PHYSICAL ACTIVITY INTERVENTIONS FOR INDIVIDUALS WITH FIBROMYALGIA: A REVIEW AND SYNTHESIS OF BEST EVIDENCE.

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ABSTRACT

Background: Fibromyalgia (FM) disorder commonly involves musculoskeletal widespread pain and other symptoms like fatigue, sleep disruption, depression and anxiety and is associated with disability, work disability and high health care utilization. An integrated approach combining pharmacological and non-pharmacological treatments is advised to manage the disorder. Among the non-pharmacological interventions exercise has been shown to help; however, details about effectiveness of different types of interventions remain unknown.

Objectives: The objective of this dissertation was to synthesize the evidence on the effectiveness of: a) Aquatic exercise interventions for adults with FM as reported in randomized control trials (RCTs), and b) any physical activity interventions for adults with FM as reported in systematic reviews. This was done by conducting a Cochrane systematic review of an aquatic training intervention and second, synthesizing the effectiveness of a variety of exercise interventions.

Methods: For the Cochrane systematic review, nine electronic databases were searched. Selection criteria included full text publication of a RCT including an aquatic exercise intervention (AQ) (exercise in water was >50% of the full intervention) and provision of between-group outcome data. Pairs of reviewers independently screened and selected articles, assessed risk of bias, and extracted data on 24 outcomes. Effects of the interventions were evaluated using mean, standardized mean differences and 95% confidence interval (MD/SMD [95% CI]). Specific computer software designed for meta-analysing and evaluating the quality of evidence were used (i.e RevMan, GradePro). The second review, the synthesis of a variety of exercise interventions or umbrella systematic review, inspected six electronic databases for the January 1st 2007 to March 31st 2012 period. We included systematic Cochrane and non-Cochrane reviews that reported on the effects of any physical activity intervention for adults with FM. Pairs of reviewers independently screened and selected articles, assessed quality of the reviews using a valid and reliable tool (AMSTAR tool), and extracted data on four outcomes. Effects of the interventions were evaluated using standardized mean differences and 95% confidence intervals (SMD [95% CI]). We planned to use RevMan software for meta-analysis but due to heterogeneity of the reviews this was not done.

Results: The Cochrane review examined 16 aquatic exercise training studies (n = 881). Nine studies compared aquatic exercise to control, five studies compared aquatic exercise to land-based exercise, and two compared aquatic to a different aquatic program. The aquatic vs control studies provided low to moderate quality evidence suggesting that aquatic training is beneficial for wellness, symptoms and fitness in adults with FM. The aquatic vs land group results suggested very low to low quality evidence that there are no differences in benefits between aquatic and land-based exercise except in muscle strength (very low quality evidence favoring land). In examining aquatic vs aquatic meta-analyses was not possible and only one difference in a major outcome was found.

The umbrella systematic review synthesis of information (n-= nine systematic reviews) found positive results for diverse exercise interventions on pain, multidimensional function, and self-reported physical function and no conclusive evidence for new (to FM) physical activity mode (i.e. qigong, tai chi). There are however, methodological weaknesses in some of the reviews which reduce applicability of the research to clinical practice. Adverse effects reported suggest there was no serious harm performing physical activity for individuals with FM.

Conclusions: Exercise interventions have the potential to positively impact individuals with FM including several outcomes like quality of life, physical functioning and pain. While some interventions had statistically significant results, methodological limitations prevented us from arriving at conclusions regarding particular elements and modes of exercise that will help inform health professional's clinical practice. On the other hand, some preliminary analysis showed that variables like age, disease duration, disease severity and pain intensity warrant further exploration. A rigorous scientific process (or quality research) as the precursor of quality evidence is crucial for validity and credibility of the information and our future understanding of the effectiveness of exercise interventions for individuals with FM.

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DEDICATION

"…it is we who are sick; it is therefore we who take the responsibility to declare our suffering, our misery, and our pain, as well as our hope"

(a group of rural Haitians in "Pathologies of Power" P. Farmer)

That's the answer – that is why I do this work.

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LIST OF ABBREVIATIONS

1RM	One repetition maximum
6MWT	6 Minute Walk Test
AAU	Activity as Usual
AB	Angela Busch
ACR	American College of Rheumatology
ACSM	American College of Sports Medicine
AE	Aerobic
AIMS	Arthritis Impact Measurement Scale
AQ	Aquatic
AMSTAR	A measurement tool to assess methodological quality of systematic reviews
Bal	Balneotherapy
BB	Brenna Bath
BC	Before Christ
BDI	Beck Depression Inventory
Biof	Biofeedback
CAM	Complementary and alternative medicine
CBT	Cognitive behavioural therapy
CES-D	Center for Epidemiologic Studies - Depression
CI (LL-UL)	Confidence interval (lower limit-upper limit)
Comp	Composite intervention
Coord	Coordination
DWR	Deep water running
ED	Education
EPICOT	Evidence, population, intervention, comparator, outcomes and timestamp
EuroQol-5d/EQ-5D	European quality of life scale

FIQ	Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
FSHC	Fibromyalgia self-help course
FX	Flexibility
HAQ	Health Assessment Questionnaire (disability scale)
HR_{max}	Maximum heart rate
HRQL	Health related quality of life
ITT	Intention to treat
JB	Julia Bidonde
Lblood • min	Liter of blood per minute
LPA	Leisure physical activity
MD	Mean differences
MDF	Multidimensional function
Meds	Medication
ml O_2 / L blood	Millilitres of oxygen / liter of blood
MVC	maximal voluntary contraction
MX	Mixed exercises
n	Number of studies
N	Number of participants
NNT	Number needed to treat
OMERACT	Outcome Measures Rheumatology
PA	Physical activity
PGWB	Psychological General Well-being
PF	Physical Function
PICO-TS	Population, Intervention, Comparators, Outcomes – Time frame, Study type
PNF	Proprioceptive neuromuscular facilitation
POMS	Profile Mood States

PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PWC170	Physical work capacity (estimated at 170 heart rate per minute)
RCT	Randomized controlled trial
Relax	Relaxation
RET	Resistance Training
RevMan	Review Manager
ROM	Range of motion
RPE	Rate of perceived exertion
RR	Risk ratio
SCL-90-R	Global Severity Index of the Symptom Checklist 90
SD	Standard deviation
SF-36/12	Short Form Health Survey
SM	Steve Milosavljevic
SMC	Standard medical care
SMD	Standardized mean differences
SMT	self-management treatment
SPA	a resort providing therapeutic bath, mineral springs, or health treatments
ST	Strength
SR	Systematic review
TAU	Treatment as usual
TENS	Transcutaneous Electrical Nerve Stimulation
TP	Tender point
US	United States
VAS	Visual analogue scale
$VO_{2\ max}$	Maximal oxygen consumption (V-volume – O2 – oxygen)
Wk(s)	Week(s)

PREFACE

This dissertation is arranged in four chapters. Chapter One is an introduction to the dissertation and includes an overview of the study design, overarching research objectives and potential relevance of the research findings. Chapter Two and Three address the research objectives outlined in Chapter One and are written so that each can be read independently as a stand-alone manuscript.

The first manuscript (presented in Chapter Two) describes a systematic review which examines the effectiveness of aquatic exercise training interventions for individuals with fibromyalgia (FM) (research objective 'a'). The first manuscript in this dissertation is part of an ongoing update of a systematic Cochrane review publication on the effectiveness of physical activity interventions for individuals with FM done by a Cochrane team. The manuscript in this dissertation is one of six planned by the team; after the six reviews proposed are completed, an overview of reviews (a review of all six Cochrane reviews planned by the team) will take place. Despite describing this first manuscript as part of an 'update', it is worth mentioning this manuscript is a stand-alone comprehensive and thorough Cochrane systematic review. The team is made up of twelve members from across Canada, including two consumers, one librarian, and nine reviewers that work with the support of the musculoskeletal group at the Cochrane Collaboration. Reviewers came from the following backgrounds: physiotherapy, dietetics and community health and epidemiology (PhD Candidate). The manuscript in this dissertation describes work conducted through a collaborative approach with the team which has been engaged doing data screening and extraction, participating in meetings and discussions, reviewing and approving the final draft of the manuscript, as well as disseminating findings to multiple audiences. Even though the team efforts are recognized, the researcher (JB) was the main leader for this manuscript.

The second manuscript (presented in Chapter Three), an umbrella systematic review (a review of Cochrane and non-Cochrane reviews), examines the effectiveness of physical activity interventions presented in systematic reviews in the last five years (research objective 'b'). The main goal of this project was to systematically identify published systematic reviews of exercise interventions for individuals with fibromyalgia and comprehensively describe and synthesize their methods, results and conclusions. This study explored the effectiveness of different exercise

interventions for individuals with fibromyalgia across sufficiently similar review questions. Description of the quality of the evidence on the effectiveness of exercise interventions for individuals with fibromyalgia were provided as well as a collection, classification and summary of evidence for individuals with fibromyalgia; and a synopsis of best evidence, to outline where the evidence is lacking and identify areas of future research. Following the manuscripts, Chapter Four presents a summary and in-depth analysis and interpretation from all reviews, the clinical implications of findings and directions for future research.

CHAPTER ONE

INTRODUCTION

Fibromyalgia (FM) is a common disorder involving widespread pain and tenderness with coexisting symptoms such as fatigue, sleep disturbances, anxiety, depression, which are associated with disability and physical de-conditioning [1]. The disorder is known to have an impact on individual's quality of life. This chapter introduces the prevalence and health care cost associated with FM and background regarding the pathophysiology of the disorder. Finally, the research objectives, methods, rational and relevance of the research described in this dissertation are introduced.

1.1 The Prevalence of Fibromyalgia and Health Care Costs

Branco [2] suggests that the prevalence of FM in the general population is estimated to be between 0.5 and 5%. In the United States (US) the prevalence has been estimated at 2% of the adult population (18 years of age and older) with a disproportionate representation among females than males (3.4% female to 0.5% male) [3;4]. The Canadian statistics are similar to the US where the self-reported prevalence of FM has been estimated at 1.1% across all ages, again with female diagnoses outnumbering male diagnoses (1.83% female to 0.33% male) [5]. The average age of onset of the disorder is between 30 and 50 years, increasing with age and then dropping off in the oldest age groups (80+ years) [6]. Although no recent prevalence studies of FM have been published and an early study by Neuman [7] suggested the prevalence of FM varies according to age groups from 1% in the 18-29 age group to 7% in the 70-79 age group. Similarly, results from The London FM study conducted in Canada [8] confirms that prevalence rises with age in females from less than 1% in women 18-30 to almost 8% in women 55-64 years to later on decline. In men, the prevalence also increases with age peaking at 2.5% in the 45-54 age group [9]. Prevalence rates among some European countries (France, Germany, Italy, Portugal, Spain) are estimated to range from 1.4% (France) to 3.7% (Italy) with fibromyalgia diagnoses being twice as common in females [2]. However, similar to other rheumatologic conditions, the prevalence of fibromyalgia in China is substantially lower than in Western countries at about 0.05% [10]. It is unclear why there are international discrepancies in the prevalence of FM, but differences in diagnosis practices might be one explanation [8].

Fibromyalgia is commonly associated with many other complaints including depressive and anxiety symptoms through the lifespan [11]. Other medical disorders associated with FM,

sometimes difficult to explain and control, are migraine headaches, irritable bowel syndrome, chronic fatigue, chronic pelvic pain, sleep disorders, and sleep apnea. [12].

FM is linked with high utilization of health care resources including primary care visits, specialist consultations (including physical therapy), pain related medications, hospitalizations and diagnostic procedure [13-15]. It is recognized that establishing a diagnosis of FM is not accomplished quickly. Due to the absence of laboratory test results and the symptoms that overlap with other conditions, it is estimated that it takes an average of five years to get an accurate diagnosis [16]; which may create concerns for individuals and increase health care services utilization. Hughes [17] showed that the rate of all primary care visits was considerably higher in FM cases compared with matched controls 10 years prior and 2.5 to 3 years after diagnosis. Neuman [7] also showed that a greater proportion of individuals with FM had physician visits and applied for disability benefits compared to those without FM. Also, the rates for prescriptions and number of diagnostic tests performed are significantly higher in individuals with FM compared with controls [17]. Data suggests health care utilization and costs expended by individuals with FM are (three times) higher when compared to a control group [17;18]. As stated above, individuals with FM have a high prevalence of comorbidities which compromises their wellness substantially, including work productivity [3] and social aspects of life.

1.2 Etiology of FM

The American College of Rheumatology (ACR) started utilizing the term "fibromyalgia". Terms such as muscular rheumatism or fibrositis were used in the past to describe poorly understood chronic pain syndromes believed to be caused by inflammation [19;20]. The ACR has not only introduced the term "fibromyalgia" but also published a set of diagnostic criteria in 1990s that is still widely used. The ACR criteria include widespread pain for greater than three months and presentation of pain on palpation of 11 or more of 18 specific tender points in the body with application of pressure applied with the dominant pad perpendicular to each site and the force increased by approximately 1 kg per second until 4 kg of pressure [21]. Diagnosis according to ACR also requires: a) pain on both left and right sides of the body, b) pain above and below the waist, and c) axial pain. However, in recent years the utility of this method has been criticized for failing to address the extent of other key somatic

complaints and secondary symptoms of FM; new diagnostic criteria (stressing the importance of symptoms and not requiring tender points) have been introduced by ACR [22;23].

The 1990's ACR criteria are still widely used by rheumatologists and other specialists for diagnostic purposes. The etiology of FM remains unknown; however, several factors have been implicated in the pathophysiology of FM, including genetic factors, stress, changes in neural structures and function, muscular physiology, hormonal factors, and inflammatory markers [24]. Although the exact origin of the disorder has not been found, research today points to several underlying factors eventually leading to the diagnosis of FM.

1.2.1 Genetic Factors

Early uncontrolled family studies as well as a recent large controlled study provided evidence for genetic factors suggesting that inherited factors may be involved in pain sensitivity in families of individuals with FM [25]. Roizenblatt [26] observed 34 children with FM and found that 71% of their mothers had undiagnosed FM. Yunus [27] observed 37 multicase families with FM with at least two affected first-degree relatives and found that 74% of the probands' siblings, 53% of children, and 30% of parents had FM. As well, there is evidence that FM co-aggregates in families with major mood, anxiety, and eating disorders, irritable bowel syndrome, and migraine [28] suggesting FM may have some underlying physiologic commonalities with some psychiatric and medical disorders. Although FM aggregates in families, no clear FM gene(s) has been identified yet.

1.2.2 Stress

Stress and environmental stressors have been linked to the development of FM either as predisposing, triggering or perpetuating factors; individuals with FM often report the onset of symptoms after a substantial stress event of period of their life [28]. Other psychosocial difficulties such as adverse life events, poor relationship with primary care takers, unsupportive emotional persons in their lives as well as feelings of insecurity are linked to the development of FM. The literature reports links to different types of abuse and psychological trauma [29] with higher prevalence rates of all forms of childhood and adult victimization, emotional abuse, physical abuse, emotional neglect, and post-traumatic stress in individuals with FM which all contribute to the experience of chronic stress [28].

1.2.3 Neural Structures and Function

There is evidence that FM is associated with increased sensitivity to pain throughout the body and a decreased capacity of descending nociceptive controls indicating dysfunction of processing of pain by the central nervous system. Individuals with FM are more sensitive to painful stimulation, due to both the peripheral and central sensitization. Jensen and colleagues applied intermittent pressure pain and showed that individuals with FM display less functional connectivity between areas involved in pain inhibition compared to healthy controls [30]. Consistent with the phenomenon of central sensitization (amplification of pain impulses within the spinal cord and brain), individuals with FM often develop hyperalgesia (increased response to painful stimuli) and allodynia (pain due to a stimulus which does not normally provoke pain) [31].

1.2.4 Muscular Physiology

A comparison of muscle performance between individuals with FM and healthy individuals suggests that muscle function is impaired in individuals with FM [32]. Casale [33] found that the motor pattern of muscle recruitment during voluntary contractions was altered in individuals with FM. Additionally, Park [34] proposed that muscle abnormalities in FM can be classified as structural, metabolic, or functional. Some muscle abnormalities described in FM include mitochondrial disturbances in Type I muscle fibres (i.e. ragged red fibres and moth-eaten fibres) [33], hypotrophy of and reductions in Type II fibers, reduced capilarization and altered microcirculation [33], abnormal muscle metabolism, and excessive agonist–antagonist co-contraction. Structural abnormalities are correlated with biochemical abnormalities (i.e. deficiency in serotonin, melatonin, cortisol and cytokines), defective energy production, and the resultant dysfunction of muscles in individuals with FM [34]. Moreover, in the presence of these symptoms, individuals with FM are often physically inactive with a tendency to live a sedentary lifestyle [35]. The exercise literature in FM shows individuals are fairly deconditioned with reduced cardiovascular capacity [36] and muscle strength and endurance [37;38]. Despite the benefits derived from exercise in helping individuals with FM to gain back their health and quality of life, as Jones [39] pointed out, it may be difficult for individuals with FM to remain active.

Although increased research has expanded our understanding of FM, the disorder is complex and continues to be challenging to manage; both pharmacologic and non-pharmacologic treatments are included in the overall care of individuals with FM. Individuals with FM are often treated with pain medicines, antidepressants, muscle relaxants, and sleep medicines. The US Food and Drug Administration approved drugs are Lyrica (pregabalin), Cymbalta (duloxetine hydrocholide) and Savella (milnacipran HCI). The effectiveness of pharmacological treatments for FM is currently the focus of vigorous debate with some medications been poorly tolerated and or not effective [40], but this discussion is beyond the scope of this dissertation. However, evidence of non-pharmacological interventions seems promising in the management of FM.

Exercise in the management of FM

Among the non-pharmacological interventions for this disorder, physical activity and exercise have shown to help reverse deconditioning and improve overall quality of life. Physical activity is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure. Common types of physical activity are: a) household activities like sweeping or cleaning, b) occupational activities like lifting boxes or walking down the hall, and c) lifestyle activities like wheeling a cart or walking around the grocery store. The concept of lifestyle physical activity (LPA) refers to physical activities performed within the household, leisure, and occupational domains (e.g., doing more walking, performing yard work, and using stairs vs elevators). These activities are integrated into daily life activities and performed in short yet accumulated bouts (5 minutes multiple times per day) toward accumulating at least 30 minutes of self-selected, moderate-intensity physical activity over the course of the day, 5 to 7 days per week [41;42]. A study by Fontaine [43] showed that accumulating 30 minutes of LPA through the day produced clinically relevant changes in physical function and pain in individuals with FM.

Exercise, a subset of physical activity, is "planned, structured, and repetitive bodily movements designed to improve or maintain physical fitness." [44]. Often, exercise is structured by the amount of time, intensity and type of activity. Aerobic exercise, strength training and flexibility training are key elements of a comprehensive fitness program. Marcus [45] pointed out that: "The most effective non-medication therapies are aerobic and strengthening exercises...p159." Several studies have demonstrated that individuals with FM are

able to perform aerobic, flexibility, and resistance training programs [46-48]. A Cochrane review [46] concluded that moderate intensity aerobic training for 12 weeks may improve overall well-being and physical function. Although researchers have speculated about the benefits of various exercise interventions for FM, details about effectiveness of specific exercise interventions, such as aquatic exercise, remain unclear. When considering aquatic exercise, potentially, the unique properties of water might provide incremental favourable outcomes. Thus, evaluating aquatic exercise training interventions serves to identify potential treatments and contribute to understanding of non-pharmacological interventions for the management of the disorder. By providing a thorough evaluation of the topic, a systematic review could serve as a useful resource helping clinicians, researchers and policy makers keep up with the steady influx of literature in the area. Also, systematic reviews, as carefully synthesize research, are at the heart of evidence based practice.

1.3 Research Objectives

Scientific and relevant evidence in clinical care is essential. High quality and trustworthy information acquired and analyzed systematically regarding the effectiveness of physical activity for individuals with FM will lead clinicians and policy makers to a more complete and individualized management of the disorder. The objectives of this dissertation were to synthesize the evidence on the effectiveness of: a) Aquatic exercise interventions for adults with FM as reported in RCTs, and b) exercise interventions for adults with FM as reported in systematic reviews. This was done utilizing two different approaches: first by conducting a Cochrane systematic review of an aquatic training intervention and second, synthesizing the effectiveness of a variety of exercise interventions.

1.4 General Overview of Study Methodology

Objective ‘a’ was addressed by way of a Cochrane systematic review, and an umbrella systematic review (or review or reviews) was conducted to address the second objective. Ethical approval was not required for this research as it dealt with secondary analysis of data found in research reports.

Using the Cochrane methodology, the first study was a systematic review with meta-analysis of randomized controlled trials. This systematic review focused on adults with

fibromyalgia involved in aquatic exercise programs. The comparison groups were either control or treatment as usual and other physical activity interventions. Twenty four outcomes were examined in this review including adverse effects and outcomes named in the Outcome Measures Rheumatology (OMERACT 9) [49] core listing.

Objective 'b' was addressed by conducting an umbrella systematic review, which examined the effectiveness of exercise interventions for individuals with fibromyalgia across multiple exercise modalities (i.e. aquatic, resistance, aerobics). The focus of the umbrella review was to systematically identify published systematic reviews (Cochrane and non-Cochrane) of exercise interventions for individuals with FM and comprehensively summarize their methods, results and conclusions. The methodological quality and clinical features of systematic reviews were examined in depth. Systematic reviews by nature have a narrow focus and present a summary of evidence from a set of trials. An umbrella review allowed us to address all the potential exercise interventions for FM, and to create a summary from several related review articles. It is an efficient way to access a body of research saving time needed to critically appraise the information and interpreting the results. The reviews were explored in depth aiming to provide high quality research evidence for health professionals and decision makers.

1.5 Rational and Relevance of the Study

Recommended best practices in the management of FM involves collaboration from different disciplines and multiple interventions (pharmacological and non-pharmacological) [50]. Physical activity is an important part of the management of FM [51]. Participation in exercise is known to help individuals with FM adapt to the process of microtrauma and repair that occurs as a result of daily physical activity perhaps by raising one's pain threshold. Participating in exercise is also important in preventing age-related loss of muscle and bone mass, managing body weight, lowering the risk of chronic conditions such as diabetes, and maintaining functional independence [44]. Therefore, individuals with FM may improve their overall health and reduce risks associated with other conditions.

Although there is abundant new research in the area, the effects of various types of physical exercise (planned, structured, and repetitive bodily movement done to improve or

maintain one or more components of physical fitness) [44] on symptoms, mental function and physical function in individuals with FM are still need to be synthesized. Through synthesis of RCTs and systematic reviews, it is hoped that answers to questions regarding the best type of exercise, intensity and delivery options for exercise interventions will begin to emerge.

Even though long-term health benefits of regular exercise for healthy individuals and those with a number of chronic conditions are widely recognized, individuals with FM have problems adhering to exercise routines. The presence of symptoms such as pain, fatigue, low levels of physical conditioning are often mentioned as barriers to exercise. By identifying the adverse effects (i.e. injuries, exacerbations) observed in studies of exercise for FM, this project may contribute to better understanding factors related to optimal program design and prescription. This information will help health care professionals and people with FM ensure that the positive effects of exercise are realized.

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CHAPTER TWO

AQUATIC EXERCISE TRAINING FOR FIBROMYALGIA

2 Manuscript #1

Evidence-based practice, which quality health services are built upon, uses best evidence derived from research as one of the principles in modern health care. Identifying effectiveness of interventions that are suited for individuals with FM is an important first step to addressing issues of management of the disorder. In light of increasing demand for evidence based information in the area of FM and physical activity, the first manuscript of this dissertation presents a Cochrane systematic review on the effectiveness of aquatic training interventions for adults with FM.

This manuscript was submitted to the Cochrane Collaboration Musculoskeletal Group for editorial review May 2013. Since then, the manuscript has been through a series of revisions and it is now in the final phases under the scrutiny of the Chief Editor of the Musculoskeletal Group. When published, the citation of the manuscript will be as follow:

> Bidonde J, Busch AJ, Webber SC, Schachter CL, Danyliw A, Overend TJ, Richards RS, Rader T. Aquatic exercise training for fibromyalgia. Cochrane Database of Systematic Reviews , Issue . Art. No.: . DOI: .

This manuscript presents an extensive and comprehensive analysis of 16 relevant RCTs conducted in different parts of the globe studying 24 outcomes relevant to practitioners and individuals with FM. Systematic reviews cannot be done by a single person. It is necessary to acknowledge that each of the many steps of data synthesis requires at least two independent researchers to be completed. As stated in the preface, this manuscript was conducted through a collaborative approach with the team (e.g., double author citation screening and study selection, double author data extraction), however, the researcher (JB) led all aspects of this manuscript.

Contributions of authors

JB: screening studies, data extraction (eight of 16 studies for this manuscript), participated in discussion regarding methods, selection of outcome measures, assessment of risk of bias, methodological analysis, data analysis (including meta-analysis) writing and reviewing manuscript, ongoing editing of manuscript and approving the final manuscript. Also, responding to editorial requests from the Cochrane editorial group; translating articles and

correspondence, communicating with authors, and facilitating finding translators for articles in other languages. Recruited and trained new reviewers.

AB: designing and reviewing protocol for review, screening, data extraction, and reviewing drafts and approving the final manuscript.

AD, CLS, RR, SCW, TR and TO: screening studies, data extraction, reviewing drafts and approving the final draft of the manuscript.

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- Mary Brachaniec and Janet Gunderson for contributing to team discussions, reviewing outcomes measures, and drafting and reviewing the plain language summary
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- Patricia Luciano-Mancini for assistance with translations from Portuguese which permitted screening data extraction for Hecker [1]
- Julia Bidonde has translated (and communicated with authors) of Arcos-Carmona [2]; Martin-Nogueras [3]; Lopez-Rodriguez [4]; Sanudo [5]; Tomas-Carus 2007 [6-8]; from Spanish to English.
- Julia Bidonde's PhD committee members for their contributions to this manuscript: Doctors Bonnie Janzen, Liz Harrison, Linda Li, Kalyani Premkumar, and Bruce Reeder.

Other:

- A poster presentation including four outcomes of this manuscript was accepted by the American College of Rheumatology and presented at the San Diego conference 2013.
- An invitation to record a podcast of this review was received January 2014, and it is now being prepared.
- Two abstracts were accepted to the International Association for the Study of Pain (IASP) conference to take place October 2014.
- Two stand-alone publications are planned based on information derived from this systematic review.

Title: *Aquatic exercise training for fibromyalgia* **(Manuscript 1)**[1]

Citation example: Bidonde J, Busch AJ, Webber SC, Schachter CL, Danyliw A, Overend TJ, Richards RS, Rader T. Aquatic exercise training for fibromyalgia. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Abstract

Background

Exercise training is commonly recommended for individuals with Fibromyalgia (FM). This review is part of the update of the "Exercise for treating fibromyalgia" review first published in 2002, and previously updated in 2007.

Objective

The objective of this systematic review was to evaluate the benefits and harms of aquatic exercise training in adults with FM.

Search methods

We searched The Cochrane Library 2013 (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, NHS Economic Evaluation Database), MEDLINE, EMBASE, CINAHL, PEDro, Dissertation Abstracts, WHO international Clinical Trials Registry Platform, and AMED from inception to October 2013 and other sources (i.e. reference lists from key journals, identified articles, meta-analyses and reviews of all types of treatment for FM). Using Cochrane methods, citations, abstracts, and full-text articles were screened. Subsequently, aquatic exercise training studies were identified.

Selection criteria

Selection criteria were: a) full text publication of an RCT of adults diagnosed with FM based on published criteria, b) between group data for an aquatic intervention and a control or other intervention. Studies were excluded if exercise in water was less than 50% of the full intervention.

Data collection and analysis

Reviewers, who were trained following a standardize protocol, independently assessed risk of bias and extracted data (24 outcomes) of which seven were designated as major outcomes: multidimensional function, self-reported physical function, pain, stiffness, muscle strength, submaximal cardiorespiratory function, withdrawal rates and adverse effects. Discordance was resolved through discussion. Interventions were evaluated using mean differences (MD) or standardized mean differences (SMD) and 95% confidence intervals (95% CI). Where two or more studies provided data for an outcome, meta-analysis was carried out.

Main Results

We included 16 aquatic exercise training studies (N = 881; 866 women and 15 men). Nine studies compared aquatic exercise to control, five studies compared aquatic exercise to land-based, and two compared aquatic to a different aquatic program.

The risk of bias related to random sequence generation (selection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), blinding of outcome assessors (detection bias) and other bias were rated as low; blinding of participants and personnel (selection and performance bias) was rated as low risk (50%) and unclear (50%).

Aquatic vs Control: Based on a 0-100 point scale, multidimensional function improved by 5.97 units (2.88 to 9.06), self-reported physical function by 4.36 units (0.94 to 7.77), pain by 6.58 units (2.48 to 10.68), and stiffness by 18.48 (0.74 to 36.22) in aquatic versus control groups. The SMD in strength was 0.63 standard deviations higher compared to the control group (0.20 to 1.05) and cardiovascular submaximal function improved by 32 meters in 6 minute walk test (17.41 to 46.03). All differences favoured the aquatic training interventions ($P < 0.05$). Withdrawals were similar in aquatic and control groups and adverse effects were poorly reported, with no serious adverse effects reported.

Aquatic vs land-based: There were no significant differences between interventions for multidimensional function, self-reported physical function, pain or stiffness: 0.91 units (-4.01 to 5.83), -5.85 units (-12.33 to 0.63), -0.75 units (-10.72 to 9.23), 2 units (-8.82 to 12.82) respectively, all based on a 100 point scale, or in submaximal cardiorespiratory function (3 seconds on 100 meter walk test, -1.77 to 7.77). A statistically significant difference between interventions was found in strength favoring land–based training (-2.40 kilo pascals grip

strength, -4.52 to -0.28). Withdrawals were similar in aquatic and land groups and adverse effects were poorly reported, with no serious adverse effects in either group.

Aquatic vs a different aquatic program: analyses (Ai Chi vs stretching in the water, exercise in pool water vs exercise in sea water), only one difference in a major outcome was found: stiffness improved by 1.00 on a 100 point scale (0.31to 1.69) favoring Ai Chi.

Authors' conclusions

The quality of evidence was rated low to moderate quality in the aquatic vs control group. Thus, further research is likely to very likely impact our confidence in the estimate of effect and may change the estimate. However, the evidence suggests that aquatic training is beneficial for improving wellness, symptoms and fitness in adults with FM. Similarly, very low to low quality evidence (meaning we are uncertain about the estimates and further research is very likely to have an important impact on our confidence in the estimate of the effect) suggests that there are no differences in benefits between aquatic and land-based exercise except in muscle strength (very low quality evidence favoring land). No serious adverse effects were reported.

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[1]Note this manuscript has gone through a thorough peer review and editorial process at the Cochrane Collaboration and is now in final editorial phase. Once published will be open access and available through the Cochrane Library at http://www.cochrane.org/

2.1 Background

2.1.1 Description of the condition

Fibromyalgia (FM) is a common chronic idiopathic condition involving widespread pain and tenderness [9]. It is often associated with other somatic complaints, disability and physical deconditioning, which negatively impact quality of life. It is estimated that 1.1% of Canadians are affected by FM across all ages, with higher prevalence among females. The prevalence of FM in Canada is similar to other parts of the world (1.1% across all ages with females diagnoses outnumbering male diagnoses) [10], with the exception of Asia where the incidence is lower [11].

Several factors have been implicated in the pathophysiology of FM, including: changes in brain and neural structure and function, muscular physiology, hormonal factors, inflammatory markers, and genetic influences [12]. Researchers have identified several abnormalities in brain and neural function in patients with FM which appear to have a genetic basis [13;14]. Various muscle abnormalities that may result in weakness, fatigue and muscle pain for individuals with FM have been described [15] and include reductions in Type II fibers, abnormal muscle metabolism, and excessive agonist–antagonist co-contraction. Consistent with these findings, individuals with FM are often less physically active and more sedentary [16] than healthy individuals. Symptoms associated with FM can have repercussions on family dynamics, employment and independence, thereby directly impacting quality of life [9]. Symptoms of FM include poor and non-restorative sleep, stiffness, muscle and body fatigue, headaches, irritable bowel syndrome, problems with memory or concentration, and mood disturbances [9].

High levels of health care utilization and health care costs associated with medical visits, drug prescriptions and diagnostic testing are commonly mentioned in the FM literature [17]. Individuals with FM are often seen by health care professionals due to concomitant medical issues (somatic comorbidities associated with FM such as depression, anxiety or fatigue) and related pharmacological treatment. Recent systematic reviews of medications for treatment of fibromyalgia (amitriptyline [18], milnacipran [19], gabapentin [20] antiepileptic drugs [21], monoamine oxidase inhibitors [22]; serotonin and noradrenaline reuptake inhibitors [23], anticonvulsants [24]) have shown only limited success. These reviews have helped to

inform recent clinical practice guidelines; Ablin [25] recommended judicious use of medical treatment given the limited evidence on efficacy and a substantial risk of side effect. On the other hand, systematic reviews of non-pharmacologic methods show that evidence is accruing which suggests positive effects for non-pharmacologic treatments in the management of fibromyalgia (exercise [26], cognitive behavior therapy [27], acupuncture [28]). In a review of clinical practice guidelines, Ablin 2013 noted "recent evidence-based interdisciplinary guidelines concur on the importance of treatments tailored to the individual patient and further emphasize the necessity of self-management strategies which include exercise and psychological techniques."

