

IDENTIFYING KEY ELEMENTS OF NON-PHARMACOLOGICAL TREATMENT PACKAGE FOR FIBROMYALGIA: EVIDENCE SYNTHESIS AND DELPHI EXERCISE

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Declaration

I hereby declare that this thesis is the result of original research. It has been conducted by myself and any assistance received is detailed below. It has not already been accepted for any degree, diploma, or other qualification. All authors and works to which reference has been made are fully acknowledged.

Study design, literature search, data extraction, analysis, interpretation, presentation and thesis writing were conducted by myself. Professor Abhishek Abhishek, Professor Weiya Zhang, Professor Michael Doherty and Dr Michelle Hall provided guidance and supervision in all aspects of the present work. In addition, Jaspreet Kaur and Dr Siew-li Goh assisted with independent validation of data extraction and risk of bias assessment for conventional and network meta-analyses. Additional statistical guidance was received from Dr Sung Ryul Shim for Bayesian network meta-analysis.

Abstract

Background

Fibromyalgia (FM) is a common condition that manifests with chronic widespread pain, fatigue, non-restorative sleep and cognitive dysfunction. FM impacts directly on health and quality of life (QoL) and is associated with a large economic burden on health care systems. Its diagnosis and management are often challenging due to heterogeneous manifestations. Non-pharmacological interventions are recommended as first-line treatment for FM. However, there are no evidence-based recommendations for which intervention(s) to offer patients with different manifestations of FM, and, which of these should be offered as core and adjunctive treatments within a package of care.

Objectives: The overall purpose of the research project was to identify key elements of a non-pharmacological treatment package for FM. The study had the following objectives:

1. To estimate the efficacy of non-pharmacologic treatments for FM using a systematic review with conventional meta-analysis (CMA) approach.
2. To estimate the relative efficacy of non-pharmacologic interventions for FM using a Bayesian network meta-analysis (NMA) approach.
3. To select the most efficacious interventions for different outcomes of FM using a Delphi exercise (consensus building) approach.

Methods

Two meta-analytical techniques, CMA and NMA, were conducted in the first stage of the project. Following this, a Delphi exercise was undertaken.

CMA and NMA: MEDLINE, EMBASE, AMED, PsycINFO, CINAHL, Web of Science were systematically searched from their dates of inception until September 2018. In addition, the first 100 articles on Google Scholar were included. Randomised controlled trials (RCTs) comparing any non-pharmacological intervention versus another non-pharmacological intervention, usual care, no treatment, waiting list or placebo/sham treatments in patients with FM aged >16 were included without language restriction. The composite score of the FM Impact Questionnaire (FIQ) was the primary outcome of interest. Pain, fatigue, sleep and depression were assessed as secondary outcomes. Usual care/placebo controlled RCTs were pooled in random-effects conventional meta-analyses (CMA) and standardised mean difference (SMD) and 95% confidence interval (CI) were calculated. Bayesian network meta-analysis (NMA) compared the treatments using usual care as a common comparator. SMDs and 95% credible intervals (CrIs) were estimated between interventions. Direct and indirect evidence were pooled using the random effect model. Modified Cochrane‘s tool was used to assess risk of bias. Publication bias was assessed using funnel plot and Egger’s test.

Delphi exercise: A three-stage Delphi exercise was designed and potential panel members were selected from experts in FM identified from the author list of international FM guidelines (EULAR, Canadian guidelines) and local

clinician advice. In the first round Delphi survey, participants were asked to confirm their professional details, select interventions that they thought should be offered to people with FM, and to rate these interventions as core or adjunctive treatment for the four key symptoms of FM (pain, fatigue, sleep disturbance and depression). They were provided a summary of current research evidence from CMA to support their decision-making. Surveys for the second and third rounds were prepared based on the items which did not achieve the consensus threshold of 70%.

Results

16,251 studies were identified and 187 RCTs (n=13,454 participants) met all inclusion criteria for the systematic review. In total, 21 non-pharmacological interventions were evaluated.

CMA: 148 RCTs (n=9,598) were included in the CMA. Exercise was the only intervention associated with significant improvements for all five outcomes [FIQ (SMD=-0.67; 95% CI -0.89, -0.45), pain (-0.84; 95% CI -1.13, -0.55), fatigue (-0.88; 95% CI -1.39, -0.37), sleep (-0.55; 95% CI -1.04, -0.06) and depression (-0.55; 95% CI -0.82, -0.28)]. Psychological treatments including cognitive behavioural therapy (CBT) and mindfulness were significantly more efficacious than usual care for FIQ, pain and depression but showed no improvement for fatigue and sleep. All exercise types were effective at relieving pain. Mind body and strengthening exercises were effective at improving fatigue, while aerobic and strengthening exercises were effective at improving sleep. All exercise types except for aerobic exercise improved depression.

NMA: 78 studies (n = 5,639 participants) met the inclusion criteria. While multidisciplinary treatment (MDT) was the best for improving pain [-1.28 (-1.84, -0.72)], sleep [-1.14 (-2.38, 0.07)] and depression [-1.20 (-1.99, -0.46)], balneotherapy and exercise were the most effective treatments for overall FIQ [-1.06 (-1.52, -0.62)] and fatigue [-0.75 (-1.35, -0.25)] respectively. Data from 47 exercise trials (n = 3,271 participants) were also analysed to examine the relative efficacy of different exercise types. Of the different types of exercise, strengthening showed the greatest benefits for FIQ [-0.76 (-1.39, -0.15)], pain [-0.94 (-1.58, -0.29)] and depression [-0.83 (-1.53, -0.14)], whereas aerobic exercise was the best for fatigue [-0.98 (-2.33, 0.18)] and sleep disorders [-0.96 (-2.08, 0.13)].

Delphi exercise: Of 48 invitees, 17 agreed to participate. These included seven rheumatologists, two physiotherapists, one psychologist, one nurse and six people from other professional backgrounds, specifically physical medicine and rehabilitation, neurology, immunology and public health. Response and completion rates for the 17 participants were 100%. Aerobic exercise, education, sleep hygiene, CBT, mindfulness, mind-body exercise and stress management were recommended for all four outcomes. Also, all these interventions except for mindfulness were voted as core in the management of FM.

Conclusions

Several non-pharmacological interventions are beneficial for FM. Some interventions appear particularly efficacious for certain FM manifestations. The results of this study should be used to guide the selection of the most

beneficial interventions according to the predominant symptom(s) of the individual patient. Further research is required to evaluate if such a strategy better improves outcomes in FM patients.

Registration

The protocol for the systematic review of non-pharmacological interventions for FM has been registered with the international prospective register of systematic reviews (PROSPERO), registration number CRD42017074982.

List of publications and presentations

Presentations at conferences

1. EULAR Annual European Congress of Rheumatology (Virtual congress, June 2020): The Comparative Efficacy of Non-Pharmacological Interventions for Fibromyalgia: A Systematic Review with Bayesian Network Meta-Analysis (poster presentation)

2. American College of Rheumatology (ACR) Annual Meeting (Atlanta, November 2019): The Efficacy of Non-Pharmacological Interventions for Fibromyalgia: A Systematic Review with Meta-Analysis (oral presentation)

3. School of Medicine – Sue Watson Oral Presentation Event (Nottingham, October 2019): The efficacy and relative efficacy of non-pharmacological interventions for fibromyalgia: A Systematic Review with Conventional and Network Meta-Analysis (oral presentation – second best presentation prize)

4. United Kingdom – Research in Musculoskeletal Epidemiology (UK-RIME) Showcase (Norwich, September 2019): The efficacy and relative efficacy of non-pharmacological interventions for fibromyalgia

Other publications from the period of this thesis

1. Abdullahi, A., Candan, S.A., Abba, M.A., Bello, A.H., Alshehri, M.A., Afamefuna Victor, E., Umar, N.A. and Kundakci, B., 2020. Neurological and musculoskeletal features of COVID-19: A systematic review and meta-analysis. *Frontiers in Neurology*, *11*, p.687.

2. Wittoek, R., Kroon, F.P., Kundakci, B., Abhishek, A., Haugen, I.K., Berenbaum, F., Conaghan, P.G., Ishimori, M.L., Smeets, W., van Der Heijde, D. and Kloppenburg, M., 2019. Report from the Hand Osteoarthritis Working Group at OMERACT 2018: update on core instrument set development. *Journal of Rheumatology*, 46(9), pp.1183-1187.

3. Kundakci, B., Sultana, A., Taylor, A. J., & Alshehri, M. A. (2018). The Effectiveness of Exercise-Based Vestibular Rehabilitation in Adult Patients with Chronic Dizziness: A Systematic Review. *F1000Research*, 7.

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List of abbreviations

ACR American College of Rheumatology

ACSM American College of Sports Medicine

CAM Complementary and Alternative Medicine

CBT Cognitive Behavioural Therapy

CI Confidence interval

CFS Chronic Fatigue Syndrome

CMA Conventional Meta-Analysis

CNS Central nervous system

CrI Credible interval

CWP Chronic Widespread Pain

COMT Catechol-O-Methyltransferase

EQ-5D EuroQol- 5 Dimension

ES Effect size

EULAR European League Against Rheumatism

FM Fibromyalgia

fMRI Functional magnetic resonance imaging

GH Growth hormone

GWAS Genome-wide association studies

HAQ Health assessment questionnaire

HOT Hyperbaric oxygen therapy

HRQoL Health related quality of life

IBS Irritable bowel syndrome

IGF-1 Insulin-like growth factor 1

ITT Intention-to-treat

LFESSQ The London Fibromyalgia Epidemiological Study Screening Questionnaire

MCMC Markov Chain Monte Carlo

MCS Mental component score

MRC Medical Research Council

n Number of participants

NMA Network Meta-Analysis

NRS Numeric rating scale

OA Osteoarthritis

PCS Physical component score

QoL Quality of life

RA Rheumatoid Arthritis

RCT Randomised Controlled Trial

SD Standard deviation

SF Short form

SMD Standardised mean difference

SPECT Single-photon emission computed tomography

SR Systematic Review

SUCRA Surface Under the Cumulative Ranking

tDCS Transcranial direct current stimulation

TMD Temporomandibular disorder

Tx treatment

VAS Visual Analogue Scale

WBV Whole body vibration

Chapter 1 INTRODUCTION

This chapter aims to present an overview of the nature of fibromyalgia (FM), and to consider aspects of its diagnosis, epidemiology, risk factors, and pathophysiology. The effectiveness of management options for FM including non-pharmacological and pharmacological treatments will then be summarised. Finally, the justification and objectives of this thesis will be stated.

1.1 Overview of the nature of fibromyalgia

FM is a common condition that manifests with chronic widespread or multiple regional pain, and with other associated symptoms of fatigue, non-restorative sleep, and cognitive dysfunction (Wolfe et al., 2010; Wolfe et al., 1990). After osteoarthritis, FM is the second most common rheumatic disease, and affects 2-8% of the whole population (Clauw, 2014). It is a common complex disorder with multiple risk factors and poorly understood pathophysiology. Diagnosis of FM is based on thorough a history and physical examination. Clinical investigations for other conditions that may cause multiple regional pain and fatigue (and any other individual symptoms that may be present) should be undertaken, but these are more to exclude or confirm an additional condition that may require treatment rather than to find an alternative diagnosis. Suggested screening should include a full blood count, an erythrocyte sedimentation rate or C-reactive protein level (to identify inflammatory musculoskeletal (MSK) diseases), thyroid function, serum calcium and alkaline phosphatase (for hyperparathyroidism) and creatine phosphokinase (CPK – for myositis) (Bair & Krebs, 2020). There is strong

and growing evidence that abnormalities within the central nervous system (CNS) lead people with FM to process and experience pain differently. Functional magnetic resonance imaging (fMRI) studies have shown that alterations in brain morphology, greater neuronal activity in pain-processing brain regions, levels of pain-related neuropeptides and neurotransmitters may amplify pain and lead to an exaggerated pain responses to experimental stimuli (central sensitisation) (O'Brien et al., 2018). Additionally, FM frequently co-exists with other chronic symptomatic conditions such as myofascial syndrome (76%), temporomandibular joint dysfunction (57%), chronic tension-type headache (48%), irritable bowel syndrome (IBS) (45%), chronic low back pain (CLBP) (39%), migraine-type headache (10%) which share the same risk factors and pathophysiology, supporting the perspective that these are different phenotypic presentations of the same disorder (Kleykamp et al., 2021).

1.2 Diagnosis

1.2.1 Clinical Features

1.2.1.1 Symptoms

1.2.1.1.1 Pain

Chronic widespread pain (CWP) is the cardinal symptom of FM. By definition, pain in FM is diffuse, non-anatomically distributed and widespread, affecting left and right sides of the body as well as above and below the waist and present for longer than 3 months (Goldenberg, 2009). Patients commonly describe their pain as if it has affected all of their body and a chief complaint of “I hurt all over” should be an alert sign of the possible diagnosis of FM for the clinician (Bair & Krebs, 2020). However, the pain often focuses on one or a few sites and a time but then slowly moves to involve another region, rather than affecting the whole body all on the same day. Pain can be aggravated by weather changes, psychological or mood changes such as anxiety or stress, repetitive movements or physical inactivity, and poor sleep (Berwick et al., 2021; Casale et al., 2019; Staud et al., 2010).

Apart from this chronic pain, patients with FM experience augmented pain response (O'Brien et al., 2018). O’Brien et al. (2018) studied the characteristics of temporal summation and conditioned pain modulation that reflect endogenous excitatory or inhibitory pain modulation mechanisms of the CNS in patients with FM and healthy participants. The results showed that FM patients exhibit a larger response to repetitive noxious stimuli and smaller response to conditioned pain modulation compared to healthy controls.

1.2.1.1.2 Fatigue

Another primary characteristic of FM is fatigue. Up to 90% people with FM have moderate to severe fatigue and common patient description for fatigue is “I am always tired.” (Arnold et al., 2019; Yunus, 1994). Physical exertion as well as prolonged inactivity may aggravate fatigue. It is generally worse in the morning and people with FM often awaken feeling more exhausted than when they went to bed (Sandıkçı & Özbalkan, 2015).

1.2.1.1.3 Sleeping dysfunction

Sleeping dysfunction including frequent awakening, difficulty in sleep onset or sleep maintenance and nonrestorative sleep is another characteristic presenting in the majority of people with FM (Smith & Haythornthwaite, 2004). Loss of deeper phases of sleep (stages three and four) may cause non-restoration and poor sleep may heighten pain. Non-restorative sleep is especially common and patients with FM often complain that they are completely unrefreshed, even if the duration and the quality of sleep appear normal (Kleinman et al., 2014; Sandıkçı & Özbalkan, 2015).

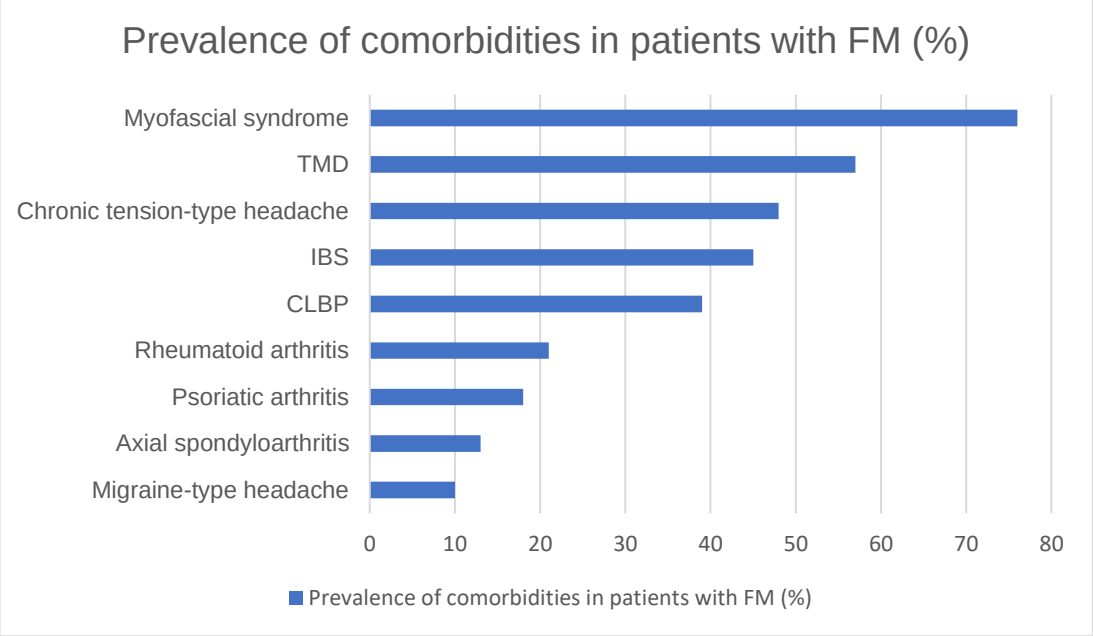
1.2.1.1.4 Cognitive disturbances and mood disorders

Another major problem of people with FM is cognitive disturbance, such as poor concentration and forgetfulness, and mood disorders. In stressful conditions such as events with lots of background noise or flashing lights, many of those who suffer from FM begin to lose mental acuity. This situation is described as “fibro-fog” by people with FM (Goldenberg, 2009). Apart from that, mood disorders may persist pain, and chronic pain may cause psychological disturbance (Glass, 2009).

1.2.1.1.5 Associated conditions

In addition to the characterising symptoms mentioned before, FM frequently co-exists with other conditions such as myofascial syndrome (76%), temporomandibular joint dysfunction (57%), chronic tension-type headache (48%), irritable bowel syndrome (IBS) (45%), chronic low back pain (CLBP) (39%), rheumatoid arthritis (21%), psoriatic arthritis (18%), axial spondyloarthritis (13%), and migraine-type headache (10%)some of which may share the same pathophysiology (Duffield et al., 2018; Kleykamp et al., 2021). Figure 1-1 shows the prevalence of comorbidities in people with FM.

Figure 1-1. Prevalence of comorbidities in people with FM (Duffield et al., 2018; Kleykamp et al., 2021)



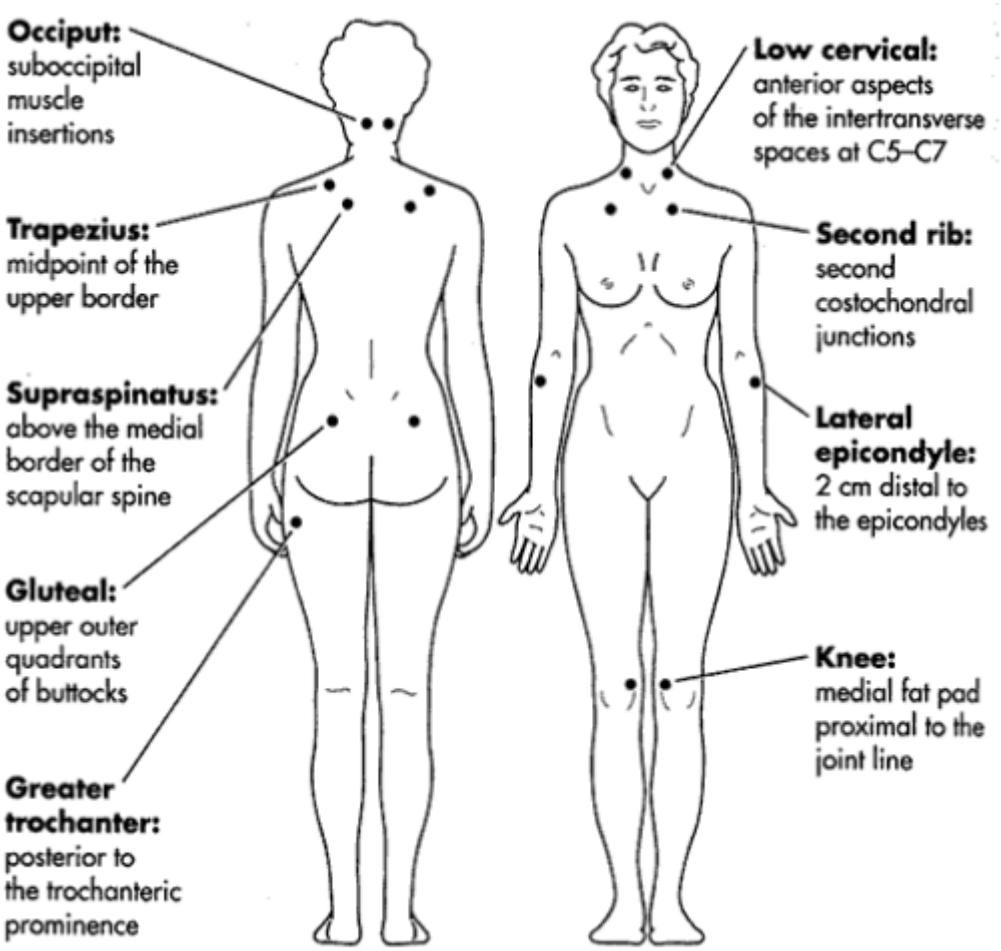
TMD: Temporomandibular joint dysfunction, IBS: Irritable bowel syndrome, CLBP: Chronic low back pain

1.2.1.2 Physical findings

The most significant physical finding related to FM is the presence of multiple hyperalgesic tender points (Wolfe et al., 1990). Figure 1-2 illustrates nine pairs of tender point sites. These locations include the upper mid-trapezius muscle, a site just distal to the lateral epicondyle (the tennis elbow location), the second costochondral junction (the site of costochondritis), the greater trochanter (the site of trochanteric bursitis of the hip), the upper medial tibia (lower medial fat pad) and the central interspinous ligament regions of the lower cervical and lumbar spine. Hyperalgesia is best evaluated by manual palpation with a digital pressure of 4 kg (clinically this equates to enough pressure applied by the examiner's index finger to just blanch the distal nail). These sites normally have a lower pain threshold to mechanical stimuli than

other parts of the body (such as the forehead) and may be tender to such palpation in healthy people, but in FM the threshold is lowered and such pressure gives a wince/withdrawal response.

Figure 1-2. Tender points in FM – ACR 1990 criteria



1.2.2 American College of Rheumatology (ACR) Criteria

In 1990, the American College of Rheumatology (ACR) introduced the first FM classification criteria (Wolfe et al., 1990). The criteria required the existence of 11 hyperalgesic tender points out of 18 specified sites and widespread pain lasting longer than 12 weeks. Although the aim of these criteria were to identify groups for research studies, not for diagnosis of individual patients, the criteria assisted in differentiation of FM from other chronic musculoskeletal pain disorders in clinical practice as well as leading to an increase in studies related to FM (Geenen & Jacobs, 2001). However, in the following years it was highlighted that tender point count was rarely performed or was performed inaccurately. Moreover, men are less likely to have hyperalgesic tender points and this makes it difficult to classify men with FM using the 1990 ACR criteria (Gracely et al., 2003). Moreover, there was uncertainty in categorising or assessing patients who improved, as they could not meet the ACR 1990 classification criteria.

The subsequent ACR 2010 and 2011 preliminary diagnostic criteria changed the definition of FM by adding its multi-symptom nature and removing the tender point examination as a requirement for diagnosis (Wolfe et al., 2011; Wolfe et al., 2010). Use of a widespread pain index (WPI) of 19 areas of the body and symptom severity score (SS) were suggested. For a diagnosis of FM, a WPI of at least 7 and an SS of at least 5 is required, or alternatively a WPI of 3-6 with an SS of 9. However, there was less emphasis on chronic pain. More recently, the 2016 revisions to the 2010/2011 diagnostic criteria again highlighted the generalised multiple regional pain as a core symptom

(Wolfe et al., 2016). Table 1-1 illustrates the differences among the ACR 1990, 2010, 2011, and 2016 criteria.

Table 1-1. Comparison of ACR criteria for diagnosing FM in 1990, 2010, 2011, and 2016

Diagnosis/classification criteria	Measures of pain	Hyperalgesic sites	Associated symptoms	Diagnosis/Classification
ACR 1990	Widespread pain noted as pain in all four quadrants (both the left and right side of the body, above and below the waist); plus axial skeletal pain (pain in the cervical spine or anterior chest or thoracic spine or low back)	Yes (≥11 out of 18)	Not specified	Widespread pain and at least 11 tender points for at least 3 months
ACR 2010	Use of WPI: a 0–19 count of the body regions reported as painful by the patient over the past week	No	Use of SSS, a score of the sum of severity of three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus somatic symptoms in general (on a 0–12 scale)	WPI ≥7 and SSS ≥5; or WPI 3–6 and SSS ≥9 Symptoms present at a similar level for at least 3 months The patient does not have a disorder that would otherwise explain the pain
ACR 2011	Use of WPI: a 0–19 count of the body regions reported as painful by the patient over the past week	No	Use of SSS, a score of the sum of severity of three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the sum of the number of the following symptoms occurring during the previous 6 months: headaches, pain or cramps in the lower abdomen and depression (on a 0–12 scale)	WPI ≥7 and SSS ≥5; or WPI 3–6 and SSS ≥9 Symptoms present at a similar level for at least 3 months The patient does not have a disorder that would otherwise sufficiently explain the pain The criteria also include a FM severity score (the sum of WPI plus SSS), which is a quantitative measurement of FM severity
ACR 2016	Generalised pain defined as pain in at least 4 out of 5 regions (left upper region, right upper region, left lower region, right lower region and axial region). Pain in the jaw, chest and abdomen are not evaluated as part of the generalised pain definition Use of WPI: a 0–19 count of the body regions reported as painful by the patient over the past week	No	Use of SSS, a score of the sum of severity of three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the sum of the number of the following symptoms occurring during the previous 6 months: headaches, pain or cramps in the lower abdomen and depression (on a 0–12 scale)	WPI ≥7 and SSS ≥5; or WPI 4–6 and SSS ≥9 The presence of generalized pain Symptoms have been present at a similar level for at least 3 months A diagnosis of FM is valid irrespective of other diagnoses and does not exclude the presence of other illnesses

ACR: American College of Rheumatology, WPI: Widespread pain index, SSS: Symptom Severity Score, FM: Fibromyalgia

1.3 Epidemiology

1.3.1 Prevalence and incidence

Numerous epidemiological studies in different settings, ethnic groups, areas and countries have been conducted to evaluate the prevalence and incidence of FM (Queiroz, 2013). Overall, these demonstrate that female gender and increasing age associate with higher prevalence (Wolfe et al., 1995). The prevalence of FM ranges from 0.4% in Greece (Andrianakos et al., 2003), to 9.3% in Tunisia (Guermazi et al., 2008) with an estimated 2.7% global prevalence (Queiroz, 2013). It affects women (4.2%) more than men (1.4%) with a prevalence ratio of 3:1 (Queiroz, 2013).

Different community settings and inconsistency in diagnostic criteria and case identification lead to varying results. In a community based study involving 3,006 participants with a mean age of 54 years in Kansas, USA, 10.6% of the general population had widespread pain, and 20.1% had single regional pain (Wolfe et al., 1995). It was reported that regional pain prevalence was similar in all age groups and in both genders. However, widespread pain had different sex and age associations. Rates increased in women and in the age group 50-69 years. Moreover, by the age of 60 years, 50% women and approximately 40% men had widespread pain lasting longer than 12 weeks. Of these, 2% (95% CI 1.4, 2.7) had FM according to the 1990 ACR criteria. It was concluded that prevalence is associated with gender and age (Wolfe et al., 1995).

The prevalence of FM has been evaluated in other countries as well. The prevalence varied from 10.5% in women aged 20 to 49 years in Arendal,

Norway (Forseth & Gran, 1992) to 3.6% in women aged 20 to 64 years from Trabzon, Turkey (Topbas et al., 2005). In a study from Mexico, 1.2% of 9-15 years aged school children were diagnosed as FM (Clark et al., 1998). On the other hand, it was present in 5.5% of people aged 65 years or older in São Paulo, Brazil (Santos et al., 2010).

Older studies have used the 1990 ACR criteria for case definition. However, fewer studies have used the more recent 2010 ACR preliminary classification criteria (Vincent et al., 2013; Wolfe et al., 2013). In spite of its increased sensitivity and decreased specificity compared to the 1990 ACR criteria, the modified criteria do not result in higher prevalence of FM (Wolfe et al., 2013).

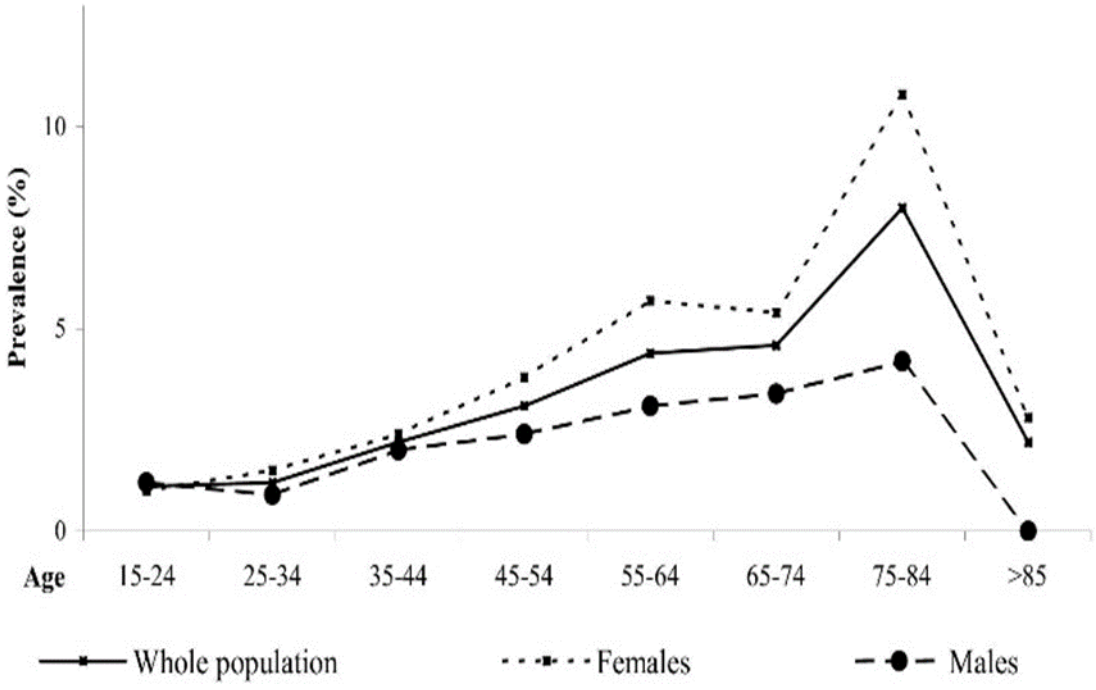
A review of 12 population-based studies assessed the incidence of physician diagnosed FM (Creed, 2020). They found that the median incidence rate of physician diagnosed FM was 3.6 per 1000 person-years ranging from 0.33 to 18.8 in eight general population cohorts. It was 14 per 1000 person-years (range 1.2-32.7) in participants with pre-existing painful conditions. Except for two studies, there was a higher incidence among women compared to men.

1.3.2 Risk Factors

1.3.2.1 Age

The prevalence of FM increases with age. It reaches peak prevalence between 60 and 79 years (more than 7% in women), and shows a downward trend above the age of 70 years (Wolfe et al., 1995). Similar results were found in another study investigating the prevalence of FM in five European countries (France, Spain, Italy, Germany, Portugal) (Branco et al., 2010). Figure 1-3 illustrates the relationship between FM and age in both genders. This shows a tail-off in the very elderly (>85 years) and may be explained by increased death rates due to associated comorbidity. Such a pattern is observed in many conditions such as knee OA (Woolf & Pfleger, 2003) or RA (Kuo et al., 2013) and might reflect a “healthy survivor effect” in that people without disease may live longer (Arrighi & Hertz-Picciotto, 1994).

Figure 1-3. Overall prevalence of FM in five different European countries per age group for both genders and the general population (Branco et al., 2010)



On the other hand, the severity of FM symptoms shows a negative correlation with age (Cronan et al., 2002). Even though the relationship between severity of FM symptoms and age is still debated, results from several studies suggest that older patients have less severe symptoms compared to their younger counterparts (Cronan et al., 2002; Jiao et al., 2014). Similarly, in people with rheumatoid arthritis (RA), younger patients have increased pain and depression compared to older patients (Wright et al., 1998). This may be due to the fact that older people are more realistic about outcomes and more stoical than younger people with chronic illness. Fleeson and Heckhausen (1997) found that older adults rated future life as less negative and their acceptance of symptoms was higher in comparison with younger people.

FM can also occur in children though there is a paucity of literature on FM at a young age. However, existing estimates of prevalence of FM in children vary widely. While it was found in 6.2% of Israeli school children (Buskila et al., 1993), in another study in Mexico (Clark et al., 1998) the prevalence of FM in school children reached only 1.2%. They both identified the cases using ACR 1990 criteria.

1.3.2.2 Gender

It is widely accepted that FM is more prevalent in women than in men (Table 1-2). Early studies suggested a prevalence ratio of 9:1 for women:men (Yunus, 2001). However, these were based on clinical diagnosis. In recent studies using classification criteria such as ACR 2011 (Wolfe et al., 2011), the proportion of women was 58.7% (Wolfe et al., 2018). Women have significantly greater intensity of pain, number of hyperalgesic tender points

(Castro-Sánchez et al., 2012), fatigue, variety of symptoms and IBS (Yunus, 2001) compared to men. Yunus (2001) also suggested that men experienced symptoms for shorter periods of time and less frequently. Similar gender differences have been reported in syndromes similar to FM in pathophysiology such as CFS, tension headache, migraine, IBS and temporomandibular disorder (TMD) (Yunus, 2002). Even though gender difference is apparent in FM and related conditions, there is still a debate regarding the reason for this difference and various factors such as biologic aspects, psychological factors or sociocultural effects have been implicated (Yunus, 2001).

Table 1-2. Adult prevalence of FM according to gender

Study	Country	Case Definition	Sample Size	Prevalence (%)	
				Women	Men
Wolfe, 1995	US	ACR 1990	3,006	3.4	0.5
White, 1999	Canada	ACR 1990	3,395	4.9	1.6
Bannwarth, 2009	France	LFESSQ and ACR 1990	3,081	2.0	0.7
Branco, 2010	Germany	LFESSQ and ACR 1990	1,002	3.9	2.5
Branco, 2010	Portugal	LFESSQ and ACR 1990	500	5.2	1.8
Branco, 2010	Spain	LFESSQ and ACR 1990	1,001	3.3	1.3
Branco, 2010	Italy	LFESSQ and ACR 1990	1,000	5.5	1.6

ACR: American College of Rheumatology, LFESSQ: the London Fibromyalgia Epidemiological Study Screening Questionnaire

Biological aspects of gender differences involve genetics, physiology and pathology. It was hypothesised that genetic factors contribute to 10% to 50% of pain severity (Mogil, 2000). Genetic variants of pain perception may differ according to gender. For instance, Belfer et al. (2013) found that the enzyme

catechol-O-methyltransferase (COMT) which reduces catecholamines such as dopamine, epinephrine and norepinephrine, is lower in women than men and this low COMT activity increases capsaicin-induced pain perception in women and reduces the efficiency of descending pain inhibition. In terms of physiologic mechanisms, women exhibit greater sensitivity to mechanical, ischaemic, electrical and cold pressure stimulation than men (Fillingim & Maixner, 1995). In a study conducted by Dessein et al. (1999), the level of adrenal androgens (testosterone and dehydroepiandrosterone) were lower in premenopausal and postmenopausal women than younger women. The authors hypothesise that androgens may be protective for FM.

Recent studies have illustrated that gender is associated with psychological distress which has an impact on pain modulation. In the general population, women showed greater depression symptoms compared with men (Kuehner, 2017). Findings from epidemiological studies show depression is more prevalent among women than man with a prevalence ratio of 2:1 (Bogren et al., 2018).

1.3.2.3 Genetic Factors

Early on in the study of FM, familial aggregation was recognised to play an important role in the development of FM (Arnold et al., 2004; Buskila & Sarzi-Puttini, 2006). Early published studies on familial occurrence of FM (Pellegrino et al., 1989; Stormorken & Brosstad, 1992) reported an autosomal dominant pattern of inheritance. Those studies did not use the ACR criteria to identify people with FM but instead used the 1981 Yunus Criteria (Yunus et al., 1981). The results, however, were supported by a family study using the ACR 1990 criteria (Arnold et al., 2004). According to

their study, first-degree relatives of probands with FM are 8.5 times more likely to develop FM when compared to probands with RA. Similarly, Buskila et al. (2006) concluded an elevated prevalence of FM in first degree relatives of FM probands.

Genetic influence on somatic symptoms has also been investigated in twin studies. It was confirmed that somatic symptoms more strongly co-aggregate in identical twins than in non-identical twins. In a twin study conducted by Kato el al. (2006), it was shown that genetic factors accounted for 48-54% of the risk for developing CWP which is a cardinal symptom of FM. No differences have been observed between genders in the magnitude or presence of genetic influence suggesting that hereditary factors may influence both genders equally in terms of developing FM (Kato et al., 2006). More recently, a series of twin studies that included 3,266 females found a heritability of CWP of 58% (Burri et al., 2015).

Research conducted in recent years that includes genome-wide association studies (GWAS) and linkage studies has expanded the knowledge of the genetic susceptibility of FM and shown the role of polymorphisms of genes in the serotoninergic, dopaminergic and catecholaminergic systems in FM (Park & Lee, 2017). FM patients have the serotonin 5-HT_{2A} receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 transporter, and COMT (Catechol-O-methyl transferase) in higher frequency (Arnold et al., 2013; Barbosa et al., 2012). These genes adversely affect monoamines and/or neuro-modulators which have a strong influence upon the stress response and both peripheral and central pain-modulating mechanisms. This then increases the predisposition to FM (Kerr & Burri, 2017).

1.3.2.4 Psychosocial Factors

Studies have demonstrated that pain is associated with psychological distress and that distress might be a cause as well as the result of FM pain (Di Tella et al., 2017). Thus, the relationship between FM and psychological distress could be bidirectional. It was also reported that psychosocial factors are not limited only to one specific period in the occurrence of FM, it may affect pain at different etiological levels. For instance, it may predispose to develop FM, and to trigger or stabilise the FM symptoms (Eich, 2000).

Many people with FM have had a history of negative experiences in childhood such as physical or sexual abuse, life stress and poor family conditions in childhood. An internet survey of 2,596 people who were diagnosed as having FM by a health care professional showed that 20.6% of the participants self-reported physical or emotional abuse in childhood and 9% reported childhood sexual abuse (Bennett et al., 2007). Similarly, in another study conducted by Jiao et al. (2015) 30% of 962 patients reported a history of abuse. Those who reported abuse specified abuse types as emotional (36%), physical (32%), sexual (25%), and verbal (7%). In contrast, a Systematic Review (SR) with MA with 23 studies including 4,640 participants found no statistically significant association between sexual abuse and a lifetime diagnosis of fibromyalgia (Odds Ratio, 1.61; 95% CI, 0.85-3.07) (Paras et al., 2009). It is hypothesised that negative experiences in childhood lead to low self-esteem, maladaptive coping strategies and unfavourable mood. As a consequence it may reduce pain threshold and tolerance even further (Winfield, 1999).

Apart from sexual victimisation, other stressful life events also might contribute to the development of FM. For instance, one study compared the impact of life events in female patients with FM and female healthy volunteers (Anderberg et al., 2000). While 51% of the 40 participants with FM rated their life events as negative, in the healthy control group this was only 28% of the 38 participants. Patients with FM also faced significantly more bullying (25.5% vs 7.9%, $p<0.05$). Furthermore, 65% of the patient group experienced daily hassles such as economic issues (45%), conflict with the partner (42.5%), bereavement of a relative or a close friend, and physical or psychological maltreatment (42.5%) before disease onset. These results are underpinned by other studies reporting higher frequency of negative life events. Van Houdenhove et al. (2002) emphasised higher prevalence of dissatisfaction with oneself, insecurity and a lack of social recognition in FM patients. Similarly, in another study by Imbierowicz and Egle (2003) it was shown that FM patients had more emotional neglect compared to the general population. Mcbeth et al. (2001) suggested that the somatisation trait or state which is the expression of personal and social distress through physical symptoms may increase risk of the development of CWP.

1.4 Pathogenesis and Pathophysiology

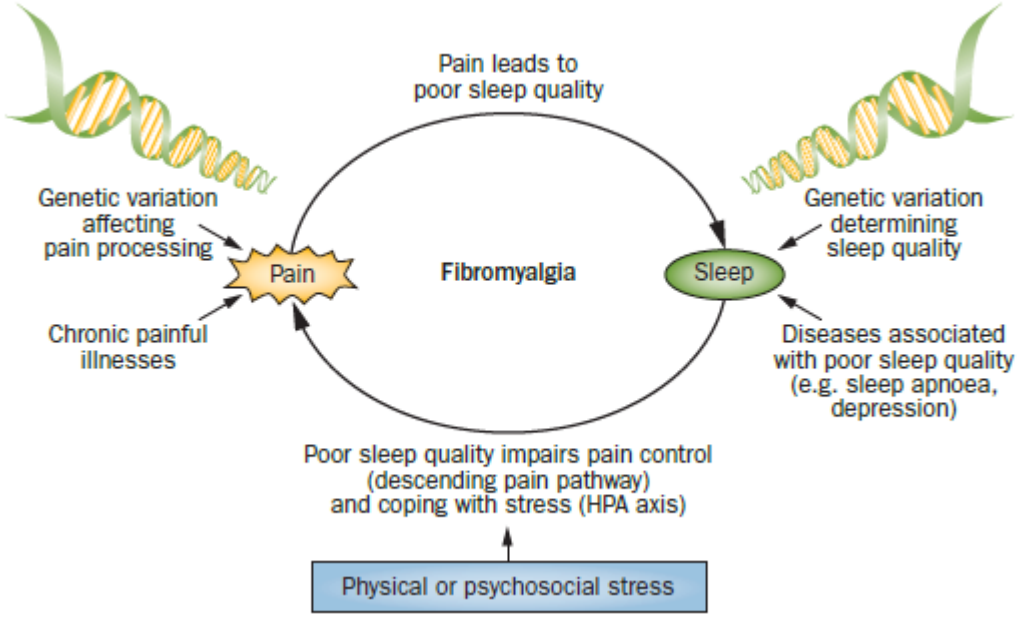
1.4.1 Altered sleep physiology

It is well documented that sleep dysfunction is a major symptom of FM (Bigatti et al., 2008; Moldofsky, 2008; Yunus et al., 1991). Common complaints include frequent awakening, difficulty in sleep onset (latency) or sleep maintenance, involuntary (restless) leg movements, and nonrestorative sleep (Choy, 2015). Several cohort studies illustrated that FM patients experienced significantly low sleep quality and their pain symptoms worsened after poor sleep (Bigatti et al., 2008; Hamilton et al., 2008; Lentz et al., 1999). In polysomnography studies, it was observed that FM patients had reduced amount of slow-wave delta sleep compared to healthy individuals that is essential for restoration (Anch et al., 1991; Sergi et al., 1999; Tononi, 2009). Also, many studies found increased alpha-delta sleep intrusion patterns during non-rapid eye movement (NREM) sleep (Dijk, 2009; Lentz et al., 1999; Sergi et al., 1999; Tononi, 2009). However, this was not unique to FM. Increased alpha-delta sleep intrusion has also been detected in insomnia (Cantero et al., 2002).

There is a reciprocal relationship in the direction of causation. Pain may cause poor sleep and decreased sleep quality may exacerbate pain (Choy, 2015) (Figure 1-4). Initially, Moldofsky et al. (1975) observed a decrease in pressure pain threshold and fibromyalgia-like myalgia and tenderness in healthy individuals after an intrusion of alpha-wave NREM sleep. Subsequent research confirmed the association between sleep deprivation and decreased pain threshold (Kundermann et al., 2004; Roehrs et al., 2006; Smith et al., 2007). It was hypothesised that loss of restorative delta sleep

and selective delta sleep deprivation for 3 nights in normal women led to an increase in pain and fatigue (Lentz et al., 1999; Moldofsky, 2009). In observational studies, sleep disorder has been shown to predispose to pain suggesting that poor-quality sleep may be aetiological for FM (Affleck et al., 1996; Bigatti et al., 2008; Mork & Nilsen, 2012).

Figure 1-4. Bidirectional relationship between sleep and pain (Choy, 2015)



1.4.2 Altered pain physiology

There is a growing body of evidence that supports altered central pain processing as a major contributor to the pathogenesis of FM (Sluka & Clauw, 2016). These alterations include an increased activation in areas of the brain dedicated to pain (Dehghan et al., 2016; Jensen et al., 2009), altered connectivity (Napadow et al., 2010), a reduced brain activity for pain anticipation and anticipatory analgesia (Pujol et al., 2009).

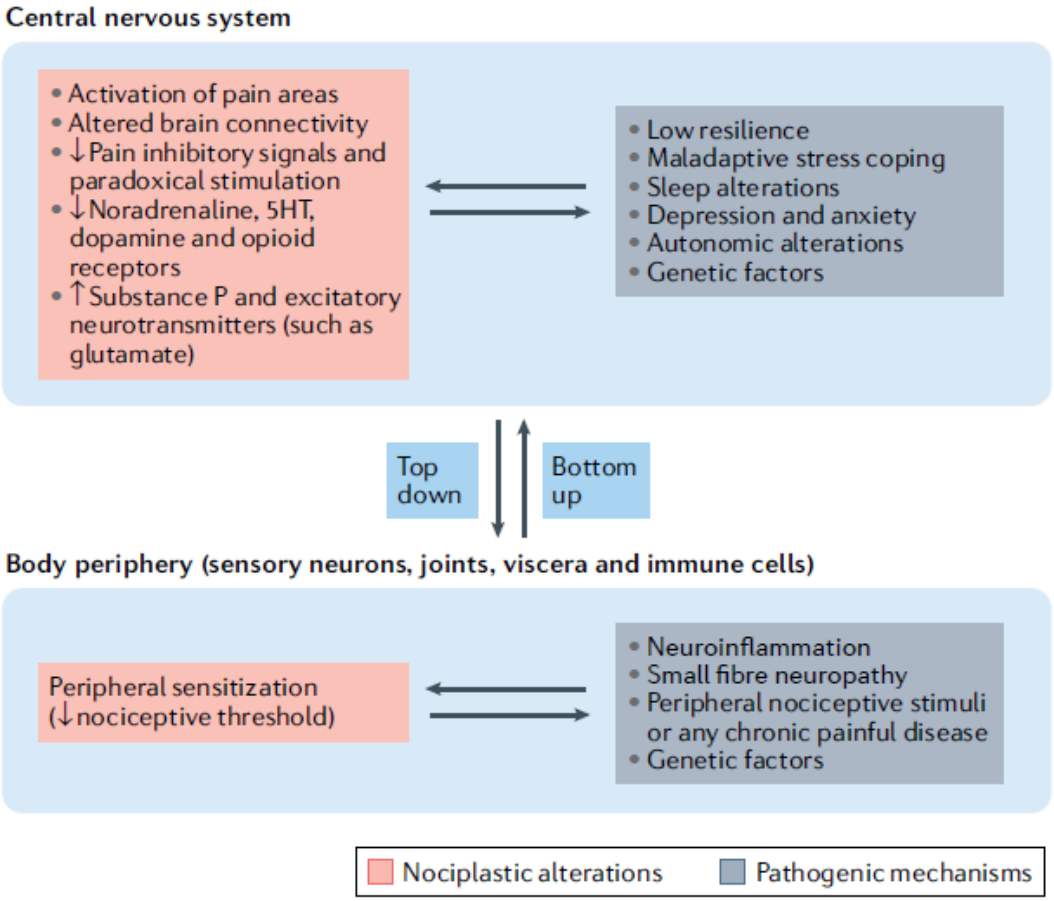
Several studies have shown there is an imbalance between the nociceptive and anti-nociceptive systems that causes an alteration in functional activation and connectivity of endogenous pain inhibitory signals (Jensen et al., 2012; Julien et al., 2005; Normand et al., 2010). At the microscopic level, it was detected that patients with FM had increased level of neurotransmitter substance P (Russell et al., 1994) and opioid (Baraniuk et al., 2004) in the cerebrospinal fluid or μ-opioid receptor availability in the amygdala, the nucleus accumbens, and the dorsal cingulate that are responsible for pain modulation (Harris et al., 2007) compared to healthy participants. Similarly, patients with FM had lower serotoninergic and noradrenergic neurotransmitters in the biological fluid (Russell et al., 1992; Yunus et al., 1992) and an attenuated brain dopaminergic activity than in healthy participants (Wood et al., 2007; Wood et al., 2007). Furthermore, fMRI studies identified decreased grey matter volume in the cortical and subcortical areas in patients with FM (Lutz et al., 2008).

It is difficult to identify the causes of these nociplastic alterations and to explain FM by a single aetiology. As mentioned in the previous sections, other factors such as genetic background, sleep, and stressful life events

also play a key role in the development of nociplastic pain and fibromyalgia.

Figure 1-5 shows the nociplastic mechanisms and pathogenic alterations in FM (Sarzi-Puttini et al., 2020).

Figure 1-5. Nociplastic mechanisms and pathogenic alterations in FM (Sarzi-Puttini et al., 2020)



5HT: 5-hydroxytryptamine

1.4.3 Environmental triggers

Environmental triggers such as exposure to physical/mechanical trauma or injury and psychosocial stressors are one of the many factors contributing to the pathophysiology of FM (Sluka & Clauw, 2016). Commonly reported physical traumas including physical injury, surgery, acute illness, and motor vehicle accidents as well as psychosocial triggers such as chronic stress, physical, sexual and emotional abuse and trauma are associated with the onset of CWP (Häuser et al., 2015; Häuser et al., 2011; Paras et al., 2009). Patients with FM have shown reduced resilience (Casale et al., 2019).

These environmental triggers may contribute to augmented pain responses by altering the function of the hypothalamic-pituitary-adrenal (HPA) axis which has a role in descending pain inhibition (Casale et al., 2019). Under conditions of acute stress, glucocorticoids and cortisol provide resilience by initiating the “fright, fight or flight” mechanism. However, during chronic stress prolonged changes in concentration of these hormones may lead to functional and structural changes in the CNS that have an impact on physical and emotional health (Spencer-Segal & Akil, 2019). As in depression, FM was found to be associated with higher levels of plasma cortisol and alteration in diurnal rhythm (Bradley, 2009). McCain et al. (1989), for instance, found a significantly higher level of plasma cortisol in patients with FM compared to those with RA. Additionally, 35% of patients with FM treated with dexamethasone had inability to suppress cortisol compared to 5% of patients with RA. These findings suggest high stress level in people with FM.

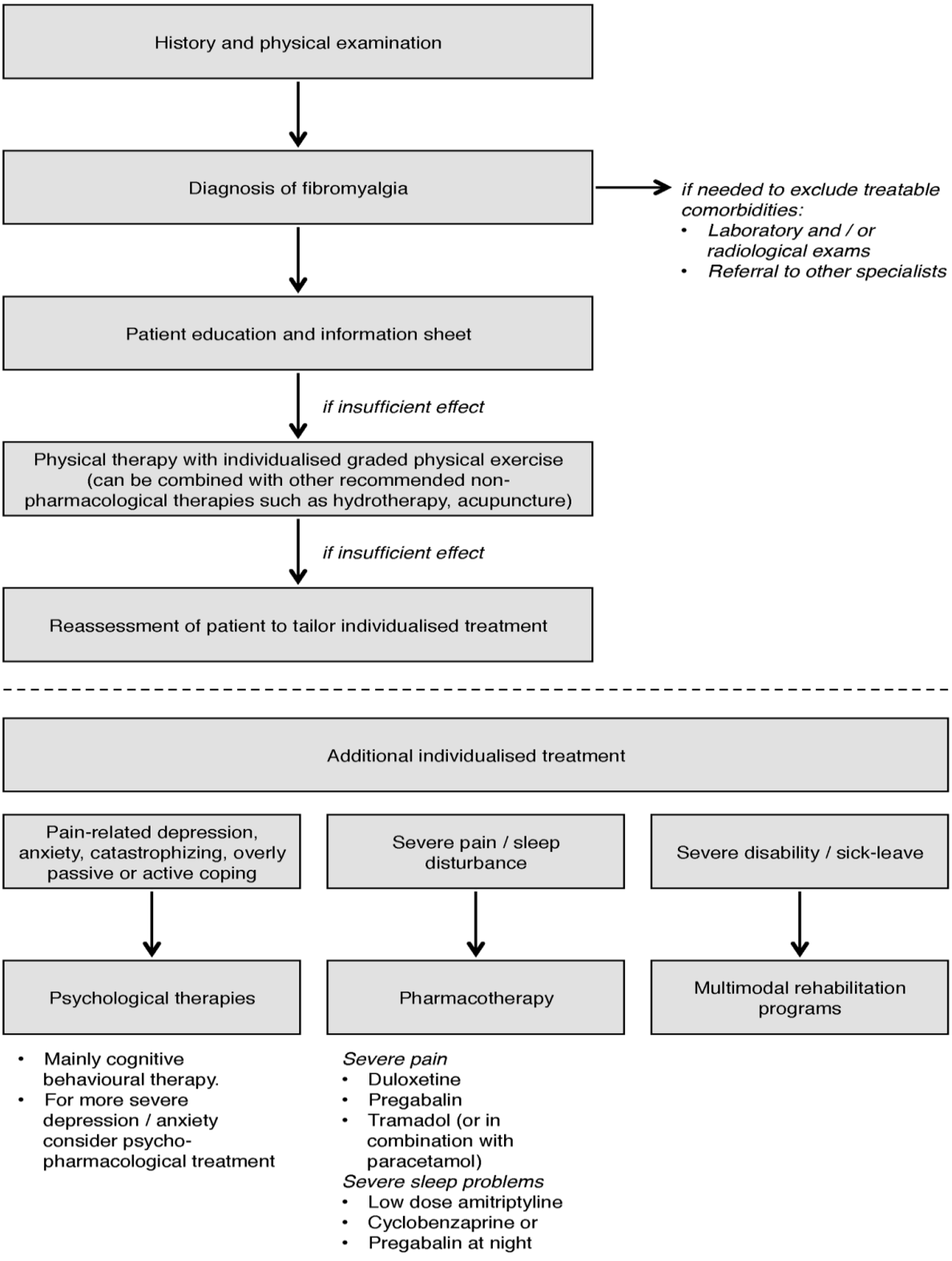
In addition to psychological stressors, certain types of infections such as Borrelia burgdorferi, Lyme disease, or viral hepatitis may trigger FM (Cassisi et al., 2011; Wormser et al., 2015).

1.5 Management

All guidelines on the management of FM support a multi-faceted approach combining non-pharmacological interventions as first-line therapy and pharmacological interventions as adjunctive treatment, with an emphasis on an individualised patient-centred approach (Fitzcharles et al., 2013; Häuser et al., 2017; Macfarlane et al., 2017). Although there are differences among guidelines regarding the strength of recommendations, which may be explained by using currently existing evidence, all guidelines (Fitzcharles et al., 2013; Häuser et al., 2017; Macfarlane et al., 2017) are in agreement on the first-line role of non-pharmacological treatments with an individualised management strategy.

Better recognition and understanding of FM have led to more treatment options for this condition. However, as there is no “cure” for this condition, the main aim is to improve health-related quality of life (HRQoL) rather than necessarily eliminating the condition (Macfarlane et al., 2017). The most recent guidelines by the European League Against Rheumatism (EULAR) in 2017 advocate the requirement of prompt diagnosis and provision of patient education for optimal treatment. They suggest non-pharmacological treatments as a first-line treatment option. Figure 1-6 illustrates management recommendations by EULAR (Macfarlane et al., 2017).

Figure 1-6. Management recommendations for FM (Macfarlane et al., 2017)



The absence of any specific “curative” management has resulted in various treatment options being prescribed and used by patients with FM (Bennett et al., 2007). In general, all the treatments for FM can be classified into two groups as pharmacological and non-pharmacological (Table 1-3).

Table 1-3. Treatments for FM

Non-pharmacological	**Pharmacological**
Patient Education	Anti-Depressants
Exercise	Analgesics and NSAIDs
Cognitive Behavioural Therapy	Anticonvulsants
Hydrotherapy and Balneotherapy	Miscellaneous medications
Complementary and Alternative Medicine	
Electrotherapy	
Sleep Hygiene	

NSAIDs: Non-steroidal anti-inflammatory drugs

1.5.1 Non-pharmacological Treatment

1.5.1.1 Patient Education

Recent evidence suggests that an educational approach should be the first step in the treatment of FM (García-Ríos et al., 2019). Patient education, by definition, is the process planned to alter patients' health behaviours or improve their health status (Hill, 1997). Information provision is a professional responsibility but it is also a treatment in its own right. Patient information should provide key features of FM and potential pathologic mechanisms in the context of a biopsychosocial framework, the prognosis of the condition and the coexisting factors. It is also important to avoid single structural or causation labels such as post-traumatic FM or post-infectious FM (Goldenberg et al., 2004). It has even been suggested that the FM diagnosis itself might result in deterioration in symptoms. However, a prospective cohort study has refuted this concern by showing that giving a diagnosis of FM had no adverse effects and may in fact be positive in terms of improving function over 18 months (White et al., 2002).

Patient education should address pain physiology and central sensitisation as well as sleep for a better understanding of the nature of FM (Ittersum et al., 2014). A basic guide to pain physiology is a good initial point to reconceptualise pain and to correct inappropriate pain beliefs. The utmost goal of patient education is to ensure that patients can better manage their condition and improve their quality of life (QoL) by increasing self-efficacy and decrease depression and catastrophic thinking (Nijs et al., 2011).

Several studies have attempted to investigate the effectiveness of patient education for FM. An SR in Spanish assessed the effectiveness of education

on pain, functionality and QoL in patients with FM (Elizagaray-García et al., 2016). Five RCTs with 330 participants were included. Three of them were combined with another active intervention. They found education in itself was not effective for the outcomes assessed.

A more recent SR conducted by García-Ríos et al. (2019) investigated the effectiveness of education techniques on pain, QoL, functionality, anxiety or catastrophisation in the management of FM. They identified 12 studies whose sample sizes ranging from 15 to 108. The educational interventions varied in terms of implementation techniques and duration of treatments. Some studies had additional treatments such as another non-pharmacological intervention or a pharmacological intervention. There were no RCTs with a high methodological quality. They concluded that there was a limited evidence for the benefits of education on pain, QoL, functionality, anxiety or catastrophisation in patients with FM.

1.5.1.2 Exercise

The term “exercise” has different meanings for different people and its meaning may also change according to context. Some people may consider a type of activity such as walking a form of exercise, whereas others would classify it as physical activity. Table 1-4 illustrates a few common words in exercise terminology. Although Goldenberg (2000) suggested using the term “activity” instead of exercise for FM patients to prevent catastrophising thoughts of sedentary FM patients, the term “exercise” will be used in this thesis.

Table 1-4. Common terminologies relating to exercise and physical activity (Ageberg et al., 2013; Chodzko-Zajko et al., 2009)

Terminology	Definition
Physical activity	Any bodily movement produced by skeletal muscles that requires energy expenditure
Physical fitness	The characteristic that people have or can achieve through physical activity or exercise
Exercise	Planned, repetitive and structured physical activity which is done with the intention of improving or maintaining physical fitness or health.
Exercise therapy	A regimen or plan of physical activities designed and prescribed for specific therapeutic goals. Its purpose is to restore normal musculoskeletal function or to reduce pain caused by diseases or injuries.

There are several reasons for the use of exercise for FM. One rationale for the use of exercise is that studies have revealed that a single episode of exercise increased the production of endogenous analgesics that lead to transient anti-nociception in humans and animals (Stagg et al., 2011). Another reason might be to compensate for the effects of long-lasting deconditioning, since patients with FM are deconditioned as compared with healthy people (Bousema et al., 2007; Elvin et al., 2006). Even though FM pain may be related to CNS pain processing abnormalities, initiating and/or maintaining central sensitisation may be caused by peripheral tissues such as muscle (Staud, 2006). Several studies have presented metabolic findings in muscle tissue due to the deconditioning (Bennett et al., 1989; Bousema et al., 2007; Elvin et al., 2006; Lund et al., 1986). Exercise may improve some of these metabolic findings and provide pain relief (Deschenes & Kraemer,

2002; Holloszy & Coyle, 1984). Fatigue may improve because as maximal aerobic capacity improves the individual will be performing activities of daily living at lower absolute percentages of maximal capacity. Also, it may decrease maladaptive fear avoidance behaviour preventing individuals to involve physical activities as in the cognitive behavioural model (Philips, 1987).

Several therapeutic benefits of exercise in the management of FM have been reported. These include alleviation of pain, improved strength and cardiovascular fitness, improved self-esteem and physical function (Redondo et al., 2004; Richards & Scott, 2002). In terms of psychological benefits, exercise may improve mental status, self-efficacy and sense of well-being (Bandura et al., 1987; Gowans et al., 2001; Marcus et al., 1992). It was also advocated that exercise, predominantly aerobic, could improve sleep pattern and encourage more delta sleep and sleep restoration (Busch et al., 2007).

Numerous reviews have been published investigating the effectiveness of different exercise interventions such as aerobic, strengthening and flexibility training and various combinations of these. The largest review, a Cochrane Review, by Busch et al. (2007) examined 47 different exercise modalities. In that study, 1,264 participants out of 2,276 from 34 included studies were assigned to exercise interventions. Exercise interventions provided significant improvements in global well-being (Effect size (ES)=0.49; 95% Confidence Interval (CI) 0.23, 0.75) and physical function (ES =0.66; 95% CI 0.41, 0.92) and reduced hyperalgesic tender point counts (ES =0.23; 95% CI -0.18, 0.65). Another SR by Busch et al. (2013) reviewed 5 trials evaluating the effectiveness of resistance exercise training. It was concluded that

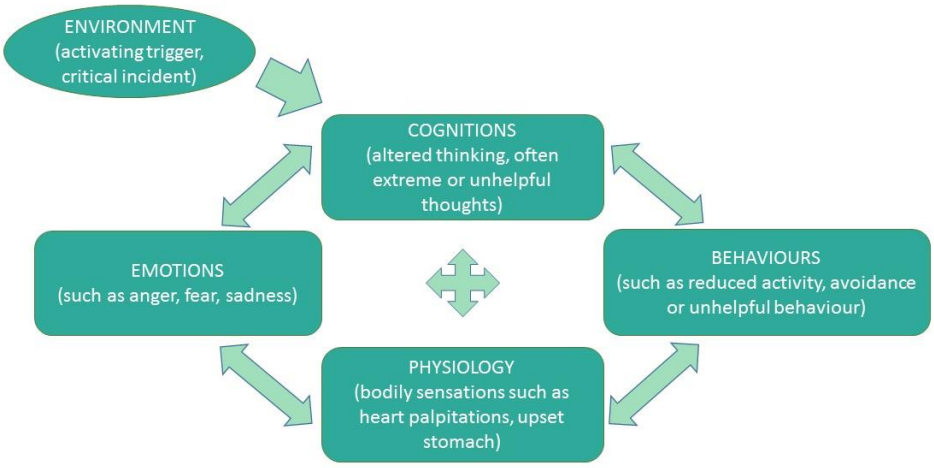
resistance exercise training showed significant improvements in pain by -3.3 cm on a 10-cm scale (95% CI -6.35 to -0.26) and in multidimensional function total reduced 16.75 units on a 100-point scale (95% CI -23.31 to -10.19) compared to controls. However, the authors rated the evidence as low quality due to the low number of studies and assessment of risk of bias. Even though the authors reported moderate quality evidence for short-term aerobic training but only limited evidence for resistance training, they could not conclude superiority of one over the other due to study limitations such as poor adherence, low quality, lack of agreement on how to assess outcomes of interest, etc. It was therefore recommended that further research is needed to prioritise them (Busch et al., 2007).

