific domains (110). We explicitly commented on missing information from the included articles and assumed these domains as unclear.

We assessed the overall quality of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (116). We judged the evidence for each outcome in the meta-analyses as high, moderate, low, or very low. Because we included RCTs only, the rating started at high certainty and was downgraded by one or two levels of concern in one of five domains: study limitation, inconsistent results, indirectness of evidence, imprecision, and publication bias (98). We used GRADEpro to rate and summarise the certainty of the final evidence (117).

#### 4.2 The SALSA study (papers II and III)

SALSA was developed in cooperation with a project group that included a GP, a rheumatologist, a senior consultant from the community rehabilitation service in Øvre Romerike, a user representative, and a representative from the local administration in Oslo. Throughout the study, project group meetings were organised so that those involved could be consulted and informed about the study progress.



## 4.2.1 Study designs

### 4.2.1.1 Randomised controlled trial (Papers II and III)

A study protocol (Paper II) of the RCT (Paper III) was registered in BMC ISRCTN96836577 and later published in BMJ Open. A published study protocol informs the scientific community about which studies are being done, avoids duplication of studies, and better coordinates research efforts (118). Paper II was reported according to the Standard Protocol Items: Recommendations for Interventional Trials (i.e., SPIRIT) guidelines and specified all interventions in detail to enhance transparency and replicability of the RCT reported in paper III (101, 115).

RCTs provide the most reliable evidence of the efficacy of complex health care interventions (119). The strength of the design is that the randomisation procedure gives all participants the same chance of being assigned to any of the intervention groups and to be as similar as possible across groups at the start of the comparison (120). The two-armed parallel RCT in this thesis was reported according to the CONSORT guidelines to improve the reporting quality and increase transparency (100). A simplified flow chart of the study is shown in figure 2.

**Figure 2. SALSA timeline**



SALSA was conducted in rural and urban communities in the South-Eastern part of Norway, including Oslo and six neighbouring rural communities in Øvre Romerike, north of Oslo. The aim was to evaluate a multicomponent rehabilitation programme that involved several interacting components delivered by health care professionals in primary health care for patients with recently diagnosed FM. Recruitment started in fall 2016 and continued until the pre-estimated number of participants was enrolled. The interventions and data collection were in progress from March 2017 to September 2019.

#### 4.2.2 Participants

Inclusion and exclusion criteria are presented in table 4.

**Table 4. PICO for inclusion and exclusion.**

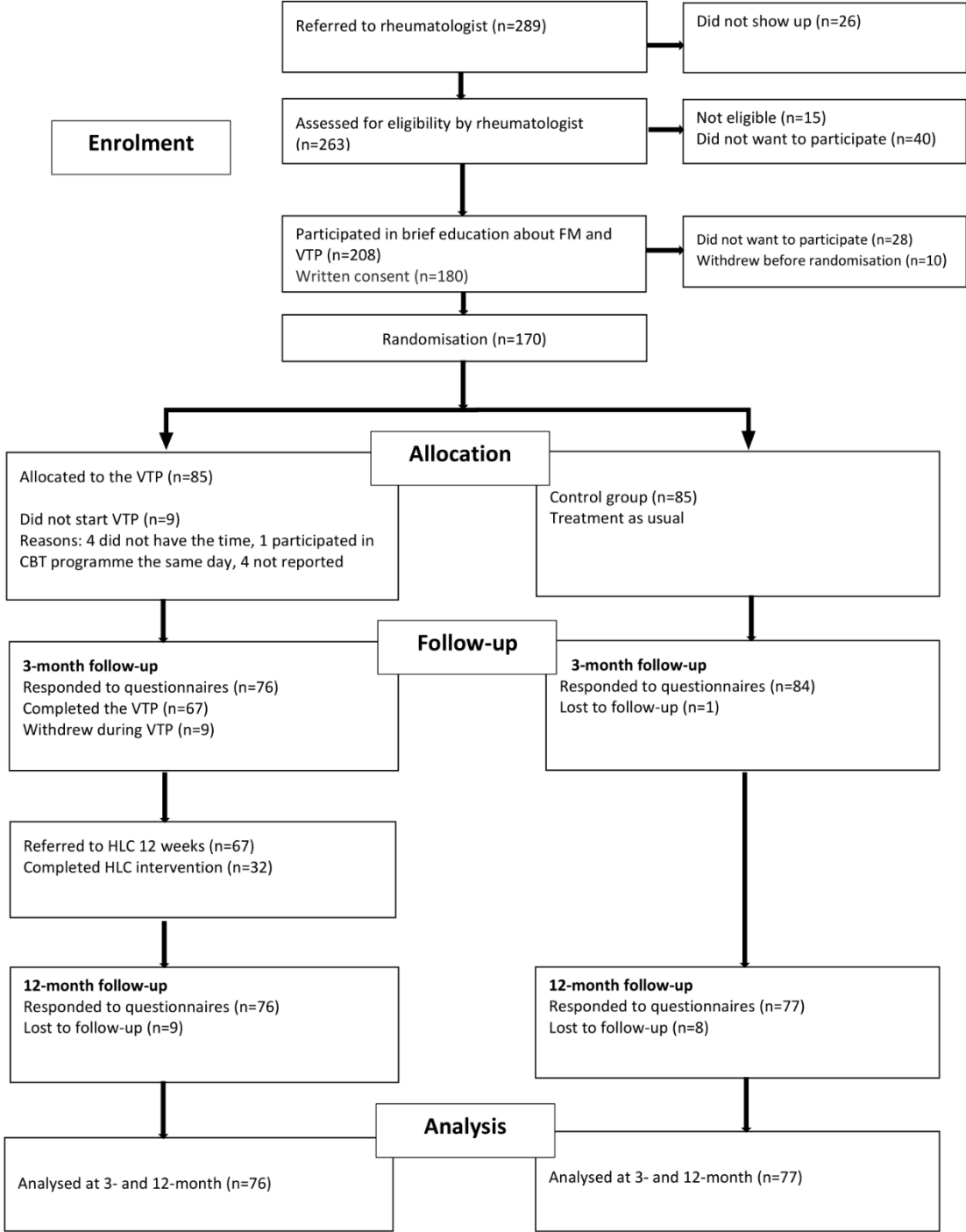
PICO element	Our criteria
<b>(P) Population</b>	
Included	<ul style="list-style-type: none"> <li>• Patients diagnosed with FM according to ACR 2010 (32)</li> <li>• Age <math>\geq</math>20 to 50 years</li> <li>• Written informed consent obtained</li> </ul>
Excluded	<ul style="list-style-type: none"> <li>• Comorbid inflammatory rheumatic disease</li> <li>• Out of work more than the 2 last years because of a pain condition</li> <li>• Serious psychiatric disorder</li> <li>• Disease that precludes physical exercise</li> <li>• Unable to understand and write Norwegian</li> </ul>
<b>(I) Interventions</b>	
	10 VTP sessions followed by physical activity counselling at a community HLC
<b>(C) Comparison</b>	
	Control group following treatment as usual
<b>(O) Outcome (s)</b>	
Included (paper III)	<ul style="list-style-type: none"> <li>• PGIC score</li> <li>• Pain, fatigue, sleep quality</li> <li>• Psychological distress</li> <li>• Mindfulness</li> <li>• Physical activity</li> <li>• Motivation and barriers of physical exercise</li> <li>• Work ability</li> <li>• Health-related quality of life</li> </ul>

#### 4.2.3 Study recruitment

The research team contacted GP offices, physical institutes, and HLCs directly in the relevant geographical areas before and during the study. We strategically approached local community leaders and GPs and encouraged them to motivate their employees and colleagues to recruit patients for the study. A flyer with study information was distributed in GP office waiting rooms and electronically on TV screens placed to reach potentially eligible patients. We scheduled presentations at regular meetings for GPs in the local communities and lunch hour meetings at GP offices to inform as many GPs and staff members as possible about the study. Two local newspapers printed interviews with the project coordinator that amplified the study information and invitation for more participants. We contacted the Norwegian Fibromyalgia Association and Norwegian Rheumatism Association to inform them about the project to reach potential patients beyond the GP offices.

Patients with widespread pain that had lasted for at least 3 months were identified and informed about the study by their GP or other recruiters. Patients who had picked up information about the study elsewhere could self-initiate participation with their GP. GPs referred interested patients to rheumatologists at Diakonhjemmet Hospital for diagnostic clarification and study eligibility assessment. Eligible and interested patients then received a letter inviting them to a 3-hour education programme and oral information about the study. The study coordinator could answer further questions and ensure that the informed consent was returned as instructed. Patients who needed more time to decide could bring their consent form home with a postage-paid return envelope. Patients were included in the study when the study coordinator received the signed consent form. Figure 3 displays the flow of study inclusion.

**Figure 3. Flow chart of participant inclusion**



## 4.2.4 Interventions

### 4.2.4.1 *The patient education programme*

A rheumatologist and a nurse invited all eligible patients to a 3-hour FM patient education programme before randomisation. The purpose was to provide basic information to the attendees about pain mechanism, psychological factors, physical activity, sleep hygiene, coping strategies, and understanding of FM. We encouraged patients to bring their partner or a relative along to share the information and knowledge. As an introduction to the methods used in the VTP, we demonstrated short mindfulness and yoga exercises. We informed the patients about the study and the timeline and that the control group would be invited to the VTP and the physical activity counselling after all study data were collected. The patients could ask questions before they consented to participate.

### 4.2.4.2 *The Vitality Training Programme*

The VTP facilitators organised and arranged the VTP groups in two communities, Jessheim in Øvre Romerike and Oslo. The VTP comprised 10 weekly 4-hour group sessions plus a booster session after about 6 months, and each group had between seven and twelve participants. The facilitators followed a manual with a thorough programme description, and every session addressed a specific topic related to living with long-lasting health challenges, as shown in table 5.

**Table 5. Topics for each VTP session.**

	Topic
Session 1	If my body could talk
Session 2	Who am I? My resources and potential
Session 3	Values—what is important to me?
Session 4	What do I need?
Session 5	Strengths and limitations
Session 6	Bad conscience
Session 7	Anger
Session 8	Joy
Session 9	Resources, potential, and choices
Session 10	If my body could talk now – and the way ahead

The facilitators invited the patients to explore these topics using various creative methods, such as music, poetry, guided imagery, drawing, and metaphors. By requiring intentional focus on emotional, cognitive, and bodily experiences, these methods provided opportunities for personal discovery. The facilitators invited the patients to maintain logs of all exercises and to share discoveries and their experiences with other group participants. Patients were encouraged to attend formal mindfulness meditation exercises, including body scan, sitting and walking meditation, and breathing exercises during the sessions. They were also provided with guided meditation audio files for practising at home between sessions. They further were encouraged to train awareness in daily activities. The VTP included gentle yoga exercises to help participants explore their physical boundaries and overcome movement barriers. Throughout the programme, patients could identify which activities were more important and healthful to them, learn how to balance activity with rest, and overcome barriers to priorities these activities.

#### *4.2.4.3 Physical exercise*

The physical activity counselling was conducted at an HLC. HLCs typically offer a 12-week programme during daytime. Interviews based on motivational interviewing, focusing on individual planning and goalsetting activities, were conducted before start-up, after 6 weeks, and at the end of week 12 (96). A physiotherapist provided physical activity counselling as part of the standard HLC interventions. Examples of activities and exercises are cycling, Nordic walking, and various group trainings customised to seasonal changes. Participants were furthered guided into exercises that they could continue after the HLC period. They also learned how to balance between activity and rest and to find the proper exercise dosage. The HLC intervention aimed to help participants set tailored goals, identify and overcome physical exercise barriers, and gradually increase their physical activity levels in mutual collaboration between the patient and the physiotherapist. The physiotherapists recorded adherence, which physical activities were performed, and any adverse events during the HLC period.

#### 4.2.4.4 Control intervention

The control group participants followed their 'treatment as usual'. The 'treatment as usual' was heterogeneous in nature and could include any management the GPs and the patients considered appropriate and any self-chosen physical activity.

#### 4.2.5 Data collection

The project coordinator registered the participants in an electronic system. Self-reported data were collected before randomisation (baseline), after the VTP (3-month), and at 12-month from baseline. Infopad© delivered an electronic solution in which participants received an e-mail with a unique link to the questionnaire at each assessment point and responded to the questionnaire on their electronic device. This risk evaluation solution followed the Code of Conduct for information security in the health care and care services (121). Patients were sent reminders over e-mail and SMS in case of non-response.

#### 4.2.6 Baseline characteristics

Baseline characteristics included sex, age, comorbidities, smoking status, education, work status, FM history in the family, and medication use.

#### 4.2.7 Outcome measures

In 2008, the Outcome Measure in Rheumatology Clinical Trials (OMERACT) recognised and recommended outcome measures for FM (122, 123). In the absence of objective measures for FM symptoms, patient-reported outcome measures are important for identifying aspects of patient health and effects of interventions (124). We have selected the included measurements according to the recommendations, in addition to measurements applied in previous research on VTP, and the aims of paper III. The 3-month assessment evaluated short-term effects of the VTP and the 12-month assessment evaluated effects of the overall multicomponent rehabilitation programme.

#### 4.2.8 Primary outcome

##### *4.2.8.1 Patient global impression of change*

We used Patient Global Impression of Change (PGIC) as the primary outcome. Patients were asked to evaluate the difference between their current and previous overall health status at 3- and 12-month follow-ups. The PGIC uses a 7-point Likert scale ranging from 1 (I feel very much worse) through 4 (no change) to 7 (I feel very much better). PGIC is considered a clinically relevant measure of overall improvement and an appropriate anchor for assessing the perceived impact of disease management (125). In our study, we considered scores of 6 and 7 to indicate clinically relevant improvements, in accordance with other studies on FM. The scores were dichotomised into 'Less than much better' (scores 1 to 5) and 'Much better' (scores 6 and 7) (126, 127).

#### 4.2.9 Secondary outcomes

##### *4.2.9.1 Pain, fatigue, and sleep quality*

We assessed pain, fatigue, and sleep quality with a numerical rating scale (NRS), which is commonly used to evaluate symptoms in rheumatic diseases (128). The scores range from 0 to 10 (best to worst) (122). Patients were asked to rate average pain, fatigue, and sleep quality over the last week at each of the three time points. For patients with chronic pain, including FM, a reduction of 1-2 points on the 0–10 NRS is interpreted as clinically important (128, 129).

##### *4.2.9.2 GHQ-12 (General Health Questionnaire-12)*

Psychological distress was assessed with the GHQ-12 (130). The questionnaire is widely used and suitable, especially in the general population in community settings and non-psychiatric clinical settings (131, 132). The original GHQ was a 60-item questionnaire designed to assess disruption in normal function and the emergence of new distressing symptoms. The GHQ-12 is a shorter version that retains many of the more extended version's desirable psychometric properties (133). Patients are asked to mark the degree to which they have experienced the designated item during the last 2 weeks compared to how they usually have felt. There are six negatively and six positively formulated questions, and each item on the scale has four



response categories from “better than usual” to “much less than usual”. The total possible scale score ranges from 0 to a maximum of 36, with higher scores indicating higher levels of psychological distress. Scores were kept as continuous for the analyses (130).

#### *4.2.9.3 EQ-5D-5L (EuroQoL 5L - health-related quality of life)*

The EQ-5D-5L (EuroQoL 5L - health-related quality of life) consists of the EQ index, also known as the EQ-5D and the EQ-VAS, and measures health-related quality of life. This scale comprises five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with three levels corresponding to no problems, some problems, and extreme problems. The patients were asked to best describe their self-perceived health that day on a 5-point Likert scale. Each health state description may be converted into a single index value (EQ-5D index score) reflecting preferences for each specific health state. The results are evaluated between 0 and 1, defining health status (0=death, 1=full health) (134). The EQ-VAS estimates generic health status using a visual analogue scale ranging from 0 (worst possible) to 100 (best possible).

#### *4.2.9.4 WPAI (Work Productivity and Activity Impairment)*

The Work Productivity and Activity Impairment (WPAI) Questionnaire is a self-administered 6-item instrument measuring work productivity loss due to general health or a specific health problem (135). It is constructed to be modified for any health problem by specifying the disease of interest in the question and has been validated for use in several diseases, including rheumatic diseases. The questionnaire assesses the impact of FM on work or other daily activities during the past 7 days (136). The six items were employment status, hours missed from work because of FM, hours missed from work for other reasons, hours worked, the degree to which FM affected work productivity while at work, and the degree to which FM affected activities outside of work. For this study, we calculated the outcomes ‘overall work impairment’ and ‘daily activity impairment’, scored on a 0–10-point scale, where 0 indicated “Health problems did not affect my work/daily activities” and 10 “Health problems completely prevented me from working/doing my daily activities” (136).

#### 4.2.9.5 FFMQ (*Five Facet Mindfulness Questionnaire*)

The Five Facet Mindfulness Questionnaire (FFMQ) was used to assess the general tendency to be mindful in daily life situations. The questionnaire is widely used and evaluated and is recommended in studies measuring the change in self-reported mindfulness over time after mindfulness-based interventions (137, 138). Trait mindfulness and mindfulness training are associated with a range of positive mental and physical health outcomes. The FFMQ can identify individuals with varying levels of trait mindfulness and provide a correlation between meditation and mindfulness (139, 140).

The questionnaire consists of 39 positively and negatively worded items characterised by five facets: 1) observing, noticing, and attending to sensations, perceptions, thoughts, and feelings; 2) describing/labelling one's experience with words; 3) acting with awareness (i.e., automatic pilot/concentration/non-distraction); 4) non-judging; and 5) non-reactivity to inner experience. Higher scores reflect more significant levels of trait mindfulness. The participants were asked to rate the degree to which several statements were true to them on a five-point Likert scale ranging from 1 (never or very rarely true) to 5 (very often or always true). The scale was reversed for negatively phrased items (137). Higher scores in FFMQ reflect more significant levels of mindfulness and are predictive of positive thinking, an overall uplifted mood, and subjective feelings of well-being (140, 141). Data were analysed and reported as a mean sum score, comprising all five facets (paper III).

#### 4.2.9.6 *Physical activity*

Three questions from the first wave of the Nord-Trøndelag Health Study (known as HUNT1) assessed physical activity, particularly leisure-time physical exercises that improve physical fitness, exemplified as walking, skiing, swimming, or other training/sport activities (142). The exercises were assessed according to frequency, intensity, and duration. If participants exercised  $\geq 1$  time per week, they continued to question two: "How hard do you push yourself?", which was rated as "I take it easy without breaking into a sweat or losing my breath", "I push myself so hard that I lose my breath and break into a sweat", or "I push myself to near-exhaustion". The average duration was rated as less than 15 minutes, 16–30 minutes, 30 minutes to 1 hour, or more than 1 hour. Each response had specified scores used when calculating the summary index of the frequency, intensity, and duration scales

(numbers for frequency [0, 0.5, 1, 2.5, 5], intensity [1, 2, 3] and duration [0.10, 0.38, 0.75, 1.0] indicate the scores used for each response when calculating the summary index). The physical activity scale ranges from 0–15, and higher scores indicate increased physical activity (142).

#### *4.2.9.7 Motivation for and barriers to physical activity*

The Exercise Beliefs and Exercise Habits questionnaire assessed motivation for and barriers to physical activity, comprising 20 items scored on a five-point Likert scale ranging from “strongly agree” to “strongly disagree” to indicate respondent beliefs. The items are divided into four sub-scores calculated and reported separately as beliefs about one’s ability to exercise (self-efficacy for exercise), barriers to exercise, benefits of exercise, and impact of exercise on muscular pain. Each item was calculated and reported separately (143).

#### *4.2.9.8 Harm at 12 months*

The questionnaire at 12 months included a question about harm. The patients were asked if they had experienced any harm because of the treatment. If the response was “yes”, the patients were asked to specify the event and report adverse events and associated major symptoms.

#### *4.2.10 Sample size and power calculation (paper III)*

We calculated sample size and power before the recruitment estimated for the primary endpoint of the study of patient-reported change, measured with the PGIC at 12-month of follow-up. We estimated that 10% in the control group would report that they felt “much better or very much better” after 12 months. At least a 20% absolute difference in improvement rate between the groups would be considered a minimum clinically relevant difference. With allowance for 10% loss to follow-up, we needed 70 participants in each group to have at least 80% power for detecting a difference at a 5% alpha level.

#### *4.2.11 Randomisation and blinding*

A statistician generated an electronic randomisation list for each geographical area. An administrative assistant not involved in data collection or the intervention successively

numbered patients. After that, each patient was allocated to the corresponding number of the randomisation list. The assistant organised equal groups in the two geographical areas and informed patients about group allocation by written letter and telephone. It was not possible to blind patients or health professionals because of the nature of the study.

Attrition bias may occur if patient data are missing because of loss to follow-up or incomplete data collection (144). Early in the process of the RCT, we experienced that participants dropped out after randomisation. We assumed that if the period between the patient education programme and randomisation was protracted, information details could have been forgotten. To prevent unnecessary and further dropouts, we introduced a mandatory information meeting before each randomisation. Everyone received refreshed study information regardless of how long it had been since the first information meeting, thus reducing the dropout after randomisation. The losses to follow-up were within our assumption of 10%. Furthermore, there was a high follow-up rate, with 76 (89%) patients in the intervention group and 77 (90%) patients in the control group completing the data collection at the 12-month follow-up, reducing the chance for attrition bias.

#### 4.2.12 Statistical methods

We presented patient baseline characteristics as descriptive statistics. Mean and standard deviation (SD) or frequency and percentage were displayed, as appropriate. We set the level of statistical significance at 5% for all relevant statistical analyses. STATA IC 14 was used in the analyses (145).

We presented continuous baseline variables as means with SDs if values were normally distributed or as medians with minimum and maximum values if the data had a skewed distribution. For categorical variables, percentage and frequency distributions were presented. We performed independent sample t-tests on two-group comparisons of normally distributed continuous baseline variables or independent sample median tests (i.e., the Mann–Whitney U test) when comparing skewed variables. If any cell had less than five entries, we used Pearson’s Chi-Square test to compare categorical variables or Fisher’s exact test.

We evaluated the effects of the multicomponent rehabilitation programme on an intention-to-treat basis, with randomised patients retaining their original allocation groups at 12-

month to provide the most realistic and unbiased answer to the question of clinical effectiveness (146).

The primary outcome (PGIC) was dichotomised, and between-group differences were tested using Chi-square statistics and Fisher's exact tests for any cell with less than five entries. For continuous secondary outcomes, we performed analysis of covariance (ANCOVA) at the 12-month follow-up, adjusted for baseline values.

#### *4.2.12.1 Analysis of covariance (ANCOVA)*

We used ANCOVA to estimate treatment effects in secondary outcomes at the 3- and 12-month follow-up adjusted for the baseline values. We used STATA V.14.0 to analyse the data (145). In effect, ANCOVA adjusts each patient's follow-up score against the baseline score but with the advantage of being unaffected by baseline differences. As an example, if by chance baseline scores are worse in the intervention group, because of regression to the mean, the treatment effect would be underestimated in a follow-up score analysis and overestimated by looking at change scores. ANCOVA gives the same answer regardless of baseline imbalance. An additional advantage of ANCOVA is that it generally has great statistical power to detect a treatment effect (147). The level of statistical significance was set to  $\leq 0.05$ .

#### *4.2.12.2 Missing data*

All analyses were performed on available data except for missing values in single items of FFMQ and GHQ-12. These missing values were imputed by calculating the mean value of the registered values multiplied by the number of questions.

### 4.3 Observational exploratory study (paper IV)

#### 4.3.1 Study design

Paper IV was an observational exploratory study. This research design is suitable when the purpose is to seek new insights into a phenomenon with little or no previous research (103).

#### 4.3.2 The study participants

Participants in this study were the same patients included in the RCT (n=170). The patient participant data used in paper IV were self-reported at referral to specialist health care (pre-baseline) and after that collected electronically using the same electronic solution as in the RCT, at baseline, 3-month, and 12-month. The total follow-up time spanned 13 and 18 months because the time from pre-baseline to baseline differed among the patients.

#### 4.3.3 Baseline characteristics

Baseline characteristics included age, sex, disease duration, number of comorbidities, education, and marital status.

#### 4.3.4 Outcome

The outcome used in this study was the PDS, which measures the magnitude and severity of FM symptoms (32, 36). PDS comprises two subscales, the WPI and the SSS. The WPI score is the number of 19 possible regions selected for self-reported pain from the Regional Pain Scale (range 0–19). The SSS score (range 0–12) is the sum of the severity scores for three symptoms (fatigue, sleep, and cognitive problems) (range for each 0–3) and the number of the following three symptoms that have bothered the patient during the previous 6 months: 1) headaches, 2) pain or cramps in the lower abdomen, and 3) depression.

The maximum PDS score is 31, with higher scores representing greater severity. The cut-off for FM diagnosis is a PDS score  $\geq 12$  (32, 33, 35). Furthermore, the symptom severity may be categorised according to the PDS score as none (0–3), mild (4–7), moderate (8–11), severe (12–19), or very severe (20–31) (36). The PDS has been translated and validated in several languages, including Norwegian (148).

#### 4.3.5 Statistical methods

Baseline characteristics in paper IV were presented as descriptive statistics. Mean and SD or frequency and percentage were displayed as appropriate. The level of statistical significance was set at 5% for all relevant statistical analyses. Stata v16 was used to analyse the data (149).

The latent class growth analysis (LCGA) was used to identify groups of patients with different symptom severity trajectories based on their responses to the PDS at the four time points. The number of trajectory groups was determined first through estimation of a sequence of models. The LCGA started with one group suggesting one type of group fitting for all patients. More trajectory groups were added one after another, each with a different number of groups, and the model was re-estimated. We used the Bayesian Information Criterion to determine which model best fit the data (150). The mean response in each group was estimated by treating time as a categorical variable. The group-specific error covariance matrix was estimated in three ways, as diagonal, commutative, or unstructured. The selected error covariance matrix was also based on the Bayesian Information Criterion (151). We used the gsem function in Stata v16 (149) to perform the LCGA. Each patient was assigned to a most likely trajectory group to identify differences in baseline characteristics between PDS trajectory groups. This assignment was determined using a posterior class probability estimate based on the four time points. Then, to compare baseline characteristics, we used two-sample t-tests and Chi-square tests as appropriate. Baseline characteristics and outcome measures applied in papers III and IV are summarised in table 6.

**Table 6. Summary of the included baseline characteristic and outcomes.**

Baseline characteristics and outcome measures included in papers III and IV			
Baseline characteristics	Scale	Paper III	Paper IV
Age	Years	X	X
Sex	Female	X	X
Intervention group	Intervention/control		X
Symptom duration	Years	X	X
Number of comorbidities	Yes/no, number	X	X
Education	Equal to or less/more than 12 years	X	X
Work status	In paid work/not in paid work	X	
Marital status	Married/living with partner	X	X
Symptom duration	Years	X	X
Comorbidities, median (min, max)	Yes/no, years	X	X
Smokers	Yes/no	X	
FM in family	Yes/no	X	
Use of medication in last 3 months	Yes/no	X	
<b>Outcome measures</b>			
Patient global impression of change	1 (I feel very much worse) through 4 (no change) to 7 (I feel very much better)	X	
Pain, fatigue, and sleep quality (NRS)	0 to 10 (best to worst)	X	
Psychological distress (GHQ-12)	(GHQ-12, mean sum score, 0–36, 0=no distress)	X	
Five Facet Mindfulness Questionnaire (FFMQ)	Mean sum score, 39–195, low to high	X	
Physical activity	(0–15, 0=inactive)	X	
Motivation for and barrier to physical activity	Likert scale “strongly agree” to “strongly disagree” in four sub-scores	X	
Work Productivity and Activity Impairment (WPAI)	Work impairment and daily impairment scored from 0–10, 10=completely impaired	X	
Health-related quality of life (EQ-5D-5L)	Index (0-1; 1=perfect health), VAS (0–100; 100=as good as it could be)	X	
Polysymptomatic distress scale	0–31, low to higher symptom severity		X
Harms	Yes/no	X	

NRS=Numeric Rating Scale; GHQ-12=General Health Questionnaire; VAS=visual analogue scale

#### 4.4 Ethical considerations

The Regional Committee for Medical and Health Research Ethics approved the study design, information strategy, written consent formula, and data security (2015/2447/REK sør-øst A). The study was conducted in accordance with the principles of the Helsinki declaration (152). The study was registered at BMC ISRCTN96836577 before the study start.

All participants received written information from the rheumatologist about the study procedures and were informed orally and as part of the patient education programme. All eligible patients who were willing to participate in the study signed informed consent. All patient participants were offered the multicomponent rehabilitation programme, including the control group after the 12-month data collection was completed. Thus, no patient received care below the current standard of each local HLC. The patients were asked to report any experienced harm or treatment side effects during the study.



Patient research partners were involved during the study, both as advisors and by testing the study questionnaire before the data collection.

## 5 Summary of study results

### 5.1 Mindfulness- and acceptance-based interventions for patients with fibromyalgia – a systematic review and meta-analyses (Paper I)

The objectives of this study were to analyse the health effects of mindfulness- and acceptance-based interventions and to explore content and delivery components in the included interventions.

The search identified 4430 papers as potentially relevant. Twenty-five of these were screened in full text. Nine met the inclusion criteria and were included in the study, all published between 2003 and 2018 (27, 153-160). The studies comprised a total of 750 patients with FM. Seven studies diagnosed FM with ACR 1990 classification criteria, and two studies relied on the ACR 2010 diagnostic criteria. The mean age ranged from 40 to 53 years. The proportion of females ranged from 95% to 100%. Health care contacts recruited study patients through media advertisements and primary and secondary health care. We pooled predefined outcomes in a meta-analysis.