Exercise is an important part of FM management [29-31]. The literature suggests that individuals with FM are often deconditioned with poor cardiovascular fitness [32], muscle strength and muscle endurance [33;34]. Whether these physiological features of deconditioning play a role in the causal pathway of FM remains unclear. However, several studies have demonstrated that individuals with FM are able to perform different types of exercise such as aerobic, flexibility, and resistance training programs [35;36]. Exercise may contribute to reduction in pain through improving the body's response to muscle microtrauma by increasing resilience, repair, and resultant adaptation as well as affecting brain processing and responses [37]. Because regular exercise is an important factor in countering age-related loss of muscle, bone mass and functional independence for the general population, it has been suggested [31] that individuals with FM may improve their overall health and moderate risks associated with other chronic conditions by engaging in regular exercises.

Despite interest and many new studies, the effects of various types of physical activity on specific symptoms, mental function and physical performance in people with FM are still unclear. As well, answers to questions regarding the best type of exercise, intensity and delivery options for exercise interventions are still needed. This review attempts to shed light on the effects of aquatic exercise on wellness, symptoms, and physical fitness to guide clinicians and patients with FM to adopt the most effective aquatic exercise training interventions for this condition. Definitions for some of the terms utilized in this review can be found in the glossary of terms (Appendix 1).

2.1.2 Description of the intervention

The traditional use of water as a medium for exercise

History shows that soaking baths, spa centres, water immersion, springs, and natural hot water springs were used for religious and healing purposes as early as 2400 BC [38]. The thermal effects of the water were considered to relieve pain and enhance relaxation [39]. Also known as pool therapy and hydrotherapy [40], aquatic exercise is defined by the Chartered Society of Physiotherapists as a therapy program designed by a qualified physiotherapist using the properties of water to improve function, ideally in a suitably heated pool [41]. Balneotherapy refers to the use of hot-water treatment to ease pain, decrease stiffness and relax muscles, and has been further developed with various forms of salt and/or sulphur treatments, mud packs, and jet streams (spa-therapy) [42].

The current use of water for therapeutic purposes

Health care practitioners currently use the physical properties of water for therapy and rehabilitation for a variety of musculoskeletal conditions (e.g., osteoarthritis, rheumatoid arthritis, fractures, tendonitis) [38;43-46;46-48]. Specific properties of water (buoyancy, resistance, flow and turbulence) are used to develop graded exercise programs. Buoyancy of the body or body segment, with or without floatation equipment, can be used to assist or to resist movements. In addition, the water viscosity itself provides resistance in all directions. During movement, submerged body parts require greater energy expenditure. This resistance can be increased or decreased by altering velocity and the directional use of water jets and turbulence. Exercise intensity can also be augmented with equipment (e.g., paddles, webbed gloves) to increase resistance of the body part moving in the water [38]. Water temperature is another important consideration when designing aquatic exercise training interventions. While most community swimming pools are heated between 26 to 28 ° Celsius (80 to 84 ° Fahrenheit), which is comfortably cool and ideal for movement, pools for therapeutic purposes are usually heated to between 30 and 32 ° Celsius (86 to 90 ° Fahrenheit).

In this review, we define aquatic exercise training intervention as “exercise conducted in a vertical standing position" in the water with the participant submerged to waist, chest or shoulder depth” [49] in a pool (indoor or outdoor). We considered only those aquatic exercise interventions that involved exercise in the water for ≥ 50% of the time. Mixed interventions

with an aquatic component in which participants spent less than 50% of the total intervention time in the water were excluded. For example, an intervention consisting of 12 sessions with 5 or less held in the pool were excluded, as the intervention outcome could not be attributed primarily to the aquatic component.

2.1.3 How the intervention might work

2.1.3.1 Pathophysiological Changes Associated with FM

The pathogenesis of FM is not completely understood. However, FM is currently thought to be a disorder of central pain processing (or central sensitivity) in which individuals have problems with sensory volume control (i.e., lower threshold of pain and other stimuli like heat, noise, odours) [50]. This hypersensitivity may be derived from neurobiologic changes related to psychological factors [51]. Research has also shown biochemical, metabolic and immunoregulatory abnormalities [50]. Other pathophysiological changes commonly found in individuals with FM are low serotonin levels [52], low levels of adenosine triphosphate in red blood cells, dysfunction of the hypothalamic-pituitary adrenal axis [53;54] low levels of growth hormone associated with poor sleep [55;56], cognitive impairment [57;58], and biochemical abnormalities producing sleep dysfunction [59].

Exercise interventions might work because exercise may contribute to reduction in pain through improving the body's response to muscle microtrauma by increasing resilience, repair, and resultant adaptation. In addition, regular exercise has been shown to improve overall health and moderate risks associated with other chronic conditions.

Ideally, in FM disease management the use of pharmacological and non-pharmacological therapies are combined. By doing this, non-pharmacological therapies such as an aquatic exercise intervention, can be part of a rehabilitation model that tackles main issues such as pain. In combining these therapeutic approaches, pharmacological treatments may help alleviate the initial symptoms of pain, and aquatic exercise interventions may help address the functional consequences of the symptoms.

2.1.4 Why it is important to do this review

This review evaluates whether aquatic exercise training has beneficial effects on FM symptoms, how long these effects might last and whether aquatic exercise training is more or less effective than land-based exercise training. It is also important to consider the effects of aquatic exercises as a non-pharmacological treatment given that not all people with FM successfully respond to pharmacological treatment and multimodal types of treatments have been shown to be more successful in the management of the disease [60]. This review also aims to document harms associated with aquatic exercise training interventions in people with FM and to determine whether aquatic exercise training should be recommended as a safe, effective component of FM management. This review will report on injuries and other adverse effects, as well as attrition rates and adherence to training protocols as these may indicate the acceptability of this form of intervention for individuals with FM.

2.2 Objective

The objective of this systematic review was to evaluate the benefits and harms of aquatic exercise training in adults with FM.

2.3 Methods

2.3.1 Types of studies

We selected randomized clinical trials (RCTs) that compared aquatic exercise training to a control group, to another exercise training protocol on land or water. Studies were included if the words randomly, random or randomization were used to describe the method of assignment of subjects to groups.

2.3.2 Types of participants

We selected studies that included adults and used published criteria for the diagnosis of FM. Recently, the American College of Rheumatology (ACR) has introduced new criteria [61;62]; however, the ACR 1990 [63] have been the dominant diagnostic criteria used for diagnosis of fibromyalgia for the past two decades. The ACR 1990 criteria include: a) widespread pain for longer than three months duration, and b) pain on digital palpation with 4

kg pressure in at least 11 of 18 tender points specified sites. Other published criteria are: Smythe 1981 [64], Yunus 1981 [65], Yunus 1982 [66], Yunus 1984 [67]. Although some differences exist between the diagnostic criteria, for the purpose of this review all were considered to be acceptable and comparable.

2.3.3 Types of interventions

Although swimming was included in our search strategy we found no studies investigating this exercise modality; thus, an aquatic exercise training intervention was defined as "exercise conducted in a vertical standing position" in the water with the participant submerged to waist, chest or shoulder depth [49] that took place in an outdoor or indoor pool. In this review, the aquatic exercise intervention was defined as a program with exercise performed in the water for ≥ 50% of the time. We did not set a specific minimum intervention duration, pool temperature, or physical location (i.e., indoor vs outdoor).

We excluded studies if the outcomes could not reasonably be attributed to aquatic exercises. For example, interventions that consisted of a mixed approach (i.e., land-based and water programs including aerobic, flexibility, and resistance training) in which participants spent less than 50% of the total intervention in the water (e.g., 12 sessions with only 2 in the pool) were excluded.

There was no restriction placed on the type of aquatic exercise equipment including flutter boards, tubing, and dumbbells. Calisthenics that used a body segment or segments moving against water resistance as the load for the exercise were also included. We were interested in comparisons in two categories: a) aquatic exercise training interventions compared to control conditions (treatment as usual, physical activity as usual, wait list control, placebo or sham, education-only, water immersion-only, and attention only), and b) aquatic exercise training compared to another exercise protocol (e.g., aerobic, strength) performed on land-based or water.

The classification of exercise intensity during cardiorespiratory exercise in this review followed the American College of Sports Medicine (ACSM) recommendation [68;69] (Appendix 2) as follows:

Table 2.1 Cardiorespiratory exercise intensity: Comparison of methods

Intensity	%VO_2 R / % HRR	% HRMax	Perceived Exertion Scale (RPE) 6-20 Scale
Very Light	<37	<57	RPE<9
Light	37-45	57-63	RPE 9 (very light) to 11 (fairly light)
Moderate	46-63	64-76	RPE 12 (fairly light) to 13 (somewhat hard)
Vigorous	64-90	77-95	RPE 14 (somewhat hard) to 17 (very hard)
Near maximal to maximal	≥ 91	≥96	RPE ≥18 (very hard)

VO_2 R: oxygen uptake reserve; HRR: hear rate reserve; HR_{max}; maximum heart rate

The use of ACSM guidelines was chosen as this represents a useful tool for debating issues and helps to standardize exercise making it comparable across different protocols. ACMS published guidelines for healthy adults and older adults with chronic diseases. We thought the later did not apply to the FM population. Therefore, considering the physiology and pathology of the condition we used guidelines for healthy individuals. In this regard, ACSM guidelines aimed to provide a roadmap for health practitioners concerned with care and exercise prescription of individuals with FM.

2.3.4 Types of outcome measures

Until recently, there was no consensus on outcomes to guide research on the effectiveness of interventions for FM. In 2004, a group of clinicians, researchers and patients under the auspices of the Outcome Measures in Rheumatology group (OMERACT) initiative set about to improve outcome measurement in FM through a data-driven interactive consensus process used previously for other rheumatic diseases [70]. Over the course of the next five years, patient focus groups [71], patient and clinician Delphi exercises [72], a systematic literature review and analysis of outcomes used in FM intervention trials [73], and analyses of psychometric properties of outcomes (i.e., face, construct, content and criterion validity in FM) [74] were conducted. Based on these efforts, OMERACT has recommended the following core set of outcomes for inclusion in all FM clinical trials: pain, fatigue, multidimensional function, tenderness, and quality of sleep [70;75]. OMERACT designated two additional outcomes,

depression and dyscognition, as important but not core, and placed anxiety, morning stiffness, imaging and biomarkers on the agenda for further research [75].

In this review, we have extracted data for 24 outcomes which include all the outcomes considered to be important by OMERACT [75]. We categorized the 24 outcomes into four main categories: wellness, FM symptoms, physical fitness, and safety and acceptability. In the wellness category, six outcomes were extracted: multidimensional function, patient rated global, clinician rated global, self-reported physical function, self-efficacy, and mental health. In the symptom category of outcomes, we extracted data for eight symptoms experienced by individuals with FM: pain, fatigue, sleep disturbance, stiffness, tenderness, depression, anxiety, and dyscognition. In the physical fitness category we extracted seven outcomes associated with physiological adaptation to exercise training: muscle strength, muscle endurance, muscle power, muscle/joint flexibility, maximum cardiorespiratory function, and submaximal cardiorespiratory function. The Cochrane handbook states "It is important that Cochrane reviews include information about the undesirable as well as desirable outcomes of the interventions examined...at least one undesirable outcome should be defined as a major outcome measure."[76]. With this in mind, the final category of outcomes was conceptualized as safety and acceptance of exercise training. This category consists of three outcome associated with possible harms - injuries, exacerbations of FM, or other adverse effects; while another outcome – attrition rates, was also considered as a form of acceptability of exercise training.

When an included study used more than one instrument to measure a particular outcome, we selected the data for extraction based on the following criteria: a) the frequency of use of the instruments in the FM literature (e.g., the Fibromyalgia Impact Questionnaire or FIQ is a disease-specific instrument commonly used in this literature), and b) documented evidence supporting the psychometric properties of the instrument or this or similar populations (e.g., validity, reliability, sensitivity, measurement properties).

Outcomes representing wellness:

This category of outcomes relates to generalized health or functioning. Tools used to measure outcomes in this category included both broad spectrum indices designed to capture an

array of tasks or characteristics to yield a single summary score (e.g., Short Form Health Survey -SF-36), and single item tests on which the respondent is asked to rate their status in an area of health using a single item scale (e.g., a visual analogue scale - VAS) on which the respondent places a mark on a 10 cm line between worst health on one end and best health on the other.

- Multidimensional Function – Multidimensional function consists of multidimensional indices used to measure general health status and/or health-related quality of life. As recommended by Choy [75], we collapsed measures of general health status or health-related quality of life or both into a single outcome. When included studies used more than one instrument to measure multidimensional function, we preferentially extracted data for the FM Impact Questionnaire (FIQ)-total [77] followed by the SF-36 total [78], the SF-12 total [79], the EuroQol-5d [80], the Arthritis Impact Measurement Scales 2 total (AIMS total) [81], the quality of life scale [82-84], and the Illness Intrusiveness Questionnaire [85].
- Patient Rated Global - Patient global assessments are commonly assessed by Likert or VAS scales. They are highly sensitive to change [70;74] and appear to be reliable [86]. We extracted data preferentially for self-perceived change VAS; followed by self-perceived change-numeric rating scale; self-perceived disease severity VAS; self-perceived disease severity-numeric rating scale; self-perceived sense of well-being-VAS [87]; and self-perceived health status numeric rating scale.
- Clinician Rated Global - Global assessments of disease severity by physicians and other health professionals using Likert or VAS are commonly used in clinical settings. We used clinician-rated disease severity measures using a VAS [88].
- Self-reported Physical Function - We preferentially extracted data for the FIQ (English or translated) physical impairment scale followed by the health assessment questionnaire disability scale (HAQ), the SF-36/Rand 36 Physical Function; the Sickness Impact Profile [89] – Physical Disability, and the Multidimensional Pain Inventory household chores scale [90;91].
- Self-Efficacy - (function) Instruments included in this review were: the arthritis Self-Efficacy Scale [92], the Chronic Pain Self - Efficacy [93], the FM Attitudes Index [94] and the Freiburg Mindfulness Inventory [95].

- Mental Health - The U.S. Surgeon General has defined mental health as "a state of successful performance of mental function, resulting in productive activities, fulfilling relationships with people, and the ability to adapt to change and to cope with adversity" [96]. In focus groups conducted by Arnold [71] participants reported that their physical and emotional ability to complete tasks of daily living was severely limited by FM because of pain, lack of energy, fatigue, and depression. Patients also expressed feelings of embarrassment, frustration, guilt, isolation, and shame. When several measures were used we chose in the following order: SF-36/Rand 36 Mental Health; psycho social scale (Sickness Impact Profile); Global Severity Index of the Symptom Checklist 90 – revised (SCL-90-R) [97]; Profile Mood States (POMS) [98]; Psychological General Well-being (PGWB) total score [99].

Outcomes representing FM symptoms:

This category of outcomes includes eight symptoms associated with FM.

- Pain – The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [100]. For the purpose of this review, we focused on one aspect of the pain experience – pain intensity. When more than one measure of pain was reported in a single study, we preferentially extracted: pain VAS (FIQ Pain, FIQ-Translated, McGill pain VAS, current pain) followed by the Numerical Pain Rating Scale, and the SF-36/Rand36 Bodily Pain scale, and the Pain Severity scale of the Multidimensional Pain Inventory.
- Fatigue – Fatigue is recognized by individuals with FM and clinicians alike as an important symptom in FM. Fatigue can be measured in a global manner, such as when an individual rates their fatigue on a single item scale, or as a multidimensional tool that breaks the fatigue experience into two or more dimensions such as general fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity, and degree of interference with activities of daily living [101]. We accepted both uni- and multi-dimensional measures for this outcome. When included studies used more than one instrument to measure fatigue, we preferentially extracted the fatigue VAS

(FIQ/FIQ-Translated Fatigue, or single item fatigue VAS) [102], followed by the SF-36/Rand36 Vitality sub-scale, the Chalder Fatigue Scale (total), the Fatigue Severity Scale and the Multidimensional Fatigue Inventory.

- Sleep Disturbance - Sleep problems are almost universal in FM, occurring in 95% of patients [101]. When included studies used more than one instrument to measure sleep, we preferentially extracted the Pittsburg Sleep Quality Index [103] followed by the Sleep Quality VAS [104], Sleep Quantity: nights/week, hours/night, hours of good to disturbed sleep, and the Hamilton Depression Sleep Items [105].
- Stiffness – In focus groups conducted by Arnold [71], individuals with FM "... remarked that their muscles were constantly tense. Participants alternately described feeling as if their muscles were 'lead jelly' or 'lead Jell-O,' and this resulted in a general inability to move with ease and a feeling of stiffness". The only measure we encountered for stiffness was the FIQ stiffness VAS.
- Tenderness - Tenderness is defined as discomfort produced as an evoked response to mechanical pressure [106;107]. Although there are concerns that measures of tenderness can be biased by cognitive and emotional aspects of pain perception, many studies support the utility of measurement of tenderness in FM using either tender point (TP) counts or pain pressure threshold [106]. When included studies used more than one instrument to measure tenderness, we preferentially extracted the TP count followed by Pain Pressure Threshold (dolorimetry score, based on at least 6 of the 18 ACR TPs) and the total myalgic score (sum/mean of ordinal rating of response to thumb pressure across 18 TPs).
- Depression - Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities [108]. In focus groups conducted by Arnold [71] the emotional disturbances most commonly experienced by participants with FM included depression and anxiety. A complete understanding of depression and how best to assess it in FM trials is still uncertain and is an active research issue [70]. However, the common practice of excluding patients with significant

depression from FM intervention studies, leads to the underestimation of the discriminatory power of these instruments [75]. We preferentially extracted the Beck Depression Inventory (BDI) total scores, Cognitive/affective sub-scale scores, BDI without FMS Symptoms; short form translated SF-36; Hamilton Depression Scale; Center for Epidemiologic Studies-Depression (CES-D) FIQ/FIQ translated – depression; mental health inventory sub-scale depression; Arthritis Impact Measurement scales – depression sub-scale; Hospital Anxiety and Depression Q-depression; Symptom checklist 90 – depression; and the Psychological General Well-Being (PGWB depression score).

- Anxiety - Anxiety is a feeling of apprehension and fear characterized by physical symptoms such as palpitations, sweating, irritability, and feelings of stress [109]. Some participants reported that acute anxiety, panic, or depression were disruptive to activities that they were trying to complete [75]. We preferentially extracted data for anxiety using the anxiety scale of the Arthritis Impact Measurement Scales, followed by the State Anxiety Inventory; the Hospital anxiety and Depression Q-anxiety; the Beck anxiety inventory; the mental health inventory sub-scale anxiety; the Symptom Checklist 90 – anxiety scale; psychological general well-being anxiety score; and the FIQ anxiety scale [110].
- Dyscognition – Dyscognition pertains to difficulty with cognitive tasks especially memory and thought processes. The term describes symptoms related to difficulty concentrating, disorganized thinking, and inability to stay focus or alert. Although OMERACT identified dyscognition as an important outcome for FM trials, it was rarely measured in the included studies. One measure we encountered in this review was the Paced Auditory Serial Addition Test [111].

Outcomes representing physical fitness:

This category, consisting of six outcomes, is associated with physiological adaptation to exercise training. There are several facets to physical fitness including: cardiovascular function (maximal capacity and submaximal endurance), body composition, muscle strength, muscle endurance, flexibility, agility, coordination, balance, power, reaction time, and speed [112]. Given the nature of the intervention, outcomes reflecting physical fitness are highly relevant.

- Muscle Strength - Muscular strength is a measure of a muscle's ability to generate force. It is commonly expressed as maximal voluntary contraction (MVC) during isometric testing; one-repetition maximum (1RM) during dynamic isotonic testing [113]; and/or peak torque muscle contraction during isokinetic testing. When more than one measure of strength was reported, we preferentially extracted dynamic test results over isometric test results, lower limb test results over upper limb results, and extensor muscle strength over flexor muscle strength.
- Muscle Endurance - Muscular endurance refers to the ability to exert submaximal force for extended periods, and it can be assessed during static or dynamic muscular contraction [114]. For the purpose of this review, when more than one measure of muscle endurance was reported we preferentially extracted: lower extremity dynamic endurance (stair step; sit to stand chair test or fatigue curve), followed by lower extremity static endurance including fatigue curve, number of squats performed in 60 seconds, fatigue index (the ratio of average power in last 5 reps to the average power in first 5 during a test of 60 repetitions), and upper extremity dynamic endurance measured using a fatigue curve and grip endurance test.
- Muscle Power - Power (the explosive aspect of strength) is defined as the rate of muscle work [115], and is the product of force and speed of movement [power = (force x distance)/time] [112]. When more than one measure of power was reported we preferentially extracted: the vertical jump test (m), horizontal jump, isokinetic power (lower extremity before upper extremity) and maximum power test (maximum power in watts on best of 3 repetitions doing squats).
- Maximum Cardiorespiratory Function - Cardiorespiratory function is the ability of the heart, lungs and circulatory system to efficiently supply oxygen and nutrients to working muscles. Rhythmic, aerobic type exercises involving large muscle groups are recommended for improving cardiovascular fitness. Maximal oxygen uptake (VO_{2max}) is accepted as the best criterion to measure cardiorespiratory fitness. Maximal oxygen uptake is the product of the maximal cardiac output (L blood • min^{-1}) and arterial-venous oxygen difference (ml O_2 / L blood). Maximal tests have the disadvantage of requiring the participant to exercise to the point of volitional fatigue and often require medical supervision and access to emergency equipment. For this

reason, maximal exercise testing is not always feasible in research, health and fitness settings. For this review, we preferentially extracted data from maximal or symptom-limited treadmill or cycle ergometer tests in units of ml/kg/min, energy expended, peak workload or test duration. We also accepted data from exercise tests which yielded predicted maximum oxygen uptake.

- Submaximal Cardiorespiratory Function or Testing - There are two major categories of submaximal tests: predictive and performance tests. Predictive tests are submaximal tests that are used to predict maximal aerobic capacity [116]. Performance tests involve measuring the responses to standardized physical activities that are typically encountered in everyday life. In this review we preferentially extracted data from work completed at a specified exercise heart rate (e.g., PWC170 test), followed by distance walked in six minutes (meters), the 2 minute walk test (meters), walking time for a set distance (seconds), anaerobic threshold test, and timed walking distance (e.g., Quarter Mile Walk Test).
- Muscle/Joint Flexibility - Flexibility is the ability to move a joint or a series of joints fluidly through the complete range of motion [114]. It is important to carry out activities of daily living, and it depends on several specific variables, including the geometry and distensibility of the joint capsule, ligaments, tendon and muscles spanning the joint [114]. Flexibility is joint specific, therefore no single test can evaluate total body flexibility. Tests quantify flexibility in terms of range of motion (ROM) expressed in degrees. For the purpose of this review the following were used: sit and reach test (commonly used to assess low back and hip joint flexibility) and ROM measures. When there were multiple ROM measures within a single study, we took the first measure in the researcher's data table.

Outcomes Representing Safety and Acceptability – Four outcomes grouped into two categories were used to represent safety and acceptability. Qualitative descriptions of any adverse events, injuries, exacerbations of pain and/or other FM symptoms were recorded. Attrition rates were also extracted as an indicator of acceptability of interventions.

Major outcomes

Based on clinician, consumers (individuals with FM) and the type of intervention reviewed we designated seven of the 24 outcomes as major outcomes. All are presented in the Summary of Findings tables (Appendix 3)

- multidimensional function (wellness)
- self-reported physical function (wellness)
- pain (symptoms)
- stiffness (symptoms)
- muscle strength (fitness)
- submaximal cardiorespiratory function (fitness)
- attrition rates* (safety and acceptability)
- adverse effects* (safety and acceptability)

  *Attrition rates and adverse effects are presented together in the Summary of Finding tables (Appendix 3). Attrition is used as a potential indicator of adverse events.

Minor outcomes

The 14 remaining outcomes were designated as minor outcomes. There were four wellness outcomes, six symptom outcomes and four physical fitness outcomes:

Minor wellness outcomes:	*Minor symptom outcomes:*	*Minor physical fitness outcomes:*
• patient rated global	• tenderness	• muscle endurance
• mental health	• fatigue	• muscle power
• self-efficacy	• sleep disturbance	• maximum cardiorespiratory function
• clinician rated (single item instrument)	• depression	• muscle flexibility
	• anxiety	
	• dyscognition	

2.3.5 Search methods for identification of studies

A comprehensive search for all physical activity interventions was conducted. The citations found in the electronic searches were screened and then classified by type of exercise training (e.g., aerobic, resistance, flexibility and yoga, aquatic exercise, mixed exercise and composite interventions, and innovative interventions).

2.3.5.1 Electronic searches

We searched the following databases from database inception to October 24, 2013 using current methods outlined in Chapter 6 of the Cochrane Handbook [117]. No language restrictions were applied. Full search strategies for each database are found in the appendices as indicated in the list.

- MEDLINE (OVID) 1946 to March Week 1 2013 October 24, 2013 (Appendix 4)
- EMBASE (OVID) EMBASE Classic+EMBASE 1947 to 2013 October 24
- Cochrane Library (Wiley) 2013 Issue 2 http://www.thecochranelibrary.com/view/0/index.html
    - Cochrane Database of Systematic Reviews (Cochrane Reviews)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Health Technology Assessment Database (HTA)
    - NHS Economic Evaluation Database (EED)
- CINAHL (Ebsco) 1982-October 24, 2013
- PEDro (www.pedro.org.au/) Accessed October 24, 2013
- Dissertation Abstracts (Proquest) Accessed October 24, 2013
- Current Controlled Trials. Accessed October 24, 2013
- WHO International Clinical Trials Registry Platform (www.who.int/ictrp/) Accessed October 24, 2013
- AMED (Allied and Complementary Medicine) (OVID) 1985 to October 2013 (accessed October 24, 2013)

2.3.5.2 Searching other resources

Reference lists from key journals, identified articles, meta-analyses and reviews of all types of treatment for FM were reviewed independently by two review authors with all promising or potential references scrutinized and appropriate titles added to the search output.

2.3.6 Data collection and analysis

2.3.6.1 Review team

The review team was made up of 12 members, including two consumers, one librarian, and nine review authors, however not all team members are listed as authors on this review. Review authors were from physical therapy, kinesiology, and dietetics backgrounds, and were trained in data extraction using a standardized orientation program designed for this review. Review authors worked in pairs (with at least one physical therapist in each pair) for the data extraction process. The team met monthly to discuss progress, clarify procedures, make decisions regarding study inclusion/exclusion, classify outcome variables, and work collaboratively in the production of this review.

2.3.6.2 Selection of studies

Review authors independently screened titles and reviewed study abstracts generated from searches using a set of criteria (see Appendix 5 - Screening and Classification Criteria - Level 1, 2 and 3). We retrieved full text publications for all promising abstracts. The methods and results sections for all non-English reports were translated, and full text reports and translations were then examined independently by two review authors to determine if the study met selection criteria. Disagreements between the two review authors and questions regarding interpretation of inclusion criteria were resolved in discussion with partners unless the pair agreed to take the issue to the team.

2.3.7 Data extraction and management

We developed electronic data extraction forms to facilitate independent data extraction and consensus. Pairs of review authors worked independently to extract the descriptive and quantitative data from the studies (i.e. characteristics of each study, details of participants, interventions, and comparators, outcomes and study design). After the data were extracted, the pairs reviewed the data together and reached a consensus. We frequently encountered questions regarding the acceptability of outcome measures used in the studies; these questions were referred to the team for resolution if not solved with partners.

2.3.8 Assessment of risk of bias in included studies

We followed the procedure to assess bias recommended in the Cochrane handbook. Two review authors independently evaluated the risk of bias in each included study using a customized form based on the Cochrane Risk of Bias Tool [76]. The tool addresses seven specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. For other sources of bias, we considered potential sources of bias such as baseline inequities despite randomization, or inequities in the duration of interventions being compared. Each criterion was rated as low, high, or unclear risk of bias. The criterion "unclear risk" was used when the assessors were unable to determine the potential for bias based on the information in the report(s) of the included study or acquired through communication with author. In such cases, the assessments were revised if the authors responded to our requests for more information. Disagreements on classifying risk of bias between the review author pairs were resolved through discussion at consensus meetings. If agreement could not be reached, the issue was referred to the review team for a decision.

2.3.9 Assessment of Congruence of Interventions with Exercise Guidelines

While exercise programs for individuals with FM commonly focus on relief of symptoms, exercise has been shown to have wide sweeping positive effects on various aspects of health when performed regularly at and beyond certain minimum volumes. We believe that this should be addressed for individuals with FM and therefore have sought to establish congruence of the exercise interventions with the widely accepted ACSM guidelines that describe the exercise dosages recommended to improve and maintain physical fitness and minimize the health effects of chronic inactivity [69]. While we have chosen to evaluate interventions against these guidelines (see Appendix 2), it is also important to acknowledge that for individuals who are deconditioned, participation in exercise that falls below the guidelines outlined in the ACSM position stand in Garber [69] can provide enough of a stimulus to cause physiological adaptations that enhance physical performance as well. While individual who are deconditioned should begin their participation in exercise at lower dosages, they will experience greater benefits as they gradually increase their exercise programs to levels within the guidelines.

We extracted data on exercise frequency, time, duration, intensity and planned progression model of each intervention, and compared the aerobic, strengthening and flexibility components of the interventions with guidelines in the 2011 ACSM Position Stand on the quantity and quality for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults [69] (see ACSM guidelines Appendix 2 and Characteristics of included studies – Appendix 6).

2.3.10 Measures of treatment effect

The outcome measures of interest were most often presented as continuous data with pre-test means, and standard deviations. We calculated change scores and estimated standard deviations for the change scores using the formula described in the Cochrane Handbook (Figure 2.1). Review Manager [118] analysis software was used: (1) to calculate effect sizes in the form of mean differences, standardized mean differences (SMD) and 95% confidence intervals (95% CI), (2) to generate forest plots to display the results, and (3) to calculate and meta-analyze attrition rates using odds ratios.

When statistically significant results were found, we also evaluated the clinical relevance of the effects in major outcomes by calculating the relative difference in change from a pooled baseline in the intervention group as compared to the change from a pooled baseline in the control or comparison group. The pooled baseline was calculated as follows:

$$\text{Pooled baseline} = (X_{1\,pre} * n_1 + X_{2pre} * n_2) / (n_1 + n_2) \quad \ldots\ldots(2.1)$$

$$\text{Relative difference (\%)} = \text{weighted mean difference /pooled baseline} \quad \ldots\ldots(2.2)$$

where the weighted mean difference was calculated in RevMan [118], $X_{1\,pre}$ and $X_{2\,pre}$ are the pre-test means in the experimental and the control groups respectively, and n_1 and n_2 are the number of participants in the experimental group and the control groups respectively. When more than one instrument was used to measure an outcome, the median and range for relative improvement were calculated. In keeping with the practice of the Philadelphia Panel, we used 15% as the level for clinical relevance [119]. Relative changes were calculated for major outcomes in the Aquatic Exercise Training vs Control analyses only.

2.3.11 Unit of analysis issues

The unit of analysis of the primary studies was individuals.

2.3.12 Dealing with missing data

When numerical data were missing, we contacted the study authors, requesting additional data required for analysis. When information needed to describe the intervention or to determine risk of bias was missing, we contacted authors using open-ended questions. When numerical data were available only in graphic form, we used Engauge version 4.1 [120] to extrapolate means and standard deviations by digitizing data point on the graphs. When unavailable, the standard deviations of the change scores were calculated using the formulae in Higgins [76] (See Figure 2.1). The correlation between baseline and end of study measurements was estimated at 0.8.

$$SD_{E,change} = \sqrt{SD^2_{E,baseline} + SD^2_{E,final} - (2 \times Corr \times SD_{E,baseline} \times SD_{E,final}}$$

Figure 2.1 Formula for calculating standard deviations of change scores based on pre and post-test standard deviations (see Section 16.1.3.2.in Higgins [76]).

2.3.13 Assessment of heterogeneity

Statistical heterogeneity among the trials was assessed using the heterogeneity statistics (chi squared, I^2). We considered values of $p < 0.1$ to be indicative of significant heterogeneity. Where $p < .1$ and or $I^2 > 50\%$, the results were examined for sources of clinical heterogeneity and methodological differences. When statistical heterogeneity was evident, we used a random effects model for meta-analysis [121]

2.3.14 Assessment of reporting biases

Methods described in the Cochrane handbook (funnel plots, statistical tests, imputation, [122]) were planned pending a large enough sample of studies (i.e., >10 studies).