Mind-body exercises such as yoga, Tai Chi and Qigong will be considered as an exercise type in this thesis. There is modest evidence to support the use of these treatments. A review of seven studies evaluated the efficacy and safety of meditative movement therapies (Qigong, Tai Chi and Yoga) in FM (Langhorst et al., 2013). Comparator treatments included waiting list, usual care and active treatment such as stretching, aerobic exercise, education and physiotherapy. At the end of therapy, improvements were seen in sleep (ES=−0.61; 95% CI −0.95 to −0.27), fatigue (ES=−0.66; 95% CI −0.99 to −0.34), depression (ES=−0.49; 95% CI −0.76 to −0.22), and HRQoL (ES=−0.59; 95% CI −0.93 to −0.24). Moreover, the significant effects on sleep and HRQoL were maintained in the longer term. There were, however, no significant improvements in pain (ES=−0.35, 95% CI −0.80 to 0.11) (Langhorst et al., 2013).

1.5.1.3 Cognitive Behavioural Therapy

Cognitive Behavioural Therapy (CBT) is a psycho-social intervention developed in the middle of the 20th century (Rachman, 1997). It combines elements of both cognitive and behavioural therapies to beneficially change patients' maladaptive patterns in cognitions such as beliefs, attitudes, emotional regulation and behaviours. Factors involved within the CBT model are illustrated in Figure 1-7 (Beck, 1979). The primary therapeutic strategies used in CBT are twofold. Firstly, maladaptive thought patterns interfering with remedial progress are identified and modified. Secondly, these behavioural interventions aim to break the vicious circle between symptoms and patterns of dysfunctional performance.(Bennett & Nelson, 2006).

Figure 1-7. Factors involved within the CBT model (Beck, 1979)



There is a growing interest in research regarding CBT. With the development of CBT, more treatment methods have become available to treat psychiatric illnesses such as depression (Butler et al., 2006) and anxiety disorders (Hofmann & Smits, 2008), which are also common in FM. Moreover, it

decreases pain, fatigue and sleeplessness as well as improves stress levels and physical condition (Bernardy et al., 2018; Goldenberg et al., 2004; Singh et al., 1998). Hence, addressing psychiatric comorbidity itself ensures a justification for the use of CBT as an adjunctive therapy for those patients with FM with sublimated anxieties or other psychiatric problems. An SR with meta-analysis evaluated the efficacy, acceptability and safety of CBT (Bernardy et al., 2018). There were 29 RCTs with 2509 participants meeting their inclusion criteria. They included only face-to-face or telephone-based CBT interventions delivered or supervised by a healthcare professional trained in an extant CBT model or framework. Overall, they found CBT was superior to the control group (usual care, waiting list, attention control) in pain (Risk difference (RD)=0.05; 95% CI 0.02 to 0.07), HRQoL (RD=0.13; 95% CI 0.00 to 0.26), fatigue (SMD=– 0–27; 95% CI −0.50 to −0.03) and negative mood (SMD=−0.43; 95% CI −0.62 to −0.24). A Cochrane Review including 23 trials with a total of 2,031 participants assessed the benefits and harms of CBT for treating FM (Bernardy et al., 2013). They included any psychological treatments based on a CBT model or framework (face to face, telephone or internet-based) delivered by a trained health care professional. Results in CBT intervention groups showed statistically significant but clinically non-significant reductions in pain by 0.5 points on a scale of 0 to 10 (-0.29; 95% CI -0.49 to -0.17), in disability by 0.7 points (-0.30; 95% CI -0.51 to -0.08) and in negative mood by 0.7 points (-0.33; 95% CI -0.49 to -0.17) compared to a variety of control groups at the end of treatment. The results were sustained long term (median 6 months), although the GRADE quality of evidence of included studies was low.

1.5.1.4 Hydrotherapy, Balneotherapy and Spa Therapy

Although the four terms hydrotherapy, aquatic therapy, balneotherapy and spa therapy were commonly used for water therapy, confusion still persists regarding their definition and the terms are often used interchangeably (Bender et al., 2005). Hydrotherapy/aquatic therapy is the general term for water therapy and employs simply ordinary water such as tap or very low mineralised water.

Balneotherapy, however, uses natural thermal mineral water including sodium, magnesium, calcium and iron etc. (Sukenik et al., 1999), natural gases (i.e. CO2, iodine, sulphur, radon) and peloids (mud) (Naumann & Sadaghiani, 2014). Spa therapy includes a number of different interventions including hydrotherapy and balneotherapy, and creates a special therapeutic context of its own through the change in environment and lifestyle (Bender et al., 2005).

It was suggested that these treatment options may alleviate FM symptoms through effects of hydrostatic pressure (i.e. buoyancy, aquatic resistance), or the effect of heat on pain nerve endings, and also non-specific contextual effects such as change of environment, spa-scenery, etc. (Naumann & Sadaghiani, 2014). Although they were commonly used in multicomponent interventions in the management of FM, current research advocates the use of hydrotherapy and balneotherapy. A Meta-Analysis performed by Langhorst et al. (2009) reviewed 10 studies with 446 participants investigating the efficacy of hydrotherapy in FM. A median treatment time of 240 (200-300) minutes hydrotherapy programme including balneo-, spa- and thalassotherapy, hydrotherapy and packing and compresses was compared

with various comparators such as no treatment, usual care, medication, etc. There were significant improvements in pain (-0.78; 95% CI -1.42, -0.13) and HRQoL (-1.67; 95% CI -2.91, -0.43) at the end of therapy in the hydrotherapy compared to other groups. Despite consistency of the evidence for both hydrotherapy and balneotherapy, there is a paucity of data to suggest superiority of one over the other (Naumann & Sadaghiani, 2014).

1.5.1.5 Complementary and Alternative Medicine

The use of Complementary and Alternative Medicine (CAM) for many chronic conditions has become increasingly popular. Almost all FM patients may at some time use CAM (Pioro-Boisset et al., 1996; Wahner-Roedler et al., 2005). However, as for several other musculoskeletal conditions, evidence supporting the use of such approaches in the management of FM is tentative at the best or does not exist.

The National Centre for Complementary and Integrative Health classifies CAM mainly into two subgroups. The first group is natural products, including vitamins, minerals, probiotics and herbs. The second group is mind and body practices, comprising acupuncture, osteopathic manipulation, chiropractic, massage therapy, hypnotherapy, relaxation techniques such as breathing exercises, guided imagery etc. In addition to these two groups, homeopathy, ayurvedic medicine, traditional Chinese medicine and traditional healers are also considered a form of CAM ("National Center for Complementary and Integrative Health (NCCIH) Website"). CAM therapies which may be beneficial in FM include acupuncture (Duncan et al., 2007), trigger point injections (Staud, 2006), chiropractic (Hains & Hains, 2000), massage

therapy (Field et al., 2002), hypnotherapy (Haanen et al., 1991) and biofeedback (Babu et al., 2007).

Although widely used by patients, there is weak evidence for use of acupuncture (Macfarlane et al., 2017). Deare et al. (2013) reviewed 9 articles (low to moderate level evidence) with 395 patients. It was concluded that while acupuncture (manual or electro-acupuncture) significantly improved stiffness (ES=-0.45; 95% CI -0.84, -0.06) up to one month after treatment, it was no better than control group including no treatment, standard treatment or sham acupuncture for pain (ES=-0.14 95% CI -0.53, 0.25), global well-being (ES=0.29; 95% CI -0.44, 1.01) and fatigue (ES=-0.10; 95% CI -0.81, 0.61). Even though electro-acupuncture provided statistically significant pain relief (-0.63; 95% CI -1.02, -0.23) the effect was short term.

According to a patient survey with 301 participants in Canada, massage is by far the most acceptable CAM intervention among patients with FM (Pioro-Boisset et al., 1996). Despite its popularity, it was not recommended in the EULAR (Carville et al.) 2016 guidelines. A meta-analysis with 9 trials performed by Li et al. (2014) evaluated the effectiveness of massage lasting 25-90 min for treating FM. Comparators included standard care, transcutaneous electrical nerve stimulation (TENS), acupuncture and guided imagery and the study duration ranged 1 to 24 weeks. Overall results showed that massage therapy was not associated with significantly decreased pain (0.37; 95% CI −0.19 to 0.93). In a subgroup analysis massage therapy of ≥5 weeks duration significantly decreased pain, but this analysis was based on lower quality studies. Likewise, the use of chiropractic

was not recommended for treating FM by EULAR due to the absence of robust interpretable data (Macfarlane et al., 2017).

The effects of psychological CAM approaches such as hypnotherapy, biofeedback and guided imagery in patients with FM have also been investigated in clinical trials. Even though some benefits were reported for each treatment modality (Bernardy et al., 2011; Glombiewski et al., 2013) the 2017 EULAR guidelines recommended not to use these treatments due to reporting of only non-supported studies or studies having serious flaws (Macfarlane et al., 2017).

Other CAM therapies such as homeopathy (Perry et al., 2010), music therapy (Crawford et al., 2014) and phyto-thermotherapy (Tenti et al., 2013) were also identified in the management of FM. Homeopathy was not recommended in the EULAR 2017 guidelines in spite of some reported benefits, and insufficient evidence was found to judge the other therapeutic approaches.

1.5.1.6 Electrotherapy and magnetic therapy

Different type of electrotherapy modalities including ultrasound, interferential currents, laser, TENS or transcranial magnetic stimulation have been investigated in the management of FM. It is hypothesised that these interventions may work through pain gate theory mechanisms proposed by Melzack (Melzack, 1996) or may activate both opioid and non-opioid endogenous pain control mechanisms and other neuroendocrine mediated systems of descending pain inhibition (Adams & Sim, 1998).

Almeida et al. (2002) evaluated the effectiveness of combined therapy comprising pulsed ultrasound and interferential current versus sham treatment on pain and sleep in patients with FM. After 12 treatment sessions, the intervention group showed significant improvements in pain and sleep complaint with decrease in tender point count (all $p<0.001$). The authors concluded that combined therapy with pulsed ultrasound and interferential current may be an effective treatment option for pain and sleep manifestations in FM. They, however, had a small sample size (17 patients).

The effectiveness of TENS in FM patients was studied by Dailey et al. (2013). Active TENS (n=43), placebo TENS (n=43) and no TENS groups (n=43) were assessed for pain, fatigue, pain pressure thresholds and functional tasks such as single-leg stance, 6-minute walk test and 5 times sit-to-stand test. The active TENS group showed significant improvements in pain, fatigue and pressure pain thresholds, but no difference in functional tasks, compared with placebo TENS and no TENS.

The efficacy of transcranial magnetic or direct current stimulation was examined by Marlow et al. (2013). Nine trials were reviewed and overall, there was little evidence to support these modalities, not all of which were analysed by intention-to treat (ITT). In addition, there were unacceptably high rates of adverse effects or drop-out due to headache.

1.5.1.7 Sleep Hygiene

Sleep disturbance with persistent non-restorative sleep is one of the hallmarks of FM and it is associated with the development and maintenance of lowered pain threshold and FM-related pain as well as fatigue (Affleck et

al., 1996; Nicassio et al., 2002). Sleep hygiene may be provided by behavioural approaches as well as advice. It includes several measures such as avoiding or minimising caffeine, alcohol, cigarette or other medications, increasing physical activity level, providing an environment that is adequately ventilated, dark and appropriately warm, avoiding heavy meals at bedtime and going to bed only when sleepy (Kamel & Gammack, 2006).

A randomised controlled trial with 47 patients with FM compared the effect of CBT, sleep hygiene advice and usual care for insomnia (Edinger et al., 2005). Subjective (sleep logs) and objective (actigraphy) total sleep time, sleep efficiency and questionnaire measures of global insomnia symptoms such as pain, psychological status and QoL were measured before and after treatments. Sleep hygiene therapy was superior in improving mental well-being and pain compared to CBT and usual care.

1.5.2 Pharmacological Treatment

To date, there is no medication which was specifically developed for the treatment of FM. Several guidelines for pharmacological treatment of FM suggest medications such as anti-depressants, NSAIDs, analgesics, anticonvulsants and miscellaneous medications including cyclobenzaprine, sodium oxybate and GH which mainly target central pain processing mechanisms (Fitzcharles et al., 2013; Macfarlane et al., 2017). Several of these pharmacological treatments have been tested in controlled trials for their effectiveness for FM and meta-analyses have been conducted on most of these management options (Häuser et al., 2013; Hauser et al., 2012; Moore et al., 2012; Moore et al., 2009; Üçeyler et al., 2013). However, overall most trials had flawed methodology including small sample sizes, inappropriate blinding and non-standardised outcome measures, and showed only short-term or trivial benefit with frequent adverse events (Goldenberg et al., 2004).

1.5.2.1 Antidepressants

It is well documented that antidepressants such as tricyclic anti-depressants specifically amitriptyline, serotonin-noradrenalin reuptake inhibitors, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors may be beneficial in the treatment of FM. These antidepressants may improve pain, fatigue, poor sleep and QoL by preventing the re-uptake of serotonin and noradrenalin into the presynaptic terminals (Staud, 2010). Low-dose amitriptyline (lower than that used in depression) provides analgesic effects by reducing spinal cord “wind up” of ascending nociceptive signals, and it also increases delta sleep (Moore et al., 2012). Two meta-analyses (Häuser

et al., 2011; Häuser et al., 2012) examined the efficacy of antidepressants in the treatment of FM and concluded that antidepressants were associated with improvement in pain, sleep disturbances, fatigue and overall well-being compared to placebo. Both studies, however, highlighted the limitations of RCTs which had small sample sizes, inappropriate blinding and non-standardised outcome measures and short-term benefit.

1.5.2.2 Analgesics and NSAIDs

Chronic widespread pain is one of the manifestations of FM. Analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids therefore are used commonly for treatment of FM. While the evidence suggests that analgesics (especially tramadol) may be helpful for FM (Biasi et al., 1998; Russell et al., 2000), there is little evidence to support the use of NSAIDs (Smith et al., 2011). Furthermore, strong opioids are not recommended due to the lack of evidence of efficacy and high risk of adverse events and possible addiction (Macfarlane et al., 2016).

Tramadol, a weak opioid, has been found to be effective in the treatment of FM. 3 RCTs versus placebo support the use of tramadol with or without paracetamol (Bennett et al., 2003; Biasi et al., 1998; Russell et al., 2000). A double-blind, crossover, placebo controlled trial with 12 patients revealed a significant reduction in pain in the tramadol group versus placebo (Biasi et al., 1998). A larger study with 100 patients also concluded that tramadol improved pain scores and pain threshold (Russell et al., 2000). Most recently, Bennett et al. (2003) compared a combination of tramadol and paracetamol with placebo and found that pain and FIQ scores were better in the treatment group. However, in this RCT, it was also reported that seizure,

nausea, constipation, vomiting, headache and somnolence were potential risks of tramadol.

There is no research evidence to support the use of NSAIDs including naproxen and ibuprofen in the management of FM. However, NSAIDs may be beneficial when combined with tricyclic medications (Goldenberg et al., 1986) or when FM is accompanied with another pain condition such as osteoarthritis (Goldenberg, 2007).

1.5.2.3 Anticonvulsants

Pregabalin and gabapentin are anticonvulsants which are used in the treatment of neuropathic pain (Dworkin et al., 2010). These two drugs are thought to work by binding the α2δ subunit of voltage-gated calcium ion channels in the CNSand this reduces calcium influx into neurons and several excitatory neurotransmitters including glutamate, norepinephrine, and substance P. This may be beneficial for conditions associated with central sensitisation and decreased activity in descending pain modulatory pathways (Dworkin et al., 2010). An SR with MA by Tzellos et al. (2010) indicated that both medications may be relatively efficacious in spite of their relatively high incidence of adverse events comprising dizziness, somnolence and dry mouth.

1.5.2.4 Miscellaneous Medications

There is at best little or no evidence to use of other medications such as sodium oxybate, cyclobenzaprine and GH.

An SR regarding Sodium oxybate revealed a modest effect size on pain (ES=0.42; 95% CI 0.11, 0.73) and moderate effect sizes on sleep problems

(ES=0.6; 95% CI 0.32, 0.91) and fatigue (ES= 0.59; 95% CI 0.25, 0.92) (Perrot & Russell, 2014). On the other hand, the use of sodium oxybate in FM was refused by The European Medicines Agency and the US Food and Drug Administration (FDA) due to concerns over safety (Perrot & Russell, 2014).

Treatment with cyclobenzaprine was evaluated in a meta-analysis of 5 RCTs with 312 patients (Tofferi et al., 2004). Results showed a significant, but small, improvement in sleep. The odds ratio for overall improvement with the medication was 3.0 (95% CI 1.6–5.6). However, 85% of patients taking cyclobenzaprine experienced adverse effects and 29% could not complete the study.

Growth hormone (GH) is sometimes recommended for treating FM as the level of GH has been found to be low in some patients with FM (the GH-somatomedin axis is involved in descending pain modulation). An SR of just two RCTs (n=74 participants) reported considerable reduction in pain (ES=1.36; 95% CI 0.01, 1.34) but an insignificant improvement in functional deficit (ES=1.24; 95% CI −0.36, 2.84) (Perrot & Russell, 2014). The medication is not approved for FM in Europe (Macfarlane et al., 2017).

1.6 Justification of the study

FM has a substantial impact on QoL and health care systems with substantially lower generic QoL scores (Hoffman & Dukes, 2008) and five-fold higher health-care expenditure (Berger et al., 2007). Its diagnosis and management are often challenging due to heterogeneous manifestations. Non-pharmacological interventions are recommended as first-line treatment for FM in multinational recommendations such as those issued by the European League Against Rheumatism (EULAR) (Macfarlane et al., 2017).

However, to our knowledge, there are no evidence-based recommendations for which intervention(s) to offer for each of the different manifestations of FM and what should be considered the core and adjunctive treatment options for FM. This is really important as the predominant symptom in FM differs from individual to individual, and personalising treatment is consistent with good clinical practice. Additionally, evidence supporting the above recommendation has not been updated comprehensively. For example, the EULAR guidelines for the management of FM (Macfarlane et al., 2017) were based on a review of SRs examining the efficacy of individual non-pharmacological interventions that were published between 2008 and 2015. Hence, the evidence from many RCTs conducted in the previous 10 years were not taken into account and the evidence base supporting the use of non-pharmacological interventions for FM needs updating and prioritising so that best available evidence can be used to guide patient-care.

All the results in this thesis will inform the development of a complex non-pharmacological treatment package for FM according to the new Medical Research Council (MRC) guidance (Craig et al., 2008). The MRC guidance suggests there are four main stages involved in the development and evaluation of a complex intervention; development, feasibility and piloting, evaluation, and implementation (Craig et al., 2008). The development phase includes:

- Identifying the evidence base - Identify the most relevant existing evidence base (SR)
- Developing theory - Best choice of intervention ensured by exploring relevant theory
- Modelling processes and outcomes - Components of intervention identified and their inter-relationship (useful to determine the design of the intervention and evaluation)

In this PhD project, conventional meta-analysis (CMA) and network meta-analysis (NMA) were used to identify existing evidence and core and adjunctive components of the complex intervention package were established by Delphi exercise.

1.7 Aims and objectives

The overall purpose of the research project was to identify key elements of a non-pharmacological treatment package for FM. The study had the following objectives:

1. To estimate the efficacy of non-pharmacologic treatments for FM using an SR with conventional meta-analysis (CMA) approach.
2. To estimate the relative efficacy of non-pharmacologic interventions for FM using a Bayesian network meta-analysis (NMA) approach.
3. To select the most efficacious interventions for different outcomes of FM using a Delphi exercise (consensus building) approach.

Chapter 2 METHODS

2.1 Background and rationale

Initially, it was planned to develop an optimal non-pharmacological treatment package for FM. Firstly, the efficacy of non-pharmacological interventions for FM were going to be evaluated using an SR with CMA. Secondly, a Delphi exercise was going to be undertaken among health care professionals to select the most effective interventions and finally, a feasibility study was going to be conducted to assess the feasibility of this complex treatment package of care for FM. However, due to the restricted time, this PhD was not going to be able to produce a detailed protocol for a complex intervention i.e. choice of therapies, number of therapy sessions, duration, and frequency. Therefore, the PhD project was reconsidered and reconceptualised and the new project title became "Identifying key elements of non-pharmacological treatment package for fibromyalgia: Evidence synthesis and Delphi exercise". Accordingly, it was decided to develop the basis of a complex non-pharmacological intervention package for FM based on the MRC framework (Craig et al., 2008).

The first step was to identify the most relevant existing evidence base. A well formulated research question and a systematic literature search are the key steps to obtain the best available evidence (Sackett, 1997). Owing to the extensive number of published trials, there is a need to synthesise the evidence from individual RCTs to know the most often used and effective interventions. SR and meta-analysis provide a comprehensive overview of available evidence on a given topic by collating and summarising all studies

pertinent to the research question (Higgins & Green, 2011). Therefore, an SR with CMA was chosen as the first study in this PhD project.

Most RCTs compare a non-pharmacological intervention against usual care, placebo or sham treatment, and there is a paucity of head-to-head comparisons. The expense of such studies and their long duration support the use an alternative approach for existing trials such as an NMA. While CMA compares two arm studies, NMA can compare multiple arm studies (i.e three or more). It can increase the precision of the ES, and also estimate the effect for an intervention that does not have direct evidence and relative efficacy between treatments, as it pools both direct and indirect evidence within the same network. Furthermore, it provides relative efficacy among interventions (Cipriani et al., 2013). For these advantages, NMA was added in this PhD project to identify the best available evidence.

The practice of evidence based medicine requires the integration of best available evidence, clinical expertise and patient preferences (Sackett, 1997). We obtained the most relevant evidence including efficacy and relative efficacy using CMA and NMA. However, some interventions such as acupuncture or balneotherapy may not be widely available across different healthcare systems. Indeed, there may be low acceptability of some of these interventions, such as psychological treatments or acupuncture, in certain cultures. Furthermore, there might be some interventions that have never been studied. Therefore, it was decided to do a Delphi exercise based on expert opinion to identify and prioritise non-pharmacological interventions for FM.

This chapter provides an overview of the methodology of the present studies which include a CMA, NMA, and the Delphi exercise. Specific methods are described within each study chapter.

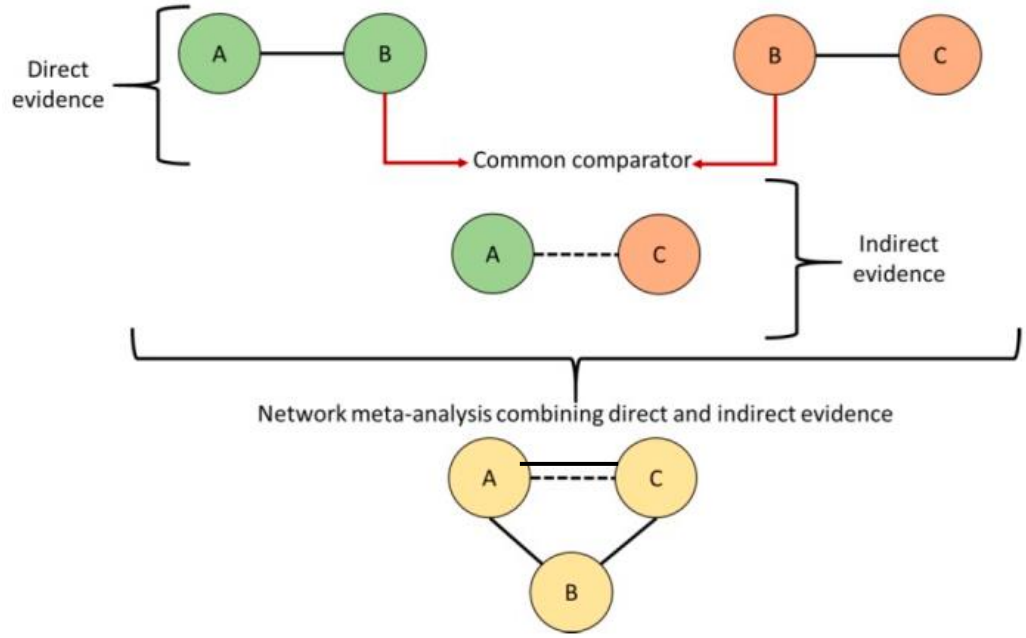
2.2 Meta-Analysis

Two meta-analytical techniques, CMA and NMA, were undertaken in the first stage of the project.

CMA combines the results from multiple studies, directly comparing an active intervention versus a control arm (e.g. exercise versus usual care, or acupuncture versus sham (placebo) acupuncture). It examines the ES of an intervention over a control arm. Furthermore, a related technique of meta-regression can identify potential determinants of efficacy.

NMA compares multiple interventions, i.e. three or more, using evidence both from direct and indirect comparisons, and combines the evidence. This analysis permits an estimation of the relative effects between two interventions through a common comparator, even if they are not compared within the same trial. It can also increase the precision of the ES as it pools both direct and indirect evidence within the same network (Cipriani et al., 2013). In indirect evidence, a common comparator is used to link different interventions. For example, existing evidence from A versus B and B versus C trials can be used to calculate the ES between A-C indirectly by using the common comparator B (Figure 2-1). Also, if there are direct comparisons between A versus C, indirect evidence will add value and increase the precision of the estimate.

Figure 2-1. Basic concept of NMA (Tonin et al., 2017)



Each circle represents an intervention (A, B and C). Solid lines show direct comparison and dashed lines are for indirect comparison. Indirect evidence for A versus C is generated using B as the common comparator.

In CMA, only the data from two arms of studies are used, whereas all arms can be used in NMA. While doing CMA, if there are more than two arms in a study, only two groups are selected and the other arms are excluded from the analysis in line with Cochrane handbook recommendations (Higgins & Green, 2011). A detailed explanation of this is given in Chapter 3. Other differences between CMA and NMA are illustrated in Table 2-1.

Table 2-1. Differences between CMA and NMA

	CMA	NMA
Types of comparison	Direct comparison only	Direct and indirect comparison
Handling of studies >2 arms	For similar comparisons, data are combined. For different comparisons, only one is selected.	All comparisons may be included as long as there is a common comparator
Model checking	By assessing study heterogeneity	Additionally, consistency checking is required between direct and indirect estimates.
Ranking	Not possible	Yes
Analysis type	Frequentist statistics	Frequentist or Bayesian statistics

2.3 Delphi exercise

The Delphi exercise is a consensus method that aims to obtain opinions or forecasts on a specific issue from a panel of independent experts. It is usually conducted through questionnaires and feedback over two or more rounds and is a rapid and cost-effective decision-making method that decreases the bias from peer pressure that may occur in an open committee vote. Anonymity supports the responses being free from bias by avoiding dominance of individual contributors (Okoli & Pawlowski, 2004). A Delphi exercise to help prioritise non-pharmacological components for the treatment of FM was conducted in the second stage of the PhD project.

The details of each of the above methods can be seen in the subsequent specific chapters.

Chapter 3 EFFICACY OF NON-PHARMACOLOGICAL INTERVENTIONS FOR FIBROMYALGIA: SYSTEMATIC REVIEW WITH CONVENTIONAL META-ANALYSIS

3.1 Introduction

This chapter evaluates the overall efficacy of all non-pharmacological interventions on five outcomes, specifically the fibromyalgia impact questionnaire (FIQ), pain, fatigue, sleep and depression, using CMA.

3.2 Methodology

3.2.1 Study selection

3.2.1.1 Types of studies

Randomised controlled trials (RCTs) (parallel or cross-over design) evaluating the efficacy of non-pharmacological interventions in people with FM were included. Quasi-randomised and non-randomised trials were excluded. Abstracts were also excluded because they provide insufficient information.

3.2.1.2 Participants

Adults (aged 16 years or over) with either physician-diagnosed FM or meeting classification diagnostic criteria, specifically those by Smythe 1986 (Smythe, 1986), Wolfe 1990 (Wolfe et al., 1990), Wolfe 2010 (Wolfe et al., 2010) and Wolfe 2016 (Wolfe et al., 2016) were included without any restriction for disease severity.

Studies including participants with other defined musculoskeletal diseases, such as RA or CFS, and studies including people younger than 16 years of age were excluded. Similarly, studies on people with CWP who did not meet classification criteria for FM, or where those criteria were not applied, were excluded.

3.2.1.3 Interventions

Studies assessing the efficacy of non-pharmacological interventions such as education, exercise, electrotherapy, balneotherapy, complementary and alternative medicine, and psychological approaches were included. However, studies that had an arm combining pharmacological and non-pharmacological interventions, or which compared a pharmacological treatment with a non-pharmacological treatment, were considered ineligible, since adding a pharmacological intervention may alter the effect size (ES). Table 3-1 illustrates the type of comparison that were eligible for the review.

Table 3-1. Types of comparisons and eligibility status

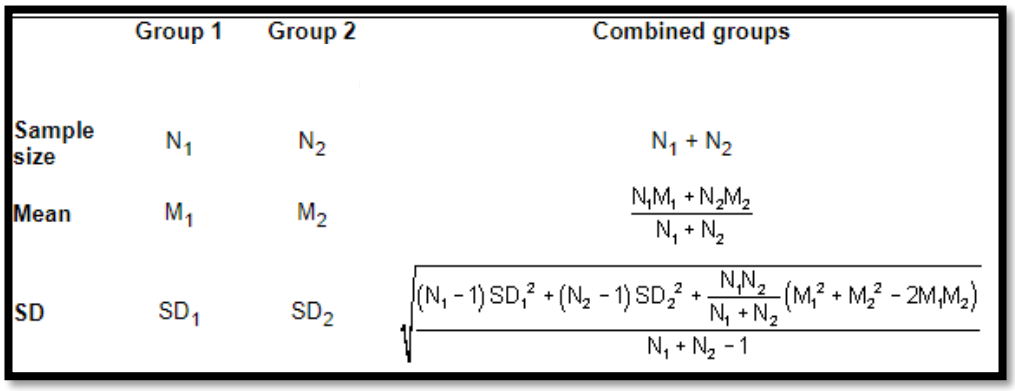
Types of comparison		Study Eligibility
Group 1	**Group 2**	
Intervention A	Non-intervention	Yes
Interventions A + B	Intervention B	Yes
Intervention A	Intervention B	No
Intervention A	Drug	No
Intervention A + Drug	Drug	No
Intervention A	Doses of intervention A*	No

*It can include a different mode, delivery methods or intensity of intervention A

If a study had more than two arms, the following steps suggested by the Cochrane handbook (Higgins & Green, 2011) were applied:

I. Intervention groups were checked to allow selection of the relevant intervention group.
II. If all intervention groups were relevant for the study, intervention types were identified.
III. If the intervention types were different from each other, the less commonly evaluated intervention among the studies included in this review was chosen.
IV. If the intervention types were similar, all intervention groups were combined into a single intervention (Figure 3-1).

Figure 3-1. Formulae for combining groups (Higgins & Green, 2011)



A modified non-pharmacological intervention classification system was prepared based on previous reviews or guidelines (Häuser et al., 2008; American College of Sports Medicine, 2013). Table 3-2 shows the classification of non-pharmacological interventions.

Table 3-2. The classification of non-pharmacological interventions

Non-pharmacological intervention types	
❖ Exercise ➢ Aerobic exercise ➢ Flexibility ➢ Mind-body ➢ Mixed* ➢ Strengthening ❖ Education ❖ Psychological interventions ➢ Cognitive behavioural therapy (CBT) ➢ Mindfulness ❖ Multidisciplinary treatment (MDT) ❖ Balneotherapy** ❖ Acupuncture ❖ Massage ❖ Manual therapy ❖ Electrotherapy ❖ Transcranial Direct Current Stimulation (tDCS) ❖ Biofeedback ❖ Nutritional supplement	❖ Homeopathy ❖ Magnetotherapy ❖ Music ❖ Weight loss ❖ Cupping Therapy ❖ Material of cloth*** ❖ Hyperbaric oxygen therapy (HOT) ❖ Topical oil ❖ Whole body vibration (WBV)

*If the exercise includes more than two components which are aerobic, strengthening, flexibility or mind-body, it was considered as mixed exercise.

**Aquatic therapy that uses a natural thermal mineral water

***Using wool shirts or t-shirt with bio-ceramic solution

3.2.1.4 Comparators

Studies comparing a non-pharmacological intervention versus a control arm including usual care, waiting list, no treatment, placebo, or sham treatment were included.

3.2.1.5 Outcomes

Although pain is the hallmark symptom of FM, the heterogeneous and complex symptomatology of FM has a significant role on HRQoL (Macfarlane et al., 2017). Therefore, to capture the overall patient-centred consequences of FM, the disease specific fibromyalgia impact questionnaire (FIQ) overall score was selected as the primary outcome, including those measured using the original FIQ (Burckhardt et al., 1991), as well as those measured using the revised questionnaire (FIQR) (Bennett et al., 2009). Secondary outcomes included pain, fatigue, sleep and depression. However, where more than one measurement scale was used for the secondary outcomes, a hierarchical selection of the measures was accepted based on OMERACT recommendations (Mease et al., 2009) and the most commonly reported outcomes. The hierarchical selection of secondary outcome measures is listed below in descending order of preference.

Secondary outcomes

1. Pain
    - Visual analogue scale (VAS) (0-10) or VAS (0-100)
    - Numeric rating scale (NRS)
    - FIQ pain subscale

- McGill pain scale
- Brief pain inventory (BPI)
- Short form (SF) 36 pain
- Multidimensional pain inventory
- Self-efficacy pain scale
- Other measurement scale

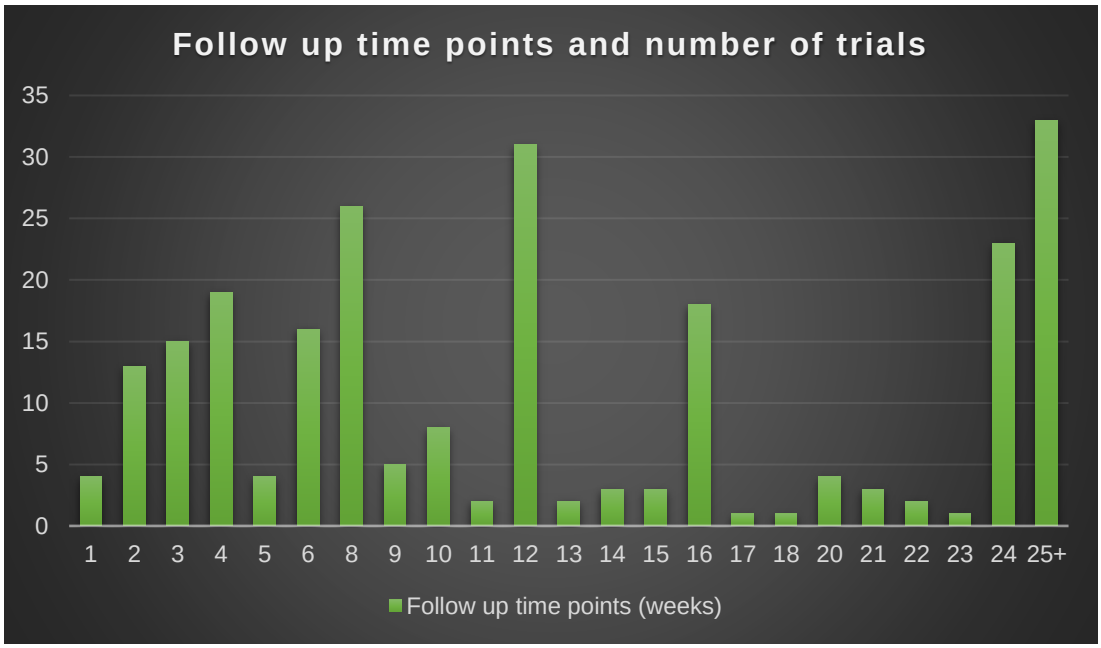
2. Fatigue
    - Multidimensional fatigue inventory
    - VAS
    - FIQ fatigue
    - Fatigue severity scale
    - Fatigue symptom inventory
    - Other measurement scale
3. Sleep
    - Pittsburgh Sleep Quality Index
    - VAS
    - FIQ sleep
    - Stanford Sleep Questionnaire
    - Other measurement scale
4. Depression
    - Beck depression inventory
    - Hamilton depression scale-Depression
    - Centre for Epidemiological Studies-Depression
    - VAS
    - FIQ depression

- Other measurement scale

3.2.1.6 Study time points

All time points at which outcomes were assessed were recorded (Figure 3-2). The most commonly reported and the median end-point which was twelve weeks, or closest to the twelve weeks, from the beginning of the study was used as the primary time point.

Figure 3-2. Follow-up time points and number of trials



3.2.2 Search strategy

A search strategy with three domains (study design, disease and intervention) was developed (Macfarlane et al., 2017; Rossy et al., 1999). Due to the absence of the search strategy of the other SRs on FM from the published literature, the treatment domain was based on treatment options included in other reviews. The key search terms were modified in accordance with the glossary of each database and combined by using Boolean operators. A search strategy designed for MEDLINE is given in Appendix 1.

For the identification of relevant studies, the following databases were systematically searched from their dates of inception until September 2017:

- Medline (OVID interface, 1946 onwards),
- Excerpta Medica Database (Embase) (OVID interface, 1974 onwards),
- Allied and Complementary Medicine Database (AMED) (OVID interface, 1985 onwards),
- PsycINFO (OVID interface, 1887 onwards),
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost interface, all years),
- Web of Science (Core Collection, 1900 onwards), and first 100 articles on Google Scholar.
- In addition, the bibliographies of previous SRs (Busch et al., 2007; Macfarlane et al., 2017; Rossy et al., 1999) were searched manually by the first author (BK) to augment the literature search.

Subsequent updated search was undertaken in September 2018.

3.2.3 Data collection

3.2.3.1 Study selection

Citations were imported to Endnote X8. After removal of duplicates, titles and abstracts were examined according to inclusion and exclusion criteria. Following this, it was decided whether the studies met inclusion criteria by full text reading. The study selection process was conducted by one reviewer (BK) and another reviewer (JK) undertook validation on a random sample (10%). Senior researchers (AA, MD, WZ, MH) were consulted to adjudicate if there was any disagreement between the two reviewers and BK was given further training if necessary.

3.2.3.2 Data extraction

A Microsoft Access database was designed and the data were extracted and entered by the first author (BK). The data extraction form included the following information:

- Trial Details
    - Study identification details (title, first author, publication year, journal)
    - Country of study
    - Language
    - Source of funding: commercial, non-commercial, no funding
    - Setting: hospital or community-based
    - Study design: parallel, cross-over
- Participant Characteristics
    - Number of participants and withdrawals

    - Diagnostic criteria
    - Demographic characteristics (mean age, mean body mass index (BMI), gender, marital status)
    - Disease duration and duration since diagnosis
- Details of the intervention
    - Types of intervention (Table 3-2. The classification of non-pharmacological interventions)
    - Comparator types
    - Delivery method of the intervention: individual or group
    - Treatment period
    - Frequency of the treatment
- Outcome characteristics
    - Types of outcome and measurement scale used
    - ITT analysis
    - Time points
    - Number of patients at baseline and follow-up periods
    - Mean change from baseline and Standard Deviation (SD) for the change or relevant statistics such as median, CI, standard error (SE)

A detailed data extraction form is shown in Appendix 2. Initially, data were extracted by BK for 25 papers and another PhD student (JK) independently performed data validation of 5 papers at random. Disagreement between reviewers (BK and JK) was resolved by senior researchers (AA, WZ) who served as adjudicators. BK proceeded to full data extraction only after >90%

agreement was reached with JK, or in case of disagreement with JK, when AA agreed with BK. Subsequently, periodic validations of 10% of the total eligible articles were done by the second reviewer (JK).

3.2.3.3 Missing data

Where the required data did not exist, authors were contacted for additional information. If this attempt was unsuccessful, the data were imputed using statistical calculations. SD was the most common missing data. Appendix 3 shows several calculation methods for SD, SD for the change and mean. Where this was not possible due to insufficient information for SD calculation, SD was substituted with the widest value from other eligible studies if the outcome scale was known. If the used outcome scale was unknown, arithmetic mean of all SDs of the same outcome were substituted (Fu et al., 2013).

3.2.4 Analysis

Microsoft Access was used to develop the database. Data were cleaned, formatted and analysed using Microsoft Access, Excel and StataSE 15.

3.2.4.1 Assessment of publication bias

Egger's test and visual inspection of funnel plot asymmetry were used to assess publication bias. Egger's test was performed where there were more than 10 studies (Higgins & Green, 2011) to detect publication bias if the p value was less than 0.05 (Egger et al., 1997).

3.2.4.2 Assessment of heterogeneity

Heterogeneity between the studies in effect measures was assessed using the I^2 statistic. This measures the inconsistency among studies and ranges from 0% to 100%. Interpretation of an I^2 value was as follows:

- 0% to 40% - might not be important;
- 30% to 60% - may represent moderate heterogeneity;
- 50% to 90% - may represent substantial heterogeneity;
- 75% to 100% - considerable heterogeneity (Higgins & Green, 2011).

3.2.4.3 Risk of bias assessment

The risk of bias was evaluated using a modified version of the Cochrane risk of bias assessment tool (Higgins et al., 2011). This consists of a checklist of seven items that assess risk of bias by evaluating the procedures of selection, detection, attrition and reporting. Compared to the narrative nature of the Cochrane tool, each question is answered as high, low or unclear risk

of bias in the modified version (Appendix 4). The seven items assessed were:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other sources of bias

This assessment was performed by one reviewer (BK), and a second reviewer (JK) validated 10% of the total eligible articles randomly. In case of disagreement, it was resolved by asking a senior third reviewer (AA).

3.2.4.4 Measures of treatment effect

Standardised mean difference or Cohen's *d* was used to measure the ES of continuous data (for FIQ, pain, fatigue, sleep, depression). Cohen's *d* is an ES statistic showing the standardised difference between two independent means in the unit of the pooled SD between the two groups. It is interpreted as small (*d* = 0.2SD), medium (*d* = 0.5SD), or large (*d* = 0.8SD) (Cohen, 1988). Mean change score from baseline was mainly used to calculate ES. Where this was not available, the end-point mean score or mean difference between intervention and control groups was used. All analyses were based on random-effects model.

3.2.4.5 Subgroup analysis

Subgroup analyses were undertaken according to patient characteristics (age, BMI), recruitment source (hospital, community-based or mixed), source of funding (non-commercial, commercial, both, or no funding) and sample size (<50).

3.2.4.6 Time dependent analysis

Time dependent analysis was conducted by selecting outcomes reported at three different time intervals (1-8 weeks, 9-15 weeks and more than 16 weeks) to measure time-dependent effects.

3.2.4.7 Meta-regression

Meta-regression was used to investigate the impact of various study characteristics on the intervention ESs. It was applied only when there were more than 10 trials (Higgins & Green, 2011).

3.2.4.8 Sensitivity analysis

The robustness of the meta-analysis results was examined by undertaking sensitivity analyses based on study risk of bias assessment, imputed data, translation studies and type of data used for the analysis.

3.3 Results

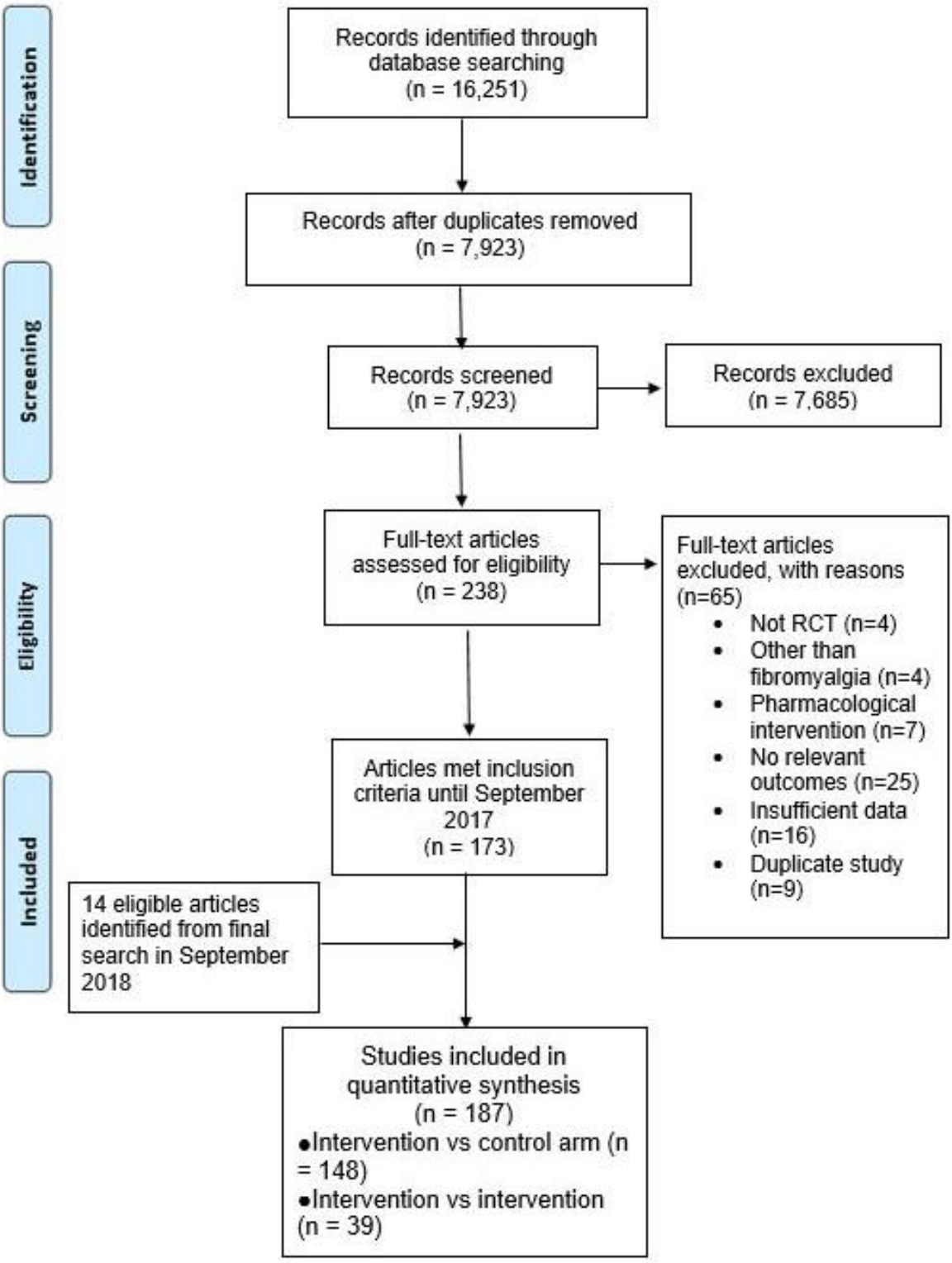
3.3.1 Study selection

A total of 16,251 records were identified from the systematic database search from the inception date of databases until September 2017. All references were exported to EndNote X7 software. Duplicates were removed and the title and abstracts of the remaining 7,923 articles were scrutinised by the first author (BK). A further 7,685 articles were excluded. The full text of 238 remaining articles were retrieved for detailed screening and data extraction. After full text screening, 65 articles that did not meet the inclusion criteria were excluded for reasons such as inclusion of conditions other than FM, pharmacological interventions, age, or duplicate publications. A total of 173 articles meeting the inclusion criteria were found.

In the update search undertaken in September 2018, a further 14 articles met the eligibility criteria. Overall, 187 articles were identified from the literature search. The characteristics of each trial are listed in Appendix 5. Figure 3-3 illustrates a detailed flow of the search results and the screening process in the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) diagram (Liberati et al., 2009).

Data extraction was undertaken by BK. Initially, the data from 25 papers were extracted and another PhD student (JK) independently performed data validation of 5 papers at random. Full data extraction was proceeded after reaching 92.6% agreement between BK and JK.

Figure 3-3. Screening flow



3.3.2 Study characteristics

Publications for 148 studies that compared an active non-pharmacological intervention to usual care, waiting list, no treatment, placebo or sham treatment were identified from the systematic literature search.

More than half (58.1%) of the studies were published after 2010 and the majority were conducted in Europe and in North and South America. 6 studies were non-English including Spanish, German, Turkish and Portuguese. The data from Turkish and Spanish studies were extracted by the first reviewer (BK) and Google Translate were used for the others.

ACR 1990 was the most commonly used FM classification criteria. ACR 2010, ACR 2016 or physician diagnosis were other used diagnostic criteria for FM. It was unclear how the diagnosis of FM was made in 4.2% of participants. Table 3-3 presents study characteristics eligible for the CMA.

Table 3-3. Summary of study characteristics for CMA

Summary of study characteristics eligible for CMA	Total (n=148)
Publication year	**No. of trials (%)**
1990-1999	9 (6.1)
2000-2009	53 (35.8)
2010-onwards	86 (58.1)
Study location	
Europe	91 (61.5)
North America	40 (27)
South America	10 (6.8)
Africa	3 (2)
Asia	3 (2)
Australia	1 (0.7)
Language	
English	142 (95.9)
Spanish	2 (1.4)
German	2 (1.4)
Turkish	1 (0.7)
Portuguese	1 (0.7)
Source of funding	
Commercial	11 (7.4)
Non-commercial	69 (46.6)
Both	1 (0.7)
No funding	6 (4.1)
Unclear	61 (41.2)
Blinding	
Participant and assessor blinded	14 (9.5)
Participant, practitioner and assessor blinded	27 (18.2)
Unblinded	102 (68.9)
Unclear	5 (3.4)
Setting	
Hospital-based	66 (44.6)
Community-based	41 (27.7)
Mixed	25 (16.9)
Unclear	16 (10.8)
Case definition for FM	
ACR 1990	86 (58.1)
ACR 2010	9 (6.1)
Physician’s diagnosis	10 (6.8)
ACR 1990 and ACR 2010	6 (4.2)
ACR 1990 and Physician’s diagnosis	28 (18.9)
ACR 1990 and ACR 2010 and Physician's diagnosis	1 (0.6)
ACR 1990 and ACR 2010 and ACR 2016	1 (0.6)
ACR 2010 and ACR 2016	1 (0.6)
Unclear	6 (4.2)
Method of delivery	
Individual	92 (62.1)
Group	46 (31.1)
Mixed	5 (3.4)
Unclear	5 (3.4)
Medium time point (IQR)	12 (6-21.5)

3.3.3 Intervention characteristics

Table 3-4 shows interventions examined in eligible studies, and participant characteristics. A total of 148 studies with 9,598 participants met the inclusion criteria. Precisely, 86.6% of the population were women and the median age of all participants was 48.8 years. The median BMI was 27.6 kg/m^2 ranging from 23.8 to 33.6. The median baseline FIQ score was 59.2.

21 non-pharmacological interventions were identified from the literature search. Additionally, different exercise types including aerobic, mind-body, mixed and strengthening, and different psychological treatments (CBT and mindfulness) and these were analysed separately.

Exercise was the most commonly investigated non-pharmacological intervention with 31 studies (n = 1,743). In exercise trials, participants were predominantly women (94.4%). Median age, BMI and baseline FIQ of the exercise group were similar to those of the overall intervention characteristics, specifically 49 years, 27.3 kg/m^2, and 58.2, respectively.

There was only one trial each for cupping therapy, hyperbaric oxygen therapy (HOT), topical oil and weight loss in FM. Other details of intervention characteristics are illustrated in Table 3-4.

Table 3-4. Interventions examined in eligible studies, and participant characteristics

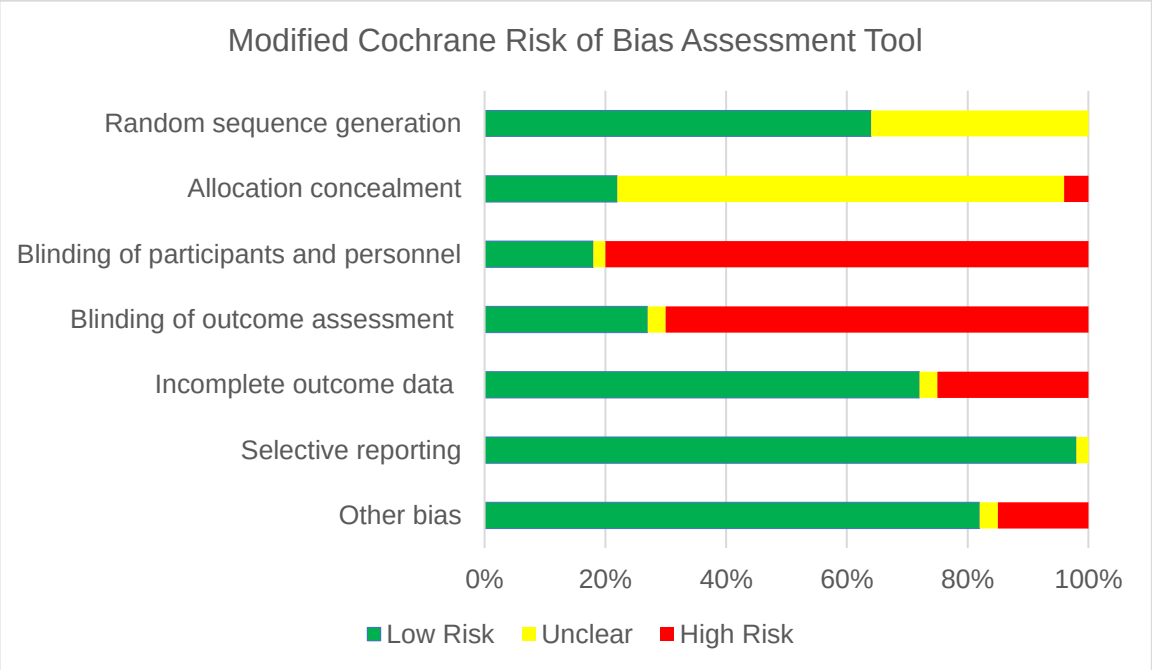
Interventions	No. of trials	No. of patients	No. of women (%)	Age, y	BMI	FIQ baseline
Exercise	31	1,743	1,646 (94.4)	49 (37-59.3)	27.3 (23.8-31.4)	58.2 (54.9-73.1)
Aerobic	8	528	516 (97.7)	46.5 (41.6-50)	28.4 (27-31.4)	64.9 (54.9-69.7)
Mind-body	9	542	523 (96.5)	48.1 (44.4-57.7)	27.2 (25.1-27.9)	53.9 (60-73.1)
Mixed	11	487	421 (86.5)	50.8 (43.5-59.3)	27.3 (23.8-29)	60.3 (48.6-72.1)
Strengthening	3	186	186 (100)	46.7 (37-51)	29 (26.7-29)	56.1 (44.3-67.3)
Education	8	901	818 (90.8)	47.2 (43-55.1)	-	56 (26.3-67.8)
Psychological Tx	23	1,975	1,639 (83)	50.8 (44.5-55.4)	27.1 (25.4-29.3)	58.6 (56.5-77.1)
CBT	6	416	409 (98.3)	49.8 (44.5-53.5)	27.1 (25.4-29.3)	64.3 (55.6-69.6)
Mindfulness	5	375	284 (75.7)	52.3 (47.6-53.4)	-	63.6 (56.5-77.1)
Multidisciplinary Tx	10	1,023	817 (79.9)	45.8 (37.4-55.4)	26.8 (24.4-28.4)	59.9 (55-72.5)
Balneotherapy	13	685	667 (97.9)	44.1 (33.4-57)	27.4 (24.8-29.2)	54.3 (17-77.1)
Acupuncture	7	443	408 (92.1)	49.1 (43.6-56.26)	27.6 (27.1-28.2)	62.3 (42.4-73.3)
Massage	2	115	-	41.2 (39.9-42.5)	26.4 (26-26.7)	61.1 (35.7-64.9)
Manual therapy	6	355	214 (60.3)	53 (47-55.5)	29 (27.5-33.1)	66.7 (57.9-71.3)
Electrotherapy	8	362	307 (84.8)	44.5 (36.4-54)	29.6 (28.8-33.6)	59.9 (41.3-67.5)
tDCS	11	469	401 (85.5)	(31.3-55.3)	(28.9-31.2)	61.4 (49.2-67.2)
Biofeedback	2	115	107 (93)	43 (35.3-44.4)	-	-
Cupping Therapy	1	95	93 (97.9)	55.3 (54.4-56.3)	28.3 (27.2-29.4)	58.8 (55.7-61.8)
Homeopathy	2	109	102 (93.6)	47.6 (43.9-49.1)	-	65.1 (64.7-65.4)
HOT	1	50	35 (70)	40.2 (39.9-40.5)	-	-
Magnetotherapy	4	255	188 (73.7)	45.6 (40.9-51.2)	25.5 (25.5-25.6)	52.4 (66-76)
Material of cloth	2	89	89 (100)	44.5 (37.4-51.5)	26.9 (26.1-27.6)	76.1 (66.6-78.8)
Music	6	297	231 (77.8)	49.6 (42.9-52.3)	-	72.5 (67.9-76.9)
Nutrition	7	309	305 (98.7)	48 (41-55)	27.4 (26.1-30.2)	61.6 (47.8-68.6)
Topical oil	1	51	51 (100)	53.4 (51.5-55.2)	-	-
WBV	2	71	71 (100)	55.4 (52.4-60.1)	(27.9-28)	56 (48.9-56.9)
Weight loss	1	86	75 (87.2)	45.6 (44.8-46.3)	32.6 (32.3-32.8)	53.9 (53.2-54.6)
Total	148	9,598	8,316 (86.6)	48.4 (31.3-60.1)	27.6 (23.8-33.6)	59.2 (17-78.8)

HOT: Hyperbaric oxygen therapy, Tx: treatment, CBT: Cognitive behavioural therapy, tDCS: Transcranial Direct Current Stimulation WBV: Whole body vibration. All values are median and range unless stated.

3.3.4 Risk of bias assessment

Table 3-5 shows the results of risk of bias assessment. Because of exclusion of non-randomised studies, there were no high risk of bias results on random sequence generation. Overall, 64% showed low risk, whereas 36% had unclear risk of bias. It was unclear if the allocation was adequately concealed in the majority (74%) of studies. There was high risk of bias with respect to blinding of participant and personnel (80%) and outcome assessment (70%). On the other hand, a low risk of bias was found for incomplete outcome data (72%), selective reporting (98%) and other bias such as group similarities at baseline (82%).