Of the nine included studies, four delivered MBSR (27, 154, 155, 158), one study delivered MBCT (157), three used ACT (156, 159, 160), and one combined mindfulness meditation and qigong movement therapy (153). Eight studies delivered the interventions in groups, and one study delivered an internet-based intervention. The follow-up period varied among the studies from 2 to 6 months after the end of treatment. They reported and assessed adherence and fidelity differently. Five studies described strategies of adherence and fidelity, two studies monitored adherence and provided a reminder phone call to absent participants, one study sent reminder e-mails, one study both provided a summary of the session to participants who were unable to attend and video recorded the instructors' activities in the session, and one study video recorded and reviewed each session to assess if the instructor followed the treatment manual. All but one study reported adherence above 80%. Excluded studies and reasons for exclusion are reported in Supplementary file 3 Table in paper I.

The meta-analyses, generating SMDs with 95% CIs, showed small to moderate pooled effects in favour of mindfulness- and acceptance-based interventions at the end of treatment for pain (SMD -0.46 [95% CI -0.75, -0.17]), depression (SMD -0.49 [95% CI -0.85, -0.12]), anxiety (SMD -0.37 [95% CI -0.71, -0.02]), sleep quality (SMD -0.33 [95% CI -0.70, 0.04]), health-

related quality of life (SMD -0.74 [95% CI -2.02, 0.54]), and mindfulness (SMD -0.40 [95% CI -0.69, -0.11]). All effect sizes decreased except for anxiety, for which there was a small increase in effect size at follow-up. We graded the certainty of the evidence as very low to moderate.

In conclusion, overall, we found small to moderate uncertain effects on pain, anxiety, depression, health-related quality of life, sleep quality, and mindfulness for female patients with FM compared to controls.

#### 5.2 Effects of a community-based multicomponent rehabilitation programme for patients with fibromyalgia: protocol for a randomised controlled trial (Paper II)

Paper II is a peer-reviewed protocol. The aim was to design and implement an RCT to evaluate the effects of a multicomponent rehabilitation programme for patients with FM. The protocol presents the aims, informs about the background of the trial and its Norwegian context. Furthermore, the inclusion and exclusion criteria were presented. Additionally, the protocol presented the methodology, including primary and secondary outcomes, and statistical analyses.

#### 5.3 Effects of a mindfulness- and acceptance-based group programme followed by physical activity for patients with fibromyalgia: a randomised controlled trial (Paper III)

The aim of this RCT was to evaluate the effects of a multicomponent rehabilitation program for patients with recently diagnosed FM.

In total, 170 patients with FM were randomised, 85 to the intervention and 85 to the control group. Except for median age (44 years in the intervention group and 41 years among controls;  $p=0.02$ ), the two groups matched well at baseline on demographic, disease variables, and all outcome measures. The  $p$  values ranged from 0.05 to 0.94.

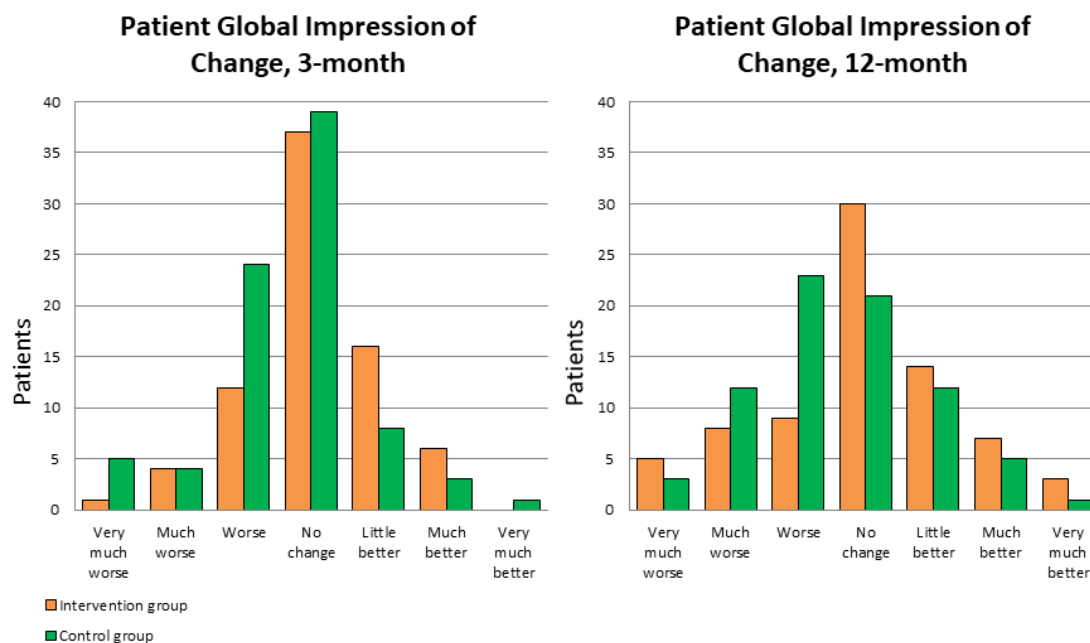
The average attendance rate in the VTP was 7.5 sessions. In total, 75 patients attended the VTP, and 67 (89%) completed five sessions or more; 21 (31%) of these patients completed all ten sessions, 20 (30%) completed nine, and nine (13%) completed eight sessions. Thirty-two patients (43%) attended the physical activity intervention after the VTP, but only a few completed the full 12-week programme.

Of 170 patients, 160 (94%) completed the data collection at 3-month and 153 (90%) at 12-month.

Analyses of the primary outcome, PGIC, showed no statistically significant differences between the intervention and control groups at the 3- and 12-month follow-ups when the PGIC was dichotomised ( $P=0.28$ ).

At the 12-month follow-up, 13% in the intervention group reported clinically relevant improvement in PGIC, i.e., 'Much better,' or 'Very much better' compared to 8% in the control group. We found statistically significant differences between groups in distribution at the 3-month follow-up ( $p=0.01$ ) but not at the 12-month follow-up ( $p=0.06$ ) (Figure 4).

**Figure 4. PGIC at the 3- and 12-month follow-ups**



No statistically significant differences were found between the groups at the 12-month follow-up in any disease-related secondary outcomes. However, there was a statistically significant improvement in favour of the intervention group in 'tendency to be mindful'. Moreover, because of a slight worsening in the control group, there was a statistically significant difference between groups in 'perceived benefits of exercise' (Table 7).

**Table 7. Secondary outcomes in paper III.**

		<b>Intervention (n=76) Mean (SD)</b>	<b>Control (n=77) Mean (SD)</b>	<b>Baseline-adjusted mean difference (95% CI)</b>	<b>P</b>
<b>Pain (NRS 0–10, 0=no pain)</b>					
	Baseline	6.7 (1.6)	6.8 (1.9)	-	-
	3 months	6.4 (1.7)	6.6 (1.8)	0.30 (-0.15 to 0.75)	0.19
	12 months	5.8 (2.1)	6.4 (1.8)	0.55 (-0.00 to 1.11)	0.05
<b>Fatigue (NRS 0–10, 0=no fatigue)</b>					
	Baseline	7.5 (2.0)	7.4 (2.0)	-	-
	3 months	7.2 (1.9)	7.1 (2.2)	-0.03 (-0.60 to 0.54)	0.92
	12 months	6.8 (2.3)	6.8 (2.3)	0.12 (-0.56 to 0.80)	0.72
<b>Sleep (NRS 0–10, 0=no sleep)</b>					
	Baseline	6.8 (2.3)	7.1 (2.5)	-	-
	3 months	6.6 (2.5)	6.9 (2.5)	0.27 (-0.42 to 0.97)	0.44
	12 months	6.5 (2.5)	6.3 (2.5)	-0.24 (-0.99 to 0.50)	0.52
<b>Psychological distress (GHQ-12, mean sum score, 0–36, 0=no distress)</b>					
	Baseline	16.5 (6.6)	19.2 (6.8)	-	-
	3 months	13.4 (6.5)	16.5 (7.0)	1.57 (-0.37 to 3.50)	0.11
	12 months	14.8 (6.8)	16.6 (6.9)	1.03 (-1.08 to 3.14)	0.34
<b>Five Facet Mindfulness Questionnaire (Mean sum score, 39–195, low to high)</b>					
	Baseline	119 (17.2)	113 (16.9)	-	-
	3 months	124 (19.1)	118 (16.3)	-1.07 (-4.73 to 2.58)	0.56
	12 months	126 (17.6)	118 (16.3)	-4.72 (-8.57 to -0.9)	0.02
<b>Physical activity (0–15, 0=inactive)</b>					
	Baseline	3.0 (2.4)	2.8 (1.8)	-	-
	3 months	2.3 (1.6)	2.7 (1.9)	0.53 (-0.04 to 1.10)	0.07
	12 months	2.9 (2.3)	2.8 (1.8)	0.10 (-0.60 to 0.79)	0.78
<b>Motivation for and barriers to physical activity</b>					
<i>Self-efficacy (4–20, low to high)</i>					
	Baseline	12.0 (2.9)	12.0 (3.2)	-	-
	3 months	12.5 (3.1)	12.6 (3.1)	0.08 (-0.70 to 0.86)	0.84
	12 months	13.1 (3.5)	12.8 (3.1)	-0.33 (-1.27 to 0.62)	0.50
<i>Barriers (3–15, low to high)</i>					
	Baseline	12.1 (2.4)	12.1 (2.0)	-	-
	3 months	11.8 (2.3)	11.8 (1.9)	-0.00 (-0.48 to 0.47)	0.99
	12 months	12.2 (2.4)	12.2 (1.7)	-0.07 (-0.61 to 0.46)	0.79
<i>Benefits (5–25, low to high)</i>					
	Baseline	20.4 (3.2)	21.1 (2.7)	-	-
	3 months	20.3 (3.0)	20.4 (2.7)	-0.19 (-0.89 to 0.50)	0.59
	12 months	20.7 (3.0)	20.1 (2.9)	-0.90 (-1.73 to -0.07)	0.03
<i>Impact (8–40, low to high)</i>					
	Baseline	28.8 (4.6)	29.0 (4.8)	-	-
	3 months	28.4 (4.8)	28.5 (4.3)	0.08 (-0.90 to 1.06)	0.87
	12 months	28.9 (5.4)	28.3 (4.6)	-0.49 (-1.63 to 0.65)	0.40
<b>Work Productivity and Activity Impairment General Health</b>					
<i>Work impairment (0–10, 10=completely impaired)</i>					
	Baseline	5.2 (2.5)	6.2 (2.2)	-	-
	3 months	5.1 (2.4)	5.4 (2.5)	-0.15 (-1.05 to 0.76)	0.75
	12 months	4.9 (3.2)	5.3 (2.9)	0.73 (-0.58 to 2.03)	0.27
<i>Daily activity impairment (0–10, 10=completely impaired)</i>					
	Baseline	7.0 (2.0)	7.1 (1.9)	-	-
	3 months	6.9 (1.7)	6.7 (2.3)	-0.25 (-0.83 to 0.34)	0.41
	12 months	6.3 (2.5)	6.5 (2.2)	0.07 (-0.65 to 0.79)	0.84
<b>EQ-5D-5L</b>					
<i>Index (0-1, 1=perfect health)</i>					
	Baseline	0.51 (0.2)	0.47 (0.2)	-	-
	3 months	0.55 (0.2)	0.53 (0.2)	0.02 (-0.05 to 0.09)	0.86
	12 months	0.54 (0.2)	0.50 (0.2)	0.04 (-0.03 to 0.11)	0.48
<i>VAS (0–100, 100=as good as it could be)</i>					
	Baseline	44.6 (16.5)	41.61 (17.0)	-	-
	3 months	46.4 (16.1)	51.5 (21.7)	-5.1 (-12.10 to 1.90)	0.03
	12 months	49.0 (20.6)	46.8 (18.5)	2.19 (-4.67 to 9.05)	0.77

NRS=Numeric Rating Scale; GHQ-12=General Health Questionnaire; EQ-5D-5L=Health-related quality of life

In conclusion, the multicomponent rehabilitation programme combining recent diagnosis and patient education with a mindfulness- and acceptance-based intervention followed by

physical activity was not more effective than recent diagnosis, patient education, and treatment as usual for patients with FM.

#### 5.4 Trajectories of change in symptom severity in patients with fibromyalgia: exploratory analyses of a randomised controlled trial (Paper IV)

This aim of this study was to identify groups of different PDS trajectories and to explore differences in baseline characteristics between these groups.

The study participants were the same patients included in the RCT, for a total of 170 patients with a mean age of 40 (SD 7.1) years, and approximately 94% were women.

A high mean PDS score was found throughout the study period. When analysing the PDS trajectories, we identified two distinct groups of PDS trajectories, with 65% of the patients classified into a group designated as “no improvement”, and 35% classified into a second group designated as “some improvement”.

At pre-baseline, the mean scores in both trajectory groups fell within the PDS category “very severe.” In the “some improvement” group, there was a stepwise decreasing proportion of patients in the category “very severe,” showing a continuous improvement across the time points. At the 12-month follow-up, 15 patients reported a PDS score <12.

The analyses showed no statistically significant differences in baseline characteristics between the two groups of PDS trajectories. However, 57% in the “some improvement” group had been randomised to the intervention group compared to 46% in the “no improvement” group ( $p=0.26$ ).

In conclusion, our findings showed individual fluctuations in symptom severity over the study period. We identified two groups of symptom trajectories, one group that improved slightly during the study period and one group with no improvements. We found no differences in baseline characteristics between the two groups.

## 6 Discussion

### 6.1 Methodological aspects

Studies were conducted and reported according to recommended guidelines for each study design to reduce the risk of bias and enhance the reliability and external and internal validity of the results (100, 115, 161).

#### 6.1.1 Study designs

In this thesis, the included study designs were chosen to investigate different aspects of relevance to the overall aims (162). Three designs were used: a systematic review with meta-analysis, a randomised controlled design, and an observational exploratory design.

##### *6.1.1.1 The systematic review*

SRs with meta-analysis of RCTs are used to estimate accumulated effects of interventions that may not be detected in individual RCTs. Methods used in SRs aim at minimising bias and providing robust and reliable findings (98, 163). Furthermore, SRs may adjust for small sample sizes and broaden the capacity to test hypotheses and detect effect patterns (164). Because there has been an increased number of published studies on mindfulness- and acceptance-based interventions for patients with FM, a SR was considered appropriate to address the first aim of this thesis. Its value depends on the reporting quality and clarity of the included studies. Poorly reported intervention details in trials will limit the reproducibility and usability of systematic reviews (165). We intended to explore this matter and used the TIDieR checklist to extract, describe, and report the content and delivery components in the included interventions to increase replicability and transparency of our results (115).

To avoid unintended duplication of our review, we predefined and reported the methodology in a study protocol that was registered in PROSPERO (108). The prospective registration also allowed readers to see how the review had developed or changed over time, promoting transparency (166, 167). The report followed the PRISMA guidelines, thus strengthening the internal and external validity (161).

### *6.1.1.2 The randomised controlled trial*

The RCT was designed to evaluate effects of the multicomponent rehabilitation programme. The randomisation distributes known and unknown factors among control and intervention groups, thus reducing the potential for confounding. To ensure concealed allocation, a statistician generated an electronic randomisation list and an administrative assistant with no other study involvement allocated patients successively to the randomisation list.

Reporting bias may occur because of selective reporting of outcomes (168). To reduce the risk of reporting bias, we registered the trial in the International Standard Randomised Controlled Trial register (ISRCTN 96836577). In addition, a study protocol was published to inform readers about the pre-planned study design, randomisation procedure, outcome measures, and data analysis (paper II). This transparency strengthened the reliability of the study and reduced the risk of reporting bias (118). The study protocol was based on selected elements of the updated EULAR recommendation for management of FM, such as prompt diagnosis, patient education, and physical activity. Furthermore, the EULAR recommendations state that cognitive-behavioural interventions might be beneficial for managing pain and developing helpful coping strategies. In this study, we have chosen to test the effects of a mindfulness- and acceptance-based behavioural intervention developed in a Norwegian context and that has shown beneficial effects in other groups of patients with musculoskeletal pain.

Patients and health professionals were not blinded to group allocation in our trial. In pragmatic randomised controlled trials including interventions with a psychoeducational approach, blinding of patients and personnel is usually not possible (169). Lack of blinding may increase the risk of performance bias and influence trial outcomes, and unblinded studies thus will always carry an overall risk of bias (98).

### *6.1.1.3 The observational exploratory study*

We used an observational exploratory study design in paper IV to further examine individual fluctuations in symptom burden among participants in the RCT. An observational study design is suitable when the goal is to describe and explore the health profile of a population (170). The rationale for these analyses was to identify groups of patients with different



symptom trajectories based on PDS scores at four time points. In addition, we explored differences in baseline characteristics between groups with different trajectories.

## 6.1.2 Study sample

### *6.1.2.1 The systematic review*

We included only randomised or quasi-randomised controlled trials in the SR. Most RCTs exclude certain categories of patients, and too-restrictive inclusion criteria might introduce selection bias as participants can become uncharacteristic and not representative for a patient population. Study participants may also receive more attention and better care regardless of their trial arm. These methodological dilemmas can threaten the generalisability and external validity of the results (171). The patients in our SR were recruited from both primary and secondary health care, increasing the external validity of the findings, although limited to the United States and Europe. To strengthen the internal validity of our results, we included patients diagnosed with FM according to the ACR 1990 or ACR 2010 criteria. The vast majority of the 750 included participants were women, and as such our results may not be applicable to men. However, this sex difference is found in other studies and may reflect the FM population (154, 156, 159).

In the SR, two independent reviewers used the ROB to evaluate the quality of evidence in each of the included trials and found overall low risk of bias in the included studies. The domain associated with a high risk of bias was blinding of participants and personnel, which may involve an overall increased bias risk (112). Other domains associated with bias risk for the studies included incomplete outcomes, such as drop-out or a high number of patients who did not complete the intervention. Although the overall risk of bias was rated as low, there will always be the potential for biased conclusions when some domains are associated with risk of bias, consequently reducing the reliability of our results.

### *6.1.2.2 The randomised controlled trial*

The patient population included in our RCT was comparable to other relevant RCTs on patients with FM regarding age and sex distribution (27, 153, 154, 156). When comparing women and men in the Norwegian population, FM is more common in women (39).

Between the ages of 20 to 55 years, the most common cause of generalised, musculoskeletal pain in women is FM (172). Because we assumed that higher age might be associated with more comorbid conditions, we defined 50 years as the upper age limit for inclusion. The intervention group had a significantly higher median age than the control group. Although the difference was small, we cannot rule out that it may have affected the results.

We intended to evaluate if participants could retain and improve their work ability, and 70% of the included patients were in paid work at baseline. A previous study suggested that multidisciplinary health care interventions should support FM patients in identifying their internal and external resources as well as promoting their development of personal skills to manage work (173). We assumed that patients with longer sick leave periods because of FM symptom severity would face difficulties in returning to work (174). We therefore excluded patients who had been out of work for more than 2 years because of their pain condition. Thus, the included participants may not be representative for the total FM patient population in Norway. The nature of the intervention also introduced another possible threat to the generalisability of the study sample. Some patients may have found the multicomponent rehabilitation programme to be too comprehensive and time-consuming. The included patients were probably a highly motivated group who were willing to invest time and effort in participation and who recognised their need for the programme. However, to strengthen the representativeness in our study, patients were recruited from both urban and rural areas and from primary and secondary health care. All patients were screened for eligibility by a rheumatologist before inclusion, and they had to fulfil the ACR 2010 diagnostic criteria for FM (148). Only two rheumatologists were involved in the screening.

### 6.1.3 Data collection

#### *6.1.3.1 The systematic review*

The validity of a SR depends on the completeness and relevance of the included studies. A strength of our SR was a comprehensive literature search thoroughly prepared in collaboration with both topic and methodological experts, and with a medical librarian who also performed the search. The search strategy was amended for each electronic database for optimal results before the search. In addition, the references in the full-text papers were

hand-searched for relevant studies. The study selection was based on pre-defined eligibility criteria. We assessed the ROB and quality of evidence using recommended tools (112, 116). These elements minimised the risk of bias for our SR. We conducted a comprehensive search including English, Swedish, Danish, Norwegian, German, French, Spanish, and Portuguese languages. Nevertheless, we may have missed relevant studies published in other languages. Publication bias may also have influenced the selection of studies because peer-reviewed journals tend to publish studies with positive outcomes and authors are more likely to publish positive results (175). We contacted five authors to clarify diagnostic criteria and randomisation procedures. Three authors did not respond, but two authors provided the requested information.

#### *6.1.3.2 The randomised controlled trial*

The data were collected by electronic questionnaires that were completed by the patients on a smartphone, tablet, or personal computer. The patients received an email with a unique link to the questionnaire at each assessment point. The solution was delivered by Infopad (<http://www.infopad.no>), was risk evaluated, and followed the highest security requirements (121). Although the questionnaire was pilot tested by user representatives, we cannot exclude a potential influence on data quality arising from patient ability to understand questions, symptom severity, mood and emotional reactions, or other difficulties they may have experienced during completion because of low health literacy. However, the number of losses to follow-up was low, and the response rate was high throughout the study.

#### *6.1.3.3 The observational exploratory study*

In this study, the outcome measures were self-reported at referral to specialist health care with pen and paper (pre-baseline) and electronically collected from baseline. A systematic review investigated the equivalence of paper and electronic administration of questionnaires in a variety of diagnoses. They found that data obtained from electronic questionnaires were comparable to those from paper questionnaires (176). These findings were supported by a randomised cross-over study for patients with FM (177). We do not believe the combination of paper and electronic questionnaire had any major impact on the

quality of the retrieved data. A strength of this study was that we repeatedly measured the included outcomes over a relatively long period with a high response rate.

#### 6.1.4 Outcome measures

Each patient included in a clinical trial is unique and may therefore experience different benefits or side effects from the same treatment. To get a broader view of interventions for patients with FM, it might be necessary to include a range of outcome measures in studies exploring nonpharmacological interventions (178).

In both the SR and the RCT, we included outcomes that were selected according to a core set of FM defined by the OMERACT, as well as from previous RCTs evaluating the VTP, and mindfulness- and acceptance-based interventions (22, 81, 179). These inclusions ensured that formally recommended and relevant outcome measures were used for the studies in this thesis. We categorised effects as end-of-treatment (3-month follow-up) and follow-up scores (12-month follow-up).

##### *6.1.4.1 Primary outcome in the RCT, Patient Global Impression of Change (PGIC)*

Our RCT was designed to detect a difference between patients who reported clinically relevant improvement in self-perceived health and those who did not, based on a pre-defined dichotomisation of the PGIC scale. The PGIC was dichotomised to provide a more clinically meaningful estimate of self-perceived impression of change compared to changes in response to, for instance, rating of FM symptom intensity. Compared to a mean change in groups of patients, the proportion of patients who report a certain change may be easier to interpret in a clinical context.

The PGIC has been used in other clinical trials testing effects of treatment for chronic pain, including FM (126, 127, 180). It has been easy to use for patients and allows them to include which construct they perceive to be most important in their health status. The latter may also be a limitation because the difference in FM aspects could render comparisons among patients problematic. There is also a risk of recall bias because of long follow-up periods. The optimal time to minimise recall bias is not established (125). A longitudinal, single-cohort observational study examined the influence of the recall period length on the validity of

global ratings of change. The results showed that patients followed for up to 6 months rated their disease as having less improvement compared to patients with shorter follow-up experiencing similar changes in disease severity measures (181). We assessed the overall PGIC, and the follow-up time between the two final timepoints was approximately 9 months. It is likely that patients could have reprioritised the importance of certain FM symptoms over time. This shift in perspective may have influenced the PGIC scoring.

#### *6.1.4.2 Secondary outcomes*

In clinical trials combining multiple components, reporting more than one outcome may be appropriate because a single measure may not sufficiently characterise the effect of holistic and multicomponent treatment (182-184). Secondary outcomes are commonly used in clinical trials evaluating multicomponent interventions (182). The 11-point NRS scales of patient perception of pain, fatigue, and sleep quality used in paper III have shown high usability in other studies (185). GHQ-12 assessment of overall psychological distress was sensitive to change in a previous RCT evaluating the VTP (81) and is relevant to exploring psychological distress in patients with FM (186). Furthermore, GHQ-12 was reported to be a consistent and reliable instrument when used in a general population sample with relatively long intervals between applications (187). Possible limitations to the use of GHQ-12 are that we could not detect separate changes in anxiety and depression, and that patients might find it difficult to consider what their “normal” or “usual” condition is considering the fluctuating severity of FM symptoms. The interpretation of the scoring therefore requires caution.

The FFMQ is widely used to assess mindfulness in daily life (188). For patients with FM, a higher level of mindfulness tends to be associated with less pain interference, lower FM impact, and better psychological health, coping skills, and mental health-related quality of life (189). VTP incorporates mindfulness training throughout the programme, and we therefore applied FFMQ (138, 141). In our RCT, we chose to report and analyse data as a mean sum score, comprising all five facets to obtain an overall measure of mindfulness. Which of these five facets are sensitive to change is thus not reported and is a limitation in our study.

Self-reported physical activity measures may both under- and overestimate physical activity compared with objective measures such as accelerometry. A systematic review found no clear trends overall in the degree to which physical activity estimates diverged across self-report compared to direct methods (190). The included PA questionnaire is reproducible and a useful measure of leisure-time physical activity (142).

People with FM report activity limitations and impaired work ability because of symptom severity, so one of the aims in the RCT was to test the impact of the interventions on work ability (174). The WPAI is constructed to be modifiable for any health problem by specifying the disease of interest in the questions (191). For this study, we specified FM in the WPAI template. We did not include presentism and absenteeism in the analyses because we wanted to measure overall impairment. Hence, in this study, we reported the results from the WPAI assessing the impact of FM symptoms on work and other daily activities during the past 7 days.

FM management should aim at improving health-related quality of life (24). We used the EQ-5D-5L to assess this outcome. This measure has shown high sensitivity and precision at the individual and group levels and is recommended for use in clinical studies (192). Moreover, the EQ-5D-5L would allow for later health economic evaluations.

In the observational exploratory study, paper IV, we included the PDS. The PDS combines symptoms and pain to provide a continuous measurement of overall symptom severity, supporting an understanding of FM and FM diagnosis by quantifying the symptoms (36). In our study, we used the PDS in patients with FM symptoms to explore PDS trajectories. We could monitor the PDS changes over a relatively long period, but a limitation was that we identified groups and presented mean differences and not individual changes across disease states. However, our results show the movements across PDS categories and might be comprehensible in communication with patients about management strategies. A limitation with the chosen measure is that we could not identify specific disease-related predictors, such as pain, depression, or sleep.

## 6.1.5 Statistical methods and data analyses/statistical considerations

### 6.1.5.1 Systematic review with meta-analysis

In our SR, we performed a meta-analysis to estimate the mean effect of the included outcome measures in the studies. We expected heterogeneity in the included studies and applied and reported a random-effects meta-analysis to address the extent and amount of variation, or heterogeneity, among the studies. This method incorporates heterogeneity and allows for the effect size to vary from study to study (98, 113). Furthermore, the studies used different instruments for outcome assessment, so that the scale of measurement differed from study to study. We therefore applied the SMD, which is calculated by dividing the mean difference between the intervention and control groups in each study by that study's SD to create an index, the SMD. The SMD reflects the difference between the distributions in the two groups even if they do not use exactly the same outcome measure (113).

An important first step in SR is to carefully consider whether studies have enough in common to be combined in a meta-analysis (98, 163). In the SR, the included studies were selected based on pre-set eligibility criteria including population, diagnostic criteria, interventions, and predefined outcome measures. All included studies aimed at testing the effects of a mindfulness- and acceptance-based intervention for patients with FM, including most of the predefined outcomes. We applied restrictions in the included intervention although we allowed for modified interventions under certain predefined criteria. One of the aims of the SR was to investigate the reporting of content and delivery components in terms of procedure, instructors, mode, length, fidelity, and adherence in the included interventions. The data were manually collected and systematically structured in the TIDieR checklist. The research team considered the studies to be sufficiently similar in design, intervention, and patient population and decided to pool the comparable outcomes in a meta-analysis.

Statistical heterogeneity reflects larger differences in the outcome of the individual studies than could be expected to result from chance alone (193). The identified heterogeneity, in terms of clinical, methodological, and statistical heterogeneity among the included studies, was considered low enough to produce generalisable results from the meta-analyses. Our test for statistical heterogeneity,  $I^2$ , varied in percentage, reflecting the total variation across

studies attributed to heterogeneity rather than chance. There was considerable heterogeneity ( $I^2 > 90\%$ ) in the comparisons of health-related quality of life at both end of treatment and follow-up. For the other outcomes, heterogeneity was considered moderate, except for the outcome 'mindfulness', with an  $I^2$  of 0% at both time points.

There has been a need for attention to the quality of evidence to reduce the risks of inappropriate guidelines and recommendations development. In 2006, the British Medical Journal requested that authors use the GRADE system to rate the quality of evidence when submitting SRs (116). Since then, GRADE has been the preferred approach, and we used it in our SR to evaluate each area of evidence in the meta-analysis. GRADE provides a framework to assess study limitations, imprecision, inconsistency, indirectness, and publication bias, graded from "very low" to "high" (194). In our SR, all trials started at "high" because we included RCTs only. However, several studies were down-graded because of study limitations, inconsistent results, and imprecision.

A common critique of meta-analyses is that researchers combine different kinds of studies in the same analysis and ignore possibly important differences across studies. However, studies brought together in a meta-analysis will always address a broader question than individual studies. Hence, clinical and methodological expertise is crucial to deciding just how similar they need to be, in addition to having skills in literature search, data extraction, statistical pooling, and rating and interpreting the evidence (97). Our research team consisted of two skilled methodologists and two experts on mindfulness- and acceptance-based interventions, who contributed throughout the entire review process.

#### *6.1.5.2 The randomised controlled trial*

As recommended by guidelines, the primary and secondary analyses followed the intention-to-treat principle (119). The intention-to-treat is the primary analysis in pragmatic trials addressing the effectiveness of a specific treatment in a real-world setting (195). This principle calls for the complete inclusion of all data from all randomised patients to evaluate the benefits and risks of a new therapy in the final analyses. This requirement applies even if patients did not receive the treatment at all (146). The intention-to-treat analysis gives the most unbiased estimate of treatments effects in an RCT but does not give the estimated treatment effect from the patients who really completed the multicomponent rehabilitation



programme (196). The reason is that the estimated effects in an intention-to-treat analysis might be diluted by patients who do not adhere to the protocol.