2.3.15 Data synthesis

When two or more sets of data were available for the same outcome, we used the RevMan [118] analyses to pool the data (meta-analysis). In order to perform meta-analysis, transformation of the point estimates of outcomes was performed: a) to express results in the same units (e.g., cm were transformed to mm), or b) to resolve differences in the direction of the scale (when scores derived from scales with higher score indicating greater health were combined with scores derived from scales with high scores indicating greater disease), change scores were modified to allow calculation of relative change or to allow pooling of data.

A fixed effects model for meta-analysis was used unless heterogeneity was evident ($I^2 >$ 50%), in which case a random effects model was used. To evaluate the magnitude of the effect, we used Cohen's guidelines (no effect < .2, small effect = .2 to .49, moderate effect = .5 to .79, large effect ≥ .80 [123].

2.3.15.1 Subgroup analysis and investigation of heterogeneity

Subgroup analysis was undertaken to explore the relative effects (as represented by the SMD) of a variety of participant and intervention related characteristics on multidimensional function, pain and muscle strength outcomes. Only studies comparing aquatics training to control were examined.

Participant Characteristics - We classified studies into high and low subgroups for each of the following participant characteristics at baseline: age, impact of FM, pain, duration of symptoms. High and low groups were determined based on 90% confidence intervals using the following steps:

- Weighted means, pooled standard errors, and 90% confidence intervals were calculated for each study.
- The studies with means below the median were candidates for the low group while studies with weighted means greater than the median were candidates for the high group.
- When the 90% confidence interval of a study of the one group overlapped with one (or more) confidence interval of the other group, it was discarded. Thus, the baseline

means of studies in the low group were statistically significantly than means of studies in the higher group ($p < 0.1$).

Characteristics of the Intervention – We planned to do subgroup analysis to determine the effects of features of the intervention on multidimensional function, pain, and strength as follows:

- Temperature of the pool: Cool (28 to 32 degrees Celsius), Temperate (33 to 36 degrees Celsius), Warm (>36 degrees Celsius)
- Duration of the program in weeks: a) < 7 weeks, b) 7 – 12 weeks, c) > 12 weeks
- Frequency of training per week: a) 1 time/week, b) 2 times/week, c) 3 times/week, d) >3 times/week
- Exercise intensity: a) very light, b) light to moderate, c) moderate, d) light to vigorous, e) non-specified, f) self-selected
- Accumulated time in the pool: a) < 1000 minutes, b) 1000 – 2000 minutes, c) > 2000 minutes

2.3.15.2 Sensitivity analysis

No sensitivity analyses were planned *a priori*. In this review, a sensitivity analysis [124] was conducted when the results of one study in the *aquatics vs control* comparisons were found be more extreme than the other studies. We carried out a sensitivity analysis by excluding the study in question from the meta-analyses and evaluating the impact on heterogeneity. Because the exclusion of the study substantially reduced the heterogeneity observed in the meta-analyses, we used the revised meta-analysis for assessment of treatment effects.

2.3.15.2.1 Summary of Findings Tables (Appendix 3)

We used Grade-Pro version 3.6 [125] to prepare summary of findings tables for the seven major outcomes for each of the three comparisons. In the summary of findings tables, we integrated analysis of quality of evidence and the magnitude of effect of the interventions. We applied the GRADE Working Group grades of evidence which considers the Risk of Bias and the body of literature to rate quality into one of four levels:

- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: We are very uncertain about the estimate.

Quality ratings were made separately for each of the seven major outcomes. Multidimensional Function, a comprehensive and encompassing outcome measure was selected among the seven outcomes variables to be highlighted in the Summary of Findings table (Appendix 3) and the Plain Language Summary. Calculations were carried out based on the guidelines of the Cochrane Musculoskeletal Review Group.

2.4 Results

2.4.1 Results of the Search

The search resulted in a total of 1986 citations. We excluded 1213 on citation screening and 609 based on abstract screening (see Figure 2.2). On examination of full text articles, we excluded 61 studies (Appendix 7) because they did not meet the selection criteria related to: a) diagnosis of FM (n = 5), b) physical activity intervention (n = 11), c) study design (n = 35), or d) outcomes (n = 9). 159 research publications described 84 RCTs with physical activity interventions for individuals with FM. The 84 RCTs were screened to identify studies which compared interventions that were exclusively aquatic exercise interventions to control groups or other interventions. Thirty-one articles describing 24 studies examining aquatic training were examined in detail; seven articles did not meet inclusion criteria; < 50% aquatic (n = 5), unspecified mix of aquatic and land (n = 2). One study [4] is awaiting assessment and four additional studies are awaiting classification. These studies will be considered when this review gets updated.

2.4.2 Included studies

Twenty three articles describing 16 studies [1;2;111;126-138] met our selection criteria and were included for analysis. Three publications by Tomas-Carus published in 2007 [6;7;139], reported additional variables from a primary study by Gusi 2006 [132]; therefore these four publications (3 by Tomas Carus and 1 by Gusi) were included but counted as one study for analysis (hereafter identified as 'Gusi 2006'). Likewise, Gowans 2002 [140] reported on additional variables from the Gowans 2001 [131] primary study and this pair was included but was also counted as one study (hereafter both reports are identified as 'Gowans 2001'). Similarly, Munguia Izquierdo 2008 [141] reported additional variables from the Munguia-Izquierdo 2007 [111] primary study and these two studies were included and counted as one (hereafter both reports are identified as 'Munguia-Izquierdo 2007'). Furthermore, two publications by Tomas-Carus, one in 2007 [8] and another one in 2009 [142], reported on additional variables from the Tomas-Carus 2008 [137] primary study so the included trio was counted as one study (hereafter identified as 'Tomas-Carus 2008'). Of 881 participants in the included studies, 866 were females with FM. There were 439 individuals assigned to aquatic exercise training intervention: 248 in the aquatic vs control comparison, 116 in the aquatic vs land-based comparison, and 65 in the aquatic vs other types of intervention comparison.

We contacted authors using open-ended questions to obtain the information needed to assess risk of bias and/or the treatment effect. We received responses from 11 authors: [1;2;111;126;130;132-134;136-138].

2.4.3 Description of intervention

The main characteristics of the studies are summarized in characteristics of included studies tables (Appendix 7) tables and described below:

2.4.3.1 Aquatic vs Control:

Settings: Nine studies were identified. Seven studies were conducted in Europe [2;111;132;136-138;143], one in North America [131] and one in South America [133]. All studies were published after 2000. Of the 16 research reports four articles written in Spanish [2;132] and [137]; two articles [132;137] had primary and secondary articles written in English and Spanish. The remaining articles were written in English.

Participants: A total of 513 females and six males with an age range of 46.3 to 48.3 years were included. FM diagnosis followed ACR 1990 criteria in all studies. Average disease duration/ was 12 years; however, some of the studies did not report this information [2;133;138]. Some studies excluded participants who were not sedentary. These included individuals who: a) were engaging in regular exercise [133], b) participating in ongoing exercise [136] , c) had a history of physical activity more strenuous than slow paced walking more than twice per week over four months prior to study [111], or d) had a history of more than 30 minutes exercise/week during 2 weeks in the last 5 years [132;137].

Figure 2.2 Study flow diagram.

[a] Discrepancy between the number of articles and studies denotes that multiple papers may have described the same study.

Characteristics of the Intervention: Water temperature was 27 to 32 degrees Celsius in three studies [2;111;133], and 33 to 37 degrees Celsius in four studies [132;136-138]. Two of the studies did not specify water temperature [131;143]. In six interventions, all sessions were performed in the water 100% of the time [111;131-133;137;143] , in one intervention, 70% of the total intervention consisted of exercise in the water [136], and the two remaining interventions consisted of exercise in the water 50% of the time [2;138]. All interventions were conducted in a supervised group setting and lasted an average of 17 weeks (range 4 to 32 weeks). Only three studies provided follow up data: Altan [138] and Gusi [132] at 12 weeks and Mannerkorpi [136] at 48 to 52 weeks. Four studies described the depth of water: Ide [133] specified participants exercised with shoulders in the water, Munguia-Izquierdo [111] at chest height, and water was at waist height in two studies [132;137]. Average session duration was 45 minutes (range 30 to 70). Frequency varied from one time per week in two studies [136;143], two times per weeks in one study [2], three times per week in five studies [111;131;132;137;138], to four times per week in one study [133]. Exercise intensity levels varied as follows:

- very light (< 57% predicted HR_{max}): Arcos-Carmona [2]
- light to moderate (57 to 76% predicted HR_{max}): Altan [138]; Tomas-Carus [137]
- moderate (64 to 76% predicted HR_{max}): Gowans & Gusi [131;132]
- light to vigorous (57 to 95% predicted HR_{max}): Munguia-Izquierdo [111]
- self-selected: Mannerkorpi 2000 [143]; Mannerkorpi 2009 [136]
- non-specified: Ide [133]

None of the studies met the ACSM exercise guidelines specified for aerobic or strength training. Only Ide [133] met the ACSM guidelines for flexibility training. There was a disagreement between review authors and trialists for one study [111] in classifying the congruence with ACSM guidelines. While Munguia-Izquierdo [111] reported "the intervention program met the minimum training standards of the American College of Sports Medicine pg 826…", the review authors evaluated the program as described as not meeting ACSM guidelines.

Types of exercise: Six studies provided an aquatic mixed intervention, including a combination of aerobics, flexibility, coordination and/or strength. Gowans [131] presented an aquatic aerobic intervention for six weeks that progressed from full exercise time in the water to fewer hours in water and more on land-based. For the purpose of this review we have used data corresponding to the period zero to six weeks (i.e., the time participants exercise 100% in the water). Two authors, Arcos-Carmona [2] and Altan [138], had the intervention split into water and land: 30 - 30 minutes for Arcos-Carmona [2] and 35 -35 minutes for Altan [138]. Ide [133] intervention had an aquatic aerobic exercise component combined with a non-exercise relaxation session.

Control: Six studies had a standardized control group. Two studies provided a specialized type of control (balneotherapy, Altan [138]), and education-relaxation [136]. One study used sedentary recreational activities [133] as a control.

2.4.3.2 Aquatic vs Land-based Training

Settings: Five studies were analyzed; two studies were conducted in Europe [130;134] and three in South America [1;126;129]. All studies were conducted after 2000. All studies but one (Hecker [1]- Portuguese) were written in English.

Participants: The studies included 203 females and one male with an average age of 44 years. All participants were diagnosed following ACR 1990 criteria. Only one study [126] had an exclusion criterion based on physical activity, wherein participants were excluded if they had exercised in the 6 weeks prior to the intervention.

Aquatic interventions: Water temperature was 27 to 32 degrees Celsius in one study [126] and 33 to 37 in two studies [130;134]. Hecker [1] water temperature was 32 to 34 degrees Celsius. One study did not report water temperature [129]. All activities were conducted in a group setting and were supervised. All but one study presented a mixed exercise intervention, including strength, aerobic, flexibility exercise plus and non-exercise relaxation components. The land-based exercises followed the same program as the aquatic exercise training intervention. Assis [126] used an aquatics aerobic intervention in the deep water part of the pool.

The average intervention duration was 13 weeks (range 3-23 weeks). Two studies carried out a follow up assessment at 19 and 24 weeks [130;134]. Duration of the individual sessions within the intervention was 60 minutes with a frequency of one time per week [1], two times per week [134] and three times per week [126;129;130]. Intensity of the intervention was reported in three studies and varied from very light [1], light to moderate [126] to light to vigorous [134]. Three studies did not meet the ACSM exercise guideline for aerobic, strength criteria [1;129;130], and information was insufficient to determine congruence in two cases [126;134]. Only de Melo Vitorino [129] met ACSM criteria for flexibility.

Land-based Interventions: All studies replicated the aquatic exercise training intervention as a land-based intervention. Authors gave these interventions different names (e.g., conventional physiotherapy, kinesiotherapy) but components such as frequency, duration, and intensity were identical. One study had a non-supervised home based exercise control [130].

2.4.2.3 Aquatic vs Aquatic

Settings: Two studies were analyzed [127;128]. One was conducted in Spain [127] and the other in Brazil [128]. Both studies were published after 2007 and were written in the English language.

Types of Interventions: Calandre [127] conducted a direct comparison of Ai Chi (Tai Chi in the water) vs stretching in water (intervention 1 and intervention 2 respectively); De Andrade [128] compared an aquatic aerobic intervention in sea water (intervention 1) to an aquatic aerobic intervention in a pool (intervention 2)

Characteristics of Intervention:

Calandre [127]: There were 73 female and eight male participants with an age range from 49 to 51 years who were diagnosed with FM according to ACR 1990 criteria. Average disease duration was 14.1 years and 15.6 years respectively. Pool temperature was 36 degrees Celcius and individuals had a warm water shower to acclimatize prior to getting in the pool. The length of the intervention was six weeks, with follow up at 10 and 18 weeks. The intervention was carried out in a supervised group setting and was 60 minutes, three times per week at intensity levels that met individual needs. The intervention did not meet ACSM exercise guidelines for

aerobic or strength but met them for flexibility. The stretching group sessions were 60 minutes long, three times per week with intensity levels to meet individual needs.

De Andrade [128]: There were 46 females with an average age of 48.3 to 48.8 years in each of the groups respectively diagnosed according to ACR 1990 criteria. Participants were excluded if they had engaged in physical activity in the three months prior to the intervention. The supervised group activity took place in an outdoor pool (during summer months) with water temperature ranging from 28 to 33 degree Celsius. The 12 week intervention consisted of three 60 minute weekly sessions, at a moderate to vigorous intensity level (50 to 75% $VO2_{max}$, 12 to 13 on the Borg RPE). The intervention did not meet ACSM exercise guidelines for aerobic, strength or flexibility training requirements. The sea water group exercised in water at shoulder level in an area with no waves, with the same duration, frequency and intensity as the pool intervention.

2.4.4 Excluded Studies

Following screening of citations and abstracts, 60 studies were excluded on the assessment of the full text article when the study did not meet the inclusion criterion for: a) diagnosis of FM (n = 5), b) physical activity intervention (n = 10), c) study design (n = 34), or d) no between group data for specified outcomes (n = 9, see Characteristics of excluded studies – Appendix 7).

2.4.5 Risk of bias in included studies

Results of the risk of bias assessment for the 16 studies are provided in in Figure 2.3 and Figure 2.4. The risk of bias assessments was based on primary article data supplemented by responses from authors.

2.4.5.1 Allocation (selection bias)

Eleven of the 16 studies used an acceptable method of random sequence generation (computer generated sequence, coin toss, drawing of cards or lots) and were rated low risk [1;2;111;126-129;133;134;136;138]. Four studies [131;132;137;143] allocation methods were unclear; only one study [130] was rated as high risk as it had not utilized an acceptable method of randomization (date of admission).

Eight studies [1;2;111;126;128;129;134;136] were rated as low risk as they utilized acceptable methods to conceal the allocation sequence such as central allocation (including telephone, web based, and pharmacy-controlled randomization) or sequentially numbered opaque sealed envelopes. Seven studies that did not present sufficient information to allow definitive judgement [130-133;137;138;143] were rated as unclear. One study [127] used an unacceptable method of allocation concealment and thus was classified as high risk.

2.4.5.2 Blinding (performance bias and detection bias)

In exercise studies, blinding of participants and care providers is very rare. Among the included studies, blinding of participants and personnel (performance bias) were rated as low risk for eight studies by review authors [1;126-129;134;136;138], and unclear rick for eight studies [2;111;130-133;137;143].

Thirteen studies blinded outcome assessors to participant group assignment (detection bias) these studies were rated by reviewers as low risk [1;2;111;126;128;129;131;134;136-138;143;144] two were rated as unclear risk [127;130] and one study was rated as high risk [132].

2.4.5.3 Incomplete outcome data (attrition bias)

Two studies that reported incomplete outcome data were rated as unclear risk; there was insufficient information provided by Gusi [132] and Gowans [131] to determine whether incomplete outcome data were adequately addressed.

Aquatic vs Control: Drop-out rates for all interventions were as follows: Altan [138] 6% (3/46) Arcos-Carmona [2] 5% (3/57 participants), Gowans [131] 2% (1/50 participants), Gusi [132] 3% (1/35 participants), Ide [133] 13% (5/40 participants), Mannerkorpi 2000 [143] 16% (11/69 participants), Mannerkorpi 2009 [136] 17% (23/134 participants), Munguia-Izquierdo [111] 5% (3/60 participants) and Tomas-Carus 9% [137] (3/33 participants). Reasons for drop out stated by authors were: failure to attend 95% of exercise sessions or missing more than 25% of activities/classes, failure to attend post measurement for personal reasons, transportation problems and employment commitments, failure to attend assessment, failure to begin exercise program due to scheduling conflicts, unknown reasons, not starting program due to randomization, concomitant disease, family reasons, move from city, falling on the street,

seeking professional support for stress, or change of medication. Only two studies used intention to treat analysis [131] and [111].

Aquatic vs land-based: Drop-out rates were as follows: Assis [126] 13% (4/30 participants), de Melo Vitorino [129] 6% (3/50 participants), Evcik [130] 3% (2/63 participants), and Jentoft [134] reported a 23% drop out rate (10/44 participants). Hecker [1] did not specify a drop-out rate but author communication clarified that "all participants in each group were followed to the end of the study." Reasons for drop out stated by authors were low attendance (< 50% of sessions), no attendance, inflammatory rheumatic disease, personal reasons, reasons not given [130], and incompatibility with work schedule. Intention- to -treat analysis was used by Assis [126] and de Melo Vitorino [129].

Aquatic vs Other: Drop-out rates were as follows: De Andrade [128] 17% (8/46 participants) and Calandre [127] 19% (15/81 participants). Reasons for drop out stated by authors were no excuse, hypertension, cardiac arrhythmia, personal problems and incompatibility with work schedule, lack of time, adverse effects like chlorine sensitivity and pain exacerbation. Calandre [127] used intention to treat analyses.

Missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups, suggesting low risk of bias in 14/16 studies. Overall we rated the risk due to incomplete outcome data low (~80%, Figure 2.4)

2.4.5.4 Selective reporting (reporting bias)

It was difficult to assess selective reporting bias because a priori research protocols were not available for any of the reviewed studies. 3/16 studies were rated as having high risk of selective reporting [127;132;137] because some of the reported outcome measures were not pre-specified and point/variability estimates were not provided for all outcomes. Unclear risk was rated on 4/16 studies [1;111;130;133]. Overall we rated the risk of selective reporting as low (~60%, Figure 2.4).

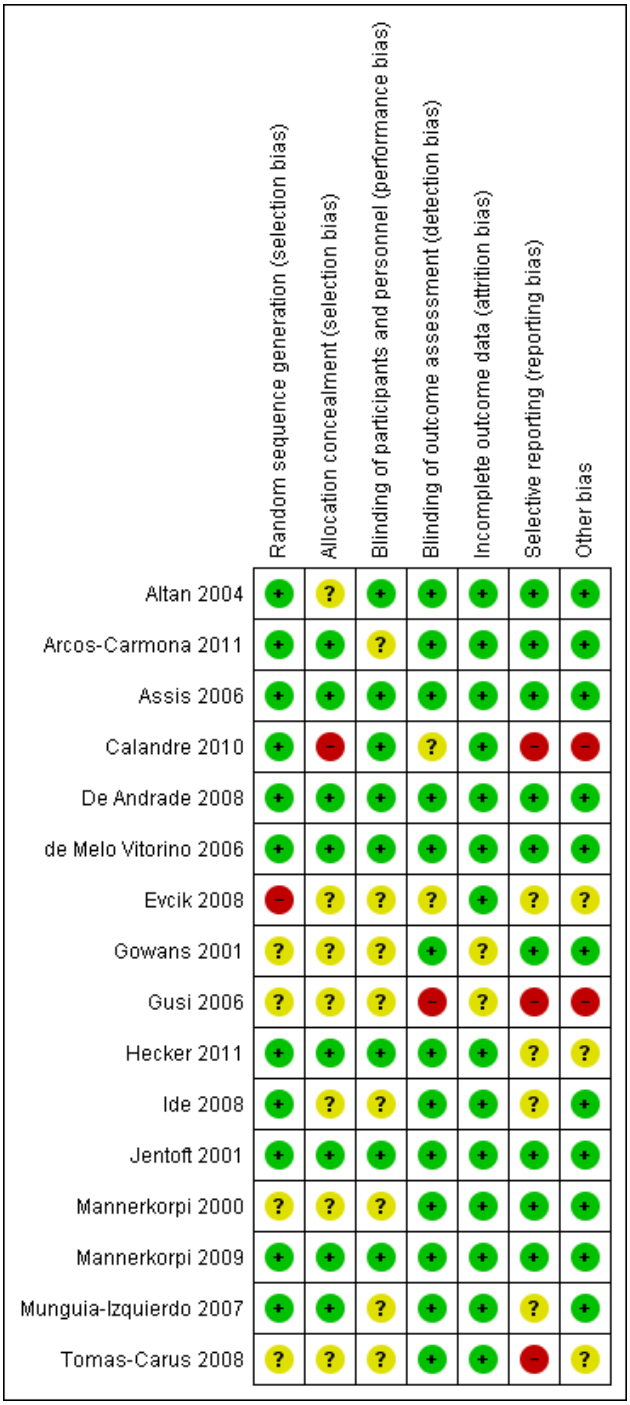

Figure 2.3 Risk of bias summary consensus: review authors' judgements about each risk of bias item for each included study. Key for colours and signs: green (+) = low risk of bias; yellow (?): unclear risk of bias; red (-): high risk of bias

Information on adverse effects was seldom included in the primary studies. Only five studies reported adverse effects. Altan [138]described participant drop out due to hypertension and cardiac arrhythmias - these participants were in the balneotherapy group. De Andrade [128] study reported "adverse events were not indicated as a cause of interruptions." There were 20 adverse events in this study (nine in pool group and 11 in sea group). Nine patients reported muscle pain in a pool group. Two patients reported first-degree burns, one patient presented with a urinary infection, and eight in sea group" (pg 149) reported muscle pain. Evcik [130] states "no side effects were observed during the program" (pg 886-7). Assis [126] states " there were 10 adverse events in the deep water running group and 16 in the land-based exercise group ... four patients in the deep water running reported muscle pain and 1 reported tinea pedis. There were 12 patients in the land-based exercise group who reported muscle pain. One of them had an impingement syndrome; another a bilateral ankle arthritis; a third a Baker cyst." (pg 61); Calandre [127] states "Fifteen patients withdrew from the trial ... three of them belonging to the Ai Chi group due to adverse reactions: one case of chlorine hypersensitivity and two cases of pain exacerbation" (pg s-16); Mannerkorpi 2000 [143] stated "main reasons for not starting or interrupting the program were lack of time due to commitments related to child care or employment, or the occurrence of infection or injury" (pg 2474).

2.4.5.5 Other potential sources of bias

Overall, we rated the risk due to other sources as low (~75%, Figure 2. 4). One study was rated high risk for other serious potential sources of bias because it reported extreme baseline imbalances in one of the outcome measures [127]. Three studies were rated unclear risk: in one of them [130] review authors considered the methodology had some flaws and many areas assessed were not discussed by authors; in another study [1] there was insufficient information to assess whether an important risk of bias existed; and in the third study [137] review authors noted there was incongruence of data among primary and companion studies.

Poor adherence is also a potential source of bias in exercise studies. None of the studies reported detailed results of systematic data collection and analysis of participant adherence to exercise performance in a way that would allow the review authors to understand the amount of exercise training actually performed by participants.

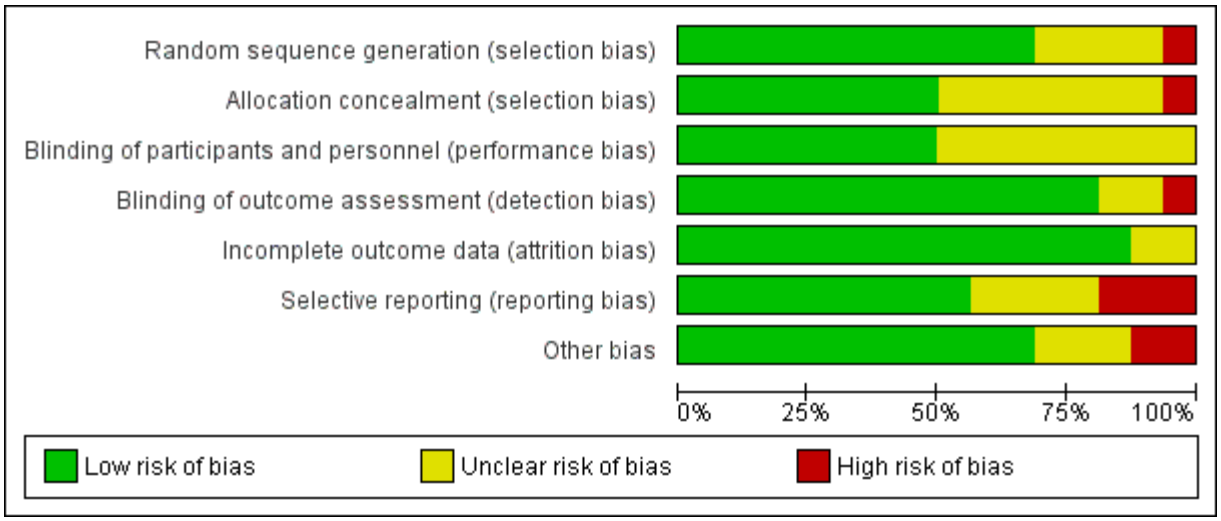

Figure 2.4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

2.4.6 Effects of the Intervention

The results related to effects of the interventions have been grouped below.

2.4.6.1 Aquatic vs control

After visually inspecting the results produced in the meta-analyses, it was apparent that one study [133] was atypical (i.e., an outlier). On reviewing Ide [133], it was noted that the intervention differed from the others; the focus of the Ide [133]intervention was on combined breathing with flexibility maneuvers in the water, whereas the other studies concentrated on aerobic and resistance training exercises. A sensitivity analysis was conducted to examine the effect on outcomes when the outliner study was removed and we decided to remove Ide [133] from the meta-analysis. This reduced heterogeneity in all but one analysis (Appendix 8). The meta-analyses results are described below and in the Summary of Findings table 1 (Appendix 3).

Wellness: Seven studies (367 participants) provided data for the major outcome measure multidimensional function [111;131;132;136-138;143] and five studies (285 participants) reported on self-reported physical function [2;132;136;137;143]. Only one study (46 participants) provided data on the minor outcome of patient rated global [138].

Among the major outcomes in the wellness category, a moderate effect was found for multidimensional function. The mean in multidimensional function in the aquatic groups improved by 5.97 FIQ units (95% CI 2.88 to 9.06, Analysis 1.1) compared to the control group. A significant effect was found in self-reported physical function with a mean reported of -4.36 FIQ units on a 100 point scale (95% CI -7.77,-0.94, Analysis 1.2); both results favoring the aquatic exercise training interventions. Among the major wellness outcomes, none of the outcomes met the threshold for clinically relevant differences (15%): relative to the control group there was a 9.4% improvement in multidimensional function outcome, and a 9.3% improvement for self-reported physical function.

Minor Wellness Outcomes: There was no evidence of an effect for patient rated global (MD -0.87 on a 10 cm VAS, 95% CI -1.74, 0.00, one study, Analysis 1.7), self-efficacy (88 participants) (MD = 9.54 , 95% CI -3.39, 22.46 Analysis 1.10), mental health (243 participants) (MD = -3.03, 95% CI -8.06, 2.01, Analysis 1.8), or clinician rated global (10 cm scale ranging 0-10 MD = 0.08 , 95% CI -0.75, 0.91, one study, 46 participants, Analysis 1.9).

Symptoms: Seven studies (382 participants) provided data on pain [2;111;132;136;138]; six studies (329 participants) assessed fatigue [2;132;136-138;143]; seven studies (368 participants) reported on tenderness [111;131;132;136-138;143] and four studies (230 participants) evaluated stiffness [132;136;137;143].

A moderate effect favouring the aquatic exercise training was found for pain with the mean pain in the aquatic group improving by -6.58 units on a 100 point scale (95% CI -10.71, -2.48, Analysis 1.3). Stiffness' mean in the aquatic group improved by 18.48 units on a 100 point scale, (95% CI -35.75,-0.93 Analysis 1.4). Among the major symptom outcomes, only one met the threshold for clinically relevant differences (15%): compared to control groups, the aquatic exercise training reduced stiffness by 26.8% following the intervention. The reduction in pain did not meet the threshold for clinical relevance (9.5% improvement).

Minor Symptom Outcomes: A small effect was found favoring the aquatic intervention in depression (362 participants) (SMD = -0.45, 95% CI -0.82, -0.08, Analysis 1.13) and tenderness (SMD = -0.47, 95% CI -0.80, -0.13 Analysis 1.12) while no evidence of an effect was found for fatigue (SMD = -0.31, 95% CI -0.75, 0.13 Analysis 1.11). A moderate effect on sleep (104 participants) was found favoring aquatics (SMD = -0.63, 95% CI -1.12, -0.14,

Analysis 1.15) anxiety (374 participants) (SMD = -0.57, 95% CI -0.95, -0.19, Analysis 1.16) and dyscognition (58 participants) (number of correct responses over 60 trials MD = -4.70, 95% CI -9.29, -0.11, one study, Analysis 1.17).

Physical fitness: Four studies (152 participants) evaluated muscle strength [131;132;137;143]; three (162 participants) evaluated muscle endurance [111;138;143]; two (64 participants) evaluated maximal cardiorespiratory function [132;137]; and three studies (194 participants) evaluated submaximal cardiorespiratory function [131;136;143].

The effects for the physical fitness training in strength and submaximal cardiorespiratory function showed a moderate effect favouring aquatic exercise training interventions: strength's mean in the aquatic group improved 0.63 standard deviations compared to the control group (95% CI 0.20, 1.05, Analysis 1.5) and submaximal cardiorespiratory function improved by 32 meters on a 6 minute walk test (95% CI 17.41, 43.03, Analysis 1.6). Clinically relevant difference was found favouring the aquatic exercise training intervention for muscle strength (37%), but submaximal cardiorespiratory function (6.5%) did not meet the 15% threshold for clinical relevance.

Minor outcome flexibility was measured in one study (30 participants) [137] and we found evidence of no effect (1.5 cms on the sit reach test, 95% CI -2.04, 5.04 Analysis 1.14). As well, evidence of no effect was found in muscle endurance (SMD = 0.00, 95% CI -0.67, 0.67 Analysis 1.19) and maximal cardiorespiratory function (SMD = 0.23, 95% CI -1.00, 1.47 Analysis 1.18).

Additional evidence: The study by Ide [133] which compared the effects of respiratory exercises with arm and trunks movements in 18 participants with fibromyalgia to 17 control participants was not meta-analyzed with the other studies due to statistical and clinical heterogeneity. Ide [133] reported a large effect favouring the aquatic exercise intervention in wellness and symptom outcomes: multidimensional function domain (MD = -20.5 on the FIQ total, 95% CI 1.70, 2.40); self-reported physical function (MD = -8.0 on the FIQ physical function scale of 0 -100, 95% CI -5.0, -11.0); mental health 10.26 on the SF36 Mental Health Scale with scale of 0 - 100, 95% CI 13.84, 6.68); pain (MD = -20.2 on the FIQ VAS with scale of 0 -100, 95% CI -16.4, -24.0); tenderness (MD = -1.48 active TPs out of 18, 95% CI -1.07, -1.89); fatigue (MD = -30.3 FIQ fatigue with scale of 0 -100, 95% CI -26.5, -34.1); and stiffness

(MD = -11.0 FIQ stiffness with scale of 0 -100, 95% CI -6.5, -15.5); depression (MD -20.3 FIQ depression with scale of 0 -100, 95% CI -16.0, -24.6); anxiety (MD = -25.0 FIQ anxiety with scale of 0 -100, 95% CI -20.8, -29.2); and sleep (MD = -5.28 on the Pittsburgh Sleep Quality Index with a scale of 0 - 21, 95% CI -4.47, -6.09).

Safety and Acceptability: Reporting of adverse effects was incomplete and sometimes absent in the studies. Mannerkorpi 2000 [143] reported an unspecified number of drop-outs due to injury and infection. Gusi [132] explicitly stated the intervention did not aggravate symptoms. Altan [138]stated that participants in the balneotherapy group dropped out due to developing hypertension and cardiac arrhythmias. In the five remaining studies, adverse effects were not addressed [2;111;131;136;137].