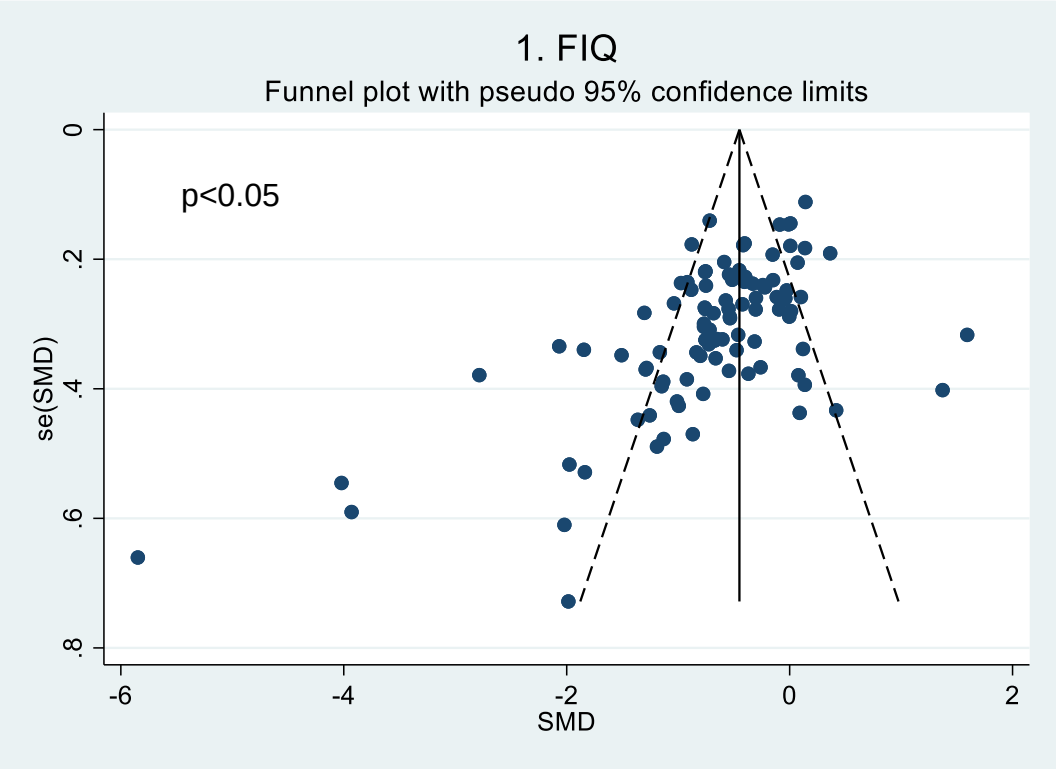
Table 3-5. Risk of bias assessment in CMA

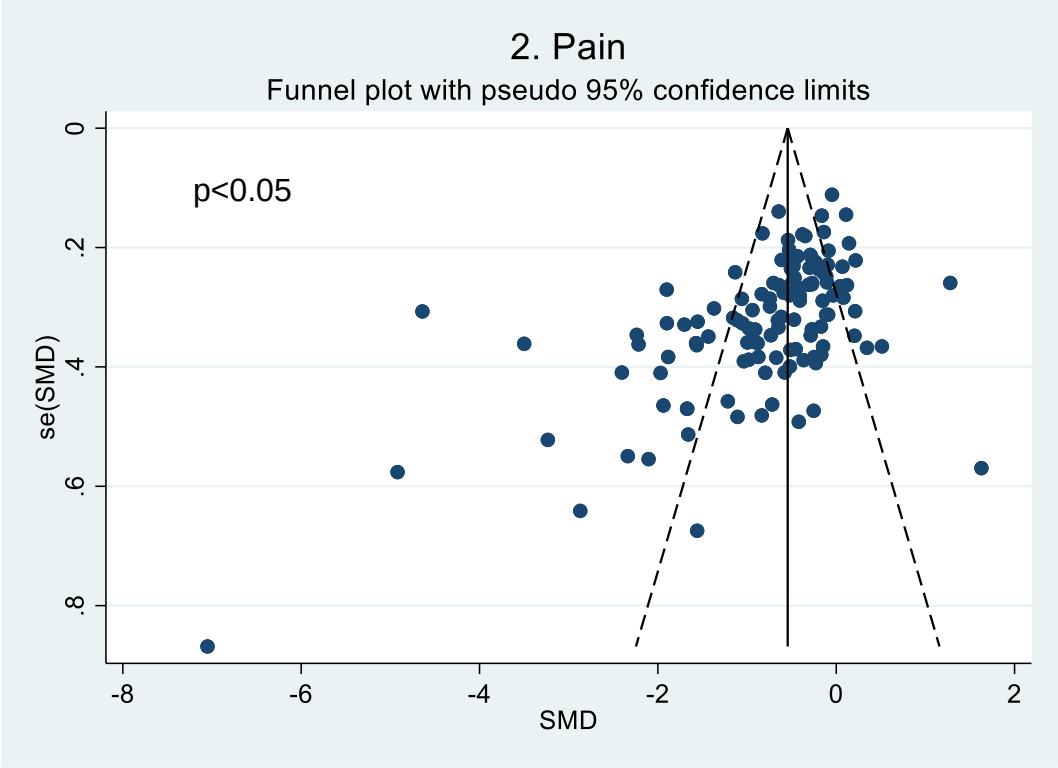


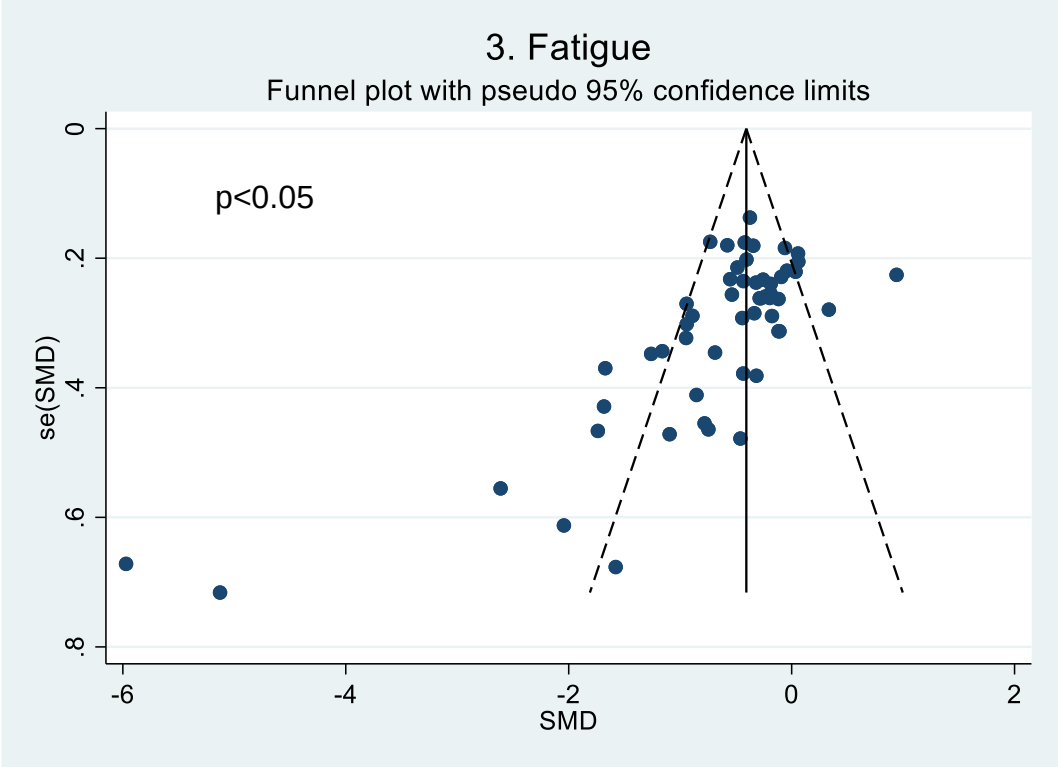
3.3.5 Publication bias and small study effects

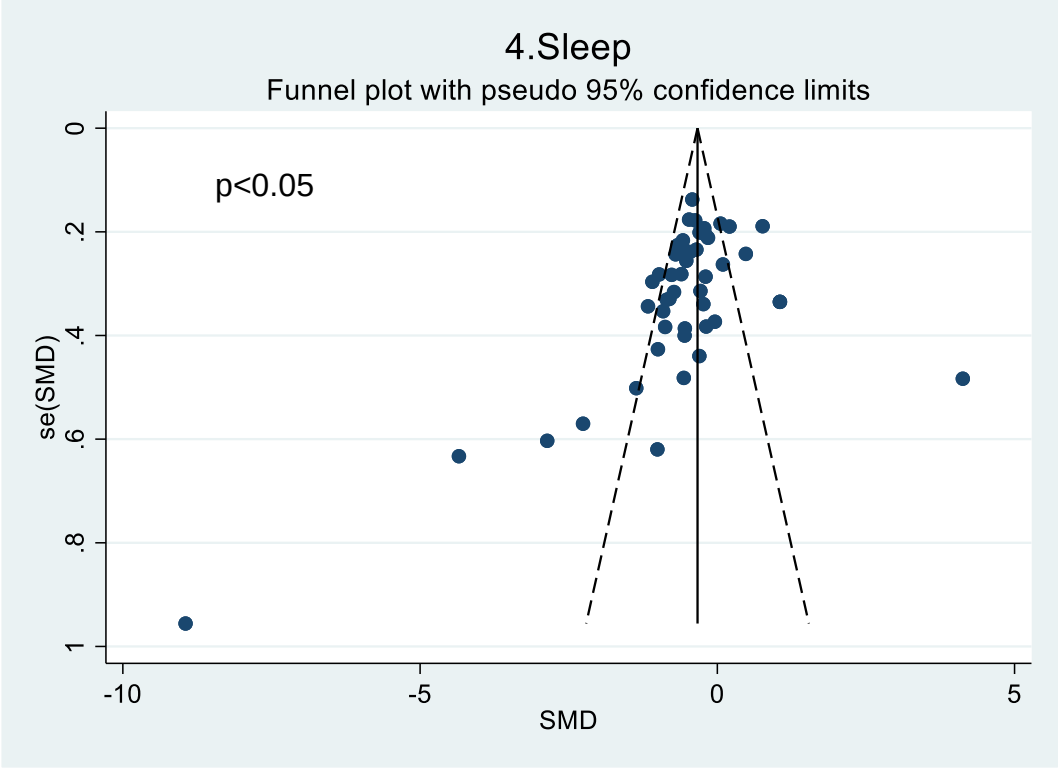
Funnel plots for FIQ, pain, fatigue, sleep and depression outcomes are presented in Figure 3-4. Overall, an asymmetry was apparent on visual inspection for all outcomes, suggesting that there was publication bias. These were confirmed by Egger's test in which the results were significant ($p<0.05$).

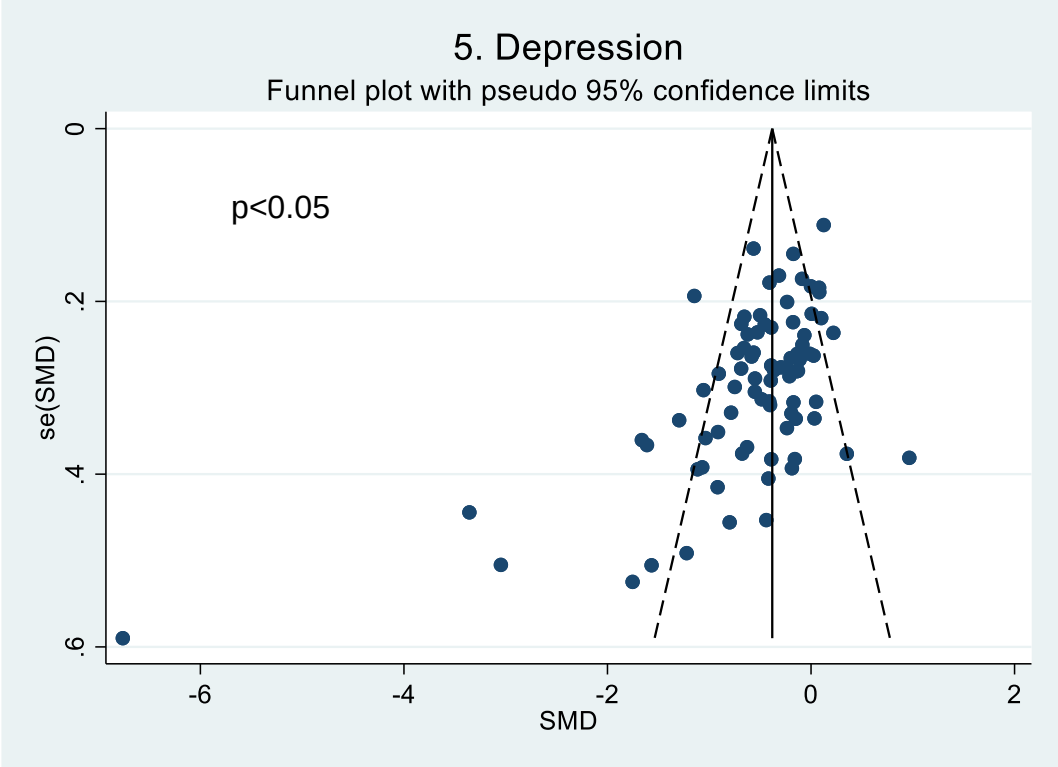
Figure 3-4. Funnel plots for non-pharmacological intervention versus control arm, showing results for FIQ, pain, fatigue, sleep and depression




2. Pain
Funnel plot with pseudo 95% confidence limits
p<0.05
se(SMD)
0
.2
.4
.6
.8
-8
-6
-4
-2
0
2
SMD


3. Fatigue
Funnel plot with pseudo 95% confidence limits
p<0.05
se(SMD)
0
.2
.4
.6
.8
-6
-4
-2
0
2
SMD


4.Sleep
Funnel plot with pseudo 95% confidence limits
p<0.05
se(SMD)
0
.2
.4
.6
.8
1
-10
-5
0
5
SMD


5. Depression
Funnel plot with pseudo 95% confidence limits
p<0.05
se(SMD)
0
.2
.4
.6
-6
-4
-2
0
2
SMD

3.3.6 Treatment effects

3.3.6.1 Exercise

Of 31 trials (1,743 participants) for exercise, 24 (n = 1,327) evaluated FIQ. The ES of exercise on FIQ was moderate (SMD -0.67; 95% CI -0.89, -0.45). Exercise interventions resulted in moderate improvements in sleep (-0.55; 95% CI -1.04, -0.06) and depression (-0.55; 95% CI -0.82, -0.28), and showed large effect sizes for pain (-0.84; 95% -1.13, -0.55) and fatigue (-0.88; 95% CI -1.39, -0.37). Table 3-6 shows the effect size of exercise relative to usual care for FIQ, pain, fatigue, sleep and depression.

Substantial heterogeneity (from 50% to 90%) was present for all outcomes. There was evidence of publication bias for FIQ, pain and fatigue outcomes ($p<0.05$) (Table 3-6).

Table 3-6. Effect size of exercise versus usual care for different outcomes

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	24	1,327	**-0.67 (-0.89, -0.45)**	0.000	71.4
Pain	24	1,225	**-0.84 (-1.13, -0.55)**	0.001	83.0
Fatigue	10	609	**-0.88 (-1.39, -0.37)**	0.006	86.9
Sleep	13	621	**-0.55 (-1.04, -0.06)**	0.292	86.8
Depression	16	865	**-0.55 (-0.82, -0.28)**	0.267	72.7

Text in bold shows significant values. Negative SMD favours the treatment group.

Different exercise types (aerobic, mind-body, mixed and strengthening) were evaluated (Table 3-7). Mixed exercise was the most commonly evaluated exercise type (11 trials, n = 487 participants). Mind-body, aerobic and strengthening exercises were examined in nine studies (n = 542 participants), eight studies (n = 528 participants) and three studies (n = 186 participants), respectively (Table 3-4).

Aerobic (-0.89; 95 CI -1.50, -0.27), mind-body (-0.52; 95 CI -0.88, -0.17) and mixed exercises (-0.70; 95% CI -0.95, -0.45) showed a significant improvement in FIQ. However, strengthening exercise (-0.67; 95% CI -1.39, 0.05) did not significantly improve FIQ. All exercise types were effective at relieving pain, namely aerobic (-0.72; 95% CI -1.37, -0.07); mind-body (-0.86; 95% CI -1.32, -0.40); mixed (-0.96; 95% CI -1.49, -0.44) and strengthening (-0.88; 95% CI -1.67, -0.09)). Mind-body (-0.99; 95% CI -1.64, -0.34) and strengthening exercises (-0.59; 95% CI -1.03, -0.16) were effective at improving fatigue, while aerobic (-1.33; 95% CI -2.55, -0.11) and strengthening exercises (-0.47; 95% CI -0.90, -0.03) were effective at improving sleep. All except for aerobic exercise improved depression (-0.73; 95% CI -1.48, 0.02) (Table 3-7).

As there were fewer than 10 studies, statistical testing for publication bias was not assessed for exercise types.

There was considerable heterogeneity in studies assessing aerobic exercise and substantial or unimportant heterogeneity in other exercise types (Table 3-7).

Table 3-7. Effect sizes of– exercise types versus usual care for FIQ, pain, fatigue, sleep and depression

	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ					
Aerobic	6	445	**-0.89 (-1.50, -0.27)**	-	87.8
Mind-body	9	446	**-0.52 (-0.88, -0.17)**	-	67.2
Mixed	7	311	**-0.70 (-0.95, -0.45)**	-	15.1
Strengthening	2	125	-0.67 (-1.39, 0.05)	-	74.3
Pain					
Aerobic	8	512	**-0.72 (-1.37, -0.07)**	-	90.6
Mind-body	7	367	**-0.86 (-1.32, -0.40)**	-	74.6
Mixed	6	200	**-0.96 (-1.49, -0.44)**	-	66.9
Strengthening	3	146	**-0.88 (-1.67, -0.09)**	-	77.9
Fatigue					
Aerobic	3	262	-1.46 (-3.05, 0.14)	-	96.0
Mind-body	4	220	**-0.99 (-1.64, -0.34)**	-	73.3
Mixed	1	41	-0.12 (-0.73, 0.50)	-	-
Strengthening	2	86	**-0.59 (-1.03, -0.16)**	-	0.0
Sleep					
Aerobic	4	259	**-1.33 (-2.55, -0.11)**	-	93.0
Mind-body	5	177	-0.03 (-0.94, 0.88)	-	87.5
Mixed	2	99	-0.64 (-1.33, 0.04)	-	63.1
Strengthening	2	86	**-0.47 (-0.90, -0.03)**	-	0.0
Depression					
Aerobic	5	277	-0.73 (-1.48, 0.02)	-	88.0
Mind-body	5	329	**-0.55 (-1.04, -0.06)**	-	77.6
Mixed	4	173	**-0.35 (-0.65, -0.04)**	-	0.0
Strengthening	2	86	**-0.74 (-1.18, -0.30)**	-	0.0

Text in bold shows significant values. Negative SMD favours treatment group.

3.3.6.2 Education

Eight studies (n = 901) assessed education that was delivered face-to-face or by a leaflet (Table 3-4). Three trials (n = 251) showed a statistical improvement for fatigue (-0.31; 95% CI -0.55, -0.06). However, education was no better than usual care for FIQ, pain, sleep and depression outcomes (Table 3-8).

Studies assessing FIQ, pain, sleep and depression showed moderate heterogeneity (30-60%) (Table 3-8).

Table 3-8. Effect size of – education versus usual care for FIQ, pain, fatigue, sleep and depression

Outcome types	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	7	713	-0.15 (-0.38, 0.08)	-	47.9
Pain	8	754	-0.18 (-0.41, 0.05)	-	49.8
Fatigue	3	251	**-0.31 (-0.55, -0.06)**	-	0.0
Sleep	3	226	-0.25 (-0.61, 0.11)	-	38.8
Depression	4	573	-0.08 (-0.35, 0.20)	-	53.1

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.3 Psychological Treatments

23 trials with 1,975 participants evaluated psychological treatments including CBT and mindfulness (Table 3-4). Psychological treatments were more efficacious than usual care for FIQ (-0.33; 95% CI -0.65, -0.02), pain (-0.44; 95% CI -0.59, -0.28) and depression (-0.35; 95% CI -0.52, -0.17). However, they showed no improvement for fatigue (-0.20; 95% CI -0.53, 0.12) and sleep (-0.42; 95% CI -0.86, 0.02) (Table 3-9).

Substantial heterogeneity for FIQ, fatigue and sleep outcomes and moderate heterogeneity for pain and sleep outcomes were observed. Egger's test did not detect publication bias in any outcome (Table 3-9).

There were six studies (n = 416) assessing CBT and five studies (n = 375) on mindfulness (Table 3-4). While CBT significantly improved FIQ (-0.35; 95% CI -0.68, -0.01) and pain (-0.54; 95% CI -1.02, -0.06), mindfulness was superior relative to usual care for fatigue (-0.49; 95% CI -0.91, -0.07). There were no significant differences in depression and sleep outcomes for both interventions (Table 3-9).

Table 3-9. Effect size of psychological treatments versus usual care for FIQ, pain, fatigue, sleep and depression

Intervention types	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ					
Psychological	14	1215	**-0.33 (-0.65, -0.02)**	0.805	85.3
CBT	3	182	**-0.35 (-0.68, -0.01)**	-	20.0
Mindfulness	4	270	-0.66 (-1.48, 0.15)	-	89.3
Pain					
Psychological	17	1290	**-0.44 (-0.59, -0.28)**	0.852	43.5
CBT	5	318	**-0.54 (-1.02, -0.06)**	-	73.4
Mindfulness	1	91	-0.29 (-0.71, 0.13)	-	-
Fatigue					
Psychological	8	870	-0.20 (-0.53, 0.12)	-	81.9
CBT	2	209	0.43 (-0.55, 1.41)	-	91.5
Mindfulness	1	91	**-0.49 (-0.91, -0.07)**	-	-
Sleep					
Psychological	6	633	-0.42 (-0.86, 0.02)	-	84.6
CBT	2	142	-1.35 (-4.20, 1.51)	-	95.3
Mindfulness	2	203	0.04 (-0.32, 0.39)	-	38.5
Depression					
Psychological T.	16	1198	**-0.35 (-0.52, -0.17)**	0.434	52.2
CBT	5	334	-0.14 (-0.40, 0.13)	-	29.9
Mindfulness	4	269	-0.46 (-0.94, 0.02)	-	69.7

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.4 Multidisciplinary treatment

10 trials with 1,023 participants on MDT showed significant improvements in four outcomes, specifically FIQ (-0.41; 95% CI -0.79, -0.03), pain (-1.33; 95%

CI -2.16, -0.49), sleep (-1.15; 95% CI -2.11, -0.18) and depression (-1.26; 95% CI -2.06, -0.45), but not fatigue (-0.58; 95% CI -1.22, 0.06) (Table 3-10).

Publication bias was assessed only for pain (10 studies, n = 978) and found a statistically significant result (p = 0.043) confirming publication bias for this outcome. Considerable heterogeneity was identified for all five outcomes (Table 3-10).

Table 3-10. Effect size of MDT versus usual care for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	6	620	**-0.41 (-0.79, -0.03)**	-	78.1
Pain	10	978	**-1.33 (-2.16, -0.49)**	0.043	96.7
Fatigue	4	242	-0.58 (-1.22, 0.06)	-	79.1
Sleep	3	190	**-1.15 (-2.11, -0.18)**	-	84.2
Depression	7	678	**-1.26 (-2.06, -0.45)**	-	95.2

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.5 Balneotherapy

13 trials with 685 participants were reviewed. These showed that balneotherapy was effective for FIQ (-1.13; 95% CI -1.64, -0.61), pain (-1.29; 95% CI -2.00, -0.58), fatigue (-0.43; 95% CI -0.81, -0.05) and depression (-0.68; 95% CI -1.23, -0.13). Evidence from three studies (n = 171) did not show any significant improvement for sleep (-0.00; 95% CI -0.62, 0.61) (Table 3-11).

Egger's test indicated that smaller studies were associated with larger effects for FIQ (11 studies, 571 participants) and pain (12 studies, 595 participants). I^2 test identified considerable heterogeneity for FIQ, pain and depression (Table 3-11).

Table 3-11. Effect Size of balneotherapy versus usual care for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	11	571	**-1.13 (-1.64, -0.61)**	0.05	87.4
Pain	12	595	**-1.29 (-2.00, -0.58)**	0.005	93.2
Fatigue	4	208	**-0.43 (-0.81, -0.05)**	-	44.3
Sleep	3	171	-0.00 (-0.62, 0.61)	-	73.7
Depression	8	367	**-0.68 (-1.23, -0.13)**	-	84.0

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.6 Acupuncture

Seven acupuncture trials (n = 443) were analysed based on their comparison groups. Five of these (n = 265) were compared to sham acupuncture and the remaining two (n = 178) were versus usual care.

While acupuncture was more effective than usual care (-0.59; 95% CI -0.99, -0.19), there was no significant effect relative to sham acupuncture (-1.18; 95% CI -2.46, 0.11) on FIQ. Acupuncture showed pain reduction compared to sham acupuncture (-1.08; 95% CI -1.79, -0.36) and usual care (-0.64; 95% CI -0.96, -0.31) as well as an improvement in fatigue (vs sham acupuncture (-0.50; 95% CI -0.90, -0.10) and vs usual care (-0.41; 95% CI -0.80, -0.01)). There were no significant differences for sleep and depression (3-12).

Considerable heterogeneity of placebo-controlled trials was observed in FIQ, pain and sleep (Table 3-12).

Table 3-12. Effect Size of acupuncture versus usual care or placebo for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	2	99	-1.18 (-2.46, 0.11)•	-	88.3
	1	100	**-0.59 (-0.99, -0.19)**	-	0.0
Pain	5	249	**-1.08 (-1.79, 0.36)•**	-	85.5
	2	158	**-0.64 (-0.96, -0.31)**	-	0.0
Fatigue	3	158	**-0.50 (-0.90, -0.10)•**	-	36.3
	1	100	**-0.41 (-0.80, -0.01)**	-	-
Sleep	2	104	1.95 (-2.29, 6.19) •	-	98.3
	1	100	-0.30 (-0.69, 0.10)	-	-
Depression	2	99	-0.63 (-1.46, 0.20) •	-	75.6
	1	100	-0.23 (-0.63, 0.16)	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

•: shows data from sham-controlled trials

3.3.6.7 Massage

The analysis of two studies comprising 83 participants showed improvements from massage on FIQ (-1.08; 95% CI -1.90, -0.26), pain (-0.76; 95% CI -1.32, -0.19), fatigue (-1.09; 95% CI -1.56, -0.63) and sleep (-0.79; 95% CI -1.23, -0.34). However, no significant improvements were seen on depression (Table 3-13).

Table 3-13. Effect Size of massage versus usual care for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	2	83	**-1.08 (-1.90, -0.26)**	-	67.5
Pain	2	83	**-0.76 (-1.32, -0.19)**	-	37.1
Fatigue	2	83	**-1.09 (-1.56, -0.63)**	-	0.0
Sleep	2	83	**-0.79 (-1.23, -0.34)**	-	0.0
Depression	2	83	-0.73 (-1.83, 0.37)	-	83.0

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.8 Manual therapy

Four (n = 205) out of six (n = 355) manual therapy studies in FM reported pain and the evidence from these trials showed significant pain relief (-0.86; 95% CI -1.32, -0.41). Manual therapy, however, was no better than usual care for FIQ, fatigue, sleep and depression (Table 3-14).

There was substantial heterogeneity in FIQ, pain and depression and considerable heterogeneity on sleep (Table 3-14).

Table 3-14. Effect Size of manual therapy versus usual care for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	4	279	-0.31 (-0.84, 0.22)	-	75.0
Pain	4	205	**-0.86 (-1.32, -0.41)**	-	53.1
Fatigue	1	48	-0.44 (-1.02, 0.13)	-	-
Sleep	2	209	0.10 (-1.22, 1.41)	-	95.4
Depression	2	209	-0.32 (-0.96, 0.32)	-	81.2

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.9 Electrotherapy

Eight studies including 362 participants investigated the effect of electrotherapy modalities including laser, TENS etc.

The synthesis of sham-controlled trials demonstrated significant improvements in FIQ (-0.88; 95% CI -1.54, -0.23), fatigue (-1.04; 95% CI -2.07, -0.01), sleep (-0.97; 95% CI -1.51, -0.43) and depression (-0.88; 95% CI -1.46, -0.29) but no improvement in pain (-0.22; 95% CI -0.86, 0.42). Electrotherapy was not superior compared to usual care for FIQ (-0.97; 95% CI -3.10, 1.15) and pain (-0.73; 95% CI -1.97, 0.51) (Table 3-15).

Heterogeneity between the studies was found to be substantial for sham-controlled trials and considerable for usual care controlled trials. No heterogeneity was detected for sleep and depression (Table 3-15).

Table 3-15. Effect Size of electrotherapy versus usual care or placebo for FIQ, pain, fatigue and sleep

and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	4	105	**-0.88 (-1.54, -0.23)•**	-	58.5
	2	120	-0.97 (-3.10, 1.15)	-	96.2
Pain	6	227	-0.22 (-0.86, 0.42)•	-	79.7
	2	120	-0.73 (-1.97, 0.51)	-	90.2
Fatigue	4	159	**-1.04 (-2.07, -0.01)•**	-	86.6
Sleep	2	60	**-0.97 (-1.51, -0.43)•**	-	0.0
	1	60	**-0.77 (-1.32, -0.21)**	-	-
Depression	2	50	**-0.88 (-1.46, -0.29)•**	-	0.0

Text in bold shows significant values. Negative SMD favours the treatment group.

•: shows data from sham-controlled trials

3.3.6.10 Transcranial direct current stimulation

The effect of tDCS in FM was studied in 11 studies with 469 participants. It was compared with sham tDCS or usual care. While it was significantly more effective than sham tDCS for all outcomes, there was no evidence for an effect of tDCS compared to usual care on pain (-0.45; 95% CI -1.18, 0.27) (Table 3-16).

Depression was the only outcome for which publication bias was assessed as there were 10 trials (n = 408). Egger's test was statistically insignificant (p = 0.256) for publication bias on this outcome (Table 3-16).

Studies assessing FIQ and sleep were homogeneous. There was, however, substantial heterogeneity in pain, fatigue and sleep (Table 3-16).

Table 3-16. Effect Size of transcranial direct current stimulation versus usual care or placebo for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	7	262	**-0.74 (-0.99, -0.48)•**	-	0.0
Pain	9	368	**-0.84 (-1.21, -0.47)•**	-	63.5
	1	30	-0.45 (-1.18, 0.27)	-	-
Fatigue	4	188	**-0.73 (-1.28, -0.19)•**	-	65.7
Sleep	2	103	**-0.57 (-0.96, -0.17)•**	-	0.0
Depression	10	408	**-0.32 (-0.52, 0.13)•**	0.256	75.6
	1	30	**-1.07 (-1.84, -0.30)**	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

•: shows data from sham-controlled trials

3.3.6.11 Biofeedback

There were two studies (n = 115) assessing the effect of biofeedback. One trial with 30 participants showed significant improvement in FIQ (-0.92; 95% CI -1.68, -0.17). However, biofeedback was no better than usual care for pain (-0.42; 95% CI -1.18, 0.33) and fatigue (-0.09; 95% CI -0.54, 0.36) (Table 3-17).

I^2 statistics demonstrated substantial heterogeneity for pain (67%) (Table 3-17).

Table 3-17. Effect Size of biofeedback versus usual care for FIQ, pain and fatigue

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	1	30	**-0.92 (-1.68, -0.17)**	-	-
Pain	2	115	-0.42 (-1.18, 0.33)	-	67.0
Fatigue	1	85	-0.09 (-0.54, 0.36)	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.12 Nutritional supplement

Any type of nutritional supplement including creatine or probiotic was examined by seven studies comprising 309 participants. Three studies (n = 120) concluded significant benefits in terms of fatigue (-0.41; 95% CI -0.77, -0.05) and sleep (-0.43; 95 % CI -0.79, -0.06). No improvements were seen in FIQ (-0.31; 95% CI -1.13, 0.50), pain (-0.29; 95% CI -0.69, 0.11) and depression (-0.04; 95% CI -0.99, 0.90) (Table 3-18).

Studies examining fatigue and sleep were homogeneous. There was, however, moderate heterogeneity for pain and substantial heterogeneity for FIQ and depression (Table 3-18).

Table 3-18. Effect Size of nutritional supplement versus placebo for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	5	230	-0.31 (-1.13, 0.50)	-	87.6
Pain	6	204	-0.29 (-0.69, 0.11)	-	46.6
Fatigue	3	120	**-0.41 (-0.77, -0.05)**	-	0.0
Sleep	3	120	**-0.43 (-0.79, -0.06)**	-	0.0
Depression	3	133	-0.04 (-0.99, 0.90)	-	84.3

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.13 Homeopathy

Two trials with 109 participants assessed homeopathy. It was effective in improving FIQ (-0.80; 95% CI -1.49, -0.12), pain (-0.73; 95% CI -1.41, -0.05), fatigue (-0.69; 95% CI -1.36, -0.01) and sleep (-0.91; 95% CI -1.60, -0.22) relative to usual care. While it was more effective than placebo for depression (-0.56; 95% CI -1.07, -0.06), no significant effects were found for fatigue (-0.19; 95% CI -0.69, 0.31) (Table 3-19).

Heterogeneity and publication bias could not be assessed due to too few trials.

Table 3-19. Effect Size of homeopathy versus usual care or placebo for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	1	36	**-0.80 (-1.49, -0.12)**	-	-
Pain	1	36	**-0.73 (-1.41, -0.05)**	-	-
Fatigue	1	62	-0.19 (-0.69, 0.31)•	-	-
	1	36	**-0.69 (-1.36, -0.01)**	-	-
Sleep	1	36	**-0.91 (-1.60, -0.22)**	-	-
Depression	1	62	**-0.56 (-1.07, -0.06)•**	-	-
	1	36	-0.15 (-0.81, 0.51)	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.14 Magnetotherapy

Four studies with 255 participants were reviewed and significant improvements were seen for FIQ (-0.69; 95% CI -1.28, -0.10), pain (-0.89; 95% CI -1.74, -0.04), fatigue (-2.61; 95% CI -3.70, -1.52) and sleep (-1.00; 95% CI -1.83, -0.16) (Table 3-20). Substantial heterogeneity was present for FIQ and pain outcomes (Table 3-20).

Table 3-20. Effect Size of magnetotherapy versus sham treatment for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	3	163	**-0.69 (-1.28, -0.10)•**	-	64.5
Pain	2	99	**-0.89 (-1.74, -0.04)•**	-	82.1
Fatigue	1	25	**-2.61 (-3.70, -1.52)•**	-	-
Sleep	1	25	**-1.00 (-1.83, -0.16)•**	-	-
Depression	1	56	-0.11 (-0.64, 0.41)•	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

●: shows data from sham-controlled trials

3.3.6.15 Music

Six studies (n = 297) examined the effect of music in FM treatment. Two studies (n = 111) found a significant improvement for depression (-0.54; 95% CI -0.92, -0.15) but there were no significant benefits for other outcomes (Table 3-21).

Studies assessing FIQ and depression were homogeneous, whereas there was substantial heterogeneity for pain (Table 3-21).

Table 3-21. Effect Size of music versus usual care for FIQ, pain, fatigue and depression

Outcomes	No. of comparison	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	2	116	-0.32 (-0.74, 0.10)	-	23.2
Pain	5	215	-0.58 (-1.24, 0.07)	-	77
Fatigue	1	41	-0.11 (-0.72, 0.50)	-	-
Depression	2	111	**-0.54 (-0.92, -0.15)**	-	0.0

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.16 Weight loss

One study with 83 participants investigated the effect of weight loss in FM and found significant improvements on FIQ (-0.54; 95% CI -0.98, -0.11), sleep (-0.66; 95% CI -1.11, -0.22) and depression outcomes (-0.68; 95% CI -1.13, -0.24) (Table 3-22).

Table 3-22. Effect Size of weight loss versus usual care for FIQ, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	1	83	**-0.54 (-0.98, -0.11)**	-	-
Sleep	1	83	**-0.66 (-1.11, -0.22)**	-	-
Depression	1	83	**-0.68 (-1.13, -0.24)**	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.17 Cupping therapy

One study (n = 95) examined the effect of cupping therapy over sham cupping in FM. It showed no significant improvements in any outcome (Table 3-23).

Table 3-23. Effect Size of cupping therapy versus sham cupping for FIQ, pain, fatigue and sleep

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	1	95	0.07 (-0.33, 0.47)	-	-
Pain	1	95	-0.09 (-0.49, 0.32)	-	-
Fatigue	1	95	0.06 (-0.34, 0.46)	-	-
Sleep	1	95	-0.20 (-0.60, 0.21)	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.18 Material of cloth

There were two trials comprising 89 patients for material of cloth as a treatment. Fatigue (-5.97; 95% CI -7.29, -4.65), sleep (-8.94; 95% CI -10.8, -7.07) and depression (-3.36; 95% CI -4.23, -2.49) showed significant improvements relative to baseline. The improvements in FIQ (-3.25; 95% CI -8.27, 1.77) and pain (-2.89; 95% CI -6.82, 1.04) were not statistically significant (Table 3-24).

Considerable heterogeneity was detected in FIQ and pain (Table 3-24).

Table 3-24. Effect Size of material of cloth versus sham treatment for FIQ, pain, fatigue, sleep and depression

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	2	89	-3.25 (-8.27, 1.77)	-	97.9
Pain	2	89	-2.89 (-6.82, 1.04)	-	97.2
Fatigue	1	50	**-5.97 (-7.29, -4.65)**	-	-
Sleep	1	50	**-8.94 (-10.8, -7.07)**	-	-
Depression	1	50	**-3.36 (-4.23, -2.49)**	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.19 Hyperbaric oxygen treatment

One study (n = 50) found that HOT significantly reduced pain (-2.22; 95% CI -2.93, -1.51) relative to normal air (Table 3-25).

Table 3-25. Effect Size of hyperbaric oxygen therapy versus sham treatment for pain

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
Pain	1	50	**-2.22 (-2.93, -1.51)**	-	-

Text in bold shows significant values. Negative SMD favours treatment group.

3.3.6.20 Topical oil

One study involving 43 participants evaluated topical oil applied to shoulders/neck and to hips/lower back pain before exercise and before going to bed. It showed no effect on pain (0.21; 95% CI -0.39, 0.81) (Table 3-26).

Table 3-26. Effect Size of topical oil versus sham oil for pain

Outcomes	No. of comparison	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
Pain	1	43	0.21 (-0.39, 0.81)	-	-

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.6.21 Whole body vibration

Two studies (n = 67) were reviewed and these showed no significant improvement on FIQ (-0.21; 95% CI -0.79, 0.37) (Table 3-27).

Table 3-27. Effect Size of whole body vibration versus usual care for FIQ

Outcomes	No. of comparisons	No. of patients	Effect Size (95% CI)	Egger's test	I^2 (%)
FIQ	2	67	-0.21 (-0.79, 0.37)	-	28.5

Text in bold shows significant values. Negative SMD favours the treatment group.

3.3.7 Generic quality of life

We undertook feasibility assessment of the data on generic QoL in the published studies to explore whether SR and CMA of the effect of non-pharmacological interventions on overall QoL could be undertaken. However, we found that the majority of the studies did not assess generic QoL and those which assessed it used a variety of outcome scales and sub-scales.

Overall, 44 studies which assessed generic QoL were identified. These studies were on 20 different interventions and reported results using 10 different scales. Short form (SF) 36 (Ware Jr & Sherbourne, 1992) was the most commonly used outcome scale (30 studies). While some studies reported mental and physical component summaries (MCS and PCS) alone, others reported a selection of the 8 subscales of SF-36 (physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH)) separately. Therefore, overall quantitative assessment of generic QoL could not be undertaken. Table 3-28 illustrates intervention types, number of studies and outcome scales used on QoL assessment.

Table 3-28. Interventions types, number of studies and outcome scales used for QoL assessment

Interventions	No. of trials	Outcome scales used
Aerobic exercise	2	SF-36 subscales (×2)
Mind-body exercise	3	SF-36 MCS-PCS (×2) Nottingham health profile
Mixed exercise	6	SF-36 subscales (×4) HAQ SF-36 overall
Strengthening exercise	1	SF-36 subscales
Education	2	SF-36 subscales SF-12 MCS-PCS
Psychological Tx	4	SF-36 subscales SF-36 MCS-PCS EQ-5D Medical outcome survey
CBT	3	SF-36 subscales SF-36 MCS-PCS (×2)
Mindfulness	1	The QoL profile for the Chronically III
MDT	3	SF-36 MCS-PCS (×3)
Balneotherapy	4	SF-36 subscales SF-36 MCS-PCS HAQ (×2)
Acupuncture	3	SF-36 subscales SF-36 MCS-PCS HAQ
Massage	1	SF-36 subscales
Manual therapy	1	HAQ
Electrotherapy	2	SF-36 subscales SF-36 MCS-PCS
tDCS	1	SF-36 MCS-PCS
Nutritional supplement	3	SF-36 subscales (×2) General health questionnaire
Homeopathy	1	EQ-5D
Music	1	HAQ
Cupping therapy	1	SF-36 subscales
Material of cloth	1	SF-12 MCS-PCS

SF: Short form, MCS: Mental component score, PCS: Physical component score, HAQ: Health assessment questionnaire, EQ-5D: EuroQol- 5 Dimension, CBT: Cognitive behavioural therapy, tDCS: Transcranial direct current stimulation

× : showing how many times that outcome was used.

3.3.8 Subgroup analysis

Subgroup analyses were undertaken on the primary-outcome FIQ for all non-pharmacological interventions as a single group as well as for exercise which was the most commonly studied intervention. The analyses were based on age, BMI, recruitment centre, source of funding and sample size. There were no studies with a mean age of older than 60 years. Hence, mean age of 50 years was set as a cut-off age. Most of the trials included female patients. Therefore, an analysis on gender could not been undertaken. Table 3-29 and Table 3-30 illustrate the detailed results for FIQ subgroup analysis together with the unadjusted univariate meta-regression p values.

The most obvious differences for FIQ outcome were observed based on funding body and sample size. Non-pharmacological interventions showed an ES of (-0.38; 95% CI -0.52, -0.23) in non-commercial studies and (-0.62; 95% CI -1.00, -0.24) in commercially funded studies. Studies involving <50 (-0.82; 95% CI -1.02, -0.63) participants showed greater FIQ improvement compared with studies with a sample size bigger than 50 participants (-0.49; 95% CI -0.64, -0.33) (Table 3-29).

Table 3-29. Subgroup analysis - Non-pharmacological intervention versus control arm (usual care, waiting list, no treatment, placebo or sham treatment): FIQ

	No. of comparison	No. of patients	Effect Size (95% CI)	I^2 (%)	p-value (univariate)
Overall	102	6,403	-0.63 (-0.76, -0.51)	81.7	
Subgroup analysis					
Age*					
<50 years old	59	3,465	-0.66 (-0.84, -0.49)	83.1	0.81
≥50 years old	36	2,385	-0.62 (-0.82, -0.42)	80.8	
Mean BMI*					
<30	28	1,689	-0.51 (-0.71, -0.32)	72.8	0.83
≥30	5	251	-0.47 (-0.72, -0.22)	0.0	
Recruitment centre*					
Hospital based	46	3,074	-0.59 (-0.75, -0.42)	77.9	0.74
Community based	26	1,797	-0.50 (-0.75, -0.26)	83.2	
Mixed	17	946	-0.52 (-0.76, -0.28)	65.8	
Source of funding*					
Non-commercial	48	3,476	-0.38 (-0.52, -0.23)	74.2	0.02
Commercial	8	495	-0.62 (-1.00, -0.24)	71.5	
No funding	4	186	-0.79 (-1.10, -0.49)	0.0	
Both	1	43	-1.51 (-2.19, -0.83)	/	
Sample size >50/ total					
Yes	53	4,776	-0.49 (-0.64, -0.33)	84.8	0.05
No	49	1,627	-0.82 (-1.02, -0.63)	71.7	

No: number, CI: Confidence Interval, FIQ: Fibromyalgia Impact Questionnaire, BMI: Body Mass Index, SD: Standard Deviation, *: Data were missing in some studies

Subgroup analysis on funding body for exercise were not carried out, as all exercise trials were non-commercially funded. Remaining covariates demonstrated a similar trend to those observed in the subgroup analysis of overall non-pharmacological interventions. While exercise was not influenced by age, BMI or recruitment centre, trials with small sample sizes found a greater magnitude of ES (-1.08; 95% CI -1.55, -0.60) relative to trials with more than 50 participants (-0.44; 95% CI -0.63, -0.26) (Table 3-30).

Table 3-30. Subgroup analysis - Exercise versus control arm (usual care, waiting list or no treatment): FIQ

	No. of comparison	No. of patients	Effect Size (95% CI)	I^2 (%)	p-value (univariate)
Overall	24	1327	-0.67 (-0.89, -0.45)	71.4	
Subgroup analysis					
Age*					
<50 years old	13	849	-0.58 (-0.90, -0.26)	78.7	0.26
≥50 years old	9	376	-0.86 (-1.11, -0.61)	23.2	
Mean BMI*					
<30	11	539	-0.68 (-0.89, -0.47)	28.7	0.51
≥30	1	84	-0.47 (-0.90, -0.03)	/	
Recruitment centre*					
Hospital based	6	434	-0.61 (-0.94, -0.27)	62.0	0.95
Community based	9	444	-0.62 (-0.91, -0.33)	51.2	
Mixed	7	392	-0.59 (-0.90, -0.27)	53.5	
Sample size >50/ total					
Yes	13	972	-0.44 (-0.63, -0.26)	49.7	0.04
No	11	355	-1.08 (-1.55, -0.60)	75.6	

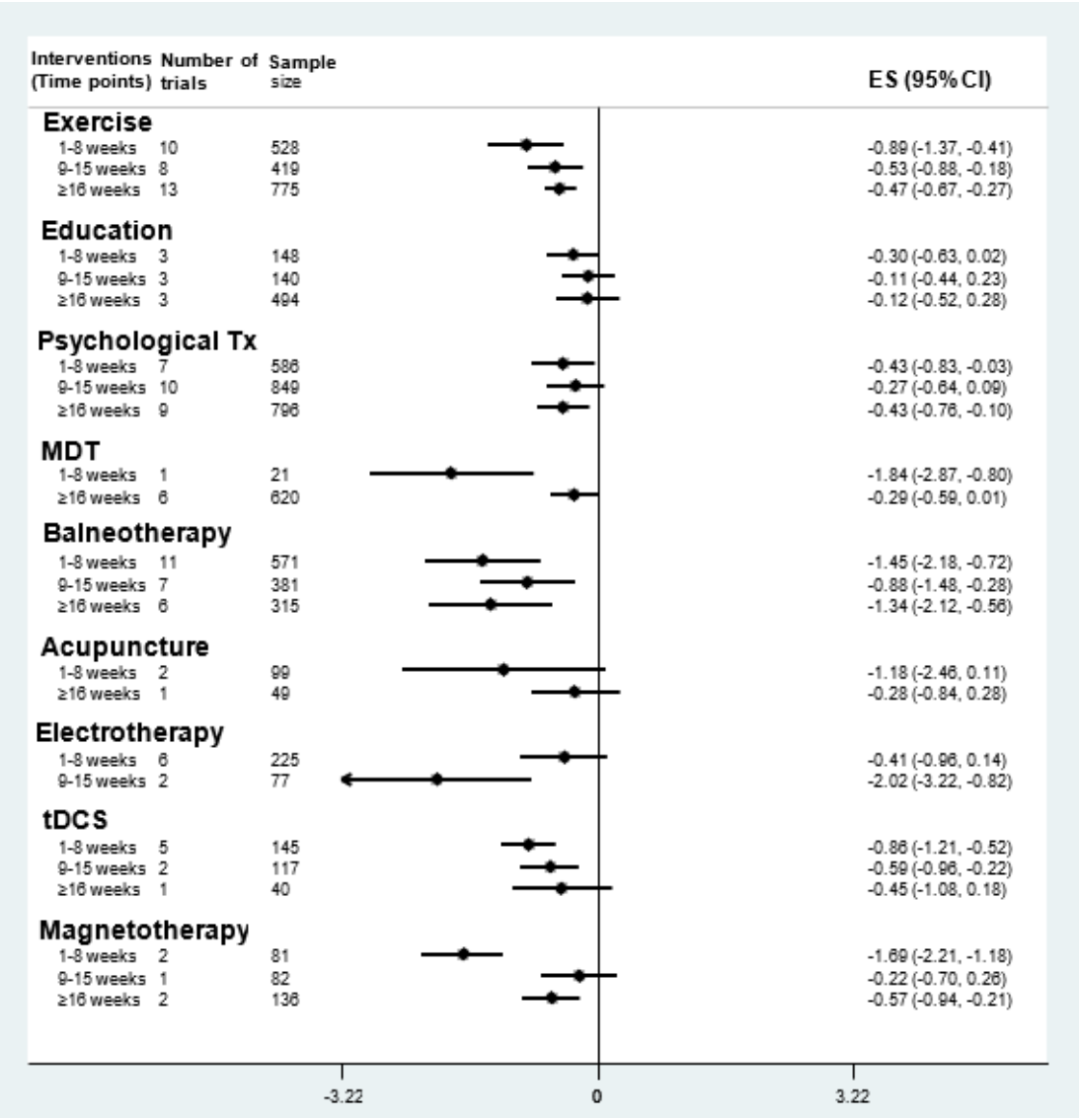
No: number, CI: Confidence Interval, FIQ: Fibromyalgia Impact Questionnaire, BMI: Body Mass Index, SD: Standard Deviation, *: Data were missing in some studies

3.3.9 Time dependant analysis

A secondary analysis for time dependant effects was undertaken on FIQ for commonly studied interventions. Post intervention follow-up time points were grouped into three intervals involving similar time periods (Figure 3-2) (e.g. 1-8 weeks, 9-15 weeks and >16 weeks).

All interventions except for electrotherapy showed a peak effect size in the first interval (1-8 weeks). From nine weeks to 15 weeks, treatment response diminished for the same interventions, whereas electrotherapy showed a greater magnitude of effect size. After 16 weeks, exercise response decreased. The benefits of balneotherapy, magnetotherapy and psychological treatments were more superior relative to the interval of 9-15 weeks. No significant results were found for the remaining interventions (Figure 3-5).

Figure 3-5. Time dependant analysis for FIQ



Tx: treatment, MDT: Multidisciplinary treatment, tDCS: Transcranial direct current stimulation

Negative SMD favours the treatment group.

3.3.10 Sensitivity analysis

Sensitivity analysis was conducted for non-pharmacological interventions and exercise for FIQ based on risk of bias assessment criteria (e.g. intention to treat use and allocation concealment), type of data included (e.g. endpoint scores rather than change scores or studies included imputed SD) and studies in different languages. All exercise trials were in English, so it was not possible to do a sensitivity analysis on language. The estimates of non-pharmacological interventions for FIQ were relatively robust. ES changes were ≤ 0.1 for overall non-pharmacological interventions (Table 3-31).

Table 3-31. Sensitivity analysis - Non-pharmacological intervention versus control arm for FIQ

	No. of comparison	**No. of patients**	**Effect Size (95% CI)**	**I^2 (%)**
Overall	102	6,403	-0.63 (-0.76, -0.51)	81.7
Sensitivity analysis				
Intention to treat use	49	3,371	-0.73 (-0.92, -0.56)	83.7
Allocation concealment	26	1,908	-0.67 (-0.87, -0.47)	76.4
Endpoint score	97	6,070	-0.57 (-0.69, -0.44)	80.5
Imputed SD	78	4,898	-0.60 (-0.74, -0.46)	82.1
Translated studies	100	6,296	-0.61 (-0.74, -0.49)	81.2

No: number, CI: Confidence Interval, Imputed SD: studies where missing SD were imputed

Sensitivity analysis on exercise trials also confirmed the overall findings, as 95% CIs were overlapping (Table 3-32).

Table 3-32. Sensitivity analysis - Exercise versus usual care for FIQ

	No. of comparison	**No. of patients**	**Effect Size (95% CI)**	**I^2 (%)**
Overall	24	1,327	-0.67 (-0.89, -0.45)	71.4
Sensitivity analysis				
Intention to treat use	10	731	-0.45 (-0.66, -0.24)	44.5
Allocation concealment	11	675	-0.87 (-1.24, -0.50)	79.0
Endpoint score	23	1,315	-0.56 (-0.79, -0.33)	74.0
Imputed SD	16	974	-0.56 (-0.76, -0.36)	54.6

No: number, CI: Confidence Interval, Imputed SD: studies where missing SD were imputed

3.4 Discussion

3.4.1 Main findings and interpretation

This is by far the most comprehensive SR and CMA including all non-pharmacological interventions and evaluating their efficacy on FIQ, pain, fatigue, sleep and depression. There were no language restrictions for the studies included in this analysis. 21 non-pharmacological interventions were identified and 148 RCTs (n=9,598) met inclusion criteria. 109 studies (n=7,677) compared active treatment to usual care, waiting list or no treatment, and 39 (n=1,921) compared treatment to placebo or sham treatment. The main results indicate that: (1) several non-pharmacological interventions are more beneficial relative to usual care or placebo for overall disease specific QoL (FIQ), pain, fatigue, sleep and depression at or around 12 weeks; (2) different intervention types benefit different outcomes; and (3) exercise appears to be the most promising non-pharmacological intervention as it was the only intervention associated with significant improvement for all outcomes. These findings were also confirmed in high quality studies and in sensitivity analysis based on the type of data used (that is, change score or raw scores).

3.4.1.1 Exercise

Studies indicate that exercise is superior to usual care and has moderate to large ES for improving FIQ, pain, sleep, fatigue and depression at or close to 12 weeks. No previous MA has assessed all exercise types for FM. However, our results are consistent with MA studies in other chronic pain

diseases such as osteoarthritis (OA) and CLBP (Goh et al., 2019; Hayden et al., 2005). Goh et al. (2019) reported significant effects of pooled exercise in OA on pain and HRQoL.

With respect to different exercise types, there are few differences with the previous literature. While we found a significant moderate ES of aerobic exercise on pain (-0.72; 95% CI -1.37, -0.07), a Cochrane review by Busch et al. (2007) reported non-significant differences (0.65; 95% CI -0.09, 1,39). This inconsistency may be due to the number of studies and sample size that were analysed. In the current study 8 aerobic exercise trials with 512 participants were meta-analysed, whereas Busch et al. (2007) examined 3 studies comprising 183 participants.

On examination of mixed exercise, the current review reported a moderate ES for FIQ (-0.70; 95% CI -0.95, -0.45) and a large ES for pain (-0.96; 95% CI -1.49, -0.44). However, another recent SR (Bidonde et al., 2019) found small, clinically unimportant improvements on FIQ (improved by 7 points on a 100 point scale) and pain (5 points on a 100 point scale). This discrepancy could be attributed to the definition of mixed exercise or to different populations studied. For example, their definition of mixed exercise was the combination of more than two exercise types (aerobic, flexibility or strengthening) whereas we additionally included mind body exercises in this list. Furthermore, the study by Bidonde et al. (2019) included other active interventions (i.e. biofeedback, CBT) or exercise types as comparators which may reduce the ES. In contrast, our study used only usual care as a comparator, and provides an estimate that may be closer to the true ES.

3.4.1.2 Education

Our study indicates that education alone may not be superior to usual care for FIQ, pain, sleep and depression. The evidence from 3 studies, however, showed significant improvements for fatigue. An SR by Sim and Adams (2002) reported modest improvement from an education program in people with FM. However, the single study included in this SR used a cognitive approach rather than education only, and improvements were not maintained at follow-up visits. Similarly, previous reviews on CLBP and chronic MSK pain (Clarke et al., 2011; Louw et al., 2016) found significant improvements. Clarke et al. (2011) (Clarke et al., 2011) evaluated two studies (n = 122) and reported statistically significant but clinically small improvements on CLBP (5 mm on the 100 mm VAS). Louw et al. (2016) (Louw et al., 2016) systematically reviewed 13 articles and reported significant findings but their population group comprised many different chronic MSK conditions. Nevertheless, it is hard to study education is a discrete component of care as it is an accepted professional responsibility and a core requirement for shared decision-making in any intervention.

3.4.1.3 Psychological treatments

When considered together, psychological interventions including CBT, mindfulness, hypnosis, acceptance and commitment therapy were more beneficial than usual care on FIQ, pain and depression. CBT and mindfulness were analysed separately. Even though our results are broadly in line with those of previous studies, some are contrary to previous studies that have assessed these interventions (Bernardy et al., 2013; Glombiewski

et al., 2010). Glombiewsk et al. (2010) (Glombiewski et al., 2010) reviewed 23 psychological treatments and, unlike our review, found significant improvements on fatigue and sleep. This discordant result may reflect the type of interventions studied. While we included 30 trials (n = 2,517 participants) and excluded studies including another non-pharmacological intervention (i.e. exercise) in combination with psychological treatments, their review was smaller (23 trials, n=1,396) and included multimodal programs if the psychological treatment accounted for at least 60% of treatment time. Because of the mixed nature of such interventions included in their study, and the difficulty in knowing accurately the percentage of time spent on the intervention from manuscripts, we classified these interventions as MDT. Similarly, our study was unable to demonstrate a significant effect of CBT on depression in contrast to an earlier review by Bernardy et al. (Bernardy et al., 2013). Again, we were strict in our definition of “CBT” as an intervention specified as “CBT” and applied by a trained professional, whereas they considered as CBT any psychological treatment based on a CBT model or framework.

3.4.1.4 MDT

MDT defines a combined non-pharmacological intervention which generally includes components of exercise, education and psychological treatment. The results of our study show that MDT is superior to usual care on FIQ, pain, sleep and depression. Also, it indicates larger ESs compared to exercise only, education only and psychological treatment only. No previous MA has assessed the effect of MDT exclusively in FM. Previous qualitative

analyses (Burckhardt, 2006; Karjalainen et al., 1999), however, suggest that MDT is effective for decreasing pain and FM impact.

3.4.1.5 Other interventions

While acupuncture was better than usual care for FIQ, pain and fatigue, it was consistently better than sham acupuncture for pain and fatigue. Balneotherapy showed significant improvements for all outcomes except for sleep. Electrotherapy was also more beneficial than sham electrotherapy for FIQ, fatigue, sleep and depression. However, these three groups were quite heterogeneous. The type of treatments differed across studies. For example, acupuncture groups included traditional acupuncture, electro-acupuncture or dry needling. Similarly, balneotherapy covered all aquatic interventions which involve a static position in either water with different minerals or sea water.

tDCS was evaluated based on different comparators (i.e. usual care and sham tDCS). Results indicate that tDCS is better than sham tDCS in all outcomes. It did not show significant pain relief, whereas it was more superior compared to usual care for depression. A recent SR with MA evaluating only pain outcome found significant improvement in pain (Chaturvedi et al., 2018). These findings, however, are contrary to those of a previous SR with MA by Zhu et al. (2017). Although they did not investigate the effect of tDCS relative to usual care, they found no significant reductions on FIQ and pain with the application of tDCS over the left dorsolateral prefrontal cortex. In comparison to our general inclusion of tDCS, they did different analyses according to stimulation site and polarity.

Finally, a number of unorthodox interventions were also analysed such as music, HOT, WBV or material of cloth etc. Some of these demonstrated quite large ESs with a wide 95% CI (Material of cloth for fatigue (-5.97; 95% CI -7.29, -4.65), for sleep (-8.94; 95% CI -10.8, -7.07) or HOT for pain (-2.22; 95% CI -2.93, -1.51). There were only one or two trials assessing these interventions and these ESs could be due to placebo effect. However, these trials were of low quality or could not be blinded.

3.4.2 Strengths

To our knowledge, this is the first CMA focusing exclusively on all non-pharmacological interventions for FM and assessing their efficacy on five different outcomes – FIQ, pain, fatigue, sleep and depression. Unlike one previous CMA (Sim & Adams, 2002), our study attempted to include all non-pharmacological interventions. There were no time, language and geographical restrictions.

Seven different databases were utilised and the literature search was complemented by a hand-search in previous SRs. The study search was updated after one year (September, 2018). Only RCTs of the highest level of research quality were synthesised in this CMA. Study selection and data extraction were validated by another researcher and senior researchers. Throughout the study selection and data extraction process, a standardised procedure was always used to be consistent.

Another important strength of this study is that interventions were analysed based on their comparison groups. The power of placebo response was first identified by Beecher (1955) and the existence of placebo and contextual effects has been observed in many settings (Abhishek & Doherty, 2013; Chen et al., 2017; Zhang et al., 2008). Therefore, a different analysis was undertaken for placebo-controlled trials. Usual care, waiting list and no treatment were grouped as usual care. Placebo and sham treatments were grouped and analysed separately.

3.4.3 Limitations

The present CMA is subject to several caveats. Firstly, in spite of the use of the most robust method to determine efficacy (i.e. RCTs), excluding other study designs may give the propensity for bias in this field. Abstracts were not included due to insufficient data. Also, unpublished trials could not be included because of the broad nature of the research question. This may lead to increased publication bias.

Secondly, more than half of the studies had a small sample size (<50). Low statistical power due to the small sample size may lead to type II error and makes it hard to draw a firm conclusion on the efficacy.

Thirdly, there was a high risk of bias for blinding and allocation concealment was unclear for most of the trials. Risks of bias across these domains have the potential to overestimate the results of the CMA. Due to the nature of most of the interventions and patient reported outcomes, it was not possible to provide blinding. However, sensitivity analysis for allocation concealment indicated that the findings were unlikely to be biased by study quality.

Fourthly, it was not possible to analyse all published evidence because of the incomplete and inconsistent outcome reporting. Visually inspected asymmetry of the funnel plots suggested that this loss of data may have biased the results. Also, studies with a small sample size and high risk of bias skewed the funnel plot to the left. This may have affected overall ES and often overestimated ES (Nüesch et al., 2010). However, we attempted to impute missing data and sensitivity analyses on imputed data indicated that results are less likely to be biased due to data imputation.

Fifthly, participants of the studies were predominantly middle-aged women living in a developed or developing country. These questions the generalisability of the findings to other populations and settings.

Finally, some groups of interventions were quite heterogeneous. For example, the electrotherapy group included different kinds of electrotherapy modalities such as TENS, laser etc. Furthermore, intervention programmes or control groups were not standardised and varied considerably between studies. Although the focus was intervention A, it could sometimes contain some element of intervention B. We were always reliant on the description of the intervention by the authors and tried to use the predominant intervention delivered. Variability in interventions and comparators such as number and duration of sessions, way of delivery, setting, and follow-up duration may have caused the heterogeneity, and could compromise the validity and reproducibility of the findings. We attempted to stratify interventions as homogeneously as we could and conducted subgroup and time dependant analyses.

3.4.4 Conclusion and future work

This CMA has systematically examined the efficacy of non-pharmacological interventions on 5 outcomes. In general, the results suggest that several non-pharmacological interventions are more efficacious relative to usual care or placebo on FIQ, pain, fatigue, sleep and depression. Exercise appears to be the most promising non-pharmacological intervention as it was the only intervention which improves all patient-centred outcomes of FM. Different intervention types preferentially benefit different outcomes. Therefore, different types of interventions can be prescribed to patients depending on their predominant symptoms.

Future research is still required to address the limitations raised in the previous section. Firstly, we require methodologically more rigorous, better quality trials with larger sample size and longer durations. Secondly, it is important to create and use standardised, consistent terminology and for investigators to fully describe the intervention programmes. To do this, future studies should investigate the optimal intervention frequency, intensity and duration. Finally, it is important to clarify the efficacy of non-pharmacological intervention in different populations and settings such as males, younger age group, undeveloped countries and different races to generalise the findings.

Chapter 4 COMPARATIVE EFFICACY OF NON-PHARMACOLOGICAL INTERVENTIONS FOR FIBROMYALGIA: A SYSTEMATIC REVIEW WITH NETWORK META ANALYSIS

4.1 Introduction

As discussed in the previous chapter, several non-pharmacological interventions are beneficial for FM. However, there is a paucity of literature regarding whether one intervention is more effective than another.

From the literature search, only 39 studies that directly compared two different non-pharmacological interventions were identified (Table 4-1). This presents difficulties in assessing the relative efficacy between interventions. Therefore, a network meta-analysis (NMA) was undertaken.

Table 4-1. Number of studies assessing two different non-pharmacological interventions

Interventions	Balneotherapy	Mind-body exercise	Land-based aerobic exercise	Electrotherapy	Kinesiotape	Massage	Mixed Exercise	Aerobic exercise	Flexibility exercise	Sleep hygiene	Occlusal splint	Mindfulness	Strengthening exercise	Pain education	Biofeedback	Vibration	tDCS
Water-based aerobic exercise	2		3														
Mixed exercise		2				2											
Massage				1					1								
Acupuncture					1												
Strengthening exercise		3						1									
Aerobic exercise		1					1		5				2		1		1
Pain education		4						1									
CBT										2				1			
Laser					1						1	1					
Mind body exercise									1								
Music																1	

This chapter evaluated the comparative efficacy of four commonly studied and commonly utilised interventions for FM (exercise, psychological

treatment, multidisciplinary treatment (MDT) and balneotherapy) with respect to patient-centred outcomes of FIQ, pain, fatigue, sleep and depression, using NMA.

4.2 Methodology

This NMA is an extension of the CMA in the previous chapter. Therefore, the eligibility criteria were extended to allow for the inclusion of head-to-head comparisons. After revising the number of studies for each intervention and their comparators, it was decided to exclude some interventions such as acupuncture, electrotherapy, biofeedback etc, either because there were not enough trials assessing these interventions or they did not have a common comparator. Otherwise the study populations, evaluated outcomes and primary time points remained the same as in the CMA and the same data collection procedure was used.

Interventions:

Only the most commonly studied interventions, specifically exercise, psychological treatment, MDT and balneotherapy, were assessed in this NMA. Table 4-2 illustrates what type of comparison would be eligible for NMA. Where studies had more than two arms, data from all arms were used for the analysis.

Table 4-2. Types of studies and eligibility status for NMA

Types of comparison		Study Eligibility
Group 1	**Group 2**	
Intervention A	Non-intervention	Yes
Intervention A+ Intervention B	Intervention B	Yes
Intervention A	Intervention B	Yes
Intervention A	Drug	No
Intervention A+ Drug	Drug	No
Intervention A	Doses of intervention A*	No

*It can include a different mode, delivery methods or intensity of intervention A

Comparators:

Comparators included non-intervention that is usual care, waiting list or no treatment or any other non-pharmacological intervention (head-to-head comparisons).

Data analysis:

A random-effects Bayesian NMA was conducted as the main analysis and a frequentist approach was used as a sensitivity analysis. While the frequentist approach exclusively used the present data ignoring what is already believed to be true, the Bayesian approach repeatedly tests the research hypothesis by incorporating the present data (likelihood) and any prior information, knowledge or external information (prior probability) (Van de Schoot et al.,

2014). Therefore, it was decided to use the Bayesian approach as the main analysis in this NMA. It has been reported that even though these two methods differ in their statistical approach, they should produce similar results with large sample sizes (Shim et al., 2019). Hence, the frequentist approach was used as a sensitivity analysis. Table 4-3 shows other differences between frequentist and Bayesian approaches (Van de Schoot et al., 2014).