The statistical analyses were described in the published study protocol, which strengthens the statistical validity of paper III. In our RCT, the primary outcome, PGIC, was dichotomised. The difference between groups was tested with Chi-square statistics and Fisher's exact tests. All secondary outcomes were continuous, and results were reported as mean values with 95% CIs of the differences. CI may provide more useful information than a p value because CI shows the uncertainty of the estimate. A 95% CI indicates the range of values in the interval that we can be confident includes the true value with a probability 0.95. The reason for choosing 95% CI and reporting the p value is convention; these values are frequently used when reporting changes, differences between groups, and statistical effects of interventions (197).

It was decided *a priori* that the secondary outcomes should be using ANCOVA for 12-month follow-up values with appropriate baseline values included as covariates. ANCOVA is considered sufficient for analysing treatment effects in RCTs for outcomes measured before and after treatment with the baseline as covariate (198). The main advantage with ANCOVA is that it adjusts for the phenomenon of "regression to the mean" (199). Furthermore, ANCOVA is an optimum statistical method for analysis of continuous outcomes in RCTs, in terms of bias, precision, and statistical power (200). Thus, it is regarded as a preferred analysis when post-treatment assessments adjusted for the pre-treatment assessments are measured (201, 202).

#### *6.1.5.3 The observational exploratory study*

Latent growth modelling methods (such as LCGA) are gaining recognition for their usefulness in identifying homogeneous subgroups within larger heterogeneous populations and identifying meaningful groups (151). The objective of using the LCGA was to estimate a set of parameters that performed the basic functions of defining the shapes of trajectories and the probability of trajectory group membership (203). In our RCT, the mean symptom burden in both the intervention and control groups was high at baseline and did not improve during the study period. We aimed to explore the sample, and the LCGA provided an opportunity to identify groups of PDS trajectories. From our results we could explore each patient's PDS

trajectory during the study period. Furthermore, the analysis reduced the complexity of the individual PDS data by identifying meaningful groups within our sample across four time points. Our results identified two groups: one with no improvement and one with some improvement. These groups were not defined before the analysis but emerged from the PDS data (203). The strength of LCGA is that it accounted for the fluctuating FM symptoms independent of treatment allocation in the RCT. It also separated the individual PDS trajectories from the sample at pre-baseline and throughout the study period. We therefore could identify different PDS trajectories in a sample with a high mean symptom burden over time.

## 6.2 Main findings

### 6.2.1 Effects of mindfulness- and acceptance-based interventions for FM patients

The mindfulness- and acceptance-based interventions included in our SR were associated with small to moderate uncertain effects on pain, depression, anxiety, sleep quality, health-related quality of life, and mindfulness.

Our findings correspond to several other studies. A systematic review that compared effects of mindfulness-based therapies (MBSR, MBCT) to control groups (waiting list, treatment as usual, or support group) showed similar reductions in FM symptoms and severity (204). Another systematic review and meta-analysis that included cognitive-behavioural therapy, MBCT, and ACT showed reduced FM symptoms such as pain, negative mood, and disability compared to control interventions (205). A recent systematic review that investigated the general effects of mindfulness-based interventions (MBSR, MBCT) in medically unexplained symptoms, including FM, showed beneficial effects on symptom severity, pain intensity, depression, and anxiety (206). We had also predefined fatigue, psychological distress, and work ability as outcome measures in the SR, but these measures were not assessed separately in any of the included studies.

Several studies have included the Fibromyalgia Impact Questionnaire, a composite measure of FM symptoms that incorporates fatigue. In our study, we wanted to assess the separate effects of fatigue, which in addition to pain is one of the most prevalent patient-reported symptoms in FM. We recognise that we might have included the Fibromyalgia Impact

Questionnaire as recommended by OMERACT, and in this way strengthened the relevance of our SR (123). However, we agree with the recommendation that future trials on mindfulness- and acceptance-based interventions for patients with FM also should include separate measurements of fatigue (122). Psychological distress is relevant to explore in patients with FM (186), but the included studies did not measure this outcome. It would be relevant to separately measure psychological distress and explore whether mindfulness- and acceptance-based interventions for patients with FM may improve psychological distress. Nine studies did include separate measures to detect changes in depression, and four studies included outcome measures for anxiety, reflecting an important aspect of mental health and distress.

None of the studies included scales to measure work ability. We believe future studies should include such measures to allow for further investigation of factors that could prevent unemployment and long-term disability.

A study evaluating how RCTs describe nonpharmacological treatment found that the majority missed essential information about the interventions (207). Implementation of nonpharmacological interventions depends on how well they are described in studies (114). One aim of our SR was to explore content and delivery components in the included interventions. We used the TIDieR checklist, which is beneficial as a research tool for clarification and reporting of content and delivery components (208). We recognise that TIDieR is a useful supplement for RCT reporting but can be less informative for the interventions we included because these were manualised and described in previous papers, books, and protocols. Hence, the authors of the included studies referred to the originators of the intervention for further details when explaining procedures used in the interventions. Most of the included studies reported relatively high adherence to the intervention. The degree of treatment fidelity was reported in only two studies, both by using video monitoring of the facilitators to assess fidelity (156, 160). Strategies to ensure that interventions can be delivered with a high level of fidelity are needed across community-based interventions (209). High levels of treatment fidelity are associated with stronger programme effects in complex interventions (210). It is possible to determine the effects of an intervention only if treatment fidelity is executed with high integrity (211). Our findings indicate the importance of including strategies to monitor and assess intervention fidelity to

enable valid conclusions about whether the intervention produces the intended outcomes. This finding corresponds to a recent systematic review investigating the general effects of mindfulness- and acceptance-based interventions and suggesting that a qualified supervisor oversaw the facilitators to ensure faithful adherence to the mindfulness theoretical fundamentals (206). However, the mindfulness- and acceptance-based interventions emphasise a dynamic relationship between facilitators and participants that is not easy to capture and measure. Furthermore, the interventions invite participants to share personal and emotional issues that require an atmosphere of trust, and monitoring fidelity might disrupt or influence the process (158). Nevertheless, we believe that strategies to improve or maintain fidelity and adherence are important and should be explored in future research.

#### 6.2.2 Effects of the multicomponent rehabilitation programme

As elaborated in section 2.2, the EULAR evidence-based recommendations for the management of FM say that patient education and nonpharmacological modalities should be the initial interventions for FM. It has been proposed that the most effective strategy, especially in cases of severe FM symptoms or disability, may be to combine psychological interventions and physical exercise in a multicomponent rehabilitation programme (24).

To date, few studies have examined which and how components of nonpharmacological treatment for patients with FM should be combined and whether their interaction has additive or synergistic effects (212). In our study, the VTP followed by physical activity for patients with recently diagnosed FM was not more effective than treatment as usual, with no differences between the groups in any disease-related secondary outcomes. These findings contrast with the conclusions of a previous systematic review investigating multiple nonpharmacological components (65). The included interventions in that review were self-management techniques and physical exercise such as aerobic training, stretching, and strengthening, and the results showed beneficial short-term effects on key FM symptoms. Häuser et al. recommended longer follow-up periods in future studies. However, knowledge of long-term effects of FM management is still limited because of the rarity of studies with longer follow-up periods (213). We therefore intended to include a relatively long follow-up period over 12 months.

Our results do correspond with the findings of a longitudinal pre–post-test study of VTP that included patients with IA and FM. Although there were reductions in psychological distress for patients with IA, there were no significant improvements in any variable for patients with FM (82). This outcome differed from that of the initial study of VTP in persons with chronic musculoskeletal pain, including FM, which documented a significant reduction in psychological distress one year after completion (214). The authors of the longitudinal study hypothesised that living with pain over a long period of time without access to relevant treatment may have led to development of maladaptive patterns of coping behaviour that could be hard to change. This possibility could explain the lack of effects for the included FM patients (82). Based on this finding, we intended to include younger patients with more recent diagnosis in our RCT.

We intended to follow EULAR recommendations with initial diagnostic clarification and assessment of comorbidities. We assumed that a prompt diagnosis would legitimise the patient's problems and provide a road to relief (25, 215). We aimed to capture patients at an early stage of FM. Studies have shown that a diagnosis of FM is associated with improved satisfaction with health and a reduction in the use of medical resources, compared to patients with FM symptoms who remain undiagnosed (216). On the other hand, a Norwegian qualitative study indicated that the diagnosis was hardly helpful for the interviewed FM patients (215). Nevertheless, the included patients in our study reported a median symptom duration of 8 years. We were therefore unable to investigate the effects of the multicomponent rehabilitation programme for FM patients with more recent disease onset. This factor may indicate that there is a considerable delay in FM diagnosis, as reported by Choy et al. (6). The extensive array of symptoms associated with FM and the gradual evolution of the condition make FM difficult to diagnose in primary care settings (6, 217). Poor knowledge and adherence to the diagnostic criteria among physicians may also lead to diagnosis delays and misdiagnoses (218). Furthermore, the presence of comorbidities increases the complexity of the clinical picture and is likely to affect the timeliness of a diagnosis (217). The patients included in our RCT reported a median of two comorbidities (range 1–6). The fact that other diagnoses were ruled out may provide relief for many patients with FM (219).

The EULAR recommendations state that patient education should be the first step to improve self-management after a diagnosis is established. We invited all patients to a 3-hour

patient education programme led by a rheumatologist and a nurse before participants were randomised. We did not assess the benefits of this programme. It is possible that some patients who were allocated to the control group ('treatment as usual') had initiated beneficial self-management strategies based on the patient education programme and thus improved their condition. We did not monitor the content of treatment as usual other than physical activity. However, to date, there is limited scientific evidence showing that patient education reduces FM symptoms (220). Because none of the groups in our study improved significantly, it is not likely that the 3-hour patient education programme promoted beneficial behaviour changes.

There has been a call for FM treatments to adopt a more holistic approach for successful outcomes (183). Furthermore, it has been advised that treatment approaches must be flexible to incorporate changes as the condition progresses, and it is likely to require the collaboration of a number of health professionals (61). There is no internationally accepted standard for minimum effective duration for FM treatment (221). We offered the VTP, a mindfulness- and acceptance-based intervention. In the published study protocol, we required that the patients attended at least 50% of the sessions to expect effects. Of the patients attending the VTP, 89% completed five sessions or more. This is a high attendance rate that is comparable to other RCTs on mindfulness- and acceptance-based interventions (153, 154).

Our study found small but statistically significant improvements in the tendency to be mindful in the intervention group compared to the control group. Meditation practice is associated with a higher level of mindfulness in daily life (222). In the VTP, patients were invited to participate in short formal mindfulness exercises, such as body scan, mindful movement, and sitting meditation with the aim to foster greater awareness of the present moment experience and bring awareness to everyday activities (223). A recent study has shown that higher levels of mindfulness are associated with less pain interference, lower FM impact, and better psychological health, coping skills, and mental health-related quality of life in clinical and community populations (189). Higher pain acceptance has been linked to better functional level and fewer symptoms in FM (224). A cross-sectional analysis of baseline data from a randomised trial demonstrated that higher mindfulness was associated with better sleep quality and less sleep disturbance in patients with FM (225). Home practise is considered essential to increasing the therapeutic effects of mindfulness- and acceptance-

based interventions (226). A limitation of our study is that we did not monitor adherence to the homework between the VTP sessions or the extent to which patients practised mindfulness training and integrated the training into their daily lives. As a result, we could not explore the relationship between home practise and clinical outcomes.

Work is an essential aspect of human social life because people spend most of their waking time working (227). Patients with FM frequently take sick leave, with significant economic consequences for them, their employers, and society (228). Previous studies have shown that nonworking patients with FM have more severe symptoms than patients who work (174, 229). Despite the high number of workers in our study, the patients reported a high symptom burden in terms of pain, fatigue, and psychological distress. FM symptom severity may, for some patients, become an obstacle to continuing to work (230). One study investigated factors associated with sick leave in patients with FM who worked and found that risk factors were related to the workplace rather than to the FM alone (227).

Consequently, interventions to improve FM management should also include contextual factors and workplace interventions should be developed (227).

In recent years, mindfulness-based approaches have been used in health and lifestyle interventions to promote physical activity (231). We assumed that the VTP would help participants overcome some of their internal barriers to physical activity. We found no support for this hypothesis. Even though 89% of the patients completed five or more of the VTP sessions, only 43% started the physical activity intervention and only 14 participated 12 times or more during the 12-week period. Poor attendance in physical activity interventions is also reported in other studies (232, 233). The HLC delivered the physical activity counselling during the daytime only. It is likely that many patients could not attend this counselling because 71% of them had paid day jobs. This obstacle might be one explanation for the high dropout rate from the HLC intervention and calls for services with more flexible opening hours.

Given the varied clinical picture associated with FM and the modest results on average for any therapy for patients with the condition, future studies should call attention to a more individualised management strategy (234). A recent systematic review showed that physical activity should be specifically tailored to the characteristics of the individual patient to be as effective as possible (235). Education and training by physiotherapists for patients with FM to initiate and remain engaged in an exercise programme have previously been

recommended (236). Although an initial aim of this study was to offer individually counselled physical activity by physiotherapist at the HLCs, the degree of individualised counselling and activities offered may have varied among HLCs. Moreover, the patients reported the physical activity they had attended in general terms such as walking, strength training, cycling, or spinning. Thus, a limitation of the RCT was that we did not monitor the degree to which the physical activity was tailored or the specific type of physical activity the patients used during the physical activity intervention. All included patients attended a 3-hour patient education programme during the study period which graded physical activity was one of the topics. In addition, we visited each HLC and provided the physiotherapists with information about the intervention and the importance of individually adjusted physical exercises for patients with FM. Thus, patients and physiotherapists received the same information before study start regarding adjusted physical activity. However, we do not have information about if and how they followed the advice and how adherent they were during the study period.

In a previous study, patients reported fear of worsening of their symptoms when they participated in physical activity (237). Of the patients in our RCT, 21 (12 in intervention and 9 in control) reported an adverse event such as aggravated pain after physical activity, which is also reported in other studies (232). It would have strengthened our study to have specifically monitored the degree to which patients were counselled to graduate exercise intensity to prevent a symptom flare. Consequently, worsening of FM symptoms during physical activity may have caused patients to quit the HLC intervention, influencing the results of the study.

In a qualitative sub-study, six patients with FM were interviewed 4 months after they had completed the VTP. These patients expressed that participating in the VTP had been important for their daily lives in terms of better self-understanding and self-acceptance and coping with the challenges of daily life. The patients continued the process after completing the VTP (238). These results are not generalisable because of the low number of attendees; however, these experiences may imply changes that the outcomes measured in the RCT did not detect. A limitation in our study is that we did not include any coping measures.

### 6.2.3 Trajectories of change in patients' symptom severity

In the observational exploratory study, we identified two groups of PDS trajectories, one group with no improvement and one with some improvement. Both groups reported mean



PDS scores within the PDS category of “very severe” at the time they were seen by a rheumatologist, pre-baseline. From baseline, the two groups diverged, and the group with some improvement showed continuous improvement across the time points. We found no differences between the groups in baseline characteristics.

These findings support a previous longitudinal study that evaluated patient-reported outcomes in FM patients at two time points over a 2-year period. The patients reported a high mean level of symptom burden although individual fluctuating symptoms were reported among the patients over time (239). Another prospective observational study described a high symptom burden for study patients from baseline assessment to a 12-month follow-up, also with fluctuating symptoms among individuals (52). Walitt et al. followed 1555 patients with FM with semi-annual observations for up to 11 years. The patients reported high levels of overall symptom severity, and only 25% showed moderate pain improvement over time (240). Although the mathematical model of LCGA identified two groups, there was only a slight difference between the two identified PDS trajectories. However, our results may be useful for clinicians and patients who want knowledge about the prognosis of FM.

A limitation of our study was that we did not include key FM symptoms as potential predictors. A previous population-based prospective twin cohort study evaluated several potential predictors for FM in 8343 participants who replied to health questionnaires in 1975, 1981, and 1990. The researchers found headache, back and neck pain, sleeping problems, and high Body Mass Index to be predictors of FM symptoms. The intensity and persistence of regional pain was associated with increased risk for FM symptoms (241). A systematic review aimed at identifying predictors of outcomes from multidisciplinary treatment in patients with FM found a higher level of depression to predict poor outcome in FM (242). A recent study showed that patients who benefitted more from a multidisciplinary group programme had lower baseline levels of anxiety, depression, and fear of pain from movement than those who experienced no improvement. They also showed more improvement on these variables throughout and after treatment (237). In our study, it would have been interesting to follow several parameters with repeated measurements, including function level.

## 7 Conclusions

### 7.1 Answers to the objectives

The overall aim of this thesis was to evaluate the effects of a multicomponent rehabilitation programme for patients with newly diagnosed FM in primary health care. The following conclusions can be drawn concerning the specific objectives:

- The SR and meta-analysis provided evidence that the mindfulness- and acceptance-based interventions included in the review were associated with small to moderate effects on pain, depression, anxiety, sleep quality, health-related quality of life, and mindfulness for patients with FM compared to controls. The effects were graded as uncertain because of study limitations, inconsistent results, and imprecision in the included trials.
- The RCT demonstrated that a multicomponent rehabilitation programme combining recent diagnosis and patient education with the VTP followed by physical activity was not more effective than recent diagnosis, patient education, and treatment as usual for patients with FM.
- The observational exploratory study identified two groups of FM trajectories: one group with no improvement and one group that improved slightly during the study period. We found no differences in baseline characteristics between the two groups.

### 7.2 Implications and future perspectives

Some areas for further research may be suggested based on the results from the studies included in this thesis:

The results from the SR demonstrated that mindfulness and acceptance-based interventions may provide beneficial health effects for patients with FM compared to controls. These positive results could aid in the development of FM management strategies. However, the evidence of the included studies was down-graded because of study limitations, inconsistent results, and imprecision, so further verification of the results from well-designed and properly reported RCTs is needed. The TIDieR checklist was found to be a useful supplement to the CONSORT checklist that may improve the reporting of RCTs. Furthermore, future trials should investigate whether strategies to improve the fidelity of and adherence to

mindfulness- and acceptance-based interventions can ensure the core intentions of the interventions to improve health outcomes. Of the included studies, the longest follow-up assessment was 6 months, and we believe that studies with longer follow-up are needed. The RCT showed no statistically significant effects of a multicomponent rehabilitation programme including the VTP followed by physical activity for patients with FM at a 12-month follow-up. Future studies should adopt a standardised approach for monitoring home practise across mindfulness- and acceptance-based interventions. Although adherence to the VTP was high, there was a high drop-out rate from the physical activity intervention. Future studies should investigate strategies to improve adherence to physical activity and how to adapt and tailor physical activity interventions to patients with FM in primary health care. We found a high symptom burden among the included patients. Thus, future research should aim at including patients with more recent disease onset and explore the effects of prompt diagnosis and patient education.

The PDS provides a useful method to quantify severity of FM symptom burden. The observational exploratory trial identified two PDS trajectories. Thus, our results showing the movements across PDS categories might be comprehensible in communication with patients about management strategies.

This thesis ends with the quote from the woman referred to in the introduction (page 1): *“I called a doctor’s office yesterday, and when I told the person on the phone that I had fibromyalgia, I was lectured that I could throw this diagnosis in the litter. It’s like nobody wants us ... I have nowhere else to go, and I’ve tried everything ...”*. Such stories tell us about the importance of increasing awareness about FM. Nevertheless, the question of how to develop management strategies to improve quality of life for people with FM is still not fully resolved.

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<b>Region:</b> REK sør-øst	<b>Saksbehandler:</b> Jakob Elster	<b>Telefon:</b> 22845530	<b>Vår dato:</b> 04.02.2016	<b>Vår referanse:</b> 2015/2447/REK sør-øst A
			<b>Deres dato:</b> 08.12.2015	<b>Deres referanse:</b>

Vår referanse må oppgis ved alle henvendelser

Heidi A. Zangi  
 Nasjonal kompetansetjeneste for revmatologisk rehabilitering

### 2015/2447 Samhandling for bedre behandling av pasienter med fibromyalgi og utbredte muskelsmerter

**Forskningsansvarlig:** Diakonhjemmet sykehus  
**Prosjektleder:** Heidi A. Zangi

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 14.01.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

#### Prosjektomtale

*Formålet med prosjektet er å evaluere en ny samhandlingsmodell for å forbedre behandlingstilbudet til personer med fibromyalgi/utbredte muskel-/skjelettsmerter.*

*Deltakerne randomiseres enten til et rehabiliteringsprogram ved Frisklivssentral i kommunen eller til oppfølging hos fastlege og eventuelt fysioterapeut (dagens praksis).*

*Rehabiliteringsprogrammet omfatter kurs i Livsstyrketrening, som strekker seg over 10 samlinger fordelt på 15 uker, samt individuell treningsveiledning i en 8-ukers periode etter kurset. De som blir randomisert til kontrollgruppen vil få tilbud om det samme behandlingstilbudet som de har i dag, og få tilbud om kurs i Livsstyrketrening etter at datainnsamlingen er avsluttet.*

*Det skal rekrutteres totalt 140 deltakere. Deltakerne skal fylle ut spørreskjema på tre tidspunkter: før randomisering, etter 16 uker og etter 52 uker. Det primære endepunktet vil være pasientens egen opplevelse av bedring skåret på en 7-punkts skala fra «mye verre» til «mye bedre».*

*Studien er et modellprosjekt som gjennomføres i samarbeid mellom Diakonhjemmet sykehus og 7 kommuner.*

#### Vurdering

Komiteen har ingen forskningsetiske innvendinger til at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll.

Komiteen har imidlertid en merknad til informasjons- og samtykkeskrivet. Det planlegges en oppfølging av deltakerne etter to år, og i informasjonsskrivet står det at hvis dette blir aktuelt, vil deltakerne bli kontaktet av prosjektleder. Komiteen mener at samtykkeskrivet bør inneholde en egen avkrysningsboks der deltakerne

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All post og e-post som inngår i saksbehandling, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff

kan gi et eksplisitt samtykke til å bli kontaktet etter to år for en oppfølgingsstudie.

Ut fra dette setter komiteen følgende vilkår for godkjenning:

Informasjonsskrivet revideres i tråd med ovenstående merknad. Revidert informasjonsskriv sendes komiteen til orientering.

### **Vedtak**

Komiteen godkjenner prosjektet i henhold til helseforskningsloven § 9 og § 33 under forutsetning av at ovennevnte vilkår oppfylles.

Det bes om at revidert informasjonsskriv innsendes til vårt arkiv.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Godkjenningen gjelder til 31.12.2019.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal oppbevares aidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding på eget skjema, jf. helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK, jf. helseforskningsloven § 11.

### *Klageadgang*

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal  
Professor dr. med.  
Leder

Jakob Elster  
seniorrådgiver

### **Kopi til:**

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## 10 Papers I – IV

## Paper I

Trond Haugmark, Kåre Birger Hagen, Geir Smedslund, Heidi A. Zangi (2019) Mindfulness- and acceptance-based interventions for patients with fibromyalgia – a systematic review and meta-analyses. PLoS ONE 14(9): e0221897. <https://doi.org/10.1371/journal-pone.0221897>

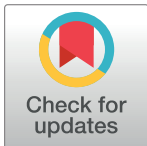
## RESEARCH ARTICLE

# Mindfulness- and acceptance-based interventions for patients with fibromyalgia – A systematic review and meta-analyses

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## Abstract

### Objectives

To analyze health effects of mindfulness- and acceptance-based interventions, including mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT) and acceptance and commitment therapy (ACT). Additionally, we aimed to explore content and delivery components in terms of procedure, instructors, mode, length, fidelity and adherence in the included interventions.

### Methods

We performed a systematic literature search in the databases MEDLINE, PsychINFO, CINAHL, EMBASE, Cochrane Central and AMED from 1990 to January 2019. We included randomized and quasi-randomized controlled trials analyzing health effects of mindfulness- and acceptance-based interventions for patients with fibromyalgia compared to no intervention, wait-list control, treatment as usual, or active interventions. MBSR combined with other treatments were included. Predefined outcomes were pain, fatigue, sleep quality, psychological distress, depression, anxiety, mindfulness, health-related quality of life and work ability. The Template for Intervention Description and Replication (TIDieR) checklist and guide was used to explore content and delivery components in the interventions. Meta-analyses were performed, and GRADE was used to assess the certainty in the evidence.

### Results

The search identified 4430 records, of which nine original trials were included. The vast majority of the participants were women. The analyses showed small to moderate effects in favor of mindfulness- and acceptance-based interventions compared to controls in pain (SMD -0.46 [95% CI -0.75, -0.17]), depression (SMD -0.49 [95% CI -0.85, -0.12]), anxiety (SMD -0.37 [95% CI -0.71, -0.02]), mindfulness (SMD -0.40 [-0.69, -0.11]), sleep quality (SMD -0.33 [-0.70, 0.04]) and health-related quality of life (SMD -0.74 [95% CI -2.02, 0.54])

## OPEN ACCESS

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at end of treatment. The effects are uncertain due to individual study limitations, inconsistent results and imprecision.

## Conclusion

Health effects of mindfulness- and acceptance-based interventions for patients with fibromyalgia are promising but uncertain. Future trials should consider investigating whether strategies to improve adherence and fidelity of mindfulness- and acceptance-based interventions can improve health outcomes.

## Introduction

Fibromyalgia (FM) is a complex and heterogeneous condition that may have important impact on patients' quality of life. Pain is the dominant symptom, but other symptoms such as non-refreshed sleep, fatigue, mood disturbance and cognitive impairment are common [1]. Current pharmacological treatments for FM are non-curative. European League Against Rheumatism (EULAR) recommends non-pharmacological therapies as first-line therapy. Individualized physical exercise should be recommended for all patients with FM. Additionally, cognitive behavioral therapy, mindfulness-based stress reduction, meditative movement, hydrotherapy or a combination of these therapies have shown promising effects for some patients, but the evidence is still insufficient [1].

Physical and emotional stress-provoking life events and stress resulting from living with pain may play a role in development of FM and exacerbation of the symptoms [2, 3]. Hence, techniques that can help patients cope with their stress-related experiences may reduce symptoms and improve wellbeing [4]. Mindfulness- and acceptance-based interventions, such as mindfulness-based stress reduction (MBSR) [5], mindfulness-based cognitive therapy (MBCT) [6] and acceptance and commitment therapy (ACT) [7] address peoples' relationship to their internal experiences. The interventions aim to train the participants to intentionally observe thoughts, emotions, and bodily sensations as they are perceived on a moment-to-moment basis with an open, non-judgmental attitude [8]. It is argued that when experiences are not judged as good or bad, positive or negative, acceptance increases and one's struggle to control what might not be controllable decreases. This should eventually lead to greater self-care and self-compassion [9].

MBSR and MBCT are typically provided as eight weekly 2–2.5 hours' group sessions plus a one-day retreat. They include practical and formal meditation training, such as body scan, sitting and walking meditation, mindful yoga movements and individual practice between sessions [5]. MBCT was adapted from MBSR to prevent recurrent depressions and replaces some of the content of MBSR with education on specific patterns of negative thinking that people with depression are vulnerable to [6]. ACT consists of a set of treatment methods and aims to focus on other cognitive skills such as the participants' ability to define and clarify values in different life domains, identify achievable goals that embody those values, and plan the future based on identified life goals. ACT can be delivered in a wide array of applications including group treatment, individual treatment, via internet and self-administered workbooks with therapist support [10]. ACT is delivered to a variety of patient populations and settings and focuses on different problems, e.g. depression, anxiety, chronic pain or the management of chronic disease [11–13]. Ultimately, the purpose is to develop psychological flexibility, which refers to the capacity to change or maintain one's behavior in open contact with thoughts and feelings [12, 14].

Systematic reviews and meta-analyses on mindfulness- and acceptance-based interventions for chronic pain conditions have showed a number of beneficial effects in patients with chronic pain, especially in the long-term [15, 16]. For patients diagnosed with FM, the evidence is scarcer. A recent systematic review and meta-analysis showed that cognitive behavioral therapies (CBT), including CBT, MBCT and ACT reduced key symptoms such as pain, negative mood and disability compared to control interventions [17]. Another systematic review on MBSR for patients with FM showed that MBSR improved health-related quality of life and reduced pain intensity compared to usual care and active control groups [18].

There has been an upsurge of mindfulness- and acceptance-based interventions across different fields of research. Although the interventions are relatively well described, there may be differences in how they are delivered and implemented [19], and details of the interventions may be lacking [20]. Hence, researchers may find it difficult to replicate the interventions in future trials [21]. Moreover, for clinicians it may be challenging to implement the interventions in clinical practice [22]. In the present systematic review we have applied the Template for Intervention Description and Replication (TIDieR) checklist and guide [23] (S1 Table) to explore the intervention components in MBSR, MBCT and ACT as they were presented in randomized controlled trials.

The aims of this study were:

- to explore content and delivery components in mindfulness- and acceptance-based interventions for patients with FM
- to analyze health effects of mindfulness- and acceptance-based interventions for patients with FM

## Materials and method

This systematic review was performed according to the Cochrane Handbook [24] and reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) [25]. The reviewers comprised two experts on mindfulness- and acceptance-based interventions (TH, HAZ) and two methodologists (GS, KBH). Inclusion criteria, methods and analyses were specified in advance, and the protocol was registered in PROSPERO (CRD42018081119).

## Search methods for identification of studies

The electronic databases MEDLINE, PsychINFO, CINAHL, EMBASE, Cochrane Central and AMED were searched from 1990 to January 25<sup>th</sup> 2019. A medical librarian developed the MEDLINE search strategy in consultation with the reviewers. The strategy was amended for each database (S1 Text) and restricted to English, Swedish, Danish, Norwegian, German, French, Spanish and Portuguese languages. The reference lists of included studies were examined for additional potentially eligible studies.