All cause withdrawal rates for the aquatic exercise training groups (n1/N1) vs comparators (n2/N2) in the aquatic exercise training vs control group were: 1/24 vs 2/22 (Altan [138]); 1/28 vs 2/28 (Arcos-Carmona [2]); 12/27 vs 8/24 (Gowans [131]); 1/18 vs 0/17 (Gusi [132]); 9/37 vs 2/32 (Mannerkorpi 2000 [143]); 9/66 vs 14/68 (Mannerkorpi 2009 [136]); 3/35 vs 1/25 (Munguia-Izquierdo [111]); 2/17 vs 1/16 (Tomas-Carus [137]). Pooled analysis resulted in a non-significant risk ratio (RR =1.13, 95% CI 0.73, 1.77, Analysis 1.20).

Long term effects:

Six studies [127;130;132;134;136;138] measured the effects of the intervention once again after the end of the supervised intervention; Altan [138] and Gusi [132] conducted a follow up at 12 weeks; Calandre [127] assessed outcomes again 12 weeks post intervention; Evcik [130] had two follow up periods at 12 and 24 weeks; Jentoft 2001[134] reported a follow up at 26 weeks post intervention; and Mannerkorpi 2009 [136] followed up at 48-52 weeks post intervention. The results of the follow up period were calculated for aquatic vs control comparison.

Three studies: Gusi [132], Altan [138], and Mannerkorpi 2009 [136] from the *aquatic vs control* comparison employed follow up testing after the intervention finished, evaluating outcomes at 12, 12, and 48-52 weeks respectively. Because of the clinical heterogeneity among these studies, we did not meta-analyse the long-term effects of aquatic exercises. Our analyses (Figure 2.5; Figure 2.6) shows the long-term effects on outcome variables of each of the studies

by displaying change from baseline to end of intervention (T2) and to follow up (T3). The data is presented in SMDs for ease of comparison. The long-term results were as follows:

- Aquatics vs control (treatment as usual, Gusi [132]): Improvement favoring Aquatics that had been observed at T2 had regressed to no difference in multidimensional function, self-rated physical function, and fatigue. The improvement in pain observed at T2 was maintained at T3. There were no between group differences at T2 or T3 in tenderness, strength, and maximal cardiorespiratory function.
- Aquatics vs Balneotherapy [138]: Improvement favoring Aquatic that had been observed at T2 was maintained at T3 in fatigue. The improvement favoring balneotherapy observed at T2 had regressed to no difference in endurance at T3. Although no difference had been observed in pain at T2, an improvement favoring Aquatic emerged at T3. There was no between group difference in multidimensional function and tenderness at either T2 or T3.
- Aquatics vs Education [136]: Improvement favoring Aquatic that had been observed in pain at T2 was not retained at T3. There was no between group difference in multidimensional function, self-reported physical function, fatigue or cardiorespiratory submaximal function at either T2 or T3.

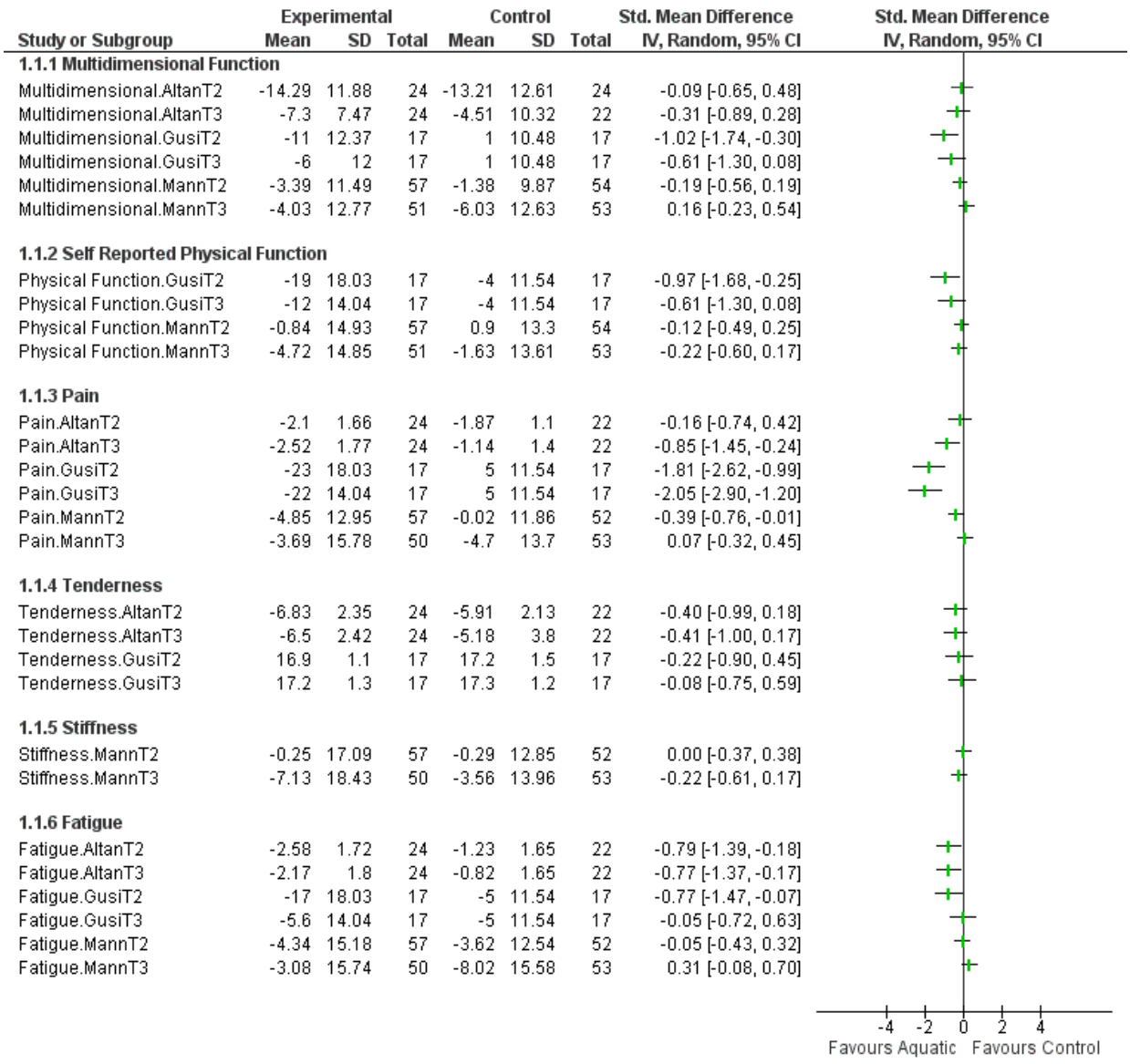

Figure 2.5. Aquatic exercise control - Follow-up analysis of wellness and symptom outcomes. Mann = Mannerkorpi. T2 display change from baseline to end of intervention, T3 display change from baseline to follow up.

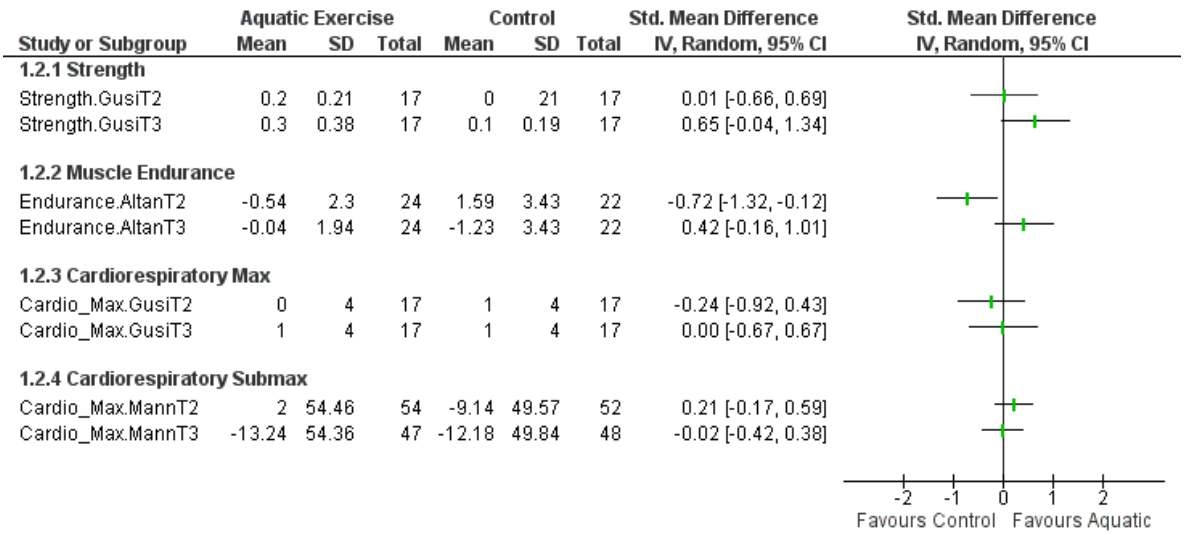

Figure 2.6. Aquatic versus Control - Follow-up fitness outcomes. Mann = Mannerkorpi, T2 display change from baseline to end of intervention, T3 display change from baseline to follow up

2.4.6.2 Aquatic Exercise Training vs Land-based Training

The meta-analyses results are described below and in the Summary of findings table 2 (Appendix 3).

Wellness: one study (61 participants) provided data on multidimensional function [130] and two studies (74 participants) reported on self-reported physical function [1;129]. Among the major outcomes in the wellness category, there was no evidence of a difference . In multidimensional function the mean difference was 0.91 mm-FIQ unit (MD 0.91 95% CI, -4.01, 5.83, one study, Analysis 2.1) or in self-reported physical function: the mean difference was -0.99 SF-36 units on a 100 point scale (95% CI -12.33, 0.63, Analysis 2.2). Only relatively small clinical differences were observed in multidimensional function and self-reported physical function, 1.4% and -2.4% respectively. There was no evidence of a difference for the minor wellness outcome mental health (74 participants) (SMD = -0.08, 95% CI -0.54, 0.38, Analysis 2.11). None of the studies provided data on patient rated global, clinician rated or self-efficacy in the wellness category.

Symptoms: four studies (169 participants) provided data on pain [1;129;130;134]; three (169 participants) assessed fatigue [1;129;134] ; one (61 participants) reported on tenderness [130]

and one (34 participants) reported on stiffness [134]. We found no evidence of a difference between aquatic and land for pain (-0.75 mm on a 100 mm scale, 95% CI -10.72, 9.23, Analysis 2.3) or stiffness (2 mm on a 100 mm scale, 95% CI -8.82, 12.82, one study, Analysis 2.6). None of the major outcomes reached the 15% threshold for clinical relevance (pain: -1% favoring aquatics, stiffness: 3% favoring land).

Minor symptoms: no evidence of a difference was found for tenderness (SMD = -0.45 95% CI -0.96, 0.06, one study, Analysis 2.4) and fatigue (SMD = -0.13, 95% CI -0.70, 0.45, Analysis 2.5). There was no evidence of a difference in the minor symptom outcome of anxiety (SMD = -0.49 95% CI -1.18, 019, one study - 34 participants) and depression (SMD = -0.11, 95% CI -0.88, 0.67). Sleep, however had a moderate effect - measured in only one study (50 participants) (total sleep time in hours MD = - 0.56, 95% CI -0.97,-0.15).

Physical Fitness: one study reported on muscle strength, muscle endurance, maximal and submaximal cardiorespiratory function [134] outcomes (34 participants). A moderate difference was found on muscle strength favouring the land-based intervention (-2.40 kilo Pascals grip strength, 95% CI -4.52, -0.28, Analysis 2.7), while no evidence of a difference was found for submaximal cardiorespiratory function (3 seconds to walk 100 meters, 95% CI -1.77, 7.77, Analysis 2.10). These differences did not meet the 15% threshold for clinical relevance: 8.7% for strength and 5% for submaximal cardiorespiratory.

Minor outcomes: There were no differences between aquatics and land-based interventions for muscle endurance (SMD = 0.13, 95% CI -0.54, 0.81, Analysis 2.8) or maximal cardiorespiratory function (SMD = -0.36, 95% CI -1.04, 0.32, Analysis 2.9). None of the studies reported on the minor outcome flexibility.

Withdrawals and Adverse Effects: adverse effects were poorly reported. Three studies did not address adverse effects in their reports [1;129;134] and one study reported no adverse effects [130]. In contrast, Assis [126] reported 10 adverse effects in the deep water running intervention: muscle pain (n = 4), tinea pedis (n = 1), and unspecified (n=5), compared to 15 in the land-based exercise intervention: muscle pain (n=12), shoulder impingement (n=1), bilateral ankle arthritis (n=1), Baker Cyst (n=1). All cause attrition for aquatic exercise training vs land-based group was: 4/30 vs 4/30 (Assis [126]); 1/25 vs 2/25 (de Melo Vitorino [129]); 2/33 vs

0/30 (Evcik [130]); and 4/22 vs 6/22 (Jentoft [134]). The odds ratio showed no significant between group differences (risk ratio = 0.91, 95% CI 0.43, 1.91, Analysis 2.15).

Additional evidence (Aquatic vs Land). The study conducted by Assis [126]could not be meta-analyzed due to skewness of the data. Contrary to our findings the 15 weeks of training employed in Assis [126] resulted in a reduction in pain intensity as measured by a visual analogue scale. As well, a 40% improvement in the patient's global assessment response was noticed in the deep water running group as compared to a land-based aerobic training program matched for training frequency, intensity and duration. The wellness outcome in the aquatic exercise intervention improved more rapidly than land-based exercise group; this was also true for depression. In the area of physical fitness, Assis [126] did not find any significant between-group differences for maximal cardiorespiratory function (which differs from findings by Jentoft [134].

2.4.6.3 Aquatic vs Aquatic

Calandre [127] conducted a direct comparison of Ai Chi (Tai Chi in water) to stretching in the water (81 participants). Ai Chi uses breathing plus the traditional movements: "Tai Chi is performed standing in shoulder-depth water using a combination of deep breathing and slow, broad movements of the arms, legs, and torso". No statistically significant between-group differences were observed for the three major outcomes measured: multidimensional function outcome (SMD = -0.35, 95% CI -0.79, 0.09), pain (SMD = -0.37, 95% CI -081, 0.07), or tenderness (SMD = 0.14, 95% CI -0.30, 0.58). There were no statistically significant differences observed for mental health (SMD = -0.19, 95% CI -0.63, 0.24), fatigue (SMD = -0.42, 95% CI -0.86, 0.03), depression (SMD = 0.16. 95% CI -0.28,0.60) and anxiety (SMD = -0.25, 95% CI -0.68 0.19), but a statistical significant result was found favouring the Ai Chi was observed in stiffness (SDM = - 0.62, 95% CI -1.07, - 0.17) and sleep (SMD = -0.45, 95% CI -0.89, -0.01). No physical fitness outcomes were measured in Calandre [127]. The only outcome approaching the 15% threshold for clinical relevance, was the stiffness value which was -14% (average) favoring Ai Chi. Regarding adverse effects, Calandre [127] stated "Fifteen patients withdrew from the trial... three of them belonging to the [Ai Chi] group due to adverse

reactions: one case of chlorine hypersensitivity and two cases of pain exacerbation" (pg S16). All cause attrition Calandre [127] was 10/42 vs 5/39 (odds ratio = 2.13, 95% CI 0.65, 6.90).

A single study in this category examined the effects of salinity of the water. In De Andrade [128], (38 participants) one group performed aerobic exercise in an outdoor pool and the other group performed the same aerobics program in sea water (no waves). Both groups improved at post-treatment in all outcomes. However, there were no statistically significant differences between the two groups with the exception of the Beck Depression Inventory (SMD = -1.88, 95% CI -2.66, -1.10), favouring the sea intervention. Both groups showed important changes in symptoms like pain, fatigue, tenderness, and sleep quality as well as wellness outcomes of multidimensional function, physical function and mental health. No physical fitness outcomes were measured in De Andrade [128]. None of the outcomes reached the 15% threshold for clinical relevance. De Andrade [128] reported that there were "20 adverse events (9 in pool group and 11 in the sea group). Nine patients reported muscle pain in pool group. Two patients reported first-degree burn...one patient presented urinary infection, and eight reported muscle pain in sea group (pg. 149). All cause attrition rates for pool vs sea water [128] were 4/23 vs 4/23 (odds ratio = 1.00, 95% CI 0.22, 4.59).

The standardized mean differences (95% CIs) for both studies on wellness, symptoms and physical fitness outcomes are summarized in Appendix 9.

2.4.6.4 Subgroup Analysis

The summary of subgroup analysis findings can be seen in Appendix 10. Regarding the subgroup analyses, we must be cautious in interpreting the results as definitive. The natural course of FM may help explain some of the results (i.e. more years living with FM, more or less pain at baseline) however, credibility of subgroup effects is low due to the same concerns with risk of bias, imprecision of results, and the low number of studies, and needs to be applied to our interpretation. Nevertheless, the subgroup analyses may point to participant and intervention related factors that may influence the effects of aquatic exercise and to potential hypothesis generating ideas for future studies.

Participant Related Subgroups:

Younger vs Older Age

The mean age of participants in three studies fell below median age (46.7 years) and were classified in the younger category [2;136;138;143], and participants in three studies [111;132;137] had ages above the median and were classified as older. On analysis of the confidence intervals, two studies [131;136] could not be classified as the 90% confidence intervals extended into both the younger and the older group (see Appendix 10). Aquatic exercise produced:

- Less improvement in multidimensional function in the younger participants (SMD = -0.33, 95% CI -0.64, -0.01) than in the older participants (SMD = -0.75, 95% CI -1.12, -0.38)
- Less improvement in pain in the younger participants (SMD = -0.39, 95% CI -0.66, -0.11) than in the older participants (SMD = -0.83, 95% CI -1.21, -0.45)

None of the studies in the younger category assessed muscle strength.

Short vs Long Disease Duration

The median value for disease duration was 9.5 years in studies comparing aquatic training to control that provided data. Of the studies with weighted mean values less than the median, three studies were classified as short disease duration [131;136;143] and three studies as long disease duration [111;132;137]. On inspection of the confidence intervals, one study [2] could not be classified as the 90% confidence intervals extended into both the lower and the higher group (see Appendix 10). Aquatic exercise produced:

- smaller improvements in multidimensional function in the short disease duration groups (SMD = -0.31, 95% CI -0.59, -0.03) as compared to the long disease duration groups (SMD = -0.75, 95% CI -1.12, -0.38)
- similar improvements in pain in the short disease duration groups (SMD = -0.41, 95% CI -0.72, -0.10) as compared to the long disease duration groups (SMD = -0.83, 95% CI -1.21, -0.45)

- smaller improvements in muscle strength in the short disease duration groups (SMD = 0.32, 95% CI -0.10, 0.74) as compared to the long disease duration groups (SMD = 1.04, 95% CI 0.51, 1.57)

Low vs High Impact of FM on Wellness

The median value for multidimensional function score (the measure used for wellness) was 62 in studies comparing aquatic training to control that provided data. Of the studies with weighted mean values less than the median, two studies were classified as low levels of impact on wellness [131;138], and three studies as high impact on wellness [111;136;143]. On inspection of the confidence intervals, two studies [132;137] could not be classified as the 90% confidence intervals extended into both the lower and the higher group (see Appendix 10). Aquatic exercise produced:

- Similar improvements in multidimensional function in the low impact (SMD = -0.35, 95% CI -0.62, -0.09) and in the high impact groups (SMD = -0.47, 95% CI -0.93, -0.02)
- Larger improvements in pain in the low impact (SMD = -0.61, 95% CI -1.04, -0.19) compared to the high impact groups (SMD = -0.16, 95% CI -0.74, 0.42)
- Similar non-significant changes in strength: low: SMD = 0.39, 95% CI -0.13, 0.91; high: SMD = 0.18, 95% CI -0.54, 0.90

Low vs High Pain at Baseline

The median value for pain was 70.9 in studies comparing aquatic training to control that provided data. Three studies [2;132;137] were classified as “low baseline pain” and three studies [111;138;143] were classified as “high baseline pain”. On inspection of the confidence interval, one study [136] could not be classified because the 90% confidence interval extended into both the lower group and the higher group (see Appendix 10). Aquatic exercise produced:

- Larger improvements in multidimensional function in the low pain groups (SMD = -1.11, 95% CI -1.64, -0.58) than in the high pain groups (SMD = -0.57, 95% CI -0.89, -0.25)
- Similar improvements in pain in the low pain (SMD = -0.60, 95% CI -0.98, -0.23) and in the high pain groups (SMD = -0.57, 95% CI -1.11, -0.03)
- Larger improvements in muscle strength in the low pain groups (SMD = 1.04, 95% CI 0.51, 1.57) compared to the high pain studies (SMD = 0.39, 95% CI -0.13, 0.91)

Intervention Related Subgroups

Length of Intervention

One study was less than seven weeks in length [131], three were 7 to 12 weeks in length [2;132;138], and four were longer than 12 weeks [111;136;137;143].

- There was no effect on multidimensional function in the shortest program (SMD = -0.17, 95% CI -0.88, 0.53), a large effect in the intermediate intervention length (SMD = -0.82, 95% CI -1.28, -0.36) and moderate effect in the longer studies (SMD = -0.52, 95% CI -0.90, -0.14)
- There was a small effect (SMD = -0.49, 95% CI -0.84, -0.14) on pain in the intermediate intervention length and moderate effect in the longer studies (SMD = -0.5, 95% CI -0.80, -0.29)
- There was no effect (SMD = 0.18, 95% CI -0.54, 0.90) on muscle strength in the shortest programs, a large effect in the intermediate intervention length (SMD = 0.93, 95% CI 0.22, 1.64) and moderate effect in the longer studies (SMD = 0.63, 95% CI 0.20, 1.06).

Accumulated Time in the Pool

The accumulated time (time in minutes x frequency x length of intervention) in the pool was <1000 minutes in three studies [2;131;143], between 1000 minutes and 2000 minutes in two studies [136;138] and more than 2000 minutes in three studies [111;132;137].

- Multidimensional function: Accumulated time of less than 1000 minutes had a small effect (SMD = -0.48, 95% CI -0.91, -0.05), 1000 to 2000 minutes had a small effect (SMD = -0.33, 95% CI -0.64, -0.01) and accumulated time of more than 2000 minutes had a moderate effect (SMD = -0.75, 95% CI -1.12, -0.38).
- Pain: Accumulated time of less than 1000 minutes had a moderate effect (SMD = -0.52, 95% CI -0.90, -0.13), 1000 to 2000 minutes had a small effect (SMD = -0.32, 95% CI -0.64, -0.00) and accumulated time of more than 2000 minutes had a large effect (SMD = -0.82, 95% CI -1.24, -0.41).
- Strength: Accumulated time of less than 1000 minutes had a small effect (SMD = 0.32, 95% CI -0.10, 0.74) whereas accumulated time of more than 2000 minutes had a large effect (SMD = 1.04, 95% CI 0.51, 1.57).

Frequency of Pool Sessions per Week

The frequency of pool sessions was once per week in two studies [136;143], twice a week in one study [2], and three times per week in five studies [111;131;132;137;138].

- Multidimensional function: Once a week had a small effect (SMD = -0.34, 95 % CI -0.65, -0.03), while three times a week had a moderate effect (SMD = -0.64, 95% CI -0.93, -0.35)
- Pain: Once a week had a small effect (SMD = -0.39, 95% CI -0.65, -0.12), twice a week had a moderate effect (SMD = -0.59, 95% CI -1.14, -0.04), and three times a week also had a moderate effect (SMD = -0.63, 95% CI -1.08, -0.17).
- Strength: Once a week had a small effect (SMD = 0.39, 95% CI -0.13, 0.91) while three times a week had a moderate effect (SMD = 0.74, 95% CI 0.31, 1.16).

Exercise Intensity

Exercise intensity was: a) very light (< 57% predicted HR_{max}) in one study [2], b) light to moderate (27 to 63% predicted HR_{max}) in two studies [137;138], c) moderate (64 to 76% predicted HR_{max}) in two studies [131;132], d) light to vigorous (77 to 95% predicted HR_{max}) in one study [111], and e) self-selected in two studies [136;143].

- Multidimensional function: interventions employing a light to moderate intensity had a large effect (SMD = -0.89, 95% CI -1.40, -0.38), those using a moderate intensity had a small effect (SMD = -0.39, 95% CI -0.92, 0.13), those using moderate intensity had a moderate effect (SMD = -0.59, 95% CI -1.43, 0.24), and a self-selected intensity had a small effect (SMD = -0.38, 95% CI -0.84, 0.07).
- Pain: interventions using a very light exercise intensity had a moderate effect (SMD = -0.59, 95% CI -1.14, -0.04), those a light to moderate intensity had a small effect (SMD = -0.25, 95% CI -0.70, 0.20), a moderate intensity had a large effect (SMD = -0.82, 95% CI -1.53, -0.12), a light to vigorous intensity had a large effect (SMD = -1.12, 95% CI -1.71, -0.54), and a self-selected intensity had a moderate effect (SMD = -0.41, 95% CI -0.72, -0.10)
- Strength: interventions having a light to moderate intensity had a large effect (SMD = 1.17, 95% CI 0.39, 1.96), a moderate intensity had a moderate effect (SMD = 0.56, 95% CI 0.05, 1.06), and a self-selected intensity had a small effect (SMD = 0.39, 95% CI -0.13, 0.91)

Temperature of the Pool

The temperature of the pool was 27 to 32 degrees Celsius (cool pool) in one study [2], 33 to 37 degrees Celsius (temperate pool) in five studies [111;132;136;137;143], and > 36 degrees Celsius (temperate pool) in two studies [131;138].

- Multidimensional function: the temperate pool had a moderate effect (SMD = -0.60, 95% CI -0.97, -0.24), and the warm pool had a small effect (SMD = -0.47, 95% CI -0.96, 0.03)
- Pain: moderate effects were seen in the cool pool (SMD = -0.52, 95% CI -0.73, -0.32) and the temperate pool (SMD = -0.57, 95% CI -0.81, -0.34), while the warm pool had no effect (SMD = -0.16, 95% CI -0.74, 0.42)
- Strength: the temperate pool had a moderate effect (SMD = 0.71, 95% CI 0.34, 1.08) while the warm pool had no effect (SMD = 0.18, 95% CI -0.54, 0.90)

2.5 Discussion

The effects of aquatic exercise training on FM have been investigated in an increasing number of studies since the publication of our last review [26]. In this review, the role of aquatic exercise training was found to be beneficial, particularly for FM symptoms. We assumed the water allowed for ease of movement and therefore promoting better conditions to exercise. However, the evidence does not yet support a standard aquatic exercise program for individuals with FM due to variability in types of exercise and wide ranges in intensity, duration and frequency of exercise recommendations.

A conflict of interest statement was not reported in seven articles [1;111;128-130;133;138], two studies provided a "none to declare" statement [2;127] and seven studies [126;131;132;134;136;137;143] reported receiving support from different sources (e.g., European social funds, regional government grant, health department funding, etc.).

2.5.1 Summary of main results

This review is one part of a series of reviews examining the effects of physical activity interventions for individuals with FM. Of the 84 studies we found that examined the effects of physical activity, only 17 studies examined aquatic exercise training where individuals remained in the water ≥50% of the time. Historical and modern beliefs about the effects of exercising in warm water make this review particularly important. In addition, aquatic exercise programs are offered in many communities. This review provides a valuable opportunity to evaluate the effects of aquatic exercise training and the benefits, risks and harms regarding this important and popular type of exercise. The main results of our review were as follows.

Aquatic vs control

Nine studies, including 513 female and six male participants diagnosed with FM according to the ACR 1990 criteria compared aquatic exercise training to control. All programs were supervised group interventions consisting of a mix of aerobic, resistance training and flexibility exercise. Six interventions were conducted exclusively in the water, one included 70% of the time in the water, and in two studies participants were in the water 50% of the time. One program was less than six weeks in duration, four were six to 12 weeks long, and four were

more than 12 weeks in duration. Frequency of sessions was at least three times per week in most studies. Average session duration was 45 minutes (range 30 to 70). The intensity of exercise varied: three studies prescribed mild or self-selected intensities, four were mild to moderate, one was mild to vigorous and in one study the intensity was not specified. While none of the studies met ACSM criteria for aerobic or resistance training, one study met the ACSM criteria for flexibility.

Eight studies were determined to be similar enough to be included in the meta-analyses (one study appeared to be an outlier and was excluded from the meta-analyses). The meta-analyses yielded two statistically significant effects in the wellness category favouring aquatic exercise training: a moderate effect on multidimensional function and a small effect on self-reported physical function. There was evidence of no effect for mental health, patient rated global, self-efficacy, and clinician rated global. The meta-analyses also produced significant results favouring aquatic exercise training in several symptoms outcomes: large effect on stiffness and moderate effect on pain, sleep, and anxiety, and small effects on tenderness and depression. When aquatic exercise training was compared to control, moderate effects were seen in strength and submaximal cardiorespiratory function. No statistically significant effects were seen in flexibility, maximal cardiorespiratory function, or in muscular endurance. These results were clinically relevant for stiffness and muscle strength.

Aquatic exercise training vs land-based training

Four studies with 203 females and one male participant diagnosed with FM according to ACR 1990 criteria compared aquatic exercise training to land-based training. All aquatic exercise training programs were supervised group interventions with most being mixed programs consisting of resistance, aerobic, flexibility training and relaxation components. The land-based exercises followed the same protocols as the aquatic exercise training interventions. One of the studies had a non-supervised home- based control program. Four aquatic intervention studies were 100% water based, while one was based in the water 65% of the time. Intervention duration was less than six weeks in two studies, between six to 12 weeks for one study, and more than 12 weeks for another. Session frequency was three times a week in three studies, two times per week in one study, and once weekly in one study. Average session

duration was 60 minutes. Exercise intensity varied from very light, light to moderate, and light to vigorous. No study met ACSM criteria for aerobic or resistance training.

Although we extracted data for 14 outcomes, only five could be meta-analysed - pain and fatigue (four studies), self-reported physical function (two studies), mental health (two studies) and depression (two studies). The meta-analyses yielded evidence of no effect in any outcome. Among the nine outcomes that could not be meta-analyzed, there were no significant differences in wellness outcomes, but there were statistically significant differences in one study in symptoms, (i.e., a moderate difference in sleep favoring aquatic exercise training). When aquatic exercise training interventions were compared to land-based interventions, one statistically significant difference was found in physical fitness; based on one study there was a moderate difference in strength favoring land-based training. No statistically significant differences were found for pain, stiffness, tenderness, fatigue, depression or anxiety, muscle endurance, maximal or submaximal cardiorespiratory function.

Aquatic vs aquatic exercise intervention

In this group, two studies were analyzed. Calandre [127] conducted a direct comparison of stretching in the water to Ai Chi (Tai Chi in the water); De Andrade [128] conducted a direct comparison of aerobic exercise in a pool to aerobic exercise in the sea. Among the 10 outcomes reported in these studies, the analyses yielded no statistically significant results in the wellness outcomes (multidimensional, self-reported physical function and mental health). There was a small effect size in symptoms - sleep (one study), a moderate effect size on stiffness (one study) and a large effect on depression (one study). No physical fitness outcomes were measured.

One study examined the effects of characteristics of the water [128]. While it is widely accepted and traditionally used in some countries, mineral water used as a medium for aquatic exercise training intervention in individuals with FM is recently seen in the literature. The single study in our review examining the effects of exercise in mineral water showed greater (but non-significant) improvement in evaluated parameters with the exception of depression which had a large effect size favouring the mineral water intervention. No physical fitness outcomes were measured.

Is aquatic exercise training safe for and acceptable to individuals with FM

All cause attrition rates were not higher for aquatic exercise training intervention than for comparators. When considering the evidence of adverse effects and attrition rates in the 16 included studies, individuals with FM were able to perform supervised aquatic exercise training safely. However, given the small number of studies and the lack of detail provided by authors on adverse effects, the evidence should be taken with caution.

Follow up data (aquatic vs control)

Follow-up data on the effects of exercise are important considering the chronic nature of FM and because exercise training is a component of recommended management of FM. Unfortunately, investigation on long term effects is limited. Few studies in our review re-evaluated outcomes weeks or months after the completion of the intervention. However, three studies examined long term follow up in the aquatic exercise training compared to control. Although the studies belong to the same comparison group, the three studies had substantial clinical heterogeneity: one compared aquatic exercise training to treatment as usual at 12 weeks, another compared aquatic exercise training to balneotherapy (specialized type of control) at 12 weeks, and a third study compared aquatic exercise training to education (specialized type of control) at 45 to 52 weeks. At follow-up, several patterns were observed:

- **regression of improvements** from post-test (T2) to follow-up (T3): multidimensional function in one out of three studies (1/3), self-related physical function 1/2, pain 1/3, fatigue 1/3, endurance 1/1
- **maintenance of improvements** observed at T2: pain 1/3, fatigue 1/3
- **no change** (no effect at either T2 or T3): multidimensional function 2/3, self-related physical function 1/2, fatigue 1/3, tenderness 2/2, strength 1/1, maximal cardiorespiratory 1/1, submaximal cardiorespiratory 1/1
- **improvement** at follow up T2 to T3: pain 1/3.