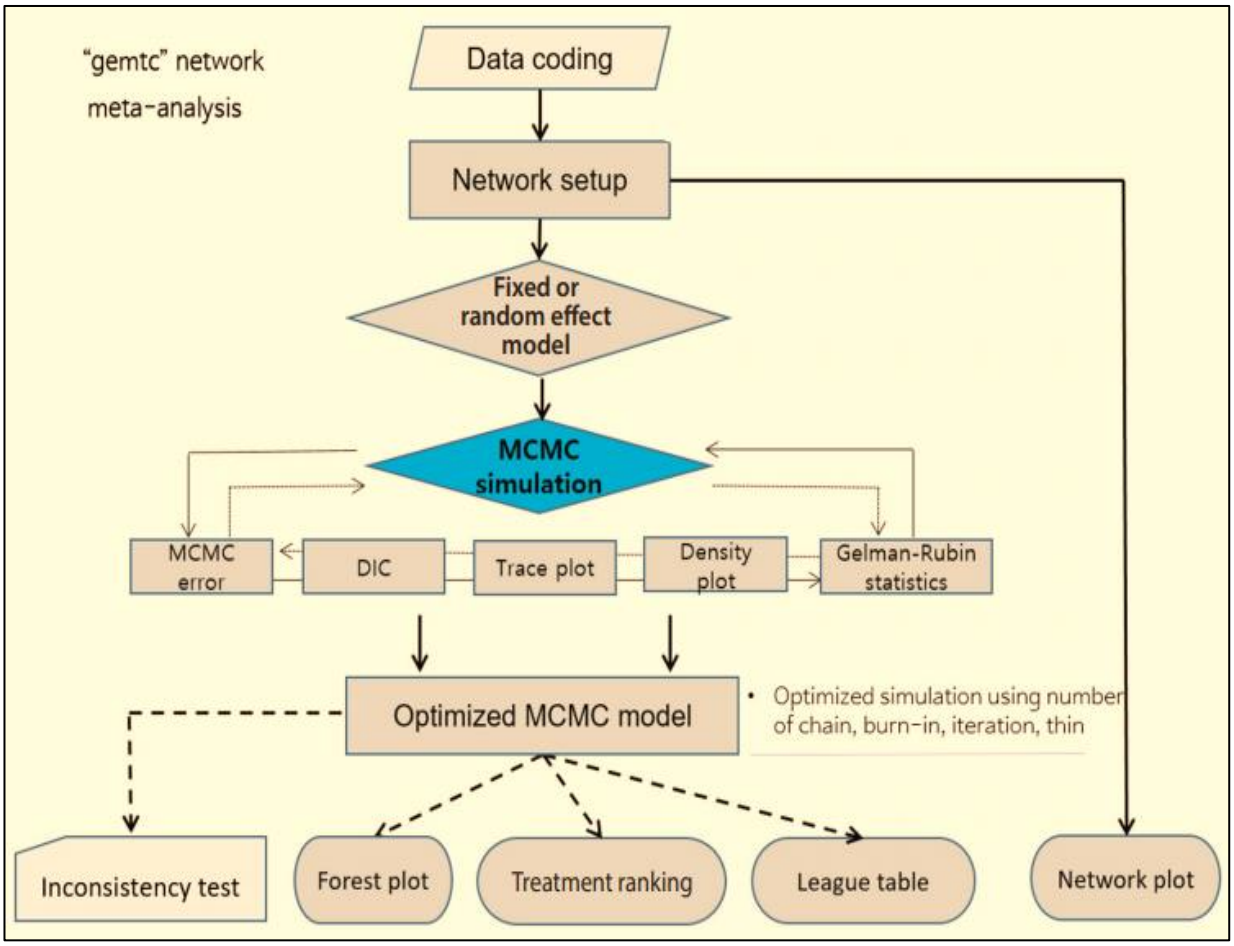
Table 4-3. Differences between Bayesian and frequentist approaches (Van de Schoot et al., 2014)

	Frequentist	**Bayesian**
Reporting of estimates	ES (95% Confidence Interval)	ES (95% Credible Interval)
Confidence interpretation	It is 95% certain that the value of interest lies between upper and lower limits.	The value of interest lies with a 95% probability in the interval.
Sample size	Large sample size is more robust.	Large sample size is not necessary.
Prior information	N/A	Incorporates prior knowledge and present data
Parameter	A population mean is unknown but has only one fixed true value.	A population mean is unknown but is not fixed. It has a distribution of random values

The Bayesian network meta-analysis was conducted in R with statistical package “gemtc” using random effect models. First, a prior distribution was selected. Second, the present data were used to calculate the likelihood that was expressed as the effect size. After that, Markov Chain Monte Carlo (MCMC) simulations were run with different values chosen arbitrarily to set a distribution which best converges the posterior distribution. A smaller MCMC

error illustrates a higher accuracy as well as good convergence. Two chains, 5,000 burn-ins with 10,000 iterations and an interval of 1 were selected for a good MCMC convergence (burn in 5000, iteration 10000 thin 1). Convergence was also confirmed by Gelman-Rubin statistics. Lastly, consistency was checked by the node-splitting method to assess the agreement between direct and indirect evidence. Figure 4-1 illustrates the flow diagram of Bayesian NMA in R using “gemtc” package (Shim et al., 2019).

Figure 4-1. Flow diagram of Bayesian NMA in R using "gemtc" package (Shim et al., 2019)



The frequentist NMA was done in STATA using “network” command (White, 2015). After setting data, a network map was generated. Following this, consistency was tested. Finally, network forest plots and a league table were produced and relative rankings of treatments were determined by surface under the cumulative ranking (SUCRA) (Shim et al., 2016).

4.3 Results

4.3.1 Study characteristics

Of 187 articles retrieved from the literature search (Figure 3-3), 77 were evaluated in this NMA. More than half of the articles (54.5%) were published after 2010 and European and North and South American countries contributed most of the eligible articles (98.7%). There was no language restriction. Two articles in Spanish and another two in German were included in the analysis. The majority of articles (94.8%) were in English.

Over half of the studies (55.8%) used non-commercial funding, whereas one study (1.3%) was funded by a commercial entity. While there was no funding source declared for two studies (2.6%), the funding body was unclear for the remaining 31 studies (40.3%).

Participants were recruited from a hospital setting in 44.6% of the studies, whereas in 27.7% of studies, participants were identified via newspapers, leaflets and community groups. In addition, 16.9% of studies found participants from both hospital and community settings. However, 10.8% of them did not report where they recruited participants from.

A large proportion – 93.5% (72/77) - of the trials were un-blinded as expected. Further details are presented in Table 4-4.

Table 4-4. Summary of study characteristics for the NMA

Summary of study characteristics eligible for NMA	Total (n=77)
Publication year	**No. of trials (%)**
1990-1999	4 (5.2)
2000-2009	31 (40.3)
2010-onwards	42 (54.5)
Study location	
Europe	51 (66.2)
North America	20 (26)
South America	5 (6.5)
Asia	1 (1.3)
Language	
English	73 (94.8)
Spanish	2 (2.6)
German	2 (2.6)
Source of funding	
Commercial	1 (1.3)
Non-commercial	43 (55.8)
No funding	2 (2.6)
Unclear	31 (40.3)
Blinding	
Participant and assessor blinded	4 (5.2)
Unblinded	72 (93.5)
Unclear	1 (1.3)
Setting	
Hospital-based	38 (44.6)
Community-based	22 (27.7)
Mixed	11 (16.9)
Unclear	6 (10.8)
Diagnostic procedure	
ACR 1990	49 (63.6)
ACR 2010	2 (2.6)
Physician diagnosis	7 (9.1)
ACR 1990 and ACR 2010	3 (3.9)
ACR 1990 and physician diagnosis	11 (14.3)
ACR 1990 and ACR 2010 and physician diagnosis	1 (1.3)
ACR 1990 and ACR 2010 and ACR 2016	1 (1.3)
Unclear	3 (3.9)
Method of delivery	
Individual	28 (36.4)
Group	42 (54.5)
Mixed	4 (5.2)
Unclear	3 (3.9)

ACR: American College of Rheumatology

4.3.2 Intervention characteristics

Of 187 studies meeting inclusion criteria, 77 studies (n = 5,639 participants) assessed exercise, psychological treatment, MDT and balneotherapy (Table 4-5). Overall, 88.3% of the participants were woman with a median age of 48.8 years ranging from 33.4 to 59.3 years. Median BMI was 27 kg/m^2.

There were 32 trials (n = 1,801 participants) that evaluated exercise versus usual care or balneotherapy. Most of the participants (94.6%) were woman. Median age was 49.1 years and median BMI was 27.9 kg/m^2. Table 4-5 illustrates intervention characteristics.

Table 4-5. Intervention characteristics for exercise, psychological treatments, MDT and balneotherapy intervention studies versus control groups (intervention, usual care or waiting list)

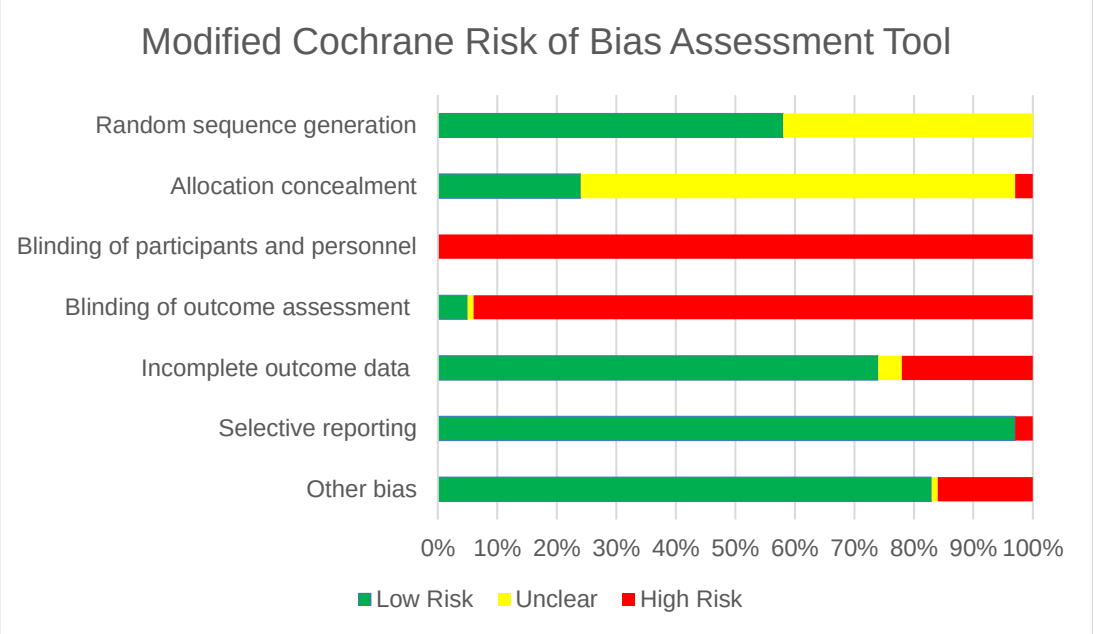
Interventions	No. of trials	No. of participants	No. of women (%)	Age, year	BMI kg/m2
Exercise	32	1,801	1,704 (94.6)	49.1 (37-59.3)	27.9 (23.8-31.4)
Psychological Tx	24	2,089	1,753 (83.9)	50.5 (43-55.4)	27.1 (25.4-29.3)
MDT	10	1,087	878 (80.8)	45.5 (37.4-55.4)	25.7 (23.8-29)
Balneotherapy	13	662	642 (97)	46.2 (33.4-57)	27.2 (24.8-29.2)
Total	77	5,639	4,977 (88.3)	48.8 (33.4-59.3)	27 (23.8-31.4)

Tx: treatment, no: number, y: year, BMI: body mass index, MDT: Multidisciplinary treatment

4.3.3 Risk of bias assessment

Table 4-6 demonstrates risk of bias assessment in the NMA. Overall, 58% of the trials adequately reported methods for random sequence generation such as using computer generation, drawing lots or tossing a coin etc. However, the remainder did not describe sufficient detail regarding the randomisation procedure. There was a high risk of bias on blinding participants and practitioners. Blinding in outcome assessment also had a high risk of bias, as outcomes were participant-reported.

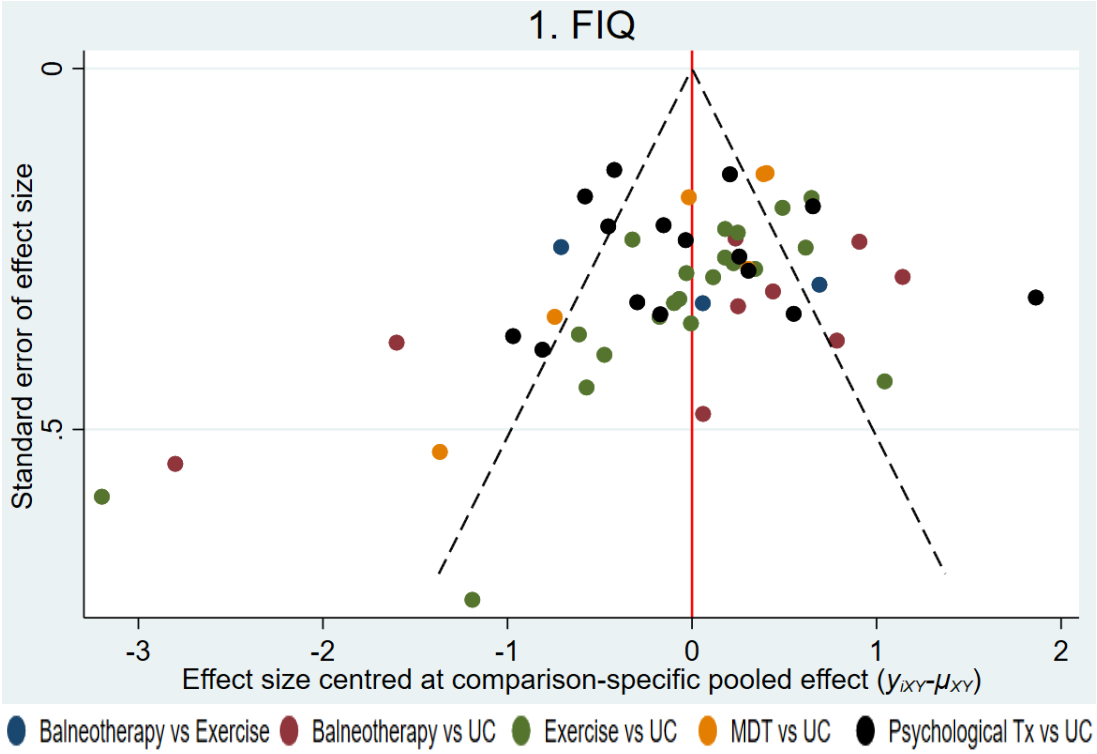
Table 4-6. Risk of bias assessment in NMA for non-pharmacological interventions



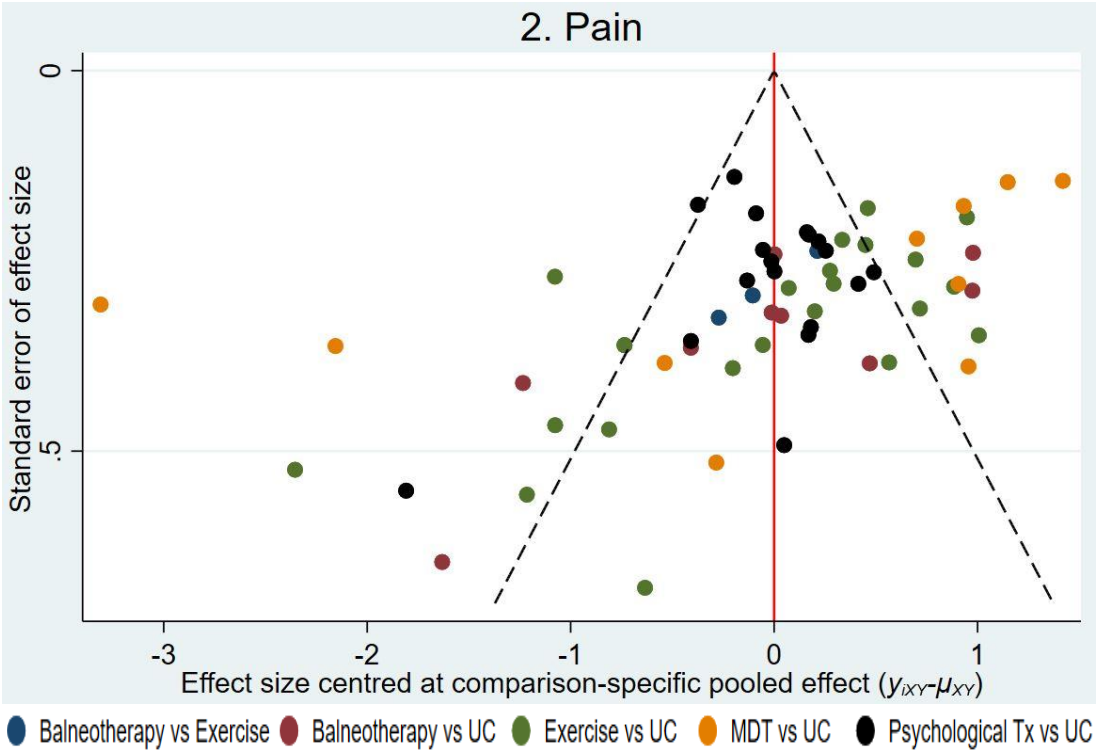
4.3.4 Publication bias

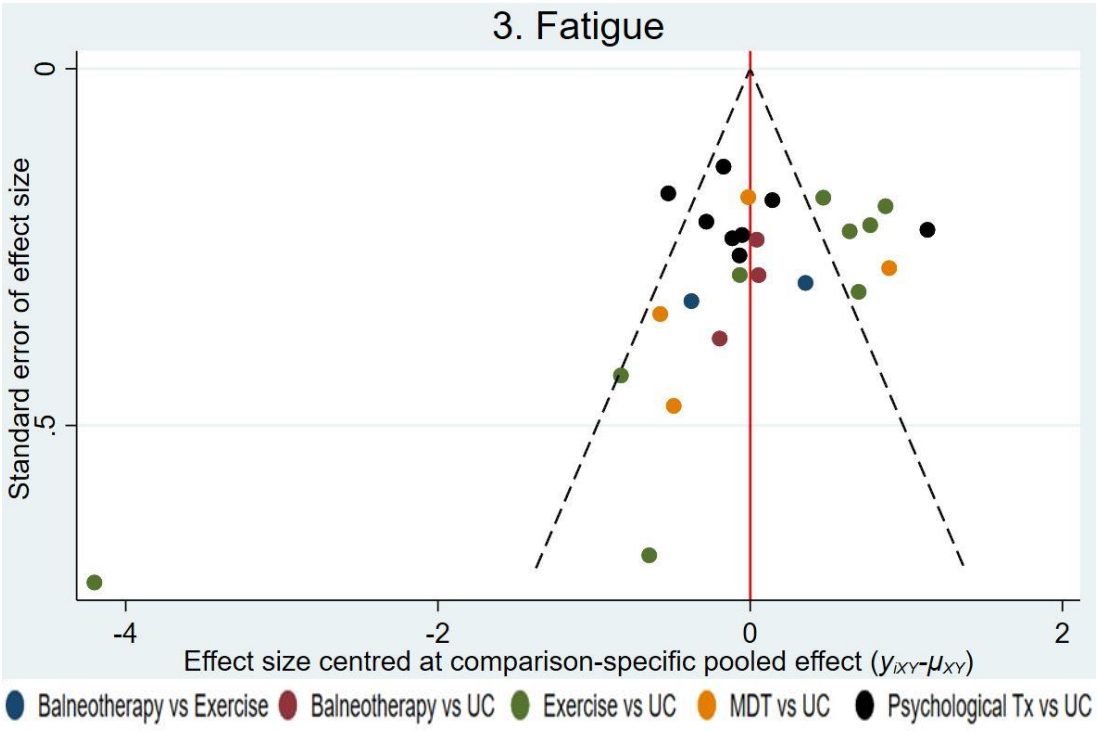
Funnel plots for FIQ, pain, fatigue, sleep and depression outcomes are presented in Figure 4-2. Overall, visually inspected asymmetry was observed for all outcomes, suggesting a publication bias.

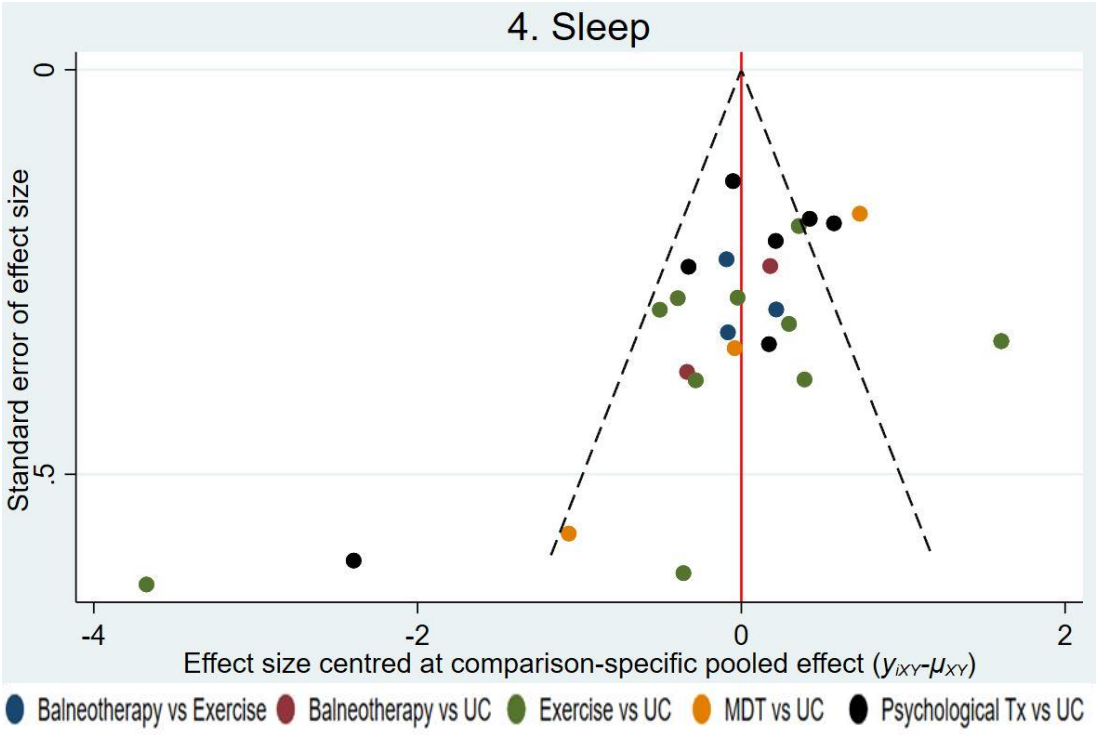
Figure 4-2. Funnel plots for the NMA of non-pharmacological interventions versus control arm (another non-pharmacological intervention, usual care) for FIQ, pain, fatigue, sleep and depression outcomes

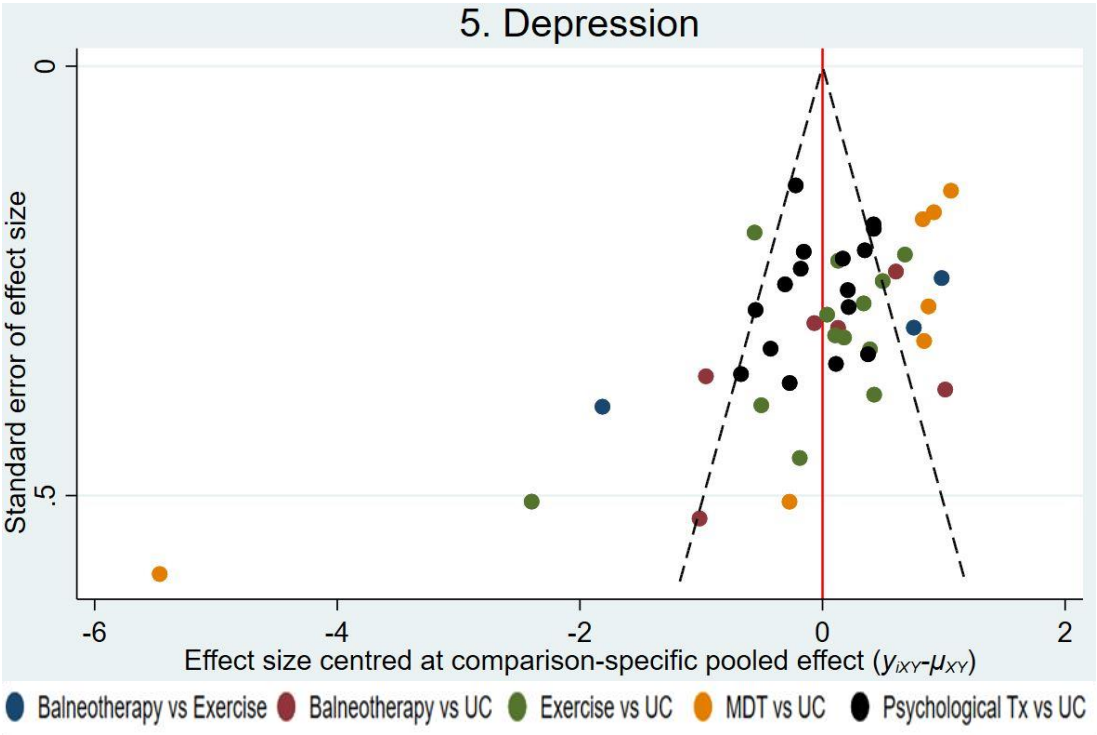


UC: Usual care, MDT: Multidisciplinary treatment, Tx: treatment


2. Pain
Standard error of effect size
0
.5
-3
-2
-1
0
1
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
Balneotherapy vs Exercise
Balneotherapy vs UC
Exercise vs UC
MDT vs UC
Psychological Tx vs UC


3. Fatigue
Standard error of effect size
0
.5
-4
-2
0
2
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
Balneotherapy vs Exercise
Balneotherapy vs UC
Exercise vs UC
MDT vs UC
Psychological Tx vs UC

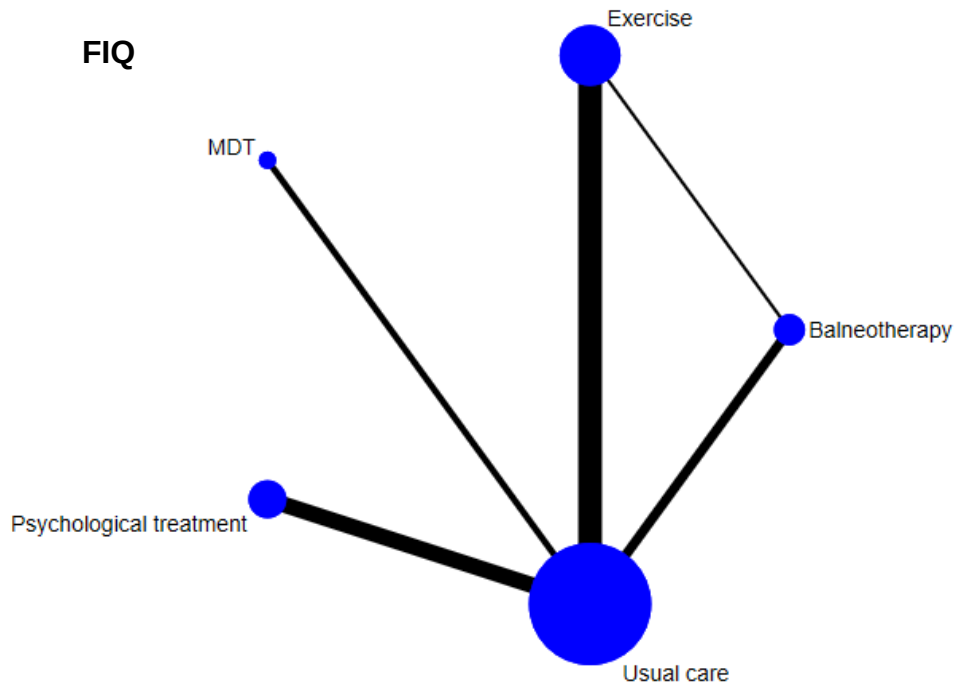

4. Sleep
Standard error of effect size
0
.5
-4
-2
0
2
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
Balneotherapy vs Exercise
Balneotherapy vs UC
Exercise vs UC
MDT vs UC
Psychological Tx vs UC


5. Depression
Standard error of effect size
0
.5
-6
-4
-2
0
2
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
Balneotherapy vs Exercise
Balneotherapy vs UC
Exercise vs UC
MDT vs UC
Psychological Tx vs UC

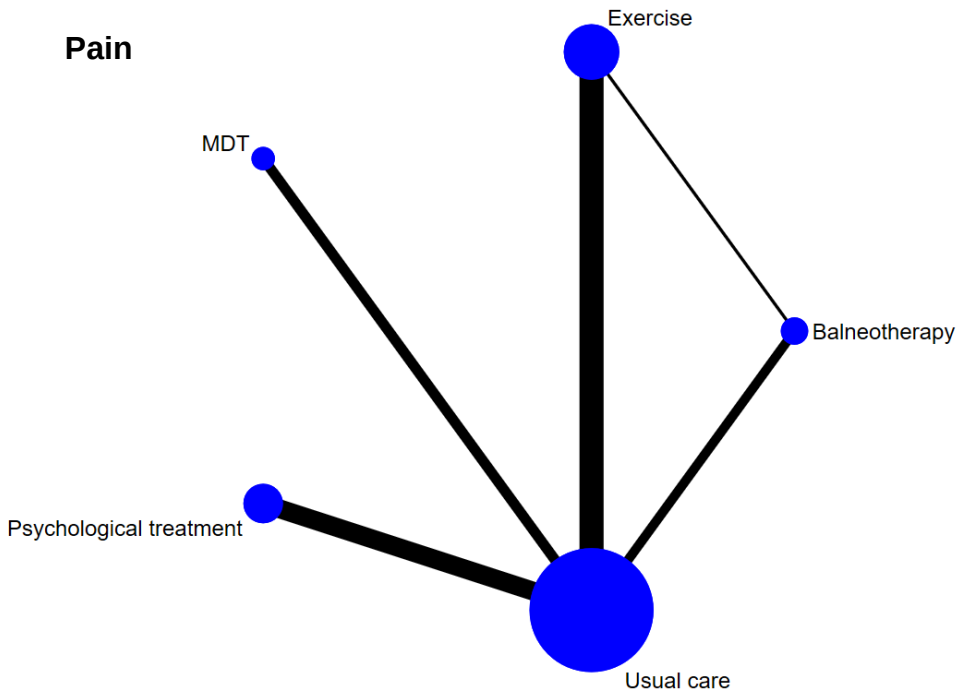
4.3.5 Network map

Figure 4-3 illustrates the generated network maps among interventions for all outcomes. All network maps showed a similar pattern. The size of the nodes, each of which represents one intervention, indicates the number of studies, and the thickness of lines connecting two nodes demonstrates the amount of relevant data. Usual care was the commonly used mutual comparator for all interventions. The only head-to-head comparison relationship was between exercise and balneotherapy.

Figure 4-3. Network maps: FIQ, pain, fatigue, sleep and depression



Exercise versus usual care: 22 studies (1,205 participants)
Psychological treatment versus usual care: 15 studies (1,250 participants)
Balneotherapy versus usual care: 9 studies (432 participants)
MDT versus usual care: 6 studies (620 participants)
Exercise versus balneotherapy: 3 studies (157 participants)



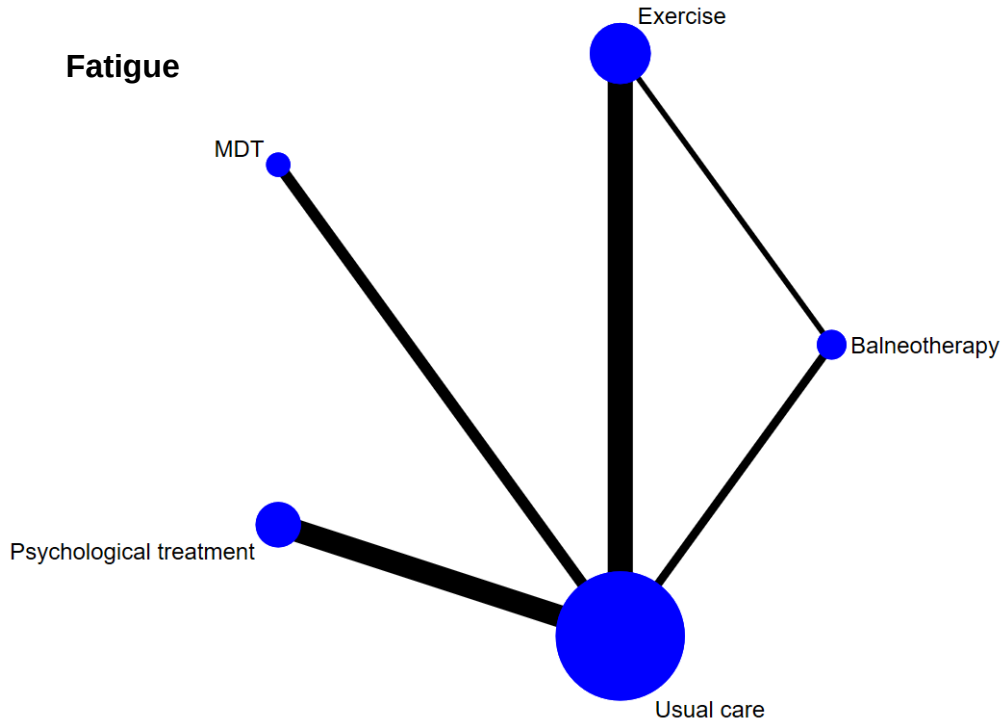
Exercise versus usual care: 23 studies (1,217 participants)

Psychological treatment versus usual care: 18 studies (1,325 participants)

Balneotherapy versus usual care: 10 studies (460 participants)

MDT versus usual care: 10 studies (978 participants)

Exercise versus balneotherapy: 3 studies (157 participants)



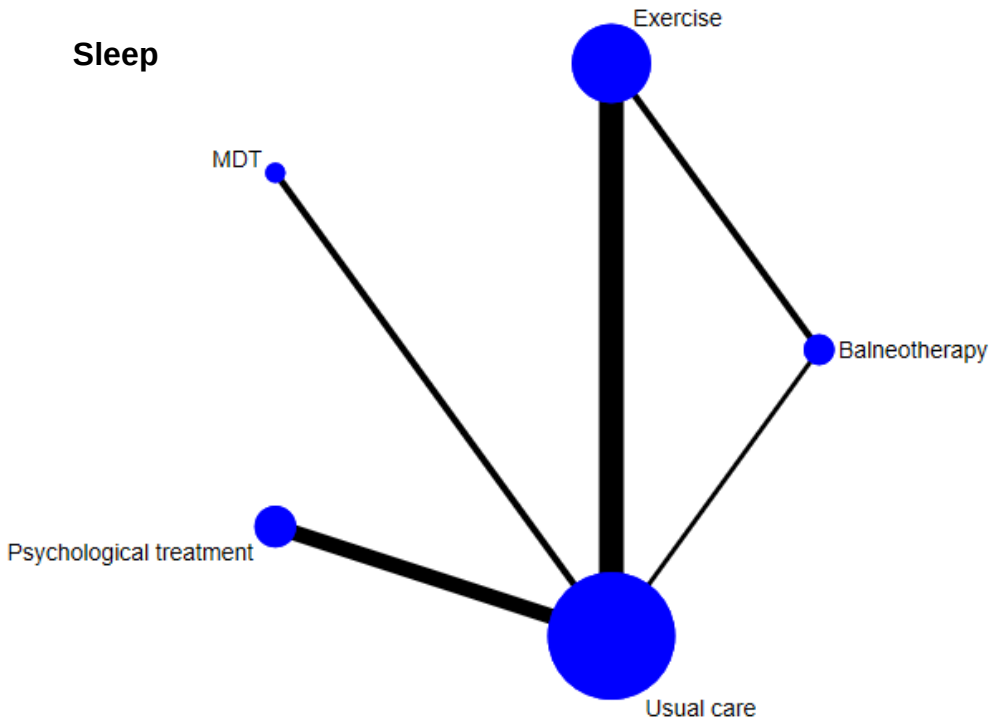
Exercise versus usual care: 9 studies (610 participants)

Psychological treatment versus usual care: 8 studies (870 participants)

Balneotherapy versus usual care: 3 studies (147 participants)

MDT versus usual care: 4 studies (242 participants)

Exercise versus balneotherapy: 2 studies (84 participants)



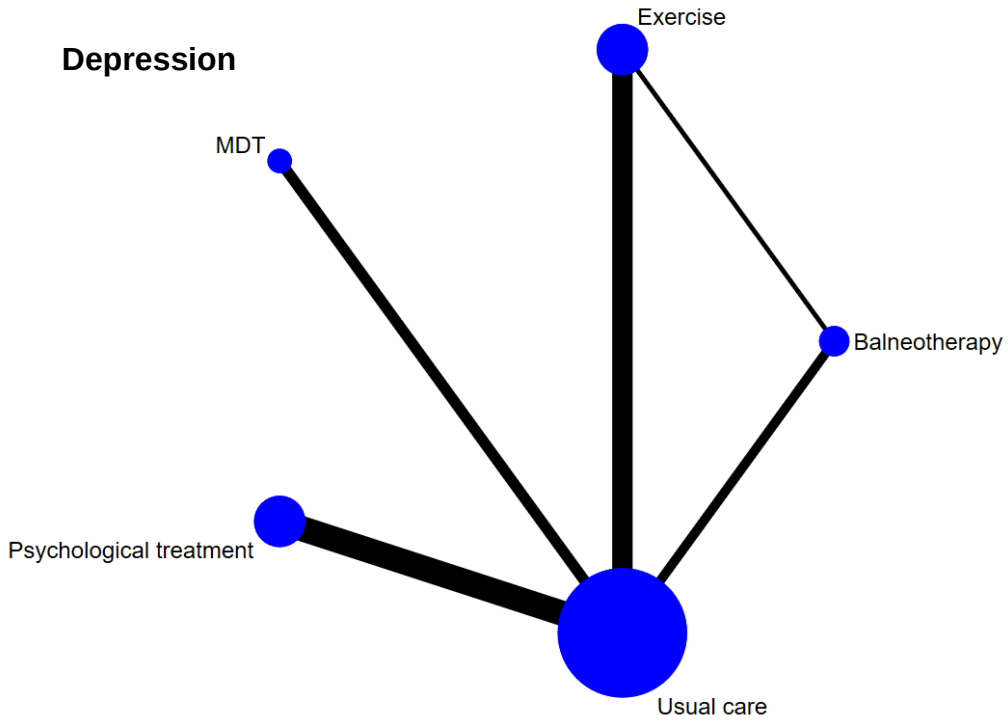
Exercise versus usual care: 11 studies (535 participants)

Psychological treatment versus usual care: 7 studies (668 participants)

Balneotherapy versus usual care: 2 studies (99 participants)

MDT versus usual care: 3 studies (190 participants)

Exercise versus balneotherapy: 3 studies (157 participants)



Exercise versus usual care: 13 studies (690 participants)

Psychological treatment versus usual care: 16 studies (1,198 participants)

Balneotherapy versus usual care: 6 studies (255 participants)

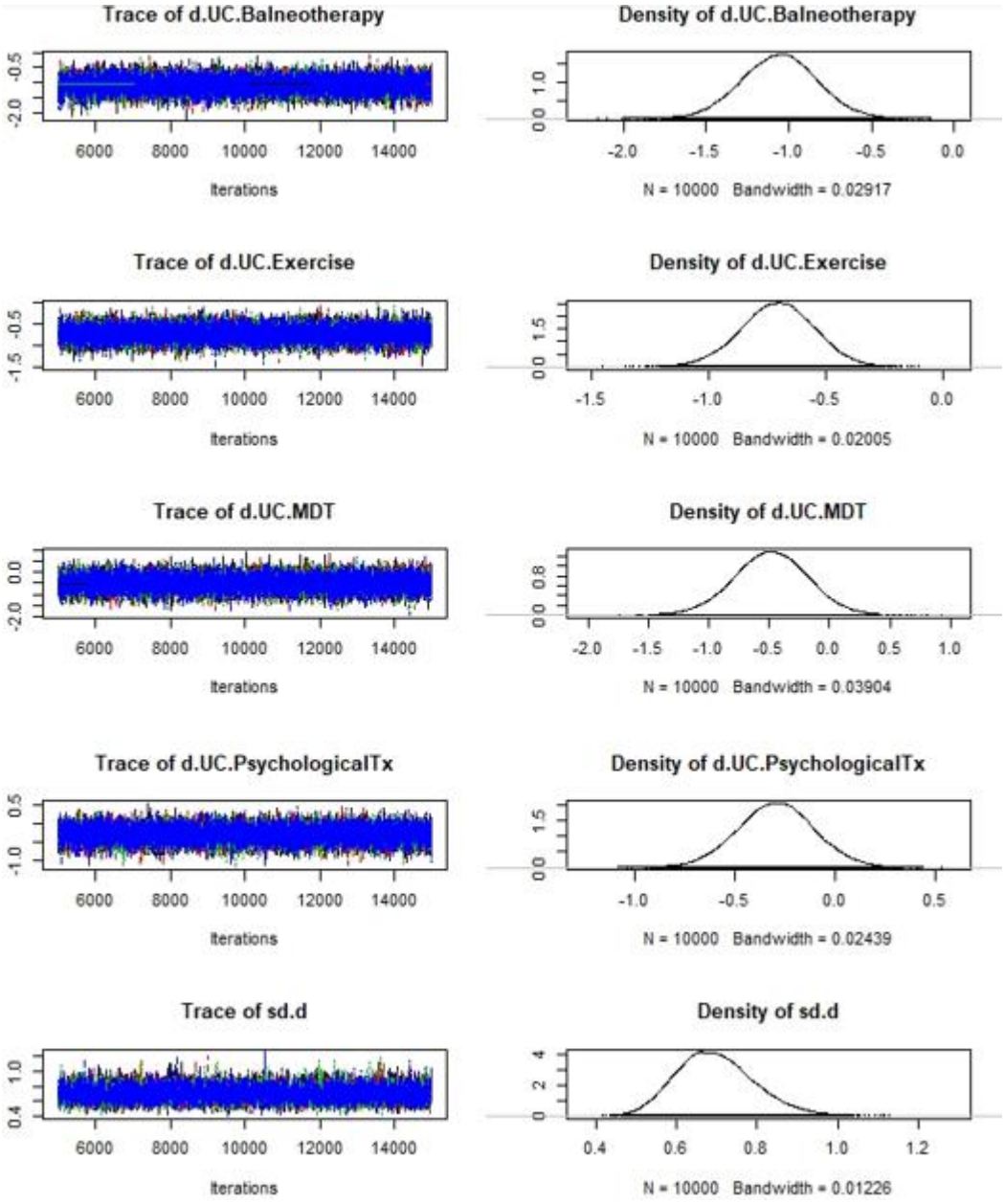
MDT versus usual care: 7 studies (678 participants)

Exercise versus balneotherapy: 3 studies (157 participants)

4.3.6 Assessing convergence

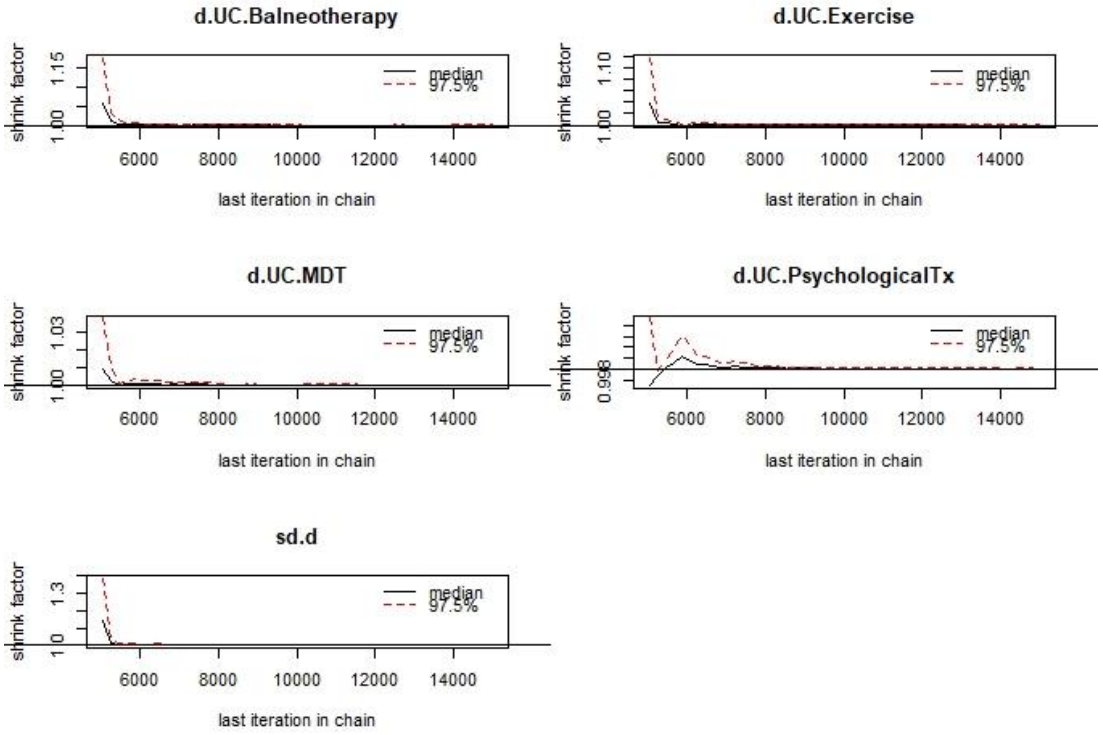
MCMC simulations and Gelman-Rubin-Brooks statistics were used to assess convergence. Several runs of MCMC simulations were performed and it was decided to use two chains, 5,000 burn-ins with 10,000 iterations and an interval of 1 (burn in 5000, iteration 10000 thin 1) for a good convergence. The trace plot which includes entangled continuous chains without a specific pattern and the density plot that shows a smooth normal distribution suggest that the data converged well (Figure 4-4)

Figure 4-4. Trace and density plots showing the results of MCMC simulation for FIQ



The Gelman-Rubin-Brooks plot showed a pattern that gradually shrinks down to zero with increasing number of iterations (Figure 4-5). This kind of pattern is indicative of good convergence.

Figure 4-5. Gelman-Rubin-Brooks plot for FIQ



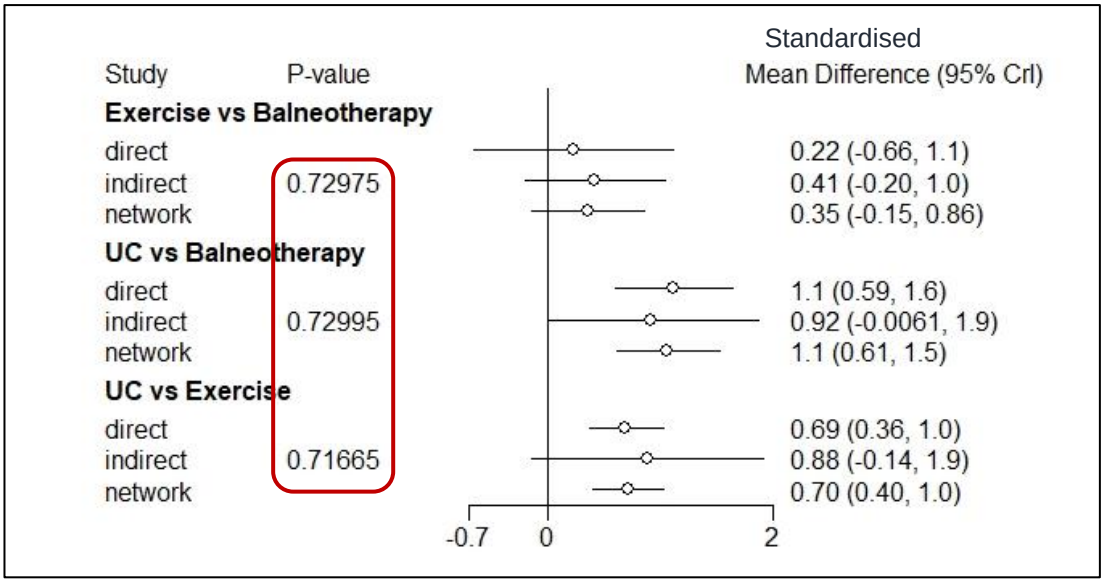
UC: Usual care, Tx: treatment, MDT: Multidisciplinary treatment

Appendix 6 illustrates MCMC simulations and Gelman-Rubin-Brooks plots for other outcomes.

4.3.7 Assessing inconsistency

The node-split method was used to assess inconsistency. Evidence from direct comparisons, indirect comparison and both through the networks were evaluated and a p value greater than 0.05 indicated consistency. Figure 4-6 demonstrates node-splitting analysis of inconsistency for FIQ. Inconsistency test for other outcomes are shown in Appendix 7.

Figure 4-6. Node-splitting analysis of inconsistency for FIQ



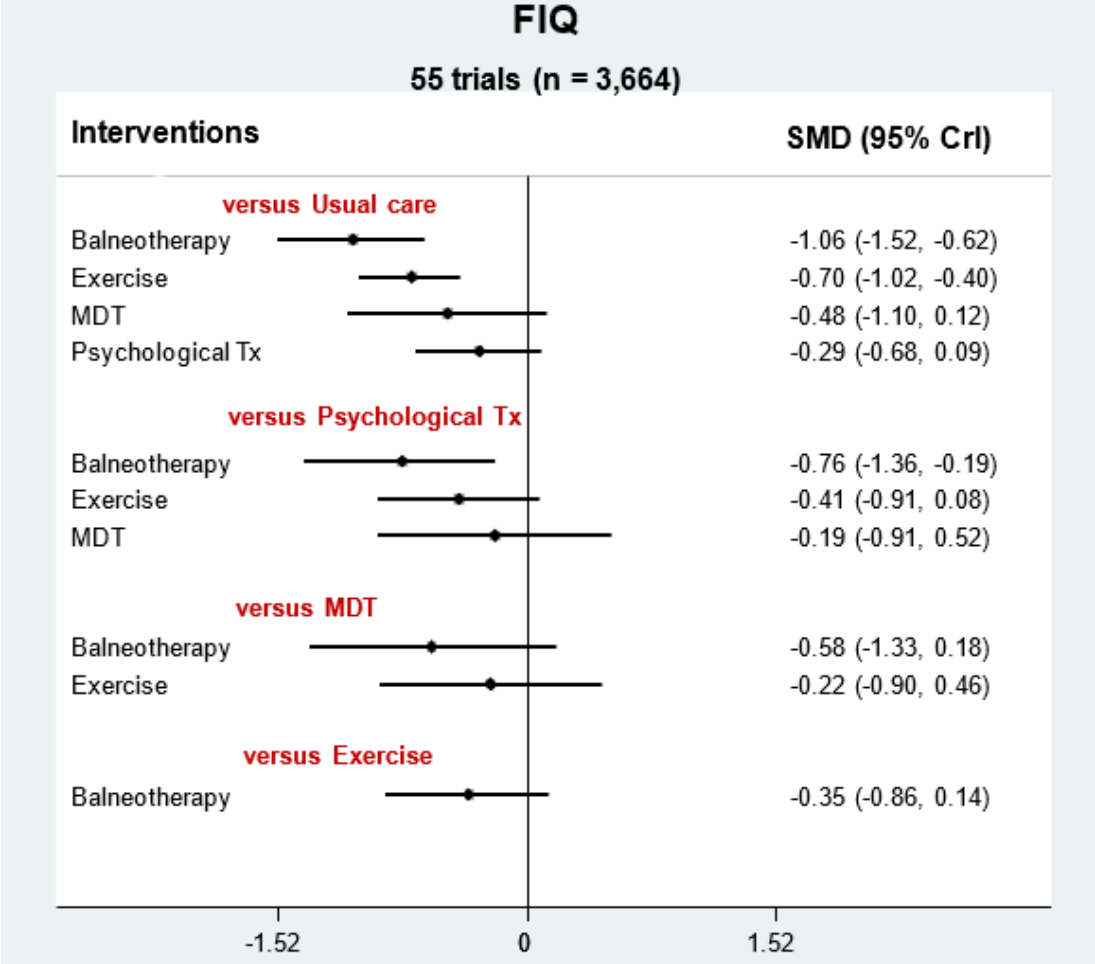
UC: Usual care, CrI: Credible interval

4.3.8 Relative efficacy of non-pharmacological interventions for different outcomes

4.3.8.1 FIQ

There were 55 trials with 3,664 participants that evaluated the effect of non-pharmacological interventions on FIQ. Balneotherapy (-1.06; 95 CrI 1.51, -0.61) and exercise (-0.70; 95% CrI -1.02, -0.40) were significantly better than usual care on FIQ. However, MDT (-0.48; 95%CrI -1.10, 0.12) and psychological treatment (-0.29; 95% CrI -0.68, 0.09) did not show a significant improvement relative to usual care. Their credible interval just crossed zero. While balneotherapy (-0.76; 95% CI -1.36, -0.19) was significantly better than psychological treatment, other interventions did not show any superiority over others (Figure 4-7).

Figure 4-7. Relative efficacy of non-pharmacological interventions on FIQ



MDT: Multidisciplinary treatment, Tx: treatment

Table 4-7 presents the Surface Under the Cumulative Ranking (SUCRA) graph and values. Based on the SUCRA values, balneotherapy would appear to be the best non-pharmacological intervention for FM on FIQ. The SUCRA value for balneotherapy was 0.96. Following this, exercise (0.69) was second best, MDT (0.49) was third best and psychological treatment (0.32) was fourth in rank.

Table 4-7. SUCRA values for FIQ in non-pharmacological intervention studies

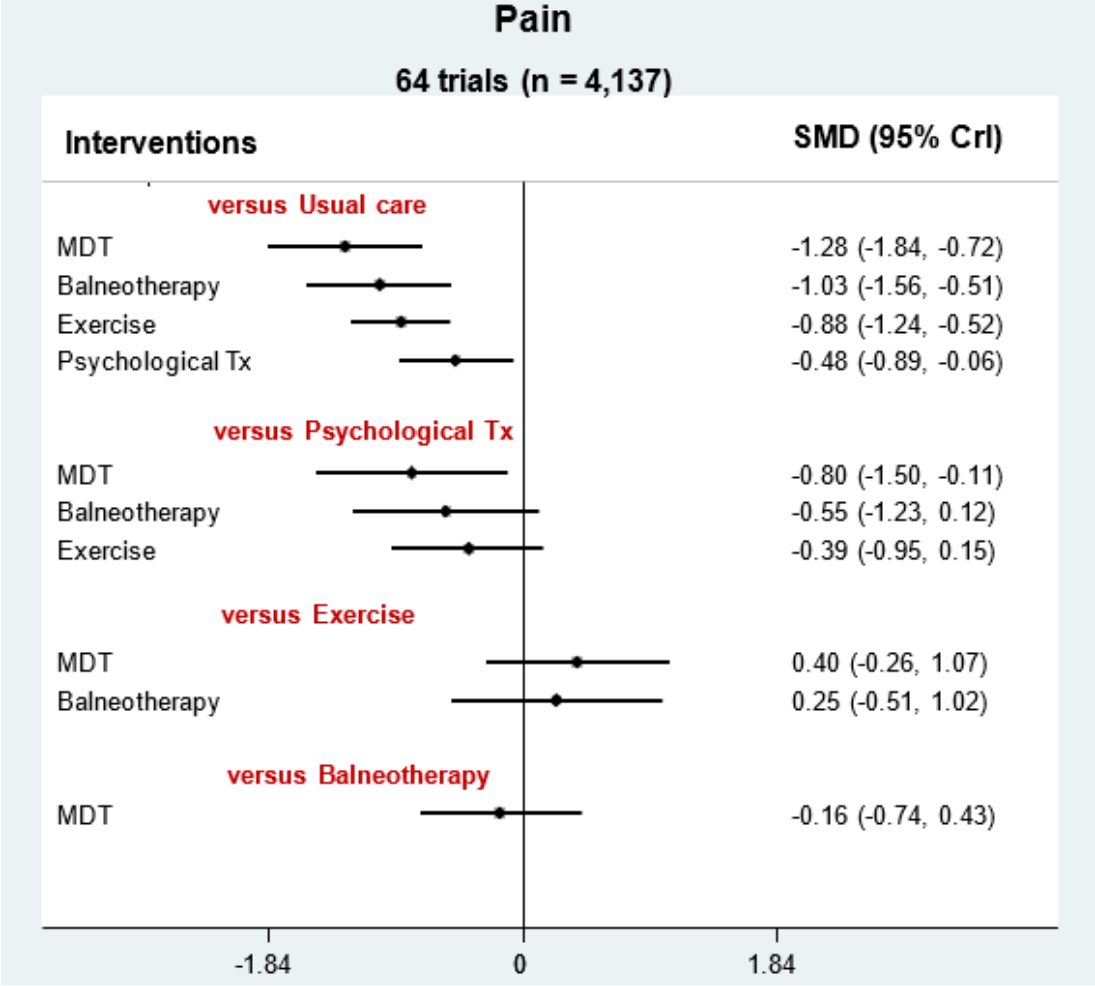
Interventions	SUCRA
Balneotherapy	0.96
Exercise	0.69
MDT	0.49
Psychological Tx	0.32
Usual care	0.03

MDT: Multidisciplinary treatment, Tx: treatment

4.3.8.2 Pain

There were 64 trials including 4,137 participants that assessed non-pharmacological interventions. All intervention types (MDT (-1.28; 95% CrI -1.84, -0.72), balneotherapy (-1.03; 95% CrI -1.56, -0.51), exercise (-0.88; 95% CrI -1.24, -0.52) and psychological treatment (-0.48; 95% CrI -0.89, -0.06)) were better than usual care for pain. MDT showed significant improvements relative to psychological treatment. However, other interventions did not significantly differ among each other (Figure 4-8).

Figure 4-8. Relative efficacy of non-pharmacological interventions on pain



MDT was observed to be the best non-pharmacological intervention for pain with a SUCRA value of 0.83. After that, balneotherapy (0.68), exercise (0.59) and psychological treatment (0.35) were ranked second, third and fourth, respectively (Table 4-8).

Table 4-8. SUCRA values for pain in non-pharmacological intervention studies

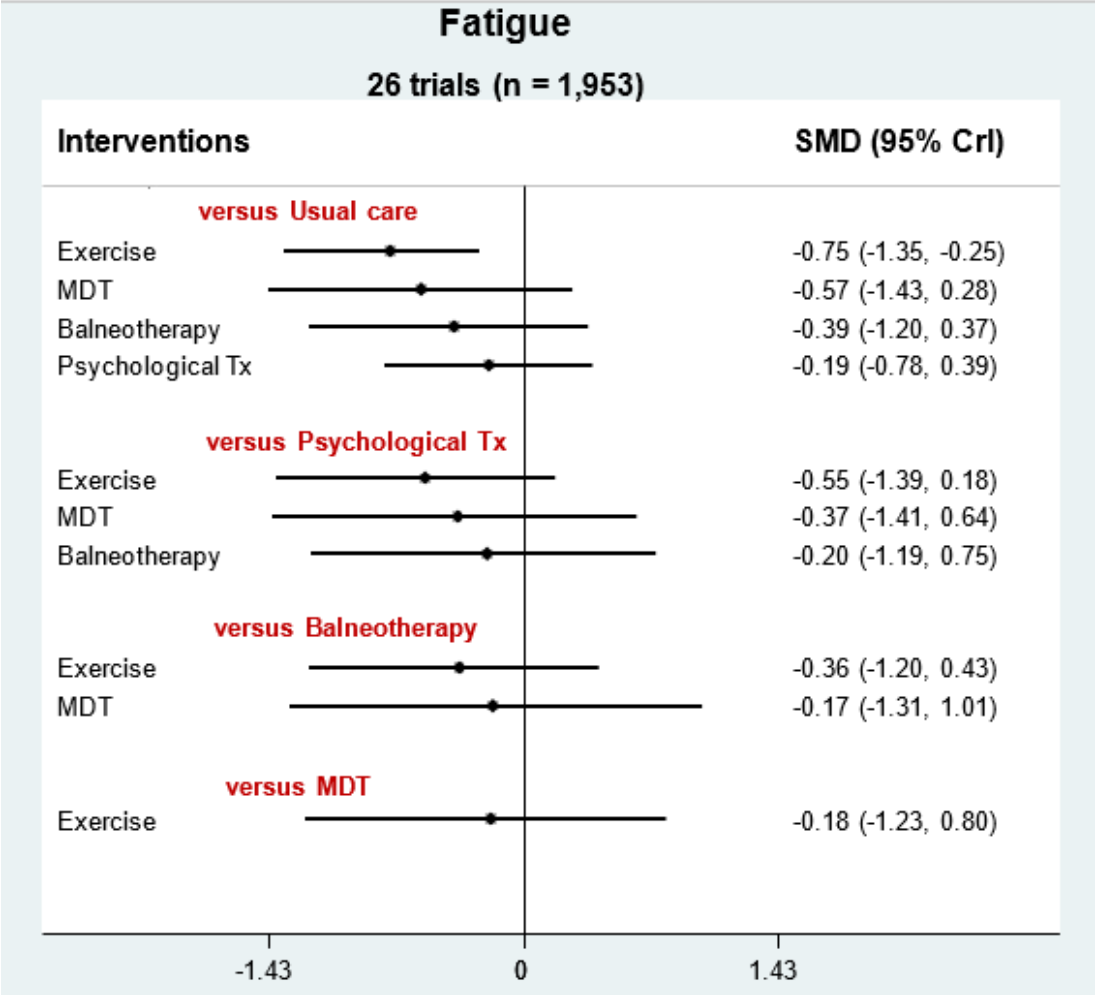
Interventions	SUCRA
MDT	0.83
Balneotherapy	0.68
Exercise	0.59
Psychological Tx	0.35
Usual care	0.03

MDT: Multidisciplinary treatment, Tx: treatment

4.3.8.3 Fatigue

There were 26 studies (n = 1,1953 participants) that evaluated fatigue. Exercise was the only intervention showing significant improvements for fatigue (-0.75; 95% CrI -1.35, -0.25) (Figure 4-9).

Figure 4-9. Relative efficacy of non-pharmacological interventions on fatigue



Exercise was ranked first. It showed a SUCRA value of 0.85. Table 4-9 illustrates SUCRA values for other interventions.