## Eligibility criteria

We included randomized controlled trials (RCTs) and quasi-randomized trials on mindfulness- and acceptance-based interventions for patients with FM. Only full-text articles published in peer-reviewed journals were included. The study population was limited to adult patients (age  $\geq 18$ ) diagnosed with FM based on the initial criteria defined by the American College of Rheumatology (ACR) in 1990 [26] or the revised ACR 2010 criteria [27].

Studies were considered if they followed the standardized format of MBSR, MBCT or ACT and were compared to no intervention, wait-list control, treatment as usual, or active

interventions. Modified interventions were considered for inclusion if they referred to the originators of the interventions in the reference list; for MBSR: Kabat-Zinn, MBCT: Teasdale, Segal, Williams, and ACT: Hayes. The interventions had to comprise 6 to 12 sessions and include group-based or online mindfulness meditation over at least 6 weeks.

Studies were included if they assessed at least one of the outcomes pain, fatigue, sleep quality, psychological distress, depression, anxiety, mindfulness, health-related quality of life or work ability. Effects were categorized as end-of-treatment and follow-up scores (2 to 6 months).

### Selection of studies

After duplicate removal, two reviewers (TH and GS) independently screened the titles and abstracts and selected studies based on the inclusion and exclusion criteria, using Rayyan screening tool [28]. The articles selected for full-text screening were examined independently by the same reviewers. Disagreements were rechecked and consensus was achieved by discussion before the final selection. A third reviewer (HAZ) was consulted in cases of dissension. When needed, study authors were contacted for additional information to clarify study eligibility and obtain further details.

### Data extraction and management

General information, population, setting, methods, and participant data were extracted by one reviewer (TH) and checked by a second reviewer (GS) using a data extraction form created for the review (S2 Table).

TH and GS used the TIDieR-checklist to extract the intervention components in each study (S1 Table). Disagreements were rechecked and consensus achieved by discussion before the final checklist was completed.

### Assessment of methodological quality

The Cochrane risk of bias tool [24] was used with six domains separately assessed: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting and other potential threats to validity. Each domain was explicitly rated by two reviewers (TH and GS) as low, high or unclear risk of bias (S1 Fig).

GRADEpro [29] was used to rate and summarize the certainty of evidence of the reported outcomes as high, moderate, low, and very low. As only RCTs were included, the rating started at high certainty and was downgraded by one or two levels for concerns in one of the five domains; study limitations, inconsistent results, indirectness of evidence, imprecision and publication bias [30].

### Statistical analysis

If the studies were sufficiently similar regarding participants, interventions, comparisons and outcomes, we conducted meta-analyses using Review Manager software (RevMan 5.3) from the Cochrane collaboration [31]. Due to clinical heterogeneity, we decided to perform and report random-effects analyses. Heterogeneity was assessed using tau-squared and I-squared statistics [32]. Considering shortcomings of the tau-squared estimator in RevMan (Der Simonian and Laird [DL]) we repeated the analyses with the Hartung-Knapp-Sidik-Jonkman (SJ) estimator in R Studio Version 1.1.463 to verify the results [33]. Since the SJ results did not differ substantially from the DL results, we decided to keep the results from the RevMan analyses. We computed standardized mean differences (SMDs) because different scales were used to measure the same outcomes.

Controls included were no intervention, wait-list controls, treatment as usual and other active interventions. In studies with more than one control arm, we calculated weighted averages. The mindfulness and health-related quality of life scales were inverted to be comparable to the other outcomes.

## Results

### Selection process

Twenty-five of 4430 articles were identified as potentially eligible and screened in full-text (Fig 1). Nine trials met the inclusion criteria. The reasons for exclusion of 16 trials are presented in S3 Table.

### Trial characteristics

The included trials were published between 2003 and 2018 totaling 750 participants (Table 1).

FM was diagnosed with ACR 1990 classification criteria in seven trials [34–40], and with ACR 2010 criteria in two trials [41, 42]. Two trials [38, 41] analyzed different outcomes within the same study population. Both were therefore included in the meta-analysis with the number of participants counted only once. Parra-Delgado et al. [37] measured pain in seven different areas of the body without reporting a sum score. The trial was therefore not included for pain outcomes in the meta-analysis. Simister et al. [42] delivered an internet-based ACT-intervention. Five authors were contacted to clarify diagnostic criteria and randomization procedures. Two authors provided the requested information; three did not respond.

### Exploration of content and delivery components in the interventions

The specific aims, content and mode of delivery of each trial are described in the TIDieR-checklist [23] (Table 2). The checklist revealed minor distinctions between trials in reporting and assessment of adherence and fidelity. These are reported below.

Five of the nine included studies, Cash et al. [41], Septhon et al. [39], Luciano et al. [36], Wicksell et al. [40] and Simister et al. [42] described strategies for adherence and fidelity. Cash et al. [41] and Septhon et al. [39] monitored attendance and absent participants received a reminder phone call to attend subsequent sessions. Wicksell et al. [40] provided a 30-minute session summary for participants who were unable to attend. Absence from five sessions resulted in discontinuation of the treatment program as well as exclusion from the study. Simister et al. [42] provided participants with weekly e-mail reminders to complete the program along with a request to contact a team member if they had any questions or concerns. Luciano et al. [36] and Wicksell et al. [40] video recorded the instructors' activities in the sessions to ensure fidelity and to assess treatment integrity. Luciano et al. [36] reviewed each group session to assess if the instructors followed the treatment manual. Schmidt et al. [38] did not monitor fidelity because they were concerned that it might disrupt or influence the intervention.

The adherence, defined as participants completing at least half of the sessions, was relatively high, i.e. above 80%, in all but one intervention. One trial reported 61% adherence [34] and the online intervention reported 100% adherence [42]. There were no differences in adherence between the interventions that reported systematic strategies to maintain or improve fidelity and interventions that did not report such strategies (S4 Table).

### Health effects

The pooled effects were small to moderate in favor of mindfulness- and acceptance-based interventions at the end of treatment for pain (SMD -0.46 [95% CI -0.75, -0.17]), depression

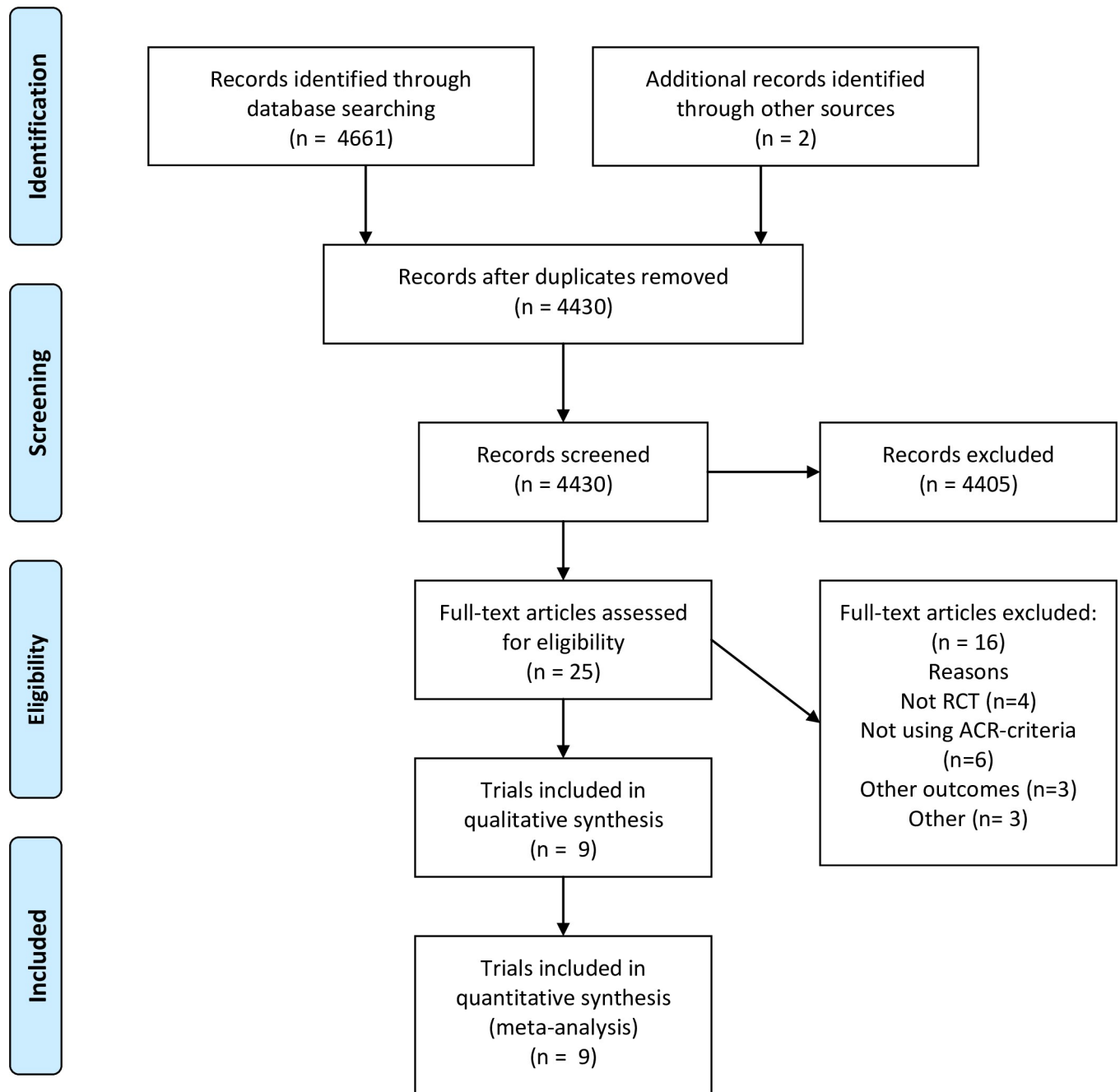


Fig 1. PRISMA flow diagram. PRISMA Study flow diagram.

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(SMD -0.49 [95% CI -0.85, -0.12]), anxiety (SMD -0.37 [95% CI -0.71, -0.02]), sleep quality (SMD -0.33 [-0.70, 0.04]), health-related quality of life (SMD -0.74 [-2.02, 0.54]) and mindfulness (SMD -0.40 [-0.69, -0.11]). At follow-up, all effect sizes decreased except for anxiety that exhibited a small increase in effect size (Fig 2 and Fig 3); (SMD -0.25 [95% CI -0.52, 0.01]), depression (SMD -0.48 [95% CI -0.77, -0.19]), anxiety (SMD -0.44 [95% CI -0.90, 0.02]), sleep quality (SMD -0.25 [-0.50, -0.00]), health-related quality of life (SMD -0.61 [-1.48, 0.26]) and

mindfulness (SMD -0.28 [-0.56, 0.01]). Study limitations, inconsistent results and imprecision in the trials (GRADE), resulted in very low to moderate certainty (S5 Table).

### Discussion

The TIDieR-checklist revealed minor differences in content and delivery components among the nine included interventions. The pooled results from nine RCTs totaling 750 patients with FM favored mindfulness- and acceptance-based interventions in all reported outcomes compared to controls. Using the GRADE criteria, the certainty of the evidence was down-graded due to study limitations, inconsistent results and imprecision. These results correspond to another recent systematic review analyzing the effects of CBTs, including ACT and MBCT, on FM [17]. The majority of the included trials applied the ACR 1990 diagnostic criteria which are favorably disposed towards women [27]. The vast majority of the study participants were middle-aged women. The result from this systematic review cannot be generalized to younger women or to men. As the ACR 2010 diagnostic criteria identify many more male patients, future trials should aim to include more men [43].

Using the TIDieR-checklist we found that the included trials provided short descriptions of the interventions and the procedures used (Item 3: Informational materials delivered and Item 4: Procedure used in the intervention) [23]. However, the trial authors referred to the originators of the interventions for further descriptions. All interventions except one were delivered as face-to-face group interventions. Simister et al. [42] delivered an individual online ACT-intervention with therapist support. Online delivery can make interventions more accessible

Table 1. Characteristics of included studies (n = 9).

Author, year, country (Ref)	Study design	Participants	Intervention	Comparison (control)	Outcome measures	Measurement time point
Astin et al. 2003, USA [34]	RCT	128 participants, mean age 48 yrs., 98.4% women in intervention and 100% in control group	n = 64, mindfulness meditation/ qigong movement therapy	n = 64, education-support group	Pain; MOS SF-36, BDI	Baseline, end of treatment (8 weeks), and at follow-up (4 months + 6 months)
Cash et al. 2015, USA [41]	RCT	91 participants, mean age 48 yrs., 100% women	n = 51, mindfulness-based stress reduction	n = 40, wait-list	Pain; VAS, SSQ, The Fatigue Symptom Inventory	Baseline, end of treatment (8 weeks) and at follow-up (2 months)
Grossman et al. 2007, Switzerland [35]	Quasi-RCT	58 participants, mean age 52 yrs., 100% women	n = 38, mindfulness-based stress reduction	n = 13, education-support group	Pain; VAS, HADS, QoL*	Baseline and at end of treatment (8 weeks)
Luciano et al. 2014, Spain [36]	RCT	156 participants, mean age 48 yrs., 96% women in both groups	n = 51, acceptance and commitment therapy	n = 52, recommended pharmacological treatment + n = 53, wait-list	HADS, Pain; VAS, EQ-5D	Baseline, end of treatment (8 weeks) and follow-up (6 months)
Parra-Delgado et al. 2013, Spain [37]	RCT	33 participants, mean age 53 yrs., 100% women	n = 17, mindfulness-based cognitive therapy	n = 16, treatment as usual	BDI, Pain; VAS**	Baseline, end of treatment (8 weeks) and follow-up (3 months)
Schmidt et al. 2011, Germany [38]	RCT	177 participants, mean age 53 yrs., 100% women	n = 59, mindfulness-based stress reduction	n = 59, education-support group + n = 59, wait-list	HRQoL (PLC), CES-D, STAI, PSQI, PPS***, FMI	Baseline, end of treatment (8 weeks) and follow-up (2 months)
Septon et al. 2007, USA [39]	RCT	91 participants, mean age 48 yrs., 100% women	n = 51, mindfulness-based stress reduction	n = 40, wait-list	BDI	Baseline, end of treatment (8 weeks) and at follow-up (2 months)
Simister et al. 2018, Canada [42]	RCT	67 participants, mean age 40 yrs., 95% women	n = 33, acceptance and commitment therapy	n = 34, treatment as usual	CES-D, SF-MPQ, PSQI, FFMQ	Baseline, end of treatment (12-weeks) and follow-up (3 months)

(Continued)



Table 1. (Continued)

Author, year, country (Ref)	Study design	Participants	Intervention	Comparison (control)	Outcome measures	Measurement time point
Wicksell et al. 2012, Sweden [40]	RCT	40 participants, mean age 45 yrs., 100% women	n = 23, acceptance and commitment therapy	n = 17, wait-list	PDI, SF-36****, BDI, STAI	Baseline, end of treatment (12-weeks) and follow-up (3–4 months)

RCT = Randomized Controlled Trial

BDI = Beck Depression Inventory; 21-question multiple-choice self-report inventory. Each question had a set of at least four possible responses, ranging in intensity

MOS SF-36 = Medical Outcome Study Shortform-36 Scores range from 0–100, Lower scores = more disability, higher scores = less disability

VAS = Visual Analogue Scale for pain intensity, 0–100, “no pain” (score of 0) and “pain as bad as it could be” or “worst imaginable pain” (score of 100)

SSQ = Stanford Sleep Questionnaire; 7-point scale with scale rating from 1 “feeling active, vital, alert, or awake” to 7 “No longer fighting sleep, sleep onset soon; having dream-like thoughts”

The Fatigue Symptom Inventory = scale composed of 14 items (one of which is not scored) designed to evaluate multiple aspects of fatigue, including its perceived severity, frequency, and interference with daily functioning

HRQoL (PLC) = The Quality of life Profile for the Chronically Ill; Questionnaire composed of 40 Likert-scaled items (scale 0–4) with 0 representing minimum and 4 representing maximum satisfaction. The items measure physical, psychological and social capacity of performance and well-being

HADS = Hospital Anxiety and Depression Scale; fourteen item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression

PPS = The Pain Perception Scale; 24-item scale that evaluates pain perception

EQ-5D = Visual analogue scale of EuroQol; EQ-5D self-reported questionnaire includes a visual analog scale (VAS), which records the respondent’s self-rated health status on a graduated (0–100) scale, with higher scores for higher HRQoL. It also includes the EQ-5D descriptive system, which comprises 5 dimensions of health

CES-D = Center for Epidemiological Studies depression inventory; 20-item, self-report measure designed to measure symptoms of depression over the past week

STAI = State-Trait-Anxiety-Inventory; 20 items for assessing trait anxiety and 20 for state anxiety. All items are rated on a 4-point scale from ‘not at all’ to ‘very much so’. Higher scores indicate greater anxiety

PSQI = Pittsburgh Sleep Quality Index; 19 individual items, creating 7 components producing one global score

FMI = Freiburg Mindfulness Inventory; a 14-item short form measuring Mindfulness

PDI = Pain Disability Index; a self-report tool used for measuring the degree of pain a patient is experiencing. Participants use a 0 (no disability) to 10 (total disability) numeric rating scale

PIPS = Psychological Inflexibility in Pain Scale; 16-item scale used to assess psychological inflexibility. Respondents are asked to rate items on a 7-point scale ranging from 1 (never true) to 7 (always true). Higher scores indicate greater levels of psychological inflexibility

SF-MPQ = Short form McGill Pain Questionnaire; 15 items asking participants to rank their typical pain experience on a 4-point Likert scale, from 0 (no pain) to 3 (severe), and maximum total score of 45

FFMQ = Five Facet Mindfulness Questionnaire; 39-items questionnaire measuring 5 facets of mindfulness

SF-36 = Short form-36 Healthy Survey, 36-item measure assessing health-related quality of life. Higher scores indicate better functioning

\*The Quality of life Profile for the Chronically Ill was reported as six dimensions and therefore not included in this review

\*\*The Visual Analogue Scale for pain intensity was measured on seven different parts of the body and not included in this review

\*\*\*The Pain Perception Scale was divided into affective and sensory and only sensory was included in this review

\*\*\*\*The short form-36 Healthy Survey provided summary for two subscales and not included in this review.

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to patients e.g. in rural areas since logistic barriers such as travel or limited access to trained therapists are eliminated [44]. As reported in S8, Simister et al. [42] obtained 100% adherence which might support further development and exploration of online interventions for FM in future research.

Crane et al. [19] have proposed that clarity regarding fidelity to the content and program structure is essential in research on mindfulness- and acceptance-based interventions. Reviewing the TIDieR-checklist Item 12 (How well intervention adherence and fidelity was assessed) we found no differences in actual adherence between trials that reported systematic strategies to improve or maintain fidelity and adherence and the trials that did not report such strategies. All over, actual adherence was relatively high in the included trials. Adherence might be influenced by other aspects that are not explored in this review or not reported in the trials. Since the included treatment interventions often deal with personal emotional issues and require an

**Table 2. TIDieR-checklist, template for intervention description and replication.** Description of content and delivery components.

Author	Item 1+2, Brief name and Why	Item 3+4, What (materials and procedures)	Item 5, Who provided	Item 6, How	Item 7, Where	Item 8, When and How much	Item 9 + 10, Tailoring and Modification	Item 11, Strategies to improve or maintain intervention fidelity and adherence	Item 12, Extent of intervention fidelity and adherence
Astin et al. 2003 [34]	Mindfulness Meditation Plus Qigong Movement Therapy. Aim: to test the potential effect of Mindfulness and Qigong	First 90 minutes of each session based on MBSR, followed by 60 minutes introduction to qigong	Mindfulness instructors not reported. Qigong taught by Chinese master	Group-based (n = 10–20)	University	8 weeks, 8 2.5-hours, All-day retreat not reported	Not reported	Not reported	26% never attended a class. Of 128 randomized into 2 groups, 50 (39%) dropped out from the study prior to 'end of treatment', 61 (48%) dropped out by week 16, and 63 (49%) failed to complete 24 week assessment
Cash et al. 2015 [41]	MBSR alleviates FM symptoms in women. Aim: to test MBSR on physiological effects	MBSR (5). Home practice assignments	Trained MBSR instructors	Group-based (n = 10–12)	University	8 weeks, 8 2.5-hours, All-day retreat reported	Not reported	Attendance monitored and absent participants received a reminder phone call to attend subsequent sessions	Of 51 randomized to intervention 42 (82%) completed 5.5 sessions. Attendance rate dropped from 90% to 57% by 4th meeting and maintained between 57 and 65%. 68% of controls provided follow-up data
Grossman et al. 2007 [35]	MBSR for FM. Aim: to compare MBSR to an active control including social support, relaxation and stretching exercises	MBSR (5). Home practice assignments	Trained MBSR instructors	Group-based (n = 10–15)	Not reported	8 weeks, 8 2.5-hours, All-day retreat reported	Not reported	Semi-structured individual interviews by instructor before/after intervention on health-related problems and expectations	Of the 58 participants, 6 (10.3%) dropped out (4 from MBSR and 2 from control). All remaining participants completed at least four sessions
Luciano et al. 2014 [36]	Effectiveness of group ACT for FM. Aim: extend findings of Wicksell 2012 with larger sample, longer follow-up and pharmacological control	ACT (7). Home practice assignments	Trained ACT instructors	Group-based (n = 10–15)	Not reported	8 weeks, 8 2.5-hours	Not reported	Video recording of instructors in sessions to insure fidelity. Interview with the participants at baseline	Of 142 participants randomized into 3 groups 20 dropped out of the study. 45 (88%) in GACT, 44 (85%) in RPR, and 47 (89%) in WL completed the study

(Continued)



Table 2. (Continued)

Author	Item 1+2, Brief name and Why	Item 3+4, What (materials and procedures)	Item 5, Who provided	Item 6, How	Item 7, Where	Item 8, When and How much	Item 9 + 10, Tailoring and Modification	Item 11, Strategies to improve or maintain intervention fidelity and adherence	Item 12, Extent of intervention fidelity and adherence
Parra Delgado et al. 2013 [37]	Effectiveness of MBCT in the treatment of FM. Aim: to examine whether MBCT may reduce the impact of the illness	MBCT (6). Home practice assignments	Trained MBCT instructors	Group-based (n = 17)	Not reported	8 weeks, 8 2.5-hours, All-day retreat not reported	Pain experience acceptance in different mediation practices, awareness of pain-related automatic thought, information on anxiety	Not reported	15 of 17 randomized to intervention group, participated. Drop-out reasons not explained. Ten attended six or more sessions (one attended four, sessions, four five, five six, three seven and two eight sessions. Controls: treatment-as-usual (n = 16), no drop-out
Schmidt et al. 2011 [38]	MBSR on FM. Aim: to include control group to replicate and extend earlier trials lacking randomization or control group	MBSR (5). Home practice assignments	Trained MBSR instructor	Group-based (n = 12)	University	8 weeks, 8 2.5-hours, All-day retreat reported	Not reported	Semi-structured individual interviews by instructor before/after intervention to help participants formulate realistic individual goals for the intervention	Of 137 participants, 25 (18%) dropped out. Similar attendance rate for both interventions (three-armed RCT)
Septhon et al. 2007 [39]	Evaluate whether MBSR provides advantage over standard treatment for depressive symptoms. Aim: to test the effects of MBSR on depressive symptoms	MBSR (5). Home practice assignments	Trained MBSR instructor	Group-based (n = 10–12)	Not reported	8 weeks, 8 2.5-hours, All-day retreat reported	Not reported	Attendance monitored and absent participants received phone call reminder for subsequent sessions	Of 91 treatment participants, 42 (46%) were considered to have completed MBSR during at least 4 of 8 weekly group sessions. Nine attended 4 sessions (18%)
Simister et al. 2018 [42]	RCT of Online ACT for FM. Aim: to evaluate the efficacy of an online ACT protocol	Online ACT (7). Homework exercises	Online platform with seven modules. Each contained written content, mp3 files and videos developed for each module	Online	Access to computer	Participants had two months to complete the program, encouraged to use approx. one week to complete each module	Online ACT protocol modified after clinical pilot study	Treatment team provided weekly e-mail reminders to complete the program and a reminder to contact a team member if any questions or concerns	All 67 intervention group participants accessed the program during treatment period. 60% practiced exercises from ACT components at least once per day, 80% more than once a week

(Continued)

Table 2. (Continued)

Author	Item 1+2, Brief name and Why	Item 3+4, What (materials and procedures)	Item 5, Who provided	Item 6, How	Item 7, Where	Item 8, When and How much	Item 9 + 10, Tailoring and Modification	Item 11, Strategies to improve or maintain intervention fidelity and adherence	Item 12, Extent of intervention fidelity and adherence
Wicksell et al. 2012 [40]	ACT for FM Aim: to evaluate the efficacy of ACT for FM	ACT (7)	Trained ACT instructors	Group-based (n = 6)	Not reported	12 weeks, 12 1,5-hours sessions	Not reported	If unable to attend a group session, individual 30-min session summary was provided prior to next session. Video recording of instructors in sessions to assess treatment integrity	3 of 23 participants (13%) in the intervention group dropped out during treatment. One of 17 dropped out in the waitlist group

FM = fibromyalgia, MBSR = mindfulness-based stress reduction, MBCT = mindfulness-based cognitive therapy, RCT = randomized controlled trial, ACT = acceptance and commitment therapy

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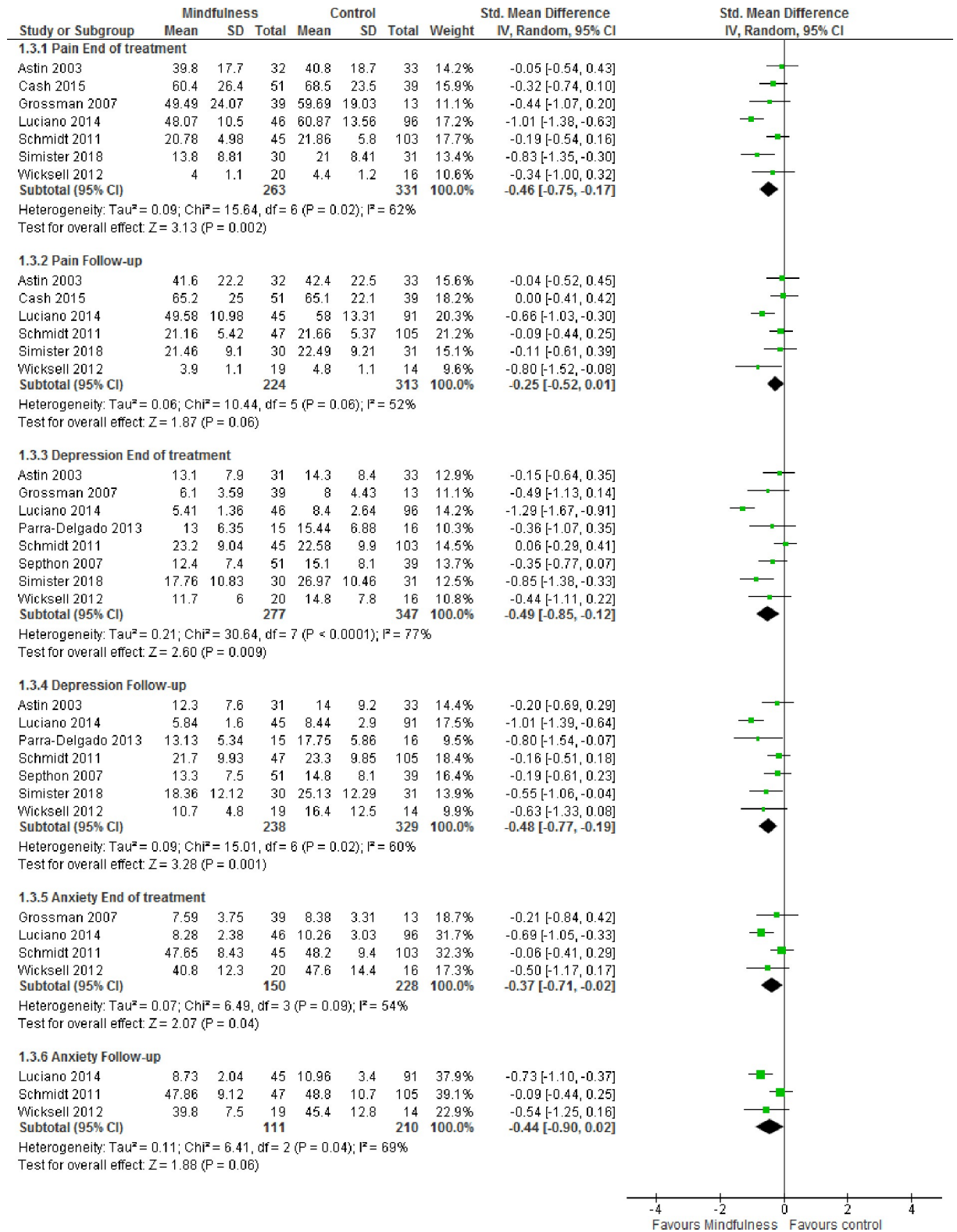
atmosphere of trust, monitoring fidelity might be disruptive or influence the process [38]. However, we believe that strategies to improve or maintain fidelity and adherence are of importance and might contribute to ensure the core intentions of the interventions in future research [19].

Fatigue and work ability were predefined outcomes in our review. Importantly; none of the included trials measured work ability, even though previous research has demonstrated that FM can have a high impact on work ability [45]. Only one trial [41] measured fatigue and consequently, this outcome was not included in the meta-analysis. Three of the nine included trials, Schmidt et al. [38], Cash et al. [41] and Simister et al. [42], measured sleep quality. Fatigue and sleep disturbances are common in FM [1], and can lower the pain threshold, trigger musculoskeletal pain and increase emotional distress [46]. Future research should include measurements for pain, fatigue, sleep and health-related quality of life to evaluate whether mindfulness- and acceptance-based interventions are more effective for particular outcomes for patients with FM [16, 47].