The literature on healthy individuals shows that when exercise training ceases, loss of physical fitness gains occur over time. We can assume this is true for individuals with FM. Pertinent questions about follow up that remain unanswered for individuals with FM include: a)

do individuals continue to exercise and at what frequency/intensity/duration after the intervention is finished? b) are wellness or symptom improvements that occurred during the study maintained and are they linked to the amount of physical activity performed during follow up?; c) if the exercise is discontinued, what happens to any gains in wellness and symptoms? Further research monitoring physical activity behavior during follow up after interventions is required to answer questions about the long term benefits of these interventions.

Subgroup Analyses

Regarding the subgroup analyses, we must be cautious in interpreting the results as definitive. The same concerns about risk of bias, imprecision of results, and the low number of studies apply to our interpretation. Nevertheless, the subgroup analyses may point to participant and intervention related factors that may influence the effects of aquatic exercise.

Subgroups based on participant characteristics: The subgroup analysis shows that older individuals (mean 48.2 to 51years) had greater improvements than younger individuals (mean 43.5 to 45.6 years) in the multidimensional function and pain outcomes. Similarly, individuals who had a longer disease duration responded better than those with a shorter duration in multidimensional function, pain, and strength. Because the upper limit of the 90% confidence interval for the younger group was 46.7 compared to the lower limit of the older group being 46.5, the two subgroups likely differed in terms of menopausal status. It is unknown if premenopausal women with FM respond differently to exercise than postmenopausal women with FM. Another possible explanation for the findings may be that the older subgroup and the subgroup with greater disease duration may have been more deconditioned at study entry; consequently, they would be more likely to experience improvement with exercise.

The subgroups with lower baseline estimates for impact of the disease had better outcomes for pain and strength, and subgroups with lower baseline estimates of pain had better outcomes in multidimensional function and strength than their counterparts. A possible explanation for these findings is that the participants with less pain and lower disease severity were better able to perform exercise and reap the benefits than those with more severe disease and more pain.

Subgroups based on exercise volume: The subgroup analyses suggested that longer programs (>12 weeks) had greater effects on multidimensional function, strength and pain than did shorter programs (<7 weeks) and intermediate length programs (7 – 12 weeks). This is consistent with findings regarding: accumulated time in the pool and frequency of pool sessions; greater amounts of accumulated time (≥ 1000 minutes) and more frequent sessions (2 and 3 times per week) showed greater effects on multidimensional function, pain and strength.

Although the subgroup analyses related to exercise intensity were hampered by overlapping categories, large effects were found in MDF, pain and strength when intensity was started at light values (57 – 63% predicted HR_{max}) and progressed either to moderate (64-76% predicted HR_{max}) or vigorous intensity (77-95% predicted HR_{max}). When the intensity was left to the participants (self-selected) the effect was moderate in pain and small in MDF and strength suggesting that without guidance regarding exercise intensity, participants may not benefit as much from the exercise. Moderate intensity (64-76% HR_{max}) exercise produced a moderate effect in MDF and strength. There were no data examining aquatic exercise performed at vigorous activity and its effect on outcomes. Very light intensity (<57% HR_{max}) was used in one study which demonstrated a moderate effect on pain.

Subgroups based on pool characteristics: Subgroup analyses showed that temperate pools (33 to 36 Degrees Celsius) produced moderate effects on MDF, pain and strength; whereas, warm pools (> that 36 Degrees Celsius) had a small effect on MDF and no effect on pain and strength. The limited amount of evidence in these analyses impeded interpretation, but perhaps warm pools may affect energy levels and reduce the participant's ability to exercise with sufficient intensity to produce long term effects. Unfortunately, other pool related factors (chemical/mineral composition of the water, ambient temperature and humidity) could not be examined as these data were not provided by most of the primary studies.

2.5.2 Overall completeness and applicability of evidence

2.5.2.1 Completeness

There were 16 studies included in this review including a total of 881 individuals diagnosed with FM (866 women and 15 men); 439 were assigned to aquatic exercise training. Given the 9:1 female:male prevalence ratio of the disease [145] we were not expecting to find a high number of male participants. However, additional studies focusing on interventions for males will shed light on whether the aquatic exercise training interventions have similar effects for men and women.

This review has included a growing body of research, as most included studies have been published since 2000. There seems to be sufficient evidence in the *aquatic vs control* comparison to confirm that this type of intervention has important short term effects on individuals with FM. However, there were too few studies comparing *aquatic interventions to land-based exercise* to make a definitive statement on which is more beneficial. There is great variability in exercise protocols, especially in mode, intensity, and frequency. There seems to be some consistency in the duration of the intervention (i.e., 60 minutes) and warm-up and cool down periods (5 to 10 minutes) across studies. However, none of the studies met the American College of Sports Medicine guideline criteria for aerobic or resistance training.

The ACSM guidelines [69] outline standard parameters to understand how much exercise is enough to improve and maintain fitness and to gain other health benefits. ACSM also reaffirms that regardless of initial level of physical conditioning of individuals, benefits of exercise outweigh the risks. In this review, despite the exercise intervention variation of included studies, the evidence shows that sedentary individuals with FM are able to perform and benefit from exercise that meets the ACSM guidelines for healthy adults. Long term effects have only recently begun to be investigated.

Until recently there has been a lack of agreement regarding core outcomes for evaluating interventions in studies on FM; with inconsistent reporting on wellness, symptoms and physical fitness outcomes. For example, one of the 16 studies reported effects on dyscognition, a symptom regarded very important by individuals with FM. Similarly, one study reported on patient rated and clinician rated global, 5/16 studies reported on strength, 4/16 on endurance, 3/16 maximal cardiorespiratory function, and 4/16 on submaximal cardiorespiratory function. The information on adverse effects is also poorly reported. Evidence of injuries,

exacerbations or adverse effects is very important and needs to be reported in a consistent and systematic form.

The effect of the characteristics of the water on the effects of exercise are still not well explored; only one study investigated the effects of water characteristics. Given the popularity of thermal waters in some countries and availability and access to sea water (compared to pool access) in other geographic regions, effects of water temperature, chemical composition and other characteristics of water warrants further attention.

2.5.2.2 Applicability of Evidence

Although aquatic exercise training has been shown to have many benefits, the optimal aquatic exercise training protocol for achieving benefits in wellness, symptoms and fitness has yet to be determined. All but one of the included studies in this review involved supervised group exercise. It is not known if unsupervised aquatic programs or home based programs for individuals with FM would yield the same results as seen in these studies.

While considering other factors that might alter the applicability of the findings, warm water pools are not easily available in small, rural, or remote communities and therefore, aquatic exercise training may need to be used in combination with other kinds of exercise training. While this review deals with exercise protocols composed mostly of aquatic exercise training (≥50% in the water) -- four studies had interventions with less than 100% of the time in the water. Therefore, results can only be generalized to similar settings. More studies in the area of aquatic exercise training in mineral water will be valuable as many regions have access to this water source but there is little current evidence to support this approach.

Most of the studies included in this review are European, American and South American in origin. We believe this may represent a small portion of the research in the area available worldwide. Participants were mostly middle age women, with few reports for any socio-demographic backgrounds. Therefore our findings are not easily generalized beyond a middle age Caucasian female population. Regardless of these limitations, the evidence of this review aims to help health professionals to make evidence based decisions about the effects of the aquatic exercise training intervention for individuals with FM in the context of their practice.

Common health and safety concerns relating to operating aquatic exercise training programs were not always mentioned in the included studies; however these must be considered. These would include issues such as water treatment; risk of rash and other skin problems; temperature of the water, environment and humidity; risk of dehydration; risk of infections; handling slips, trips and falls; and the number and qualifications of personnel present in the facility.

2.5.3 Quality of the evidence

Based on the *aquatic vs control* comparison, statistically significant benefits of aquatic exercise training have been found in wellness, symptoms and physical fitness. The intervention group sample sizes in the nine studies ranged from 15 to 57 participants. Although most of the individual studies were underpowered, the meta-analyses in the aquatics vs control comparisons for wellness and symptoms provided a sufficient pooled sample size to detect differences for most variables. We found moderate quality evidence for benefits in multidimensional function (wellness), self-reported physical function (wellness), pain (symptoms), and submaximal cardiovascular (physical fitness). The rating of quality of the evidence was downgraded due to potential limitations related to imprecision of the estimates (i.e. total cumulative sample size is lower than 400). We also found low quality evidence for benefits in stiffness (symptoms) and muscle strength (fitness). Once again, the rating of the quality of the evidence was downgraded due to potential limitations related to imprecision and limitations related to unclear and low risk of bias). Regarding harms, no serious injuries were reported, but reporting was poor in this body of studies. Attrition ranged between 13% to 44% and adherence to the prescribed training programs was generally poorly reported.

We rated the evidence as very low to low in the *aquatic vs land-based* comparisons (rating of the quality of the evidence was downgraded because of limitations related to imprecision (i.e., total cumulative sample size lower than 400), or limitations related to unclear and low risk of bias, and heterogeneity of the sample). We found data for 14 outcomes; our analyses identified significant differences for only two outcomes – one favoring land-based exercise (muscle strength) and one favoring aquatic exercise (sleep). Based on these results, no clear preference could be found for land-based vs water-based exercise.

2.5.4 Potential biases in the review process

There are limitations inherent in the primary literature including incomplete description of the exercise protocols, inadequate sample sizes, inappropriate designs for assessing mixed exercise programs, and inadequate documentation of adverse effects and adherence to exercise prescriptions. In our review process, we attempted to control for biases as follows:

- We did not limit our search to English-only publications
- We contacted primary authors for clarification and additional information where indicated, although responses were not always obtained
- We examined clinical sources of heterogeneity
- Our description of the results was based on a careful consideration of intervention characteristics, study population, methodological rigour, pre-identification of levels of evidence and group discussion of evidence tables to reach consensus
- We used a multi-disciplinary team with expertise in critical appraisal, pain, clinical rheumatology, physical therapy, exercise physiology, library sciences, and knowledge translation
- Where researchers evaluated treatment effects at multiple points, we used the data points closest to 12 weeks to standardize our comparisons

2.5.5 Agreements and disagreements with other studies or reviews

Over the past decade, there have been several reviews regarding aquatic exercise training for FM. Based on their relevancy, we have chosen to comment on: Gowans [146], Langhorst [147], Lima [148], McVeigh [149], and Perraton 2009 [150].

Gowans [146] reviewed eight RCTs published between 2000 and 2007 to determine the physiological effects of exercise in warm water. Our review excluded one of the eight studies because aquatic exercise training did not make up $\geq$ 50% of the treatment time. It is not surprising that our results are in general agreement with Gowans [146]. We do differ in our findings related to long term effects: Gowans [146] suggested that exercise-induced improvements in physical function, pain and mood may continue for up to two years. In our review, only three studies of the aquatic vs control comparison had a follow up. Our results were non-significant for physical function at the end of the intervention and follow up; pain

however, was less at the end of the intervention but had regressed to baseline values at follow up. Gowans [146] pointed out that pool exercise may be better tolerated as an initial means of exercise by individuals with arthritis in weight bearing joints (because of water buoyancy) or by individuals who fear exercise will exacerbate their pain -- which may be the case in individuals with FM. Gowans [146] also recommended that future studies should reassess subjects at multiple time points to determine the time course of exercise-induced improvements and further explore the effects of pool exercise on mood and sleep quality.

Langhorst [147] conducted a systematic review on 13 primary studies published to December 2008 evaluating hydrotherapy (with and without exercise) in FM. Hydrotherapy included spa, balneotherapy and thalassotherapy, and packing and compresses. Inclusion criteria were poorly defined; for example it is not clear if nonrandomized studies were included. Based on the range of types of interventions included, and differences in review methods, the Langhorst [147] report differs considerably from our review. In contrast to our review, methodological quality was assessed by the van Tulder score (we used the Cochrane Risk of Bias Tool). Also in contrast to our review, Langhorst [147] found only two of 13 studies to have adequate randomization, whereas we rated 11 out of 16 studies to have adequate sequence generation. Despite these fundamental differences, Langhorst [147] also found evidence for reduction of pain and improved health-related quality of life at the end of therapy. Langhorst [147]also reported that there was moderate evidence that the reduction of pain and improvement of Health Related Quality Of Life could be maintained at follow-up (median 14 weeks). Our results do not support this - in our review pain regressed to close to baseline values at follow up evaluation.

Lima [148] conducted a systematic review on 18 studies published from 1950 to December 2012, 14 of which overlap with this review. Lima [148], examined 10 outcomes while this review investigated the effects of aquatic exercise on 21 outcomes. There are several similarities in these reviews. For example, Lima [148] had three equally formed comparison groups, both reviews agreed on the diversity of the outcome measures utilized, variation of exercise programs, time of follow up, and incompleteness of information in RCTs. In both reviews, subgroup analysis based on the duration of the intervention was undertaken, and despite the use of different cut points in determining the subgroups both reviews concurred longer intervention were more successful. In Lima's [148] case durations longer than 20 weeks

were most successful than shorter interventions; whereas, in our review, interventions longer than 7 weeks were more successful than shorter interventions.

An important disagreement is seen in the terminology used within Lima's review; authors use interchangeably the terms 'aquatic physical therapy', 'aquatic exercise programs', and 'aquatic therapy'; as well, the conceptualization of the physical function outcome and the test utilized to measure it differs in these reviews. Although both reviews utilized the Cochrane risk of bias tools, there are differences in results regarding the rigor of the studies affecting the conclusions of the reviews. Lima [148] points out that there is low methodological rigor in the RCTs included. Our review shows low to unclear risk of bias for most studies with the exception of blinding of personnel who deliver the intervention which is rated as high risk.

In agreement with our review, Lima's [148] found significant results for aquatic vs control group multidimensional function, stiffness and cardiorespiratory sub-maximal outcomes (what he called physical function). Lima's [148] analysis of follow up was conducted in two studies and two outcome measures (pain and depression) we agree in one study and one outcome measure (pain) showing the same results. Our findings do not support Lima's [148] recommendations related to water temperature; our evidence shows a moderate effect on multidimensional function, pain and strength after exercising in *temperate water* (33-36 degrees Celcius); whereas Lima [148] recommended temperature should not exceed 30/33 degrees Celcius. Both reviews agree that three pool sessions per week is the most beneficial for individuals with FM.

McVeigh [149] examined the effectiveness of hydrotherapy in the management of FM; the literature search involved 10 major databases from 1990 -2006. McVeigh [149] found 10 studies meeting their criteria, five of which were included in our review. The authors arrived at the conclusion that the mean methodological quality of studies included was 4.5/9 on the van Tulder scale. Similar to our review, McVeigh [149] study defined aquatic interventions as water-based interventions consisting of more than 50% of the treatment. However, in our review the aquatic exercise training interventions had to be active, consisting in large part of exercise in the water rather than soaking or floating in the water as with balneotherapy or some spa interventions. Nevertheless, our results from the *aquatic vs control* comparison support McVeigh's [149] conclusions that there are positive outcomes for pain, health-status and

tenderness. However, this was not found to be the case when the aquatic exercise training intervention was compared to a land-based intervention. In addition, McVeigh [149] presented strong evidence for the use of hydrotherapy in the management of FM. Our results differ in that we found strong evidence of an effect of the aquatic exercise training interventions in pain, multidimensional function and submaximal cardiorespiratory outcomes; this was not true for other wellness, symptoms or physical fitness outcomes in our review.

Perraton [150] conducted a systematic review of randomized controlled trials published between 1998 and 2009 to summarize the components of hydrotherapy programs in individuals with FM. Only trials that reported significant FM-related outcomes were included in this review. Data relating to the components of hydrotherapy programs (exercise type, duration, frequency and intensity, environmental factors, and service delivery) were analyzed. Eleven RCTs were included in this review. Aerobic aquatic exercise featured in all 11 trials and the majority of hydrotherapy programs included either a strengthening or flexibility component. There was a strong overlap with our review, with nine of the 11 studies in Perraton [150] included in our review. In agreement with Perraton [150], our included studies had a similar composition of exercise mode which included either aerobic training on its own or in combination with resistance training or flexibility. Great variability was noted in both the environmental components (e.g., water temperature, depth) of hydrotherapy programs and service delivery in Perraton [150] studies. In our review included programs were conducted in group settings and mostly delivered by physiotherapists. Our review also found that aerobic training, warm up and cool-down periods and relaxation exercises are common features of hydrotherapy programs and that treatment duration is commonly 60 minutes. A frequency of three sessions per week and an intensity equivalent to 60% – 80% maximum heart rate were the most commonly reported exercise prescription parameters noted in Perraton [150]; our review included study programs run 1-4 times per week at intensities ranging from 40% to 80% maxHR. The chemical or mineral content of the water was not described in Perraton [150] and that was also true for studies included in our review.

2.6 Conclusions

2.6.1 Implications for practice

The improvement in wellness and symptoms resulting from aquatic exercise training found in this review could be very important in the management of FM. The improvement in pain may be due in part to the warmth of the water which provides immediate benefits for muscle pain or stiffness [151] that often limit exercise tolerance on land. Because almost all the participants in the primary studies were females, it is unclear if the results of the review can be generalized to males. Exercise in water may be an appealing way to begin exercising especially for participants who are deconditioned such as those in the primary studies in this review. As such, exercise in warm water may be particularly beneficial as an initial means to exercise without exacerbating pain for individuals with FM who have been sedentary. One may assume that the sense of pleasure that arises from exercising in warm water may help with adherence and influence compliance. However, without details on the characteristics of exercise actually performed, we cannot be certain of the actual exercise volume performed by participants. We can, however, take a broader look at exercise performed by comparing attrition rates, and we note that there were no significant differences in attrition rates between water and land-based interventions, suggesting both intervention were well tolerated and accepted by participants.

Heterogeneity among study protocols and inconsistencies in reporting exercise parameters and outcomes makes interpretation of results challenging. Consequently, it is unclear what exercise protocols (intensity, duration, frequency, mode, temperature and salinity of the water), for aquatic training will yield optimal results for adults with FM. However, the heterogeneity of protocols also leads us to speculate that the benefits of aquatic exercise training are fairly robust as they were achieved in such a variety of conditions.

Results of this review may reinforce the benefits of using water for therapeutic treatment of pain. Water as an exercise medium offers advantages and disadvantages: while some exercises in water are made easier (e.g., jumping), others such as walking are more difficult. Individualized therapeutic programs developed according to participants' baseline physical activity levels and pain may be most beneficial.

Subgroup analyses suggested that programming may need to consider different responses based on age, disease duration, disease severity and pain intensity when planning exercise programs and when setting treatment goals. The length of the program allows for

adaptation and conditioning, and may lead to behavioral change with regards to adapting a physical activity routine. Regarding exercise intensity, the common approach of starting with light intensity and progressing to moderate or vigorous intensity seems to be supported; whereas leaving the intensity decisions completely to the participant (self-selected intensity) does not seem to be as effective.

The subgroup analyses for length of intervention and accumulated time in the pool as described in Appendix 10 have potential implications for practice. People with FM may need to consider continuing with the intervention even when they appear to have little initial effect. These analyses showed the intervention effect is higher when the intervention is longer either in weeks or minutes. Also care providers may need to consider planning interventions with sufficient dosage/duration to be effective. The dosage implications are an important factor for future research.

2.6.2 Implications for research

Several implications for further research arose from this review. We have used the EPICOT approach to describing implications for future research [152].

Evidence: There are insufficient studies to allow adequate meta-analysis of the effects of aquatic exercise training compared to land-based interventions and other types of interventions. The evidence in reduction of pain warrants further work; this is the most common symptom complaint in this population. Long term effects are poorly understood. The sample size of individual studies was generally small with only one study exceeding 50 participants per group.

In terms of methodological quality of RCTs, allocation concealment is not adequately addressed in most studies. Therefore, it is not possible to assess the extent to which selection bias may have occurred in these studies. The recent trend to publication of *a priori* trial protocols will allow improved evaluation of selective reporting bias. The accumulation of more studies will permit better evaluation of publication bias.

Population: The majority of the individuals included in our review were women; there is no evidence to describe the effects of aquatic exercise training on men with FM. The population

consisted primarily of middle age Caucasian women living in developed countries, which makes results difficult to generalize to other contexts.

Information is scarce about individuals' beliefs and prior experiences with exercise which may impact beliefs about and adherence to exercise. Most studies state that participants were sedentary (without quantification) but there is no information about previous exercise experience. As well there is little description of lifestyle physical activity prior to and during exercise interventions which also may add to the total number of hours the individual is actively moving and may contribute to the presence or absence of conditioning and symptoms. It is also unclear if disease duration impacts adherence to exercise interventions.

Intervention: More detail with respect to exercise frequency, intensity and mode is needed to more precisely identify exercise volume and to determine if the prescribed exercise protocol meets current recommendations. Adherence to protocols needs to be tracked more carefully and reported in detail to add to the understanding of individuals' tolerance to prescribed exercise. Individuals may need to be coached to exercise in a gradually progressive manner to avoid flare-ups and worsening of pain. However, optimal planned progression and intensity recommendations are not clear.

Comparators: In this review aquatic exercise training was compared to control, land-based and other type of interventions via direct comparison. The evidence would be strengthened with more studies in each category.

Outcomes: Cognitive dysfunction is rated by many individuals with FM as their most distressing symptom [153]; yet, it was measured by only one study in this review [111]. Another important outcome to clinicians and consumers (individuals with FM) are clinician and patient global assessment [74] again measured in this review only by one set of researchers. This may be due to the nature of our search not being set to capture this body of literature and the fact that OMERACT recommendations are relatively new.

There was a tendency in the RCTs of this review to focus more on symptoms and less on physical fitness outcome measures. This has an impact on the quality of the evidence in this area. There was only one study in several instances presenting physical fitness outcomes which did not allow us to meta-analyze results. This is an important issue when considering the quality of evidence related to aquatic exercise training and FM.

Improved documentation is needed in the area of adverse effects (injuries, exacerbations and other associated adverse effects). Long-term outcomes need to be assessed at least to 12 weeks of follow up. It would also be helpful to know if positive outcomes lead to health related behavioral change. This behavioral change (i.e., exercising on her/his own) needs to be measured.

Timestamp: This review should be updated in 3 to 5 years.

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APPENDICES

Table of Appendices

Appendix 1 - Glossary of Terms

Term	Definition
Balneotherapy	The term derived from the Latin word balneum which means bath. Balneotherapy involves bathing in mineral or thermal water, and sometimes exercise. Usually the natural spring or welled water is 20 C˚ or higher
Biomarkers	In medicine, a biomarker is a term often used to refer to measurable characteristic that reflects the severity or presence of some disease state. It is often an indicator of a particular disease state or some other psychological state of an organism.
Detraining	Losing the physical and health effects gained during exercise training by stopping exercise
Exercise	Physical activity that is planned, structured, and repetitive and [that] has as a final or intermediate objective the improvement or maintenance of physical fitness [69]
Exercise Training	Program that is designed to meet individual health and physical fitness goals; a single exercise session should include a warm-up, stretching, conditioning and cool down components. The rate of progression depends on the individual's health status, exercise tolerance
Hydrotherapy	A warm water (above 30C) exercise intervention in which participant immerse at waist or shoulder height
Mental health	The individual's level of psychological well-being or an absence of a mental disorder. It may include the ability to enjoy life or adapt to different circumstances and demands.
Multidimensional function	A single score derived from either a general health questionnaire (e.g., SF-36, EuroQol 5d) or a disease-specific questionnaire (FM Impact Questionnaire) that attempts to summarize the many components of health.
Muscle endurance	The ability to produce force repetitively
Muscle strength	A physical test of the amount of force a muscle can generate.
OMERACT	OMERACT (Outcome Measures in Rheumatology) is an independent initiative of international health professionals interested in outcome measures in rheumatology. Over the last 20 years, OMERACT has served a critical role in the development and validation of clinical and radiographic outcome measures in rheumatoid arthritis, osteoarthritis, psoriatic arthritis, FM, and other rheumatic diseases (www.omeract.org). OMERACT is linked to the Cochrane Collaboration Musculoskeletal Review Group where the outcomes endorsed by OMERACT are recommended for use in Cochrane Systematic Reviews.
Physical Activity	Any bodily movement produced by skeletal muscles that results in energy expenditure above resting (basal) levels. Physical activity broadly

	encompasses exercise, sports, and physical activities done as part of daily living, occupation, leisure, and active transportation [69]
Physical Fitness	The ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy [leisure] pursuits and to meet unforeseen emergencies. Physical fitness is operationalized as ‘‘[a set of] measurable health and skill-related attributes.’’
Physical Function	The capacity of an individual to carry out the physical activities of daily living. Physical function reflects motor function and control, physical fitness, and habitual physical activity and is an independent predictor of functional independence, disability, morbidity.
PWC-170	Test that measures aerobic fitness. PWC stands for physical work capacity. PWC-170 estimates the working capacity at a heart rate of 170 beats per minute. A cycle ergometer, clock and/or hear rate monitor are needed.
Skewness	Not every distribution of data is symmetric - sets of data that are not symmetric are said to be asymmetric. The measure of how asymmetric a distribution can be is called skewness.
Sleep disturbance	A score derived from a questionnaire that measures sleep quantity and quality. The Medical Outcomes Survey Sleep Scale measures 6 dimensions of sleep (initiation, staying asleep, quantity, adequacy, drowsiness, shortness of breath, snoring).
Symptoms	Patients' perceptions of "an abnormal" physical, emotional, or cognitive state
Tenderness	Pain evoked by tactile pressure
Thalassotherapy	A combination of bathing in sea water in a marine climate with solar radiation and exercise

Appendix 2

2011 ACSM Position Stand: Guidance for Prescribing Exercise

The following recommendations are from Garber 2011 [69]

Recommendations for Cardiorespiratory fitness

- Moderate intensity cardiorespiratory exercise training for ≥30 minutes/day on ≥5 days per week for a total of ≥150 minutes per week, vigorous intensity cardiorespiratory exercise training for ≥20 minutes/day on ≥3 days per week (≥75 minutes/week), or a combination of moderate and vigorous intensity exercise to achieve a total energy expenditure of ≥500 – 1000 MET min/week.

Recommendations for muscular fitness (strengthening)

- On 2–3 days per week, adults should also perform resistance exercises for each of the major muscle groups, and neuromotor exercise involving balance, agility, and coordination.
- Two to four sets of resistance exercise per muscle group are recommended but even a single set of exercise may significantly improve muscle strength and size.
- Rest interval between sets if more than one set is performed: 2-3 minutes
- Resistance equivalent of 60-80% of one repetition max (1RM) effort. For novices 60-70% of 1RM is recommended, for experienced exercises ≥80% may be appropriate.
- The selected resistance should permit the completion of 8-12 repetitions per set or the number needed to induce muscle fatigue but not exhaustion.
- For people who wish to focus on improving muscular endurance, a lower intensity (<50% of 1RM) can be used with 15-25 repetitions in no more than 2 sets.

Recommendations for Flexibility

- A series of flexibility exercises for each major muscle–tendon groups with a total of 60 seconds per exercise on ≥ 2 days per week is recommended. A series of exercises targeting the major muscle-tendon units of the shoulder girdle, chest, neck, trunk, lower back, hips, posterior and anterior legs, and ankles are recommended. For most individuals, this routine can be completed within 10 minutes.
- Stretches should be held for 1-30 seconds at the point of tightness or slight discomfort. Older persons may realize greater improvements in range of motion with longer stretching durations (30-60 seconds). A 20%-75% maximum contraction held for 3-6 seconds followed by a 10 to 30 second assisted stretch is recommended for propioceptive neuromuscular facilitation (PNF) techniques.
- Repeating each flexibility exercise two to four times is effective.

Appendix 3 - Summary of findings tables

1.Aquatic Training compared to Control

Aquatic Training vs Control						
Patient or population: Adults with FM **Settings:** Supervised group intervention **Intervention:** Aquatic Training						
Outcomes	**Assumed Risk** **Control**	**Corresponding Risk** **Aquatic exercise Training**	**Relative effect** **(95% CI)***	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Multidimensional Function Self -report questionnaire FIQ -total (range 0-100mm, lower scores indicate greater health). Follow-up: 4 to 32 weeks	The mean change in multidimensional function in the control group was -1.28[1] Weighted mean score at baseline (all participants): 63.77	The mean multidimensional function in the aquatic groups improved by 5.97 FIQ units (2.88 to 9.06) compared to the control groups.[2]		367 (7 studies)	⊕⊕⊕⊖ **Moderate**[3]	MD -5.97, 95% CI -9.06,-2.88 p < 0.05 Absolute Difference: 5.97 FIQ units (2.88 to 9.06). Relative percent change: -9.4% (-14.2%, -4.5%) NNT: 5 (3 to 9)
Self-Reported Physical Function FIQ physical function scale and SF-36 physical function scale (transformed range 0 - 100mm, lower scores indicate greater health). Follow-up: 4 to 32 weeks	The mean change in self-reported physical function was -0.59[1] Weighted mean score at baseline (all participants): 46.82	The mean self-reported physical function in the aquatic groups improved by 4.36 FIQ units (0.94 to 7.77) compared to the control groups.[4]		285 (5 studies)	⊕⊕⊕⊖ **Moderate**[3]	MD -4.36, 95% CI -7.77,-0.94 p < 0.05 Absolute Difference: 4.36 FIQ units (0.94 to 7.77). Relative percent change: -9.3% (-16%, -2%) NNT: 6 (3 to 22)

Pain Self-reported questionnaires (i.e., FIQ pain, SF-36 bodily pain, current pain VAS) (transformed range 0 - 100mm, lower scores indicate greater health). Follow-up: 4 to 32 weeks	The mean pain in the control group was -1.94[1] Weighted mean score at baseline (all participants): 69.59	The mean pain in the aquatic groups improved by 6.59 units (2.48 to 10.71) compared to the control groups[2]	382 (7 studies)	⊕⊕⊖⊖ **Low**[3,5,7]	MD -6.59, 95% CI -10.71,-2.48 p < 0.05 Absolute Difference: 6.58 units (2.48 to 10.71) Relative percent change: -9.5% (-15.3%, -3.7%) NNT: 5 (3 to 8)
Stiffness Self-reported questionnaire FIQ Stiffness scale (0-100 mm, lower scores indicate greater health). Follow-up: 4 to 32 weeks	The mean stiffness in the control group was 1.66 mm[1] Weighted mean score at baseline (all participants): 69.42	The mean in stiffness in the aquatic groups improved by 18.34 mm (0.93 to 35.75) compared to the control groups[6]	230 (4 studies)	⊕⊕⊖⊖ **Low**[3,5,7]	MD -18.34, 95% CI -35.75,-0.93 p < 0.05 Absolute Difference: 18.34 mm (0.93 to 35.75) Relative percent change: -26.8% (-52.2%, -1.1%) NNT: 3 (2 to 24)
Muscle Strength Isokinetic strength of knee extension and hand grip. Higher scores indicate greater health Follow-up: 12 to 32 weeks	The mean change in muscle strength in Newton meters was -0.30.[1]	The mean in muscle strength in the aquatic groups improved 0.63 standard deviations (0.20 to 1.05 higher) compared to the control groups	152 (4 studies)	⊕⊕⊖⊖ **Low**[3,7]	SMD 0.63, 95% CI 0.20, 1.05 p < 0.05 moderate effect Absolute Difference: 0.63 standard deviations (0.20 to 1.05 higher) Relative percent change: 37.0% (11.7, 61.6%) NNT: 4 (3 to 12)
Submaximum Cardiorespiratory 6 minute walk test (6MWT)	The mean change in sub maximum cardiorespiratory was -5.6 [1]	The mean in sub maximum cardiorespiratory in the aquatic groups improved	213 (3 studies)	⊕⊕⊖⊖ **Low**	MD 37.03, 95% CI 4.14,69.92 p < 0.05 Absolute Difference: 37 meters walked in

(distance in meters). Higher scores indicate greater health. Follow-up: 6 to 26 weeks	Weighted mean score at baseline (all participants): 484.81 m	by 37 meters walked in 6 minutes (4.14 to 69.92 m) compared to the control groups				6 minutes (4.14 to 69.92m) Relative percent change: 6.5% (3.6%, 9.4%) NNT: 5 (3 to 9)
Withdrawals and Adverse effects[7]	All cause withdrawal in Control Groups: 33/232 (14.2%)	All cause withdrawal in Aquatic Groups: 38/252 (15.1%)	Risk Ratio: 1.13 (0.73, 1.77)	472 (8 studies)	⊕⊕⊖⊖ **Low**[9,10]	One study: no adverse effects, one study: no aggravation of symptoms, one study: unspecified number of drop outs due to injury and infection, five studies did not address adverse effects at all.

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.