Table 4-9. SUCRA values for fatigue in non-pharmacological intervention studies

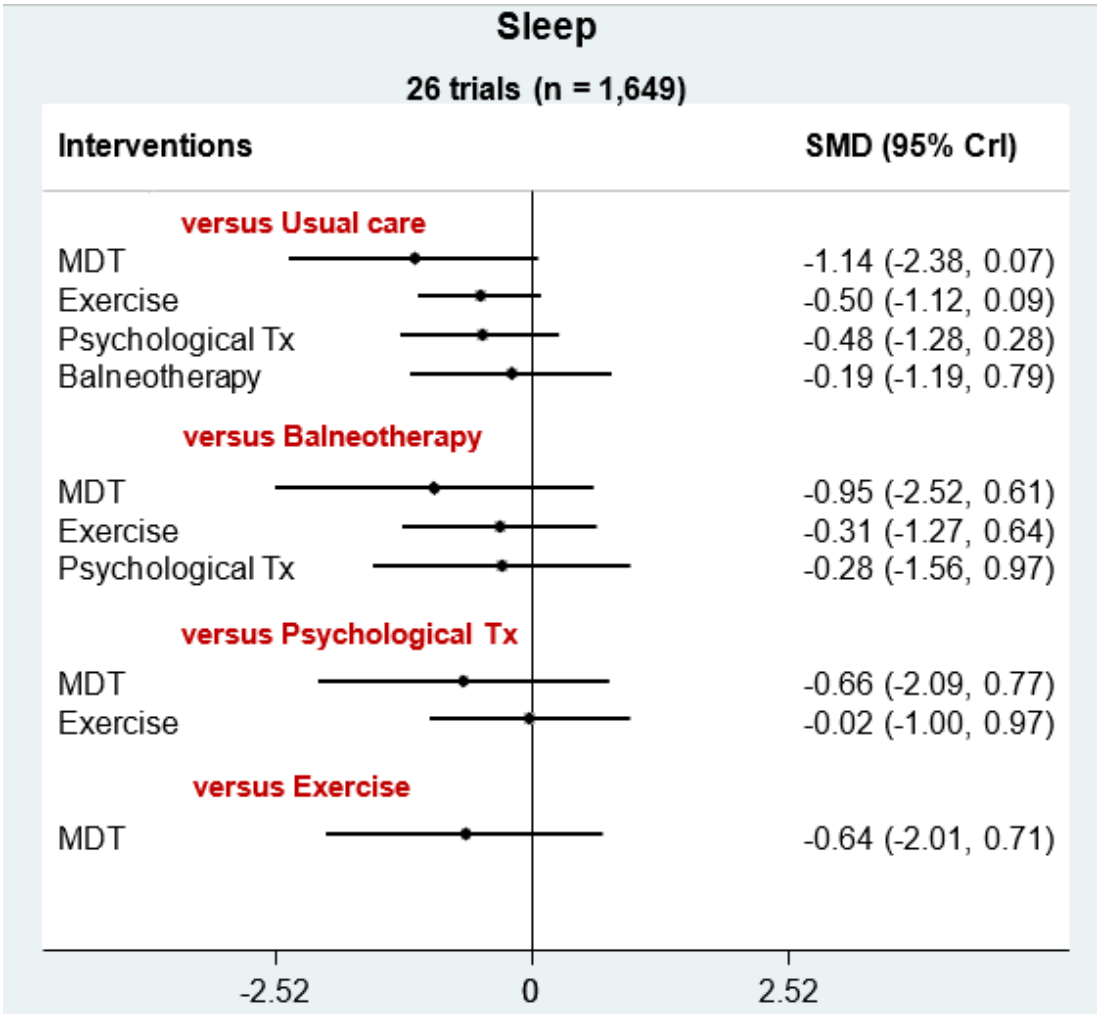
Interventions	SUCRA
Exercise	0.85
MDT	0.67
Balneotherapy	0.52
Psychological Tx	0.34
Usual care	0.12

MDT: Multidisciplinary treatment, Tx: treatment

4.3.8.4 Sleep

Although MDT (-1.14; 95% CI -2.38, 0.07) and exercise (-0.50; 95% CI -1.12, 0.09) just crossed the border, no interventions showed significant changes on sleep relative to usual care. Similarly, none of them was superior over other non-pharmacological interventions (Figure 4-10).

Figure 4-10. Relative efficacy of non-pharmacological interventions on sleep



MDT (0.74) may be the most effective treatment option for sleep (Table 4-10).

Table 4-10. SUCRA values for sleep in non-pharmacological intervention studies

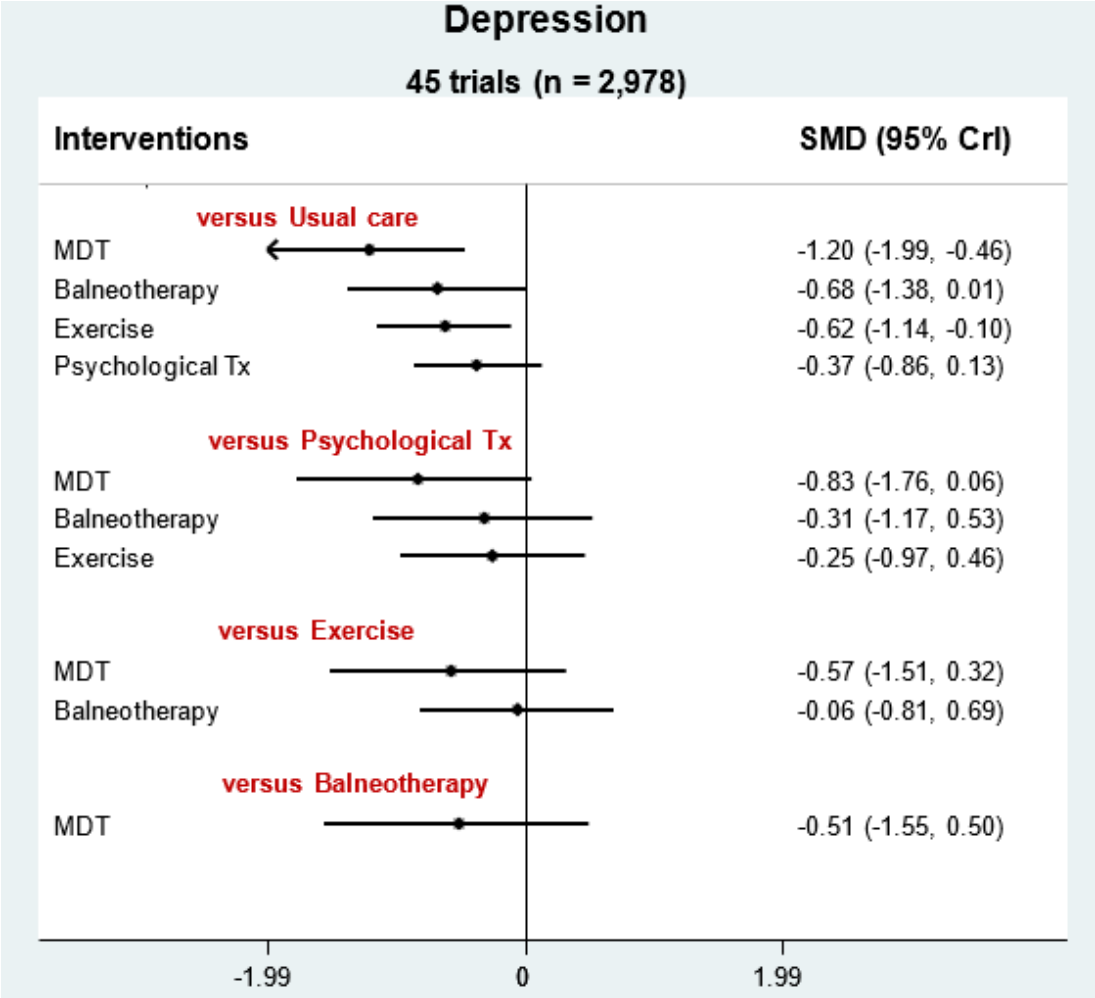
Interventions	SUCRA
MDT	0.74
Exercise	0.67
Psychological Tx	0.52
Balneotherapy	0.35
Usual care	0.12

MDT: Multidisciplinary treatment, Tx: treatment

4.3.8.5 Depression

Based on the analysis of 45 trials comprising 2,978 participants, MDT (-1.20; 95% CrI -1.99, -0.46) and exercise (-0.62; 95% CrI -1.14, -0.10) significantly improved depression in participants with FM (Figure 4-11).

Figure 4-11. Relative efficacy of non-pharmacological interventions on depression



MDT had the highest SUCRA value (0.80), indicating that it may be the best intervention for depression (Table 4-11).

Table 4-11. SUCRA values for sleep in non-pharmacological intervention studies

Interventions	SUCRA
MDT	0.80
Balneotherapy	0.69
Exercise	0.57
Psychological Tx	0.44
Usual care	0.13

MDT: Multidisciplinary treatment, Tx: treatment

4.3.9 Sensitivity analysis

The robustness of the study results was checked by comparing Bayesian and frequentist analyses. Table 4-12 illustrates the Bayesian and frequentist results for the four interventions (balneotherapy, exercise, MDT and psychological treatment) on five outcomes – FIQ, pain, fatigue, sleep and depression. The results of these two analyses were mostly in agreement. The differences were that MDT showed significant improvements for sleep (-1.14; 95% CI -2.26, -0.02) and balneotherapy was significantly better than usual care for depression (-0.68; 95% CI -1.34, -0.02) based on the frequentist NMA. However, these improvements were not significant according to Bayesian NMA.

Table 4-12. Bayesian and frequentist NMAs of non-pharmacological interventions

Outcomes (Interventions)	Bayesian	Frequentist
FIQ	**vs. usual care**	**vs. usual care**
Balneotherapy	-1.06 (-1.52, -0.62)	-1.06 (-1.50, -0.62)
Exercise	-0.70 (-1.02, -0.40)	-0.70 (-1.01, -0.40)
MDT	-0.48 (-1.10, 0.12)	-0.48 (-1.07, 0.10)
Psychological treatment	-0.29 (-0.68, 0.09)	-0.29 (-0.66, 0.08)
Pain	**vs. usual care**	**vs. usual care**
Balneotherapy	-1.03 (-1.56, -0.51)	-1.03 (-1.55, -0.52)
Exercise	-0.88 (-1.24, -0.51)	-0.88 (-1.23, -0.53)
MDT	-1.28 (-1.84, -0.72)	-1.28 (-1.82, -0.73)
Psychological treatment	-0.48 (-0.89, -0.06)	-0.48 (-0.88, -0.08)
Fatigue	**vs. usual care**	**vs. usual care**
Balneotherapy	-0.39 (-1.20, 0.37)	-0.40 (-1.11, 0.31)
Exercise	-0.75 (-1.35, -0.25)	-0.76 (-1.26, -0.25)
MDT	-0.57 (-1.43, 0.28)	-0.58 (-1.34, 0.19)
Psychological treatment	-0.19 (-0.78, 0.39)	-0.20 (-0.71, 0.32)
Sleep	**vs. usual care**	**vs. usual care**
Balneotherapy	-0.19 (-1.19, 0.79)	-0.19 (-1.09, 0.71)
Exercise	-0.50 (-1.12, 0.09)	-0.50 (-1.05, 0.06)
MDT	-1.14 (-2.38, 0.07)	-1.14 (-2.26, -0.02)
Psychological treatment	-0.48 (-1.28, 0.28)	-0.48 (-1.19, 0.23)
Depression	**vs. usual care**	**vs. usual care**
Balneotherapy	-0.68 (-1.38, 0.01)	-0.68 (-1.34, -0.02)
Exercise	-0.62 (-1.14, -0.1)	-0.62 (-1.11, -0.13)
MDT	-1.20 (-1.99, -0.46)	-1.20 (-1.93, -0.47)
Psychological treatment	-0.37 (-0.86, 0.13)	-0.37 (-0.84, 0.10)

MDT: Multidisciplinary treatment, vs: versus

4.4 Discussion

4.4.1 Main findings and interpretations

This study is the first to provide direct comparision between four commonly used non-pharmacological therapies, specifically exercise, balneotherapy, psychological treatment and MDT, through an NMA. In total 78 studies (n = 5,639 participants) were included in this NMA. The main findings are: [1] all non-pharmaological interventions were significantly more effective than usual care for pain, with MDT being the best, followed by balneotherapy, exercise and psychological treatment; [2] only two treatments (balneotherapy and exercise) were effective for FIQ, one treatment was effective for fatigue, none were effective for sleep and two were effective for depression (MDT and exercise); and [3] psychological treatment was the least effective accross all outcomes and was significanly inferior to MDT for pain and to balneotherapy for FIQ.

These results seem to be consistent with the previous research conducted by Nüesch et al. (2013) except for the ranking of interventions and the effect of MDT on fatigue. While they found MDT significantly improved fatigue, in our study MDT was not effective for fatigue. A possible explanation for this might be that they used trials from both non-pharmacological and pharmacological interventions whereas our study only included trials from non-pharmacological interventions. Furthermore, our study has more non-pharmacological studies. The study by Nüesch et al. was the only previous NMA in FM and evaluated the effect of pharmacological and non-pharmacological interventions on four different outcomes – pain, QoL,

fatigue, and sleep. In terms of non-pharmacological interventions, they included aerobic exercise, balneotherapy, CBT and MDT. Although they defined the exercise group as aerobic exercise, it also included other exercise types. However, we used any type of exercise.

In our study, it was clearly apparent that MDT was the best treatment for two outcomes (pain, and depression) and second best and third best for fatigue and FIQ, respectively. The conceptual basis for this may be explained by the biopsychosocial model of illness, as persistent pain and other features of FM lead to a combination of physical, psychological and social disabilities. Therefore, exercise combined with psychological and educational intervention may have increased the ES.

Psychological treatment was only effective for pain and was the least effective treatment for all outcomes, and there were no treatments that were better than usual care for sleep. Nüesch et al. (2013) also could not show the efficacy of non-pharmacological interventions for sleep outcome. Similarly, psychological treatments were not significantly superior to usual care for fatigue and sleep according to our CMA results (Chapter 3). These results are likely to relate to heterogeneity in intervention groups. For example, while exercise includes any type of exercise (aerobic, flexibility, mind-body, mixed or strengthening), CBT, mindfulness., hypnosis and acceptance and commitment treatment were pooled as one intervention in the psychological treatment group.

4.4.2 Strengths

Our study has several strengths. Firstly, to our knowledge, this is the first Bayesian NMA focusing exclusively on non-pharmacological interventions for FM. An extensive literature search was undertaken in seven different databases and four most commonly studied non-pharmacological interventions were investigated on disease specific QoL (FIQ) and four main manifestations of FM (pain, fatigue, sleep and depression). Unlike other reviews, disease specific QoL (FIQ) were analysed separately rather than combining with other generic QoL scales. Secondly, we tried to keep the control group (mutual comparator) as homogenenous as possible. For example, control groups including minimally active interventons (e.g. education, attention control etc) or placebo/sham treatments were not considered as usual care. Thirdly, NMA allowed comparison of interventions for different outcomes and facilitated more precise results by combining direct and indirect evidence. Finally, the frequentist approach was also conducted to confirm the results.

4.4.3 Limitations

There are several limitations to this NMA. Firstly, most of the trials had small sample size and were hampered by unclear risk of bias for allocation concealment and high risk of bias for blinding due to the nature of the interventions. This may have caused an overestimation of the results, which therefore need to be interpreted with caution. Secondly, we evaluated only the most commonly studied non-pharmacological interventions (>10 trials). Although there are other widely used non-pharmacological interventions

such as acupuncture, its comparison group was mainly sham treatment, so it was not possible to build a network. Thirdly, the only head-to-head comparison was between exercise and balneotherapy. Therefore, we mainly used indirect comparison in our analysis. Including more head-to-head comparison trials could have increased the precision of ES (Cipriani et al., 2013). Therefore, results should be interpreted in caution. Fourthly, intervention groups were somewhat heterogeneous. For example, the balneotherapy group included hydrotherapy, spa therapy or thalassotherapy. Similarly, psychological treatments included any psychological interventions such as CBT, mindfulness etc. Finally, the sensitivity analysis was only based on the frequentist approach, as there were not enough studies that included different study characteristics, such as patient mean age, or that included more than 50 participants. These study characteristics could affect the results and overestimate ESs.

4.4.4 Conclusion and future work

This Bayesian NMA compared widely used non-pharmacological interventions for FM. Several non-pharmacological interventions are beneficial for FM. However, the effect size varies between interventions and outcomes. MDT was ranked first for pain, sleep and depression outcomes. Balneotherapy was the best treatment for FIQ, whereas exercise was the most efficacious intervention for fatigue. Psychological treatment was only effective for pain but not other outcomes. Exercise appears to be the most promising non-pharmacological intervention, as it was effective for all outcomes except sleep. The results of this study may be used to guide the

selection of the most effective non-pharmacological interventions according to the predominant symptom in individual patients.

Future research is warranted to address the previously mentioned caveats. High methodological quality RCTs with larger sample size are required. It is important to conduct these trials with different age groups, gender and ethnicity to allow determination of the generalisability of the results. More head-to-head comparisons between different non-pharmacological interventions are also necessary to find more precise results combining direct and indirect evidence, as in our study balneotherapy vs. exercise was the only head-to-head comparison.

Chapter 5 COMPARATIVE EFFICACY OF EXERCISE TYPES FOR FIBROMYALGIA: A SYSTEMATIC REVIEW WITH NETWORK META ANALYSIS

5.1 Introduction

This chapter evaluates the relative efficacy of five exercise types (aerobic, flexibility, mind-body, mixed and strengthening exercises) in five outcomes of FM (FIQ, pain, fatigue, sleep and depression) using Bayesian NMA.

5.2 Methods

This NMA differs from that described in the preceding chapter in that the intervention group was limited to different exercise types. The literature search and analysis methodology was otherwise identical.

Interventions:

Aerobic, flexibility, mind-body, mixed and strengthening exercise

Comparators:

The comparison group was extended to include another exercise type (e.g. aerobic versus flexibility).

5.3 Results

5.3.1 Study characteristics

Of 187 articles retrieved from the literature search, 47 were included in this NMA. Nearly half of the articles (44.7%) were published after 2010 and all were conducted in European and North and South American countries. Two studies (4.3%) were in Spanish and the data from those studies were extracted by the first reviewer (BK). The remaining 45 articles were in English.

While 33 studies (70.2%) used non-commercial funding, the funding source for the remaining 14 studies (29.8%) was unclear.

Participants were recruited from a hospital setting in 38.8% of studies, whereas 34% of studies identified participants from community settings such as community groups, newspapers or leaflets. In addition, 19.2% of studies found participants from both hospital and community settings. However, 8.5% of studies did not report where they recruited participants. Table 5-1 presents further details of study characteristics.

Table 5-1. Summary of study characteristics for the NMA of exercise types

Summary of study characteristics eligible for NMA	Total (n=47)
Study characteristics	
Publication year	**No. of trials (%)**
1980-1989	1 (2.1)
1990-1999	3 (6.4)
2000-2009	22 (46.8)
2010-onwards	21 (44.7)
Study location	
Europe	27 (57.5)
North America	16 (34)
South America	4 (8.5)
Language	
English	45 (95.7)
Spanish	2 (4.3)
Source of funding	
Non-commercial	33 (70.2)
Unclear	14 (29.8)
Blinding	
Participant and assessor blinded	4 (5.2)
Un-blinded	72 (93.5)
Unclear	1 (1.3)
Setting	
Hospital-based	18 (38.3)
Community-based	16 (34)
Mixed	9 (19.2)
Unclear	4 (8.5)
Diagnostic procedure	
ACR 1990	31 (66)
ACR 2010	2 (4.3)
Physician diagnosis	1 (2.1)
ACR 1990 and ACR 2010	4 (8.5)
ACR 1990 and physician diagnosis	6 (12.8)
Smythe's criteria	1 (2.1)
ACR 1990 and ACR 2010 and ACR 2016	1 (2.1)
Unclear	1 (2.1)
Way of delivery	
Individual	14 (29.8)
Group	29 (61.7)
Mixed	1 (2.1)
Unclear	3 (6.4)

ACR: American College of Rheumatology

5.3.2 Intervention characteristics

Of 187 studies meeting inclusion criteria for both CMA and NMA in the previous chapters, 47 studies (n = 3,271 participants) assessed exercise types including aerobic, flexibility, mind-body, mixed and strengthening (Table 5-2). Overall, 96.1% of the participants were women with a median age of 50.8 years ranging from 37 to 59.3 years. Median BMI was 28 kg/m^2.

Aerobic exercise was the most commonly studied type with 21 studies (n = 1,136 participants). Nearly all participants were women (97.5%). Median age was 46 years and median BMI was 29.3 kg/m^2. Table 5-2 presents intervention characteristics of the studies evaluating different types of exercise.

Table 5-2. Intervention characteristics of studies examining different exercise types versus control group (usual care or another exercise type)

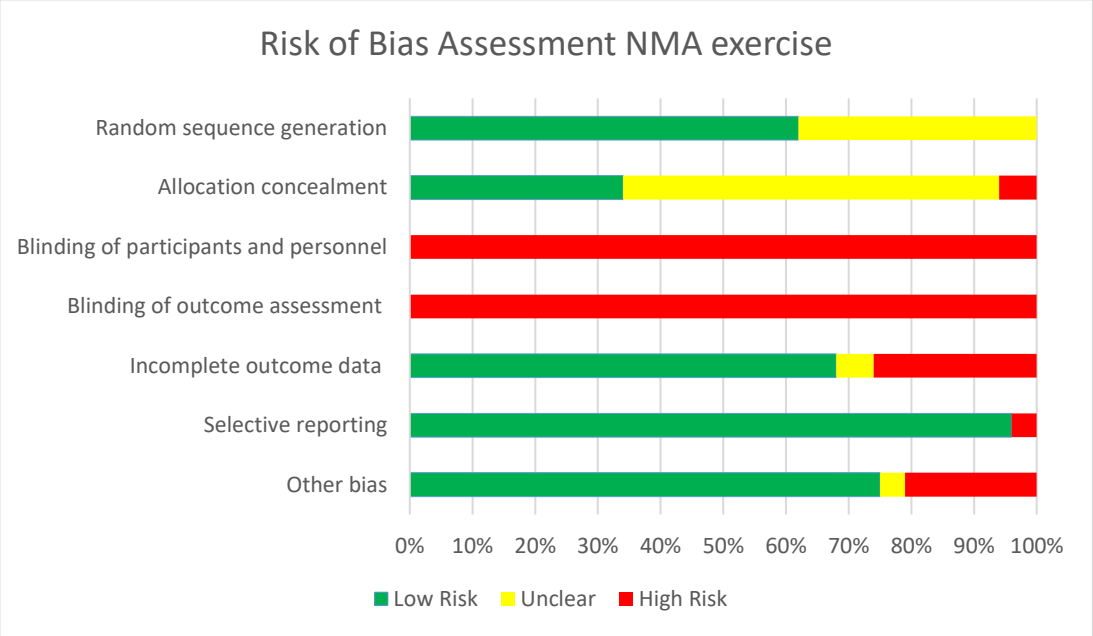
Interventions	No. of trials	No. of patients	No. of women (%)	Age, y	BMI
Aerobic	21	1,136	1,107 (97.5)	46 (39-58)	29.3 (25.6-31.4)
Flexibility	6	235	225 (95.7)	48.5 (44-55.3)	28 (28-28)
Mind-body	15	934	878 (94)	52.1 (44.4-57.7)	28.7 (25.1-30.1
Mixed	15	625	613 (98.1)	51.2 (42.8-59.3)	28 (23.8-30)
Strengthening	8	341	318 (93.2)	46.4 (37-50.8)	27.4 (26.2-29)
Total	47	3,271	3,141 (96.1)	50.8 (37-59.3)	28 (23.8-31.4)

Tx: treatment, no: number, y: year, BMI: body mass index

5.3.3 Risk of bias assessment

Table 5-3 demonstrates risk of bias assessment in the NMA for exercise types. While 62% of all studies reported an adequate randomisation procedure, it was unclear for the remaining 38% of studies. Allocation concealment was unclear for the majority of studies (60%). Due to the nature of the interventions and outcomes, blinding of participants and personnel or outcome assessors was not possible for any of the studies.

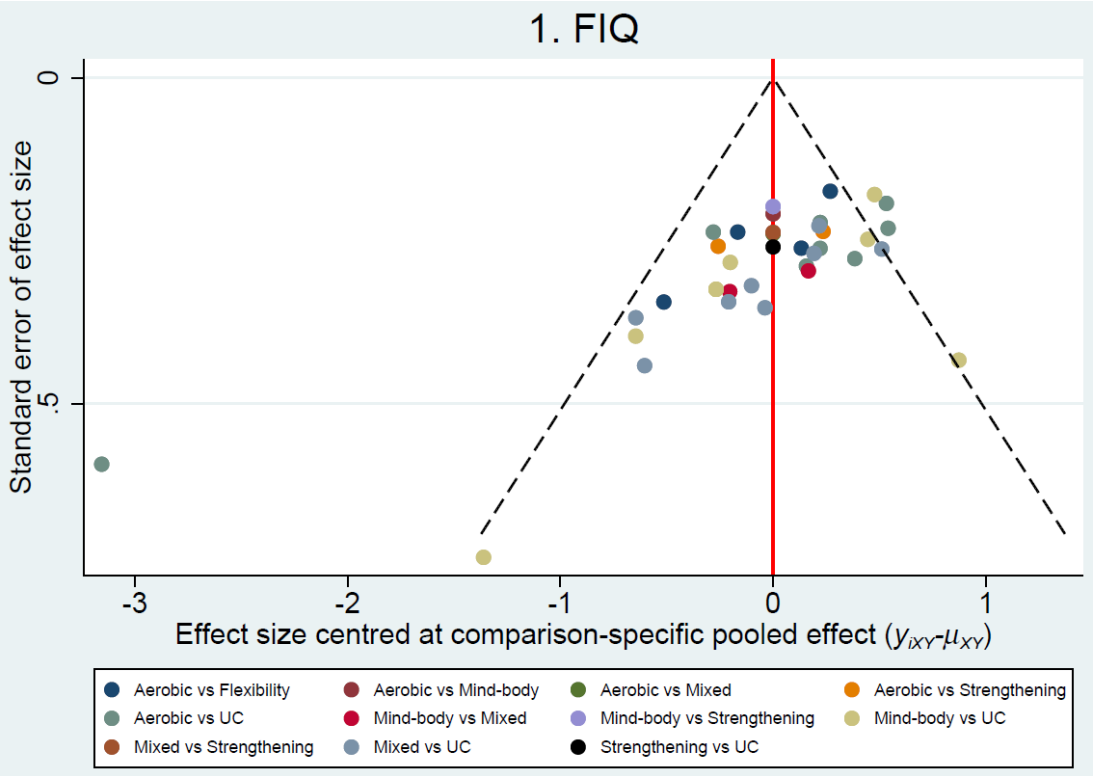
Table 5-3. Risk of bias assessment in the NMA for exercise types



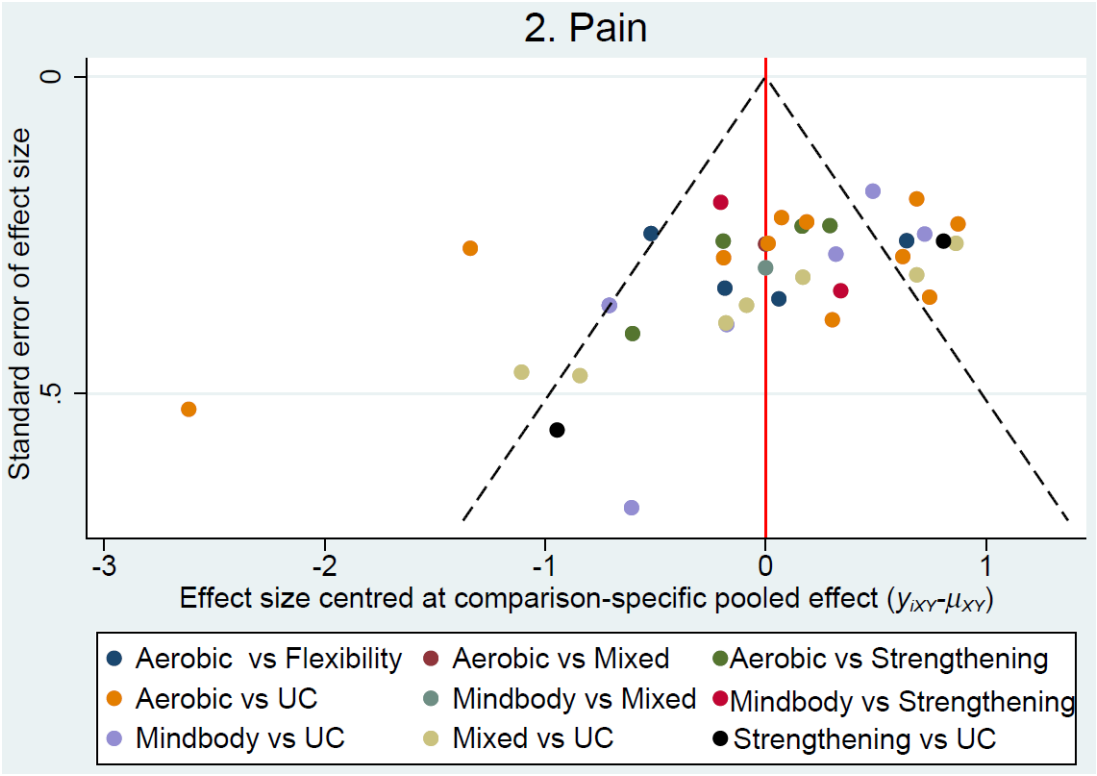
5.3.4 Publication bias

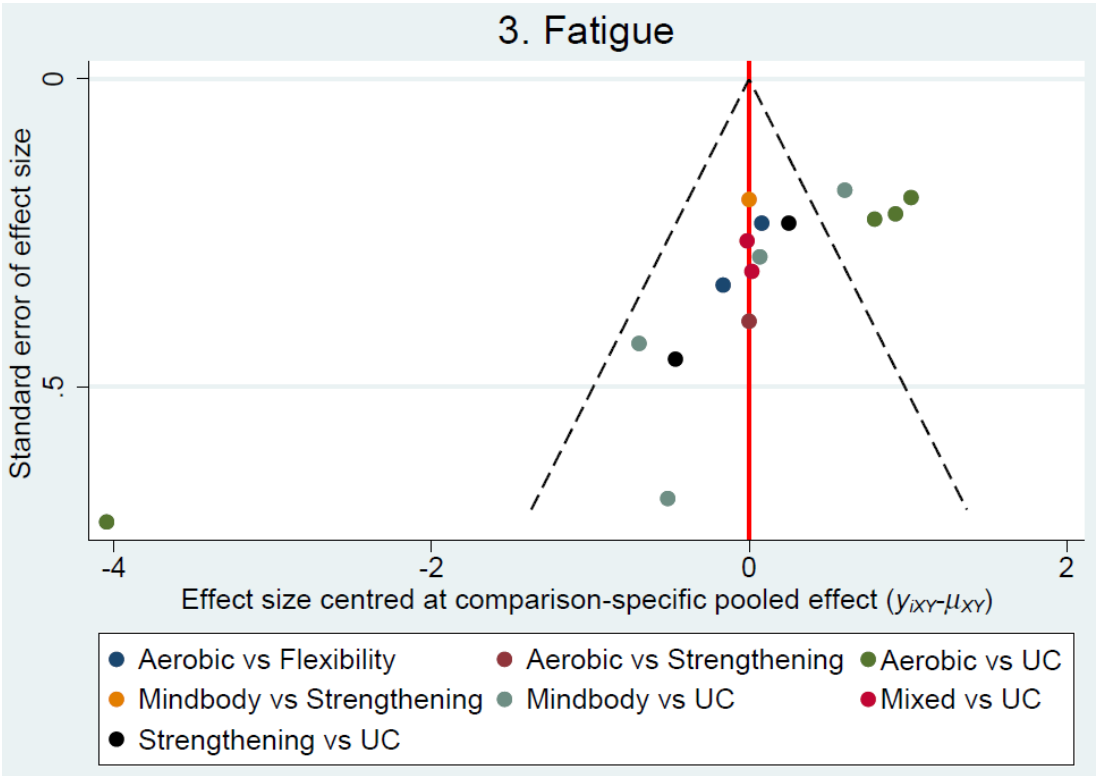
Figure 5-1 presents funnel plots for FIQ, pain, fatigue, sleep and depression outcomes. Overall, observed asymmetry in the funnel plots is indicative of a publication bias for all outcomes.

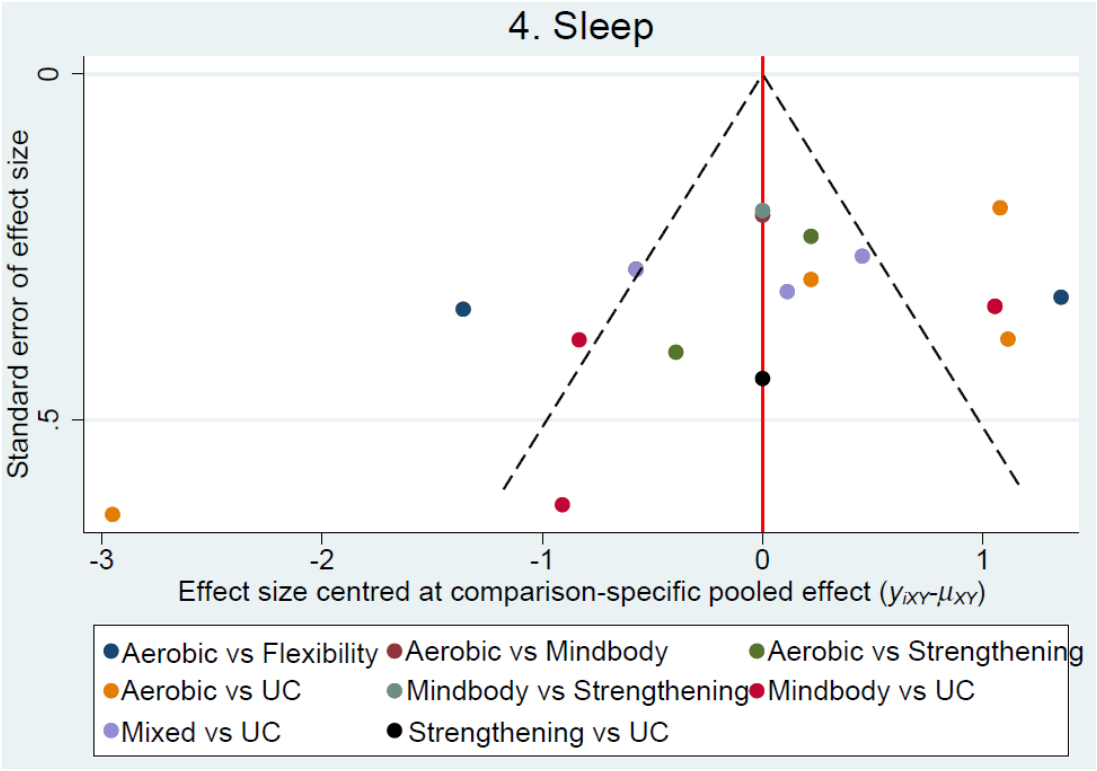
Figure 5-1. Funnel plots for the NMA of different exercise types versus control arm (another exercise type or usual care) for FIQ, pain, fatigue, sleep and depression outcomes

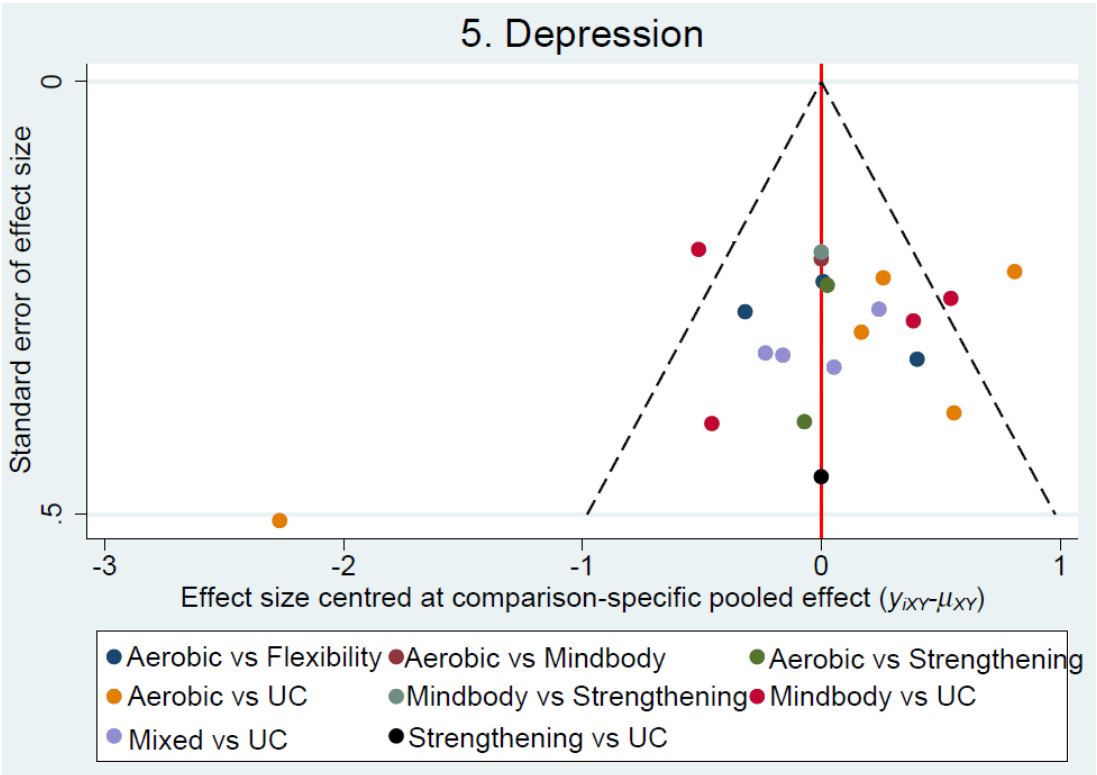


UC: Usual care


2. Pain
Standard error of effect size
0
.5
-3
-2
-1
0
1
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
Aerobic vs Flexibility
Aerobic vs Mixed
Aerobic vs Strengthening
Aerobic vs UC
Mindbody vs Mixed
Mindbody vs Strengthening
Mindbody vs UC
Mixed vs UC
Strengthening vs UC


3. Fatigue
Standard error of effect size
0
.5
-4
-2
0
2
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
Aerobic vs Flexibility
Aerobic vs Strengthening
Aerobic vs UC
Mindbody vs Strengthening
Mindbody vs UC
Mixed vs UC
Strengthening vs UC

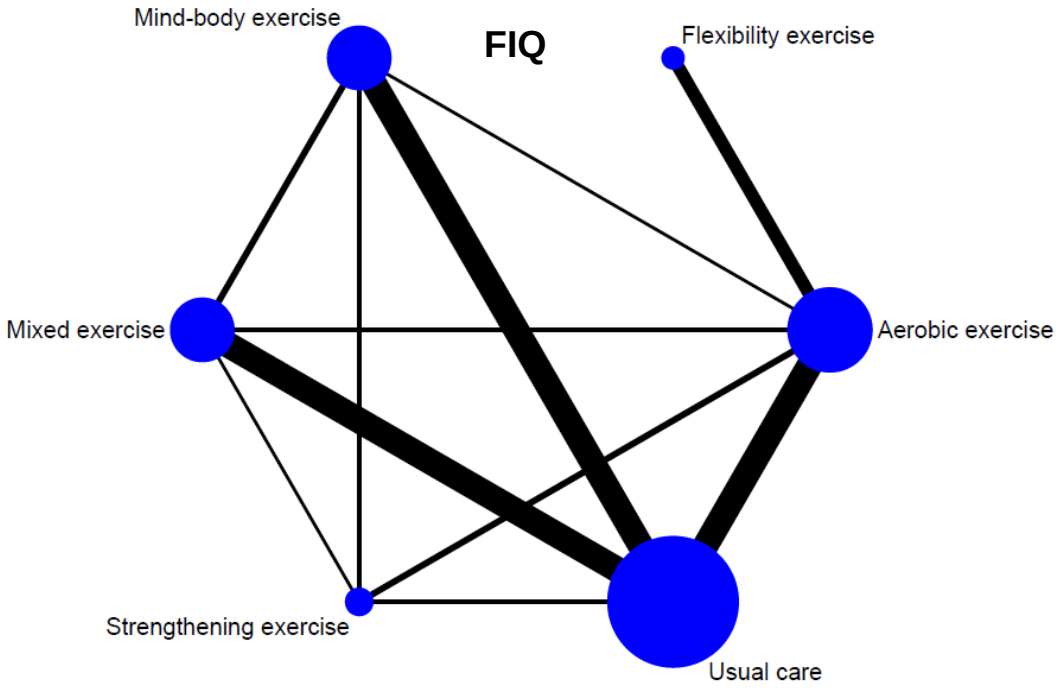

4. Sleep
Standard error of effect size
0
.5
-3
-2
-1
0
1
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
Aerobic vs Flexibility
Aerobic vs Mindbody
Aerobic vs Strengthening
Aerobic vs UC
Mindbody vs Strengthening
Mindbody vs UC
Mixed vs UC
Strengthening vs UC


5. Depression
Standard error of effect size
0
.5
-3
-2
-1
0
1
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
Aerobic vs Flexibility
Aerobic vs Mindbody
Aerobic vs Strengthening
Aerobic vs UC
Mindbody vs Strengthening
Mindbody vs UC
Mixed vs UC
Strengthening vs UC

5.3.5 Network map

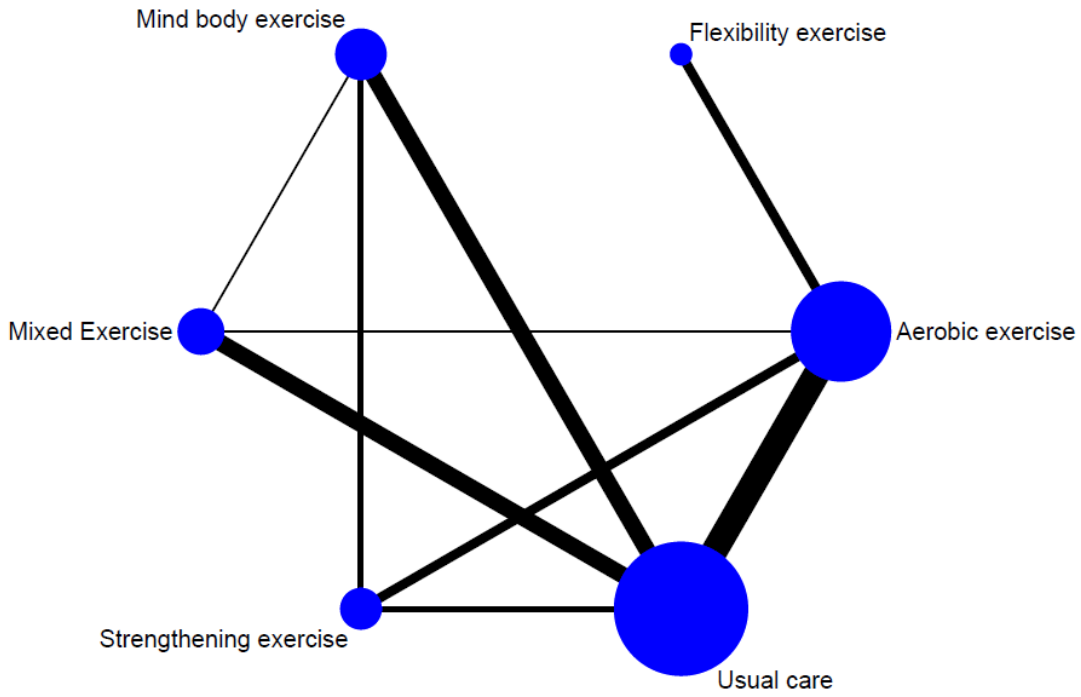
Figure 5-2 demonstrates the generated network maps among exercise types for all outcomes. The nodes representing an exercise type were well connected for FIQ and pain outcomes. Network maps for fatigue, sleep and depression showed a similar pattern. Usual care was the most commonly used comparator in the included trials.

Figure 5-2. Network maps: FIQ, pain, fatigue, sleep and depression



Aerobic versus usual care: 8 studies (581 participants)
Mind-body versus usual care: 8 studies (389 participants)
Mixed versus usual care: 8 studies (369 participants)
Strengthening versus usual care: 1 study (60 participants)
Aerobic versus flexibility: 4 studies (308 participants)
Aerobic versus mind-body: 1 study (111 participants)
Aerobic versus mixed: 1 study (70 participants)
Aerobic versus strengthening: 2 studies (133 participants)
Mind-body versus mixed: 2 studies (87 participants)
Mind-body versus strengthening: 1 study (105 participants)
Mixed vs strengthening: 1 study (73 participants)

Pain



Aerobic versus usual care: 11 studies (735 participants)

Mind-body versus usual care: 7 studies (367 participants)

Mixed versus usual care: 7 studies (258 participants)

Strengthening versus usual care: 2 studies (81 participants)

Aerobic versus flexibility: 4 studies (209 participants)

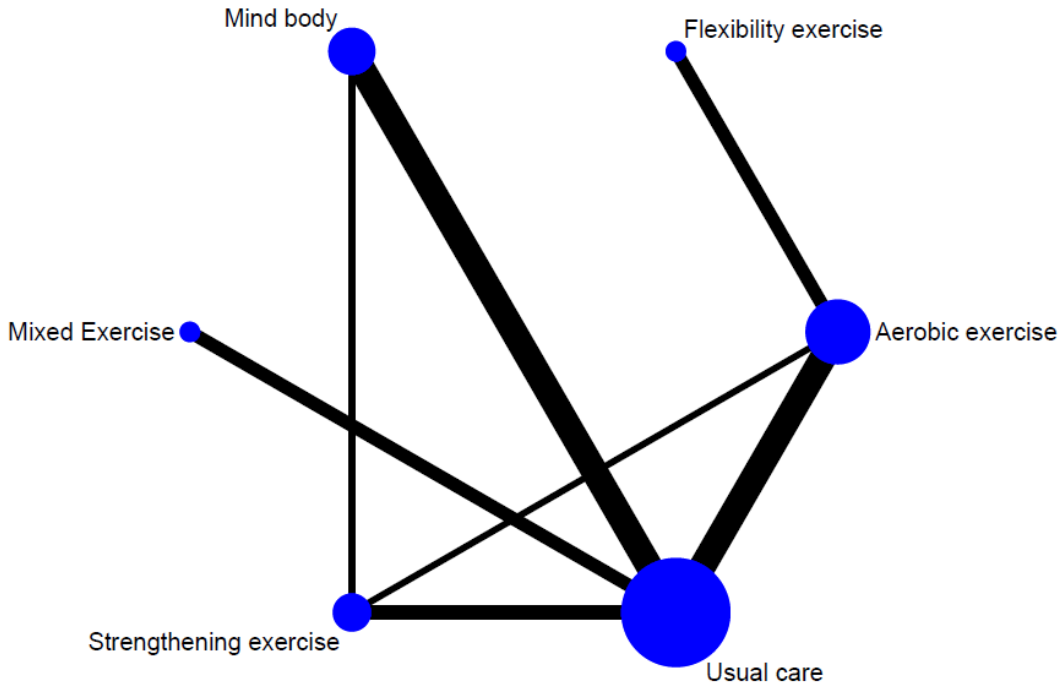
Aerobic versus mixed: 1 study (61 participants)

Aerobic versus strengthening: 4 studies (231 participants)

Mind-body versus mixed: 1 study (49 participants)

Mind-body versus strengthening: 2 studies (145 participants)

Fatigue



Aerobic versus usual care: 4 studies (349 participants)

Mind-body versus usual care: 4 studies (220 participants)

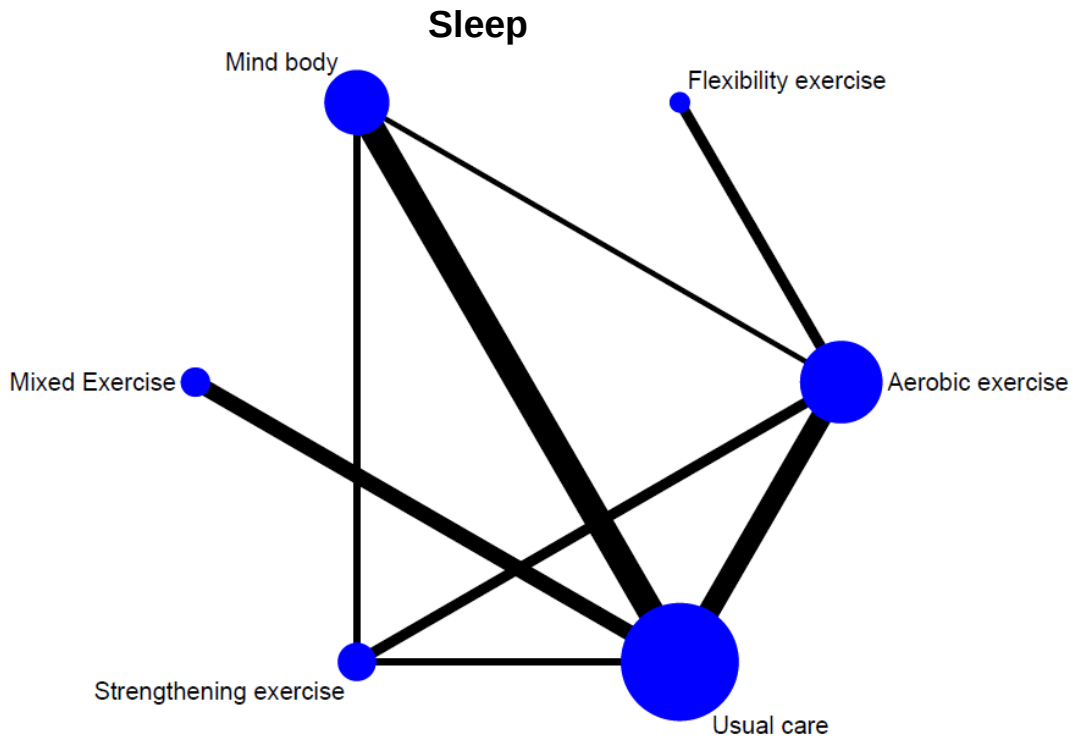
Mixed versus usual care: 2 studies (99 participants)

Strengthening versus usual care: 2 studies (94 participants)

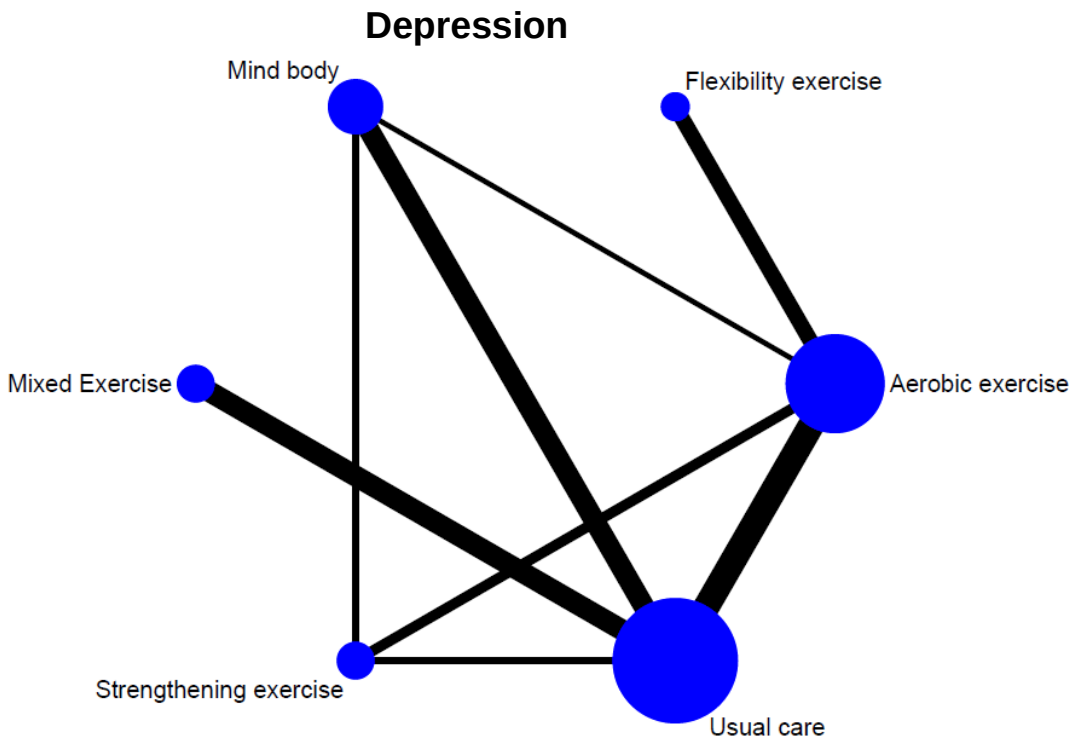
Aerobic versus flexibility: 2 studies (115 participants)

Aerobic versus strengthening: 1 study (26 participants)

Mind-body versus strengthening: 1 study (105 participants)



Aerobic versus usual care:	4 studies (259 participants)
Mind-body versus usual care:	5 studies (177 participants)
Mixed versus usual care:	3 studies (57 participants)
Strengthening vs usual care:	1 study (21 participants)
Aerobic versus flexibility:	2 study (115 participants)
Aerobic versus mind-body:	1 study (111 participants)
Aerobic versus strengthening:	2 studies (99 participants)
Mind-body versus strengthening:	1 study (105 participants)



Aerobic versus usual care:	5 studies (277 participants)
Mind-body versus usual care:	4 studies (272 participants)
Mixed versus usual care:	4 studies (178 participants)
Strengthening vs usual care:	1 study (21 participants)
Aerobic versus flexibility:	3 studies (175 participants)
Aerobic versus mind-body:	1 study (111 participants)
Aerobic versus strengthening:	2 studies (99 participants)
Mind-body versus strengthening:	1 study (105 participants)

5.3.6 Assessing convergence

Two chains, 5,000 burn-ins with 10,000 iterations and an interval of 1 (burn in 5000, iteration 10000 thin 1) were used. Trace and density plots (Figure 5-3) as well as the Gelman-Rubin-Brooks plot suggest that the data converged well.

Figure 5-3. Trace and density plots showing the results of MCMC simulation for FIQ

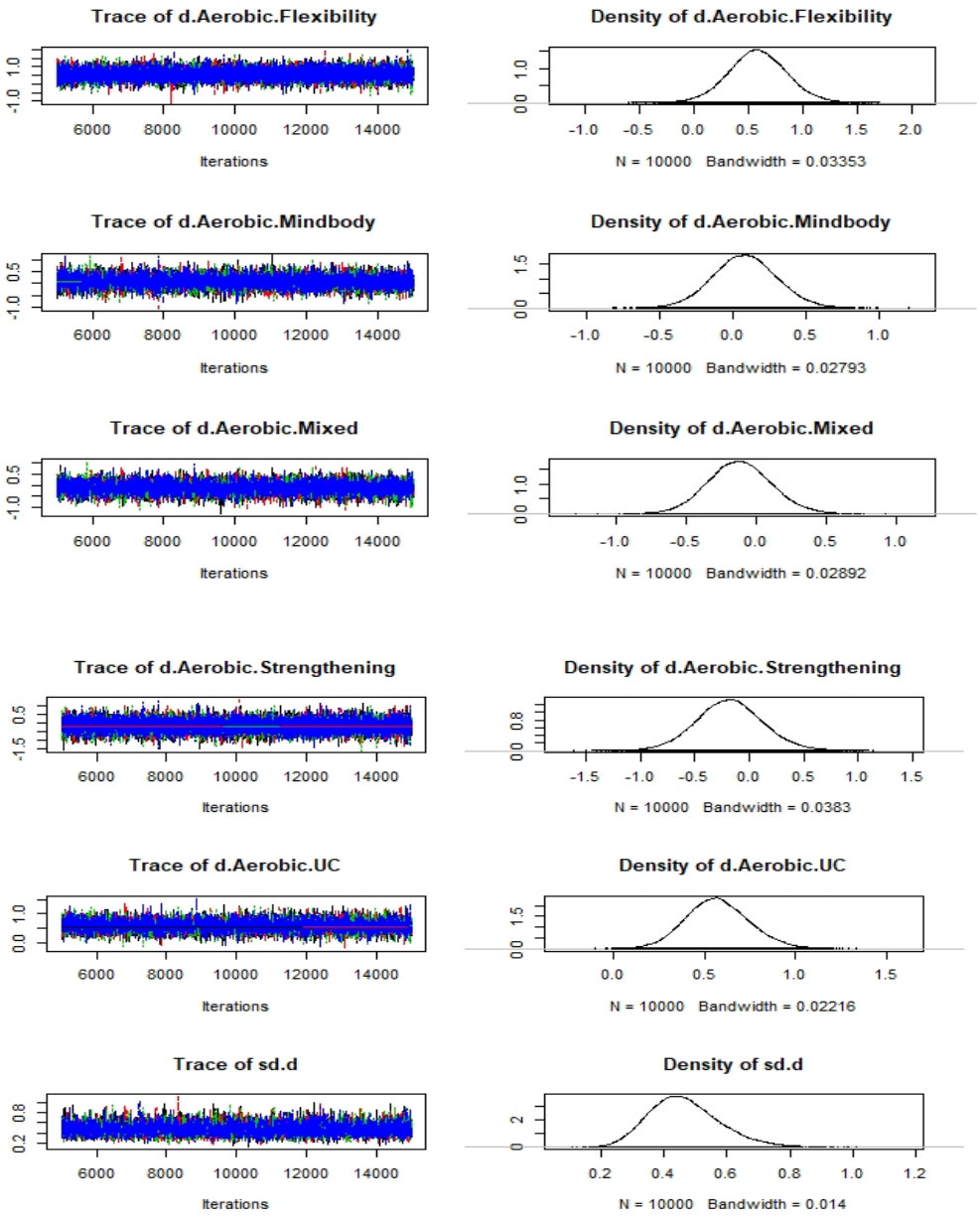
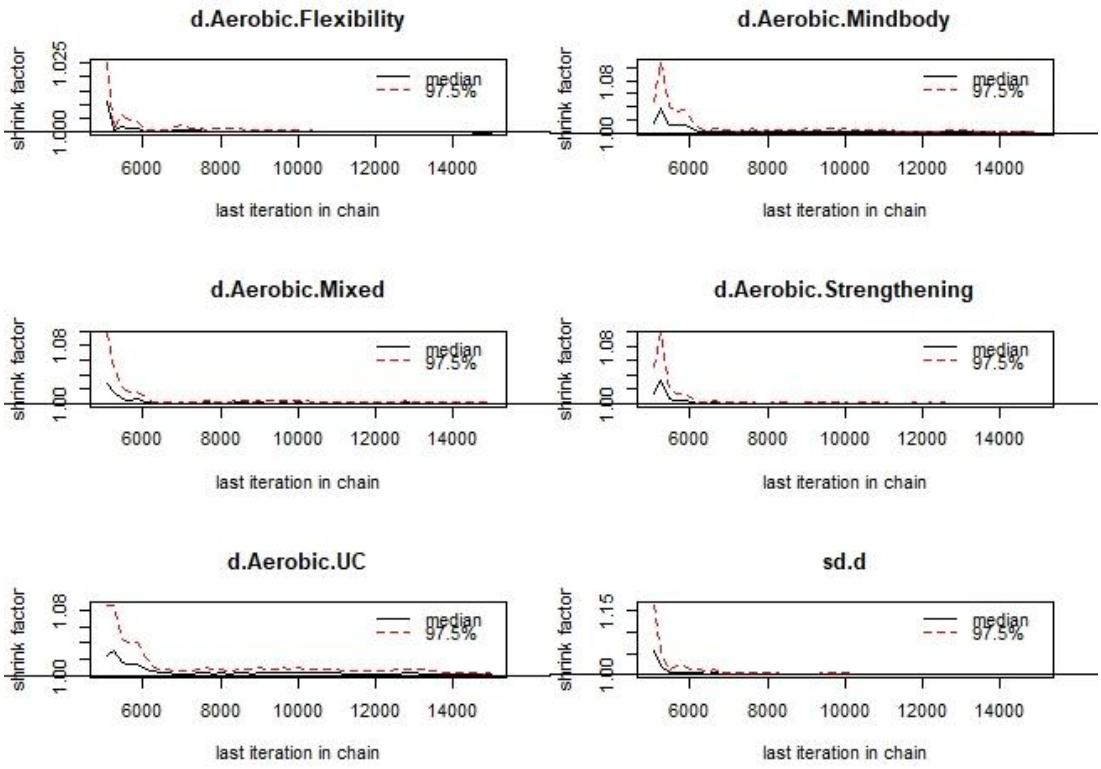


Figure 5-4. Gelman-Rubin-Brooks plot for FIQ

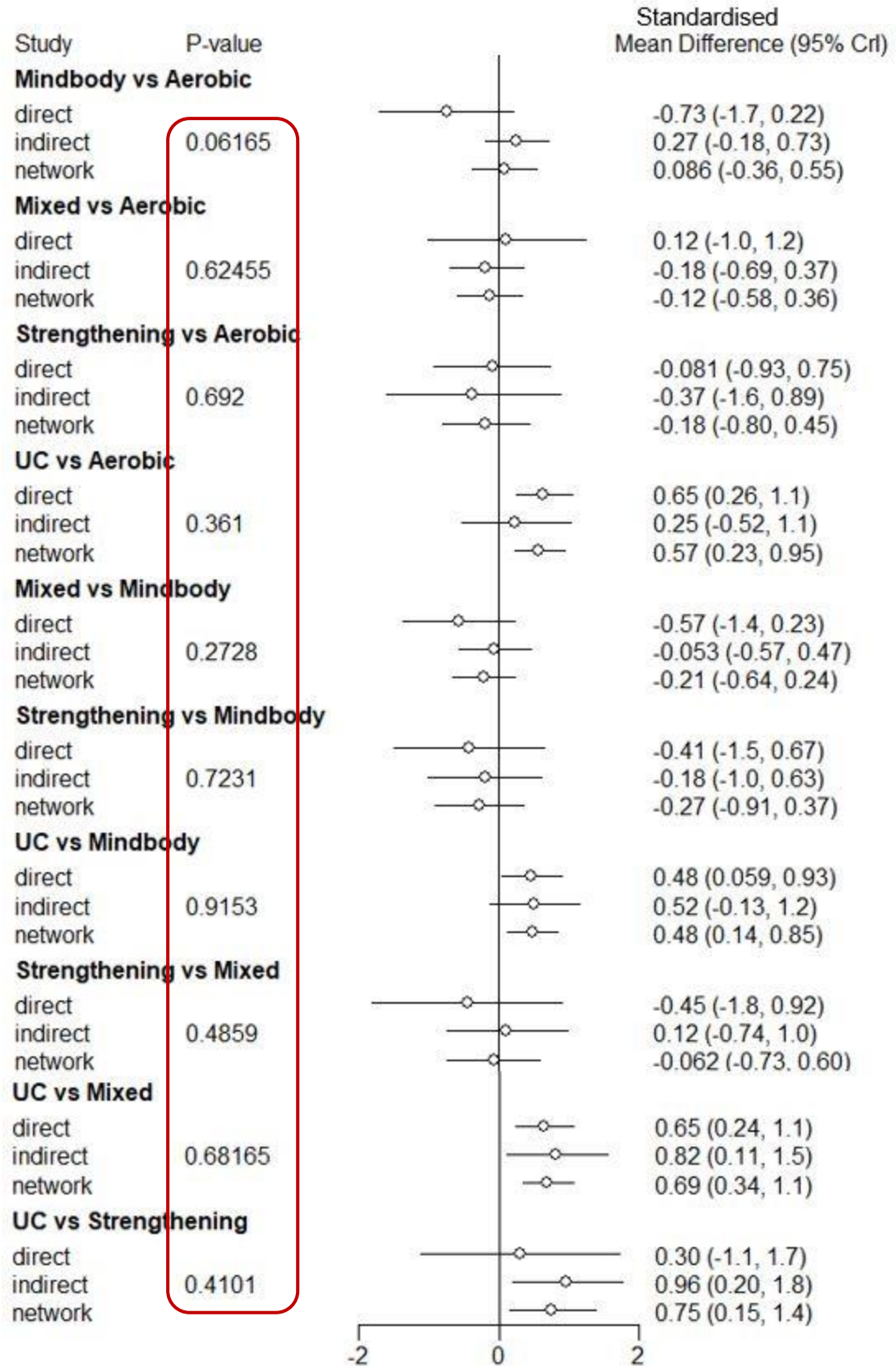


Appendix 8 illustrates MCMC simulations and Gelman-Rubin-Brooks plots for the other outcomes.