We did not include the Fibromyalgia Impact Questionnaire (FIQ) which captures the overall impact of FM symptomatology [48]. The reason for excluding FIQ was that it does not allow separate measures of pain, fatigue, depression and anxiety.

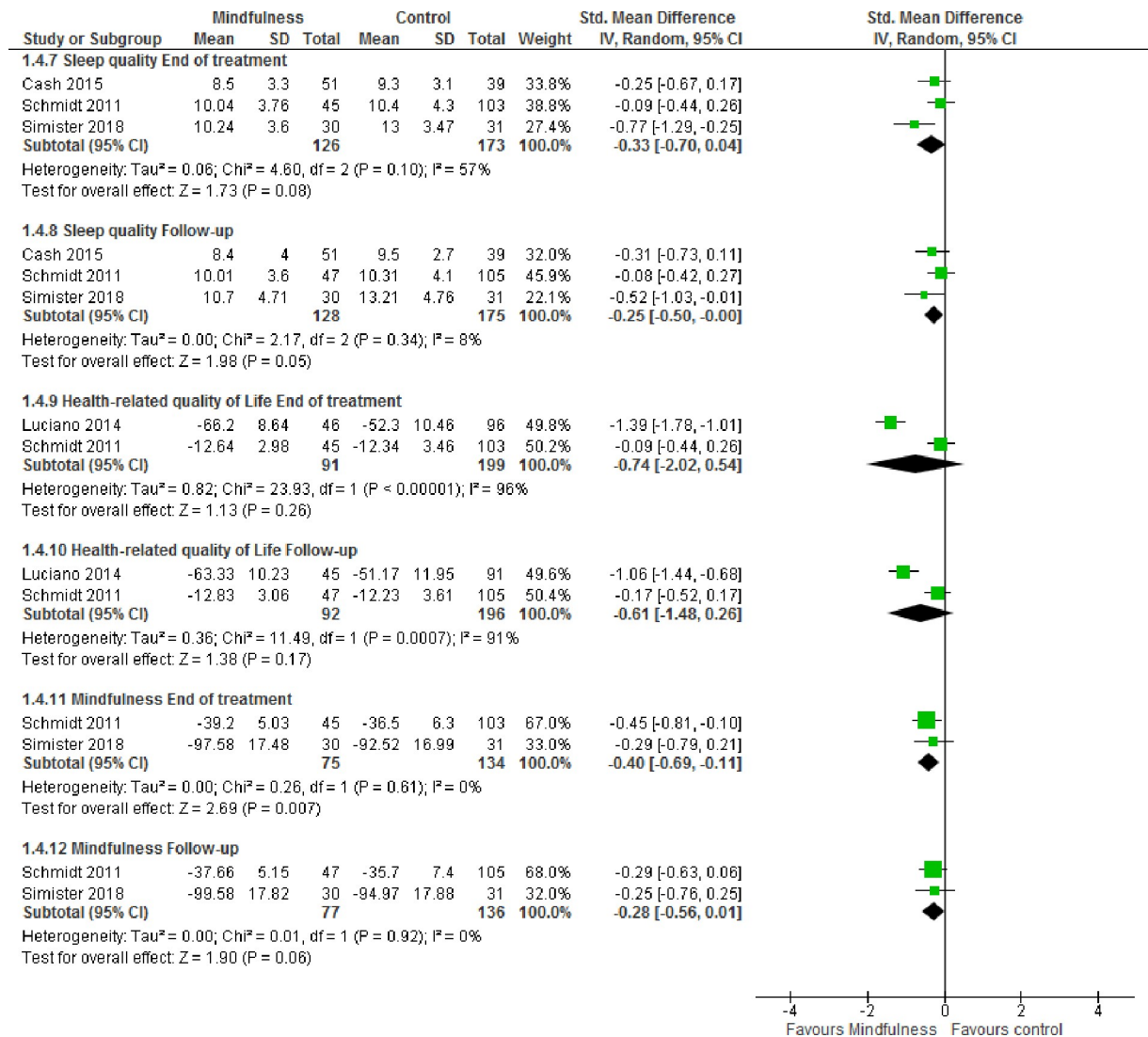
A previous systematic review and meta-analysis on mindfulness- and acceptance-based interventions for patients with chronic pain conditions have reported beneficial long-term effects on pain, depression, anxiety and health-related quality of life [15]. The longest follow-up assessment in the trials included in our review was six months. Future studies with longer follow-up periods are needed.

We estimated tau-squared using both the DL and the SJ estimator. The Knapp-Hartung approach (SJ) is known to suit systematic reviews including few studies, particularly when dealing with 5 or fewer trials [49]. The RevMan uses the DL method and is known as the standard estimator [31]. We have chosen to report the results from the meta-analyses computed in RevMan since the results were mainly similar and the small differences had no influence on the conclusion.



**Fig 2. Forest plot for meta-analyses of effects of mindfulness- and acceptance-based interventions.** Random-effects meta-analyses of effects of mindfulness- and acceptance-based interventions on pain, depression and anxiety at end of treatment (8-weeks) and follow-up (2–6 months).

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**Fig 3. Forest plot for meta-analyses of effects of mindfulness- and acceptance-based interventions.** Random-effects meta-analyses of effects of mindfulness- and acceptance-based interventions on sleep quality, health-related quality of life and mindfulness at end of treatment (8-weeks) and follow-up (2–6 months).

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To our best knowledge, this review is the first to use the TIDieR-checklist to describe and explore content and delivery components in mindfulness- and acceptance-based interventions. The included trials met fairly rigorous criteria. Some studies were excluded because ACR diagnostic criteria had not been followed or the randomization procedures were not clearly reported. We contacted the authors of these studies and if they did not respond, the trials were excluded.

The TIDieR-checklist may be appropriate to use in conjunction with the CONSORT-checklist [50] when reporting randomized controlled trials. We expected that the TIDieR-checklist would be appropriate for description and exploration of mindfulness- and acceptance-based interventions. MBSR and MBCT are relatively clearly described and manualized interventions and major differences were not revealed in any TIDieR items except for the items describing fidelity and adherence as discussed above. The TIDieR-checklist might be more suitable for exploring more complex interventions that are not described in manuals.

Nevertheless, the TIDieR-checklist allows the authors to better describe interventions in sufficient details to make replication possible [23].

Adopting the optimal version of mindfulness- and acceptance-based interventions might be difficult due to the heterogeneity between the included trials [22]. Some of the pooled effects were also based on a small number of trials. Users of mindfulness- and acceptance-based interventions should consider the effects against risk of bias, adherence, and fidelity in the included trials (Tables 1, 2) [20]. Future trials should investigate whether strategies to improve adherence and fidelity of mindfulness- and acceptance-based interventions can improve health outcomes.

## Conclusions

Overall, the mindfulness- and acceptance-based interventions included in this review were associated with small to moderate uncertain effects on pain, depression, anxiety, sleep quality, health-related quality of life and mindfulness for female patients with FM compared to controls. In our review we found no association between the mindfulness- and acceptance-based interventions that reported strategies to improve adherence and fidelity and trials that did not report such strategies. Future trials should monitor adherence and fidelity to explore this association more extensively. There was heterogeneity between trials, and down-grading in GRADE resulted in very low, low and moderate certainty of evidence. Only limited conclusions can therefore be drawn. The TIDieR-checklist is a useful supplement that can improve the reporting of RCTs but might be less informative for manualized interventions.

## Supporting information

### **S1 Table. TIDieR-checklist.**

(PDF)

### **S2 Table. Data extraction form created for the review.**

(PDF)

### **S3 Table. Excluded studies with reasons.**

(XLSX)

### **S4 Table. Item 11 and 12 in TIDieR-checklist specified.**

(PDF)

### **S5 Table. GRADE evidence profile.**

(PDF)

### **S6 Table. PRISMA-checklist.**

(PDF)

### **S1 Text. Search strategy for MEDLINE.**

(PDF)

**S1 Fig. Risk of bias summary.** The review authors' judgements of the risk of bias of each included study.

(PDF)

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# TIDieR-checklist

Author Year	Brief name	Recipient	Why	What (materials)	What (procedures)	Who provided	How	Where	When and how much	Tailoring	Modification of intervention throughout trial	Strategies to improve or maintain intervention fidelity	Extent of intervention on fidelity

# Data extraction form (trial)

(Title)

## 1. General Information

<b>Person extracting data (name)</b>	
<b>Date form completed</b>	
<b>Report title</b> <i>(title of paper/ abstract/ report that data are extracted from)</i>	
<b>Study country</b>	

## 2. Population and setting

<b>Recruitment details</b>	Number of people screened: Number of people eligible: Number of people recruited: Number of people randomized:
<b>Notes:</b>	

## 3. Methods

	<b>Descriptions as stated in report/paper</b>	<b>Location in text</b> <i>(pg &amp; ¶/fig/table)</i>
<b>Aim of study</b>		
<b>Design</b> <i>(e.g. parallel, cluster)</i>		
<b>Control group</b> (What did the control group receive?)	Wait-list <input type="checkbox"/> no intervention <input type="checkbox"/> treatment as usual <input type="checkbox"/> <b>Other active treatment:</b> <b>Describe:</b>	
<b>Notes:</b>		

## 4. Risk of Bias assessment

See [Chapter 8](#) of the Cochrane Handbook and *The Cochrane collaboration tool for assessing risk of bias; criteria for judging risk of bias in the 'Risk of bias' assessment tool*

Domain	Risk of bias			Support for judgement (describe)	Location in text (pg & ¶/fig/table)
	Low risk	High risk	Unclear		
<b>Random sequence generation</b> <i>(selection bias)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Allocation concealment</b> <i>(selection bias)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Blinding of participants and personnel</b> <i>(performance bias)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Outcome group: All/	
<b>Blinding of outcome assessment: self-reported outcomes</b> <i>(detection bias)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Outcome group: All/	
<b>Blinding of outcome assessment: objective outcomes</b> <i>(detection bias)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Outcome group: All/	
<b>Incomplete outcome data</b> <i>(attrition bias)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Selective outcome reporting?</b> <i>(reporting bias)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Other bias</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Notes:</b>					

## 5. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Setting;			Location in text (pg & ¶/fig/table)
<b>Specific intervention</b>				
<b>Number of participants</b>	<b>Total:</b>	<b>Intervention:</b>	<b>Comparison:</b>	
<b>% Female</b>	<b>Total:</b>	<b>Intervention:</b>	<b>Comparison:</b>	
<b>Age</b>	<b>Total:</b>	<b>Intervention:</b>	<b>Comparison:</b>	

<b>Diagnose criteria</b>				
<b>Sample size</b>		<b>Intervention:</b>	<b>Comparison</b>	
<b>Comments from the authors</b>				
<b>Notes:</b>				

## 6. Outcomes / results (In Revman)

Copy and paste table for each outcome

### Primary time point

	Outcome	Result	Location in text (pg & ¶/fig/table)
Post-intervention	Pain		
	Fatigue		
	Sleep quality		
	Psychological stress		
	Depression		
	Anxiety		
	Mindfulness		
	Quality of Life		
	Work participation ability		

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Key conclusions of study authors		
Notes:		

Adverse Events	
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### Exclusion after data extraction

**Reasons for exclusion:** (study design? participants? interventions/ outcomes? attrition? bias?)

### Dates:

**Date entered into RevMan and by whom?**

**Date checked and by whom?**

Excluded studies with reasons

Author, year, country	Title	Reasons
Amutio 2015, Spain (51)	Mindfulness training for reducing anger, anxiety, and depression in fibromyalgia patients	Could not verify the use of ACR criteria for FM
Amutio 2018, Spain (46)	Effects of Mindfulness Training on Sleep Problems in Patients with Fibromyalgia	Could not verify the use of ACR criteria for FM
Carter 2007, US (52)	Fibromyalgia patients less depressed after mindfulness meditation than after waitlist	Not available in full text
Davis 2013, US (53)	An Online Mindfulness Intervention Targeting Socioemotional Regulation in Fibromyalgia: Results of a RCT	Could not verify the use of ACR criteria for FM
Finkbeck 2013, Sweden (54)	Mindfulness therapy for somatization disorder and functional somatic syndromes - Randomised trial with one-year follow-up	Different diagnoses included. Could not verify the use of ACR criteria for FM
Grossman 2017, Germany (55)	Mindfulness-based intervention does not influence cardiac autonomic control or the pattern of visceral activity in the digestive tract in patients with irritable bowel syndrome: A randomized controlled trial	Did not include outcomes intended for the present review
Grodenberg 1994, US (56)	A randomized study of stress reduction, cognitive behavioral treatment, and progressive FM	Not a RCT
Kaplan 1993, US (57)	The impact of a meditation-based stress reduction program on FM: A randomized controlled trial	Did not include outcomes intended for the present review
Ludman 2017, Spain (8)	Co-utility of group Acceptance and Commitment Therapy for FM vs recommended drugs	Same study as Wickell
Oksa 2012, Sweden (40)	Acceptance and commitment therapy for fibromyalgia: A randomized controlled trial	Not a RCT
Simpall 2009, Canada (59)	A randomized study of the effects of mindfulness-based stress reduction on pain, mood, and quality of life in patients with fibromyalgia, chronic fatigue syndrome, and fibromyalgia	The intervention did not include mindfulness- and acceptance-based interventions
Stal 2016, Germany (60)	The effects of long- and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial	Did not include outcomes intended for the present review
Steiner 2014, US (64)	Assessing the Efficacy of Acceptance and Commitment Therapy in Reducing Value-based action in FM: results from a randomized pilot of Acceptance and Commitment Therapy	Could not verify the use of ACR criteria for FM
Steiner 2013, US (61)	Meditation awareness training for the treatment of FM: A randomized controlled trial	Not a RCT
Van Gordon 2017, UK (62)	Mindfulness-based stress reduction and Sense of Coherence among women with FM	Did not include outcomes intended for the present review
Wicksell 2007, US (63)	ACR = american college of rheumatology; FM = fibromyalgia; RCT = randomized controlled trial; MBSR = mindfulness-based stress reduction	

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42. Amutio A, Ferraz C, de Cidre-Cabreriz A, Ferraz C, de Cidre-Cabreriz A, Ferraz C, et al. Mindfulness-based stress reduction for reducing anger, anxiety, and depression in fibromyalgia patients. *Frontiers in Psychology*. 2015; 6:1015. Published PMID: 26154385.

43. Carter R, Carlson L, McGee R, et al. Mindfulness-based stress reduction for fibromyalgia: A randomized controlled trial. *Journal of Behavioral Medicine*. 2007;32(3):201. Published PMID: 17420835.

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49. Ludman J, D'Amico F, Finkbecker M, Agard J, Benhabib-Sarraf M, et al. Capacity of Group Acceptance and Commitment Therapy for Fibromyalgia versus Recommended Drugs: An Economic Analysis. *PLoS ONE*. 2013;8(12):e82323. doi: 10.1371/journal.pone.0082323.

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53. Carter R, Carlson L, McGee R, et al. Mindfulness-based stress reduction for fibromyalgia: A randomized controlled trial. *Journal of Behavioral Medicine*. 2007;32(3):201. Published PMID: 17420835.

54. Davis C, Zaura A, An Online Mindfulness Intervention Targeting Socioemotional Regulation in Fibromyalgia: Results of a Randomized Controlled Trial. *Annals of Behavioral Medicine*. 2013;46(3):273-84. doi: 10.1007/s12160-013-9513-7.

55. Finkbeck U, Arendt M, Ortolan E, Walchli H, Rehdiger A, Schneider A, et al. Mindfulness-based intervention for somatization disorder and functional somatic syndromes - randomized trial with one-year follow-up. *Journal of Psychosomatic Research*. 2013;74(1):31-40. doi: 10.1016/j.jpsyres.2012.09.006. Published PMID: 236933001.

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57. Grodenberg D, Kaplan KJ, Nadelman MG, Brody R, Smith S, Schmidt CH. A Controlled Study of a Stress-Reduction, Cognitive Behavioral Treatment Program in Fibromyalgia. *General Hospital Psychiatry*. 1993;15(5):284-9. doi: 10.1016/0193-9891(93)90020-0.

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62. Amutio A, Ferraz C, de Cidre-Cabreriz A, Ferraz C, de Cidre-Cabreriz A, Ferraz C, et al. Mindfulness-based stress reduction for reducing anger, anxiety, and depression in fibromyalgia patients. *Frontiers in Psychology*. 2015; 6:1015. Published PMID: 26154385.

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**Table over item 11 and 12 in TIDieR-checklist specified**

<b>Authors</b>	<b>Strategies to improve or maintain intervention adherence and fidelity</b>	<b>Extent of intervention adherence</b>	<b>Effect size, follow-up</b>
Luciano et al. (36) (ACT)	Instructors were video recorded, participants were interviewed before intervention	n=45: 88% completed the intervention	Pain: -0.66, depression: -1.01, anxiety: -0.73, health-related quality of life: -1.06
Wicksell et al. (40) (ACT)	Instructors were video recorded. If unable to attend a session, 30-minutes summary were provided	n=19: 87% completed the intervention	Pain: -0.80, depression: -0.63, anxiety: -0.54
Simister et al. (42) (Online ACT)	E-mail reminders to participants	n=30: 100% completed the intervention	Pain: -0.11, depression: -0.55, sleep quality: -0.52, mindfulness: -0.25
Cash et al. (41) (MBSR)	Attendance monitored and absence tracked	n=51: 82% completed at least 4 of 8 sessions	Pain: 0.00, sleep quality: -0.31
Septon et al. (39) (MBSR)	Attendance monitored and absence tracked	n=51: 82% completed at least 4 of 8 sessions	Depression: -0.19
Astin et al. (34) (MBSR)	No strategies reported	n=31: 61% completed the intervention	Pain: -0.04, depression: -0.20
Grossmann et al. (35) (MBSR)	No strategies reported	n=39: 88% completed at least 4 of 8 sessions	*Pain: -0.01, depression: -0.49, anxiety: -0.21,
Schmidt et al. (38) (MBSR)	No strategies reported	n=45: 89% completed at least 4 of 8 sessions	Pain: -0.09, depression: -0.16, anxiety: -0.09, sleep quality: -0.08, health-related quality of life: -0.17, mindfulness: -0.29
Parra Delgado et al. (37) (MBCT)	No strategies reported	n=15: 88% completed the intervention	Depression: -0.80

\*End of treatment data.

## GRADE evidence profile

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control	Relative (95% CI)	Absolute (95% CI)	

### Pain End of treatment

7	randomised trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	not serious	none	263	331	-	SMD 0.46 SD lower (0.75 lower to 0.17 lower)	⊕⊕○○ LOW
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### Pain Follow-up

6	randomised trials	serious <sup>c</sup>	not serious	not serious	serious <sup>d</sup>	none	224	313	-	SMD 0.25 SD lower (0.52 lower to 0.01 higher)	⊕⊕○○ LOW
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### Depression End of treatment

8	randomised trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	not serious	none	277	347	-	SMD 0.49 SD lower (0.85 lower to 0.12 lower)	⊕⊕○○ LOW
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### Depression Follow-up

7	randomised trials	serious <sup>c</sup>	serious <sup>b</sup>	not serious	not serious	none	238	329	-	SMD 0.48 SD lower (0.77 lower to 0.19 lower)	⊕⊕○○ LOW
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### Anxiety End of treatment

4	randomised trials	serious <sup>a</sup>	not serious	not serious	not serious	none	150	228	-	SMD 0.37 SD lower (0.71 lower to 0.02 lower)	⊕⊕⊕○ MODERATE
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### Anxiety Follow-up

3	randomised trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>d</sup>	none	111	210	-	SMD 0.44 SD lower (0.9 lower to 0.02 higher)	⊕○○○ VERY LOW
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**Sleep quality End of treatment**

3	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>d</sup>	none	126	173	-	SMD 0.33 SD lower (0.7 lower to 0.04 higher)	⊕⊕○○ LOW
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**Sleep quality Follow-up**

3	randomised trials	serious <sup>a</sup>	not serious	not serious	not serious	none	128	175	-	SMD 0.25 SD lower (0.5 lower to 0 )	⊕⊕⊕○ MODERATE
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**Health-related quality of Life End of treatment**

2	randomised trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>d</sup>	none	92	152	-	SMD 0.62 SD lower (1.52 lower to 0.28 higher)	⊕○○○ VERY LOW
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**Health-related quality of Life Follow-up**

2	randomised trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>d</sup>	none	92	152	-	SMD 0.62 SD lower (1.52 lower to 0.28 higher)	⊕○○○ VERY LOW
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**Mindfulness End of treatment**

2	randomised trials	serious <sup>a</sup>	not serious	not serious	not serious	none	75	134	-	SMD 0.4 SD lower (0.69 lower to 0.11 lower)	⊕⊕⊕○ MODERATE
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**Mindfulness Follow-up**

2	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>d</sup>	none	77	136	-	SMD 0.28 SD lower (0.56 lower to 0.01 higher)	⊕⊕○○ LOW
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**Fatigue - not measured**

									-	0 (0 to 0)	-
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**Workability - not measured**

									-	0 (0 to 0)	-
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CI: Confidence interval; SMD: Standardised mean difference

## Explanations

- a. The Risk of Bias show High Risk on attrition bias, selection bias and performance bias. In addition there are some uncertainty and unclear risk.
- b. The p-value is low and the I-square is high.
- c. The Risk of Bias show High Risk on attrition bias and performance bias. In addition there are some uncertainty and unclear risk.
- d. The confidence interval goes from a large effect in favor of mindfulness to a small effect in favor of control.
- e. The Risk of Bias show High Risk on performance bias. In addition there are some uncertainty and unclear risk.

MEDLINE

Search Strategy:

- 
- 1 Fibromyalgia/ (8417)
  - 2 Chronic Pain/ (10259)
  - 3 fibromyalg\*.tw,kf. (9869)
  - 4 (chronic adj1 widespread adj1 pain).tw,kf. (803)
  - 5 or/1-4 (21108)
  - 6 Mindfulness/ (1728)
  - 7 "Acceptance and Commitment Therapy"/ (230)
  - 8 mindfulness\*.tw,kf. (4958)
  - 9 (acceptance and commitment therap\*).tw,kf. (648)
  - 10 ((awareness adj6 attention) and (medit\* or vipassana)).tw,kf. (75)
  - 11 or/6-10 (5692)
  - 12 5 and 11 (235)
  - 13 randomized controlled trial.pt. (505234)
  - 14 controlled clinical trial.pt. (100418)
  - 15 (randomized or placebo or randomly or trial or groups).ab. (2593502)
  - 16 or/13-15 (2740891)
  - 17 12 and 16 (111)
  - 18 limit 17 to yr="1990 -Current" (111)

## Risk of bias summary

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Astin 2003	+	+	+	+	-	?	+
Cash 2015	+	?	?	+	?	?	+
Grossman 2007	-	-	+	+	-	?	?
Luciano 2014	+	+	-	+	+	?	?
Parra-Delgado 2013	+	?	-	+	+	?	+
Schmidt 2011	+	+	+	+	+	+	+
Septon 2007	+	?	?	+	?	?	+
Simister 2018	+	+	-	+	+	?	+
Wicksell 2012	?	+	-	?	+	?	+

### Reasons for high risk of bias

Astin 2003 et al. (34): Incomplete outcomes; 26 % never attended a class. Of 128 randomized into 2 groups, 50 (39%) dropped out from the study prior to 'end of treatment', 61 (48%) dropped out by week 16, and 63 (49%) failed to complete 24 week assessment.

Grossman 2007 et al. (35): Random sequence generation; quote p. 228: 'A quasi-random allocation to treatments was based upon alternation of small groups of patients according to time of enrollment'. Allocation concealment; Alternation of small groups of patients according to time of enrollment. The first 31 patients who enrolled comprised the initial two MBSR groups; the next consecutive 15 patients formed the control group, which was then followed with subsequent MBSR groups. Incomplete outcomes; 26 of 58 participants in follow-up.

Luciano 2014 et al. (36): Blinding of participants and personnel; Not blinded.

Parra-Delgado 2013 et al. (37): Blinding of participants and personnel; Participants were probably aware of assignment.

Simister 2018 et al. (42): Blinding of participants and personnel; quote p. 743: 'a registered physiotherapist...remained blind to participants' assigned condition for the duration of the study'. Participants were probably aware of assignment

Wicksell 2012 et al. (40): Blinding of participants and personnel; Wait-list control.

## Paper II

Trond Haugmark, Kåre Birger Hagen, Sella Aarrestad Provan, Elisebeth Bærheim, Heidi A. Zangi (2018) Effects of a community-based multicomponent rehabilitation programme for patients with fibromyalgia: protocol for a randomized controlled trial. *BMJ Open* 2018;8:e021004. doi: 10.1136/bmjopen-2017-021004

# BMJ Open Effects of a community-based multicomponent rehabilitation programme for patients with fibromyalgia: protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** People with fibromyalgia (FM) suffer from symptoms such as widespread pain, non-refreshing sleep, fatigue and reduced quality of life. Effects of pharmacological treatment are questionable and non-pharmacological treatments are recommended as first-line therapy. To date the majority of patients with FM in Norway are not offered any targeted treatment. The aim of this randomised controlled trial is to investigate the effects of a community-based multicomponent rehabilitation programme comprising an acceptance-based and mindfulness-based group intervention, the Vitality Training Programme (VTP), followed by tailored physical activity counselling.

**Materials and methods** General practitioners refer potential participants to a rheumatologist in specialist healthcare for diagnostic clarification and assessment of comorbidities. Inclusion criteria are widespread pain/FM  $\geq 3$  months, age 20–50 and work participation (minimum part-time) within the last 2 years. The intervention group attends the VTP comprising 10 weekly 4 hour group sessions plus a booster session after 6 months. Thereafter, they receive 12 weeks of individually tailored physical exercise counselled by physiotherapists at community-based Healthy Life Centers. The control group follows treatment as usual. The primary outcome is Patient Global Impression of Change. Secondary outcomes include self-reported pain, fatigue and sleep quality, psychological distress, mindfulness, health-related quality of life, physical activity, work ability and exercise beliefs and habits. To achieve a power of 80% and allow for 10% dropout, 70 participants are needed in each arm. All analyses will be conducted on intention-to-treat bases and measured as differences between groups at 12 months follow-up.

**Ethics and dissemination** The study is approved and granted by the Norwegian South-Eastern Regional Health Authority (reference 2016015). Ethics approval was obtained from Regional Committee for Medical and Health Research Ethics (reference 2015/2447/REK sør-øst A). Results will be submitted to appropriate journals and presented in relevant conferences and social media.

**Trial registration** ISRCTN 96836577.

## Strengths and limitations of this study

- The multicomponent rehabilitation programme consists of modalities that have previously been found to be effective for people with rheumatic and musculoskeletal diseases.
- Sustainability of effects will be measured at 1-year follow-up.
- The inclusion of patients from both rural and urban communities will enhance the generalisability of the results.
- It is not possible to examine the effectiveness of single components of the programme.
- Some participants may experience the multicomponent rehabilitation programme to be too comprehensive and time-consuming.

## INTRODUCTION

Fibromyalgia (FM) is a heterogeneous and still unexplained disease that poses major personal and societal challenges in terms of disease burden, non-fatal health loss and costs.<sup>1,2</sup> It is one of the most common chronic pain conditions with an estimated prevalence of 2% worldwide.<sup>3</sup> In Norway, it is estimated that FM affects as much as 6% of the women and 3% of the men.<sup>4</sup> The cardinal symptom of FM is widespread pain characterised by reduced pressure pain thresholds and hyperalgesia. In 2010, the American College of Rheumatology (ACR) introduced new diagnostic criteria that also included other somatic symptoms, such as non-refreshing sleep, fatigue, difficulties with memory and concentration, irritable bowel syndrome, headache and depression.<sup>5</sup> The complexity of FM symptoms commonly reduces patients' well-being and has an important influence on their quality of life.<sup>6</sup> In Norway, FM is a common cause of sick leave, disability benefit

and extensive use of healthcare services.<sup>4</sup> Although the FM diagnosis has become increasingly recognised during the last decades, there are still some physicians who question its validity. Several patients experience disbelief, lack of understanding and stigmatisation from their general practitioners (GPs) as well as from the social security systems, colleagues and family.<sup>3,7</sup>

Current treatments for FM are non-curative and the efficacy of pharmacological treatment alone is questionable.<sup>8</sup> Recent updated evidence-based recommendations from the European League Against Rheumatism conclude that optimal management requires prompt diagnosis and thereafter a graduated follow-up.<sup>9</sup> The initial management of FM should focus on patient education and non-pharmacological interventions, such as graded physical exercise and individually tailored psychological therapies for those with mood disorder or unhelpful coping strategies. The interventions may be combined in multicomponent rehabilitation programmes. Pharmacotherapy is only recommended for severe pain and sleep disturbances.<sup>9</sup>

In Norway, the main responsibility for management of FM is assigned to the primary healthcare services.<sup>10</sup> Some patients with FM are referred to physiotherapists and a few to rehabilitation in specialist care. However, to date, the majority of patients with FM are not offered any tailored treatment in the primary healthcare.