[1] Mean difference in control group(s) (posttest scores-pretest scores)
[2]Moderate effect (SMD =.50 to .79)
[3] Potential limitations related to imprecision (i.e., total (cumulative) sample size is lower than 400)
[4] Statistical heterogeneity (i^2 > 50%).
[5] Small effect (SMD = .20 to .49)
[6] Large effect (SMD = > .80)
[7] Potential limitations related to, high, unclear and low risk of bias.
[8]Whithdrawals may be associated with frequency, intensity, etc. in which case interventions should try to maximize retention focusing in these events. As adverse effects are still poorly reported, attrition may be taken as an indicator of adverse effect
[9]Incomplete documentation of adverse effects in at least five studies.
[10]Wide confidence interval

2. Aquatic Training compared to Land-based Training

Aquatic training compared to Land-based training for FM

Patient or population: Adults with FM **Settings:** Supervised group

Outcomes	Assumed Risk Land-Based Training	Corresponding Risk Aquatic Training	Relative Effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Multidimensional Function Self- report questionnaire FIQ-total (range 0-100 mm, higher scores mean worse function) Follow-up: 4 weeks	The mean change in multidimensional function was -8.21[1] Weighted Mean score at baseline: 64.4	The mean difference in multidimensional function was 0.91 mm better in the land-based (-4.01 to 5.83) than the aquatic groups		61 (1 study)	⊕⊖⊖⊖ **Very Low**[2,3,4]	MD 0.91, 95% CI -4.01, 5.83. Absolute Difference: 0.91mm (-4.01 to 5.83) Relative Difference: 1.4% (-6.2%, 9.05)
Self-Reported Physical Function SF-36 (0-100, transformed so higher scores mean poorer function). Follow-up: 3 to 23 weeks	The mean change in self-reported physical function was 27.44 SF-36 units[1] Weighted mean score at baseline: 32.16	The mean difference in self-reported physical function was -5.85 units (-12.33, 0.63)		74 (2 studies)	⊕⊖⊖⊖ **Very Low**[3,4,5]	MD -5.85, 95% CI -12.33, 0.63. Absolute Difference: -5.85 on a scale of 0-100 (-12.33, 0.63) Relative Difference: 2.4% (-41.4%, 36.7%)
Pain Self-reported measures FIQ pain, SF-36 bodily pain and VAS (transformed range 0 - 100mm, higher scores mean more pain).Follow-up: 3 to 23 weeks	The mean change in pain was -21.48 Weighted mean score at baseline: 75.64	The mean in pain was -0.75 mm (-10.72, 9.23) better in the aquatic groups than in land-based groups.		169 (4 studies)	⊕⊕⊖⊖ **Low**[3]	MD -0.75, 95% CI -10.72, 9.23. Absolute Difference: -0.75 mm (-10.72 to 9.23) Relative Difference in Change score: -1.1% (-15.3%, 13.2%)

Stiffness Self-reported measures FIQ stiffness (0-100mm) Follow-up: 20 weeks	The mean change in stiffness was -18[1] Weighted mean score at baseline: 75.64	The mean in stiffness was 0.20 mm (-0.88 to 1.28) better in the land-based group		34 (1 study)	⨁⊖⊖⊖ **Very Low**[2,3,4]	MD 2.00, 95% CI -8.82, 12.82 Absolute Difference: 0.20 mm (-0.88 to 1.28) better in the land-based group Relative Difference in change score: 2.6% (-11.7%, 16.9%) favouring land- based intervention
Muscle Strength Grip Strength Kilo Pascals (kPa). Higher scores mean health. Follow-up: 20 weeks	The mean change in muscle strength was 3.3 kPa[1] Weighted mean score at baseline: 28.57	The mean in muscle strength was 2.40 kPa (0.28, 4.52) better in the land-based group		34 (1 study)	⨁⊖⊖⊖ **Very Low**[2,3,4]	MD -2.40, 95% CI -4.52, -0.28, $p < 0.05$, effect favoring land-based exercise.[7] Absolute Difference: 2.40 kPa (0.28 to 4.52) better in the land-based group. Relative Difference in change score: -8.7% (-16.4%, 1.0%) favouring land-based intervention NNT: 4 (2 to 60)
Submaximal Cardiorespiratory function Walking Time (seconds required to complete 100 meters) Follow-up: 20 weeks	The mean change in submaximal cardiorespiratory function was 60.1 seconds[1] Weighted mean score at baseline: 60.08	The mean difference in submaximal cardiorespiratory function was 3 seconds (-1.77, 7.77) better in the aquatic group		34 (1 study)	⨁⊖⊖⊖ **Very Low**[2,3,4]	MD 3.00 95% CI -1.77, 7.77. Absolute Difference: 3 seconds (-1.77 to 7.77) better in the aquatic group Relative Difference in change score: 5.0% (-2.9%, 12.9%) favouring the land-based intervention
Withdrawals and adverse effects[8]	All cause withdrawal in Control	All cause withdrawal in Control Groups: 11/110 (10%)	RR: 0.91 (0.43, 1.91)	217 (4 studies)	⨁⨁⊖⊖ **Low**[4]	One study: no adverse effects either group, one study described several musculoskeletal adverse

	Groups:12/107 (10.7%)	effects in both groups and one instance of tinea pedis no aggravation of symptoms, and three studies did not address adverse effects at all.[8]

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.**Very low quality:** We are very uncertain about the estimate.

[1] Mean difference in control group(s) (posttest scores-pretest scores)
[2]Evidence based on a single study
[3] Potential limitations related to imprecision (i.e., total (cumulative) sample size is lower than 400)
[4]Potential limitations related to high, unclear, and low risk of bias.
[5]Evidence based on two small studies.
[6]Statistical heterogeneity (i^2 >50%)
[7]Moderate effect favouring the land based exercise (SMD =.50 to .79)
[8]Whithdrawals may be associated with frequency, intensity, etc. in which case interventions should try to maximize retention focusing in these events. As adverse effects are still poorly reported, attrition (or withdrawal) may be taken as an indicator of adverse effects.
[9]Incomplete documentation of adverse effects in at least three studies.

Appendix 4
Medline (OVID) Search Strategy

1. Fibromyalgia/
2. Fibromyalgi$.tw.
3. fibrositis.tw.
4. or/1-3
5. exp Exercise/
6. Physical Exertion/
7. Physical Fitness/
8. exp Physical Endurance/
9. exp Sports/
10. Pliability/
11. exertion$.tw.
12. exercis$.tw.
13. sport$.tw.
14. ((physical or motion) adj5 (fitness or therapy or therapies)).tw.
15. (physical$ adj2 endur$).tw.
16. manipulat$.tw.
17. (skate$ or skating).tw.
18. jog$.tw.
19. swim$.tw.
20. bicycl$.tw.
21. (cycle$ or cycling).tw.
22. walk$.tw.
23. (row or rows or rowing).tw.
24. weight train$.tw.
25. muscle strength$.tw.
26. exp Yoga/
27. yoga.tw.
28. exp Tai Ji/
29. tai chi.tw.
30. Ai Chi.tw.
31. exp Vibration/
32. vibration.tw.
33. pilates.tw.
34. or/5-33
35. 4 and 34

Appendix 5

Screening Selection Criteria

Level One screen

Based solely on the title of the report:

1. Does the study deal exclusively with Fibromyalgia? No – exclude, Yes or uncertain - go to step two
2. Does it include Exercise? No – exclude, Yes or uncertain – go to step three
3. Does the study deal exclusively with Adults? No – exclude, Yes or uncertain – go to step four
4. Is it an RCT? No – exclude, Yes or uncertain – Include

Level Two screen

Based solely on the abstract of the report:

1. Does the study deal exclusively with Fibromyalgia? No – exclude, Yes or uncertain - go to step two
2. Does it include Exercise? No – exclude, Yes or uncertain – go to step three
3. Does the study deal exclusively with Adults? No – exclude, Yes or uncertain – go to step four
4. Is it an RCT? No – exclude, Yes or uncertain – Include

Level Three screen

Based on the full text of the report:

1. Does the study deal exclusively with Fibromyalgia? No - exclude, Yes-go to step two, Uncertain - add to list of questions for author and proceed to step two
2. Is the diagnosis of Fibromyalgia based on published criteria? No - exclude, Yes - go to step three, Uncertain - add to list of questions for author and proceed to step 3
3. Does the study deal exclusively with Adults? No-exclude, Yes-go onto step 4, Uncertain - add to list of questions for author and proceed to step 4
4. Is it an RCT? (the study uses terms such as "random", "randomized", "RCT", or "randomization" to describe the study design or assignment of subjects to groups) No - exclude, Yes - go onto step 5, Uncertain - add to list of questions for author and proceed to step 5
5. Does it include Exercise (the study involves at least one intervention that includes exercise)? No - exclude, Yes - go on to step 6, Uncertain - add to list of questions for author and proceed to step 6
6. Is between group data provided for the outcomes? No (the study contains ONLY FM, or b) results are reported such that effects on FM cannot be isolated - **exclude,** Yes - **include** the

study, Yes but uncertain about one or more of steps 1-5 reserve judgement until authors are contacted

Level Four screen (classification of the study using team's intervention listing)

1. Classification of Design
    - Number of interventions
    - Type of Comparisons:
        - Head to Head comparison?
        - Exercise to control?
        - Composite to control?
2. Control group
    - Classify type of control
3. Exercise
    - Enter the type of exercise interventions used in the study
    - Complete the naming of the intervention groups

Appendix 6

Characteristics of included studies

Altan 2004 [138]

Methods	2 groups: aquatic exercises vs balneotherapy - both in mineral water. Length: 12wks plus 12 wks follow-up Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE 46:0, AGE: 43.14 (6.39) to 43.91 (6.26). INCLUSION: diagnosis of FM according to ACR 1990. EXCLUSION: rheumatoid disease, unstable hypertension, severe cardiopulmonary problems, heat intolerance, psychiatric disorder affecting compliance, abnormal blood count and chemistry, ESR, urinalysis. All patients were instructed to discontinue nonsteroidal anti-inflammatory drug medication throughout the study period.
Interventions	**a) Aquatic exercise in heated pool** (37 ºC) (n=24) Supervised aquatic Intervention: **F**REQUENCY: 3 times per week, **D**URATION: 35 minutes, **I**NTENSITY: 60-75% HRmax, **M**ODE: FX was performed to maximum length - active ROM plus static stretches: Ae: jumping, walking back and forth in the pool. Out of the pool exercises: bending back and forth, squatting, and relaxing with deep breath. Slow swimming as part of relaxation. **b) No exercise-balneotherapy** (n=22) Supervised balneotherapy: **F**REQUENCY: 3 times per wk. **D**URATION: 35 minutes; **M**ode: women were instructed not to perform any exercise during the sessions.
Outcomes	Pain, tender points, fatigue, sleep, stiffness, health related quality of life, muscle endurance, patient-rated disability, clinician-rated disability, depression. Measurements at: Pre - Post: 12 weeks - Follow up: 24 wks
Congruence with ACSM	No - only 20 minutes of aerobic activity
Injuries, Exacerbations, Other Adverse	**a) Aquatic exercise in heated pool:** none stated. **b) Balneotheraphy:** 3 dropouts because of hypertension (n=1) and cardiac arrhythmia (n=2) (other adverse)
Notes	Country: Turkey Language: English. Author contacted: response received. Funding sources/declaration of interest: none stated

Arcos-Carmona 2011 [2]

Methods	2 groups: Experimental vs placebo. Length: 10wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE 53:0, AGE: 44.4 (9.25). INCLUSION: diagnosis of FM according to ACR 1990. EXCLUSION: memory loss, participating in other pharmacological therapies, infectious diseases, hypotension and respiratory alterations that could limit participation in the treatment.
Interventions	**a) Experimental Group** (28 ºC) (n=27) Supervised aquatic intervention: **F**REQUENCY: 2 times per wk, **D**URATION: 60 minutes (30 minutes in the water and 30 minutes in land following Jacobson relaxation); **I**NTENSITY:40% of relative medium; **M**ODE:walks, jumps, grabbing, general mobility **b) Placebo** (n=26) Sham treatment with disconnected magnet therapy device. Participants were lying prone and the machine was covered so the they could not see the machine was disconnected. **F**REQUENCY**:** 2-times per wk; **D**URATION: 10 minutes at cervical level, 10 minutes lumbar level.
Outcomes	Sleep, pain, fatigue, health related quality of life, self-rated physical function, mental health, anxiety, depression Measurements at: Pre - Post: 10 weeks
Congruence with ACSM	No - only 2 times per week
Injuries, Exacerbations, Other Adverse	Unspecified injuries, exacerbations or other adverse effects.
Notes	Country: Spain - Language: Spanish. Article translated - Author contacted: response received. Funding sources/declaration of interest: authors declared no conflict of interest (pg 401)

Assis 2006 [126]

Methods	2 groups: deep water running vs land-based exercises. Length: 15 wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE: 60:0 AGE: 42.17(10.05) to 43.43 (10.76). INCLUSION: Diagnosis of FM (ACR1990), literate, and kept in an unchanged drug regimen for the last 4 weeks before starting the study. EXCLUSION: symptomatic cardiac failure, uncontrolled thyroid disturbances, body mass index equal or greater than 40, infectious contagious skin diseases, coronary, pulmonary, neurologic and rheumatic diseases limiting or hindering their ability to exercise, and those who had performed regular physical activity in the 6 weeks before the trial were not included. Years since onset of FM at entry/complaint duration: Deep water running (DWR): 7years - land-based group: 5 years
Interventions	**a) Deep water running in heated pool** (28-31 °C) (n=30) Supervised aquatic Intervention: **F**REQUENCY:3 times per wk. **D**URATION: 60 minutes (warm up:10', Ae:40', cool down:10') **I**NTENSITY: 60-75% HR_{max}. Low to moderate (at researcher calculated anaerobic threshold). **M**ODE:DWR **b) Land-based exercise:** (n=30) Supervised land-based intervention: **F**REQUENCY: 3 times per wk; **D**URATION: 60 minutes (Warm up:10', Ae:40', cool down:10'); **I**NTENSITY: 60-75% HR_{max}. Intensity: moderate (at researcher calculated anaerobic threshold); **M**ODE: outdoor walking and jogging.
Outcomes	Pain, patient rated global, health related quality of life, depression, self-reported physical function, submaximal cardiorespiratory, maximal cardiorespiratory, mental health, anxiety Measurements at: Pre - Middle: 8 weeks - Post: 15 wks
Congruence with ACSM	Not enough information to judge
Injuries, Exacerbations, Other Adverse	**a) DWR:** impingement syndrome; muscle pain (exacerbation) **b) Land - based exercise:** 2 events = bilateral ankle arthritis , Bakerys cyst; tinea pedis (injury); muscle pain (exacerbation)
Notes	Country: Brazil - Article Language: English. Author contacted: response received. Funding sources/declaration of interest: Supported by a grant from FAPESP (Research Support Fund of the State of Sao Paulo) (pg 57)

Calandre 2010 [127]

Methods	2 groups: Stretching in the water vs Tai Chi in the water (Ai Chi). Length: 6 wks - Follow up at 10 and 18 wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE: MALE 73:8; AGE 51 (8) to 49 (8.4).INCLUSION: Diagnosis of FM (ACR1990).EXCLUSION: those who never attended a swimming pool, had disease susceptible to worsen with warm water exercise such as coronary disease, allergy to chlorine, etc. Participants followed their pharmacological treatment during study and follow up period. Years since onset of FM at entry 14.1 (8.4) to 15.6 (8.7)
Interventions	**a) Ai Chi** (pool temperature 36 °C preceded by warm shower to condition the body 34.5-35.5 °C) (n=42) Supervised aquatic intervention. **F**REQUENCY: 3 times per wk **D**URATION: 60 minutes (first and last 10 minutes patient relax, 40 minutes exercises) **I**NTENSITY: to individual needs depending on degree of pain and fatigue **M**ODE: patients were taught the 16 movements which constitute the Tai Chi therapy without the help of any material - they use a combination of deep breathing and slow, broad movements of the arms, legs and torso **b) Stretching in the water** (pool temperature 36° C preceded by warm shower to condition the body 34.5-35.5 °C) (n=39) Supervised aquatic intervention. **F**REQUENCY: 3 times per wk **D**URATION: 60 minutes (first and last 10 minutes patient relax, 40 minutes exercises) **I**NTENSITY: to individual needs depending on degree of pain and fatigue **M**ODE: in order to facilitate stretching participants were given 1mt long wooden sticks, 1.5mt flexible tube. Stretching was performed over muscles of main body areas: cervical, upper and lower extremities and trunk.
Outcomes	Pain, fatigue, sleep disturbance, stiffness, tender points, health related quality of life, physical function, depression, anxiety. Measurements at: Pre - Post: 6 wks - Follow up 1: 10 wks - Follow up 2: 18 wks
Congruence with ACSM	No applicable
Injuries, Exacerbations, Other Adverse	Injuries unspecified for either group; **a) Ai Chi:** pain exacerbation; chlorine hypersensitivity (n=1) (other adverse)
Notes	Country: Spain - Language: English. Author contacted: n/a. Funding sources/declaration of interest: article states "none declared" (pg S-13)

De Andrade 2008 [128]

Methods	2 groups: aerobic aquatic exercises vs aerobic aquatic exercises in sea water (Thalassotherapy). Length: 12wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE: 23:0 AGE: 48.8(9.9) to 48.3 (8.9). INCLUSION: diagnosis of FM (ACR1990), be without physical activity at least 3 months. EXCLUSION: pregnancy, infectious contagious skin disease, coronary, pulmonary, neurological or other limiting rheumatic diseases. Years since onset of FM at entry: not specified
Interventions	**a) Aerobic aquatic exercises** (28-33 °C) (n=23) Supervised aerobic aquatic exercise in outdoor pool during summer months . **F**REQUENCY: once a day-3-times per week **D**URATION: 60 minutes (10 minutes stretching, 40 minutes low impact aerobic,10 minutes relaxation) **I**NTENSITY: training level was set at 50-75% of $VO2_{max}$. or levels 12 to 13 on BORG scale **M**ODE: racing against the water resistance, bicycling simulation, stationary march, shoulders and elbows bending and extension with dumbbells, punches in the air, multidirectional kicks against water resistance, pushing and pulling floater against water resistance, stepping and sinking the floaters with feet and jumping jacks and low jumps using calf for leverage. **b) Aerobic aquatic exercises in sea water (Thalassotherapy)** (n= 23) Supervised aerobic thalassotherapy performed in sea water - no waves and water stood at shoulder level of participants **F**REQUENCY: once a day-3 times per wk; **D**URATION: 60 minutes (10 minutes stretching, 40 minutes low impact aerobic-10 minutes relaxation); **I**NTENSITY: training level was set at 50-75% of $VO2_{max}$. or levels 12 to 13 on BORG scale **M**ODE: racing against the water resistance, bicycling simulation, stationary march, shoulders and elbows bending and extension with dumbbells, punches in the air, multidirectional kicks against water resistance, pushing and pulling floater against water resistance, stepping and sinking the floaters with feed and jumping jacks and low jumps using calf for leverage.
Outcomes	Pain, fatigue, tender points, sleep, health related quality of life, depression, self-rated physical function, mental health. Measurements at: Pre- Post: 12 wks
Congruence with ACSM	No - only 3 times a week or 120 minutes of aerobic exercise
Injuries, Exacerbations, Other Adverse	**a) Aquatic exercises:** muscle pain (n=9) (exacerbation); urinary infection (n=1) (other adverse) **b) Aquatic exercises in sea water:** first degree burn (n=2) (injuries); muscle pain (n=8) (exacerbation);
Notes	Country: Brazil Language: English. Author contacted: n/a. Funding sources/declaration of interest: non stated

de Melo Vitorino 2006 [129]

Methods	2 groups: Hydrotherapy vs Conventional Physiotherapy. Length: 3 wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE 25:0 ; AGE 48.9 (9.2) to 46.6 (8.4); INCLUSION: diagnosis of FM according to ACR (1990). EXCLUSION: no contraindications to pool treatment. Years since onset of disease/symptoms: unspecified
Interventions	**a) Hydrotherapy** (temperature unspecified) (n =19) Supervised aquatic intervention. **F**REQUENCY: 3 times per wk. **D**URATION: 60 minutes (warm up: 5', FX: 6', AE: 30', FX: 6', Relax: 13') **I**NTENSITY: unspecified. **M**ODE: jumping walking, sliding with arm movement vs resistance. Flexibility - unspecified **b) Conventional Physiotherapy** (n=19) Supervised conventional intervention. **F**REQUENCY: 3 times per week; **D**URATION: 60 minutes; (Infrared at beginning 10', FX 5' x 2; AE: 30', Relax: 10) **I**NTENSITY: unspecified; **M**ODE: AE:leg-ergometry, FX-unspecified,
Outcomes	Sleep, self-rated physical function, pain, fatigue, mental health. Measurements at: Pre - Post: 3 wks
Congruence with ACSM	No - Intensity unspecified
Injuries, Exacerbations, Other Adverse	**a) Hydrotherapy:** unspecified injuries, exacerbations or adverse effects. **b) Conventional Physiotherapy:** unspecified injuries, exacerbations or adverse effects.
Notes	Country: Brazil Language: English. Author contacted: n/a. Funding sources/declaration of interest: none stated

Evcik 2008 [130]

Methods	2 groups: Aquatic exercise program vs home-based exercise program. Length: 5 wks plus 19 wks follow up. Study Design: Randomized clinical trial with parallel group
Participants	FEMALES: MALES, 62:1 AGE: 42.8 (7.6) to 43.8 (7.7). INCLUSION: diagnosis of FM according the ACR (1990).EXCLUSION: severe cardiovascular disease, unstable hypertension, malignancy, inflammatory joint disease, heat intolerance and pregnancy, use of antidepressive or nonsteroidal anti-inflammatory drugs, exercise regularly. Years since onset of FM at entry (in years): 3
Interventions	**a) Aquatic exercise program** (33 °C) (n=31) Supervised aquatic mixed program. **F**REQUENCY: 3 times per wk; **D**URATION: 60 minutes (35 minutes aquatic- 20 minutes poolside exercises such as warming up active range of motion and relaxation); **I**NTENSITY: unspecified; **M**ODE: stretches, walking, jogging and low impact swimming. **b) Home-based exercise program** (n=30) Exercises were demonstrated on one occasion and participants were given written advice. **F**REQUENCY: 3 times per wk; **D**URATION: 60 minutes; **I**NTENSITY: unspecified; **M**ODE: aerobic, general mobility, flexibility and relaxation.
Outcomes	Pain, tender points, fatigue, stiffness, sleep disturbance, paresthesia, irritable bowel, pseudo Raynaud's, sicca symptoms, headache, bladder dysfunction, depression, health related quality of life Measurements at: Pre - Post: 4 weeks, Follow up 1: 12 wks, Follow up 2: 24 wks
Congruence with ACSM	Not enough information to judge - intensity not stated
Injuries, Exacerbations, Other Adverse	Authors stated "no side effects were observed during the program" pg 886-87
Notes	Country: Turkey Language: English. Author contacted: Response received. Funding sources/declaration of interest: none stated

Gowans 2001 [131]

Methods	2 groups: Aerobic vs untreated control. Length: 23 wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE 44:6 AGE: 44.6 (8.7) to 49.9 (7.3); INCLUSION meet diagnostic criteria and be willing to comply with the experimental protocol EXCLUSION diagnosis of high blood pressure or symptomatic cardiac disease, other serious systemic diseases (e.g., cancer, diabetes) intention of changing medications for anxiety or depression or seek professional treatment for anxiety or depression during the study period, and be enrolled in or intended to begin an AE exercise program. Years since disease symptoms [Mean (SD)]: 6.4 (7) to 11.6 (10.4) years; duration of diagnosis: 3.2 (3.3) to 3.5 (3.2) years.
Interventions	**a) Aerobic** (warm water pool - temperature not specified) (n=27) Classes for the first 6 weeks were conducted in a warm therapeutic pool. At 7 week subjects progressed to 2 walking classes in a gym and 1 pool class. Data for this review was extracted to represent the aquatic exercise training at 6 week mark. **F**REQUENCY: 3 hospital based classes per wk; **D**URATION: 30 minutes (20 minutes aerobic); **I**NTENSITY: low to moderate 60-75% age-adjusted HR_{max}; **M**ODE: water (warm) walking/running progressing to land walking/running **b) Wait list control** (n=23): "continue ad libitum activity"
Outcomes	Depression, submaximal cardiovascular, anxiety, mental health, tender points, strength, health related quality of life, self-efficacy. Measurements at: Pre - Middle: 6 wks- Post: 23 wks
Congruence with ACSM	No - only 20 minutes of aerobic exercise
Injuries, Exacerbations, Other Adverse	No reported injuries, exacerbations or other adverse effects.
Notes	Country: Canada Language: English. Author contacted: n/a. Funding sources/declaration of interest: the work was supported by a grant from the Toronto Hospital Auxiliary Women's Health Project on Women and Arthritis (pg 528)

Gusi 2006 [132]

Methods	2 groups: Aquatic exercise vs control. Length: 12 wks plus 12 wks follow up. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE; 35:0.AGE: 51(9) - 51 (10). INCLUSION: diagnosis of FM according the ACR (1990). EXCLUSION: any severe disorder of the spine (e.g., prolapsed disk, spinal stenosis), severe trauma, frequent migraines, peripheral nerve entrapment, inflammatory rheumatic diseases, and severe psychiatric illness. Participants with diseases the prevent physical loading, pregnant, those who attended another psychological or physical therapy or history of more than 30 minutes exercise session per week during 2 weeks in the last 5 years. Years since onset of disease/symptoms: 24 and 19 years
Interventions	**a) Aquatic exercise** (33 °C) (n=17) Supervised exercises in waist high warm pool. **F**REQUENCY: 3 times per wk; **D**URATION: 60 minutes (10 minutes warm up, 2 x 10 minutes aerobic, 10 minutes strength, 10 minutes cool down); **I**NTENSITY: Aerobic 65-75% HR_{max}, Strength slow pace; **M**ODE: aerobic-unspecified; strength-low extremity exercises (knee flexion and extension) against water resistance **b) Control** (n=17) The control group continue to follow normal daily activities, and did not performed any form of exercise as those in the exercise group.
Outcomes	Pain, health related quality of life, self-reported physical function, strength Measurements at: Pre - Post: 12 wks - Follow up: 24 wks
Congruence with ACSM	No - Only 20' 3 times per week
Injuries, Exacerbations, Other Adverse	No injuries, exacerbation or other adverse effects specified; authors mentioned " strength training in water did not aggravated the symptoms" pg 71
Notes	Country: Spain Language: English (2) and Spanish (2). Spanish articles translated. Author contacted: response received. Funding sources/declaration of interest: Support received from the European Social Funds and Regional Government of Extremadura (pg 66)

Hecker 2011 [1]

Methods	2 groups (hydrokinesiotherapy and kinesiotherapy). LENGTH: 23 wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE = 24:0, AGE(yrs): 47.5 to 45.3 INCLUSION: females with a diagnose of FM for at least 2 years, without diagnoses of associated diseases, not engaged in regular physical activities and that were not on any medication. EXCLUSION: patients with pathologies that would prevent attending less than 75% of the visits to either group. Also it were excluded the patients that were taking any kind of medication as well those who started taking medication during the study. DURATION OF ILLNESS (yrs):3 to 4.5.
Interventions	**a) Hydrokinesiotherapy** (32-34 ºC) (n=12) **F**REQUENCY:1 time per wk. **D**URATION: 60 minutes (15' FX, 15' aerobic, 15' unloaded AROM, 15' flexibility) **I**NTENSITY: 40% - low intensity for the aerobic portion. **M**ODE: AE working major muscle groups of the lower limbs, upper limbs, trunk and neck. **b) Kinesiotherapy** (n=12) **F**REQUENCY: 1 time per wk. **D**URATION: 60 minutes (15' FX, 15' AE, 15' unloaded AROM, 15' flexibility) **I**NTENSITY: 40% - low intensity for the AE portion. **M**ODE: AE working major muscle groups of the lower limbs, upper limbs, trunk and neck.
Outcomes	Pain, Fatigue, Physical Function, Mental Health, Global well-being, multidimensional function Measurements at: Pre - Post: 23 weeks
Congruence with ACSM	No - frequency 1 per week and no description of intensity
Injuries, Exacerbations, Other Adverse	No injuries, exacerbations or other adverse effects specified.
Notes	Country: Brazil Language: Portuguese. Article translated. Author contacted: response received. Funding sources/declaration of interest: none stated

Ide 2008 [133]

Methods	2 groups: Aquatic respiratory exercise-based program vs control. Length: 4 wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE 40:0 AGE 46.61 (9.8) to 45.47 (8.65).INCLUSION: diagnosis of FM according the ACR (1990), time availability, means of transportation and acceptance of training routine. EXCLUSION: the presence of musculoskeletal, respiratory, neurological, cardiovascular, skin diseases or hydrophobia reported. Participants enrolled in any other regular exercise activity or institutionalised were excluded. Years since onset of disease/symptoms: unspecified
Interventions	**a) Aquatic respiratory exercise-based program** (32 °C) (n=20) Exercise program performed in a 1.05m deep heated pool - participants were asked to keep their shoulders in the water. **F**REQUENCY:4 times wk; **D**URATION:60 minutes (5 minutes warm up walking, jogging and running, 45 minutes general exercises and specific breathing patterns, 10 minutes cool down free floating and breathing; **I**NTENSITY: unspecified. **M**ODE: Shoulder, hip and trunk movement combined with breathing exercises **b) Control** (n=20) Non-exercise program involved no exercises, no health related issues and consisted of recreational card games, music and general interest seminars **F**REQUENCY: 1 time wk **D**URATION: 60 minutes
Outcomes	Pain, dyspnea, tender points, anxiety, sleep disturbance, fatigue, stiffness, health related quality of life, self-reported physical function, mental health, depression, patient-rated global Measurements at: Pre - Post: 4 weeks
Congruence with ACSM	No - intensity unspecified
Injuries, Exacerbations, Other Adverse	No injuries, exacerbations or other adverse effects specified.
Notes	Country: Brazil Language: English. Author contacted: response received. Funding sources/declaration of interest: none stated

Jentoft 2001 [134]

Methods	2 groups: Aquatic exercise program vs land-based exercise program. Length: 20 wks plus 6 months follow up. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE= 34:0, AGE: 39.4 (8.8) to 42.9(8.6). INCLUSION: Diagnosis of FM (ACR 1990). EXCLUSION: Inflammatory rheumatic disease, hypothyroidism, heart and lung disease, pregnancy. Years since onset of disease/symptoms (years): 11.1
Interventions	**a) Aquatic exercise program** (34 °C) (n=18) Supervised program based on an aquatic adaptation of the Norwegian Aerobic Fitness Model. **F**REQUENCY: 2 times wk; **D**URATION: 60 minutes; **I**NTENSITY: 60-80% HR_{max} age adjusted; **M**ODE: dynamic muscle work accompanied by music (aerobic dance, stretching, strengthening). **b) Land-based exercise program** (n=16) Supervised program based on the original form of the Norwegian Aerobic Fitness Model. Strength for thighs and trunk: Gymnastic hall with normal room temperature and a wooden floor was used. **F**REQUENCY: 2 times wk; **D**URATION: 60 minutes; **I**NTENSITY: 60-80% HR_{max} age adjusted; **M**ODE: dynamic muscle work accompanied by music (aerobic dance, stretching, strengthening).
Outcomes	Pain, fatigue, sleep, stiffness, tender points, patient global rating, self-rated physical function, submaximal cardiovascular, maximal cardiovascular, strength, endurance, self-efficacy, depression, anxiety. Measurements at: Pre - Post: 20 wks - Follow up: 46 wks
Congruence with ACSM	Not enough information to judge
Injuries, Exacerbations, Other Adverse	No injuries, exacerbations or other adverse effects specified.
Notes	Country: Norway Language: English. Author contacted: Response received. Funding sources/declaration of interest: Support from the Norwegian Ministry of Health and Social Affairs/Rogaland County Council, Department of Health and Social Services, and by the Haugesund Women's Public Health Association (pg 42)

Mannerkorpi 2000 [143]

Methods	2 groups: Aquatic exercise program vs control. LENGTH: 24 wks (includes 6 weeks of education). Study Design: Randomized clinical trial with parallel group
Participants	FEMALE: MALE 57:0 AGE: 45(8) to 47 (11.6) INCLUSION: Diagnosis of FM (ACR1990). EXCLUSION: rheumatic diseases, severe somatic or psychiatric disorders, inability to understand Swedish, chlorine allergy, plans to start other treatments during study period. Years since onset of disease/symptoms: 8.4(6) to 8.9 (7.2) years
Interventions	**a) Aquatic exercise program (**pool temperature - unspecified) (n=28) Supervised exercise program in groups of 6-10 participants. **F**REQUENCY: 1 time per wk; **D**URATION: 35 minutes; **I**NTENSITY: self-selected below pain and fatigue threshold; **M**ODE: endurance, FX, coordination and relax Supervised education program **F**REQUENCY: 1 time per wk per 6 wks; **D**URATION: 60 minutes. The aim was to introduce strategies to cope with FM symptoms and encourage physical activity. Based on active participation of the patients **b) Control Group** (n=29) treatment as usual
Outcomes	Submaximal cardiovascular, health related quality of life, pain, self-rated physical function, stiffness, anxiety, depression, fatigue, mental health, tender points, endurance, strength, flexibility, self-efficacy. Measurements at: Pre - Post: 26 wks
Congruence with ACSM	No - frequency 1 per week, intensity unspecified, session duration 35' including all components
Injuries, Exacerbations, Other Adverse	"Main reasons for not starting or interrupting the program were lack of time due to commitments relating to child care or employment, or the occurrence of infection or injury" pg 2474
Notes	Country: Sweden Language: English. Author contacted: n/a. Funding sources/declaration of interest: Supported by grants from the Swedish Rheumatism Association the Vardal Foundation, and the Lansforsakringsbolagen Research Foundation (pg 2473)