5.3.7 Assessing inconsistency

Evidence from direct comparisons, indirect comparisons and both through the networks were evaluated using the node-split method and a p value greater than 0.05 indicated consistency. Figure 5-5 shows node-splitting analysis of inconsistency for FIQ. Inconsistency test for other outcomes are shown in Appendix 9.

Figure 5-5. Node-splitting analysis of inconsistency for FIQ



UC: Usual care, CrI: Credible interval, vs: versus

5.3.8 Relative efficacy of exercise types in different outcomes

5.3.8.1 FIQ

There were 37 studies with 2,286 participants that evaluated the effect of five different exercise types on FIQ. All exercise types (strengthening (-0.76; 95% CrI -1.39, -0.15), mixed (-0.69; 95% CrI -1.06, -0.34), aerobic (-0.57; 95% CrI -0.95, -0.24) and mind-body (-0.49; 95% CrI -0.85, -0.15)), apart from flexibility (0.00; 95% CrI -0.67, 0.64), showed a significant improvement relative to usual care on FIQ. While aerobic exercise (-0.58; 95% CrI -1.12, -0.04) was significantly better than flexibility exercise, other exercise types did not significantly differ from each other (Figure 5-6).

Figure 5-6. Relative efficacy of exercise types on FIQ

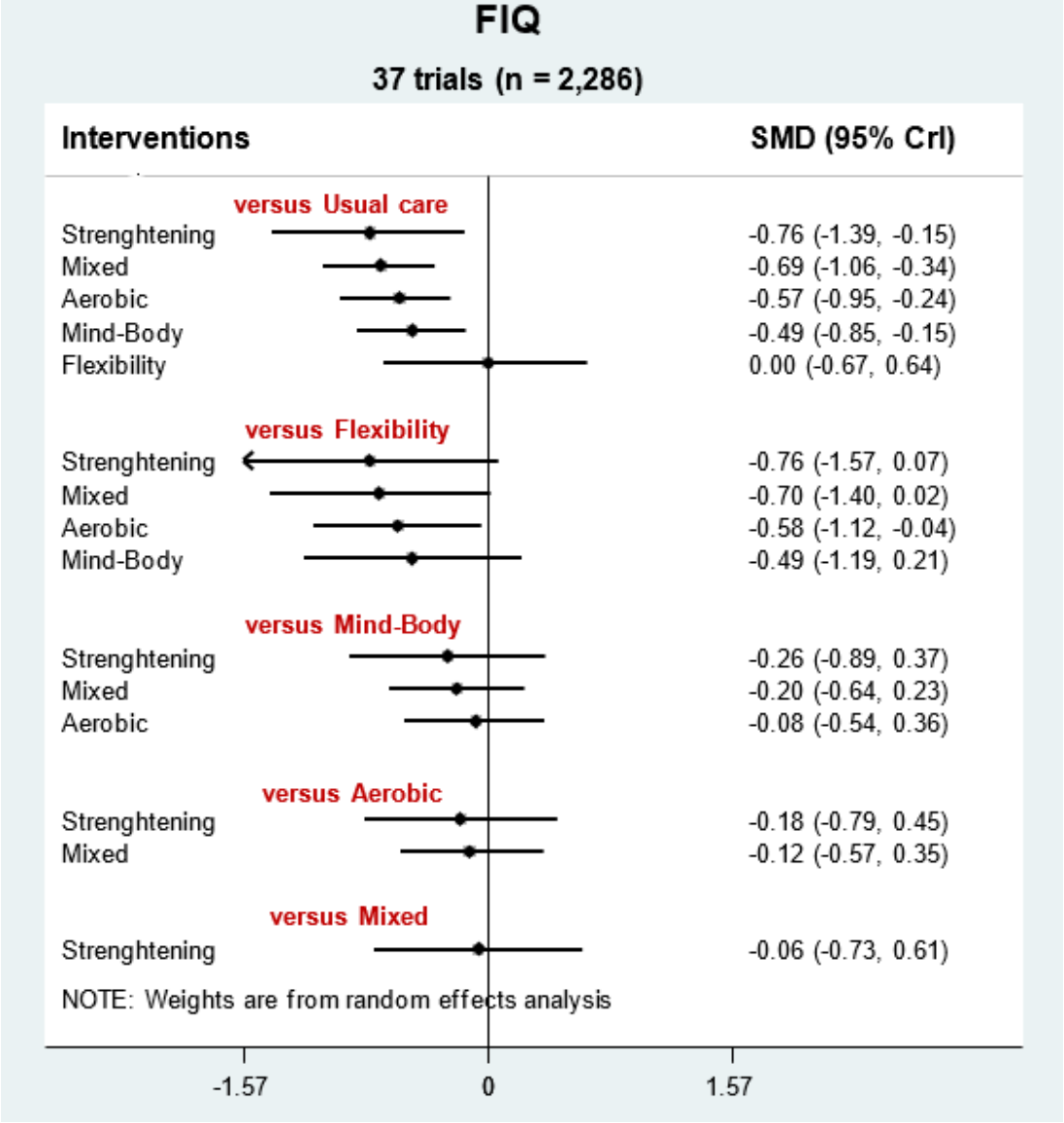


Table 5-4 presents the SUCRA graph and values. Based on the SUCRA, strengthening exercise (0.81) would appear to be the best exercise type for improving FIQ in people with FM. Following this, mixed (0.79) was second best, aerobic (0.64) was third best, mind-body (0.53) was fourth best and flexibility (0.13) was fifth in rank.

Table 5-4. SUCRA values for FIQ in studies of different exercise types

Interventions	SUCRA
Strengthening	0.81
Mixed	0.79
Aerobic	0.64
Mind-body	0.53
Flexibility	0.13
Usual care	0.11

5.3.8.2 Pain

Pain outcome was assessed in 39 trials with 2,136 participants. All exercise types (strengthening (-0.94; 95% CrI -1.58, -0.30), mixed (-0.78; 95% CrI -1.31, -0.25), aerobic (-0.72; 95% CrI -1.16, -0.32) and mind-body (-0.63; 95% CrI -1.15, -0.11)), apart from flexibility (-0.13; 95% CrI -1.02, 0.73), were significantly better than usual care. When different exercises were compared with each other, none showed any superiority over the others (Figure 5-7).

Figure 5-7. Relative efficacy of exercise types on pain

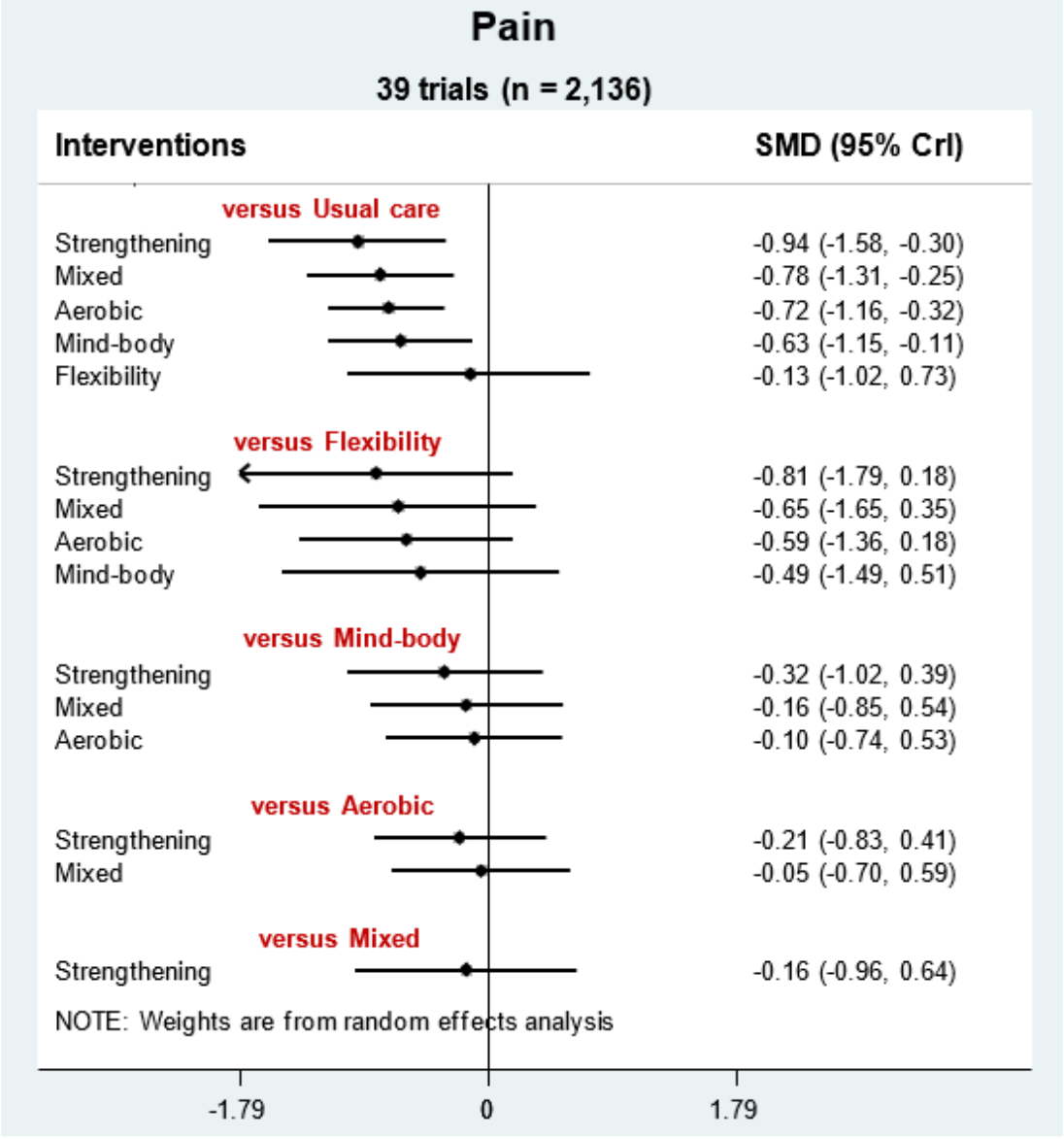


Table 5-5 illustrates SUCRA graph and values for pain outcome. Strengthening was ranked as the best exercise type for pain with a SUCRA score of 0.83. After strengthening, mixed (0.70), aerobic (0.65), mind-body (0.54) and flexibility (0.20) were ranked second, third, fourth and fifth, respectively.

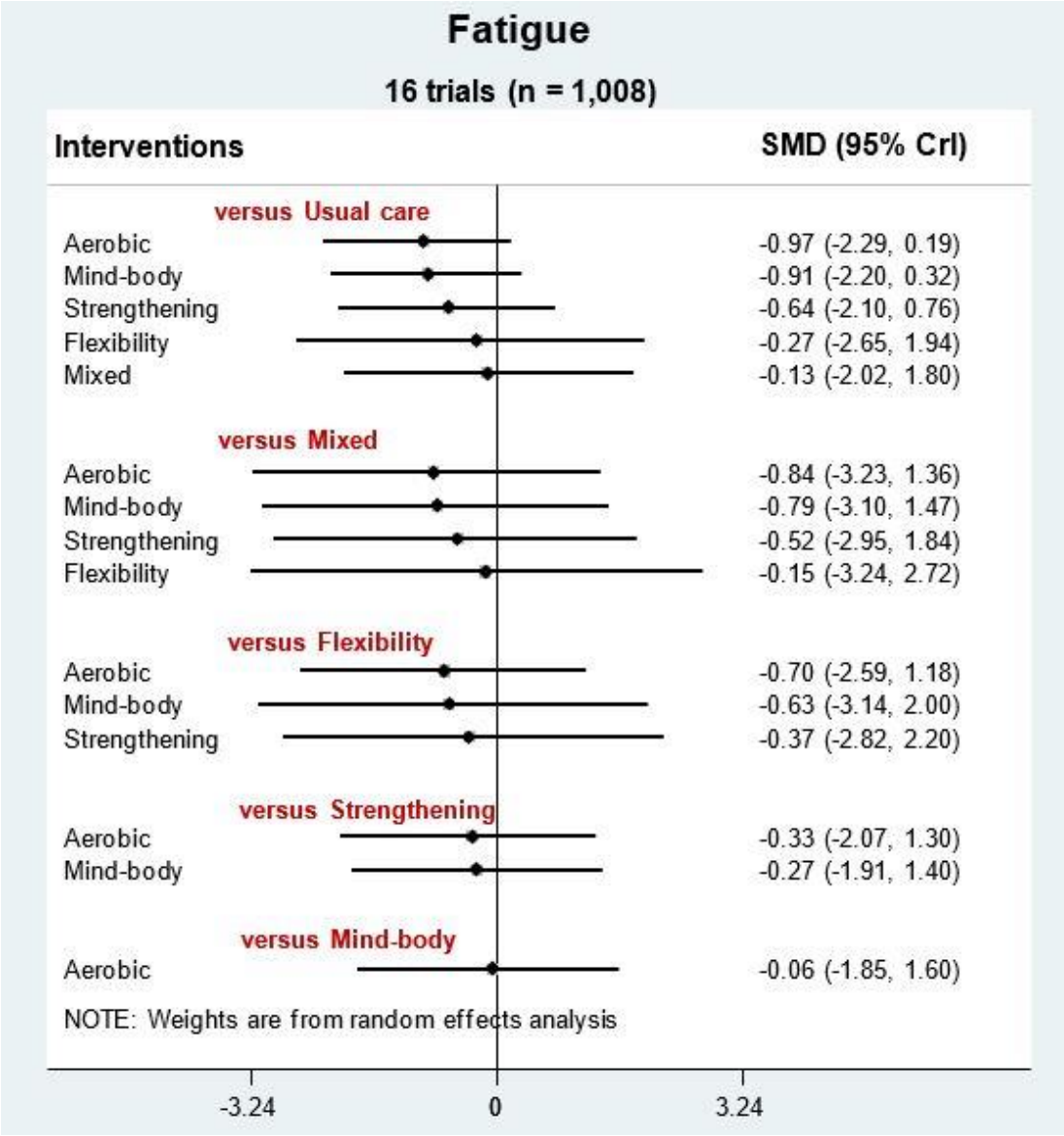
Table 5-5. SUCRA values for pain in studies of different exercise types

Interventions	SUCRA
Strengthening	0.83
Mixed	0.70
Aerobic	0.65
Mind-body	0.54
Flexibility	0.20
Usual care	0.11

5.3.8.3 Fatigue

Based on the analysis of 16 trials (n = 1,008 participants) that evaluated fatigue, none of the exercise types showed significant improvements relative to usual care. Moreover, there were no significant differences between the exercise types (Figure 5-8).

Figure 5-8. Relative efficacy of exercise types on fatigue



Aerobic exercise was observed to be the best exercise type for fatigue with a SUCRA value of 0.75. Table 5-6 illustrate SUCRA graph and values for other exercise types on fatigue outcome.

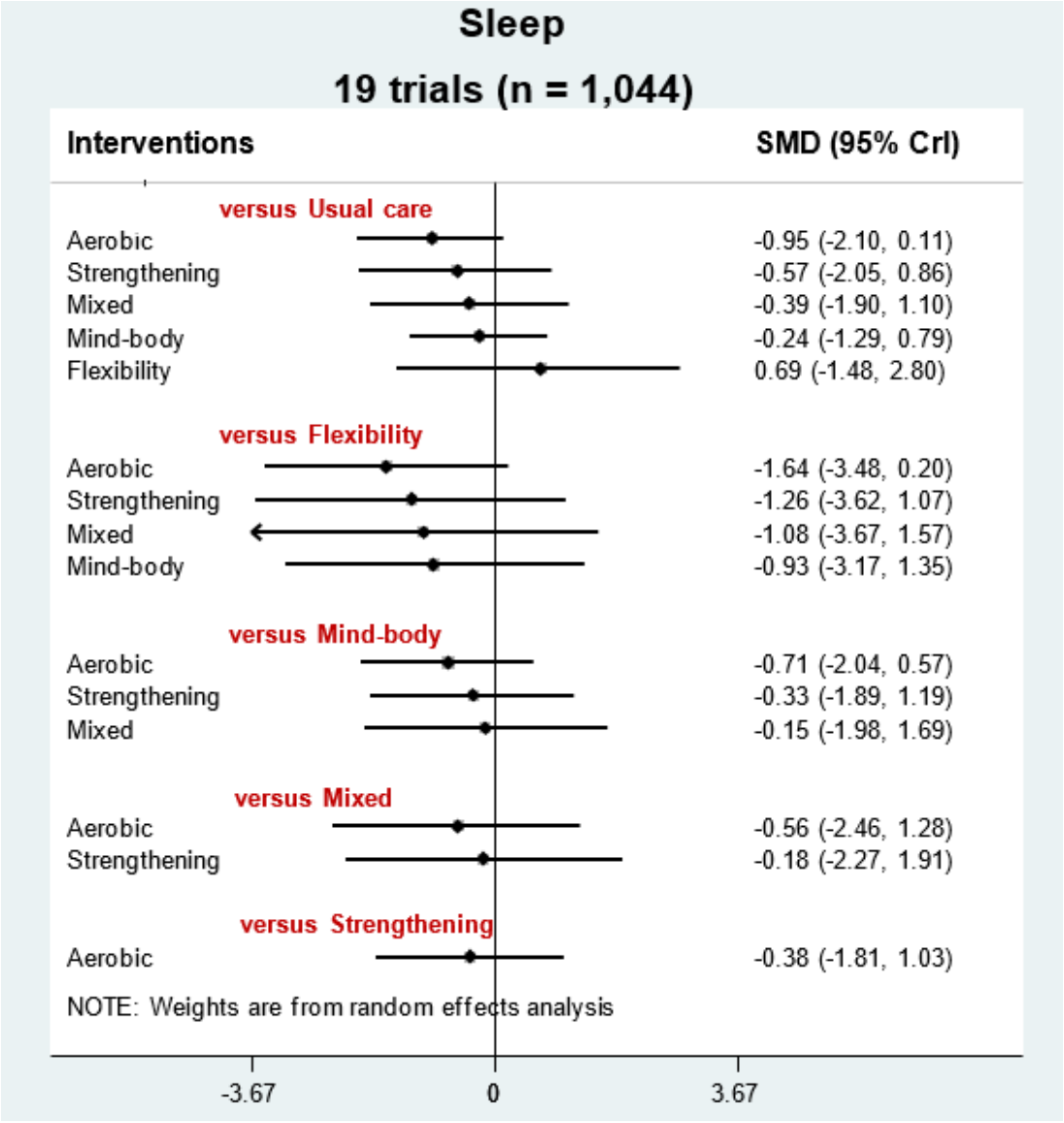
Table 5-6. SUCRA values for fatigue in studies of different exercise types

Interventions	SUCRA
Aerobic	0.75
Mind-body	0.71
Strengthening	0.57
Flexibility	0.41
Mixed	0.35
Usual care	0.22

5.3.8.4 Sleep

Sleep outcome was investigated in 19 trials (n = 1,044 participants) and it was found that none of the exercise types could significantly improve sleep more than usual care. There were no significant differences between the exercise types (Figure 5-9).

Figure 5-9. Relative efficacy of exercise types on sleep



Aerobic exercise had the highest SUCRA value (0.85), indicating that it may be the best exercise type for sleep. Table 5-7 shows SUCRA values for other exercise types on sleep outcome.

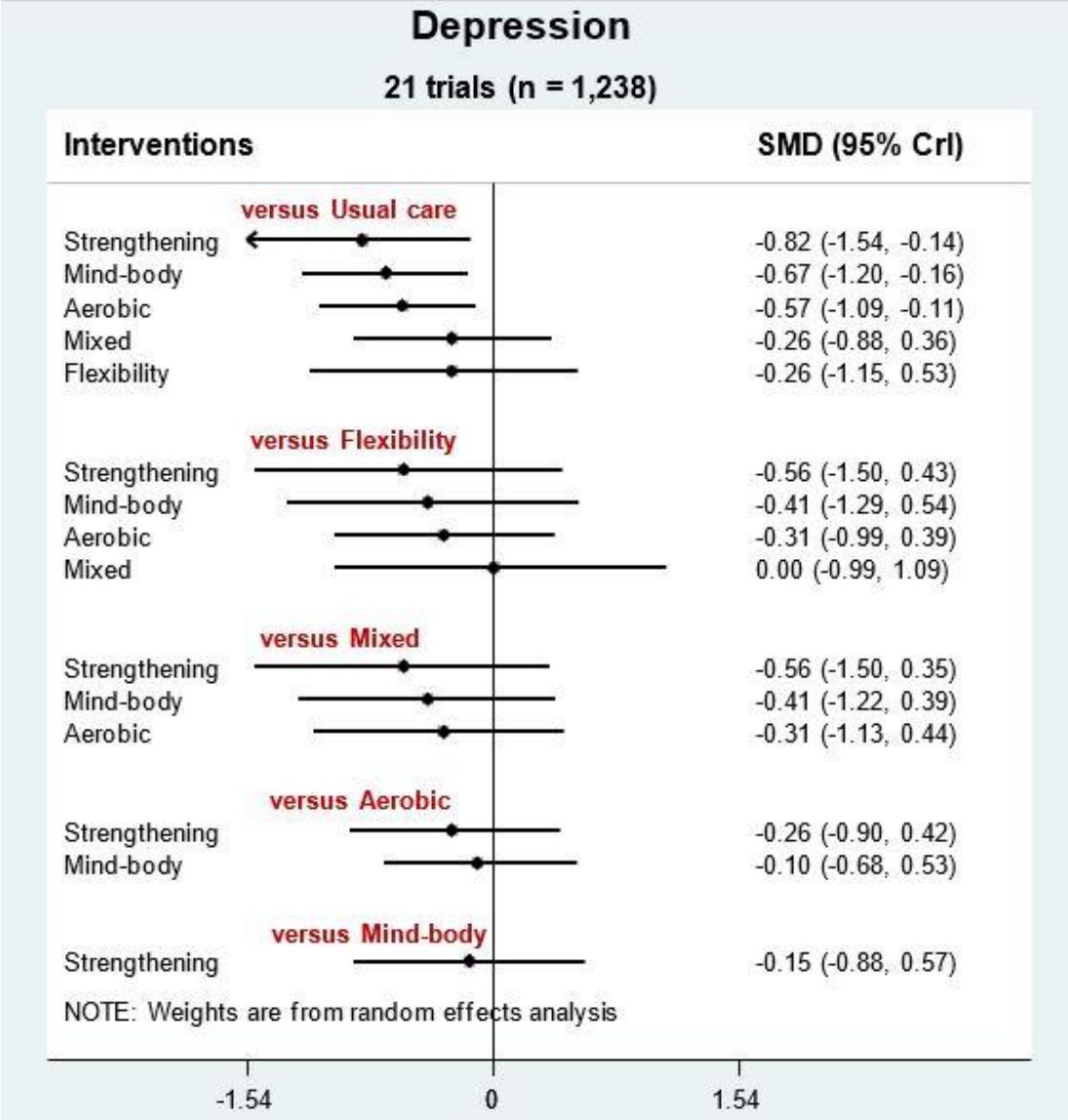
Table 5-7. SUCRA values for sleep in studies of different exercise types

Interventions	SUCRA
Aerobic	0.85
Strengthening	0.64
Mixed	0.56
Mind-body	0.48
Usual care	0.32
Flexibility	0.16

5.3.8.5 Depression

There were 21 trials comprising 1,238 participants that evaluated the effect of the five different exercise types on depression. Strengthening (-0.82; 95% CrI -1.54, -0.14), mind body (-0.67; 95% CrI -1.20, -0.16) and aerobic exercises (-0.57; 95% CrI -1.09, -0.11) significantly improved depression in patients with FM. However, mixed (-0.26; 95% CrI -0.88, 0.36) and flexibility exercises (-0.26; 95% CrI -1.15, 0.53) did not show any significant improvement. Also, there was no significant difference between strengthening, mind body and aerobic exercise (Figure 5-10).

Figure 5-10. Relative efficacy of exercise types on depression



Strengthening exercise (0.85) may be the most effective exercise type for depression in patients with FM. Table 5-8 show SUCRA graph and values for other exercise types on depression outcome.

Table 5-8. SUCRA values for depression in studies of different exercise types

Interventions	SUCRA
Strengthening	0.85
Mind-body	0.73
Aerobic	0.64
Mixed	0.35
Flexibility	0.34
Usual care	0.09

5.3.9 Sensitivity analysis

Sensitivity analysis was conducted based on the Bayesian and frequentist analyses of the exercise types. Table 5-9 presents the results of Bayesian and frequentist approaches for the five exercise types (aerobic, flexibility, mind-body, mixed and strengthening exercises) on five outcomes – FIQ, pain, fatigue, sleep and depression. The results of these two approaches were all in agreement.

Table 5-9. Bayesian and frequentist NMAs of exercise types compared to usual care

Outcomes (Interventions)	Bayesian	Frequentist
FIQ	**vs. usual care**	**vs. usual care**
Aerobic	-0.57 (-0.95, -0.24)	-0.57 (-0.90, -0.23)
Flexibility	0.00 (-0.67, 0.64)	0.01 (-0.59, 0.61)
Mind-body	-0.49 (-0.85, -0.15)	-0.49 (-0.81, -0.16)
Mixed	-0.69 (-1.06, -0.34)	-0.69 (-1.01, -0.36)
Strengthening	-0.76 (-1.39, -0.15)	-0.75 (-1.30, -0.20)
Pain	**vs. usual care**	**vs. usual care**
Aerobic	-0.72 (-1.16, -0.32)	-0.72 (-1.12, -0.32)
Flexibility	-0.13 (-1.02, 0.73)	-0.13 (-0.96, 0.71)
Mind-body	-0.63 (-1.15, -0.11)	-0.62 (-1.11, -0.13)
Mixed	-0.78 (-1.31, -0.25)	-0.78 (-1.29, -0.28)
Strengthening	-0.94 (-1.58, -0.30)	-0.92 (-1.53, -0.31)
Fatigue	**vs. usual care**	**vs. usual care**
Aerobic	-0.97 (-2.29, 0.19)	-0.99 (-2.04, 0.07)
Flexibility	-0.27 (-2.65, 1.94)	-0.30 (-2.18, 1.59)
Mind-body	-0.91 (-2.20, 0.32)	-0.92 (-1.96, 0.13)
Mixed	-0.13 (-2.02, 1.80)	-0.13 (-1.69, 1.43)
Strengthening	-0.64 (-2.10, 0.76)	-0.65 (-1.83, 0.53)
Sleep	**vs. usual care**	**vs. usual care**
Aerobic	-0.95 (-2.10, 0.11)	-0.95 (-1.91, 0.00)
Flexibility	0.69 (-1.48, 2.80)	0.69 (-1.16, 2.54)
Mind-body	-0.24 (-1.29, 0.79)	-0.24 (-1.14, 0.66)
Mixed	-0.39 (-1.90, 1.10)	-0.39 (-1.68, 0.89)
Strengthening	-0.57 (-2.05, 0.86)	-0.57 (-1.84, 0.69)
Depression	**vs. usual care**	**vs. usual care**
Aerobic	-0.57 (-1.09, -0.11)	-0.57 (-1.01, -0.14)
Flexibility	-0.26 (-1.15, 0.53)	-0.27 (-1.01, 0.47)
Mind-body	-0.67 (-1.20, -0.16)	-0.67 (-1.12, -0.22)
Mixed	-0.26 (-0.88, 0.36)	-0.26 (-0.80, 0.28)
Strengthening	-0.82 (-1.54, -0.14)	-0.83 (-1.44, -0.21)

5.4 Discussion

5.4.1 Main findings and interpretations

This study is the first to provide direct comparison among five different exercise types, namely aerobic, flexibility, mind-body, mixed and strengthening exercises through a network meta-analysis. There were 47 studies (3,271 participants) included in the analysis. The main findings are: [1] all exercise types, except for flexibility, were significantly more efficacious than usual care on FIQ and pain, with strengthening being the most effective exercise type followed by mixed, aerobic, mind-body and flexibility exercise; [2] none of the exercise types showed significant improvements for fatigue or sleep - however, aerobic exercise was ranked as the best exercise type for fatigue and sleep, although there was no statistically significant difference of all types of exercises over usual care; and [3] flexibility exercise was the least effective exercise across all outcomes and failed to show significant improvements on any outcome.

These findings are consistent with previous research related to the efficacy of exercise types on FM (Bidonde et al., 2019; Busch et al., 2007; Busch et al., 2013; Kim et al., 2019; Nüesch et al., 2013). The only previous NMA in FM by Nüesch et al. (2013) reported that while aerobic exercise significantly improved health related quality of life (HRQoL), pain and fatigue, it was no better than usual care for sleep. Although their results corroborate our findings except for fatigue, their definition for the aerobic exercise was broader than ours. For example, they included endurance training or whole body vibration within the aerobic exercise group. One previous CMA

assessing the efficacy of aerobic exercise on FM included 13 articles (n = 839 participants) for HRQoL, pain, fatigue, stiffness and physical function (Bidonde et al., 2017). This also found clinically meaningful (15% improvement level) and significant improvements for HRQoL and pain. Our CMA results (Chapter 3) also demonstrated no significant benefits of aerobic exercise for fatigue.

Strengthening exercise was the most beneficial exercise type for FIQ, pain and depression. This is in line with the Cochrane SR conducted by Busch et al. (2013) which included five trials on strengthening exercise (versus usual care or another type of exercise). This SR found that strengthening exercise was more beneficial on FIQ and pain. However, they reported that aerobic exercise was better than strengthening on pain which is contrary to our findings. We found no significant differences between strengthening and aerobic exercise. This result may be explained by the fact that we performed a Bayesian NMA incorporating prior knowledge and present data between direct and indirect evidence. However, they included only one study and conducted a CMA using solely direct evidence.

Flexibility exercise did not show significant improvements for any outcome compared to any comparator. Even though there was no RCT comparing flexibility exercise versus usual care, NMA enabled us to calculate the ES of flexibility exercise versus usual care through indirect evidence. Kim et al. (2019) also reported no significant results of flexibility exercise on FIQ, pain and fatigue relative to different comparators such as aerobic, strengthening or mind-body exercises.

5.4.2 Strengths

This is the first NMA assessing the relative efficacy of different types of exercises for five different outcomes - disease specific QoL (FIQ), pain, fatigue, sleep and depression. The American College of Sports Medicine's (ACSM) recommendation for exercise classification was extended and mind-body exercise (e.g. tai chi, yoga) and mixed exercise (if the exercise program includes more than two exercise types) were added to aerobic, flexibility and strengthening. This enabled us to make the interventions group more homogeneous. An extensive literature search was run in seven different databases with no language or year restrictions. NMA allowed comparison between different types of exercise and facilitated more precise results by combining direct and indirect evidence. The convergence was good and there was no inconsistency between direct and indirect evidence. The Frequentist method was also performed to check the robustness of our results.

5.4.3 Limitations

This study has several limitations. Firstly, we were reliant on the author definition of exercise type or control group. Even though they specified an individual exercise type, the intervention may have included different exercises. Secondly, most of the studies had a small sample size ($n<50$). Thirdly, due to the nature of exercise, blinding is impossible and allocation concealment was unclear for most of them. Finally, visual asymmetry in funnel plots is suggestive of small study effects.

5.4.4 Conclusion and future work

This Bayesian NMA confirms that exercise has clear benefits for people with FM, though different types of exercise benefit different outcomes. The results of this study may be used to guide the selection of the most effective exercise types according to the predominant symptom in individual patients. Strengthening exercise may be the best for FIQ, pain and depression, whereas aerobic exercise may be the most effective exercise type for fatigue and sleep. Although there is a ranking of different exercise types, none were found to be superior over another apart from aerobic being superior to flexibility for FIQ. Further research is still required to confirm if the hierarchy observed is consistent across all patients with FM.

Chapter 6 NON-PHARMACOLOGICAL INTERVENTIONS FOR FM: DELPHI EXERCISE FOR RECOMMENDATIONS AND PRIORITISATION

6.1 Introduction

This chapter presents a Delphi exercise that was conducted to identify and prioritise non-pharmacological treatments for FM.

6.2 Methods

6.2.1 Identification of panel members

Potential panel members were selected from the author list of international FM guidelines (Burckhardt et al., 2005; Fitzcharles et al., 2013; Macfarlane et al., 2017), and prominent clinicians and academics identified through the literature review. People were included if they met the following criteria:

- A health care professional (rheumatologist, general practitioner (GP), physiotherapist, nurse, psychologist or occupational therapist) of any nationality, with expertise in the management of FM or
- An academic with a health care background from any nationality who has undertaken research in FM

People with no experience in FM and non-healthcare professional academics were excluded.

In total, 48 world-wide experts in the field of FM were invited and an invitation letter (Appendix 10) was emailed to all the potential panel members in August 2019.

6.2.2 Survey procedure

The survey was prepared in Microsoft Word and email was used to send it to the participants. An electronic survey method was chosen as it aided completion of the survey within the specified deadline and was accessible for all participants. Emails were sent separately to each expert to allow the panel members to remain anonymous from each other.

The first-round survey was emailed to the participants on 18th August 2019. Three rounds were set and each round took 2 weeks to complete. After one week for each round, a reminder e-mail was sent to the participants. If a participant did not complete the survey within the specified deadline, they were excluded from any subsequent rounds of the Delphi exercise.

6.2.3 The Delphi survey

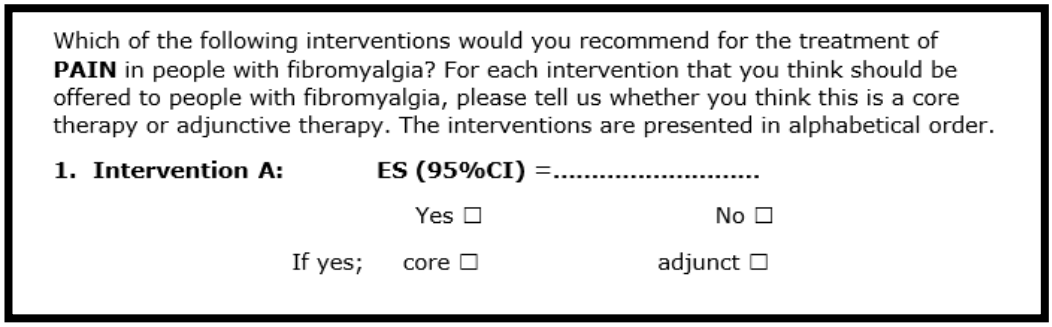
In the first round, a Delphi survey (Appendix 11) was prepared to identify and prioritise non-pharmacological treatments for FM. The survey for the first round included 5 sections:

- professional details
- pain
- fatigue
- sleep
- depression

In the professional details section, they were asked about their years of experience, professional background (Rheumatology, General Practice, Physiotherapy, Psychology, Occupational Therapy etc.) and primary role (academic, clinician or both).

In the subsequent sections, participants were asked to select interventions that they thought should be offered to people with FM and to rate these interventions as core or adjunctive treatment for each of the four common manifestations of FM (pain, fatigue, sleep and depression). In addition, there was a section for any additional intervention suggestions for each domain. Our meta-analysis results were also provided to summarise current research evidence. Figure 5-11 presents an example question type.

Figure 5-11. An example of question type in the first round Delphi exercise


Which of the following interventions would you recommend for the treatment of **PAIN** in people with fibromyalgia? For each intervention that you think should be offered to people with fibromyalgia, please tell us whether you think this is a core therapy or adjunctive therapy. The interventions are presented in alphabetical order.

1. Intervention A: **ES (95%CI)** =.....

Yes ☐ No ☐

If yes; core ☐ adjunct ☐

Surveys for the second and third rounds were prepared based on the items which did not achieve consensus.

6.2.4 Determining consensus

There is no universally accepted cut-off score for achieving consensus in a Delphi survey. However, the published literature describes thresholds ranging from 55% to 100% (Williams & Webb, 1994). A 70% cut-off score was set for the level of consensus for this study, as it is consistent with many other publications including OMERACT (Wells et al., 2014; Williams & Webb, 1994). Items receiving more than 70% of positive votes were accepted, those receiving less than 30% were rejected, and those obtaining between 30-70% were recirculated in the following round to allow a further vote to achieve

consensus. Delphi rounds were repeated until stability of votes for the items which did not reach consensus.

6.3 Results

Of 48 invitees, 19 responded to the invitation and 17 agreed to participate in the Delphi exercise.

Response and completion rates for the 17 participants were 100%. There were seven rheumatologists, two physiotherapists, one psychologist, one nurse and six people from other professional backgrounds, specifically physical medicine and rehabilitation, neurology, immunology and public health (Figure 5-12). Eight participants worked as clinical academics, seven were non-clinical academics and two were clinicians (Figure 5-13). Most (15 out of 17) had experience of FM for more than 10 years, and two had 5 to 10 years of experience (Figure 5-14).

Figure 5-12. Professional backgrounds of Delphi panel members

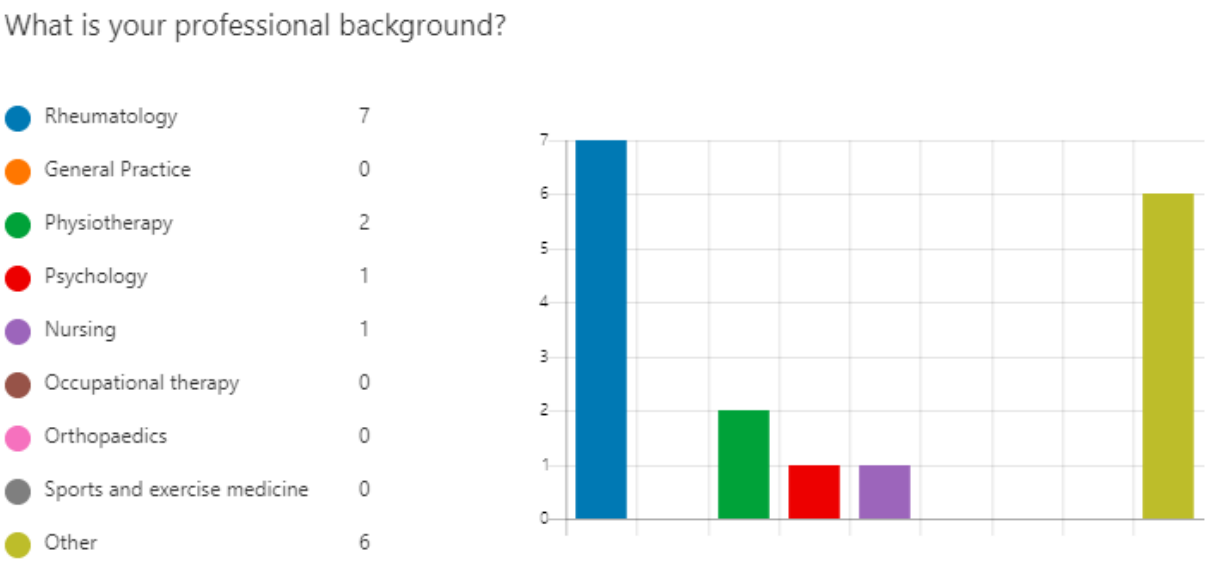


Figure 5-13. Primary roles of Delphi panel members



Figure 5-14. Years in practice of Delphi panel members



6.3.1 First round

6.3.1.1 Pain

Table 5-10 presents the interventions which were accepted (supported by at least 70% participants), rejected (supported by fewer than 30% participants) or did not achieve consensus (supported by between 30 and 70% participants) from the first round of the Delphi exercise for pain. Acupuncture, balneotherapy, biofeedback, massage and weight loss needed to be re-voted. Other interventions were also suggested by the members of the Delphi panel, namely clear understanding of the crucial role of stress, determination to "build well-being/happiness, goal setting, hot bath and local heating, orthotics, pacing, postural training, periods of relaxation/enjoyment during the day, stress management and sleep hygiene.

Table 5-10. First round results - accepted, no consensus and rejected interventions for pain

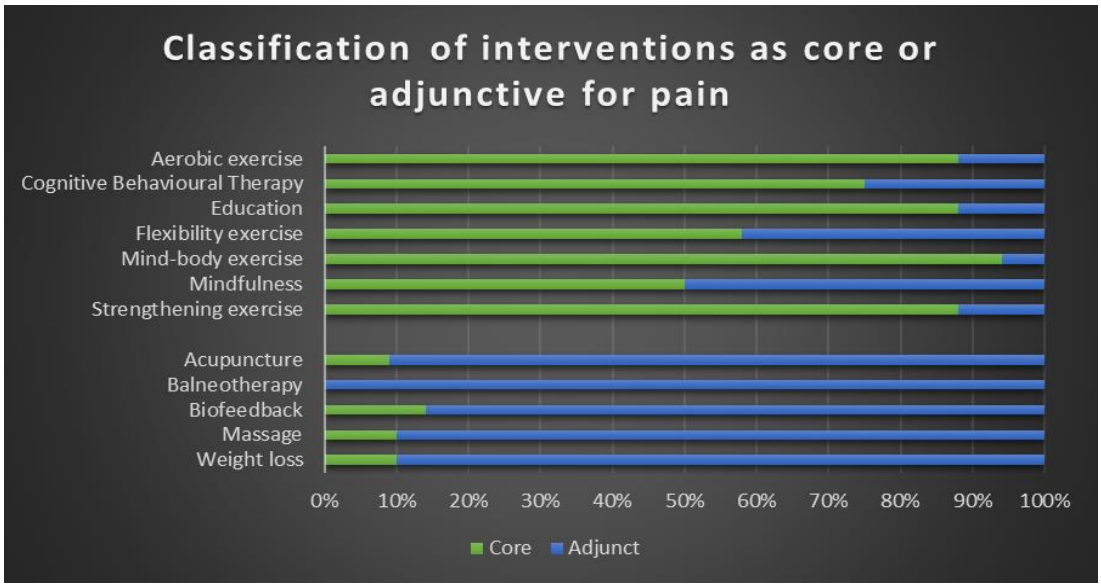
ACCEPTED		
Intervention	**Yes (%)**	**No (%)**
Aerobic exercise	94	6
Cognitive Behavioural Therapy	94	6
Education	94	6
Flexibility exercise	71	29
Mind-body exercise	94	6
Mindfulness	82	18
Strengthening exercise	88	12

NO CONSENSUS		
Intervention	**Yes (%)**	**No (%)**
Acupuncture	65	35
Balneotherapy	47	53
Biofeedback	41	59
Massage	59	41
Weight loss	59	41

REJECTED		
Intervention	**Yes (%)**	**No (%)**
Cupping	0	100
Electrotherapy	24	76
Homeopathy	6	94
Hyperbaric oxygen therapy	18	82
Magnetotherapy	6	94
Manual therapy	29	71
Material of cloth	6	94
Music	18	82
Nutritional supplement	18	82
Transcranial direct current stimulation	29	71
Whole body vibration	6	94

Figure 5-15 shows the classification of interventions (accepted and no consensus) as core or adjunctive for pain by the members of the Delphi panel. All accepted interventions except for mindfulness were voted as core interventions for pain outcome, whereas there was disagreement for mindfulness as to whether it should be core or adjunctive.

Figure 5-15. Classification of interventions as core or adjunctive for pain



6.3.1.2 Fatigue

Table 5-11 demonstrates the interventions which were accepted, rejected or did not achieve consensus from the first round of the Delphi exercise for fatigue. Acupuncture, balneotherapy, flexibility exercise, massage and weight loss were voted between 30 and 70% and did not reach consensus. Other interventions suggested by the Delphi panel members were dietary modification, goal setting, pacing, stress management and sleep hygiene.

Table 5-11. First round results - accepted, no consensus and rejected interventions for fatigue

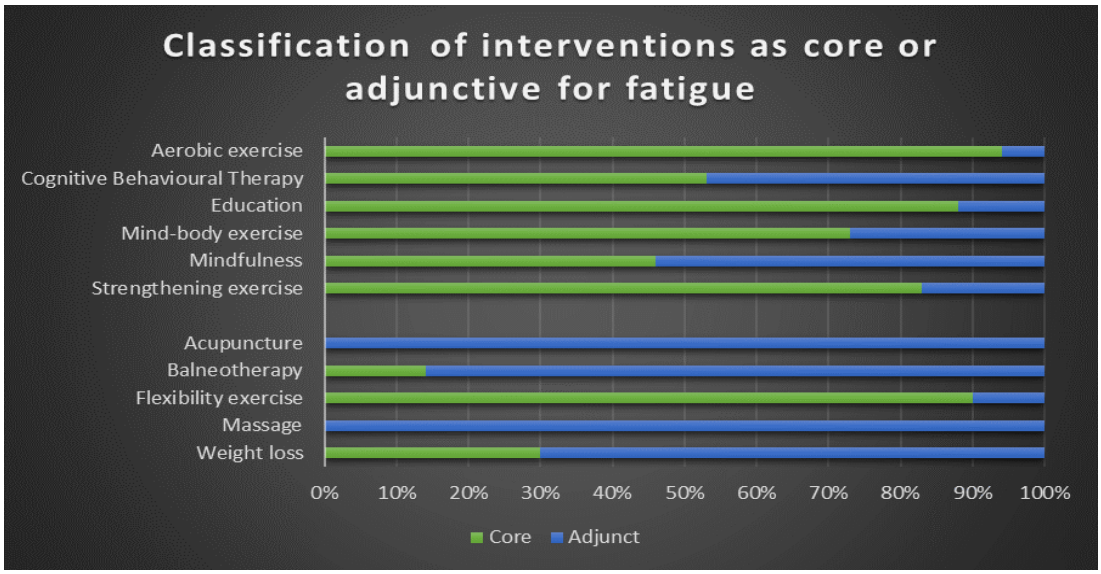
ACCEPTED		
Intervention	**Yes (%)**	**No (%)**
Aerobic exercise	94	6
Cognitive Behavioural Therapy	88	12
Education	94	6
Mind-body exercise	88	12
Mindfulness	76	24
Strengthening exercise	71	29

NO CONSENSUS		
Intervention	**Yes (%)**	**No (%)**
Acupuncture	41	59
Balneotherapy	41	59
Flexibility exercise	59	41
Massage	41	59
Weight loss	59	41

REJECTED		
Intervention	**Yes (%)**	**No (%)**
Biofeedback	18	82
Cupping	0	100
Electrotherapy	0	100
Homeopathy	6	94
Hyperbaric oxygen therapy	18	82
Magnetotherapy	12	88
Manual therapy	6	94
Material of cloth	6	94
Music	18	82
Nutritional supplement	29	71
Transcranial direct current stimulation	12	88
Whole body vibration	0	100

Figure 5-16 shows the classification of interventions (accepted and no consensus) as core or adjunctive for fatigue by the members of the Delphi panel. While mindfulness (55% as adjunctive) was suggested as an adjunctive intervention, the rest of the accepted interventions were voted as core.

Figure 5-16. Classification of interventions as core or adjunctive for fatigue



6.3.1.3 Sleep

Table 5-12 demonstrates the interventions which were accepted, rejected and did not achieve consensus from the first round of the Delphi exercise for sleep. Flexibility exercise, massage, mindfulness, music, nutritional supplement, strengthening exercise and weight loss did not reach consensus. The members of the Delphi panel suggested other interventions such as clear understanding of the crucial role of stress, determination to "build well-being/happiness, dietary modification, hot bath and local heat, pacing, periods of relaxation/enjoyment during the day, stress management, and sleep hygiene.

Table 5-12. First round results - accepted, no consensus and rejected interventions for sleep

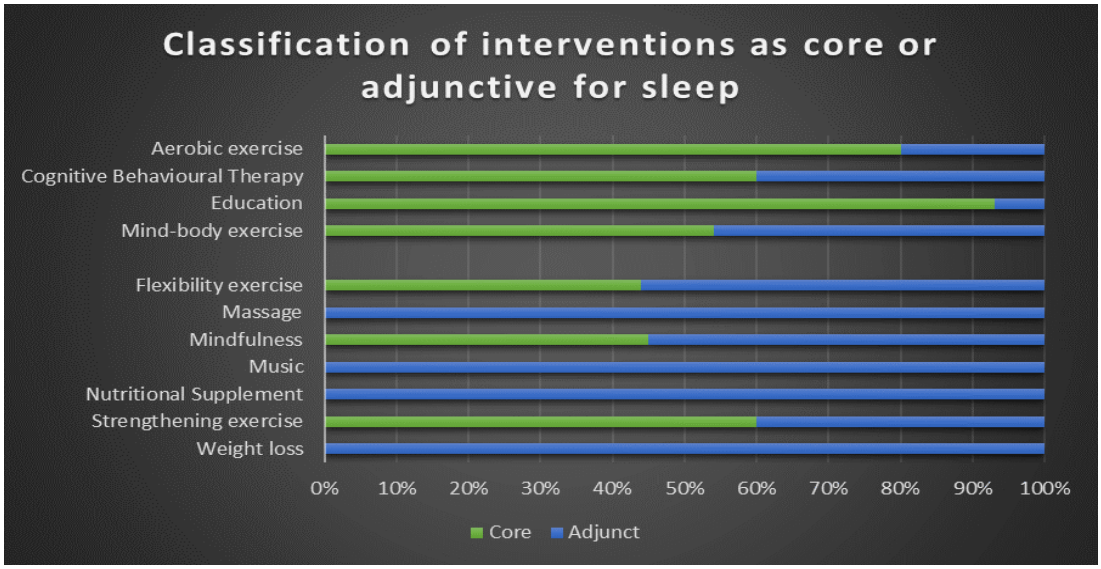
ACCEPTED		
Intervention	**Yes (%)**	**No (%)**
Aerobic exercise	88	12
Cognitive Behavioural Therapy	88	12
Education	88	12
Mind-body exercise	76	24

NO CONSENSUS		
Intervention	**Yes (%)**	**No (%)**
Flexibility exercise	53	47
Massage	47	53
Mindfulness	65	35
Music	53	47
Nutritional supplement	35	65
Strengthening exercise	59	41
Weight loss	53	47

REJECTED		
Intervention	**Yes (%)**	**No (%)**
Acupuncture	24	76
Balneotherapy	18	82
Biofeedback	29	71
Cupping	0	100
Electrotherapy	6	94
Homeopathy	0	100
Hyperbaric Oxygen therapy	6	94
Magnetotherapy	6	94
Manual therapy	6	94
Material of cloth	18	82
Transcranial direct current stimulation	12	88
Whole body vibration	0	100

Figure 5-17 shows the classification of interventions (accepted and no consensus) as core or adjunctive for sleep by the members of the Delphi panel. All accepted interventions (aerobic exercise (80%), CBT (60%), education (93%) and mind-body exercise (54%)) were suggested as core.

Figure 5-17. Classification of interventions as core or adjunctive for sleep



6.3.1.4 Depression

Table 5-13 presents the interventions which were accepted, rejected or did not achieve consensus from the first round of the Delphi exercise for depression. Flexibility exercise, massage, music, strengthening exercise and weight loss were carried to the second round as they did not reach consensus. Clear understanding of the crucial role of stress, determination to "build well-being/happiness, goal setting, hot bath and local heat, periods of relaxation/enjoyment during the day, stress management, and sleep hygiene were the other interventions suggested by the Delphi panel.

Table 5-13. First round results - accepted, no consensus and rejected interventions for depression

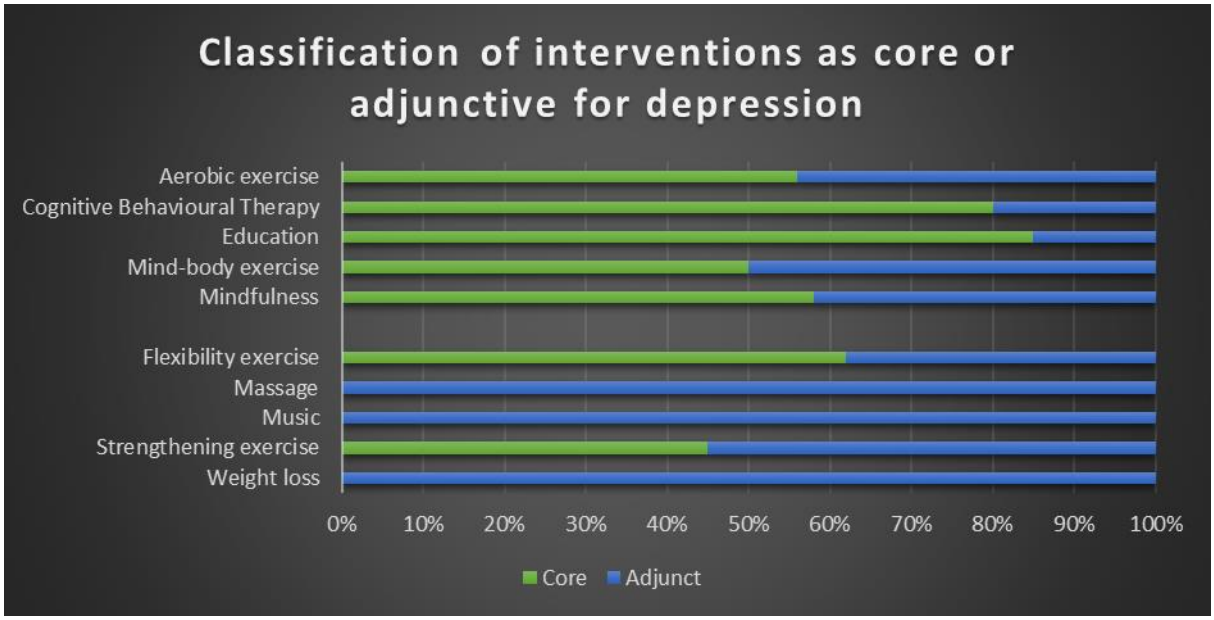
ACCEPTED		
Intervention	**Yes (%)**	**No (%)**
Aerobic exercise	94	6
Cognitive Behavioural Therapy	88	12
Education	76	24
Mind-body exercise	82	18
Mindfulness	71	29

NO CONSENSUS		
Intervention	**Yes (%)**	**No (%)**
Flexibility exercise	47	53
Massage	35	65
Music	41	59
Strengthening exercise	65	35
Weight loss	53	47

REJECTED		
Intervention	**Yes (%)**	**No (%)**
Acupuncture	12	88
Balneotherapy	18	82
Biofeedback	24	76
Cupping	0	100
Electrotherapy	0	100
Homeopathy	0	100
Hyperbaric oxygen therapy	0	100
Magnetotherapy	0	100
Manual therapy	0	100
Material of cloth	0	100
Nutritional supplement	29	71
Transcranial direct current stimulation	29	71
Whole body vibration	6	94

Figure 5-18 shows the classification of interventions (accepted and no consensus) as core or adjunctive for depression by the members of the Delphi panel. All accepted interventions except for mind-body exercise were voted as core interventions for depression outcome. There was disagreement for mind-body exercise, as it was equally voted as a core (50%) and an adjunctive (50%) intervention.

Figure 5-18. Classification of interventions as core or adjunctive for depression



6.3.2 Second round

6.3.2.1 Pain

Table 5-14 presents the interventions which were accepted, rejected or did not achieve consensus from the second round of the Delphi exercise for pain. Interventions suggested by the Delphi panel members such as clear understanding of the crucial role of stress, goal setting, hot bath and local heat, pacing, periods of relaxation/enjoyment during the day, stress management and sleep hygiene were accepted. Orthotics was rejected. There was no clear consensus for the other interventions.

Table 5-14. Second round results - accepted, no consensus and rejected interventions for pain

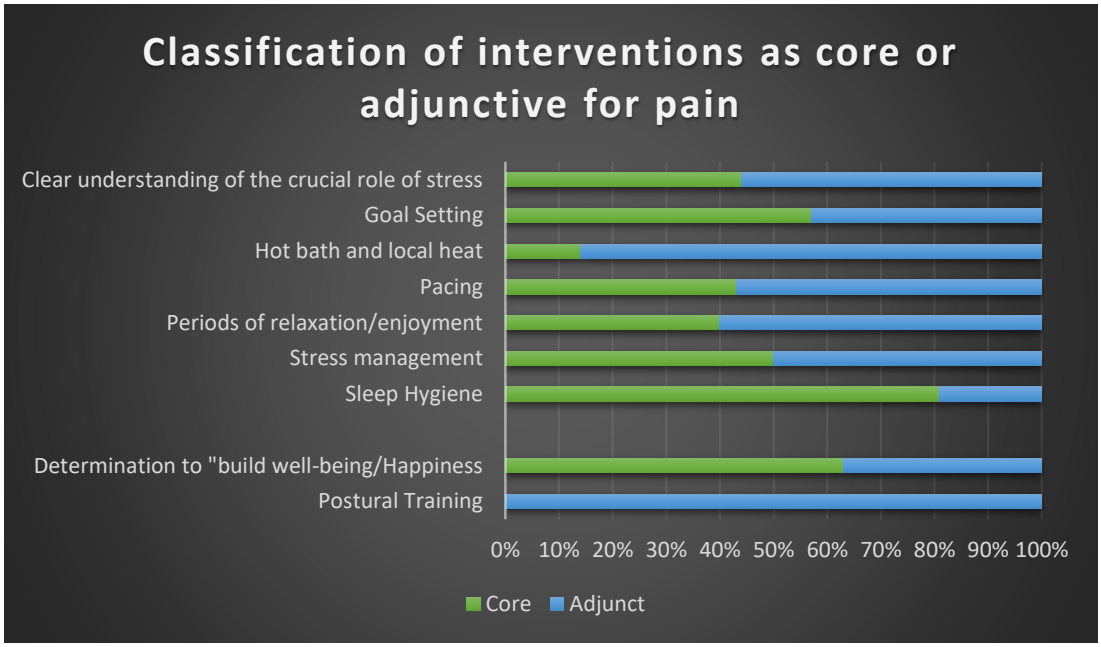
ACCEPTED		
Interventions	**Yes (%)**	**No (%)**
Clear understanding of the crucial role of stress	94	6
Goal setting	82	18
Hot bath and local heat	82	18
Pacing	82	18
Periods of relaxation/enjoyment during the day	88	12
Stress management	94	6
Sleep hygiene	94	6

NO CONSENSUS		
Interventions	**Yes (%)**	**No (%)**
Acupuncture	59	41
Balneotherapy	47	53
Biofeedback	35	65
Determination to "build well-being/happiness”	47	53
Massage	47	53
Postural training	59	41
Weight loss	44	56

REJECTED		
Interventions	**Yes (%)**	**No (%)**
Orthotics	6	94

Figure 5-19 shows the classification of interventions suggested by Delphi panel members (accepted and no consensus) as core or adjunctive for pain. Accepted interventions apart from hot bath and local heat and periods of relaxation/enjoyment were suggested as core interventions in a treatment package of FM for pain. 86% of the panel members that suggested hot bath and local heat as a treatment option voted it as an adjunctive treatment for pain.

Figure 5-19. Classification of interventions as core or adjunctive for pain



6.3.2.2 Fatigue

Table 5-15 presents the interventions which were accepted, rejected or did not achieve consensus from the second round of the Delphi exercise for fatigue. Interventions suggested by the Delphi panel including goal setting, pacing, stress management and sleep hygiene were accepted. However, acupuncture, balneotherapy, flexibility exercise and massage were rejected in the second round. There was no consensus for dietary modifications and weight loss.

Table 5-15. Second round results - accepted, no consensus and rejected interventions for fatigue

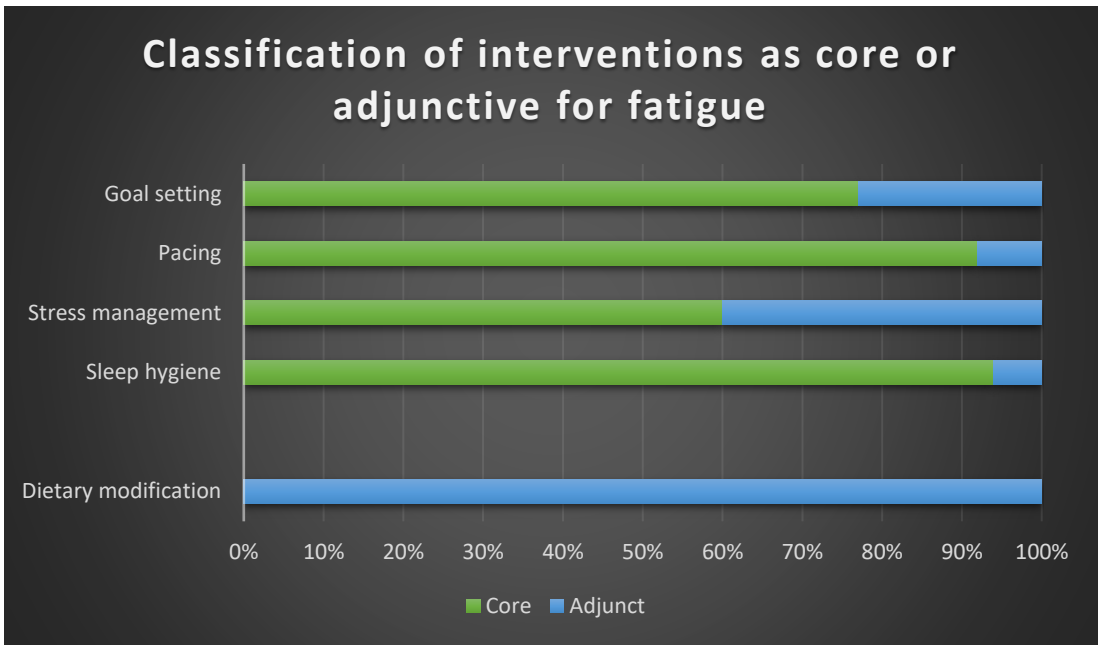
ACCEPTED		
Intervention	**Yes (%)**	**No (%)**
Goal Setting	76	24
Pacing	76	24
Stress management	88	12
Sleep hygiene	100	0

NO CONSENSUS		
Intervention	**Yes (%)**	**No (%)**
Dietary modification	41	59
Weight loss	65	35

REJECTED		
Intervention	**Yes (%)**	**No (%)**
Acupuncture	6	94
Balneotherapy	24	76
Flexibility exercise	18	82
Massage	6	94

Figure 5-20 shows the classification of interventions suggested by Delphi panel members (accepted and no consensus) as core or adjunctive for fatigue. All accepted interventions were suggested as core treatment options for fatigue.

Figure 5-20. Classification of interventions as core or adjunctive for fatigue



6.3.2.3 Sleep

Table 5-16 presents the interventions which were accepted, did not achieve consensus or were rejected from the second round of the Delphi exercise for sleep. Interventions suggested by the Delphi panel such as clear understanding of the crucial role of stress, hot bath and local heat, periods of relaxation/enjoyment during the day, stress management and sleep hygiene and mindfulness which could not achieve consensus from the first round were accepted. Flexibility exercise, massage and nutritional supplement were rejected.