### Mindfulness-based and acceptance-based training for patients with FM

It has been shown that women with FM may have maladaptive emotion regulation styles, such as difficulty in identifying and expressing feelings, which amplify pain and impede their adjustment to the disease. Moreover, women with FM commonly experience stressful and negative emotions related to depressive mood and anxiety.<sup>11,12</sup> In mindfulness-based and acceptance-based therapies, participants learn to accept their experiences of pain and stressful thoughts and emotions as part of human life that one can relate to rather than judging them as good or bad, positive or negative and thus fostering better emotional regulation.<sup>13</sup> The core aspect of mindfulness is training in moment-to-moment awareness of internal experiences, such as thoughts, emotions and body sensations with an attitude of openness, curiosity, patience and acceptance.<sup>14</sup> Increased acceptance is believed to decrease the struggle to control what might not be controllable and seems to be associated with better treatment outcomes for pain patients.<sup>15</sup> Systematic reviews on mindfulness training for patients with FM have shown evidence for small, but significant improvements of pain, depression, anxiety and quality of life.<sup>16,17</sup>

A Norwegian mindfulness-based and acceptance-based group intervention, the Vitality Training Programme (VTP) was developed for patients with chronic musculoskeletal pain in the late 1990s.<sup>18</sup> It was later adjusted for patients with inflammatory arthritis (IA).<sup>19</sup> The VTP incorporates mindfulness training, values-based

action and various creative methods. The main goals are to enhance participants' awareness of their health promoting resources and to strengthen their inner authority and abilities to make conscious choices in line with their personal values. Two randomised controlled trials on the VTP, one in patients with chronic musculoskeletal pain, including FM, and one in patients with IA, showed reduced psychological distress, improved pain coping and mental well-being in the intervention groups compared with the control groups. The group with IA also showed decreased fatigue and increased self-efficacy. The effects were sustained or increased at 1-year follow-up.<sup>19,20</sup> However, a longitudinal pre-post-test study on the VTP in patients with IA and FM showed substantial improvements in the IA group, but no changes in the FM group.<sup>21</sup> The reason for these differences remains unclear, but it may be related to the long symptoms duration without any targeted treatment in the patients with FM. On average, these patients had experienced pain symptoms more than 10 years before they were diagnosed with FM. Living with pain over many years without access to relevant treatment might lead to development of maladaptive coping strategies that may be difficult to change. Hence, it was suggested that future studies should investigate effects of the VTP in patients with FM with more recent disease onset.<sup>21,22</sup> The VTP is implemented in some rheumatology specialist departments and in specialist rehabilitation, but to date there is no systematic implementation and evaluation in primary healthcare.

### Physical exercise for patients with FM

Physical exercise has been defined as physical activity that is planned, structured and repetitive with the goal to maintain or improve physical fitness, that is, cardiorespiratory endurance, muscular strength and flexibility.<sup>23</sup> Studies have demonstrated that compared with healthy women people with FM are less physically active.<sup>24</sup> Two systematic reviews on physical exercise in patients with FM found evidence that aerobic exercise reduces pain, fatigue and depressed mood and improves health-related quality of life and physical fitness.<sup>25,26</sup> The amount and intensity of initial aerobic exercises should be adapted to the individual level of physical fitness and patients should start at a level just below their capacity and gradually increase the duration and intensity.<sup>25</sup> Studies have demonstrated that appropriately progressed muscle strengthening activities is safe and effective for individuals with FM and should be considered as part of a multicomponent rehabilitation programme.<sup>26</sup>

Since 2004, Healthy Life Centres (HLCs) have been established in most Norwegian municipalities.<sup>27</sup> The HLCs are based on a salutogenic framework aiming at strengthening peoples' capacities to use their own health resources and make health-friendly choices. They provide low-threshold easily accessible activities and interventions targeted at supporting behavioural changes and management of lifestyle issues, such as indoor and outdoor physical activity, healthy diet



courses, smoking cessation and short mental health interventions. The physical activity interventions include aerobic and strengthening exercises usually twice a week for a 12-week period. Some HLCs also offer yoga and mindfulness exercises. Health professionals working at HLCs are mainly physiotherapists and nutritionists. All are educated in Motivational interviewing (MI), which is both a treatment philosophy and a set of methods employed to help people increase intrinsic motivation by exploring and resolving ambivalence about behavioural change. MI has demonstrated effectiveness for clients regardless of problem severity, age and gender.<sup>28</sup> One of the main groups that use HLCs is people with chronic pain condition, including FM. However, many patients with FM are reluctant to participate in the general exercises because they are afraid of increasing their pain. For patients with FM, it seems to be important that the exercise programmes are individually tailored and that the graded approach is followed.

### Aim and research questions

The overall aim of this trial is to evaluate the effects of a multicomponent rehabilitation programme for patients with newly diagnosed FM delivered in primary healthcare.

The primary objective is to study the hypothesis that patients with newly diagnosed FM who participate in a community-based multicomponent rehabilitation programme will improve their self-perceived health compared with patients who follow their 'treatment as usual'. The rehabilitation programme comprises the VTP plus 12 weeks physical activity counselling at a HCL.

More specifically, the study will investigate the following research questions:

1. Does a community-based multicomponent rehabilitation programme relieve symptoms burden of patients with newly diagnosed FM in terms of reduced pain, fatigue, sleep disturbances and psychological distress?
2. Does a community-based multicomponent rehabilitation programme increase physical activity of patients with FM?
3. Does a community-based multicomponent rehabilitation programme increase work ability of patients with newly diagnosed FM?

### Trial development and design

A project group including a patient representative, two GPs, a representative for community rehabilitation service, a rheumatologist and health professionals educated as VTP facilitators have been involved in the project development and will be consulted throughout the trial. The study is a pragmatic parallel randomised controlled trial with two arms (ISRCTN 96836577). The multicomponent rehabilitation programme is a complex intervention with several interacting components, such as a group intervention with several interactive methods plus individually tailored physical exercise counselling. The project group has followed the new Medical Research Council guidance for Developing and evaluating complex interventions.<sup>29</sup>

The protocol has been developed in line with the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials)<sup>30</sup> (online supplementary file 1).

## METHODS

### Study setting and recruitment of participants

The trial is a collaboration between the rheumatology specialist department at Diakonhjemmet Hospital in Oslo, two municipal districts in the city of Oslo and six rural municipalities in geographical proximity to Oslo. GPs and physiotherapists in the eight municipalities will identify potential patients and refer the patients to a rheumatologist at Diakonhjemmet Hospital for diagnosis clarification and assessment of comorbidities. To enhance recruitment, the project coordinator (TH) and the project leader (HAZ) have visited all GP offices in the eight municipalities and written information is sent by email and per post. Moreover, flyers have been distributed to offices and waiting areas for potential patients informing them to contact their GP if they are in the target group for the project. Information is also shared in relevant website and social media.

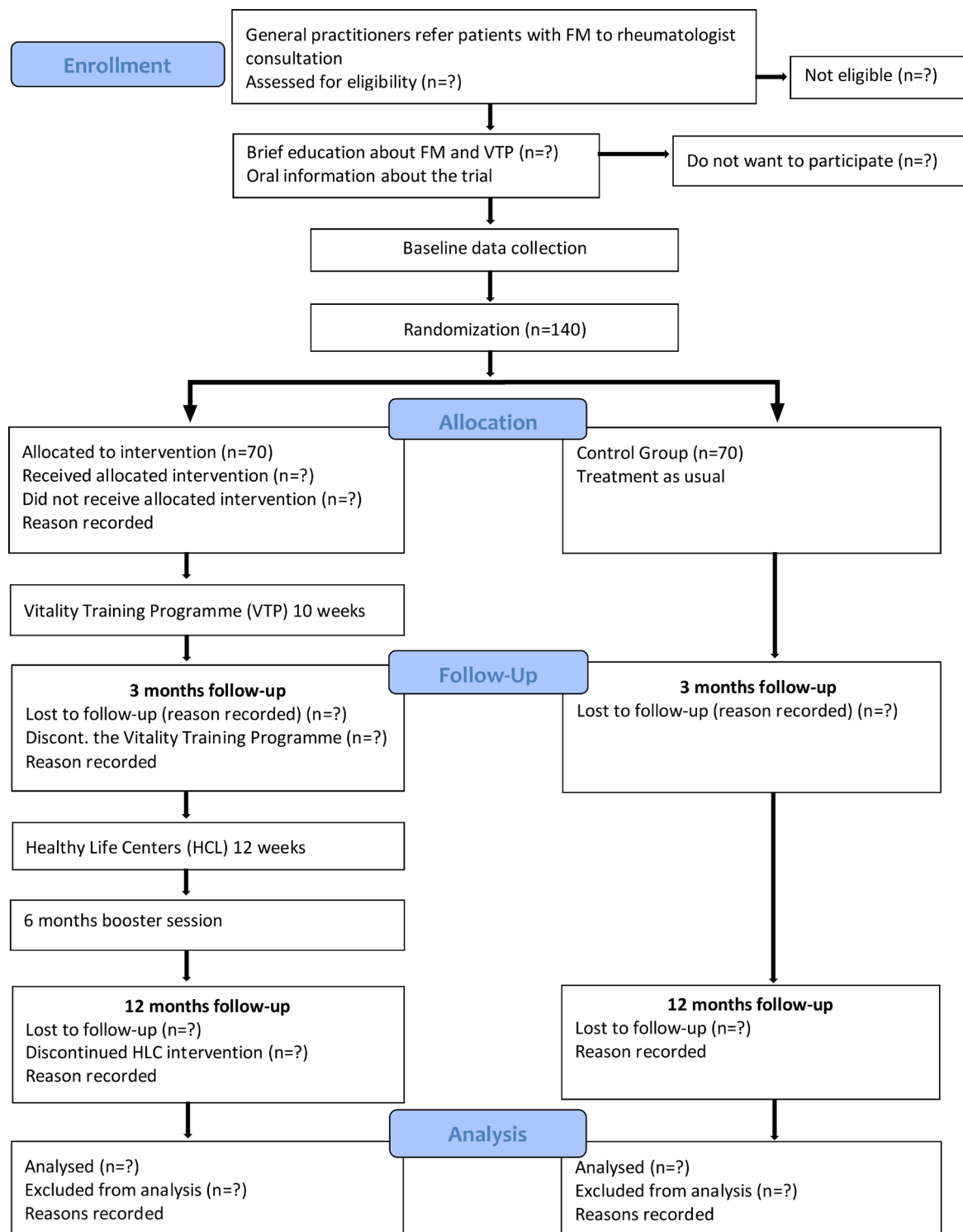
Patients will be examined and screened for eligibility by the rheumatologist. All eligible patients will be offered a 3-hour FM group education programme by a rheumatologist and a nurse, aimed at providing basic understanding about FM, pain mechanisms, psychological factors, physical activity and coping strategies. Short mindfulness and yoga exercises will be introduced. This programme is currently part of standard care for patients with FM at Diakonhjemmet Hospital. Additionally, the project coordinator will inform about the VTP and present the logistics of the study. The patients have the opportunity to ask questions before they consent to participate. The programme will be arranged regularly throughout the recruitment period until the target sample size is obtained.

The multicomponent rehabilitation programme will be conducted in the municipalities. HAZ and TH will organise the VTP at central places in Oslo and the rural municipalities. The physical exercise will take place at a HCL in the participants' home communities. If the community has not yet established a HCL, the participants will be referred to a HCL in a nearby community. Participants will follow the HLC's ordinary 12-week physical activity counselling and exercise programme (figure 1).

### Eligibility criteria

Patients are eligible for inclusion if they are diagnosed with FM according to the ACR 2010 criteria for FM<sup>5</sup> and aged between 20 and 50 years. Patients will be excluded if they have a comorbid inflammatory rheumatic disease, have been out of work for more than 2 years due to their pain condition, have a serious psychiatric disorder, have another disease that does not allow physical exercise or are unable to understand and write Norwegian.





**Figure 1** Study flowchart. FM, fibromyalgia.

## Interventions

### The Vitality Training Programme

The VTP comprises 10 weekly 4-hour group sessions plus a booster session after about 6 months. Each group have between 8 and 12 participants. Every session addresses a specific topic related to living with long-lasting health challenges: If my body could talk/Who am I?/Values—what is important to me?/What do I need?/Strengths and limitations/Bad conscience/Anger/Joy/Resources,

potentials and choices/The way ahead<sup>18 19</sup> (online supplementary file 2). The participants are invited to explore these topics by using various creative methods, such as guided imagery, music, drawing, poetry and metaphors. The purpose is to provide opportunities for personal discoveries by intentionally attending to emotional, cognitive and bodily experiences. Participants are also invited to write logs from all exercises and to share their experiences and discoveries with other group participants.

Moreover, participants are invited to attend to mindfulness meditation exercises, that is, body scan, sitting and walking meditation and breathing exercises. They are provided with guided mindfulness audio files and are encouraged to practice these exercises in everyday life and to train awareness in daily activities. Moreover, the VTP includes gentle yoga exercises that can help participants explore their physical boundaries and overcome barriers to movement. Throughout the programme, participants learn how to balance rest with activity, identify activities that are important and healthful to them and how to overcome barriers to prioritise these activities (values-based action).

All groups have two facilitators who are certified through a 1 year university training programme (30 crd) at VID Specialized University in Oslo. They follow a manual with a thorough programme description.<sup>18</sup> Adherence to the intervention, that is, attendance in group sessions will be recorded by the group facilitators. The participants need to attend at least 50% of the sessions to expect effect. They will also be asked to report any adverse events (online supplementary file 3).

#### Individual physical activity counselling and tailored physical exercise

After completing the VTP, participants will be offered individual physical activity counselling by a physiotherapist at the HLCs. Interviews based on MI with focus on individual planning and goalsetting on activity and participation level will be conducted before start-up, after 6 weeks and at the end of week 12. The goals will be defined by the participant in collaboration with a physiotherapist. A common goal may be to reduce pain. An activity plan may be to perform strengthening and aerobic exercises, for example, cycling or Nordic walking three times a week. Another aim is to learn the balance between activity and rest and find the right dosage of the exercises. The purpose of the counselling is to help participants identify and overcome barriers to physical activity, to find exercises that can be easily continued in their everyday life and gradually increase their levels of physical activity. The physical exercise will be adapted to each participant's individual level of physical fitness. The physiotherapists will record adherence to the HLC intervention and any adverse events during the 12-week period.

#### Control group

Patients randomised to the control group will not receive any intervention other than the 3-hour FM education. They will follow their 'treatment as usual' in primary care, that is, GP consultations and any physical activity they may choose. At the FM course, all participants are told that they can follow any new information as they would like. This means that control group participants may initiate life-style changes on their own initiative. There are no restrictions on participation in physical activities during the trial. The control group will be offered the VTP after

completion of the last data collection, that is, 1 year after inclusion.

#### Outcomes

Outcome measures are selected according to the core set of domains for FM defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT).<sup>31 32</sup> All outcomes are self-reported.

Primary outcome will be Patient Global Impression of Change (PGIC) that evaluates overall health status as perceived by the patient in a 7-point single-item scale ranging from 1 ('I feel very much worse') through 4 ('no change') to 7 ('I feel very much better') 1 year after inclusion.<sup>33</sup> Scores of 6 and 7 are considered clinically relevant improvement.<sup>34</sup> This measure has previously been used in FM trials.<sup>33 35 36</sup>

Secondary outcomes related to the specific research questions will be collected at baseline, 3 and 12 months. The outcomes include:

- ▶ *Pain, fatigue and sleep quality* assessed by Numerical Rating Scales scored from 0 to 10 (10 is intolerable pain/fatigue/very bad sleep quality).
- ▶ *Psychological distress* assessed by the General Health Questionnaire-12 (GHQ-12), a widely used screening instrument measuring aspects of psychological health during the last 2 weeks.<sup>37</sup> The GHQ-12 comprises six positively phrased items, indicating psychological health, and six negatively phrased items, indicating psychological distress. The respondents are requested to compare their current status with what they consider as their 'normal' condition on a four-point Likert scale, scored from 0 (less than usual) to 3 (much more than usual). This gives a possible sum score between 0 (no distress at all) and 36 (much more distress than usual).<sup>37 38</sup>
- ▶ *Mindfulness* assessed by The Five Factor Mindfulness Questionnaire (FFMQ) that measures a general tendency to be mindful in daily life. FFMQ comprises 39 items rated on a five-point Likert scale from 1 (never or very rarely true) to 5 (always or almost always true).<sup>39 40</sup>
- ▶ *Health-related quality of life* assessed by the EuroQol (EQ-5D-5 L) comprising five dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is scored on five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Additionally, 'perceived health today' is scored from 0 (as bad as it could be) to 100 (as good as it could be).<sup>41</sup> The instrument has been validated in similar populations<sup>42</sup> and in Norwegian context.<sup>43</sup>
- ▶ *Physical activity* assessed by three questions addressing the average number of times exercising each week and the average intensity and average duration each week.<sup>44</sup>
- ▶ *Motivation and barriers for physical activity* assessed by the Exercise Beliefs and Exercise Habits questionnaire comprising 20 items that reflect beliefs about

one's ability to exercise, barriers to exercise, benefits of exercise and impact of exercise on muscular pain. Items are scored on a five-point Likert scale, ranging from strongly agree to strongly disagree.<sup>45</sup>

- ▶ *Work ability* assessed by the Work Productivity and Activity Impairment General Health V2.1 (WPAI:GH) that comprises six questions to determine employment status, hours missed from work because of health problems or other reasons, hours actually worked, the degree to which health problems affected work productivity while at work and activities outside of work.<sup>46</sup> WPAI outcomes are expressed as impairment percentages with higher numbers indicating greater impairment and less productivity.

Moreover, the data collection includes self-reported healthcare consumption, that is, visits to GP, rheumatologist, physiotherapist and other healthcare professionals, use of medication and alternative treatments. Self-reported adverse events will be collected electronically at 12 months. The respondents report if they have or have not experienced any adverse events. If relevant, the respondents report whether they perceived the events caused by the VTP or the HLC intervention with the possibility to elaborate (online supplementary file 3).

### Sample size

Sample size calculation is based on the primary outcome assuming that 10% in the control group will report that they 'feel much better' or 'very much better' after 12 months<sup>35</sup> and that at least a 20% absolute difference in improvement rate between the groups can be considered as a minimal clinically relevant difference. We anticipate 10% losses to follow-up and will need 70 participants in each group to have at least 80% power of detecting differences with 5% alpha level.

### Randomisation and allocation concealment

A statistician has generated an electronic randomisation list based on blocks of 20–24 for each geographical area to ensure approximately equal sample sizes. Participants will be given consecutive numbers. A secretary not involved in the data collection or the intervention will allocate each participant to the corresponding number on the randomisation list and inform the patients about group allocation by telephone and written letter. Due to the nature of the implementation strategy, it is not possible to blind the patients or the health professionals. The project leader and the research coordinator who are responsible for the data collection and data analyses will not be aware of group allocation.

### Data collection

Participant flow is shown in [figure 1](#). Data will be collected electronically by a solution delivered by Infopad (<http://www.infopad.no>) before randomisation (baseline), after the VTP (3 months) and at 12 months from baseline. This electronic solution is risk evaluated and follows the Code

of Conduct for information security in the healthcare and care services.<sup>47</sup>

Participants will be registered in the electronic system by the project coordinator. Participants receive an email with a unique link to the questionnaire at each assessment point and can respond to the questionnaire on their individual electronic device (computer, mobile phone or tablet). Participants who do not possess an electronic device will receive a paper version of the questionnaire.

### Statistical analysis

The treatment effects will be analysed on an intention-to-treat basis with all randomised participants retaining their original allocated group and measured as differences between groups at 12 months. Analyses of covariance will be used for continuous outcomes with baseline values as covariates. Logistic regression analyses for dichotomous outcomes. The level of significance will be set to  $p \leq 0.05$  and the confidence level to 95%. We will use the STATA V.14.0 (Texas, USA) to analyse the data.

### Ethical approval

Study design, information strategy, written consent formula and data security are approved by the Regional Committee for Medical and Health Research Ethics (2015/2447/REK sør-øst A). The trial will be carried out in accordance with the Helsinki Declaration. Participants will receive written and oral information about the study processes and interventions before they sign a written declaration of voluntary participation. They have the right to withdraw from the study at any time without any explanation.

All included participants will receive a consultation with a rheumatologist and a brief patient education intervention that either corresponds to or is better than their currently provided care. Participants who are randomised to the multicomponent rehabilitation programme will receive a potentially more effective intervention. Control group participants will receive the current standard of care that is delivered in their respective community. Thus, no participants will receive an intervention that is below standard treatment. Any potential adverse events will be registered throughout the trial period. All personal information about potential and enrolled patients as well as patient consent forms will be securely stored in paper formats in a locked closet in a locked room. Electronic data will be stored in a password protected solution (<http://www.infopad.no>) during the study and for 5 years after completion. The project leader (HAZ) will regularly review the data collection process and ensure that the data are collected, stored and handled in accordance with the current guidelines. The data are only available to the project leader (HAZ), the project coordinator (TH) and the project secretary.

### Patient and public involvement

The VTP was developed in the 1990s in close collaboration with people with chronic musculoskeletal pain.<sup>18</sup>

The burden of the intervention has been assessed in the two previous randomised controlled trials.<sup>18 22</sup> The present project emerged from informal conversations between the project manager (KBH), the project leader (HAZ) and the leader of the FM group in the Norwegian Rheumatism Association (EB). Further development of the project, such as study design, research questions and recruitment of patients has been thoroughly discussed with representatives for the Patient Advisory Board at the rheumatology department at Diakonhjemmet Hospital. The electronic questionnaire has been tested and amended by user representatives.

In addition to publishing in international peer-reviewed journals, the results of the study will be disseminated through various information channels to the project group members and the public, including websites, social media, national and international networks, conferences and congresses. Moreover, the results will be published in a yearly special issue of the journal of the Norwegian Rheumatism Association that focuses on recent research and communicated to patients in relevant meetings arranged by this association.

## DISCUSSION

FM is a complex chronic condition with extensive use of healthcare services and important impact on patients' quality of life. Current pharmacological treatments for patients with FM are not curative and initial management should be non-pharmacological.<sup>9</sup> Patients with FM should be treated in primary healthcare, but to date the majority of patients with FM are not offered any targeted interventions. This paper describes the rationale and design of an RCT investigating the effects of a multicomponent community-based rehabilitation programme for patients with FM. The rehabilitation programme will fill a gap in the management of people with FM and if found effective, can be recommended as a rehabilitation model for people with FM in primary healthcare. We aim at reaching patients at an early stage of their disease to prevent further development of disability and therefore we will include only patients of 50 years and below and patients who have not been out of work for more than 2 years due to their pain condition. The design of the multicomponent rehabilitation programme is based on updated international recommendations for management of FM, including a group-based coping intervention to strengthen patients' health promoting resources (the VTP) and graded physical exercise.<sup>9</sup> The rationale for offering patients the VTP before the physical activity counselling is that many patients may have previous stressful life experiences and emotional burdens that may be a barrier to lifestyle change.<sup>48</sup> Throughout the VTP, the participants may acquire alternative coping strategies and more constructive ways to deal with stress, which may facilitate their participation in physical exercise. The individual physical activity counselling will follow the current practice at the HLCs and thus ensure the feasibility of

the intervention and strengthen the external validity of the study. The inclusion of patients from both rural and urban communities will also enhance the generalisability of the results.

Some participants may experience the multicomponent rehabilitation programme to be too comprehensive and recruiting sufficient number of patients may be a challenge. GPs in the respective municipalities will be approached with information about the project before and during the study period. Moreover, potential participants will be given extensive information about the programme before they consent to participate and again before they start the VTP in order to enhance adherence. Previous research shows that behavioural change takes time and that interventions that include multiple strategies are more successful.<sup>49</sup> Many patients with FM express frustration about the lack of treatment possibilities and have felt neglected by the healthcare system.<sup>50</sup> They are likely to be motivated to receive any treatment that can improve their condition. Moreover, the Norwegian social security system can provide 'sick-leave for single treatment days' to facilitate participation during work time.

The effect of the intervention will be measured in accordance with its aims and content. The validity of the primary outcome measure, PGIC, has been assessed in a prospective observational cohort study in patients with FM and was found to be a clinically relevant measure to assess perceived impact of disease management.<sup>33</sup> The secondary outcomes are based on a recommended core set from OMERACT<sup>32</sup> and thus enable comparison with results from other studies.

The study has been developed in close collaboration with a project group comprising a patient partner, a rheumatologist, two GPs and a health professional representing rehabilitation service in one of the communities. If the intervention is proven effective, this group will contribute to disseminating and implementing the results in clinical practice.

## Trial status

Enrolment for the trial began in November 2016 and recruitment is still in progress. Data collection will continue until the target sample size is reached, approximately December 2018.

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**Contributors** HAZ, KBH and EB conceived the project idea and designed the study. TH, HAZ and SAP are responsible for recruitment. TH and HAZ are responsible for acquisition of data and data management. TH has drafted the manuscript. HAZ has critically revised the manuscript. SAP, KBH and EB have read and approved the final manuscript.

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**Competing interests** None declared.

**Patient consent** Not required.



**Ethics approval** The researchers have obtained approval from the Regional Committee for Medical and Health Research Ethics in South East Norway (2015/2447/REK sørøst A). Written consent to participate will be collected before enrolment to the trial.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## **Online Supplementary file 2**

### **Example from group session 6: Anger**

The first part of the programme is common in all sessions: Participants are invited to share their reflection on experiences from home exercises after previous session in group of three to four persons. They are encouraged to read their reflective diaries for each other and to share and listen with an open, non-judgemental attitude without discussing or giving advice. Next, participants are invited to take part in an awareness exercise instructed by one of the group facilitators. They are guided to attend to their thoughts, feelings and bodily senses in the present moment with openness, acceptance and curiosity. After the exercise, they are invited to share their experiences with one other person in the group.

In the next part of the session, the group facilitators introduce the topic “anger” by giving a short introduction about relationship between chronic illness and emotions and the purpose of addressing emotions. The participants are then invited to take part in an exercise with awareness of anger, introduced by one of the facilitators: “Think of the word anger... or to be angry. Notice what you become aware of... thoughts, maybe concrete situations, perhaps memories from the past... Are the situations that you become aware of new or old? Maybe both?... What do you experience in your body right now when you think of anger or being angry?... Also note whether the word anger or being angry evokes any other feelings...”

Awareness of anger is continued in movement to music. The music allows participants to express anger with their body and they are invited to let their bodies do what they want to do while listening to the music. Then, written hypothetical sentences are used to enhance discovery to tacit knowledge, for example: “If there are any other emotions related to my feeling of anger, it must be...” Participants are further invited to share and reflect upon experiences and discoveries from the exercise in small groups and in a plenary session.

The next exercise is a guided imagery intending to help individuals to connect to their experiences of anger in the present moment, and to explore its meaning. Further, crayons and white paper are used to draw an image of anger as experienced here and now. Again, participants are invited to share and reflect in small groups and in plenary, with focus on new discoveries and the consequences of these discoveries from the participants' daily life. Finally, they write a diary about their experiences from the whole session.

Before closing the session, participants are asked to be aware of how they relate both to their own anger and anger from others in their daily lives. They are provided with guided mindfulness audio files and are encouraged to practice these exercises in everyday life and to train awareness in daily activities. They are asked to write reflective diaries about their thoughts, emotions and bodily senses. The session ends with a relaxation exercise. Each session follows the same structure with exercise adapted to the particular topic.

The group facilitators in the SALSA trial are health professionals, such as nurses and physiotherapists, and certified through a one-year university training programme (30 crd) at VID Specialized University in Oslo.



## Online Supplementary file 3

### Self-reported adverse events assessed at 12-months.

Have you carried out any type of treatment during the last year? (With treatment we mean medication, physical exercise, self-management course or any alternative treatments) Yes/ No Have you experienced any adverse event as a result of the treatment? Yes/ No If yes, which adverse events as a result of treatment? Elaborate In your opinion, which treatment(s) do you think the adverse event was/were caused by? Elaborate

### Paper III

Trond Haugmark, Kåre Birger Hagen, Geir Smedslund, Sella Aarrestad Provan, Heidi A. Zangi. Effects of a mindfulness-based and acceptance-based group programme followed by physical activity for patients with fibromyalgia: a randomised controlled trial. *BMJ Open* 2021;11:e046943. doi:10.1136/bmjopen-2020-046943

# BMJ Open Effects of a mindfulness-based and acceptance-based group programme followed by physical activity for patients with fibromyalgia: a randomised controlled trial

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## ABSTRACT

**Introduction** Non-pharmacological approaches are recommended as first-line treatment for patients with fibromyalgia. This randomised controlled trial investigated the effects of a multicomponent rehabilitation programme for patients with recently diagnosed fibromyalgia in primary and secondary healthcare.

**Methods** Patients with widespread pain  $\geq 3$  months were referred to rheumatologists for diagnostic clarification and assessment of study eligibility. Inclusion criteria were age 20–50 years, engaged in work or studies at present or during the past 2 years, and fibromyalgia diagnosed according to the American College of Rheumatology 2010 criteria. All eligible patients participated in a short patient education programme before inclusion and randomisation. The multicomponent programme, a 10-session mindfulness-based and acceptance-based group programme followed by 12 weeks of physical activity counselling was evaluated in comparison with treatment as usual, that is, no treatment or any other treatment of their choice. The primary outcome was the Patient Global Impression of Change (PGIC). Secondary outcomes were self-reported pain, fatigue, sleep quality, psychological distress, physical activity, health-related quality of life and work ability at 12-month follow-up.

**Results** In total, 170 patients were randomised, 1:1, intervention:control. Overall, the multicomponent rehabilitation programme was not more effective than treatment as usual; 13% in the intervention group and 8% in the control group reported clinically relevant improvement in PGIC ( $p=0.28$ ). No statistically significant between-group differences were found in any disease-related secondary outcomes. There were significant between-group differences in patient's tendency to be mindful ( $p=0.016$ ) and perceived benefits of exercise ( $p=0.033$ ) in favour of the intervention group.

**Conclusions** A multicomponent rehabilitation programme combining patient education with a mindfulness-based and acceptance-based group programme followed by physical activity counselling was not more effective than patient education and treatment as usual for patients with recently diagnosed fibromyalgia at 12-month follow-up.

## Strengths and limitations of this study

- This pragmatic randomised controlled trial was conducted according to a predefined published protocol.
- The main treatment effects were analysed on an intention-to-treat basis at 12-month follow-up, with all randomised patients retaining their original allocated groups.
- Although we intended to capture patients with fibromyalgia at an early stage of their disease, the included patients reported median symptoms duration of 8 years.
- There was a high drop-out rate from the physical activity intervention.
- We did not monitor the content of 'treatment as usual' in the control group other than physical activity.