Mannerkorpi 2009 [136]

Methods	2 groups (Pool and education and Education only), LENGTH: 20 wks - follow up 48 to 52. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE = 134:0 MEAN POOLED AGE (yrs): 45.64 (22-60 minutes-max).INCLUSION: women with FM between ages of 18-60 years and pain at manual palpation at 11 out of 18 examined TPs (ACR 1990).EXCLUSION: other severe somatic psychiatric disorders such as stroke or schizophrenia, inability to understand Swedish, allergy to chlorine, ongoing exercise therapy supervised by a physical therapist, or plans to start such therapy during the study period. DURATION of Symptoms (yrs ± SD): 10.6 (7.2)
Interventions	**a) Pool and Education group:** (33 ºC) (n= 68) Pool - **F**REQUENCY**:** 1 time per wk **D**URATION**:** 45 minutes total **I**NTENSITY**:** participant determined at low to moderate - median value for exertion (6-20) measured by Borg scale for perceived exertion **M**ODE**:** aquatic aerobic, walking, jogging on flotation devise with arm movement. Aquatic flexibility/coordination: active and passive arm/trunk movements. Additional breathing exercises and body awareness. Education - **F**REQUENCY**:** 1 wk per 6 wks **D**URATION**:** 6-1hr sessions **M**ODE**:** discussions and practical exercises (relaxation) **b) Education Group** (n= 66) **F**REQUENCY**:** 1 wk per 6 wks **D**URATION**:** 6-1hr sessions **M**ODE**:** discussions and practical exercises (relax)
Outcomes	Multidimensional function, Pain, Fatigue, Tenderness, Self-reported physical function, Mental Health, Depression, Anxiety, submaximal cardiorespiratory function (outcome data specific to FM participants received upon request). Measurements at: Pre - Post: 20 weeks
Congruence with ACSM	No - 1 time per wk, 45 minutes total
Injuries, Exacerbations, Other Adverse	No injuries as reported from personal communication with the author. No severe exacerbations related to the program were documented.
Notes	Country: Sweden. Author contacted: Yes - responses received. Funding sources/declaration of interest: Financial support was provided by the Swedish Research Council, The Health and Medical Care Executive Board of Vastra Gotaland Region, the Swedish Rheumatism Association, the Lansforsakringsbolagens Research Foundation, the Rheumatic Pain Society in Goteborg/RiG, the Goteborg Region Foundation for Rheumatology Research/GSFR and ALF at Sahlgrenska University Hospital (pg 759)

Munguia-Izquierdo 2007 [111]

Methods	3 groups: Aquatic mixed - FM control - healthy control. Length: 16 wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE: MALE 78:0 AGE (yrs ± SD): 50(7), 46 (8) and 47(10) INCLUSION: Diagnosis of FM (ACR1990). EXCLUSION: morbid obesity, cardiopulmonary disease, uncontrolled endocrine or allergic disturbances, severe trauma, frequent migraines, inflammatory rheumatic disease, and severe psychiatric illness. Pregnant women, those with restriction for physical loading, those who attended another physical or psychological therapy, and those with a history of regular physical activity more strenuous than slow-paced walking a maximum of 2 times per week over 4 months prior to study entry were excluded from final analysis. Years since onset of disease/symptoms (years ± SD): 14(10) to 14(9) (healthy group n/a)
Interventions	**a) Aquatic mixed:** (32 ºC) (n=35) Supervised aquatic mixed (at chest high): **F**REQUENCY: 3 times per wk; Aerobic: **D**URATION: 20-30 minutes; **I**NTENSITY: low to vigorous in chest deep water (50-80% of predicted HR_{max}); Strength for all major muscle groups: **D**URATION: 20-30 minutes: **I**NTENSITY: slow pace **M**ODE: resistance from water and aquatic materials **b) Healthy controls:** (n=25) matched for age, weight, body mass index, and educational and physical activity levels to FM participants. **c) FM control:** (n=25) instructed not to change their habits regarding physical activities during the period
Outcomes	Tender points, Pain, health related quality of life, cognitive function, endurance, anxiety, sleep disturbance. Measurements at: Pre- Post: 16 wks
Congruence with ACSM	From review authors: No - aerobic duration was only 20-30 minutes; 3 times per wk From authors: "The intervention program met the minimum training standards of the American College of Sports Medicine" pg 826
Injuries, Exacerbations, Other Adverse	No injuries, exacerbations or other adverse effects specified.
Notes	Country: Spain Language: English (2). Author contacted: response received. Funding sources/declaration of interest: Work supported by the European Social Funds and Regional Government of Aragon (pg 824)

Tomas-Carus 2008 [137]

Methods	2 groups: Aquatic mixed vs FM control. Length: 34 wks. Study Design: Randomized clinical trial with parallel group
Participants	FEMALE:MALE 30:0 AGE (years ± SD) : 50.7-50.9 (10.6-6.7) INCLUSION: diagnosis of FM (ACR) EXCLUSION: history of severe trauma, frequent migraines, peripheral nerve entrapment, inflammatory rheumatic diseases; severe psychiatric illness, other diseases that prevent physical loading and pregnancy, attendance at another psychological or physical therapy or regular physical exercise with more than one exercise session of 30 minutes per week during a 2 week period in the last 5 years. Years since onset of disease/symptoms (years ± SD): 20.1 (8) for the exercise group and 19.4 (6.9) control.
Interventions	**a) Aquatic mixed (aerobic-strength):** (33 ºC) (n=15) **F**REQUENCY: 3 times per wk; **D**URATION: total 60 minutes in waist deep warm water. AE: 20 minutes; **I**NTENSITY: light to moderate 60-65% HR_{max}; **M**ODE: walking; ST and FX; **D**URATION: 20 minutes; **I**NTENSITY: 4 x 10 reps for each exercise - "light loads"; **M**ODE: lower extremity against water resistance, raising arms with light loads and elastic bands **b) FM control:** (n=15) The control group continue to follow normal daily activities, and did not performed any form of exercise as those in the exercise group.
Outcomes	Pain, fatigue, morning tiredness, stiffness, tender points, health related quality of life, physical function, cardiovascular maximum oxygen uptake, strength, endurance, flexibility, balance, anxiety, depression. Measurements at: Pre - Post 32 wks
Congruence with ACSM	No - Only 20 minutes, 3 times per wk
Injuries, Exacerbations, Other Adverse	No injuries, exacerbations or other adverse effects specified.
Notes	Country: Spain. Funding sources/declaration of interest: Study co-financed by the Regional Government of Extremadura and the Health Department (pg 251)

Appendix 7
Characteristics of excluded studies

Author	Reasons for exclusion
Bailey 1999 [154]; Dal 2011 [155]; Dawson 2003 [156]; Gandhi 2000 [157]; Geel 2002 [158]; Gowans 2004 [159]; Han 1998 [160]; Hoeger 2011 [161]; Huyser 1997 [162]; Jones 2011 [163]; Kadetoff 2010 [164]; Karper 2001 [165]; Kesiktas 2011 [166]; Khalsa 2009 [167]; Kingsley 2010 [168]; Klug 1989 [169]; Lange 2011 [170]; Mannerkorpi 2002 [135]; Mason 1998 [171]; Meiworm 2000 [172]; Meyer 2000 [173]; Mobily 2001 [174]; Nielen 2000 [175]; Nijs 2004 [176]; Offenbacher 2000 [177]; Piso 2001 [178]; Pfeiffer 2003 [179]; Rooks 2002 [180]; Salek 2005 [181]; Suman 2009 [182]; Tiidus 1997 [183]; Thijssen 1992 [184]; Uhlemann 2007 [185]; Worrel 2001[186]; Zijlstra 2005[187]	Non RCT
Astin 2003 [188]; Casanueva-Fernandez 2012 [189]; Castro-Sanchez 2011 [190]; daSilva 2007 [191]; Lorig 2008 [192]; Kendall 2000 [193]; Newcomb 2011 [194]; Oncel 1994 [195]; Vlaeyen1996 [196]; Williams 2010 [197]	Did not meet exercise criteria or effect of exercise could not be isolated
Ahlgren 2001 [198]; Guarino 2001 {248}; Kingsley 2005 [199]; Peters 2002 [200]; Santana 2010 [201]; Thieme 2003 {320}	Not published FM diagnosis confirmation
Matsumoto 2011 [202]	FM data could not be isolated
Alentorn-Geli 2009 [203]; Bakker 1995 [204]; Carbonell-Baeza 2011 [205]; Carbonell-Baeza 2012 [206]; Finset 2004 [207]; McCain 1986 [208]; Mutlu 2013 [209]; Sigl-Erkel 2011 [210]	Proposal, protocol, provision of data issues (i.e. between group not done),

Appendix 8

Results of Sensitivity Analysis

Comparison of heterogeneity (I^2) of the meta-analyses –with Ide [133] included vs excluded

	With Ide 2008 included in Meta-analysis Heterogeneity statistics (I^2)	With Ide 2008 excluded from Meta-analysis Heterogeneity statistics (I^2)	Difference in I^2
Multidimensional function	Chi^2 = 45.24, df = 7 (P < 0.00001); I^2 = 85%	Chi^2 = 18.71, df = 6 (P = 0.005); I^2 = 68%	17% less
Self-reported Function	Chi^2 = 16.86, df = 5 (P = 0.005); I^2 = 70%	Chi^2 = 6.98, df = 4 (P = 0.14); I^2 = 43%	27% less
Pain	Chi^2 = 34.03, df = 7 (P < 0.0001); I^2 = 79%	Chi^2 = 7.15, df = 6 (P = 0.31); I^2 = 16%	63% less
Tenderness	Chi^2 = 30.26, df = 7 (P < 0.0001); I^2 = 77%	Chi^2 = 14.25, df = 6 (P = 0.03); I^2 = 58%	19% less
Fatigue	Chi^2 = 67.94, df = 6 (P < 0.00001); I^2 = 91%	Chi^2 = 18.17, df = 5 (P = 0.003); I^2 = 72%	19% less
Stiffness	Chi^2 = 18.92, df = 4 (P = 0.0008); I^2 = 79%	Chi^2 = 22.65, df = 3 (P < 0.0001); I^2 = 87%	8% more
Mental Health	Chi^2 = 23.57, df = 4 (P < 0.0001); I^2 = 83%	Chi^2 = 8.44, df = 3 (P = 0.04); I^2 = 64%	19% less
Sleep	Chi^2 = 30.70, df = 2 (P < 0.00001); I^2 = 93%	Chi^2 = 1.47, df = 1 (P = 0.22); I^2 = 32%	61% less
Depression	Chi^2 = 43.27, df = 7 (P < 0.00001); I^2 = 84%	Chi^2 = 17.04, df = 6 (P = 0.009); I^2 = 65%	19% less
Anxiety	Chi^2 = 12.85, df = 7 (P = 0.08); I^2 = 46%	Chi^2 = 6.34, df = 6 (P = 0.39); I^2 = 5%	41% less

Appendix 9

Primary Wellness Outcomes in Aquatic vs Aquatic RCTs (SMDs, 95% CIs)[a]

Study	Intervention 1	Intervention 2	Multidimensional Function[b]	Self-Reported Physical Function[b]
Calandre 2010	Aquatic Flexibility	Ai Chi (Aquatic Tai Chi)	-0.35 (-0.79, 0.09)	n/a
de Andrade 2008	Aquatic Aerobic	Aquatic Aerobic Training in sea water	-0,17 (-0.81, 0.47)	-0.26 (-0.90, 0.38)

Notes:
[a] *Random Effects Model*
[b] *Negative Numbers mean the results favor intervention 1*
References [127;128]

Primary Symptoms Outcomes in Aquatic vs Aquatic RCTs (SMDs, 95% CIs)[a]

Study	Intervention 1	Intervention 2	Pain[b]	Stiffness[b]
Calandre 2010	Aquatic Flexibility	Ai Chi (Aquatic Tai Chi)	-0.37 (-0.81, 0.07)	-0.62 (-1.07, -0.17)
de Andrade 2008	Aquatic Aerobic	Aquatic Aerobic in sea water	-0.06 (-0.07, 0.58)	n/a

Notes:
[a] *Random Effects Model*
[b] *Negative Numbers mean the results favor intervention 1*
References [127;128]

Primary Fitness Outcomes in Aquatic vs Aquatic RCTs (SMDs, 95% CIs)[a]

Study	Intervention 1	Intervention 2	Strength	Submaximal Cardiorespiratory function
Calandre 2010	Aquatic Flexibility	Ai Chi (Aquatic Tai Chi)	n/a	n/a
de Andrade 2008	Aquatic Aerobic	Aquatic Aerobic Training in sea water	n/a	n/a

Notes:
[a] *Random Effects Model*
[b] *Negative Numbers mean the results favor intervention 1*
References [127;128]

Appendix 10

Subgroups Analysis Based on Participant Related Characteristics

Subgroup	Study	N	Mean	90%CI LL	90%CI UL
Younger vs Older age					
YOUNGER	Altan 2004 [138]	46	43.5	42.00	45.02
YOUNGER	Arcos-Carmona 2011[2]	53	44.0	42.29	45.64
YOUNGER	Mannerkorpi 2009 [130]	132	45.64	44.59	46.69
---	Mannerkorpi 2000 [143]	57	46.0	43.87	48.17
---	Gowans 2001[131]	31	47.3	44.97	49.60
OLDER	Munguia-Izquierdo [111]	53	48.2	46.52	49.85
OLDER	Tomas-Carus [137]	30	50.8	48.19	53.41
OLDER	Gusi [132]	34	51.0	48.37	53.63
Short vs Long disease duration					
SHORT	Gowans 2001[131]	31	8.9	6.4	11.5
SHORT	Mannerkorpi 2000 [143]	57	8.7	7.2	10.1
SHORT	Mannerkorpi 2009 [136]	132	5.1	4.4	5.9
---	Arcos-Carmona [2]	53	9.5	8.0	11.1
LONG	Gusi [132]	34	21.5	19.1	23.9
LONG	Munguia-Izquierdo [111]	53	14.0	11.9	16.1
LONG	Tomas-Carus [137]	30	19.8	17.6	21.9
Low vs High Impact of FM at baseline					
LOW	Gowans 2001[131]	31	55.7	52.4	59.1
LOW	Altan [138]	46	60.1	57.2	63.1
---	Gusi [132]	34	61.0	56.0	66.0
---	Tomas-Carus [137]	30	62.0	58.3	65.7
HIGH	Mannerkorpi 2009 [136]	132	65.5	63.2	67.8
HIGH	Munguia-Izquierdo [111]	53	66.0	62.8	69.3
HIGH	Mannerkorpi 2000 [143]	57	68.0	65.6	70.4
Low vs High Pain at Baseline					
LOW	Arcos-Carmona [2]	53	57.5	56.3	58.8
LOW	Tomas-Carus [137]	30	60.0	53.8	66.2
LOW	Gusi [132]	34	63.5	56.4	70.6
---	Mannerkorpi 2009 [136]	132	70.9	68.3	73.5
HIGH	Mannerkorpi 2000 [143]	57	75.5	71	79.9
HIGH	Munguia-Izquierdo [111]	53	75.7	70.9	80.5
HIGH	Altan [138]	46	77.1	72.8	81.5

Subgroup Analysis – Effects of Subject Characteristics on Multidimensional Function, Pain and Strength

Subgroup	**Multidimensional function** *Number of studies (participants), SMD [95% CI]*	**Pain** *Number of studies (participants), SMD [95% CI]*	**Strength** *Number of studies (participants), SMD [95% CI]*
Age[a]			
Younger	2 (157), -0.33 [-0.64, -0.01]	3 (208), -0.39 [-0.66, -0.11]	---
Older	3 (122), -0.75 [-1.12, -0.38]	3 (117), -0.83 [-1.21, -0.45]	---
Test for subgroup differences	*Chi^2 = 2.87, p = 0.09, I^2 = 65.2%*[b]	*Chi^2 = 3.46, p = 0.06, I^2 = 71.1%*[b]	---
Duration of FM[c]			
Short Duration	3 (199), -0.31 [-0.59, -0.03]	2 (166), -0.41 [-0.72, -0.10]	2 (88), 0.32 [-0.10, 0.74]
Long Duration	3 (122), -0.75 [-1.12, -0.38]	3 (117), -0.83 [-1.21, -0.45]	2 (64), 1.04 [0.51, 1.57]
Test for subgroup differences	*Chi^2 = 3.34, p = 0.07, I^2 = 70.1%*[b]	*Chi^2 = 2.88, p = 0.09, I^2 = 65.3%*[b]	*Chi^2 = 4.41, p = 0.04, I^2 = 77.3%*[b]
Impact of FM at Baseline[d]			
Low Impact	3 (226), -0.35 [-0.62, -0.09]	3 (219), -0.61 [-1.04, -0.19]	1 (58), 0.39 [-0.13, 0.91]
High Impact	2 (77), -0.47 [-0.93, -0.02]	1 (46), -0.16 [-0.74, 0.42]	1 (30), 0.18 [-0.54, 0.90]
Total	5 (303), -0.38 [-0.61, -0.15]	4 (265), -0.51 [-0.87, -0.15]	2 (88), 0.32 [-0.10, 0.74]
Test for subgroup differences	*Chi^2 = 0.19, p = 0.66, I^2 = 0%*[e]	*Chi^2 = 1.52, p = 0.22, I^2 = 34.3%*[e]	*Chi^2 = 0.21, p = 0.65 I^2 = 0%*[e]
Pain at Baseline[f]			
Low Pain at Baseline	2 (64), -1.11 [-1.64, -0.58]	3 (117), -0.60 [-0.98, -0.23]	2 (64), 1.04 [0.51, 1.57]
High Pain at Baseline	3 (161), -0.57 [-0.89, -0.25]	3 (156), -0.57 [-1.11, -0.03]	1 (58), 0.39 [-0.13, 0.91]
Test for subgroup differences	*Chi^2 = 2.95, p = 0.09, I^2 = 66.2%*[b]	*Chi^2 = 0.01, p = 0.93, I^2 = 0%*[e]	*Chi^2 = 2.97, p = 0.08, I^2 = 66.4%*[b]
Length of Program			
< 7 weeks	1 (31), -0.17 [-0.88, 0.53]	---	1 (30), 0.18 [-0.54, 0.90]

7 to 12 weeks	2 (80), -0.82 [-1.28, -0.36]	3 (133), -0.49 [-0.84, -0.14]	1 (34), 0.93 [0.22, 1.64]
> 12 weeks	4 (256), -0.52 [-0.90, -0.14]	4 (249), -0.54 [-0.80, -0.29]	2 (88), 0.63 [0.20, 1.06]
Test for subgroup differences	*Chi² = 2.44, p = 0.29, I² = 18.2%*[e]	*Chi² = 0.05, p = 0.82, I² = 0%*[b]	*Chi² = 2.15, p = 0.34, I² = 6.9%*[b]
Accumulated time in the pool			
< 1000 min in pool	2 (88), -0.48 [-0.91, -0.05]	2 (110), -0.52 [-0.90, -0.13]	2 (88), 0.32 [-0.10, 0.74]
1000 to 2000 min in pool	2 (157), -0.33 [-0.64, -0.01]	2 (155), -0.32 [-0.64, -0.00]	---
> 2000 min in pool	3 (122), -0.75 [-1.12, -0.38]	3 (117), -0.82 [-1.24, -0.41]	2 (64), 1.04 [0.51, 1.57]
Test for subgroup differences	*Chi² = 2.88, p = 0.24, I² = 30.5%*[b]	*Chi² = 3.60, p = 0.17, I² = 44.4%*[e]	*Chi² = 4.41, p = 0.04, I² = 77.3%*[b]
Exercise Frequency			
One pool session per week	2 (168), -0.34 [-0.65, -0.03]	1 (218), -0.39 [-0.65, -0.12]	1 (58), 0.39 [-0.13, 0.91]
Two pool sessions per week	---	1 (53), -0.59 [-1.14, -0.04]	---
Three pool sessions per week	5 (199), -0.64 [-0.93, -0.35]	4 (163), -0.63 [-1.08, -0.17]	3 (94), 0.74 [0.31, 1.16]
Test for subgroup differences	*Chi² = 1.92, p = 0.17, I² = 47.9%*[b]	*Chi² = 1.02, p = 0.60, I² = 0%*[e]	*Chi² = 1.05, p = 0.31, I² = 4.5%*[b]
Exercise intensity			
Very Light Intensity	---	1 (53), -0.59 [-1.14, -0.04]	---
Light to Moderate Intensity	2 (76), -0.89 [-1.40, -0.38]	2 (76), -0.25 [-0.70, 0.20]	1 (30), 1.17 [0.39, 1.96]
Light to Vigorous Intensity	1 (58), -0.39 [-0.92, 0.13]	1 (34), -0.82 [-1.53, -0.12]	2 (64), 0.56 [0.05, 1.06]
Moderate Intensity	2 (65), -0.59 [-1.43, 0.24]	1 (53), -1.12 [-1.71, -0.54]	---
Self-selected Intensity	2 (168),0 -0.38 [-0.84, 0.07]	2 (166), -0.41 [-0.72, -0.10]	1 (58), 0.39 [-0.13, 0.91]
Test for subgroup differences	*Chi² = 2.58, p = 0.46, I² = 0%*[e]	*Chi² = 6.72, p = 0.15, I² = 40.4%*[e]	*Chi² = 2.71, p = 0.26, I² = 26.3%*[b]
Pool Temperature			
Cool (27 to 32º Celsius)	---	1 (53), -0.59 [-1.14, -0.04]	---

Temperate (33 - 36° Celsius)	5 (290), -0.60 [-0.97, -0.24]	5 (283), -0.57 [-0.81, -0.34]	3 (122), 0.71 [0.34, 1.08]
Warm (> 36° Celsius)	2 (77), -0.47 [-0.96, 0.03]	1 (46), -0.16 [-0.74, 0.42]	1 (30), 0.18 [-0.54, 0.90]
Test for subgroup differences	*$Chi^2 = 0.19$, $p = 0.66$, $I^2 = 0\%$*[e]	*$Chi^2 = 1.74$, $p = 0.42$, $I^2 = 0\%$*[b]	*$Chi^2 = 1.65$, $p = 0.20$, $I^2 = 39.2\%$*[b]

[a] The median of mean age of participants in the studies comparing aquatic training to control was 46.7 years. Studies with a mean age younger than 46.7 were classified as "younger" and studies in which the mean age was above the median were classified as "older".

[b] Statistical method - Inverse Variance, Fixed Effects Model

[c] The median value for disease duration was 9.5 years in studies comparing aquatic training to control that provided data. Studies with weighted mean values less than 9.5 were classified as "Short Duration" and studies with disease duration > 9.5 years were classified as "Long Duration".

[d] The median value for multidimensional function score (the measure used for wellness) at baseline was 62 / 100. Studies with weighted mean values less than the median were classified as "low impact" and studies weighted mean values greater than the median were classified as "high impact" on wellness at baseline.

[e] Statistical method - Inverse Variance, Random Effects Model

[f] The median value for pain at baseline was 70.9 / 100 in studies comparing aquatic training to control that provided data. Studies below the median were classified as "low pain at baseline" and those above were classified as "high pain at baseline".

Data and analyses

Aquatic vs Control (after Sensitivity Analysis)

	Studies	Part	Statistical Method	Effect Estimate
1.1 Multidimensional Function	7	367	Mean Difference (IV, Random, 95% CI)	-5.97 [-9.06, -2.88]
1.2 Self-Reported Physical Function	5	285	Mean Difference (IV, Random, 95% CI)	-4.35 [-7.77, -0.94]
1.3 Pain	7	382	Mean Difference (IV, Random, 95% CI)	-6.59 [-10.71, -2.48]
1.4 Stiffness	4	230	Mean Difference (IV, Random, 95% CI)	-18.34 [-35.75, -0.93]
1.5 Muscle Strength	4	152	Mean Difference (IV, Random, 95% CI)	5.83 [-2.41, 14.08]
1.6 SubMaximum cardiorespiratory	3	194	Mean Difference (IV, Fixed, 95% CI)	31.72 [17.41, 46.03]
1.7 Patient rated global	1		Mean Difference (IV, Random, 95% CI)	No totals
1.8 Mental Health	4	243	Mean Difference (IV, Random, 95% CI)	-3.03 [-8.06, 2.01]
1.9 Clinician rated global	1		Mean Difference (IV, Random, 95% CI)	No totals
1.10 Self -efficacy	2	88	Mean Difference (IV, Random, 95% CI)	9.54 [-3.39, 22.46]
1.11 Fatigue	6	329	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.75, 0.13]
1.12 Tenderness	7	368	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.80, -0.13]
1.13 Depression	7	362	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.82, -0.08]
1.14 Flexibility	1		Mean Difference (IV, Random, 95% CI)	No totals
1.15 Sleep	2	104	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.12, -0.14]
1.16 Anxiety	7	374	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.95, -0.19]
1.17 Dyscognition	1		Mean Difference (IV, Random, 95% CI)	No totals
1.18 Maximum cardiorespiratory function	2	64	Std. Mean Difference (IV, Random, 95% CI)	0.23 [-1.00, 1.47]
1.19 Muscle Endurance	3	162	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.67, 0.67]
1.20 Attrition	8	484	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.73, 1.77]

2 Aquatic vs Land-based

Outcome or Subgroup	Studies	Part	Statistical Method	Effect Estimate
2.1 Multidimensional Function	1		Mean Difference (IV, Random, 95% CI)	No totals
2.2 Self-Reported Physical Function	2	74	Mean Difference (IV, Fixed, 95% CI)	-5.85 [-12.33, 0.63]
2.3 Pain	4	169	Mean Difference (IV, Random, 95% CI)	-0.75 [-10.72, 9.23]
2.4 Tenderness	1		Std. Mean Difference (IV, Random, 95% CI)	No totals
2.5 Fatigue	4	169	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.70, 0.45]
2.6 Stiffness	1		Std. Mean Difference (IV, Random, 95% CI)	No totals
2.7 Muscle Strength	1		Mean Difference (IV, Random, 95% CI)	No totals
2.8 Muscle Endurance	1		Mean Difference (IV, Random, 95% CI)	No totals
2.9 Maximum cardiorespiratory function	1		Mean Difference (IV, Random, 95% CI)	No totals
2.10 Submaximal cardiorespiratory function	1		Mean Difference (IV, Random, 95% CI)	No totals
2.11 Mental Health	2	74	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.54, 0.38]
2.12 Sleep	1		Mean Difference (IV, Random, 95% CI)	No totals
2.13 Depression	2	95	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.88, 0.67]
2.14 Anxiety	1		Std. Mean Difference (IV, Random, 95% CI)	No totals
2.15 Attrition	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.15.1 AQ vs Land	4	217	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.43, 1.91]

3 Aquatic vs Aquatic - See Appendix 9

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CHAPTER THREE

AN UMBRELLA SYSTEMATIC REVIEW WITH SYNTHESIS OF BEST EVIDENCE

3 Manuscript #2

The second manuscript aimed to summarize the effects of physical activity interventions for adults with FM as presented in systematic reviews from 2007 to 2012. Given the proliferation of review articles in the last 5 to 10 years, this step was deemed to be timely and important. Also, we considered the relevance of reviews' information for influencing clinical practice and decision making.

This manuscript was circulated among co-authors and researcher committee members in December 2013. Since then, an abstract was submitted and accepted to the Current Rheumatology Reviews Journal. A potential citation of the manuscript is as follow:

> Bidonde J, Busch AJ, Bath B, Milosavljevic S. Physical Activity for Adults with Fibromyalgia: An Umbrella Systematic Review with Synthesis of Best Evidence. Curr Rheum Reviews [Year], [Issue], [pages]

Contributions of authors

JB: screening studies, data extraction (9 systematic reviews for this manuscript), participated in discussion regarding methods, selection of outcome measures, assessment of risk of bias, methodological analysis, writing and reviewing manuscript and approving the final manuscript.

AB: screening studies, data extraction, participating in discussion regarding methods, assessment studies' quality, reviewing manuscript, and approving the final manuscript.

BB, SM: data extraction and appraisal of JB and AB authored reviews, reviewing manuscript, reviewing drafts and approving the final draft of the manuscript.

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Abstract

The objective of this umbrella systematic review was to identify, evaluate, and synthesize systematic reviews of physical activity interventions for adults with fibromyalgia (FM) focussing on four outcomes: pain, multidimensional function (wellness or quality of life), physical function (self-reported physical function or measured physical fitness) and adverse effects. A further objective was to link these outcomes with details of the interventions so as to guide and shape future practice and research. Electronic databases including Medline, EMBASE, CINHAL, AMED, the Cochrane Library, and DARE, were searched for the January 1st 2007 to March 31st 2012 period. Nine systematic reviews (60 RCTs with 3816 participants) were included. Meta-analysis was not conducted due to the heterogeneity of the sample. We found positive results of diverse exercise interventions on pain, multidimensional function, and self-reported physical function, and no supporting evidence for new (to FM) modalities (i.e. qigong, tai chi). There were no adverse effects reported. The variability of the interventions in the reviews prevented us from answering important clinical questions to guide practical decisions about optimal modes or dosages (i.e. frequency, intensity, duration). Finally, the number of review articles is proliferating, leading researchers and reviewers to consider the rigor and quality of the information being reviewed. As well, consumers of these reviews (i.e. clinicians, individuals with FM) should not rely on them without careful consideration.

Keywords: adult, best evidence, fibromyalgia, interventions, physical activity, synthesis, systematic review, umbrella review

3.1 Background

Fibromyalgia (FM), a disorder of unknown etiology, is reported to be "the third most common rheumatic condition after low back pain and osteoarthritis [1]." The prevalence of this disorder is estimated to be 2 to 3% worldwide, affecting women more frequently than men [2]. Individuals with FM report pain and other symptoms that affect their day-to-day social and work life. Silverman and colleagues [3] pointed out that the economic impact of fibromyalgia disorder is significant, similar to rheumatoid arthritis, and added "more emergency department utilization, physician and physical therapy visits than individuals with rheumatoid arthritis."[3] Fibromyalgia is associated with generalized body pain and tenderness [4;5], and many other symptoms including fatigue, lack of or disturbed sleep (wakening un-refreshed), stiffness, depression, and cognitive problems [6]. Even when the optimal treatment of FM is not straightforward, individuals with FM can benefit from pharmacological and non-pharmacological interventions (including physical activity). There is evidence suggesting low dose antidepressants, cardiovascular exercise, cognitive behavioural therapy, and patient education are effective in the management of FM [2;7]. This umbrella systematic review focuses on evidence from systematic review articles published in the last five years evaluating physical activity interventions for the management of FM.

Despite a need for information regarding effective interventions, health professionals are often overwhelmed by the growth of literature on the topic. A strategy to address this issue is to access/refer to/utilize/turn to review articles on the topic. Historically, it is accepted that systematic reviews of high quality randomized controlled trials (RCTs) yield the highest level of evidence regarding effectiveness of an intervention [8]. Systematic reviews often present a rigorous and complete overview of primary research on a particular topic. The essential aim of a systematic review is "…to minimize bias in locating selecting, coding, and aggregating individual studies" [9]. Systematic reviews draw out best available evidence and therefore have an important role in evidence-based healthcare [10]. Systematic reviews of interventions provide clinicians with opportunity to identify, understand and implement best available interventions into clinical practice, inform decision making, plan future research agendas, or help strengthen the link between research evidence and optimal health care. Knowledge synthesized from reviews can improve patient care if it is utilized and applied appropriately in clinical, policy, and administrative settings [11]. Despite the potential value of systematic review articles to

clinicians and policy makers, it is essential to recognize systematic reviews can be of variable quality and scope [12;13]. In order to benefit from these reviews, a critical step for clinicians, health professionals, researchers, and consumers is the ability to distinguish and appraise their quality.

A review of reviews (also called 'umbrella review') provides an evaluation and synthesis of published reviews and should be considered as a new level in the hierarchy of evidence. An umbrella review provides an efficient way to access a body of research, and is a logical way to contrast and compare information and interpret results. An umbrella review, as an overarching approach, synthesizes and allows the creation of a summary of several individual review articles into a single document. It also compiles evidence on the benefits and harms from multiple reviews, identifies information gaps [14], and describes the quality of the evidence.