Table 5-16. Second round results - accepted, no consensus and rejected interventions for sleep

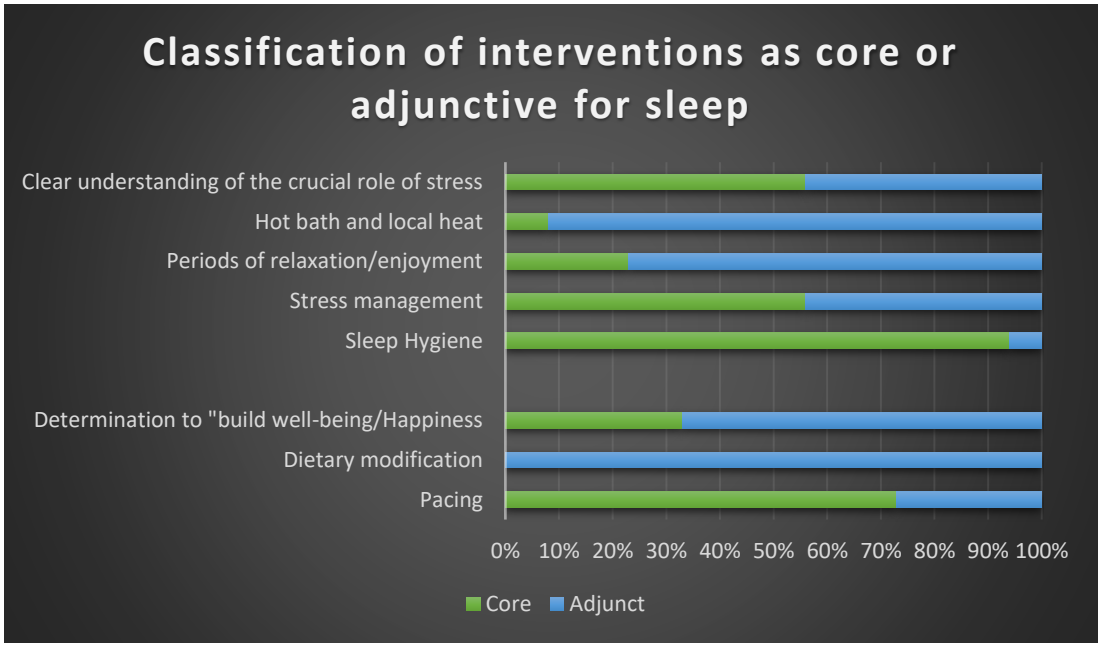
ACCEPTED		
Interventions	**Yes (%)**	**No (%)**
Clear understanding of the crucial role of stress	94	6
Hot bath and local heat	71	29
Mindfulness	76	24
Periods of relaxation/enjoyment during the day	76	24
Stress management	94	6
Sleep hygiene	100	0

NO CONSENSUS		
Interventions	**Yes (%)**	**No (%)**
Determination to "build well-being/happiness"	53	47
Dietary modification	41	59
Music	35	65
Pacing	65	35
Strengthening exercise	35	65
Weight loss	53	47

REJECTED		
Interventions	**Yes (%)**	**No (%)**
Flexibility exercise	18	82
Massage	24	76
Nutritional Supplement	6	94

Figure 5-21 shows the classification of interventions suggested by Delphi panel members (accepted and no consensus) as core or adjunctive for sleep. Clear understanding of the crucial role of stress (56%), stress management (56%) and sleep hygiene (94%) were suggested as core, whereas hot bath and local heat (92%) and periods of relaxation/enjoyment during the day (77%) were voted as adjunctive treatment options.

Figure 5-21. Classification of interventions as core or adjunctive for sleep



6.3.2.4 Depression

Table 5-17 presents the interventions which were accepted, rejected or did not achieve consensus from the second round of the Delphi exercise for depression. Accepted interventions were clear understanding of the crucial role of stress, determination to "build well-being/happiness", goal setting, periods of relaxation/enjoyment during the day, stress management and sleep hygiene. On the other hand, flexibility exercise, hot bath and local heat, massage and music were rejected.

Table 5-17. Second round results - accepted, no consensus and rejected interventions for depression

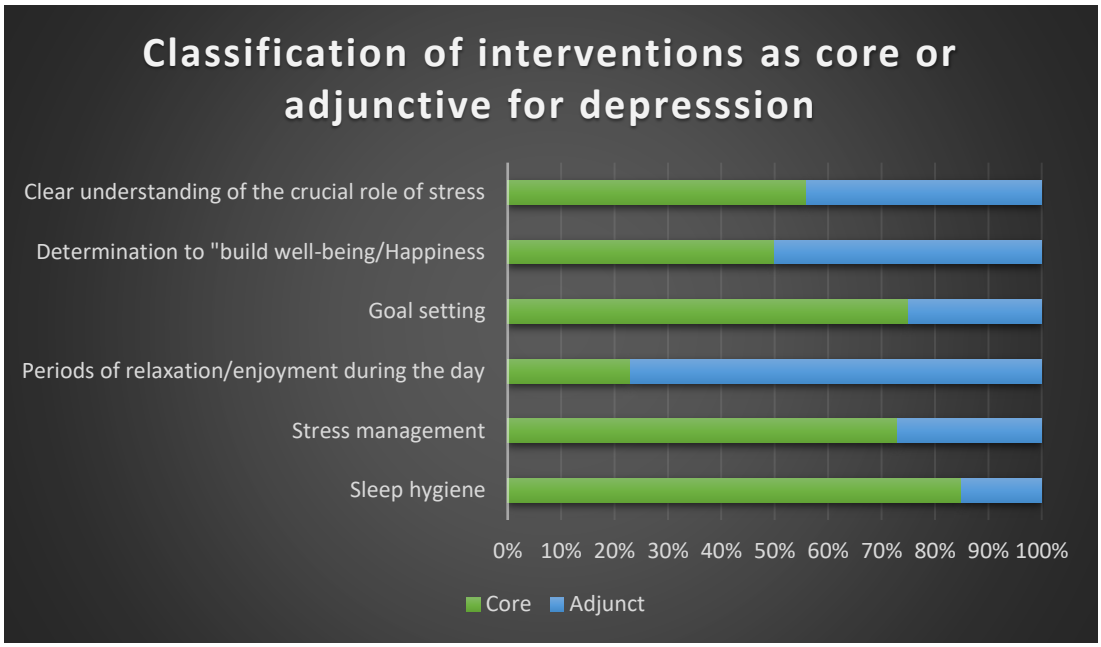
ACCEPTED		
Interventions	**Yes (%)**	**No (%)**
Clear understanding of the crucial role of stress	94	6
Determination to "build well-being/happiness"	71	29
Goal setting	71	29
Periods of relaxation/enjoyment during the day	76	24
Stress management	88	12
Sleep hygiene	76	24

NO CONSENSUS		
Interventions	**Yes (%)**	**No (%)**
Strengthening exercise	41	59
Weight loss	41	59

REJECTED		
Interventions	**Yes (%)**	**No (%)**
Flexibility exercise	24	76
Hot bath and local heat	6	94
Massage	12	88
Music	24	76

Figure 5-22 shows the classification of interventions suggested by Delphi panel members (accepted and no consensus) as core or adjunctive for depression. Clear understanding of the crucial role of stress (56%), goal setting (75%), stress management (73%) and sleep hygiene (85%) were suggested as core, whereas periods of relaxation/enjoyment during the day was suggested as adjunctive treatment. Determination to "build well-being/happiness" was equally voted as core and adjunctive.

Figure 5-22. Classification of interventions as core or adjunctive for depression



6.3.3 Third round

It was decided to stop the Delphi after 3 rounds as there was stability in the items which did not reach consensus.

6.3.3.1 Pain

Table 5-18 presents the interventions which were rejected or did not achieve consensus from the third round of the Delphi exercise for pain. Biofeedback and determination to “build well-being/happiness” were rejected.

Table 5-18. Third round results - no consensus and rejected interventions for pain

NO CONSENSUS		
Interventions	**Yes (%)**	**No (%)**
Acupuncture	41	59
Balneotherapy	41	59
Massage	41	59
Postural Training	41	59
Weight loss	53	47

REJECTED		
Interventions	**Yes (%)**	**No (%)**
Biofeedback	29	71
Determination to “build well-being/happiness”	29	71

6.3.3.2 Fatigue

Table 5-19 presents the interventions which were rejected or did not achieve consensus from the third round of the Delphi exercise for fatigue. Dietary modification was rejected by the Delphi panel. There was no consensus for weight loss.

Table 5-19. Third round results - no consensus and rejected interventions for fatigue

NO CONSENSUS		
Interventions	**Yes (%)**	**No (%)**
Weight loss	53	47

REJECTED		
Interventions	**Yes (%)**	**No (%)**
Dietary modification	29	71

6.3.3.3 Sleep

Table 5-20 presents the interventions which were accepted, rejected or did not achieve consensus from the third round of the Delphi exercise for sleep. Pacing was accepted by 82% of the Delphi panel, whereas strengthening exercise was rejected by 72% of the panel members.

Table 5-20. Third round results - accepted, no consensus and rejected interventions for sleep

ACCEPTED		
Interventions	**Yes (%)**	**No (%)**
Pacing	82	18

NO CONSENSUS		
Interventions	**Yes (%)**	**No (%)**
Determination to "build well-being/Happiness	47	53
Dietary modification	35	65
Music	41	59
Weight loss	53	47

REJECTED		
Interventions	**Yes (%)**	**No (%)**
Strengthening exercise	24	76

6.3.3.4 Depression

Table 5-21 presents the interventions which were rejected or did not achieve consensus from the third round of the Delphi exercise for depression. While weight loss was rejected, there was no consensus on strengthening exercise.

Table 5-21. Third round results - no consensus and rejected interventions for depression

NO CONSENSUS		
Interventions	**Yes (%)**	**No (%)**
Strengthening exercise	35	65

REJECTED		
Interventions	**Yes (%)**	**No (%)**
Weight loss	24	76

6.3.4 Summary of the results

Table 5-22 indicates the accepted interventions for pain, fatigue, sleep and depression as well as their classification as core or adjunctive in a treatment package for FM.

Table 5-22. The classification of accepted non-pharmacological interventions as core or adjunctive for pain, fatigue, sleep and depression

Interventions	Pain	Fatigue	Sleep	Depression
Aerobic exercise				
Education				
Sleep hygiene				
Cognitive behavioural therapy				
Mind-body exercise				
Stress management				
Goal setting				
Mindfulness				
Pacing				
Clear understanding of the crucial role of stress				
Strengthening exercise				
Flexibility exercise				
Music				
Periods of relaxation/enjoyment during the day				
Hot bath and local heat				
Determination to "build well-being/Happiness”				

Green: core, yellow: adjunctive, red: not recommended

6.4 Discussion

6.4.1 Main findings and interpretations

This Delphi exercise identified 14 non-pharmacological interventions for pain, 10 for fatigue, 12 for sleep and 11 for depression that expert clinicians and academics suggested as potentially accessible and beneficial for the four common manifestations of FM. These interventions were also prioritised as core or adjunctive based on expert opinion. This may provide a basis for a non-pharmacological treatment package for FM according to the predominant symptoms of individual patients.

Suggested interventions by the Delphi panel for all symptoms are mainly exercise, education and psychological treatments such as CBT and mindfulness. These results are in agreement with recent studies on FM and management of other chronic pain diseases. The most recent EULAR guidelines (Macfarlane et al., 2017) recommend education and graded physical activity as first line treatment options for the management of FM. If there is insufficient effect, they then recommend mainly CBT for pain related depression or catastrophising.

MDT defines a combined non-pharmacological intervention which generally includes components of exercise, education and psychological treatment. No previous MA has assessed the effect of MDT exclusively in FM. A previous qualitative analysis (Burckhardt, 2006), however, suggests that MDT is effective for decreasing pain and fibromyalgia impact. An MA on FM and chronic musculoskeletal pain (7 trials, n = 1,050 participants) (Karjalainen et al., 1999) reported that education combined with exercise showed

improvement in long-term follow up and that behavioural treatment and stress management seemed to be important components. Similarly, a multidisciplinary approach including education, exercise and a psychological intervention was beneficial for other chronic pain diseases such as CLBP (Kamper et al., 2015) and OA (Kloppenburg et al., 2019).

Rejected interventions that are mainly complementary and alternative medicines (CAMs) were also consistent with the previous literature. The quantitative synthesis of the RCTs (chapter 3) found no significant results for interventions such as cupping therapy, HOT, WBV, manual therapy etc. On the other hand, some interventions that provided significant improvements such as acupuncture, balneotherapy or weight loss were also rejected or were not able to reach consensus. A possible explanation for this result may be bias against this kind of intervention by members of the Delphi panel who were predominantly physicians. A study assessing cross-cultural differences in general practitioners' (GP) attitudes towards CAM indicated that many GPs in Germany and the United Kingdom are prejudiced against CAM and concerned about its availability (Schmidt et al., 2002). Similarly, despite the large effect of balneotherapy, it was rejected by the Delphi panel. We asked them to vote for interventions based not just on research evidence, but also on perceived patient preference and their knowledge and experiences in terms of efficacy, acceptability, availability, cost etc. Therefore, some of these other considerations may have let to its rejection.

6.4.2 Strengths

This Delphi exercise included prominent academics and clinicians from a variety of backgrounds, often with involvement in international FM guideline development groups. All participants completed all three rounds of the Delphi exercise. Our MA and NMA results were given in summary form and they were asked to vote by considering research evidence, their knowledge and experience of treating patients with FM and patient preferences. A very comprehensive non-pharmacological intervention list was presented but the survey also allowed them to suggest any other non-pharmacological intervention by the panel members.

6.4.3 Limitations

There were several limitations in this Delphi exercise. Firstly, the panel members of the Delphi exercise were predominantly physicians. This may have caused a biased perspective towards some interventions. Secondly, patients were not included in this study due to the time constraints and the challenges of collecting a large sample of representative patients (e.g. a spectrum of ages, gender, severity, country of residence etc.). However, it was important to involve patients in design, conduct or analysis stage of the studies to make them more relevant to end users (Boote et al., 2015; Frank et al., 2014), reduce waste in research (Salman et al., 2014) and to improve research quality (Kearney et al., 2017). Thirdly, the titles of some interventions were quite general or ambiguous, for example, electrotherapy included several modalities such as laser, TENS etc., and music intervention referred to listening to any type of music either therapeutic or for pleasure.

The panel members might misinterpret the intervention due to this ambiguity in intervention names, and this may over or underestimate the percentage of agreement for a specific intervention. Fourthly, ESs and 95% CI of the interventions were provided to the participants based on our findings. However, other parameters which were not provided would also be important to interpret these ESs such as sample size, number of study or heterogeneity. Also, this may have introduced a bias in terms of social desirability bias. Even though we reminded them to use not only research evidence but also their previous experience and patient preferences, participants might have wanted to appear to be supporting the research evidence.

6.4.4 Conclusion

This Delphi exercise appears to have provided a fair representation of the expert practitioner and researcher perspective of the non-pharmacological treatment package for FM. Agreement was reached on a set of non-pharmacological interventions based on four different manifestations of FM including pain, fatigue, sleep and depression. These interventions were prioritised as either core or adjunctive. This information will inform the future development of a complex non-pharmacological treatment package for FM, which will subsequently be tested in clinical research.

Chapter 7 CONCLUSION

In this doctoral thesis, CMA of RCTs was used to examine the efficacy of 21 different non-pharmacological interventions, NMA was used to examine the relative efficacy between four representative interventions (exercise, psychological treatment, MDT and balneotherapy), as well as between five different exercise types (aerobic, flexibility, mind-body, mixed and strengthening). The latter also aimed to increase the precision of estimates of each treatment by using both direct and indirect evidence. Less frequently studied interventions for which there were only a few RCTs were not included in the NMA. Most of the results of NMA were consistent with with those of CMA. However, there were few differences. For example, while some exercise types (i.e. aerobic and strengthening) showed significant improvements for sleep based on CMA results, they were not significantly better than usual care according to NMA results. This may be explained by the fact that NMA combined both direct and indirect evidence. In CMA, 13 exercise trials with 621 participants were included. However, in NMA, 19 exercise studies including 1,044 participants were analysed. Additionally, NMA estimated the efficacy of other interventions such as flexibility exercise that does not have direct evidence. Following these two studies, a Delphi exercise was undertaken to select the most effective and accessible non-pharmacological interventions considering research evidence, expert knowledge and experience as well as patient preferences.

Exercise, psychological treatment, MDT, balneotherapy, massage, electrotherapy, tDCS, biofeedback, homeopathy, magnetotherapy and weight loss were effective for improving FIQ on CMA. Of the interventions

that were compared in NMA, balneotherapy was the most effective treatment for FIQ according to NMA. Following this, exercise was second best. Specifically, looking at exercise types, strengthening exercise would appear to be the best exercise type for improving FIQ in people with FM.

Exercise, psychological treatment, MDT, balneotherapy, acupuncture, massage, manual therapy, tDCS, homeopathy, magnetotherapy and HOT significantly improved pain in patients with FM. NMA results showed that MDT was the best treatment option among four non-pharmacological interventions and strengthening exercise was the most effective exercise type compared to the others. Delphi results supported the use of aerobic, flexibility, mind-body and strengthening exercises, education, CBT, sleep hygiene and goal setting as core interventions, and stress management, mindfulness, pacing, clear understanding of the crucial role of stress, periods of relaxation/enjoyment during the day, and hot bath and local heat as adjunctive interventions.

Exercise, education, balneotherapy, acupuncture, massage, electrotherapy, tDCS, nutritional supplement, magnetotherapy, and material of cloth were effective for fatigue on CMA. Exercise was ranked first for fatigue and specifically looking at exercise types, aerobic exercise was better than other exercise types. Aerobic, mind-body and strengthening exercises, education, CBT, sleep hygiene, pacing, stress management, and goal setting were suggested as core and mindfulness was suggested as adjunctive in the management of fatigue on FM by the Delphi panel.

In terms of sleep outcome, exercise, MDT, massage, electrotherapy, tDCS, nutritional supplement, homeopathy, magnetotherapy, music, weight loss, and material of cloth were effective based on CMA. According to NMA of a selected few interventions, MDT and aerobic exercise were the best treatments for fatigue. While aerobic and mind-body exercises, education, CBT, sleep hygiene, pacing, stress management and clear understanding of the crucial role of stress were suggested as core, mindfulness, music, periods of relaxation/enjoyment during the day and hot bath and local heat were suggested as adjunctive non-pharmacological interventions for sleep.

Exercise, psychological treatment, MDT, balneotherapy, electrotherapy, tDCS, homeopathy, music, weight loss, and material of cloth significantly improved depression based on CMA. However, on NMA, of the interventions that were compared, MDT was the best treatment for improving depression. Looking at exercise types, strengthening was the most effective intervention. The Delphi panel suggested aerobic exercise, education, CBT, sleep hygiene, stress management, mindfulness, clear understanding of the crucial role of stress, and goal setting as core interventions, and mind-body exercise, periods of relaxation/enjoyment during the day, and determination to "build well-being/happiness as adjunctive interventions.

In alignment with the MRC guidance for complex intervention development (Craig et al., 2008), the evidence presented in this thesis should now progress to consider the development of relevant theory. This will identify the mechanisms underpinning the interventions and which of these are necessary in the development of an overall complex package. A modelling

phase can then test assumptions about the intervention and the outcomes before refining the intervention with input from stakeholders.

Further feasibility and piloting work will be required to ensure acceptability and feasibility of intervention delivery and the feasibility of conducting a full RCT.

Overall, non-pharmacological interventions are beneficial for people with FM but some interventions appear more efficacious than others for different FM outcomes. Exercise was the most promising non-pharmacological intervention for relieving multiple FM symptoms, though different types of exercise benefit different outcomes. Psychological treatments including cognitive behavioural therapy (CBT) and mindfulness were significantly more efficacious than usual care for FIQ, pain and depression but showed no improvement for fatigue and sleep. These findings suggest that different types of non-pharmacological interventions can be selected for patients in an individualised manner depending on their predominant symptoms. The results of this study may be used to guide the selection of the most beneficial interventions according to the predominant symptom of individual patients.

This study has also provided a fair representation of the expert practitioner and researcher view of a non-pharmacological treatment package for FM. Agreement was reached on a set of non-pharmacological interventions based on four different manifestations of FM including pain, fatigue, sleep and depression. These interventions were prioritised as core or adjunctive. The results in this doctoral thesis will inform the development of a complex non-pharmacological treatment package for FM.

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Appendices

Appendix 1 A search strategy designed for MEDLINE

1 Randomized Controlled Trial.mp.
2 Controlled Clinical Trial.mp.
3 random*.mp.
4 trial.mp.
5 Single-Blind Method/
6 Double-Blind Method/
7 1 or 2 or 3 or 4 or 5 or 6
8 fibromyalgia.mp.
9 fibrositis.mp.
10 chronic widespread pain.mp.
11 Chronic Pain/
12 multiple regional pain.mp.
13 widespread pain.mp.
14 psychogenic rheumatism.mp.
15 8 or 9 or 10 or 11 or 12 or 13 or 14
16 non-pharmacological treatment.mp.
17 patient education.mp.
18 pain education.mp.
19 pain management.mp.
20 self-management.mp.
21 Education/
22 advice.mp.
23 exercise.mp.
24 physical activity.mp.
25 physiotherapy.mp.
26 electrotherapy.mp.
27 tens.mp.
28 magnetotherapy.mp.
29 sleep hygiene.mp.

30 complementary medicine.mp.

31 alternative medicine.mp.

32 chinese medicine.mp.

33 acupuncture.mp.

34 dry needling.mp.

35 homeopathy.mp.

36 food supplement.mp.

37 nutraceutical.mp.

38 Dietary Supplements/

39 balneotherapy.mp.

40 hydrotherapy.mp.

41 psychological therapy.mp.

42 cognitive behavioural therapy.mp.

43 mindfulness.mp.

44 hypnotherapy.mp.

45 meditation.mp.

46 (Acceptance and Commitment Therapy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

47 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48 7 and 15 and 47

Appendix 2 Data extraction form

DATA EXTRACTION FORM

Date of review : enter a date. **ID of reviewer :** enter initials

Title of article : enter article title.

Author(s) : Click here to enter text.

A. Study characteristics

Country: Country where study was done. **Year:** State study date

Language: Click here to enter text.

Funding: **Public ☐** **Commercial (Fully ☐** **Partially ☐** **Unclear ☐)**

Unclear ☐ **Others:**

Diagnosis made using: Smythe 1981 ☐ **Yunus 1981☐** **Yunus 1984☐** **ACR 1990 ☐** **ACR 2010 ☐** **Physician's diagnosis ☐**

Unclear ☐ **Others:**Click here to enter text.

Grouping:

Control	Intervention 1	Intervention 2
Detail description: Enter description of exercise details	Detail description: Enter description of exercise details	Detail description: Enter description of exercise details

Design: Parallel ☐ Crossover ☐ Others: Other types

Primary Outcome: Click here to enter text.

B. Participant Characteristics

Demographic	**Control**	**Intervention 1**	**Intervention 2**	**Total**
Number of participants				
Number of withdrawals				
Age (mean ± SD)				
Female%				
Treatment Period				
Follow-up Period				

C. Outcome

I. Health Related Quality of Life (FIQ)

Group (Intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

II. Pain

Group (Intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

III. Fatigue

Group (Intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

IV. Sleep

Group (Intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

V. Depression

Group (Intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

Appendix 3 Calculation methods for SD

Calculations	Notes
SD from SE and CI • $SD = SE \times \sqrt{N}$ • $SD = \frac{(UpCI - LwCI) \times \sqrt{N}}{3.92}$ SD from median • $SD \cong \frac{1}{12}\left(\frac{(a-2m+b)^2}{4} + (b-a)^2\right)$ SD from interquartile range • $SD \cong \frac{q_3 - q_1}{1.35}$ SD of the change from baseline • $SD = \sqrt{SD_{baseline}^2 + SD_{final}^2 - \left(2 \times r \times SD_{baseline} \times SD_{final}\right)}$ Mean from median • $x = \frac{a+2m+b}{4}$	SD = standard deviation SE = standard error CI = Confidence Interval N = sample size UpCI = upper confidence interval LwCI = lower confidence interval a = minimum value b = maximum value m = median q_3 = third quartile q_1 = first quartile x = mean

Appendix 4 Modified Cochrane Risk of Bias Assessment Tool

Domain	Description	High risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer assessment
Selection bias **Random sequence generation**	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	Random sequence generation method should produce comparable groups	Not described in sufficient detail	**High Low Unclear**
Selection bias **Allocation concealment**	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrollment	Selection bias (biased allocation to interventions) due to inadequate concealment o allocations prior to assignment	Intervention allocations likely could not have been foreseen in before or during enrollment	Not described in sufficient detail	**High Low Unclear**
Performance bias **Blinding (participants and personnel)**	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	**High Low Unclear**
Detection bias **Blinding (outcome assessment)**	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	**High Low Unclear**
Attrition bias **Incomplete outcome data**	Described the completeness of outcome data for each main outcome including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with tota randomized participants), reasons for	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusi ons to permit judgment (e.g., number randomized not stated, no reasons for missing data provided)	**High Low Unclear**

	attrition/exclusions where reported.				
Reporting bias **Selective reporting**	Stated how the possibility of selective outcome reporting was examined by the authors and what was found	Reporting bias due to selective outcome reporting	Selective outcome reporting bias not detected	Insufficient information to permit judgment†	**High Low Unclear**
Other bias **Other sources of bias**	Any important concerns about bias not addressed above*	Bias due to problems not covered elsewhere in the table	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias	**High Low Unclear**

Appendix 5 Characteristics of included studies and references

Study (Author, year)	Interventions Assessed	Outcomes assessed	Number of patients randomised	% of female	Mean Age (years)	Mean BMI (kg/m^2)	Setting	Duration of intervention
Acosta-Gallego 2018 [1]	ME (WB)/ME (LB)	FIQ/Pain/Fatigue/Depression	90	100	58.15	27.66	Unclear	20 weeks
Albers 2018 [2]	MT/WL	FIQ/Pain	50	96	55.02	-	Mixed	12 weeks
Alfano 2001 [3]	MGT/PLA/UC	FIQ/Pain	119	69	45.36	-	Mixed	24 weeks
Alparslan 2016 [4]	MUS/UC	Pain	37	95	43.59	-	Hospital	2 weeks
Altan 2004 [5]	AEX/BAL	FIQ/Pain/Fatigue/Sleep/Depression	50	100	43.53	-	Hospital	12 weeks
Altan 2009 [6]	ME/MBE	FIQ/Pain	50	100	49.10	-	Hospital	12 weeks
Alves 2013 [7]	FS/PLA	FIQ/Pain/Fatigue/Sleep/Depression	32	100	48.85	27.40	Hospital	16 weeks
Amirova 2017 [8]	MBE/WL	FIQ/Pain/Fatigue/Depression	189	94	49.18	-	Community	4 weeks
Amris 2014 [9]	MDT/WL	FIQ/Pain/Depression	191	100	44.30	26.95	Hospital	2 weeks
Anderson 2007 [10]	MDT/UC	FIQ/Pain/Fatigue/Depression	52	98	37.90	24.80	Hospital	4 weeks
Arcos-Carmon 2011 [11]	ME/UC	Depression	56	-	-	-	Mixed	10 weeks
Ardic 2007 [12]	BAL/UC	FIQ/Pain/Depression	24	100	46.15	-	Hospital	3 weeks
Assis 2006 [13]	AEX(WB)/AEX(LB)	FIQ/Pain/Depression	60	100	42.80	27.10	Hospital	15 weeks
Astin 2003 [14]	MBE/UC	FIQ/Pain/Depression	128	99	-	-	Mixed	8 weeks
Babu 2007 [15]	BIO/UC	FIQ/Pain	30	73	39.25	-	Hospital	6 days
Bagdatli 2015 [16]	BAL/UC	FIQ/Pain/Fatigue/Sleep/Depression	70	100	43.97	25.72	Hospital	2 weeks
Baptista 2012 [17]	AEX/WL	FIQ/Pain/Depression	80	100	49.30	-	Hospital	16 weeks
Bazzichi 2013 [18]	BAL/BAL	FIQ/Pain/Fatigue/Depression	41	95	53.39	-	Community	2 weeks
Bell 2004 [19]	HOM/PLA	Fatigue/Depression	62	94	48.48	-	Community	16 weeks
Bircan 2008 [20]	AEX/SEX	Pain/Fatigue/Sleep/Depression	30	100	47.15	-	Hospital	8 weeks
Blunt 1997 [21]	MT/WL	Pain	21	-	48.96	-	Hospital	4 weeks
Bongi 2010 [22]	MBE/WL	FIQ/Pain/Sleep	41	93	45.42	-	Community	8 weeks

Bongi 2012 [23]	MBE/MBE	FIQ/Pain/Sleep/Depression	38	-	57.24	-	Unclear	7 weeks
Bongi 2016 [24]	MBE/EDU	FIQ/Pain/Sleep/Depression	44	-	52.33	-	Unclear	16 weeks
Brattberg 2008 [25]	PTx/WL	Pain/Depression	86	-	-	-	Community	8 weeks
Broderick 2005 [26]	PTx/UC	Pain/Fatigue/Depression	92	100	49.74	-	Mixed	3 weeks
Burckhardt 1994 [27]	EDU/WL	FIQ/Pain/Fatigue/Sleep/Depression	86	100	-	-	Hospital	6 weeks
Buskila 2001 [28]	BAL/UC	FIQ/Pain/Fatigue/Depression	48	100	54.45	-	Hospital	10 days
Calandre 2009 [29]	FEX/MBE	FIQ/Pain/Fatigue/Sleep/Depression	81	90	49.96	-	Hospital	6 weeks
Carleton 2011 [30]	PTx/UC	Pain	21	90	51.20	-	Community	4 weeks
Carson 2010 [31]	MBE/UC	FIQ/Pain/Fatigue/Sleep/Depression	53	100	53.72	-	Community	8 weeks
Casanueva 2014 [32]	AC/UC	FIQ/Pain/Fatigue/Sleep/Depression	120	92	53.54	27.64	Unclear	6 weeks
Cash 2015 [33]	MIN/WL	FIQ/Pain/Fatigue/Sleep	91	-	-	-	Community	8 weeks
Castro-Sanchez 2011 [34]	MAS/PLA	FIQ/Pain/Fatigue/Sleep	94	-	54.40	-	Community	20 weeks
Castro-Sanchez 2014 [35]	MT/UC	FIQ/Pain/Sleep/Depression	89	54	53.51	-	Community	5 weeks
Castro-Sanchez 2017 [36]	AC/TAP	Pain	64	92	45.81	-	Community	4 weeks
Ceca 2017 [37]	MAS/WL	FIQ/Pain/Fatigue/Sleep/Depression	66	-	-	-	Community	20 weeks
Cedraschi 2004 [38]	MDT/WL	FIQ/Pain/Fatigue/Sleep/Depression	164	93	49.34	-	Hospital	6 weeks
Celenay 2017 [39]	MAS/UC	FIQ/Pain/Fatigue/Sleep/Depression	49	100	41.23	26.36	Hospital	6 weeks
Chesky 1997 [40]	MUS/UC	Pain	26	92	48.85	-	Mixed	immediate
Clarke-Jenssen 2014 [41]	MDT/UC	Pain	129	92	45.66	28.01	Hospital	4 weeks
Colbert 1999 [42]	MGT/PLA	FIQ/Pain/Fatigue/Sleep	30	-	49.66	-	Mixed	16 weeks
Da Costa 2005 [43]	ME/UC	FIQ	79	100	50.77	28.05	Mixed	12 weeks
Dailey 2013 [44]	ET/PLA	Pain/Fatigue	86	98	49.10	33.60	Mixed	3 weeks
Davis 2013 [45]	MIN/EDU	Pain	79	-	-	-	Community	6 weeks
De Andrade 2008 [46]	BAL/AEX (WB)	FIQ/Pain/Fatigue/Sleep/Depression	46	100	48.55	-	Unclear	12 weeks
Deluze 1992 [47]	AC/PLA	Pain/Sleep	70	77	47.87	-	Hospital	3 weeks
Donmez 2005 [48]	BAL/UC	FIQ/Pain/Fatigue/Sleep/Depression	30	100	43.21	-	Hospital	2 weeks
Edinger 2005 [49]	CBT/UC	Pain/Sleep	29	97	49.42	26.92	Community	6 weeks

Edwards 2000 [50]	FS/PLA	Pain/Fatigue/Sleep	24	100	45.60	-	Unclear	12 weeks
Ekici 2008 [51]	ME/CTM	Pain/Depression	51	100	37.27	23.06	Hospital	4 weeks
Ekici 2009 [52]	MLD/CTM	FIQ/Pain/Fatigue/Depression	53	100	37.88	23.24	Hospital	3 weeks
Ekici 2017 [53]	ME/CTM	FIQ/Pain/Fatigue/Sleep/Depression	43	100	36.99	22.85	Hospital	4 weeks
Ericsson 2016 [54]	SEX/MBE	Fatigue/Sleep/Depression	130	100	51.44	28.01	Community	15 weeks
Evcik 2002 [55]	BAL/UC	FIQ/Pain/Depression	42	74	41.76	-	Unclear	3 weeks
Evcik 2008 [56]	AEX/ME	Pain	63	100	43.32	26.70	Hospital	5 weeks
Fagerlund 2015 [57]	tDCS/PLA	FIQ/Pain/Depression	48	94	48.61	-	Community	5 days
Falcao 2008 [58]	CBT/UC	FIQ/Pain/Depression	60	100	45.67	-	Hospital	10 weeks
Fernandes 2016 [59]	AEX(WB)/AEX (LB)	FIQ/Pain	75	100	48.78	25.93	Hospital	12 weeks
Field 2003 [60]	FEX/SEX	Pain	40	-	-	-	Community	3 weeks
Fioravanti 2007 [61]	BAL/UC	FIQ/Pain	80	98	47.40	-	Hospital	2 weeks
Fioravanti 2009 [62]	BAL/UC	FIQ	56	100	51.07	-	Unclear	10 days
Fitzgibbon 2018 [63]	tDCS/PLA	FIQ/Pain/Fatigue/Depression	26	92	45.61	-	Community	4 weeks
Fontaine 2010 [64]	AEX/UC	FIQ/Pain/Fatigue/Depression	84	96	47.58	30.68	Mixed	12 weeks
Fors 2000 [65]	EDU/PTx/UC	Pain	58	-	-	-	Community	30 minutes
Friesen 2017 [66]	EDU/WL	FIQ/Pain/Fatigue/Depression	60	95	47.50	-	Mixed	8 weeks
Garcia-Martinez 2012 [67]	ME/UC	FIQ/Pain	28	100	58.95	28.30	Community	12 weeks
Gillis 2006 [68]	PTx/UC	FIQ/Pain/Fatigue/Sleep	83	-	-	-	Mixed	4 days
Gowans 1999 [69]	ME/WL	Pain/Fatigue/Sleep/Depression	45	78	45.42	-	Hospital	6 weeks
Gowans 2001 [70]	AEX/UC	FIQ/Pain/Depression	50	88	46.99	-	Mixed	23 weeks
Gur 2002 [71]	ET/PLA	Pain/Fatigue/Sleep	40	100	-	-	Hospital	2 weeks
Hakkinen 2001 [72]	SEX/UC	Pain/Fatigue/Sleep/Depression	21	100	38.05	-	Unclear	21 weeks
Hammond 2006 [73]	EDU/UC	FIQ/Pain/Fatigue/Sleep/Depression	183	90	48.53	-	Hospital	10 weeks
Hargrove 2012 [74]	tDCS/PLA	FIQ/Pain/Fatigue/Sleep/Depression	91	92	52.66	-	Hospital	11 weeks
Harris 2005 [75]	AC/PLA	Pain/Fatigue	114	93	47.40	-	Community	9 weeks
Hedman 2018 [76]	PTx/WL	FIQ/Pain/Fatigue	140	98	50.55	-	Community	10 weeks

Hooten 2012 [77]	SEX/AEX	Pain	72	90	46.55	-	Hospital	3 weeks
Ide 2008 [78]	AEX/UC	FIQ/Pain/Fatigue/Sleep/Depression	40	100	46.04	-	Unclear	4 weeks
Ittersum 2014 [79]	EDU/MBE	FIQ/Pain/Fatigue/Sleep/Depression	105	93	46.71	-	Hospital	2 weeks
Izquierdo 2007 [80]	AEX/UC	FIQ/Pain/Sleep	60	100	48.33	27.00	Community	16 weeks
Jensen 2012 [81]	CBT/WL	Pain/Depression	43	100	45.50	25.69	Hospital	12 weeks
Jones 2012 [82]	MBE/EDU	FIQ/Pain/Sleep	101	93	54.04	30.50	Mixed	12 weeks
Kayo 2012 [83]	SEX/AEX/UC	FIQ/Pain	90	100	46.83	26.40	Hospital	16 weeks
Keel 1998 [84]	MDT/UC	Pain	32	75	49.00	-	Hospital	15 weeks
Kesiktas 2011 [85]	BAL/UC	Pain/Depression	56	100	44.68	-	Hospital	3 weeks
Khedr 2017 [86]	tDCS/PLA	Pain/Depression	40	95	32.60	-	Hospital	2 weeks
Kibar 2015 [87]	MBE/UC	FIQ/Depression	68	96	48.14	27.23	Hospital	6 weeks
King 2002 [88]	EDU/AEX/WL	FIQ/Pain	170	100	46.08	-	Unclear	12 weeks
Kiyak 2009 [89]	MoC/PLA	FIQ/Pain/Fatigue/Sleep/Depression	50	100	37.40	-	Hospital	6 weeks
Kocyigit 2016 [90]	BAL/UC	FIQ/Pain/Fatigue	66	100	42.11	27.80	Hospital	4 weeks
Kravitz 2006 [91]	tDCS/PLA	Pain/Fatigue/Depression	64	92	46.97	-	Mixed	11 weeks
Kulcu 2009 [92]	ET/UC	FIQ/Pain/Sleep	60	95	37.00	-	Hospital	3 weeks
Kurt 2016 [93]	BAL/ME/UC	FIQ/Pain/Sleep/Depression	120	100	38.38	-	Hospital	3 weeks
Lami 2018 [94]	CBT/UC	FIQ/Pain/Fatigue/Depression	126	100	50.13	-	Mixed	9 weeks
Lange 2011 [95]	MDT/UC	Pain/Depression	166	-	54.34	-	Hospital	3 weeks
Larsson 2015 [96]	SEX/MBE	FIQ/Pain	130	100	51.44	28.01	Community	15 weeks
Lauche 2016 [97]	CUP/PLA/UC	FIQ/Pain/Fatigue/Sleep	141	99	55.81	28.26	Community	2.5 weeks
Lazaridou 2017 [98]	CBT/EDU	Pain/Depression	17	82	45.70	-	Community	4 weeks
Lemstra 2005 [99]	MDT/UC	Pain/Depression	79	85	49.43	-	Hospital	6 weeks
Liu 2012 [100]	MBE/UC	FIQ/Pain/Fatigue/Sleep	14	100	56.50	-	Mixed	6 weeks
LopezRodrigues 2012 [101]	AEX/FEX	FIQ/Pain/Fatigue/Sleep/Depression	70	100	55.40	-	Hospital	12 weeks
LopezRodriguez 2013 [102]	AEX/FEX	FIQ/Pain/Fatigue/Sleep/Depression	76	100	54.84	-	Community	12 weeks
Luciano 2011 [103]	PTx/UC	FIQ/Pain/Fatigue/Sleep/Depression	216	98	55.30	-	Hospital	9 weeks

Maddali 2010 [104]	MBE/WL	FIQ/Pain/Sleep	44	93	45.50	-	Community	8 weeks
Maestú 2013 [105]	MGT/PLA	Pain	67	100	-	-	Community	8 weeks
Mannerkopi 2004 [106]	MBE/UC	FIQ	36	100	45.00	-	Unclear	12 weeks
Martin 1996 [107]	MBE/ME	FIQ	60	97	44.80	-	Mixed	6 weeks
Martin 2006 [108]	AC/PLA	FIQ/Pain/Fatigue/Sleep/Depression	50	98	49.80	-	Hospital	2-3 weeks
Martinez 2013 [109]	CBT/SH	FIQ/Pain/Fatigue/Sleep/Depression	64	100	47.60	-	Hospital	6 weeks
MartínNogueras 2012 [110]	ME/UC	Pain	29	100	50.42	-	Community	12 weeks
Mason 1998 [111]	MDT/UC	FIQ/Pain/Fatigue/Sleep/Depression	21	100	44.68	-	Hospital	4 weeks
McCain 1986 [112]	AEX/FEX	Pain	34	85	42.71	-	Hospital	20 weeks
Meiworm 2000 [113]	AEX/UC	Pain	39	92	46.23	-	Hospital	12 weeks
Mendonca 2016 [114]	tDCS/UC	Pain/Depression	45	98	47.47	-	Mixed	4 weeks
Mercadie 2015 [115]	MUS/UC	Pain/Fatigue	44	100	51.40	-	Community	4 weeks
Merchant 2001 [116]	FS/PLA	FIQ	86	98	47.10	-	Unclear	12 weeks
Mhalla 2011 [117]	tDCS/PLA	FIQ/Depression	40	-	50.70	-	Unclear	21 weeks
Miró 2011 [118]	CBT/SH	FIQ/Pain/Sleep/Depression	44	100	47.07	-	Hospital	6 weeks
Mirzaei 2018 [119]	FS/PLA	FIQ/Pain/Fatigue/Sleep/Depression	74	100	41.55	-	Hospital	8 weeks
Molinari 2018 [120]	PTx/UC	Pain/Depression	80	100	51.08	-	Hospital	4 weeks
Molina-Torres 2016 [121]	ET/OS	Pain/Sleep	58	95	51.40	-	Community	12 weeks
Montero-Marin 2018 [122]	MIN/UC	FIQ/Depression	42	100	51.45	-	Hospital	8 weeks
Moustafa 2015 [123]	MT/UC	FIQ/Sleep/Depression	120	43	52.45	-	Hospital	12 weeks
Munguia 2008 [124]	ME/UC	FIQ/Sleep	60	100	48.33	27.00	Hospital	16 weeks
Mutlu 2013 [125]	ET/UC	FIQ/Pain	66	100	44.47	28.89	Hospital	12 weeks
Olivares 2011 [126]	WBV/UC	FIQ	41	100	52.69	-	Community	12 weeks
Oliver 2001 [127]	EDU/UC	FIQ/Pain/Depression	600	95	53.93	-	Community	52 weeks
Onieva-Zafra 2013 [128]	MUS/UC	Pain/Depression	60	97	51.80	-	Community	4 weeks
Onieva-Zafra 2015 [129]	PTx/UC	Pain/Depression	60	3	52.47	-	Community	8 weeks
Ozkurt 2012 [130]	BAL/UC	FIQ/Pain/Depression	50	100	48.84	-	Hospital	2 weeks

Panton 2009 [131]	MT/UC	FIQ	27	100	48.67	31.19	Unclear	16 weeks
Panton 2013 [132]	ET/PLA	FIQ/Pain	41	100	52.88	30.65	Community	4 weeks
Paolucci 2016 [133]	ME/UC	FIQ	62	100	50.35	24.65	Hospital	5 weeks
Parra-Delgado 2013 [134]	MIN/UC	FIQ/Depression	33	100	52.92	-	Community	8 weeks
Passard 2007 [135]	tDCS/PLA	FIQ/Pain/Fatigue/Sleep/Depression	30	100	53.95	-	Unclear	2 weeks
Picard 2013 [136]	PTx/WL	FIQ/Pain/Fatigue/Depression	62	100	48.70	-	Hospital	5sessiones
Ramsay 2000 [137]	AEX (S)/AEX (US)	Pain/Depression	74	-	-	-	Hospital	12 weeks
Rasmussen 2017 [138]	MDT/WL	FIQ/Pain	187	100	44.35	26.95	Hospital	2 weeks
Relton 2009 [139]	HOM/UC	FIQ/Pain/Fatigue/Sleep/Depression	47	94	45.69	-	Hospital	22 weeks
Richards 2002 [140]	AEX/FEX	FIQ	136	93	46.52	-	Hospital	12 weeks
Rodriguez 2015 [141]	MT/UC	Pain/Fatigue	48	81	53.05	28.35	Community	8 weeks
Roman 2018 [142]	FS/PLA	FIQ/Pain/Depression	40	100	52.64	29.82	Community	8 weeks
Rooks 2007 [143]	SEX/UC	FIQ/Pain/Fatigue/Sleep/Depression	207	100	49.75	29.25	Mixed	16 weeks
Ruaro 2014 [144]	ET/PLA	FIQ/Pain/Fatigue/Sleep/Depression	20	95	41.40	-	Unclear	4 weeks
Rus 2017 [145]	FS/PLA	FIQ/Pain	23	100	50.78	26.37	Community	3 weeks
Rutledge 2007 [146]	TO/PLA	Pain	51	100	53.31	-	Mixed	12 weeks
Santos 2017 [147]	MoC/PLA	FIQ/Pain	39	100	51.50	26.87	Community	8 weeks
Sañudo 2010 [148]	WBV/UC	FIQ	30	100	59.01	-	Mixed	6 weeks
Sañudo 2011 [149]	ME/UC	FIQ/Pain/Depression	42	100	55.82	28.61	Community	24 weeks
Sañudo 2012 [150]	ME/UC	FIQ/Depression	41	100	-	-	Mixed	24 weeks
Sanudo 2015 [151]	AEX/UC	Pain/Sleep/Depression	32	100	56.50	29.65	Community	24 weeks
Saral 2016 [152]	MDT/UC	FIQ/Pain/Fatigue/Sleep/Depression	66	100	41.73	24.30	Hospital	10 weeks
Schachter 2003 [153]	AEX/UC	FIQ/Pain/Fatigue/Sleep	143	100	41.83	-	Hospital	16 weeks
Schmidt 2011 [154]	MIN/WL	FIQ/Sleep/Depression	177	100	52.53	-	Mixed	8 weeks
Senna 2012 [155]	WEI/UC	FIQ/Sleep/Depression	86	91	45.55	32.55	Hospital	6 months
Sephton 2007 [156]	MIN/WL	Depression	91	100	48.05	-	Community	8 weeks
Short 2011 [157]	tDCS/PLA	FIQ/Pain/Depression	20	85	52.94	-	Mixed	2 weeks

Soares 2002 [158]	EDU/CBT	FIQ/Pain/Sleep	53	100	45.04	-	Hospital	10 weeks
Stival 2014 [159]	AC/PLA	Pain	36	86	50.83	-	Hospital	1 session
Stuifbergen 2010 [160]	PTx/UC/WL	FIQ	234	100	-	-	Community	8 weeks
Sutbeyaz 2009 [161]	MGT/PLA	FIQ/Pain/Depression	56	100	41.93	25.52	Hospital	3 weeks
Targino 2008 [162]	AC/UC	Pain	58	100	51.71	-	Hospital	10 weeks
Taylor 2009 [163]	ET/PLA	FIQ/Pain/Fatigue	19	-	48.00	-	Mixed	6 weeks
Tekin 2014 [164]	tDCS/PLA	Pain/Depression	52	90	44.37	-	Hospital	10 weeks
Tomas-Carus 2007 [165]	ME/UC	FIQ/Pain	35	100	51.00	27.00	Community	12 weeks
Tomas-Carus 2009 [166]	ME/UC	Pain	30	100	50.80	27.70	Community	32 weeks
Tomas-Carus 2018 [167]	MBE/UC	FIQ/Pain/Fatigue/Sleep/Depression	35	100	52.50	26.46	Community	12 weeks
Torres 2018 [168]	MUS/UC	FIQ/Pain/Depression	70	100	51.36	-	Community	12 weeks
Ugurlu 2017 [169]	AC/PLA	FIQ/Pain/Fatigue/Depression	50	100	45.44	-	Unclear	8 weeks
Valencia 2009 [170]	FEX/MAS	FIQ	20	100	55.25	-	Community	12 weeks
Valim 2003 [171]	FEX/AEX	FIQ/Pain/Depression	76	100	45.50	27.00	Hospital	20 weeks
Vallejo 2015 [172]	CBT/WL	FIQ/Depression	60	100	51.55	-	Hospital	10 weeks
Van Gordon 2017 [173]	MIN/CBT	FIQ/Pain/Sleep	148	83	46.88	-	Mixed	8 weeks
Van Ooster 2013 [174]	EDU/UC	FIQ/Pain	30	87	45.85	-	Hospital	2sessiones
Van Santen 2002 [175]	BIO/UC	Pain/Fatigue	143	100	44.81	-	Hospital	24 weeks
Vayvay 2016 [176]	ET/PLA	FIQ/Pain/Depression	45	-	37.47	26.43	Hospital	3 weeks
Verkaik 2014 [177]	PTx/UC	FIQ/Pain	70	99	47.51	-	Community	8 weeks
Walz 2013 [178]	BAL/UC	FIQ/Pain	94	96	54.10	27.86	Hospital	3 weeks
Wang 2010 [179]	MBE/EDU	FIQ/Pain/Sleep/Depression	66	86	50.10	32.70	Hospital	12 weeks
Wang 2018 [180]	MBE/AEX	FIQ/Sleep/Depression	226	92	51.63	30.07	Mixed	24 weeks
Weber 2015 [181]	MUS/UC	FIQ	120	-	48.28	-	Hospital	5 weeks
Wepner 2014 [182]	FS/PLA	Pain	30	93	48.37	-	Mixed	20 weeks
Wicksell 2013 [183]	PTx/WL	FIQ/Pain/Depression	40	100	45.10	-	Hospital	12 weeks
Williams 2010 [184]	CBT/UC	Pain/Fatigue/Sleep/Depression	118	95	50.46	28.68	Hospital	24 weeks

Yagci 2014 [185]	tDCS/PLA	FIQ/Pain/Depression	28	100	44.13	30.03	Unclear	2 weeks
Yildiz 2004 [186]	HOT/PLA	Pain	50	70	40.18	-	Unclear	3 weeks
Yurtkuran 1996 [187]	BAL/UC	Pain	40	93	35.45	-	Hospital	2 weeks

AC: Acupuncture, AEX: Aerobic exercise, BAL: Balneotherapy, BIO: Biofeedback, CBT: Cognitive behavioural therapy, CUP: Cupping therapy, EDU: Education, ET: Electrotherapy, FEX: Flexibility exercise FS: Food supplement, HOM: Homeopathy, HOT: Hyperbaric oxygen therapy, LB: Land based, MAS: Massage, MBE: Mind-body exercise, MDT: Multidisciplinary treatment, ME: Mixed exercise, MGT: Magnetotherapy, MIN: Mindfulness, MLD MoC: Material of cloth, MT: Manual therapy, MUS PTx: Psychological treatment, S: Supervised, SEX: Strengthening exercise, TAP: Taping, tDCS: Transcranial direct current stimulation, TO: Topical oil, UC: Usual care, US: Unsupervised, WB: Water based, WBV: Whole body vibration, WL: Waiting list, WEI: Weight loss

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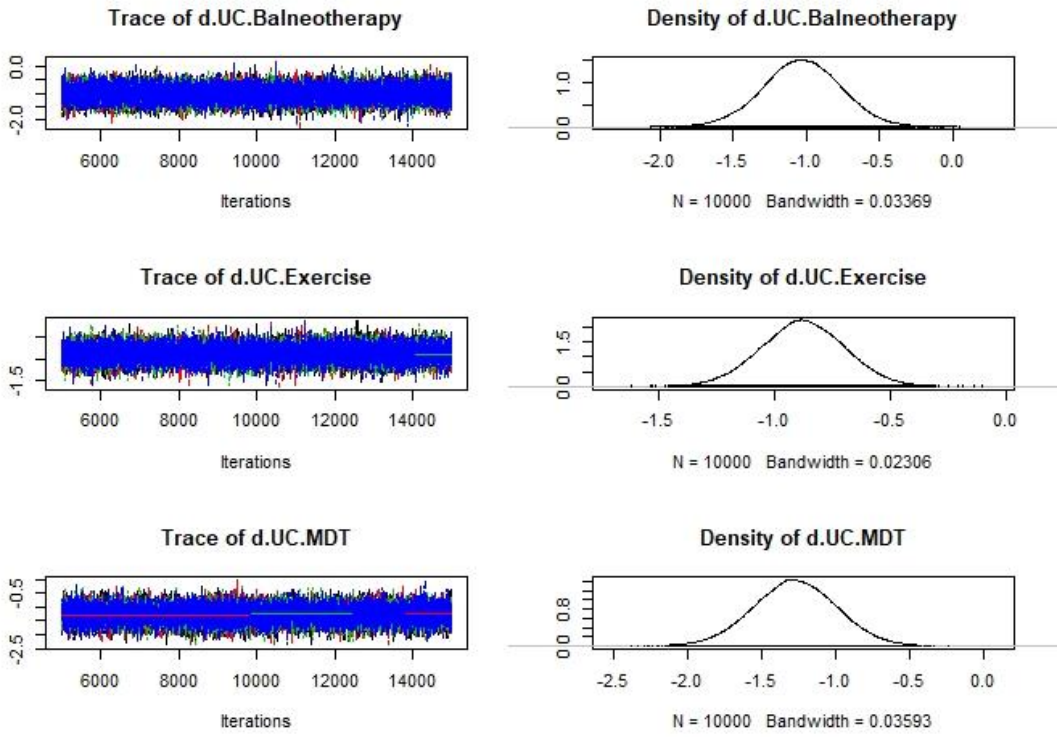
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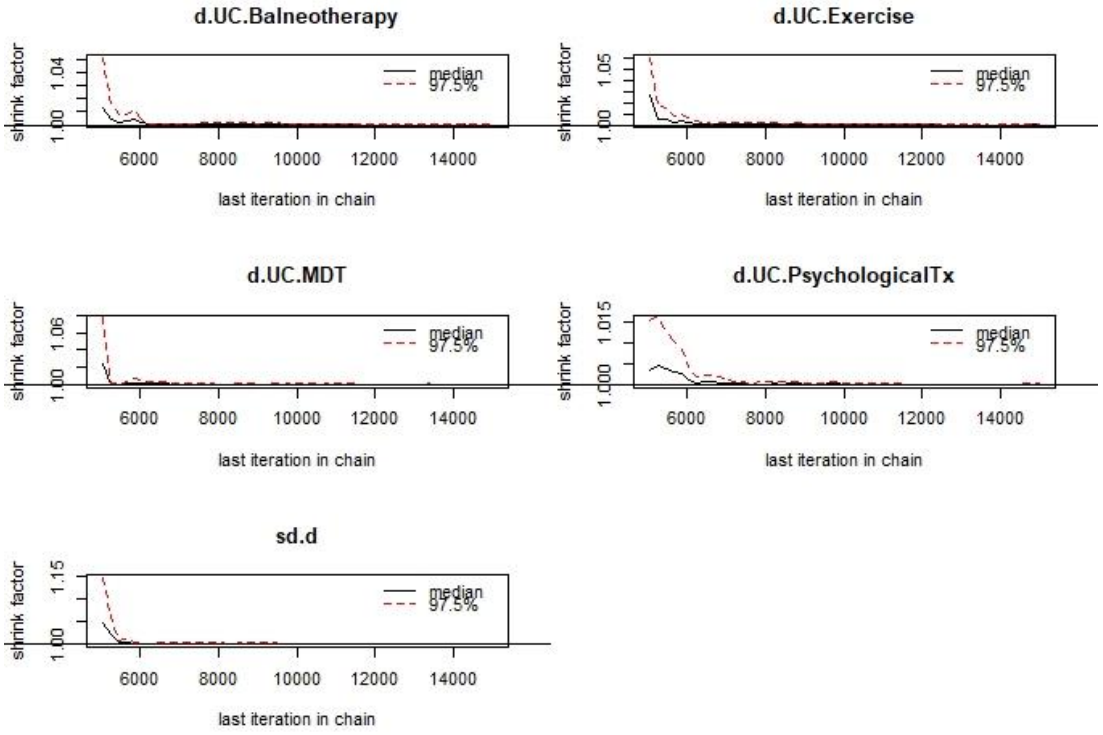
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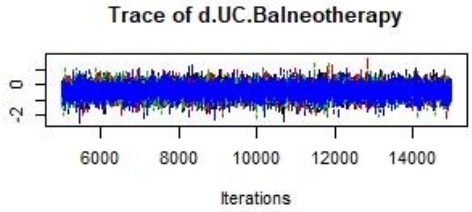
Appendix 6 MCMC simulations and Gelman-Rubin-Brooks plots for non-pharmacological interventions in pain, fatigue, sleep and depression

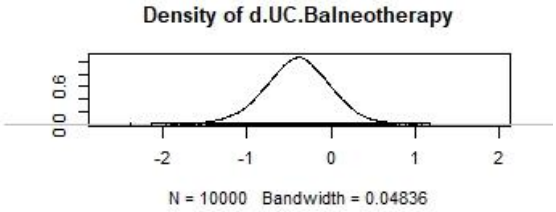
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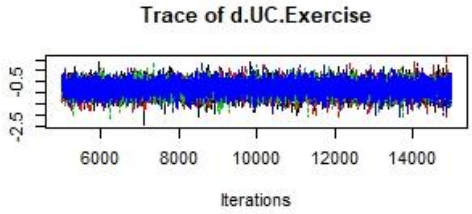


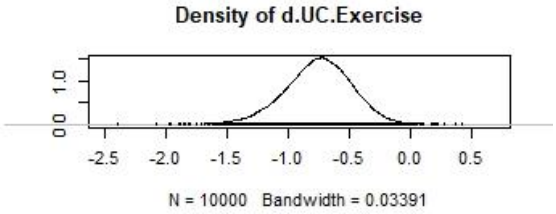

d.UC.Balneotherapy
shrink factor
1.00
1.04
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.UC.Exercise
shrink factor
1.00
1.05
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.UC.MDT
shrink factor
1.00
1.06
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.UC.PsychologicalTx
shrink factor
1.000
1.015
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
sd.d
shrink factor
1.00
1.15
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain

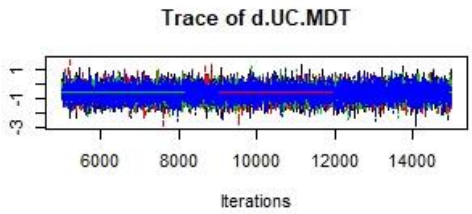
- Trace, density plots and Gelman-Rubin-Brooks plot for fatigue

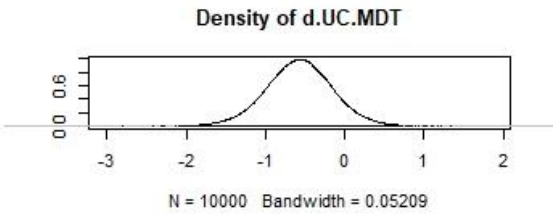


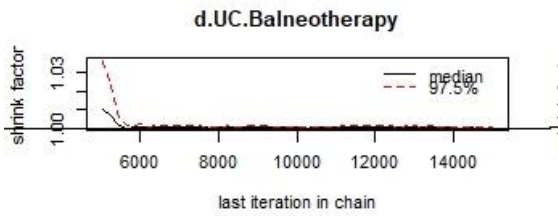


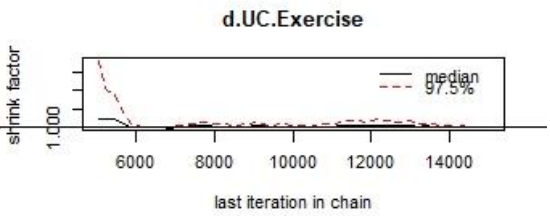


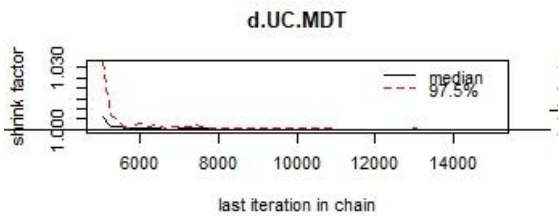


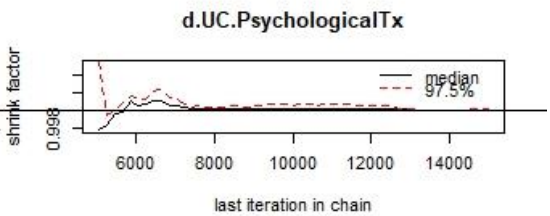


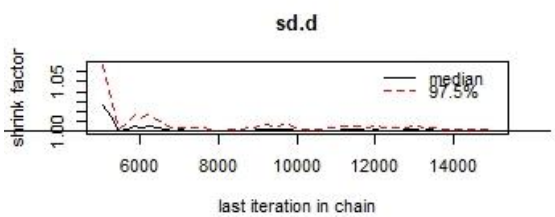




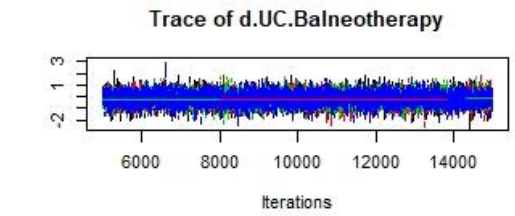


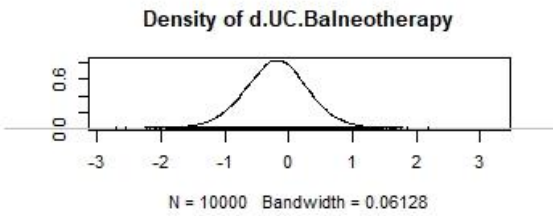


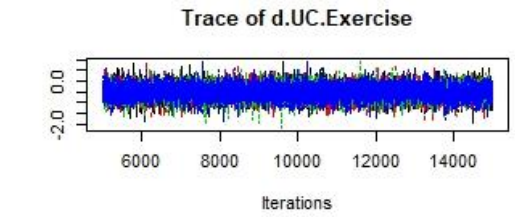


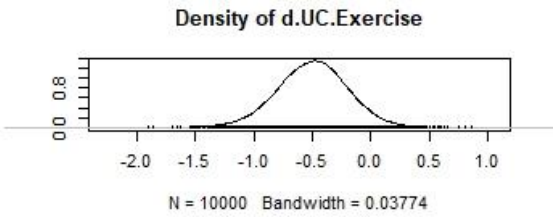


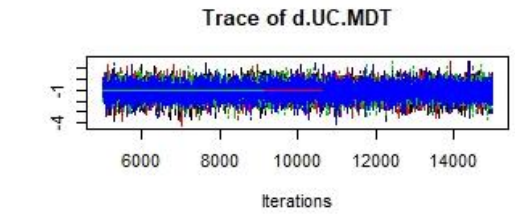
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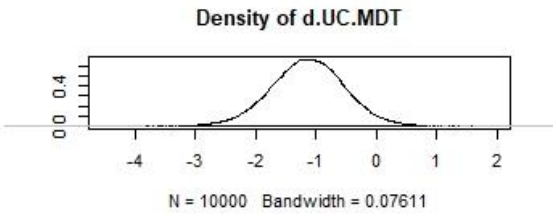