**Trial registration number** BMC Registry (ISRCTN96836577).

## INTRODUCTION

Fibromyalgia (FM) is characterised by widespread pain and symptoms such as fatigue, unrefreshed sleep, mood disturbances and cognitive impairment that have persisted more than 3 months without any alternative explanation.<sup>1</sup> Patients report unpredictable symptoms that vary in terms of expression and intensity, and reduced quality of life.<sup>2–5</sup> The estimated prevalence of FM in the general population worldwide is between 2% and 7%, with women being predominantly affected.<sup>6</sup> Many patients experience lack of understanding from their primary care physicians, insufficient healthcare and deficient treatment.<sup>7 8</sup>

For optimal management of FM, the European League Against Rheumatism (EULAR) recommends prompt diagnosis and patient education as first-line treatment. The



effects of pharmacological treatments are inadequate.<sup>4</sup> The management should aim at improving patients' health-related quality of life and initially focus on non-pharmacological modalities.<sup>4 9</sup> Individualised physical exercise is recommended for all patients with FM. Cognitive-behavioural therapy, mindfulness-based stress reduction, meditative movement (ie, qigong, yoga, tai chi), and hydrotherapy have shown promising effects for some patients, although the evidence is still insufficient.<sup>4</sup> Further, multicomponent programmes combining physical exercise with either of these modalities have shown beneficial synergetic effects on FM symptoms in terms of reduced pain and FM impact, and increased physical fitness at the end of treatment.<sup>4 10</sup>

Three recent systematic reviews and meta-analyses have shown that mindfulness-based and acceptance-based interventions had short-term small-to-moderate effects on pain, depression, anxiety, sleep quality and health-related quality of life in patients with FM.<sup>11–13</sup> Systematic reviews and meta-analyses on physical exercise in patients with FM have shown beneficial effects on symptoms, such as pain, sleep and physical function.<sup>14–18</sup>

A Norwegian mindfulness-based and acceptance-based intervention, the Vitality Training Programme (VTP), aimed at strengthening participants' health-promoting resources and ability to make choices in accordance with own values, has been evaluated in two randomised controlled trials in persons with chronic musculoskeletal pain and inflammatory arthritis (IA). The VTP improved pain, fatigue, psychological distress, pain coping, and self-efficacy for pain and other symptoms.<sup>19 20</sup> The effects persisted at 12-month follow-up in both studies. However, a preceding longitudinal pre/post-test study on the VTP in patients with IA and FM showed substantial improvements in patients with IA, but no changes in patients with FM.<sup>21</sup> In a nested qualitative study, the patients with FM described how they had struggled for years to be believed and taken seriously.<sup>22</sup> The authors suggested that the lack of effects in patients with FM might have been related to long symptoms duration without recognition and treatment, which may have led to the development of maladaptive patterns of coping strategies that are difficult to change. They proposed that future studies should investigate the effects of the VTP in patients with FM at an early stage of their disease.

The aim of the present randomised controlled trial was to study the effects of a community-based multicomponent rehabilitation programme comprising the VTP followed by 12 weeks of physical activity (PA) counselling in patients with recently diagnosed FM. More specifically, we examined whether the multicomponent rehabilitation programme improved patients' self-perceived health, pain, fatigue, sleep quality, psychological distress, PA and work ability, compared with treatment as usual, that is, no treatment or any other treatment of their choice.

## METHODS

### Study design

We conducted a two-armed parallel randomised controlled trial in rural and urban communities in the southeastern part of Norway. Patients were allocated to the VTP and PA (intervention group) or treatment as usual (control group). More details can be found in the published protocol (ISRCTN 96836577).<sup>23</sup> We followed the Consolidated Standards of Reporting Trials in this report.<sup>24 25</sup>

### Participants

General practitioners and physiotherapists referred patients who had widespread pain that had lasted for at least 3 months to rheumatologists in specialist health-care for diagnostic clarification and assessment of study eligibility. Inclusion criteria were age 20–50 years and FM diagnosed according to the American College of Rheumatology 2010 criteria.<sup>1 26</sup> Patients were excluded if they had an inflammatory rheumatic disease, had a severe psychiatric disorder, another disease that did not allow PA, or if they were unable to understand or write Norwegian. We also excluded patients who had been out of work for more than 2 years.

### Procedure and interventions

All eligible patients received a 3-hour patient education programme and oral information about the study. Patients who agreed to participate completed written informed consent before inclusion. The VTP was organised in the local communities with 7–12 patients in each group. It comprised 10 weekly 4-hour sessions plus a booster session after approximately 6 months. Every session addressed a specific topic: If my body could talk/Who am I?/My resources and potentials/Values—what is important to me?/What do I need?/Strengths and limitations/Bad conscience/Anger/Joy/Resources, potentials and choices/Closure and the way ahead. These were explored by various creative methods, such as guided imagery, music, drawing, poetry, metaphors and reflections. The patients wrote logs after all exercises and shared their experiences with other group participants.

Moreover, patients were invited to attend mindfulness meditation, that is, body scan, sitting and walking meditation, and gentle yoga exercises.<sup>27</sup> They were encouraged to listen to guided mindfulness meditation audio files and practise awareness in their daily activities between sessions.<sup>28</sup> The group facilitators were experienced nurses and physiotherapists, who were certified by a 1-year post-graduate training programme (30 credits). The facilitators followed a standardised manual with a thorough programme description and monitored the attendance throughout the programme. Based on previous studies, the patients needed to attend at least five sessions to expect effect.<sup>20 23</sup> Online supplemental file 1 describes an example of the structure and content of one of the sessions.

The PA counselling was conducted at a Healthy Life Centre (HLC), which is a low threshold healthcare service provided in Norwegian communities designed as easily accessible generic services aimed at lifestyle changes. HLCs typically offer a 12-week programme during daytime, comprising individual counselling based on motivational interviewing, individual and group PAs.<sup>29</sup> A physiotherapist provided the individual PA counselling. This intervention aimed at helping patients to set tailored goals, identifying and overcoming barriers to PA, and guiding them into exercises that they could continue after the 12-week period to increase the level of PA gradually.

Control group patients did not receive any organised intervention other than diagnostic clarification and the patient education session but were free to attend any treatment and activity at their own initiative. The control group was offered the VTP and the HLC intervention after completion of the data collection at 12-month follow-up.

### Outcomes

The outcome measures were selected according to a core set of domains for FM defined by the Outcome Measures in Rheumatology Clinical Trials.<sup>30 31</sup> Self-reported questionnaires comprising baseline demographics and all outcome measures were collected electronically before randomisation (baseline), after the VTP (3 months) and at 12 months from baseline.

#### Primary outcome: Patient Global Impression of Change

Patient Global Impression of Change (PGIC) is a validated ordinal 7-point self-reported scale that measures how patients feel that their health has changed from they entered the trial to post-intervention data collections. The scale ranges from 1 (I feel very much worse) through 4 (no change) to 7 (I feel very much better).<sup>32</sup> Scores 6 and 7 are considered a clinically relevant improvement. PGIC has previously been used in FM trials and is recommended as a core measure to improve the applicability of information from clinical trials to clinical practice.<sup>33–35</sup> Higher scores in PGIC have been associated with more significant improvements in key FM symptoms and correlate well with FM outcomes.<sup>33</sup> The scores can be dichotomised into 'Less than much better' (scores 1–5) and 'Much better' (scores 6 and 7).<sup>34</sup>

#### Secondary outcomes

Pain, fatigue and sleep quality were assessed by Numerical Rating Scale scored from 0 to 10 (10 is intolerable pain/fatigue/very bad sleep).<sup>31</sup> Psychological distress was assessed by the General Health Questionnaire-12 (GHQ-12) that comprises six positively phrased items indicating psychological health and six negatively phrased items indicating psychological distress.<sup>36</sup> The respondents scored their condition during the last 2 weeks compared with what they perceived as their 'normal' condition on a 4-point Likert scale, reported from 0 (less than usual) to 3 (much more than usual). The scale was reversed for negatively phrased items. Data were analysed and

reported as mean sum score; higher scores represented higher psychological distress.<sup>37 38</sup> A general tendency to be mindful in daily life situations was assessed by the Five Facet Mindfulness Questionnaire (FFMQ) that comprises 39 items rated on a 5-point Likert scale from 1 (never true) to 5 (always true).<sup>39</sup> Higher scores reflected higher levels of mindfulness. The scale was reversed for negatively phrased items. Data were analysed and reported as a mean sum score, comprising all five facets. PA was assessed by three questions from the Nord-Trøndelag Health Study.<sup>40</sup> The questions measure frequency, intensity and duration of leisure-time physical exercises such as walking, skiing, swimming or other training/sport activities that improve physical fitness. A summary index of weekly PA was calculated from the frequency, intensity and duration scales with scores from 0 to 15. Higher scores indicate increased PA. Motivation and barriers for PA were assessed by the Exercise Beliefs and Exercise Habits Questionnaire comprising 20 items scored on a 5-point Likert scale ranging from 'strongly agree' to 'strongly disagree'.<sup>41</sup> The items were divided into four subscales calculated and reported separately as beliefs about one's ability to exercise, barriers to exercise, benefits of exercise and impact of exercise on muscular pain. Work ability was assessed by the Work Productivity and Activity Impairment General Health V.2.1 (WPAI:GH) comprising six questions to determine employment status; hours missed from work because of health problems or other reasons; and hours worked.<sup>42</sup> Higher scores indicate more significant impairment and less productivity. For this study, we calculated the outcomes 'overall work impairment' and 'daily activity impairment'. Health-related quality of life was assessed with EuroQol (EQ-5D-5L) comprising five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression scored on five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ-5D-5L scores range between 0 and 1, 0 indicates death and 1 indicates perfect health.<sup>43</sup> Second, the participants rate their overall health on a 0–100 hash-marked, vertical Visual Analogue Scale, 0 is as bad as it could be and 100 as good as it could be.<sup>44</sup>

#### Harms

Patients were asked to report adverse events at 12 months and major symptoms that were associated with these events.

#### Randomisation and blinding

A statistician generated an electronic randomisation list for each geographical area to ensure approximately equal sample sizes. A research assistant not involved in the study generated the allocation sequence and assigned patients to study groups. Further, the facilitators of the VTP groups organised and administered the enrolment. Due to the nature of the intervention, it was not possible to blind the patients and the VTP facilitators to group allocation. The project leader and the research coordinator who were



responsible for the data collection and data analysis were blinded to the allocation.

### Sample size

Sample size calculation was based on the primary outcome assuming that 10% in the control group would report clinically relevant improvement at 12-month follow-up, and that at least 20% absolute difference in improvement rate between the groups would be considered a minimum clinically relevant difference. With allowance for 10% losses to follow-up, 70 patients in each group were needed to have at least 80% power of detecting differences with 5% alpha level.

### Statistical analyses

Mean values and SD were calculated for continuous variables or as median with minimum and maximum values if skewed. Frequency numbers and percentages were calculated for categorical variables. Baseline differences in patients' characteristics between intervention and control group were assessed by independent group t-test or Mann-Whitney U test for continuous variables. For categorical variables, we used Pearson's  $X^2$  test or Fisher's exact test when the expected cell count fell below five. The treatment effects were analysed on an intention-to-treat basis with all randomised patients retaining their original allocated groups at 12 months. The distribution of the primary outcome (PGIC) was analysed as an ordinal variable by Mann-Whitney U test. When dichotomised, the difference between groups was tested with  $X^2$  statistics and Fisher's exact tests. Treatment effects in secondary outcomes were estimated by analysis of covariance (ANCOVA) at 3-month and 12-month follow-up adjusted for the baseline values. The level of statistical significance was set to  $\leq 0.05$ . We used STATA V.14.0<sup>45</sup> to analyse the data. Missing values in single items of FFMQ and GHQ-12 were imputed by calculating the mean value of the registered values multiplied with the number of questions.

### Patient and public involvement

Representatives from the Patient Advisory Board at the Diakonhjemmet Hospital were involved in the development of the study, such as study design, research questions and recruitment of patients. The electronic questionnaires were tested and amended by user representatives. More information is described elsewhere.<sup>23</sup>

## RESULTS

Of the 289 patients who were referred to the rheumatologists, 208 (72%) were eligible for inclusion. A total of 170 consented to participate and were randomised; 85 to the intervention group and 85 to the control group. **Figure 1** illustrates the flow of patients through the study.

The intervention group had a significant higher median age ( $p=0.02$ ) and symptoms duration in years ( $p=0.05$ ) compared with the control group. All other

baseline characteristics were equally distributed between the groups (**table 1**).

Of the 75 patients who attended the VTP, 67 (89%) completed five sessions or more; 21 (31%) of these patients completed all 10 sessions, 20 (30%) completed nine, and 9 (13%) completed eight sessions. The average attendance rate was 7.5 sessions. Thirty-two patients (43%) attended the PA intervention after the VTP, but only 14 patients participated more than 12 times during the 12-week programme. The data collection was completed by 160 (94%) at 3 months and 153 (90%) at 12 months. Recruitment of patients started in September 2016 and ended in August 2018. Electronic data collection started in February 2017 and ended in September 2019 when the complete 12-month follow-up data were attained.

### Patient Global Impression of Change

The median PGIC score was 4 (range 1–7) in both groups at 3-month and 12-month follow-up. However, we found statistically significant differences between the groups in distribution of the PGIC scores at 3-month follow-up ( $p=0.01$ ), but not at 12-month follow-up ( $p=0.06$ ). The distribution across all response categories is shown in **figure 2**.

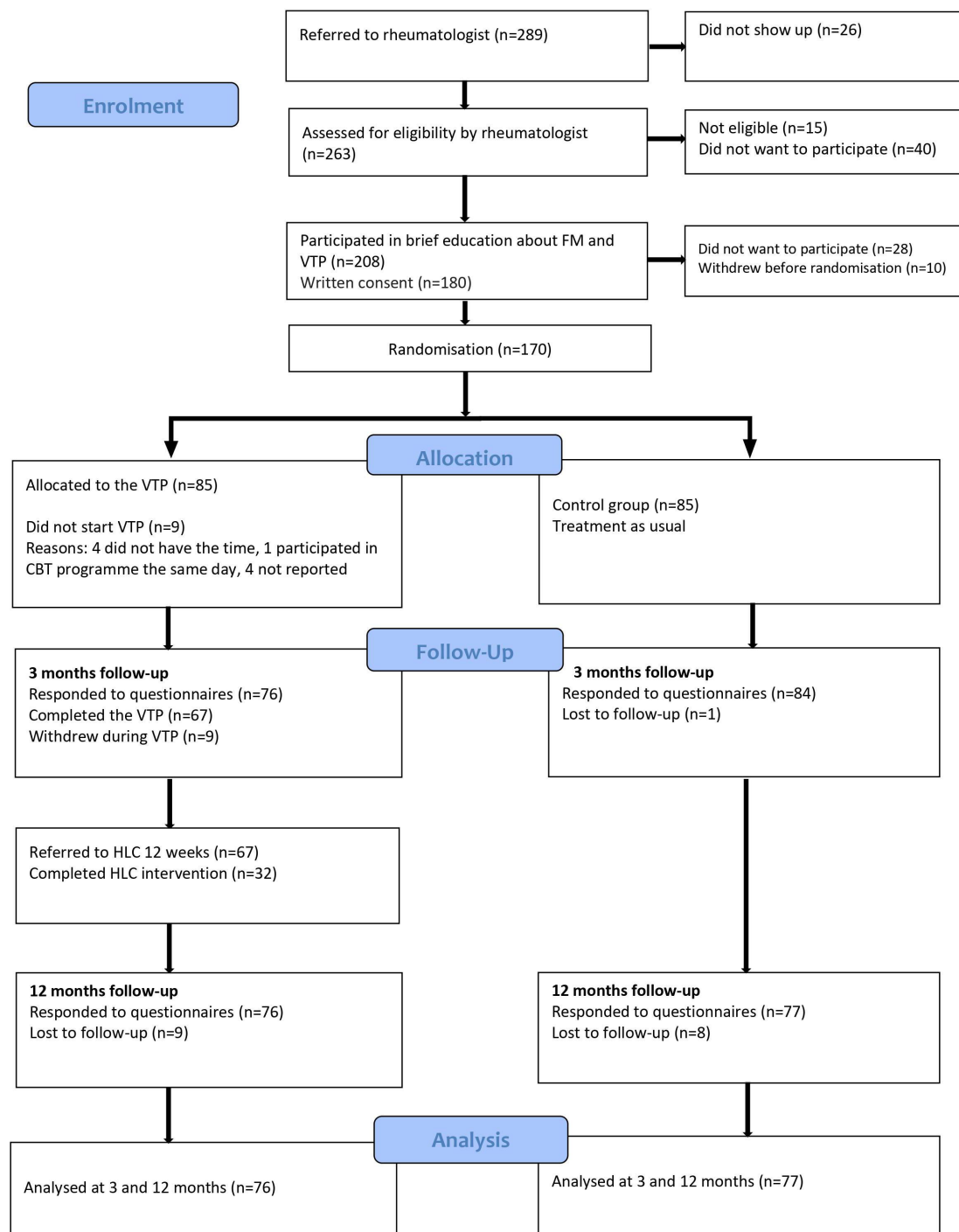
There were no statistically significant differences between the intervention group and the control group at 3-month and 12-month follow-ups when the PGIC was dichotomised into 'Less than much better' and 'Much better'. At 12-month follow-up, 13% in the intervention group reported 'Much better' compared with 8% in the control group (**table 2**).

### Secondary outcomes

There were no statistically significant differences between the groups at 12-month follow-up in any disease-related outcomes (**table 3**). However, there was a statistically significant improvement in favour of the intervention group in 'general tendency to be mindful'. Moreover, there was a statistically significant difference between groups in 'perceived benefits of exercise' due to a small deterioration in the control group (**table 3**). The numbers of people working, assessed by the WPAI:GH, were 56 (67%) at baseline and 48 (64%) at 12-month follow-up in the intervention group, compared with 52 (61%) at baseline and 50 (64%) at 12-month follow-up in the control group.

### Harms

A total of 34 patients reported adverse events: 21 (28%) in the intervention group and 13 (17%) in the control group. Increased pain and fatigue were the most frequent adverse events. Thirteen (nine in the intervention group and four in the control group) related the events to medication; 21 (12 in intervention and 9 in control) to PA; 4 in the intervention group related the events to the VTP; 2 (one in intervention and one in control) related the events to alternative treatment.



**Figure 1** Flow chart of patients. CBT, cognitive-behavioural therapy; FM, fibromyalgia.

## DISCUSSION

In this pragmatic randomised controlled trial, we examined the effects of a multicomponent rehabilitation programme for patients with FM. The study demonstrated that a mindfulness-based and acceptance-based intervention, the VTP, followed by PA counselling in patients with recently diagnosed FM was not more effective than treatment as usual. Only 13% in the intervention group reported clinically relevant improvement in self-perceived health status at 12-month follow-up compared with 8% in the control group. We did not observe differences

between the groups in any disease-related secondary outcomes. However, there were statistically significant differences between groups in ‘tendency to be mindful’ and ‘perceived benefits of exercise’ in favour of the intervention group. The latter was due to a slight deterioration in the control group.

The results of this trial both negate and support earlier studies on the VTP for patients with FM. One randomised controlled trial in patients with musculoskeletal pain conditions, including FM, demonstrated substantial health improvements.<sup>19</sup> In contrast, a longitudinal study

**Table 1** Patients' characteristics at baseline

Variables	All patients (n=170)	Intervention group (n=85)	Control group (n=85)	P value
Age, years, median (min, max)	42 (24, 52)	44 (26, 52)	41 (24, 51)	0.02*
Gender, women	159 (94%)	78 (92%)	81 (95%)	0.54†
Education				0.60‡
Primary/middle school (1–10 years)	20 (12%)	8 (9%)	12 (14%)	
Upper secondary school/vocational 10–12 years	68 (40%)	36 (42%)	32 (38%)	
Bachelor/university >12 years	81 (48%)	40 (47%)	41 (48%)	
Work status				
Currently in paid work	119 (70%)	59 (69%)	60 (71%)	0.94‡
Not in paid work	48 (28%)	24 (28%)	24 (28%)	0.94‡
In paid work but on sick leave (100%)	8 (17%)	3 (13%)	5 (21%)	
Work assessment allowance	35 (73%)	20 (83%)	15 (62%)	
Unemployed	4 (8%)	1 (4%)	3 (13%)	
Student	1 (2%)		1 (4%)	
Married/living with partner	120 (71%)	54 (64%)	66 (78%)	0.06‡
Symptoms duration, years, median, (min, max)	8 (1, 32)	10 (1, 32)	7 (1, 30)	0.05*
Comorbidities, median (min, max)	2 (1, 6)	2 (1, 6)	2 (1, 6)	0.24*
Smokers	23 (14%)	14 (17%)	9 (11%)	0.25‡
FM in family	57 (34%)	27 (32%)	30 (35%)	0.55‡
Use of medication in the last 3 months				
Pain medications	149 (88%)	73 (86%)	76 (89%)	0.64‡
Hypnotics	51 (30%)	27 (32%)	24 (28%)	0.63‡
Antidepressants	20 (12%)	8 (9%)	12 (14%)	0.48‡
Anxiolytics	8 (5%)	2 (2%)	6 (7%)	0.28†

Values are means (SD) or numbers (%).

\*Mann-Whitney U test,

†Fisher's exact test.

‡Pearson's X<sup>2</sup> test.

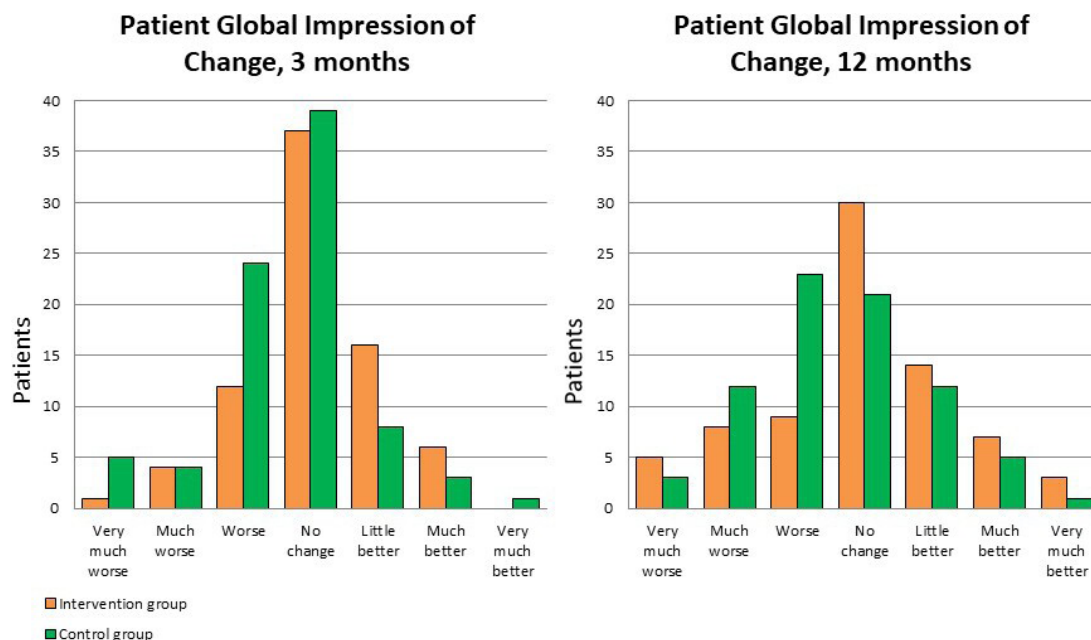
FM, fibromyalgia.

in patients with IA and FM showed improvements in the IA group, but not in the FM group.<sup>21</sup> Based on the latter study, it was hypothesised that the lack of effects in patients with FM might have been related to living with distressing symptoms over a long time without receiving any diagnosis. The present study aimed to improve the management of FM by following the EULAR recommendations for management of FM in a Norwegian context. We assumed that offering patients who had been recently diagnosed with FM a mindfulness-based and acceptance-based intervention might help them overcome some of their internal barriers to PA before they attended a PA intervention. However, we found no support for this assumption.

There were statistically significant differences between the groups in distribution of the PGIC scores at 3-month follow-up, but not at 12 months. This corresponds to other studies on mindfulness-based and acceptance-based interventions that have shown beneficial short-term

effects, but no evidence for long-term effects.<sup>10 11</sup> Our primary outcome, the PGIC scale, was dichotomised to distinguish between those who reported clinically relevant improvement in self-perceived health and those who did not. This has also been performed in previous studies, in which clinically relevant improvements have been shown.<sup>33 34</sup> However, we did not find any clinically relevant differences between the groups in our study. Previous systematic reviews and meta-analyses on mindfulness-based and acceptance-based interventions have shown small-to-moderate beneficial effects on pain, sleep quality and health-related quality of life for patients with FM.<sup>10–13</sup> In the present study, we did not see any of these effects. However, we found a statistically significant effect in 'tendency to be mindful'. Improvement in mindfulness may be associated with enhanced mental health outcomes.<sup>39 46</sup> Longer follow-up may be needed to see if this improvement will result in effects in other outcomes, such as perceived health status and PA.





**Figure 2** The distribution of PGIC scores. PGIC, Patient Global Impression of Change.

As many as 57% of the patients never attended the HLC intervention, and they did not report any increase in PA at 12-month follow-up. Twelve of the 32 patients who took part in the HLC intervention reported adverse events, such as increased pain and fatigue, which may have been one reason for quitting the training. This corresponds to other studies, which have shown that many patients report PA to be challenging, and that adherence to exercise interventions is poor.<sup>18 47–49</sup> A recent systematic review showed that PA should be tailored to individual characteristics to be effective.<sup>50</sup> Given the varied clinical picture associated with FM, the initial objective of the HLC intervention was to adapt the PA to each patient's physical condition and individual preferences. The patients reported the type of PA they performed in general terms, such as walking, strength training, cycling, spinning, etc. A limitation of our study is that we did not monitor to which degree the physiotherapists at the HLC adapted the PA to the individual patient's condition, nor did we monitor if the patients experienced that the PA was individually tailored. Further studies are needed to explore ways to improve adherence to PA.

Because we wanted to investigate if it was possible to prevent work loss and improve work participation, we excluded patients that had been out of work for more than 2 years. Long-term absence from work due to illness

has been identified as a risk factor for transition into disability pension.<sup>51 52</sup> Seventy-one per cent of the patients in our study had paid work. Previous studies have shown that non-working patients with FM have more severe symptoms than working patients.<sup>53 54</sup> Despite the high number of workers in our study, the patients reported high symptom burden, in terms of pain, fatigue and psychological distress.

Because we assumed that higher age might be associated with more comorbid conditions, we defined 50 years as the upper age limit for inclusion. Nevertheless, the median number of comorbidities in the included patients was 2.

Although we intended to capture patients with FM at an early stage of their disease, the included patients reported median symptoms duration of 8 years. These findings, although contrary to our expectations, correspond to other studies, which have shown that patients wait a significant time before presenting symptoms to a physician.<sup>55</sup> Further, there may be a delay in diagnosis in primary healthcare due to an overlap of symptoms with other conditions and patients may have difficulties in communicating their symptoms.<sup>56</sup> Other reasons for the delay in diagnosis and treatment may be lack of knowledge and understanding of FM from primary care physicians.<sup>57</sup>

**Table 2** Effect of intervention, primary outcome: Patient Global Impression of Change (PGIC)

PGIC	3 months		P value	12 months		P value
	Intervention (n=76)	Control (n=84)		Intervention (n=76)	Control (n=77)	
Much better (scores 6 and 7), n (%)	6 (7.9)	4 (4.8)	0.52*	10 (13.2)	6 (7.8)	0.28†

\*Fisher's exact test.

†Pearson's  $\chi^2$  test.

**Table 3** Effects of intervention, secondary outcomes estimated by ANCOVA adjusted for baseline scores

	Intervention (n=76) mean (SD)	Control (n=77) mean (SD)	Baseline-adjusted mean difference (95% CI)	P value
<b>Pain (NRS 0–10, 0=no pain)</b>				
Baseline	6.7 (1.6)	6.8 (1.9)	–	–
3 months	6.4 (1.7)	6.6 (1.8)	0.30 (–0.15 to 0.75)	0.19
12 months	5.8 (2.1)	6.4 (1.8)	0.55 (–0.00 to 1.11)	0.05
<b>Fatigue (NRS 0–10, 0=no fatigue)</b>				
Baseline	7.5 (2.0)	7.4 (2.0)	–	–
3 months	7.2 (1.9)	7.1 (2.2)	–0.03 (–0.60 to 0.54)	0.92
12 months	6.8 (2.3)	6.8 (2.3)	0.12 (–0.56 to 0.80)	0.72
<b>Sleep (NRS 0–10, 0=no sleep)</b>				
Baseline	6.8 (2.3)	7.1 (2.5)	–	–
3 months	6.6 (2.5)	6.9 (2.5)	0.27 (–0.42 to 0.97)	0.44
12 months	6.5 (2.5)	6.3 (2.5)	–0.24 (–0.99 to 0.50)	0.52
<b>Psychological distress (GHQ-12, mean sum score, 0–36, 0=no distress)</b>				
Baseline	16.5 (6.6)	19.2 (6.8)	–	–
3 months	13.4 (6.5)	16.5 (7.0)	1.57 (–0.37 to 3.50)	0.11
12 months	14.8 (6.8)	16.6 (6.9)	1.03 (–1.08 to 3.14)	0.34
<b>Five Facet Mindfulness Questionnaire (mean sum score, 39–195, low to high)</b>				
Baseline	119 (17.2)	113 (16.9)	–	–
3 months	124 (19.1)	118 (16.3)	–1.07 (–4.73 to 2.58)	0.56
12 months	126 (17.6)	118 (16.3)	–4.72 (–8.57 to –0.9)	0.02
<b>Physical activity (0–15, 0=inactive)</b>				
Baseline	3.0 (2.4)	2.8 (1.8)	–	–
3 months	2.3 (1.6)	2.7 (1.9)	0.53 (–0.04 to 1.10)	0.07
12 months	2.9 (2.3)	2.8 (1.8)	0.10 (–0.60 to 0.79)	0.78
<b>Motivation and barriers for physical activity</b>				
<b>Self-efficacy (4–20, low to high)</b>				
Baseline	12.0 (2.9)	12.0 (3.2)	–	–
3 months	12.5 (3.1)	12.6 (3.1)	0.08 (–0.70 to 0.86)	0.84
12 months	13.1 (3.5)	12.8 (3.1)	–0.33 (–1.27 to 0.62)	0.50
<b>Barriers (3–15, low to high)</b>				
Baseline	12.1 (2.4)	12.1 (2.0)	–	–
3 months	11.8 (2.3)	11.8 (1.9)	–0.00 (–0.48 to 0.47)	0.99
12 months	12.2 (2.4)	12.2 (1.7)	–0.07 (–0.61 to 0.46)	0.79
<b>Benefits (5–25, low to high)</b>				
Baseline	20.4 (3.2)	21.1 (2.7)	–	–
3 months	20.3 (3.0)	20.4 (2.7)	–0.19 (–0.89 to 0.50)	0.59
12 months	20.7 (3.0)	20.1 (2.9)	–0.90 (–1.73 to –0.07)	0.03
<b>Impact (8–40, low to high)</b>				
Baseline	28.8 (4.6)	29.0 (4.8)	–	–
3 months	28.4 (4.8)	28.5 (4.3)	0.08 (–0.90 to 1.06)	0.87
12 months	28.9 (5.4)	28.3 (4.6)	–0.49 (–1.63 to 0.65)	0.40
<b>Work Productivity and Activity Impairment General Health</b>				
<b>Work impairment (0–10, 10=completely impaired)</b>				

Continued

Table 3 Continued

	Intervention (n=76) mean (SD)	Control (n=77) mean (SD)	Baseline-adjusted mean difference (95% CI)	P value
Baseline	5.2 (2.5)	6.2 (2.2)	–	–
3 months	5.1 (2.4)	5.4 (2.5)	–0.15 (–1.05 to 0.76)	0.75
12 months	4.9 (3.2)	5.3 (2.9)	0.73 (–0.58 to 2.03)	0.27
Daily activity impairment (0–10, 10=completely impaired)				
Baseline	7.0 (2.0)	7.1 (1.9)	–	–
3 months	6.9 (1.7)	6.7 (2.3)	–0.25 (–0.83 to 0.34)	0.41
12 months	6.3 (2.5)	6.5 (2.2)	0.07 (–0.65 to 0.79)	0.84
EQ-5D-5L				
Index (0–1, 1=perfect health)				
Baseline	0.51 (0.2)	0.47 (0.2)	–	–
3 months	0.55 (0.2)	0.53 (0.2)	0.02 (–0.05 to 0.09)	0.86
12 months	0.54 (0.2)	0.50 (0.2)	0.04 (–0.03 to 0.11)	0.48
VAS (0–100, 100=as good as it could be)				
Baseline	44.6 (16.5)	41.61 (17.0)	–	–
3 months	46.4 (16.1)	51.5 (21.7)	–5.1 (–12.10 to 1.90)	0.03
12 months	49.0 (20.6)	46.8 (18.5)	2.19 (–4.67 to 9.05)	0.77

ANCOVA, analysis of covariance; GHQ-12, General Health Questionnaire-12; NRS, Numerical Rating Scale; VAS, Visual Analogue Scale.

This study was conducted according to a predefined published protocol.<sup>23</sup> It was well powered, and all included patients were allocated to the groups to which they were randomised, ensuring valid treatment comparisons and assessment of treatment effects.<sup>58</sup> The losses to follow-up were within our assumption of 10%. We had predefined that patients needed to attend at least 50% of the sessions to expect effects of the VTP intervention, and nearly 90% attended more than half of the VTP sessions.<sup>23</sup> This attendance rate is comparable with other studies on mindfulness-based and acceptance-based interventions.<sup>13</sup> The percentage of patients with complete follow-up data was high. The VTP facilitators were certified and followed a manualised programme, which improves transparency and replication.<sup>59</sup> Moreover, the 12-month follow-up time was relatively long, and in line with what has been asked for in previous research.<sup>13</sup>

Several limitations need to be mentioned. First, before randomisation, all study participants received a short patient education session, which is recommended as a first-line intervention by the EULAR recommendations. This might have served as a validation of the FM diagnosis and may have provided the patients with knowledge and information about possible coping strategies. The control group could include strategies and activities at their own initiative. We did not monitor the content of ‘treatment as usual’ in the control group other than PA. Thus, we do not know if the patients had initiated beneficial self-management strategies during the control period.

Second, our study was a pragmatic randomised controlled trial, which makes it difficult to differentiate

between the effects of the various interventions and to interpret the lack of effects. Moreover, we did not monitor the adherence to the homework between the VTP sessions. Consequently, we do not know to what extent the patients practised mindfulness training and integrated the training in their daily life. A recent review on mindfulness-based and acceptance-based interventions showed a small but significant association between the extent of formal practice and positive intervention outcomes.<sup>60</sup> It is recommended that future research should adopt a standardised approach for monitoring home practice across mindfulness-based and acceptance-based interventions.<sup>61</sup> Further, we included already existing HLCs in the communities. The activities offered vary between centres, and consequently, it was not possible to standardise the frequency, intensity, duration, progression or type of exercise. Moreover, the HLCs offer PA counselling at daytime only, making the intervention challenging to combine with a daytime job. Subsequently, a PA intervention with more flexible access might have increased the patient participation.

Third, we did not include any coping measures, such as self-efficacy, to assess the coping with their symptoms. We used the GHQ-12 to assess mental health status because this was found to be sensitive to change in previous studies on the VTP. The GHQ-12 does not capture more severe symptoms of depression and anxiety but is a widely used instrument to assess psychological distress.

Finally, we could have applied other statistical analyses, such as linear mixed models rather than ANCOVA, to estimate effects. However, ANCOVA was chosen because



it has shown great power and low variability when compared with other traditional analyses approaches, and it is regarded as a preferred analysis when post-treatment assessments adjusted for the pretreatment assessments are measured.<sup>62 63</sup> We did not adjust for multiple comparisons.

This study has demonstrated that a multicomponent rehabilitation programme combining recent diagnosis and patient education with a mindfulness-based and acceptance-based intervention followed by PA counselling was not more effective than recent diagnosis, patient education and treatment as usual for patients with FM.

There was a high drop-out rate from the PA intervention. Further, studies on how to adapt and tailor PA interventions to patients with FM are needed.

Our intention to include patients at an early stage of the disease was not fulfilled. The patients reported high symptom burden and had a median symptom duration of 8 years. Thus, future research should aim at including patients with more recent disease onset and explore the effects of prompt diagnosis and patient education.

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## Supplementary file

### *Online Supplementary file 1*

#### Example from group session 6 in the Vitality Training Programme: Anger

The first part of the program is standard in all sessions: Participants are invited to share their reflection on experiences from home exercises after the previous session in groups of three to four persons. They are encouraged to read their reflective diaries for each other and to share and listen with an open, non-judgmental attitude without discussing or giving advice. Next, participants are invited to take part in an awareness exercise instructed by one of the group facilitators. They are guided to attend to their thoughts, feelings and bodily senses in the present moment with openness, acceptance and curiosity. After the exercise, they are invited to share their experiences with one other person in the group. In the next part of the session, the group facilitators introduce the topic "anger" by giving a short introduction about relationship between chronic illness and emotions and the purpose of addressing emotions. The participants are then invited to take part in an exercise with awareness of anger, introduced by one of the facilitators: "Think of the word anger... or to be angry. Notice what you become aware of... thoughts, maybe concrete situations, perhaps memories from the past... Are the situations that you become aware of new or old? Maybe both?... What do you experience in your body right now when you think of anger or being angry?... Also note whether the word anger or being angry evokes any other feelings..." Awareness of anger is continued in movement to music. The music allows participants to express anger with their body, and they are invited to let their bodies do what they want to do while listening to the music. Then, written hypothetical sentences are used to enhance discovery to tacit knowledge, for example: "If there are any other emotions related to my feeling of anger, it must be..." Participants are further invited to share and reflect upon experiences and discoveries from the exercise in small groups and in a plenary session. The next exercise is a guided imagery intending to help individuals connect to their experiences of anger in the present moment, and to explore its meaning. Further, crayons and white paper are used to draw an image of anger as experienced here and now. Again, participants are invited to share and reflect in small groups and in plenary, with focus on new discoveries and the consequences of these discoveries from the participants' daily life. Finally, they write a diary about their experiences from the whole session. Before closing the session, participants are asked to be aware of how they relate both to their own anger and anger from others in their daily lives. They are provided with guided mindfulness audio files and are encouraged to practice these exercises in everyday life and to train awareness in daily activities. They are asked to write reflective diaries about their thoughts, emotions and bodily senses.

Each session follows the same structure with exercise adapted to the particular topic. The group facilitators are health professionals, such as nurses and physiotherapists, and certified through a one-year university training programme (30 credits) at VID Specialized University in Oslo.

## Paper IV

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# Trajectories of change in symptom severity in patients with fibromyalgia: exploratory analyses of a randomised controlled trial

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## Abstract

The clinical picture of fibromyalgia (FM) symptoms fluctuates, and the symptom severity varies within and between patients. The current study aimed to identify groups of PDS trajectories and to explore differences in baseline characteristics between the potential groups of trajectories. We included patients from a completed randomised controlled trial, in total 170 patients diagnosed with FM according to the ACR 2010 criteria. The mean age was 40 years, and 94% were women. Symptom severity was assessed by the Polysymptomatic distress scale (PDS) [range 0 (no symptoms) to 31] at four timepoints over 13–18 months. Latent class growth analysis was used to identify patient trajectories based on their response pattern on the PDS. Potential differences in baseline characteristics between the trajectories were compared using appropriate statistical tests. Two distinct PDS trajectories were identified with 110 patients (65%) classified as the “no improvement” group and 60 (35%) as the “some improvement” group. Mean PDS scores at pre-baseline were  $\geq 20$  in both groups. At 12 months, the groups diverged, mean (SD) PDS score was 14 (3.82) in the “some improvement” group and 21 (4.12) in the “no improvement” group. There were no significant differences in baseline characteristics between the groups of PDS trajectories. We identified one group of FM patients that improved slightly during the study period and one group that not improved. There were no differences in baseline characteristics between the two groups.

**Keywords** Fibromyalgia · Polysymptomatic distress scale · Latent class growth analysis · Trajectory

## Introduction

Fibromyalgia (FM) patients have been shown to suffer from heavy symptom burden over time [1]. The underlying mechanisms of FM are not fully understood, and to date, there is no curative treatment [2].

The first American College of Rheumatology (ACR) classification criteria for FM were based on the doctor’s examination of bilateral pain in the axial skeleton in upper and lower parts of the body; at least 11 of 18 tender points were needed to be diagnosed with FM [3]. In 2010, new diagnostic FM criteria were developed [4]. These criteria recognized that FM patients in addition to pain could have co-occurring symptoms, such as fatigue, non-restorative sleep, mood disturbances, and cognitive impairment that fluctuate and vary in terms of expression and intensity within and between patients, at different times and intervals [5, 6]. The criteria were based on the assessment of two scales, the Widespread pain index (WPI) and the Symptom severity scale (SSS), that were summed up in

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the Polysymptomatic distress scale (PDS) and measures the magnitude and severity of FM symptoms [4, 7]. It was suggested that patients' FM-associated symptoms might be graded on a continuum as "fibromyalgianess", rather than a discrete diagnosis [7, 8]. The PDS scores can also be categorised into none, mild, moderate, severe, and very severe to better assess and interpret the severity of symptoms [7]. In 2011, the ACR 2010 criteria were modified to allow for self-report of FM severity in clinical research [9]. The PDS has been translated and validated in several languages, including Norwegian [10].

We have conducted a randomised controlled trial (RCT) to evaluate the effects of a mindfulness- and acceptance-based group-intervention, the Vitality Training Programme (VTP), followed by supervised physical exercise, compared to treatment as usual, for patients with recently diagnosed FM [11]. The VTP comprised 10 four-hour sessions once a week and aimed to enhance patients' health-promoting resources [12, 13]. All eligible participants received a three-hour patient education programme to provide a basic understanding of FM, pain mechanisms, psychological factors, physical activity, and coping strategies before inclusion and randomisation. Control group participants did not receive any organised intervention other than diagnostic clarification and the patient education programme, but they were free to attend any treatment and activity of their own choice. The outcomes in the RCT were self-perceived change in health status, pain, fatigue, sleep quality and psychological distress. Outcomes were assessed at baseline, three and 12-month follow-up. We found no statistically significant differences between the groups in any outcomes during follow-up. The PDS was assessed at all time-points, but was not included as an outcome measure in the RCT.

The mean symptom burden in the RCT was high in both groups at baseline and did not improve throughout the study period. Based on these results, the aim of the present study was to explore if we could identify groups of PDS trajectories during the study period. Furthermore, we aimed to explore if there were any differences in baseline characteristics between the groups of PDS trajectories.

## Methods

### Study overview

This study was an exploratory analysis of data from a completed RCT in patients with FM that was conducted from 2016 to 2019. Study details are described elsewhere (ISRCTN 96836577) [11]. The study was approved by the Regional Committee for Medical and Health Research Ethics (2015/2447/REK sør-øst A).

### Participants and procedures

All randomised patients in the RCT were included in the present study ( $n = 170$ ). The patients were recruited from rural and urban areas in the South-Eastern part of Norway. General practitioners (GPs) referred patients with widespread pain lasting for more than 3 months to specialist health care rheumatologists for diagnostic clarification and assessment of study eligibility. Eligibility criteria were patients aged 20–50 who were engaged in work or studies at present or during the past 2 years and diagnosed with FM according to the ACR 2010 criteria.

### Outcome

The outcome in the present study was the PDS comprising two subscales, the WPI and the SSS. The WPI score is a 0–19 (worst) summary count of 19 painful regions from the self-reported Regional Pain Scale. The SSS is a 0–12 (worst) measure of symptom severity that includes fatigue, sleep, and cognitive problems (range 0–9) and the sum (range 0–3) of symptoms from headaches (range 0–1), pain or cramp in lower abdomen (range 0–1) and depression (range 0–1) that patients have been bothered with during the previous 6 months [7, 14]. The PDS is the sum score of the SSS and WPI, making the maximum score of PDS 31. Higher scores represent higher severity and more extensive symptoms. The cut-off for FM-diagnosis is PDS score  $\geq 12$  [4]. Furthermore, the symptom severity may be categorised according to the PDS score from none (0–3), mild (4–7), moderate (8–11), severe (12–19), to very severe (20–31) [7, 10].

### Baseline characteristics

Baseline characteristics included age, gender, disease duration, number of comorbidities, education, and marital status.

### Data collection

The PDS was self-reported at referral to specialist health care (pre-baseline) and collected electronically at inclusion in the study (baseline), after the VTP (3 months), and at 12-month follow-up. The time from pre-baseline to baseline differed in individual patients; thus, the total follow-up time spanned from 13 and 18 months.

### Statistical analysis

Latent class growth analysis (LCGA) was used to identify groups of patients with similar symptom severity trajectories based on patients' responses on the PDS at four time-points.

The number of trajectory groups was determined by first estimating a sequence of models, each with a different number of groups, and then selecting the one with the best-fit. The model sequence started with a single group, and the group number was successively increased, and the model re-estimated. The Bayesian Information Criterion (BIC) was used to identify the best-fitted model and a corresponding number of trajectory groups [15]. The mean response within each group was estimated by treating time as a categorical variable, while the group-specific error covariance matrix was estimated in three different ways, treating it as diagonal, exchangeable, and unstructured. The selected error covariance matrix was also based on the BIC [16]. The LCGA was carried out using the function `gsem` in Stata v16 [17]. Each patient was assigned to their most likely trajectory class to identify differences in baseline characteristics between the groups of PDS trajectories. This was determined by the posterior class probability estimate based on the four time-points. Baseline characteristics were then compared using two-sample *t*-tests and Chi-square tests as appropriate.

## Results

A total of 170 patients were included in the present analyses. The mean (SD) age was 40 (7.1) years, 94% were women, the mean (SD) symptom duration was 10 (7.7) years, and the median number of comorbidities was 2 (range 1–6). The mean (SD) PDS score was high throughout the study period (pre-baseline: 21 (4.2), baseline: 21 (4.5), 3 months: 19 (5.4), 12 months: 18 (5.3)). However,

there were individual variations in the PDS trajectories across time-points for all included patients.

## Trajectories of change

Two distinct groups of PDS trajectories were identified with 65% of the patients classified into the first group denoted “no improvement” and 35% into the second group denoted “some improvement” (Fig. 1).

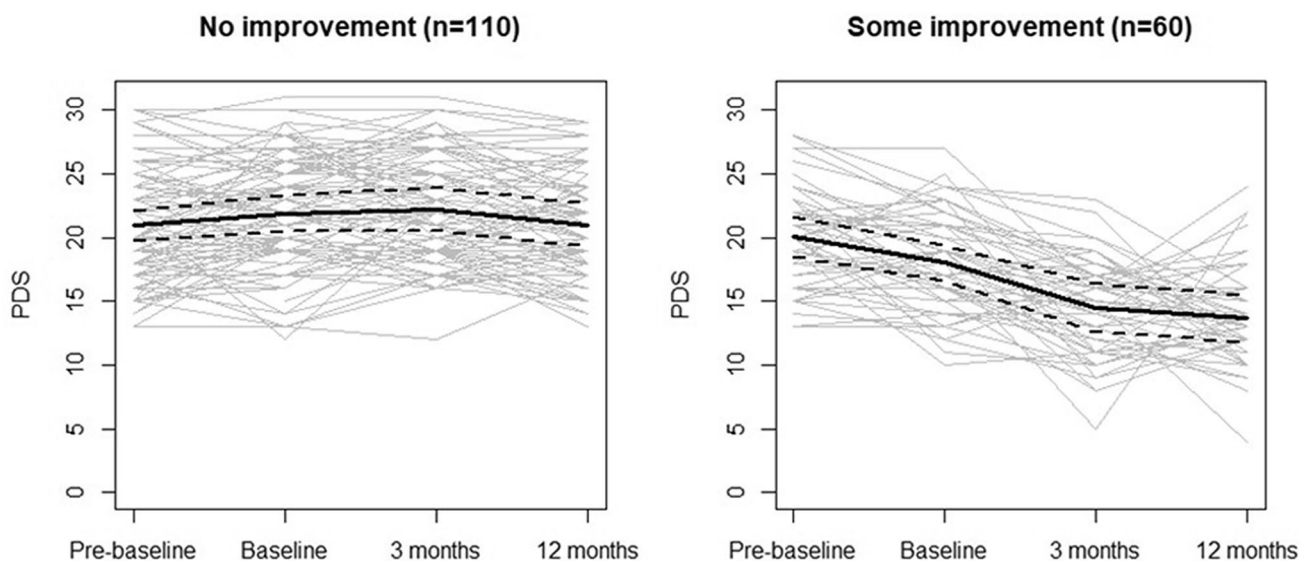
At pre-baseline, the mean scores in both trajectory groups fell within the PDS category “very severe”. The scores diverged between the groups at all time-points from baseline, and the estimated trajectories displayed significant differences in PDS scores (Table 1). In the “some improvement” group, 15 patients reported PDS score < 12 at 12-month follow-up.

**Table 1** PDS scores across time-points in the two groups

Characteristic	No improvement, <i>n</i> = 110	Some improvement, <i>n</i> = 60	<i>P</i> value*
Pre-baseline PDS	20.95 (4.46)	20.05 (3.72)	0.18
Baseline PDS	21.9 (4.31)	18.02 (3.74)	<0.001
3-month PDS	22.17 (4.04)	14.53 (3.68)	<0.001
12-month PDS	20.96 (4.12)	13.66 (3.82)	<0.001

Data are mean (SD)

\*Differences between groups assessed by *t* tests



**Fig. 1** Trajectories of the PDS measured at four time-points. The solid lines show the mean and the dotted lines show the 95% CI

### Changes of PDS categories across time-points

In the “some improvement” trajectory, the number of patients in the category “very severe” decreased, whereas the proportion of patients in the “severe” and “moderate” categories increased stepwise across the time-points. In the group of “no improvement”, the numbers were stable across all time-points (Fig. 2).

### Differences in baseline characteristics between groups of PDS trajectories

There were no statistically significant differences in baseline characteristics between the two groups of PDS trajectories (Table 2). However, 57% in the “some improvement” group had been randomised to the intervention group compared to 46% in the “no improvement” group ( $p=0.26$ ).

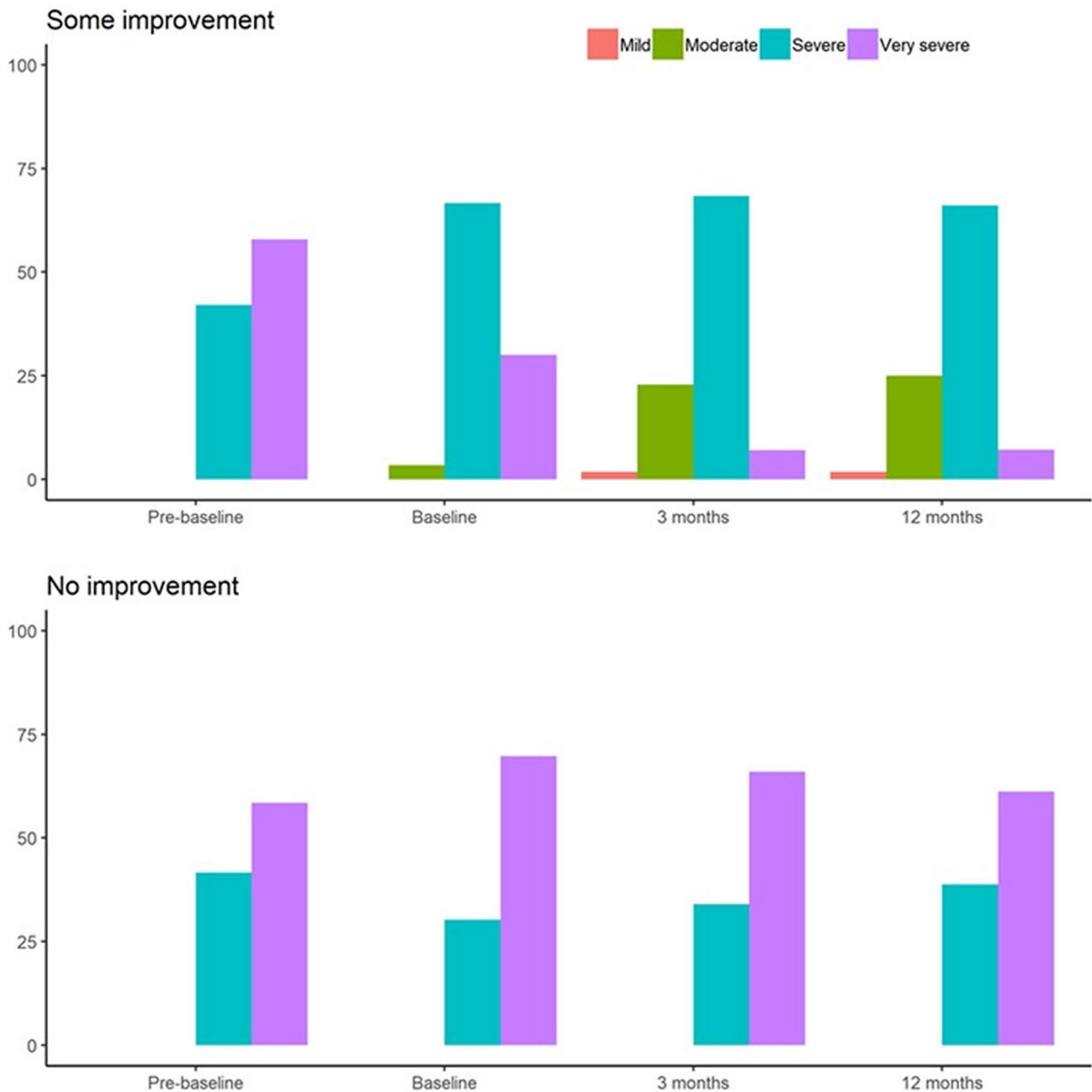


Fig. 2 Changes of PDS categories across time-points

**Table 2** Differences in baseline characteristics between groups of PDS trajectories

Characteristic	No improvement ( <i>n</i> = 110)	Some improvement ( <i>n</i> = 60)	<i>P</i> value
Age (mean) (years)	40.38 (7.32)	41.25 (6.94)	0.45
Female <i>n</i> (%)	104 (95%)	55 (92%)	0.69
Intervention group <i>n</i> (%)	51 (46%)	34 (57%)	0.26
Living with partner (%)	73 (66%)	47 (78%)	0.10
Symptoms duration (mean) (years)	10.17 (7.09)	10.88 (8.82)	0.60
Number of comorbidities (mean)	1.99 (1.05)	2.08 (1.38)	0.72
Education <i>n</i> (%)			0.45
Primary/ lower secondary school (1–10 years)	14 (13%)	6 (10%)	
Vocational school (10–12 years)	26 (24%)	21 (35%)	
Upper secondary school (10–12 years)	16 (15%)	5 (8%)	
Bachelor/ University < 4 years	30 (28%)	18 (30%)	
Bachelor/ University > 4 years	23 (21%)	10 (17%)	

## Discussion

In this exploratory study, we have examined repeated self-reported PDS scores in patients with FM to identify potential PDS trajectories in FM patients. The mean PDS score was high throughout the study period for all patients, though there were individual variations throughout the study period. We identified two distinct groups of trajectories, labelled as “no improvement” and “some improvement”. The mean PDS scores in the two groups displayed significant and increasingly diverging differences from the time they were seen by a rheumatologist (pre-baseline) to baseline, and from baseline to 12 months. In the group “some improvement” there was a stepwise decreasing proportion of patients in the category “very severe” and a corresponding increase in the categories “severe” and “moderate” showing a continuously improvement across the time-points. By the end of the study, 15 patients no longer fulfilled the criteria for FM-diagnosis (PDS  $\geq$  12). The patients in the group “no improvement” reported no mean changes in severity across the four time-points. We found no differences in baseline characteristics between the two PDS trajectories. Although not statistically significant, a higher proportion of the patients in the group “some improvement” had been randomised to the intervention group in the RCT compared to the patients in the “no improvement” group.

These results are similar to those of an observational study that tracked 1555 patients with FM with semi-annual questionnaires for up to 11 years [18]. The majority of the included patients reported high levels of symptoms and no change in overall symptom severity over time, only 25% of the patients reported a slight trend toward improvement. Another longitudinal study observed patients with FM at two time-points over 2 years and reported high levels of disease burden at both time-points [1]. Furthermore, the patients included in our study reported fluctuating FM symptoms

and transition between categories of symptoms severity over time, which has also been found in other longitudinal studies [19, 20].

Because the patients in our study had participated in an RCT in which both groups had received an intervention (patient education  $\pm$  VTP and exercise) and attention, we would have expected improvement over time. The lack of time-effect was, therefore, somewhat surprising. It might be that the patients need longer time to integrate new strategies to manage stress into their daily lives.

A longitudinal study that followed 166 women with FM and chronic widespread pain (CWP) for 10–12 years after an RCT found that a majority of the included women showed improvement of pain over time [21]. Moreover, the study showed that reduced stress levels contributed to improvement over time. We, therefore, consider it a limitation of the RCT that the follow-up time was only 12 months.

A limitation of this study was that we did not include disease-related symptom variables as potential predictors. A systematic review that aimed to identify predictors of outcomes from multidisciplinary treatment in patients with FM showed that a higher level of depression predicted poorer outcomes [22]. Other predictors were baseline status, specific patient profiles, belief in fate, disability, and pain. Another study examined patients with FM after completion of a multidisciplinary group programme and found that the improvers reported lower baseline anxiety, depression and less fear of pain due to movement than the non-improvers [23].

Strength of the present study was that all patients at the point of inclusion fulfilled the ACR 2010 diagnostic criteria for FM [24]. Recruitment from both rural and urban areas ensured a heterogeneous sample. Moreover, the time-points for data collection were distributed over more than a year, reducing the potential bias of seasonal FM symptoms variations. The LCGA is a statistical model that estimates the

number of trajectories present based on BIC. The LCGA allowed us to examine trajectories of PDS over the study period and to our knowledge few studies have used this method in studies in patients with FM [16]. A limitation of the model is that the trajectories may not be clinically relevant, in that the improvements are mean differences and not individual movements across disease states. Although four time-points is sufficient for LCGA, the inclusion of more time-points would have provided a more detailed picture of groups of PDS trajectories [25]. Finally, we consider it a strength that we could repeatedly monitor PDS changes over a relatively long period in a sample of FM patients with high symptoms burden.

Previously, it has been proposed that in clinical settings, the use of the PDS provides a method to quantify severity and may be a way to overcome the difficulties and uncertainty of binary diagnosis in research settings [26]. Furthermore, knowledge of longitudinal patient movements across the PDS categories might be comprehensible in communication with patients about management strategies.

## Conclusion

In this exploratory study we found individual variations in symptom severity among patients with FM who had been included in an RCT. We identified two groups of FM trajectories, one group that improved slightly during the study period and one group with no improvements. We found no differences in baseline characteristics between the two groups.

**Author contributions** KBH and HAZ contributed to the initial design of the project. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by TH, JS and SAP. All authors contributed to the interpretation of the data. The first draft of the manuscript was written by TH, and all authors commented and revised previous versions of the manuscript. All authors read and approved the final manuscript.

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## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflict of interest.

**Ethics approval** This study was performed in line with the principals of the Declaration of Helsinki. Study design, information strategy, written consent formula and data security are approved by the Regional Committee for Medical and Health Research Ethics (2015/2447/REK sør-øst A).

**Informed consent** Informed consent was obtained from all individuals patients included in the study.

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