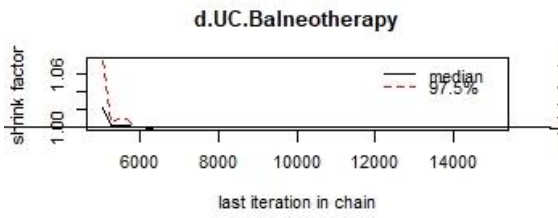


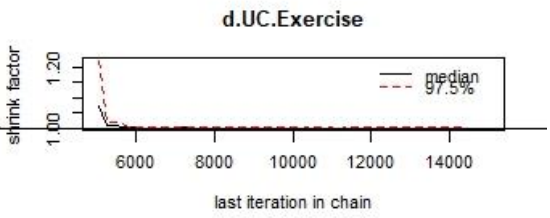


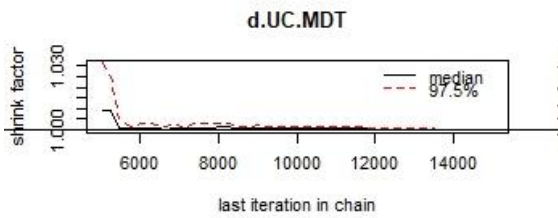


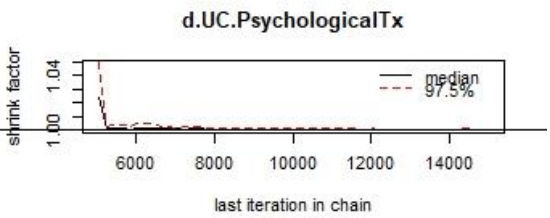


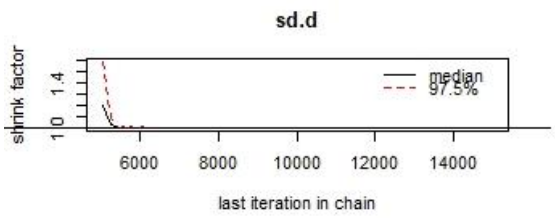




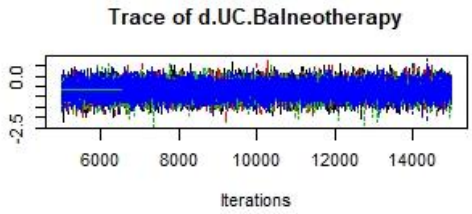


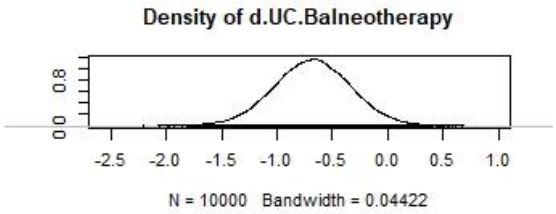


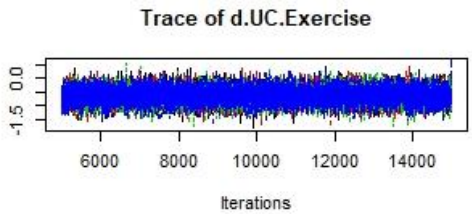


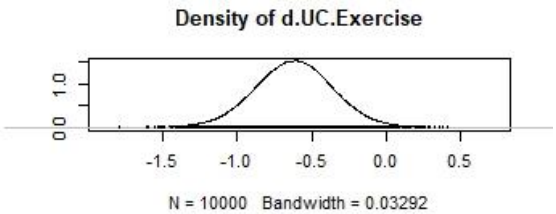


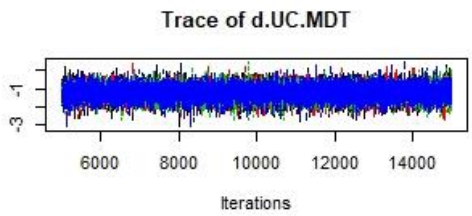
- Trace, density plots and Gelman-Rubin-Brooks plot for depression

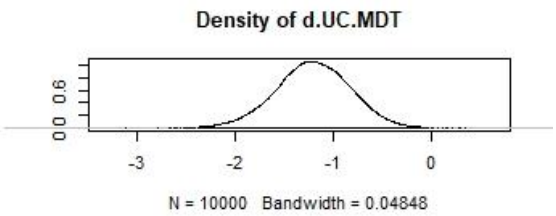


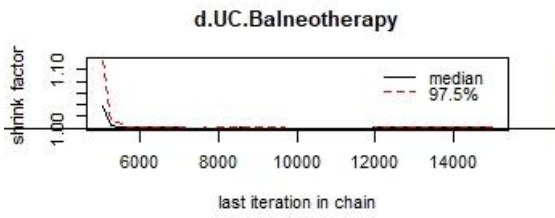


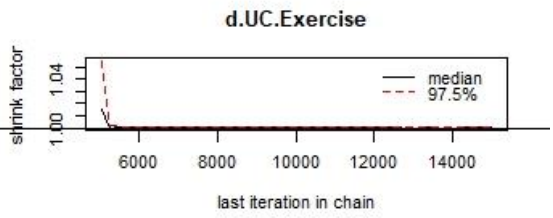


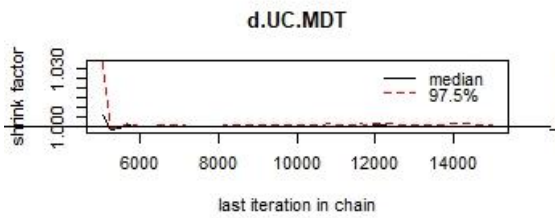


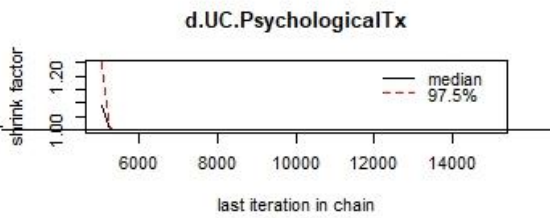


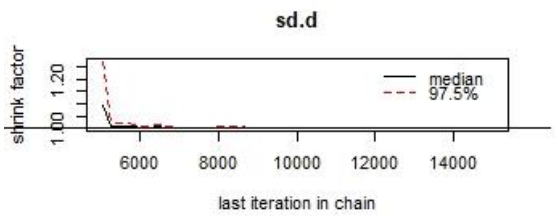






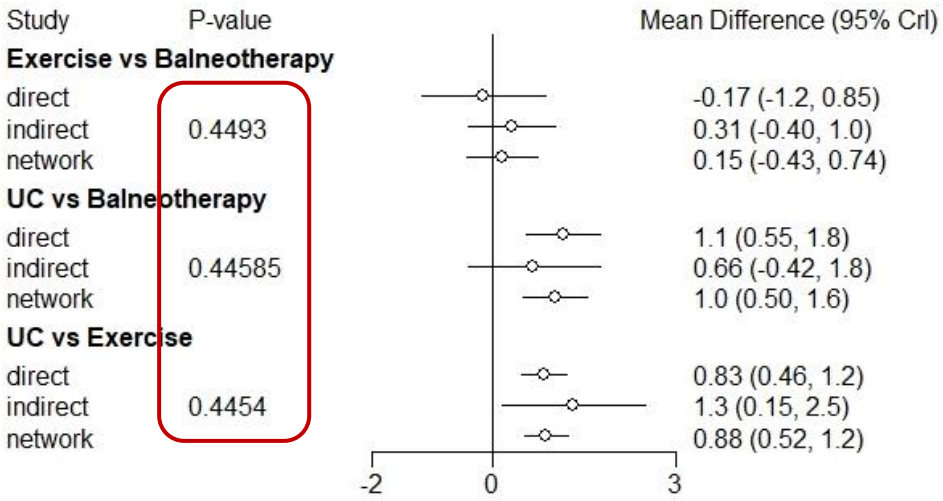




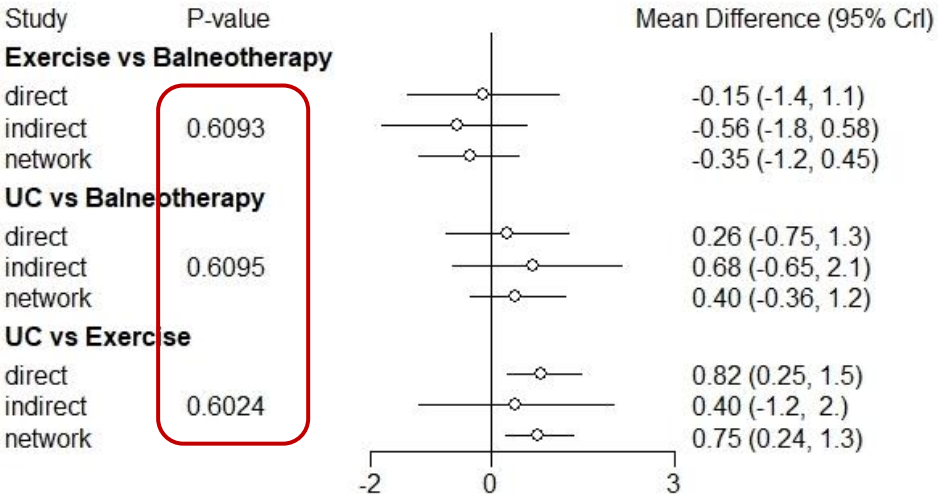


Appendix 7 Node splitting analysis of inconsistency for non-pharmacological interventions in pain, fatigue, sleep and depression

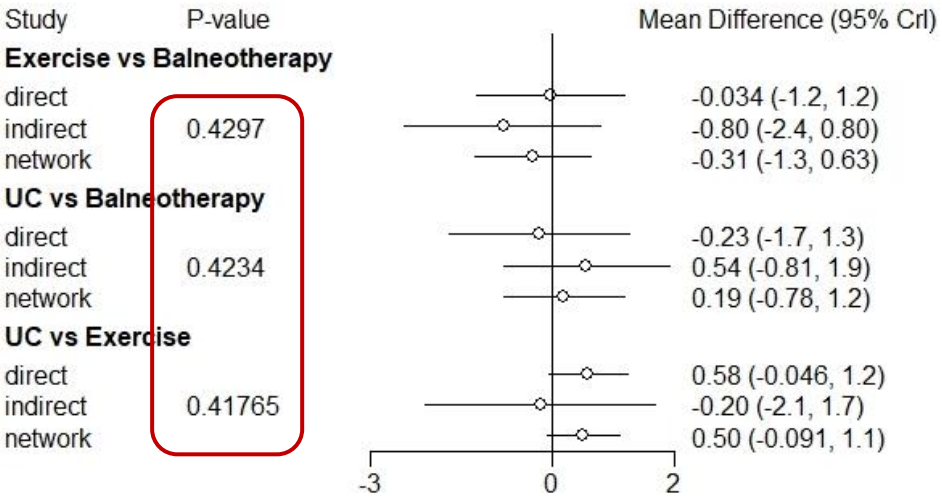
- Node-splitting analysis of inconsistency for pain



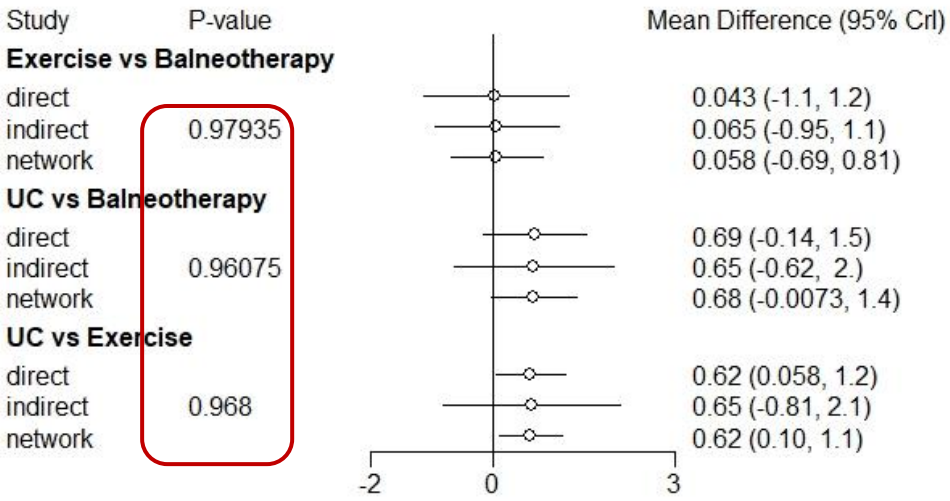
- Node-splitting analysis of inconsistency for fatigue



- Node-splitting analysis of inconsistency for sleep

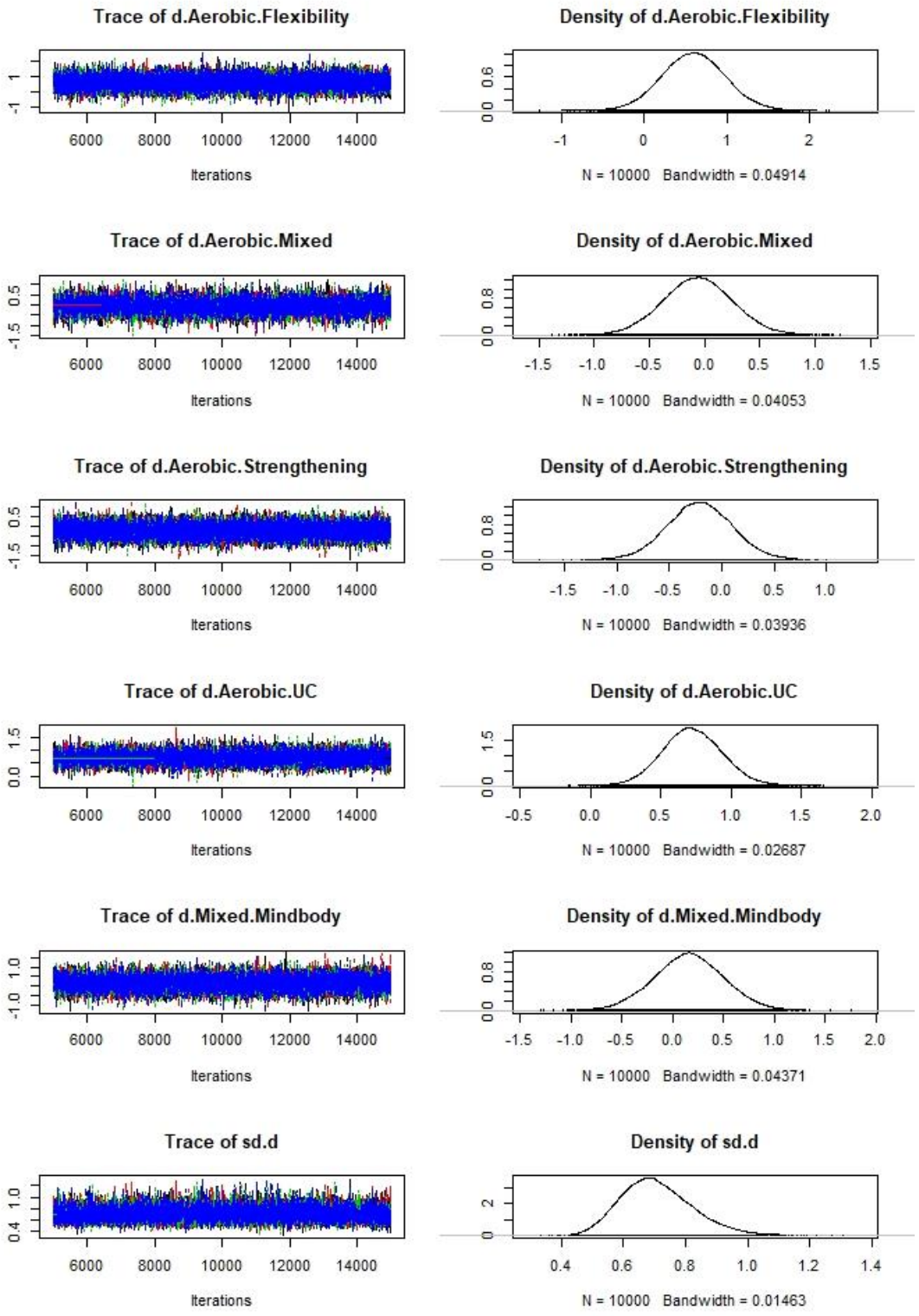


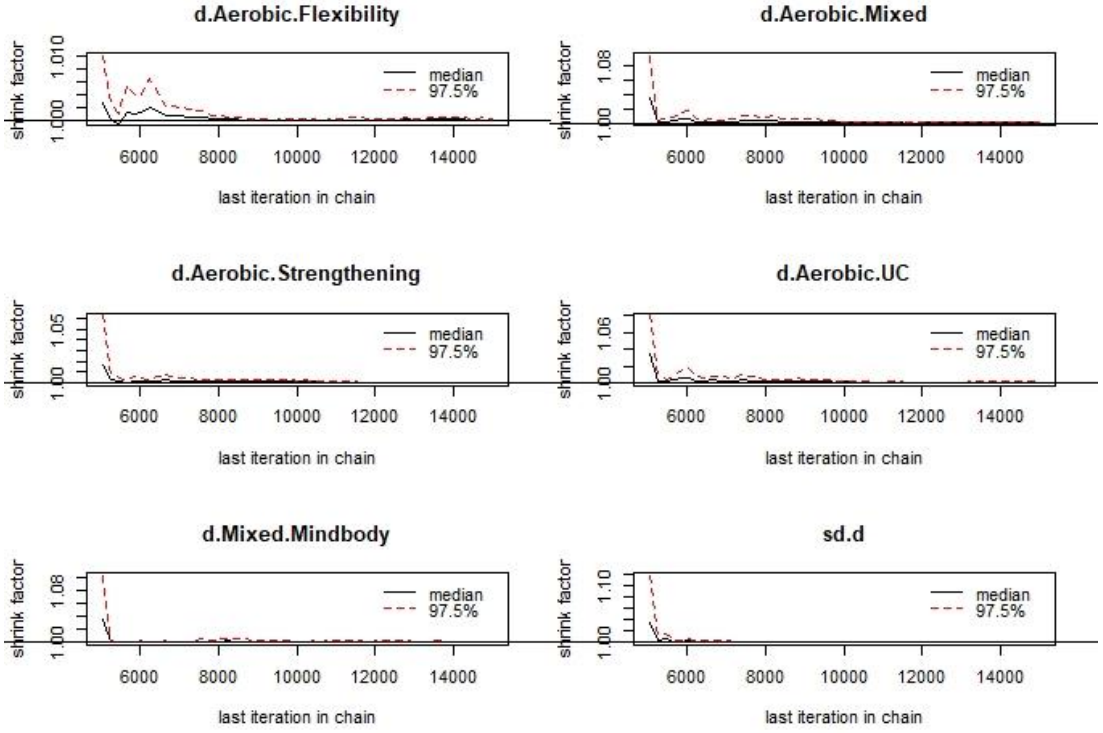
- Node-splitting analysis of inconsistency for depression



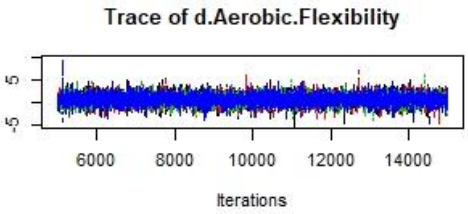
Appendix 8 MCMC simulations and Gelman-Rubin-Brooks plots for exercise types in pain, fatigue, sleep and depression

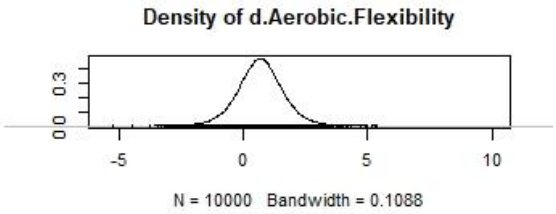
- Trace, density plots and Gelman-Rubin-Brooks plot for pain

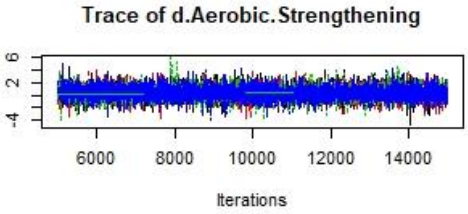


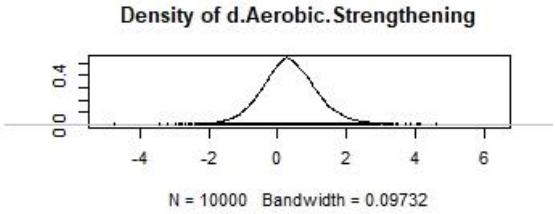

d.Aerobic.Flexibility
d.Aerobic.Mixed
d.Aerobic.Strengthening
d.Aerobic.UC
d.Mixed.Mindbody
sd.d
shrink factor
median
97.5%
last iteration in chain
6000
8000
10000
12000
14000

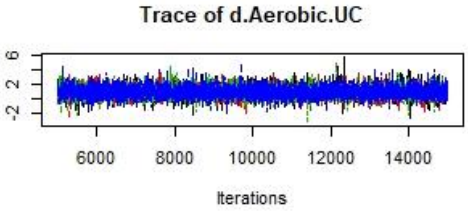
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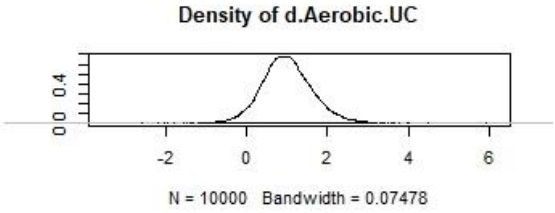


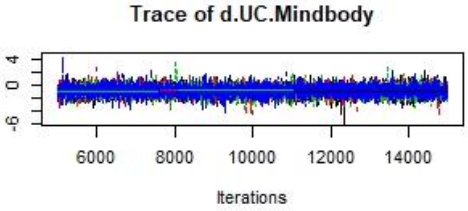


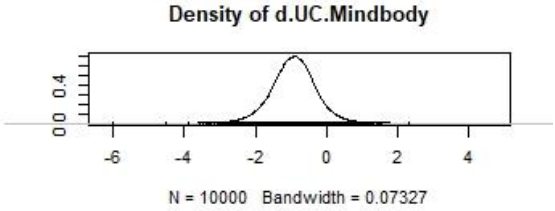


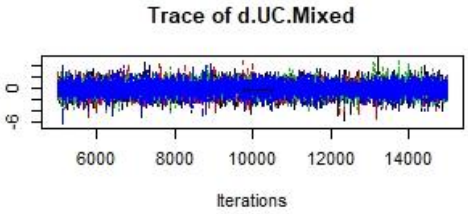


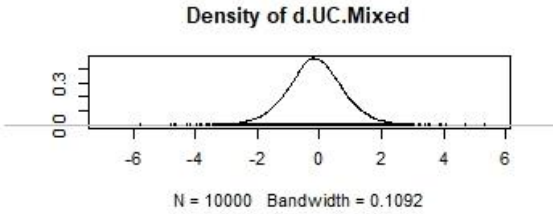


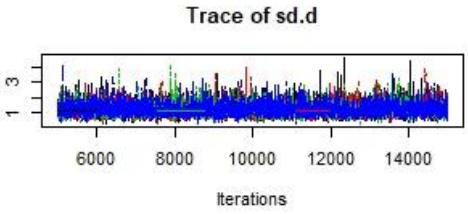


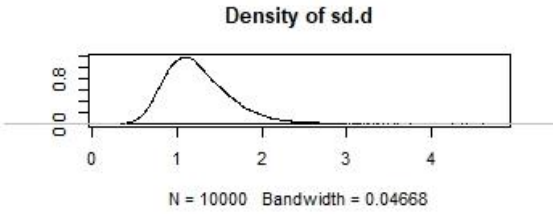


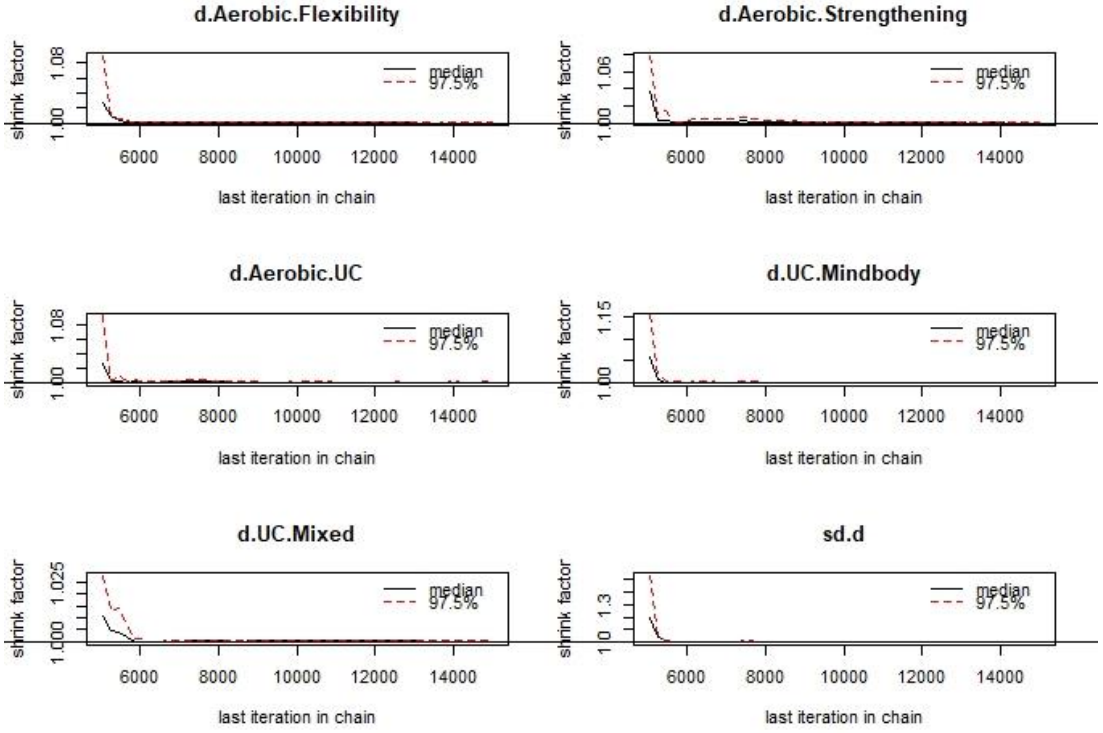




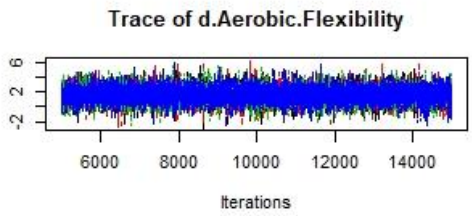


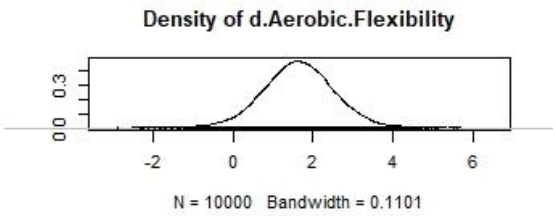


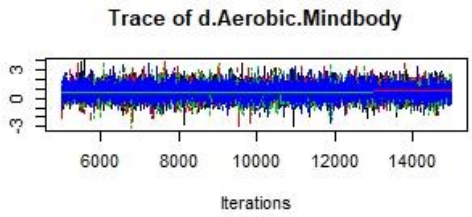


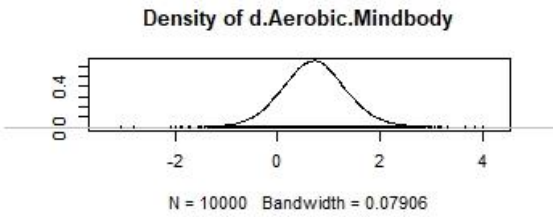

d.Aerobic.Flexibility
d.Aerobic.Strengthening
d.Aerobic.UC
d.UC.Mindbody
d.UC.Mixed
sd.d
shrink factor
median
97.5%
last iteration in chain
6000
8000
10000
12000
14000

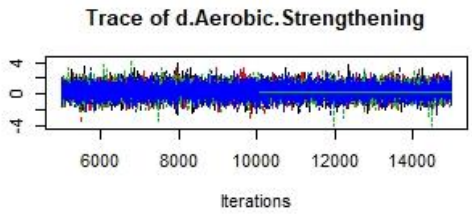
- Trace, density plots and Gelman-Rubin-Brooks plot for sleep

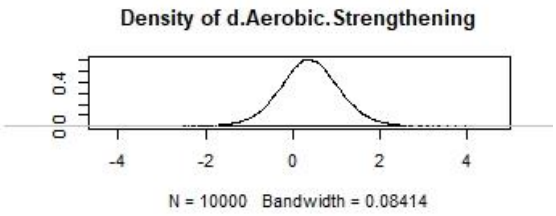


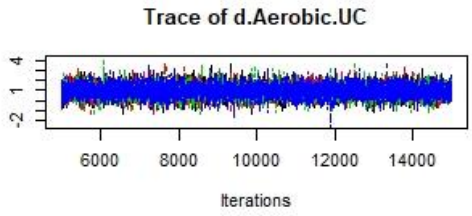


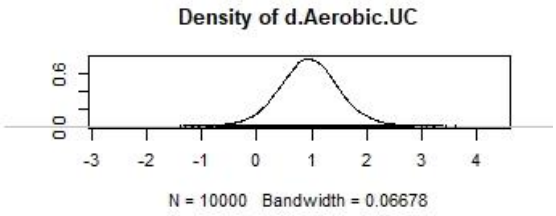


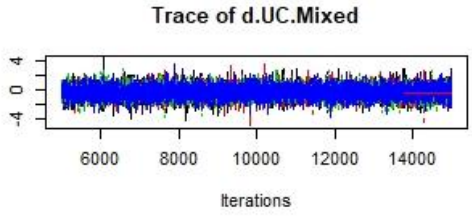


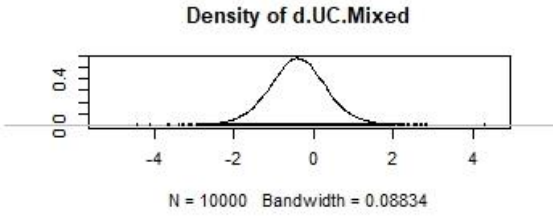


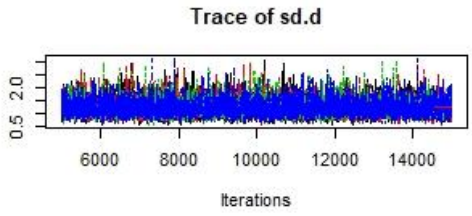


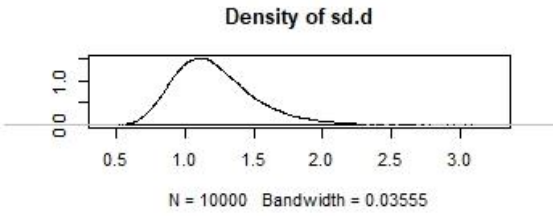


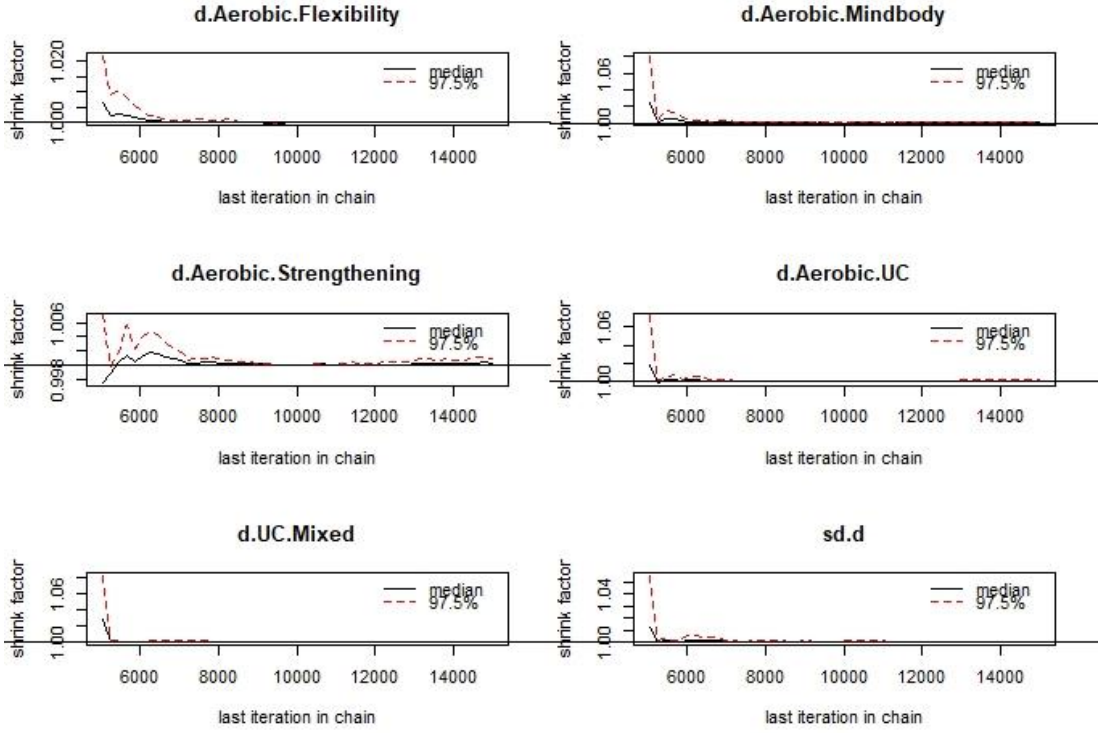




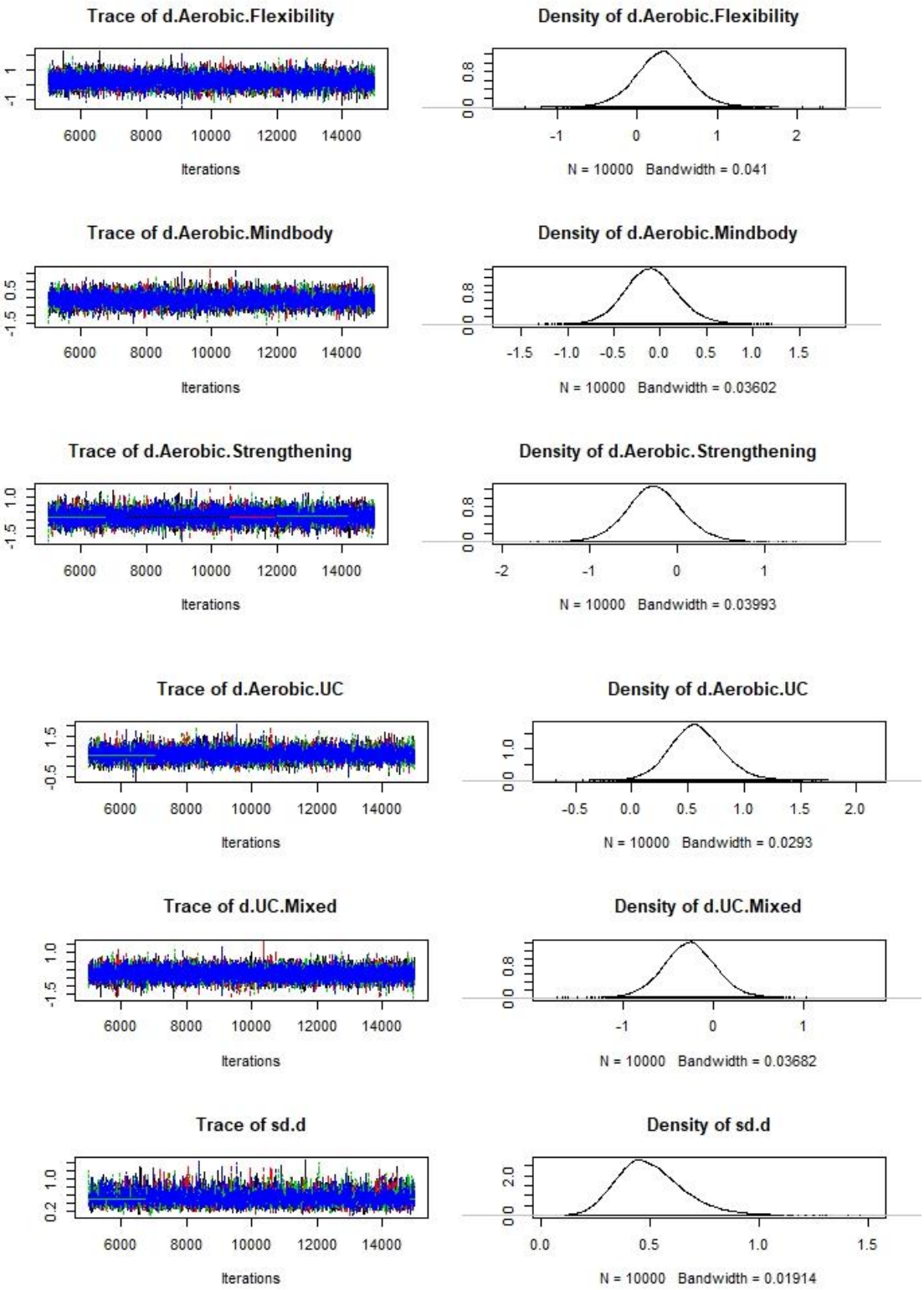


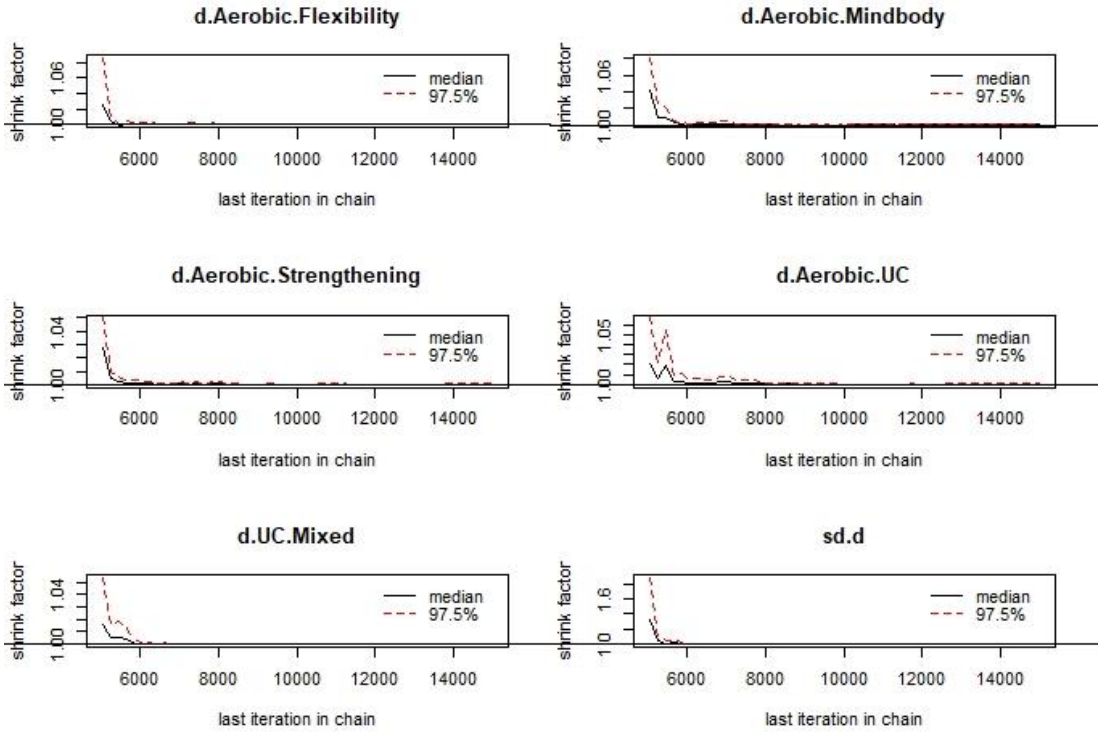





d.Aerobic.Flexibility
shrink factor
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1.020
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.Aerobic.Mindbody
shrink factor
1.00
1.06
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.Aerobic.Strengthening
shrink factor
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1.006
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.Aerobic.UC
shrink factor
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1.06
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.UC.Mixed
shrink factor
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1.06
median
97.5%
6000
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10000
12000
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last iteration in chain

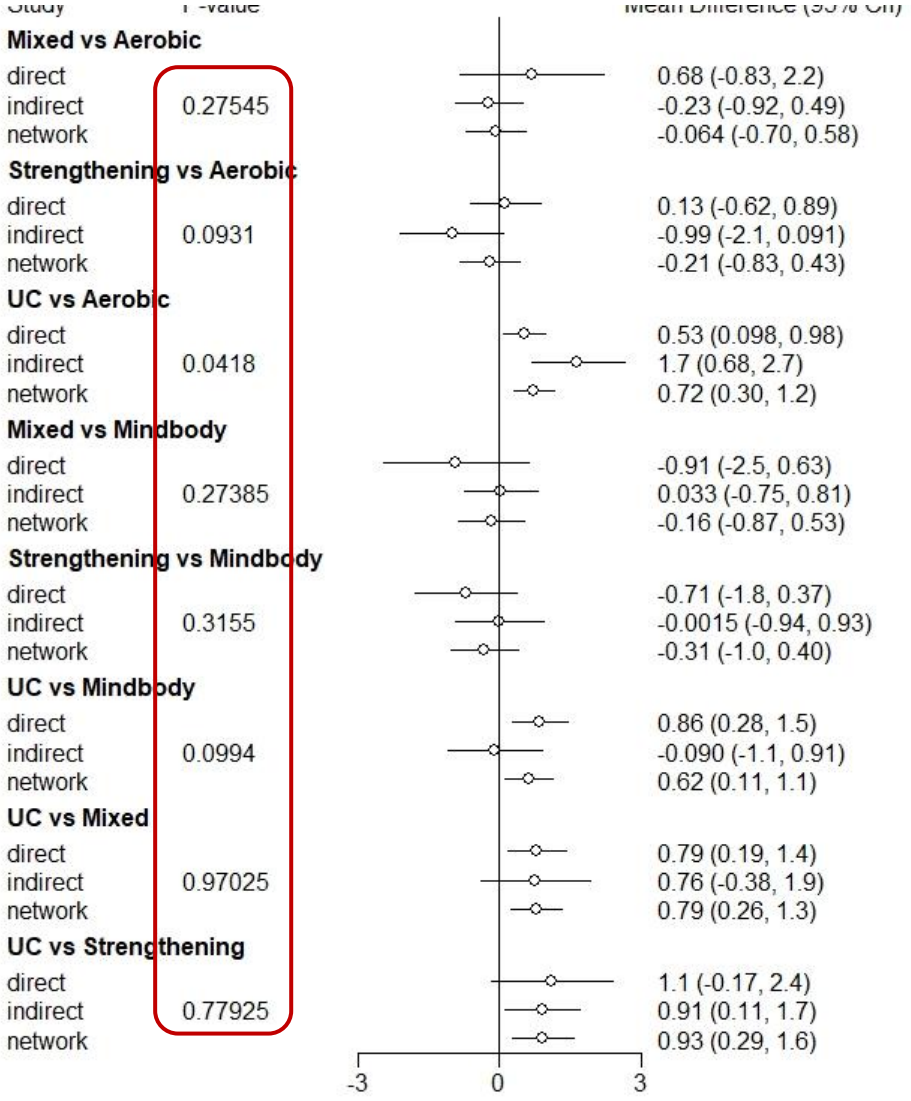
- Trace, density plots and Gelman-Rubin-Brooks plot for depression



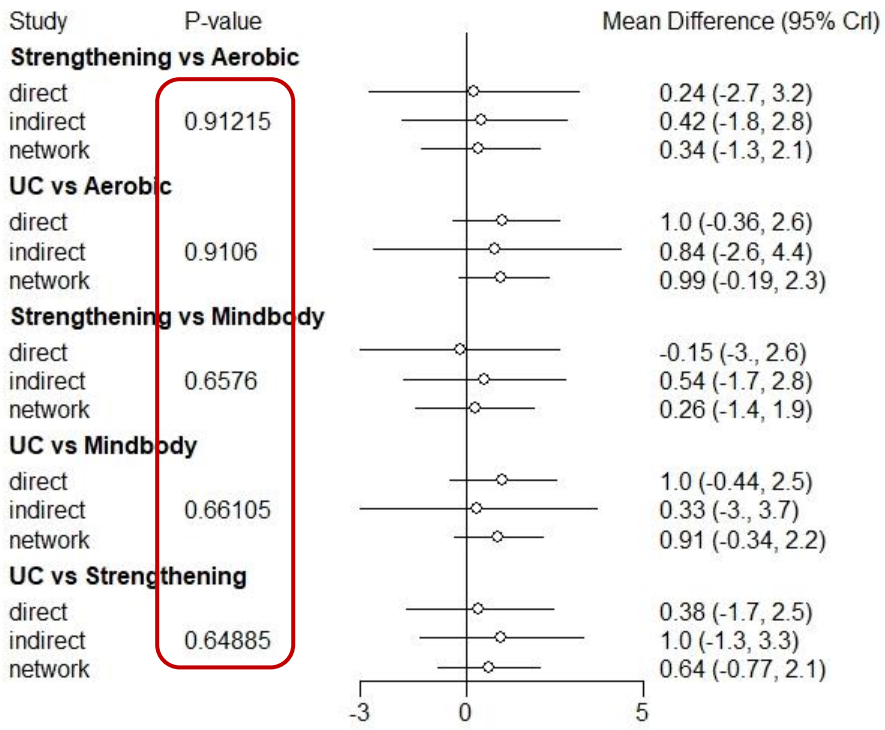

d.Aerobic.Flexibility
shrink factor
1.00
1.06
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.Aerobic.Mindbody
shrink factor
1.00
1.06
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.Aerobic.Strengthening
shrink factor
1.00
1.04
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.Aerobic.UC
shrink factor
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1.05
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
d.UC.Mixed
shrink factor
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1.04
median
97.5%
6000
8000
10000
12000
14000
last iteration in chain
sd.d
shrink factor
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8000
10000
12000
14000
last iteration in chain

Appendix 9 Node splitting analysis of inconsistency for exercise types in pain, fatigue, sleep and depression

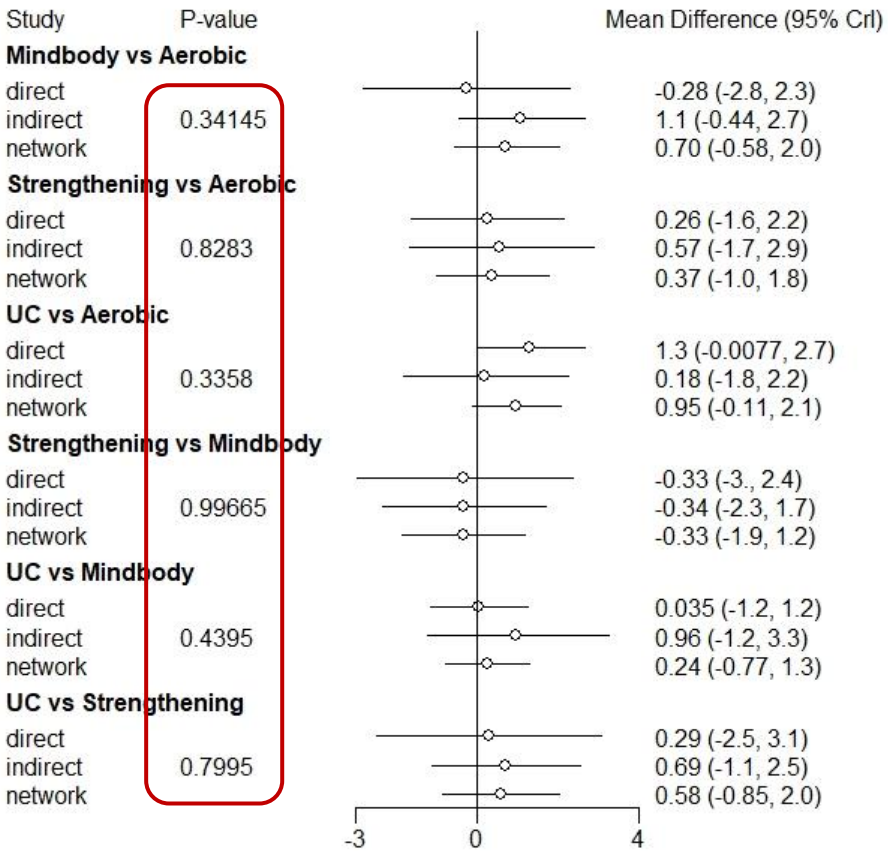
- Node-splitting analysis of inconsistency for pain



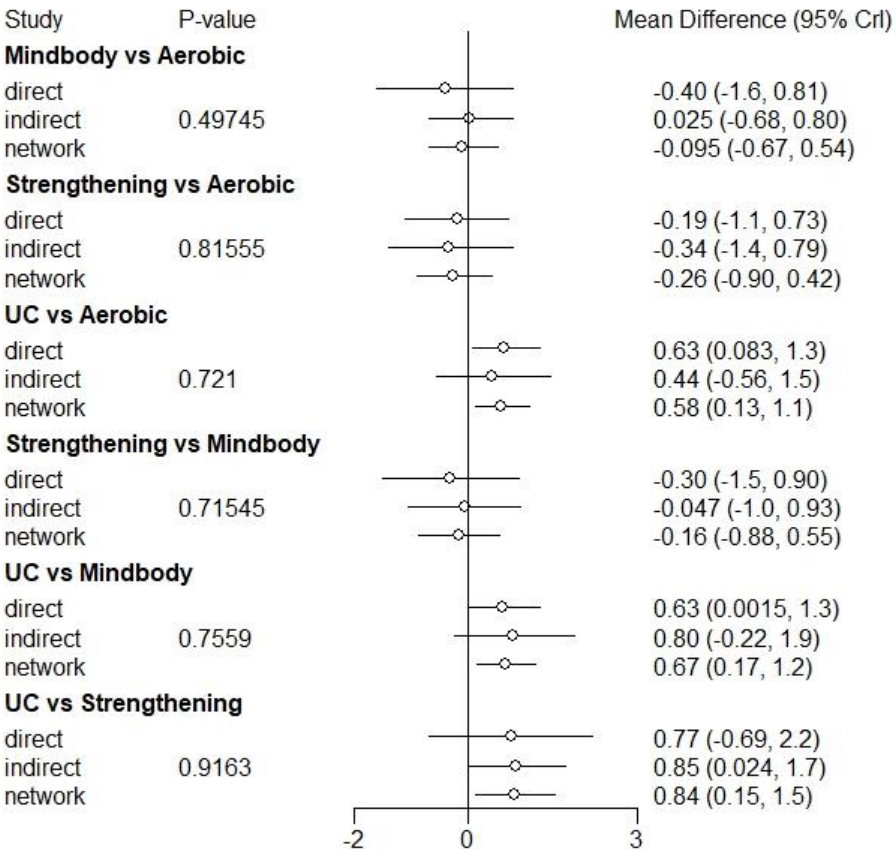
- Node-splitting analysis of inconsistency for fatigue



- Node-splitting analysis of inconsistency for sleep



- Node-splitting analysis of inconsistency for depression



Appendix 10 Delphi invitation letter

Dear …….,

My name is Burak Kundakci, and I am a PhD student at the University of Nottingham, UK. My supervisors are Dr Abhishek Abhishek, Prof Michael Doherty, Prof Weiya Zhang, and Dr Michelle Hall.

My PhD project aims to evaluate the efficacy of all non-pharmacological treatments for fibromyalgia and to build expert consensus on their use in the management of different manifestations of fibromyalgia.

Given your expertise in this field, I would like to invite you to participate in a Delphi exercise to identify key components of a non-pharmacological treatment package for fibromyalgia that can be tailored to individual patient needs.

If you are happy to participate, I will provide a summary of the results of our unpublished systematic review for your interest, and invite you to combine your knowledge of the research literature with your personal opinion and experience to vote on each intervention.

The responses from the first round will inform subsequent rounds where you will be asked to vote (agree/disagree) with the statements generated. Items that do not achieve consensus will enter the next round for further voting. Voting rounds will continue until all statements are agreed. It is anticipated that no more than four rounds will be required, and each may take approximately 20-30 minutes to complete.

As for all participants who complete the Delphi exercise, you will be invited to be a co-author of the resulting publication, or acknowledged for your contribution, whichever you prefer.

I fully appreciate that your time is always at a premium, but I would be very grateful if you would consider participating in this survey. Please contact me if you have any questions about the Delphi exercise.

Kind regards,

Burak Kundakci

PhD student

School of Medicine, Academic Rheumatology, University of Nottingham

Room A26, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB

Appendix 11 First round Delphi survey

Delphi Survey Round 1: Non-pharmacological interventions for fibromyalgia: recommendations and prioritisation exercise

Thank you for agreeing to participate in the Delphi exercise to identify and prioritise non-pharmacological treatments for fibromyalgia. For your interest, I have given an effect size (ES) and its 95% confidence interval (CI) for each treatment from our recent systematic review (unpublished so please keep in confidence). Clinically ES=0.2 is small, 0.5 moderate and 0.8 or more is large. The 95%CI is a possible variation of this measure, so please use the lower limit for a safer judgement.

This is the first round of the Delphi study. Please consider research evidence, your knowledge and experience of treating patients with fibromyalgia and patient preferences, to tell us if you would recommend the following treatments for four common manifestations (pain, fatigue, sleep and depression) of fibromyalgia. It is anticipated that this step of the Delphi exercise will take approximately 20-30 minutes.

Section 1

Professional details (We need this information to see the difference between professionals. Your individual answers will not be exposed to others either within or outside of this panel so please feel free to answer, or skip this section if you wish)

Can you please provide some details about your professional background and your current role?

1. **Full name:**
2. **Years in practice:**
   a. **0-5☐ 5-10☐ >10 years☐**
3. **What is your professional background?**
   a. Rheumatology
   b. General Practice
   c. Physiotherapy
   d. Psychology
   e. Occupational therapy
   f. Orthopaedics
   g. Sports and exercise medicine
   h. Other (……)
4. **What is your primary role?**
   a. Academic
   b. Clinician
   c. Clinical academic
   d. Other (……)

Section 2

Which of the following interventions would you recommend for the treatment of **PAIN** in people with fibromyalgia? For each intervention that you think should be offered to people with fibromyalgia, please tell us whether you think this is a core therapy or adjunctive therapy. The interventions are presented in alphabetical order.

1. **Acupuncture: ES (95%CI) = -1.08 (-0.36 to -1.79)**

   yes ☐ no ☐

   If yes; core ☐ adjunct ☐

2. **Balneotherapy ES (95%CI) = 1.29 (0.58 to 2.00)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

3. Biofeedback **ES (95%CI) = -0.42 (-1.18, 0.33)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

4. Cupping **ES (95%CI) = -0.09 (-0.49, 0.32)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

5. Education **ES (95%CI) = -0.18 (-0.41, 0.05)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

6. Electrotherapy **ES (95%CI) =-0.22 (-0.86, 0.42)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

7. Exercise

Aerobic **ES (95%CI) = -0.72 (-1.37, -0.07)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Flexibility **ES (95%CI) = -0.13 (-1.01, 0.75)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Strengthening **ES (95%CI) = -0.88 (-1.67, -0.09)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mind-body **ES (95%CI) = -0.86 (-1.32, -0.40)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mixed **ES (95%CI) = -0.96 (-1.49, -0.44)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

8. Homeopathy **ES (95%CI) = -0.73 (-1.41, -0.05)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

9. Hyperbaric oxygen therapy **ES (95%CI) = -2.22 (-2.93, -1.51)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

10. Magnetotherapy **ES (95%CI) = -0.89 (-1.74, -0.04)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

11. Manual therapy **ES (95%CI) = -0.86 (-1.32, -0.41)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

12. Massage **ES (95%CI) = -0.76 (-1.32, -0.19)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

13. Material of cloth **ES (95%CI) = -2.89 (-6.82, 1.04)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

14.Music **ES (95%CI) = -0.58 (-1.24, 0.07)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

15.Nutritional Supplement **ES (95%CI) = -0.29 (-0.69, 0.11)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

16.Psychological Treatments
Cognitive Behavioural Therapy **ES (95%CI) = -0.54 (-1.02, -0.06)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

Mindfulness **ES (95%CI) = -0.29 (-0.71, 0.13)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

17.Transcranial direct current stimulation ES (95%CI) = -0.84 (-1.21, -0.47)

yes ☐ no ☐
If yes; core ☐ adjunct ☐

18.Whole Body Vibration **ES (95%CI)= -**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

19.Weight loss **ES (95%CI) = -**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

20.Other(s): List any other intervention(s) you think should be in the treatment package for fibromyalgia and please specify whether it is core or adjunct.

……

Section 3

Which of the following interventions would you recommend for the treatment of **FATIGUE** in people with fibromyalgia? For each intervention that you think should be offered to people with fibromyalgia, please tell us whether you think this is a core therapy or adjunctive therapy. The interventions are presented in alphabetical order.

1. **Acupuncture:** **ES (95%CI) = -0.50 (-0.90, -0.10)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

2. **Balneotherapy** **ES (95%CI) = -0.43 (-0.81, -0.05)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

3. **Biofeedback** **ES (95%CI) = -0.09 (-0.54, 0.36)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

4. **Cupping** **ES (95%CI) = 0.06 (-0.34, 0.46)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

5. **Education** **ES (95%CI) = -0.31 (-0.55, -0.06)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

6. **Electrotherapy** **ES (95%CI) = -1.04 (-2.07, -0.01**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

7. **Exercise**

Aerobic **ES (95%CI) = -1.46 (-3.05, 0.14)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Flexibility **ES (95%CI) = -0.28 (-2.66, 1.91)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Strengthening **ES (95%CI) = -0.59 (-1.03, -0.16)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mind-body **ES (95%CI) = -0.99 (-1.64, -0.34)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mixed **ES (95%CI) = -0.12 (-0.73, 0.50)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

8. Homeopathy **ES (95%CI) = -0.19 (-0.69, 0.31)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

9. Hyperbaric oxygen therapy **ES (95%CI) = -**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

10. Magnetotherapy **ES (95%CI) = -2.61 (-3.70, -1.52)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

11. Manual therapy **ES (95%CI) = -0.44 (-1.02, 0.13)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

12.Massage **ES (95%CI) = -1.09 (-1.56, -0.63)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

13.Material of cloth **ES (95%CI) = -5.97 (-7.29, -4.65)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

14.Music **ES (95%CI) = -0.11 (-0.72, 0.50)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

15.Nutritional Supplement **ES (95%CI) = -0.41 (-0.77, -0.05)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

16.Psychological Treatments

Cognitive Behavioural Therapy **ES (95%CI) = 0.43 (-0.55, 1.41)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mindfulness **ES (95%CI) = -0.49 (-0.91, -0.07)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

17.Transcranial Direct Current Stimulation ES (95%CI) = -0.73 (-1.28, -0.19)

yes ☐ no ☐

If yes; core ☐ adjunct ☐

18.Whole Body Vibration **ES (95%CI) = -**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

19. Weight loss **ES (95%CI) = -**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

20. Other(s): List any other intervention(s) you think should be in the treatment package for fibromyalgia and please specify whether it is core or adjunct.

……

Section 4

Which of the following interventions would you recommend for the treatment of **SLEEP** in people with fibromyalgia? For each intervention that you think should be offered to people with fibromyalgia, please tell us whether you think this is a core therapy or adjunctive therapy. The interventions are presented in alphabetical order.

1. Acupuncture: **ES (95%CI) = 1.95 (-2.29, 6.19)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

2. Balneotherapy **ES (95%CI) = -0.00 (-0.62, 0.61)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

3. Biofeedback **ES (95%CI) = -**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

4. Cupping **ES (95%CI) = -0.20 (-0.60, 0.21)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

5. Education **ES (95%CI) = -0.25 (-0.61, 0.11)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

6. Electrotherapy **ES (95%CI) = -0.97 (-1.51, -0.43)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

7. Exercise

Aerobic **ES (95%CI) = -1.33 (-2.55, -0.11)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Flexibility **ES (95%CI) = 0.69 (-1.46, 2.81)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Strengthening **ES (95%CI) = -0.47 (-0.90, -0.03)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mind-body **ES (95%CI) = -0.03 (-0.94, 0.88)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mixed **ES (95%CI) = -0.64 (-1.33, 0.04)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

8. Homeopathy **ES (95%CI) = -0.91 (-1.60, -0.22)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

9. Hyperbaric oxygen therapy **ES (95%CI) = -**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

10. Magnetotherapy **ES (95%CI) = -1.00 (-1.83, -0.16)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

11. Manual therapy **ES (95%CI) = 0.10 (-1.22, 1.41)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

12. Massage **ES (95%CI) = -0.79 (-1.23, -0.34)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

13. Material of cloth **ES (95%CI) = -8.94 (-10.8, -7.07)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

14. Music **ES (95%CI) = -**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

15. Nutritional Supplement **ES (95%CI) = -0.43 (-0.79, -0.06)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

16. Psychological Treatments

Cognitive Behavioural Therapy **ES (95%CI) = -1.35 (-4.20, 1.51)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mindfulness **ES (95%CI) = 0.04 (-0.32, 0.39)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

17. Transcranial Direct Current Stimulation ES (95%CI) = -0.57 (-0.96, -0.17)

yes ☐ no ☐
If yes; core ☐ adjunct ☐

18. Whole Body Vibration ES (95%CI) = -

yes ☐ no ☐
If yes; core ☐ adjunct ☐

19. Weight loss ES (95%CI) = -0.66 (-1.11, -0.22)

yes ☐ no ☐
If yes; core ☐ adjunct ☐

20. Other(s): List any other intervention(s) you think should be in the treatment package for fibromyalgia and please specify whether it is core or adjunct.

……

Section 5

Which of the following interventions would you recommend for the treatment of **DEPRESSION** in people with fibromyalgia? For each intervention that you think should be offered to people with fibromyalgia, please tell us whether you think this is a core therapy or adjunctive therapy. The interventions are presented in alphabetical order.

1. Acupuncture: ES (95%CI) = -0.63 (-1.46, 0.20)

yes ☐ no ☐
If yes; core ☐ adjunct ☐

2. Balneotherapy ES (95%CI) = -0.68 (-1.23, -0.13)

yes ☐ no ☐
If yes; core ☐ adjunct ☐

3. Biofeedback ES (95%CI) = -

yes ☐ no ☐
If yes; core ☐ adjunct ☐

4. Cupping **ES (95%CI) = -**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

5. Education **ES (95%CI) = -0.08 (-0.35, 0.20)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

6. Electrotherapy **ES (95%CI) = -0.88 (-1.46, -0.29)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

7. Exercise

Aerobic **ES (95%CI) = -0.73 (-1.48, 0.02)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Flexibility **ES (95%CI) = -0.26 (-1.14, 0.53)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Strengthening **ES (95%CI) = -0.74 (-1.18, -0.30)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mind-body **ES (95%CI) = -0.55 (-1.04, -0.06)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

Mixed **ES (95%CI) = -0.35 (-0.65, -0.04)**

yes ☐ no ☐

If yes; core ☐ adjunct ☐

8. Homeopathy **ES (95%CI) = -0.56 (-1.07, -0.06)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

9. Hyperbaric oxygen therapy **ES (95%CI) = -**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

10. Magnetotherapy **ES (95%CI) = -0.11 (-0.64, 0.41)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

11. Manual therapy **ES (95%CI) = -0.32 (-0.96, 0.32)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

12. Massage **ES (95%CI) = -0.73 (-1.83, 0.37)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

13. Material of cloth **ES (95%CI) = -3.36 (-4.23, -2.49)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

14. Music **ES (95%CI) = -0.54 (-0.92, -0.15)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

15. Nutritional Supplement **ES (95%CI) = -0.04 (-0.99, 0.90)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

16. Psychological Treatments
Cognitive Behavioural Therapy **ES (95%CI) = -0.14 (-0.40, 0.13)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

Mindfulness **ES (95%CI) = -0.46 (-0.94, 0.02)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

17. Transcranial Direct Current Stimulation ES (95%CI) = -0.32 (-0.52, -0.13)

yes ☐ no ☐
If yes; core ☐ adjunct ☐

18. Whole Body Vibration **ES (95%CI) = -**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

19. Weight loss **ES (95%CI) = -0.68 (-1.13, -0.24)**

yes ☐ no ☐
If yes; core ☐ adjunct ☐

20. Other(s): List any other intervention(s) you think should be in the treatment package for fibromyalgia and please specify whether it is core or adjunct.

……