The purpose of this umbrella review was to evaluate the quality of systematic reviews of physical activity interventions for adults with FM and to comprehensively describe and synthesize their findings. It focuses on four outcomes: pain, multidimensional function (MDF) (i.e. wellness or quality of life), physical function (self-reported physical function or physical fitness), and adverse effects. A further objective of the review was to link these outcomes with details of the interventions so as to guide and shape future practice and research.

3.2 Methods

This umbrella systematic review was guided by the procedures described in the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [15]. PRISMA recommends the conduct of systematic reviews to be published in the study protocol. However, even when all other procedures were followed, there was no published protocol to guide this review as recommended by PRISMA.

For the purpose of this umbrella review, we focused on existing systematic reviews of RCTs that evaluate physical activity interventions for the treatment of FM. Although there is no standard definition of a systematic review (SR) [16] we followed the key characteristics of a systematic review as stated by Cochrane Collaboration [17]. Although the definitions of physical activity and exercise have been discussed in Chapter 1, as a reminder *physical activity* is defined as any bodily movement produced by the contraction of skeletal muscles that substantially

increases energy expenditure and *exercise* is planned, structured, and repetitive exercise for the purpose of improving or maintaining one or more components of physical fitness [18].

3.2.1 Sources and Searches

The search strategy was carried out with the assistance of a medical librarian specializing in systematic reviews to identify all published reviews in the area of physical activity interventions for adults with FM. Six electronic databases utilized in the health fields including, Medline, EMBASE, CINHAL, AMED, the Cochrane Library, and DARE, were searched for the January 1st 2007 to March 31st 2013 period. Examples of key topic areas in the search strategy were 'physical activity', 'exercise' or 'physical activity interventions', 'fibromyalgia' or 'fibromyalgia syndrome', and 'review' or 'systematic review' or 'meta-analysis'. The computerized complete search strategy is summarized and presented in Appendix 1. The search was not restricted by specific languages. Reference lists from retrieved reviews were also examined to identify additional reviews.

3.2.2 Study Selection

Two authors (JB & AB) independently screened titles and abstracts to identify relevant studies. Potentially relevant full-text articles were obtained and assessed independently against inclusion criteria by the same two investigators. The PICO-TS framework (population, intervention, comparison, outcome, time, and study type) was used to evaluate the suitability of trials for inclusion (see Table 3.1). We included full text reports of systematic reviews of intervention studies which: a) cited their purpose as investigating the effect of physical activity interventions for adults diagnosed with FM, b) were published in English, Spanish or French (JB was literate in all three and could translate as needed), and c) included analysis on primary articles dealing with adults diagnosed with FM according to accepted and published criteria [19-25], and d) meeting at least three of five criteria of a systematic review according to Cochrane Collaboration (described below).

Table 3.1. PICO-TS criteria.

Population	Adults of either gender diagnosed with FM according to a published criteria
Intervention	Any intervention in which participants perform a program of regular physical activity over a period of time
Comparison	Any control or comparison group
Outcomes	Multidimensional function (i.e. well-being or quality of life), pain, physical function (self-report or observational test), or adverse effects.
Time frame	January 2007 to March 2013
Study **T**ype	Systematic Review (meeting at least three of five criteria characterizing a systematic review) of RCTs

Reviews were identified by assessing five essential features of SRs described by the Cochrane Collaboration [6;26]. We treated these features (i.e., items) as an instrument to determine suitability for inclusion. The items, each assigned a score of one, were: a) a focused question (i.e. contains PICO-TS statement); b) a comprehensive, systematic and explicit search (i.e. more than one database and other sources searched, keywords or mesh terms given); c) the use of explicit criteria to include and exclude RCTs; d) explicit methods of extracting and synthesising study findings (quantitative) and e) inferences made were evidence based. Reviews were evaluated and a score was assigned; scores ranged from 0 to 5, with one point for each item. Reviews having a score of three points or higher were considered to be SRs and included in this review. Exclusion criteria were: (1) SR assessment of less than three points, (2) those that did not fit all PICO-TS, and (3) clinical practice guidelines. Examples of reviews that were excluded were narrative reviews, reviews with no identified search strategy, and reviews of aquatic interventions that did not involve bodily movement (i.e., soaking in the water).

3.2.3 Quality Assessment

The quality of included reviews was independently assessed using the AMSTAR methodological quality measurement tool [27;28] by pairs of authors (AB+JB and SM+BB). Based on a pilot test of the AMSTAR tool and communication with the AMSTAR's developer, descriptions for items were refined and operationalized. The eleven AMSTAR items were scored (yes/no) to evaluate the adequacy of the important components of the method: search,

selection criteria, validity assessment, and synthesis. To avoid conflict of interest, authors (AB, JB) did not assess the SRs they had authored.

Interrater reliability analysis using Kappa statistic [29] was calculated using SPSS software version v 20 to determine consistency among raters. The following equation was used:

$$\kappa = \frac{\Pr(a) - \Pr(e)}{1 - \Pr(e)}, \quad \text{.....(3.1)}$$

where Pr(*a*) is the relative observed agreement among rater or 'reviewers', and Pr(*e*) is the hypothetical probability of chance agreement, using the observed data to calculate the probabilities of each observer randomly saying each category. If the raters are in complete agreement then $\kappa = 1$. If there is no agreement among the raters other than what would be expected by chance (as defined by Pr(*e*)), $\kappa = 0$. We interpreted Kappa statistics using the Landis and Koch approach [30]: value of 0 = poor, 0.01 to 0.20 = slight, 0.21 to 0.40 = fair, 0.41 to 0.60 = moderate, 0.61 to 0.80 = substantial, 0.81 to 1 = almost perfect/ perfect agreement.

3.2.4 Data Extraction

Data were extracted at two levels; first we extracted data regarding the reviews, and then we went beyond what was presented in the reviews and carefully inspected the included studies (RCTs). The following data were extracted:

3.2.4.1 Details of the characteristics of the reviews:

We extracted the following details from the reviews: a) author(s), b) year of publication, c) research question(s), d) comparators included (all types including head to head interventions), e) number of databases searched, f) period searched (in years), g) number of *RCTs* included, h) outcomes investigated in agreement with this review goals, i) age of participants included, j) duration of disease, and k) a brief summary of the characteristics of the included reviews. Regarding item g, we counted the number of included *RCTs* instead of number of separate publications (RCTs); whereas some review authors counted each publication as a separate study. Where this was the case, there were discordances between authors' count and our count. For example, Lima indicated that 27 RCTs were reviewed; whereas, after double and sometimes quadruple research publications for the same study were removed, we counted the total number

of studies in Lima as 18. Appendix 2 shows the references for all publications (primary and companion articles).

3.2.4.2 Overlap among RCTs included in the included Systematic Reviews

We investigated the degree to which the reviews shared the same RCTs (overlap) and the number of RCTs that were unique to each review.

3.2.4.3 Data Synthesis: Analysis and classification of RCTs

A detailed inspection of included RCTs in each review was undertaken to identify and classify the interventions and the comparators brought together (and/or pooled). In order to accomplish this task, included studies were sought and read; following a simple in-house abbreviation system the interventions were then represented (i.e. flexibility = FX, aerobics = AE, aquatics = AQ, mixed = MX, etc., see List of Abbreviations page xii). We completed this classification for the included studies in each review with the aim to understand the clinical characteristics of the interventions pooled in the reviews. Classification and differentiation of the interventions are highly relevant for health practitioners; attention to classification of the interventions is not frequently provided in reviews nor is it considered in the AMSTAR tool.

In addition, data related to exercise training variables such as: a) exercise frequency b) length of the intervention in minutes c) intensity d) duration of the intervention and follow up, and pool temperature were extracted.

3.2.4.4 Findings and conclusions from SRs

Quantitative or narrative data were extracted for the outcomes of interest (i.e., pain, multidimensional function, physical fitness, and adverse effects) including effect sizes and 95% confidence intervals provided by meta-analyses when applicable. Cohen's categories [31] (i.e., 0.20 to 0.49 small effect, 0.50 to 0.79 moderate effect, and $\geq$ 0.80 large effect) were used to interpret standardized mean differences (SMDs) when available.

3.3 Results

3.3.1 Search Results

The literature search identified 17 reviews, which were retrieved; all were in in English. Four reviews did not meet inclusion criteria and were excluded [32-35]. Full texts of 13 reviews were further screened for systematic review status. Out of these 13 reviews, only nine had three or more features of a systematic review as defined by the Cochrane Collaboration and met our inclusion criteria: five reviews scored five points [36-40], three reviews scored four points [41-43] and one scored three points [44]. Results of the search and screening are presented in the PRISMA diagram (Figure 3.1) and in Table 3.2.

3.3.2 Quality Assessment – AMSTAR

The quality assessment of the nine reviews is presented in Table 3.3. The quality of the reviews varied significantly (range 1 to 10) with three studies having high values (8, 10, 10) [36;37;41] four studies medium values (5,5,7,7) [38;40;42;44] and two studies scoring lower values (1,4) [39;43].

The Kappa analysis of inter-rater agreement on the use of the AMSTAR tool indicated there was moderate agreement among observers (overall Kappa = 0.600) for the nine included reviews (see Table 3.3). The itemized analysis shows there were perfect agreements in questions 10 and 11 and almost perfect for question five, substantial agreements in questions one, four, seven and nine , moderate agreement in questions two and three, slight agreement in question eight, and fair agreement in question six.

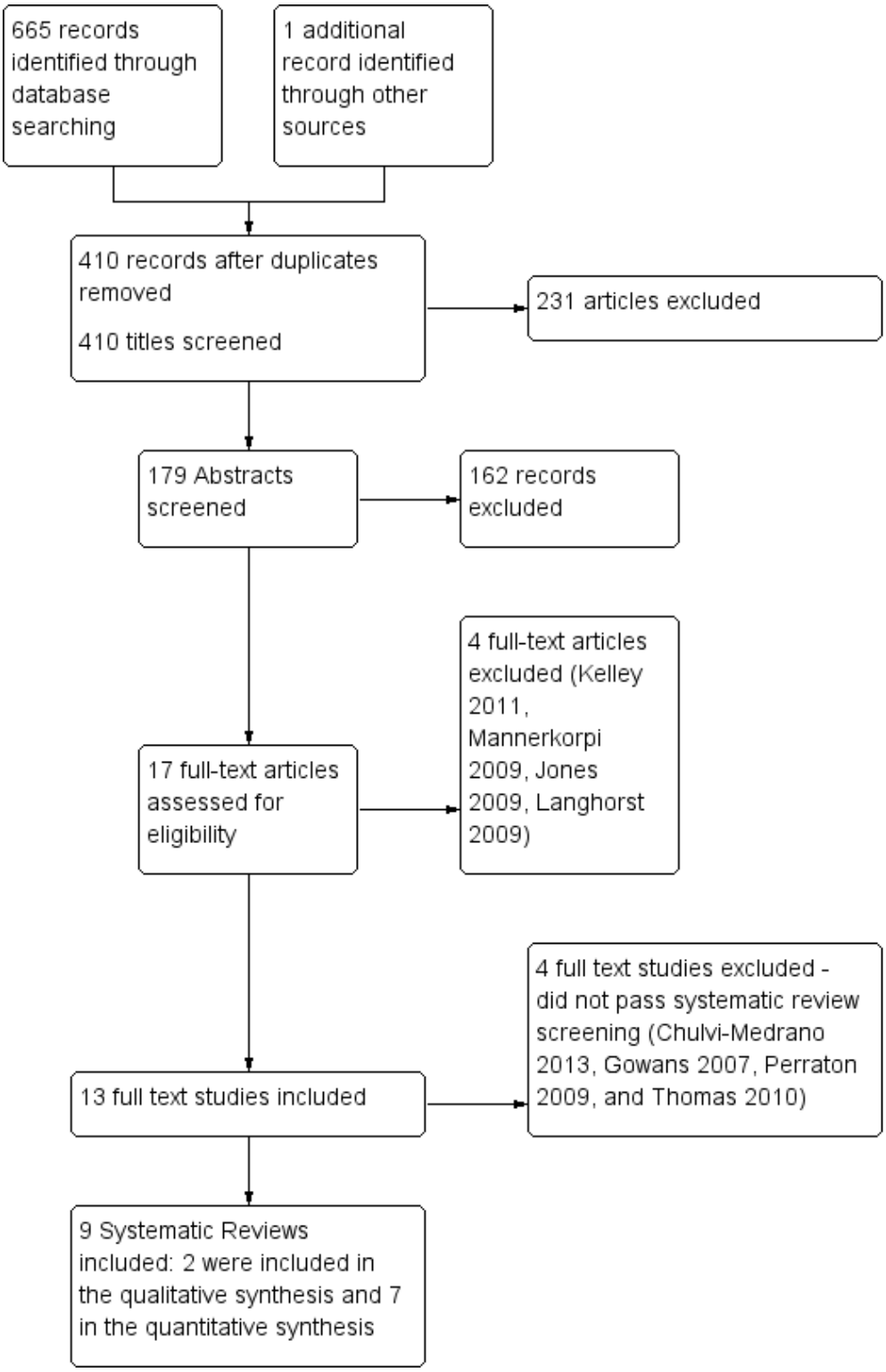


Figure 3.1. Study flow diagram of selected reviews.

Table 3.2. Systematic reviews screening (consensus).

	Question	**Sources & Search**		**Synthesis**		**Inferences**	
Review Authors	Focussed Question	Comprehensive and explicit search	Use of explicit criteria to include/exclude studies	Explicit methods of extracting and synthesising study findings-quantitative summary	Quantitative synthesis not applicable	Evidence-based	**Total - I**ncluded **or E**xcluded
Bidonde	1	1	1	1		1	5 – I
Busch 2013	1	1	1	1		1	5 – I
Chan 2012	1	1	1	0.5	0.5	1	5 – I
Chulvi-Medrano 2013	0	0	0	0		0	0 - E
Gowans 2007	0	0	0	0		1	1 – E
Hauser 2010	1	1	1	1		0	4 – I
Kelley 2010	1	0	1	1		1	4 – I
Lima 2013	1	1	1	1		1	5 – I
McVeigh 2008	0	1	1	0.5	0.5	0	3 – I
Mist 2013	1	1	0	1		1	4 – I
Perraton 2009	0	1	1	0		0	2 – E
Ramel 2009	1	1	1	1		1	5 – I
Thomas 2010	1	0	0	0	0.5	0	1.5 – E

Bidonde [36], Busch [37], Chan [38], Chulvi-Medrano [45] Gowans [46]Hauser [41], Kelley [42], Lima [39], McVeigh [44], Mist [43], Perraton [47] Ramel [40] and Thomas [48]

0= no: 1=yes: 0.5 = synthesis question may have 2 parts

Table 3.3. AMSTAR consensus scores and questions, and Kappa agreement and interpretation.

AMSTAR Question	Bidonde [36]	Busch [37]	Chan [38]	Hauser [41]	Kelley [42]	Lima [39]	McVeigh [44]	Mist [43]	Ramel [40]	Measure of Agreement (Kappa)	Kappa Interpretation
1	Y	Y	N	Y	N	N	N	N	N	.759	Substantial agreement
2	Y	Y	N	Y	Y	N	Y	N	N	.462	Moderate agreement
3	Y	Y	Y	Y	Y	Y	Y	N	Y	.429	Moderate agreement
4	Y	Y	Y	Y	Y	N	Y	N	N	.714	Substantial agreement
5	Y	Y	N	Y	N	N	Y	N	N	.811	Almost perfect
6	Y	Y	Y	N	Y	Y	Y	N	Y	.286	Fair agreement
7	Y	Y	Y	Y	Y	Y	Y	N	Y	.696	Substantial agreement
8	Y	Y	N	N	N	N	N	N	Y	.176	Slight agreement
9	Y	Y	Y	Y	Y	Y	Y	N	Y	.714	Substantial agreement
10	N	Y	N	Y	Y	N	N	Y	N	1	Perfect agreement
11	Y	N	N	N	N	N	N	N	N	1	Perfect agreement
Total Score	**10**	**10**	**5**	**8**	**7**	**4**	**7**	**1**	**5**	.600	Moderate agreement

AMSTAR Questions

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of the publication used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies assessed and documented?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Were potential conflict of interest (for systematic review and included studies) included

3.3.3 Key features of the Reviews

The review components (i.e., question under review, intervention, number and years of databases searched, number of studies included, outcomes included, number of participants included, age and disease duration) are compiled in Table 3.4. An in depth description of interventions in the primary studies compared can be seen in Appendix 3. Below is a summary of the key features of the included reviews:

- Review questions investigated the effects of specific mode of physical activity (e.g., aerobic, resistance, aquatics, Qigong, yoga) in seven reviews, or a specific outcome irrespective of intervention type (i.e., multidimensional function, pain) in two reviews.
- The years searched in the included reviews ranged from inception of the database to 2013 in three reviews [36;37;39], inception to 2009 in Hauser and Ramel [40;41], 'up to Feb 2011' [38] and specific years (1980 to 2008) in Kelley [42] and McVeigh [44] (1990 - 2006). Mist [43] did not specified years of the search.
- The number of databases searched varied between five and 13, and the number of RCTs included ranged from four to 35.
- The population under study was predominantly female adults diagnosed with FM with the exception of Chan [38], Hauser [41] and Mist [43] who each included an RCT involving children (8 to 18 years old).
- RCTs compared an intervention to a control group (e.g., treatment as usual, education, waiting list), a similar type intervention (i.e., strength vs flexibility) either utilizing a similar or a different medium (e.g., water, land); or a non-exercise intervention (e.g., cognitive behavioural therapy, medication).
- Eight reviews investigated the effect of an intervention on multidimensional function [36-39;41-44] with one focussing on multidimensional function exclusively [42]; eight reviews investigated the effect of the intervention on pain [36-41;43;44] with one focussing on pain exclusively [40]. Effects of the intervention on physical function were investigated by six reviews [36-39;41;44]. Adverse effects were reported in six reviews [36;37;39;41;43;44]. The median number of participants included in the reviews was 670 (range from 219 to 2494). This number may not be precise as some authors had companion articles and had counted participants more than once.

- The reporting of age was different among the reviews: some authors reported mean years and standard deviations, others minimum and maximum range, median, etc.
- Duration of FM was not reported in three reviews [39;41;43] and varied from 4 months to 42 years in the remaining reviews.
- Of the 9 reviews two were from Canada [36;37], one from China [38], one from Germany [41], one from England [44], one from Brazil [39], and three from the United States [40;42;43]; all middle to high income countries (the authors' institutional affiliation was used to determine precedence of the review).
- Conflict of interest statement /competing interest / disclosure of funding or financial contribution provided in the following reviews: Bidonde [35], Busch [36], Chan [37], Hauser [40], Kelley [44], Lima, Mist [42], and Ramel [39]. No comments were found in McVeigh [43].

Table 3.4 Characteristics of the Included Reviews.

Review, AMSTAR Score	Focus of Question, Comparator(s)	Search - number of databases, years searched	RCTs Included	Outcomes MDF | PF | Pain | AdE				Number of Participants (female: male)	Age of Part	Disease Duration
Studies with Meta-Analysis										
Bidonde (in press) AMSTAR = 10	The benefits and harms of aquatic (AQ) exercise training in adults with FM; Comparators: a) Control, b) land-based, c) other AQ	9, Data base inception to Oct 2013	16	✓	✓	✓	✓	881 (866:15)	46.3 to 48.3 years	12 years (6 to 24)
Busch 2013 AMSTAR = 10	The benefits and harms of resistance exercise training (RET) in adults with FM; Comparators: a) Control, b)FX, c) AE	9, Data base inception to Oct 2013	5	✓	✓	✓	✓	219 (no males)	Means (SD): 37 (6) to 60.2 (2.5) years	3.85 (SD 3.31) to 12.4 (4)
Hauser 2010 AMSTAR = 8	The efficacy of different types and volumes of AE in FM; Comparator: Control (AE, MX, FX, ST, Biof, SMT, ED, CBT, Bal, Relax, qigong)	5, Through 2009	34	✓	✓	✓	✓	2494[c] (most studies are composed of females)	Median of the mean ages: 45 (range 13-59)	Not reported

Review, AMSTAR Score	Focus of Question, Comparator(s)	Search - number of databases, years searched	RCTs Included	Outcomes MDF | PF | Pain | AdE				Number of Participants (female: male)	Age of Part	Disease Duration
Kelley 2010 AMSTAR = 7	The effects of exercise on global well-being using a single instrument ; Comparators: a) Control(TAU+ comp/ED)	6, 1980 - 2008	7	✓				473 (467:6)	18-73 min to max age	8 to 24 years
Lima 2013 AMSTAR = 4	The effectiveness of aquatic physical therapy in the treatment of FM; Comparators: a) Control, b) land-based, c) other	12, 1950-Dec 2012	18	✓	✓	✓	✓	1265[c,d]	Not included in aggregate form	Not reported
Mist 2013 AMSTAR = 1	Effects of land based and alternative medicine FM exercise studies; Comparators: a) Control+ED+daily activities, b) wait list, c) ED+control, d) control+home exercise program	5, Unclear	Sep-16	✓	✓	✓	✓	832[c]	Not included in aggregate form	Not reported

Review, AMSTAR Score	Focus of Question, Comparator(s)	Search - number of databases, years searched	RCTs Included	Outcomes MDF | PF | Pain | AdE			Number of Participants (female: male)	Age of Part	Disease Duration
Ramel 2009 AMSTAR = 5	The efficacy of exercise on pain relief in patients with FM; Comparator: Control+ED+FSHC	8, Data base inception to Mar 2009	10			✓	767 (752:15)	47 (18-75) average years	3 to 42 years
Studies without meta-analysis									
Chan 2012 AMSTAR = 6	The effects of Qigong exercise for patients with FM; Comparators: Education/support, waiting list, daily activities and aerobics	13, up to Feb 2011	4	✓	✓	✓	251[c]	8 to 73 min-max range	1 article average of 10 years
McVeigh 2008[b] AMSTAR = 7	The effects of hydrotherapy in the management of FM.; Comparators: Control, land-based	10, 1990-2005/6	4 / 10	✓	✓	✓	183 (515:57)	18-72 min-max range	5.4 months to 42 years

Bidonde [36], Busch [37], Chan [38], Hauser [41], Kelley [42], Lima [39], McVeigh [44], Mist [43], and Ramel [40]

[a] Mist included 16 studies but only 9 were RCTs and were examined for this review;

[b]McVeigh included 10 studies but only 4 were RCTs with an exercise component and were examined for this review.

[c]A female:male breakdown was not provided.

[d]Primary and companion studies included – participants' count may not be accurate.

AE: aerobic, AdE: adverse effects, Comp: composite, FX: flexibility, Meds: medication, MX: mixed exercises, MDF: multidimensional function, PF: physical function, SMT: Self-management treatment.

3.3.4 Other important components of the nine reviews

Bidonde review [36]

Definition of the intervention: Aquatic exercise was defined as exercise conducted in a vertical position where participants spent more than50% of the time in water. The interventions were mixed (i.e., two or more components such as flexibility, strength) *Stratification (subgroup analysis and long term effects):* Inspection of the (meta) analyses showed that the authors tried to control for clinical heterogeneity by pooling studies based on similar interventions. The analyses were stratified as follows:

1.Comparison1 (aquatic vs control): Aquatic was compared to a traditional control group (e.g., treatment as usual) or a specialized type of control (e.g., education, soaking in water with no exercise). Bidonde noted the following decisions regarding meta-analyses: for Gowans 2001 [49] the data collected at six weeks (phase of the intervention when participants spend more than 50% of the time in the water) were used, for Mannerkorpi 2009 [50] only data for FM condition only were used, and data from Ide 2008 [51] was excluded after noting clinical heterogeneity confirmed using sensitivity analysis.

2.Comparison 2 (aquatic vs land): Aquatic interventions were compared to similar interventions on land. Meta-analyses were performed for pain (n=4) and physical function outcomes (n=2). Bidonde excluded one study [52] from meta-analyses based on skewness of the data as reported in RCT publication.

3.Comparison 3 (aquatic vs other type of aquatic): included two different and unique comparisons that took place in the water. No meta-analysis was possible due to the heterogeneity of the interventions. Both studies reported results for MDF and pain and only one reported effects on physical function.

Subgroup analysis: Subgroup analyses were carried out for:

a) Participant related characteristics: 1) Age: younger vs old age; 2) Disease duration: short vs long disease duration; 3) Impact of the Disease: low vs high impact of FM; 4) Pain: low vs high pain at baseline;

b) Intervention related characteristics: 1) Length of the intervention; 2) Accumulated time: 3) Frequency: 4) Intensity; 5) Pool Temperature.

Long Term effects: Analyses were provided for wellness (multidimensional, self-reported, physical function), symptoms (pain, tenderness, stiffness, and fatigue) and physical fitness (strength, endurance, cardiorespiratory maximal, and cardiorespiratory submaximal).

Statistical heterogeneity was controlled in the aquatic vs control group by the sensitivity analysis and by using a random effects model. The researchers described the number of studies in each comparison group was insufficient to test for publication bias (less than 10 studies in each comparison).

Conclusions: Bidonde concluded that there was low to moderate quality evidence that aquatic training is beneficial for improving multidimensional, pain, and physical fitness in adults with FM. Authors also concluded that there is very low to low quality evidence suggesting that there were no differences in benefits between aquatic and land-based exercise. Regarding adverse effects, authors stated that no serious adverse effects resulting from aquatic training were reported in any of the included RCTs.

Busch review [37]

Definition of the intervention: Resistance training intervention was defined as exercise performed against a progressive resistance (loading) with the intention of improving muscle strength, muscle endurance and/or power.

Stratification: Busch presented three comparisons: resistance vs control, resistance vs aerobics, and resistance vs flexibility. Studies in each stratum were clearly similar therefore presenting low risk of clinical heterogeneity. Authors stated too few studies were found to undertake publication bias analysis.

Conclusions: Busch concluded that there is low quality evidence that moderate to high intensity resistance improves MDF, physical function or pain in women with FM. Busch concluded that there is low quality evidence that aerobic is superior to moderate intensity resistance for improving MDF in women with FM. There is low quality evidence that

low intensity resistance is superior to flexibility exercise training in women with FM for improvements of pain and MDF. There is low quality evidence that women with FM can safely perform moderate to high intensity resistance.

Chan review [38]

Definition of the intervention: Chan's included studies presented different types of Qigong. Qigong was defined as "a general term for a large range of traditional Chinese energy exercises and therapies and a form of Chinese medical practice" Chan later added that there are two forms of Qigong, "*internal Qigong* which is self-directed and involves the use of movements, meditation an control of breathing pattern whereas *external Qigong* is usually performed by a trained practitioner using their hands to direct qi energy onto the patient for treatment."

Stratification/subgroup analysis: none

Conclusion: The authors acknowledged there was great variability in the dosage and the quality of the Qigong exercise across studies. Chan concluded that "it is still too early to draw a conclusion about the effectiveness of Qigong exercise for FM" (p 646). Authors acknowledged average sample size in the studies was low, increasing the probabilities of type II errors, and intention to treat analysis was only used in one RCT, suggesting the possibility of bias existing in included studies. A source of clinical heterogeneity in this review may have been introduced by including participants of any age (one study including children) [53]. In addition, selective publishing and reporting may be a major cause of bias on the included studies.

Hauser's review [41]

Definition of the intervention: Aerobic exercise was defined as a protocol in which: a) at least 50% of the training sessions consisted of aerobic exercise, b) "the reported target heart rate was at least 40% maximum heart rate (HR_{max})"or the exercise involved "at least one-sixth of the skeletal muscles", and c) the length of aerobic exceeded the time with other types of exercise the time spent stretching and/or strengthening in mixed exercise protocols.

The authors presented main characteristics of the studies including length and intensity of the aerobic intervention. However, documentation of synthesis of the above characteristics (i.e 40% HR max, one-sixth of skeletal muscles involved or more than 50% aerobic in mixed exercise interventions) remains unclear. For example, in Martin 1996, exercise included 20 minutes of aerobic and 20 minutes of either strength or flexibility. It is, unclear how benefits of the intervention could be attributed solely to the effects of aerobic exercise.

Stratification (and subgroup analysis): Aerobic interventions were compared to a control group or between land-based vs water-based. In this review 'control' was loosely defined and included things like therapy as usual, non-supervised pool activities, strengthening exercises, education, biofeedback, usual care, cognitive behavioural therapy, supervised relaxation, supervised stretching, and hot packs among others.

Subgroup analysis for the effect on pain at post treatment included:

a) Type of exercise (land-based, water based, mixed), b) type of exercise (aerobic only, aerobic combined with other exercise), c) duration of the intervention (less than 7 weeks, 7 to 12 weeks, more than 12 weeks), d) frequency of training, e) total duration aerobic exercise, f) intensity of aerobic, and g) type of control group.

Hauser evaluated statistical heterogeneity, the impact of risk of bias in primary studies on effects of aerobic and mixed exercise (sensitivity analysis) and the potential for publication bias. No evidence of publication bias was found in this review. Although statistical heterogeneity was ruled out, it is quite likely that there was considerable clinical heterogeneity present in the meta-analyses (e.g., including studies of participants of 'any age' led to inclusion of one study of children).

Conclusion: Hauser and colleagues concluded that an aerobic programme for individuals with FM should consist of land-based or water-based exercises of light to moderate intensity, two or three times per week for at least four weeks and that the patient should be motivated to continue exercise after participating in an exercise programme. Although Hauser assessed the quality of individual studies, there is no direct reference to study quality in author's conclusions.

Kelley review [42]

Definition of the intervention: The interventions were "exercise only intervention group (aerobic, strength training, or both), community-accessible exercise intervention defined as those interventions that could be performed and made available to non-institutionalized persons in community settings, and exercise intervention of at least four weeks…"

Conclusions: Kelley concluded that exercise improves multidimensional function in women with FM and that research in men and optimal exercise programs are needed. Although Kelley assessed the quality of individual studies, it did not appear to have been considered in stating these conclusions. By reducing the outcome measure to one, Kelley helped reduce measurement heterogeneity. However, Kelley included a study [54] that had not published criteria for the diagnosis of FM – which increases heterogeneity of the pooled interventions. Furthermore, there is a risk of increased clinical heterogeneity by combining different modes of exercise. Kelley's results provided evidence that exercise improves multidimensional function; however the review adds little our understanding of the optimal intervention for fibromyalgia due to the heterogeneity of the interventions evaluated.

Lima's review [39]

Definition of the intervention: Lima did not provide either the definition of 'aquatic physical therapy' or the time participants spent in the water. Despite calling the intervention 'physical therapy' the reader is left wondering why and what operational definitions author used.

Stratification (and subgroup analysis): Inspection of the (meta) analyses showed that the authors tried to control for clinical heterogeneity by pooling studies based on similar interventions. Lima used a fixed or random effects statistical model for meta-analysis according to the heterogeneity of the pooled studies.

The analyses were stratified as follows:

1.Comparison 1 (Aquatic vs no treatment) is partitioned into three sub-comparisons according to length of the intervention. This comparison shows aquatic mixed interventions – with two or more components - compared to controls (e.g., groups receiving treatment as usual or specialized types of controls like education). Meta-analyses were performed for several outcomes including pain, MDF, and physical function.

2.Comparison 2 (aquatic vs land) shows aquatic mixed interventions – with three components (i.e. aerobic, flexibility, strength) – compared to similar interventions on land. Meta-analysis was performed on pain variable. One of the studies included in this comparison [52] presents data in interquartile ranges. The authors did not mention how they have dealt with the skewedness of the data in their analysis.

3.Comparison 3 (aquatic vs other) shows six different and unique comparisons. No meta-analysis was possible due to the heterogeneity of the interventions.

Subgroup Analysis: Lima evaluated aquatic vs control for durations of a) 4-8 week, b) 9-20 weeks, and c) more than 20 weeks.

Follow up Analysis: An aquatic vs control follow up analysis of two studies was included by Lima. These studies were formed by two diverse interventions.

Conclusion: Lima concluded that an aquatic 'physical therapy' intervention of 20 weeks or longer was effective for three outcomes when compared to the control group. Author suggests the studies reviewed have a high risk of bias showing flaws in allocation concealment, blinding of the assessors and analysis. Researchers highlighted the lack of standardization and variety of outcome measures utilized, the variation of the exercise programs, time of follow up and incompleteness of the information played a role in providing accurate results.

McVeigh's review [44]

Definition of the intervention: McVeigh defined hydrotherapy as interventions in which 50% of the time is spent in the water; however, structured physical activity or exercise training was not a required component of the intervention. McVeigh's included 4 RCTs

with an exercise intervention (aerobic, strength and flexibility compared to control, land intervention and education). Ziljstra's study [55] (who included an exercise intervention) was not considered in this review as this author's design is not an RCT.

Stratification/subgroup analysis: none

Conclusion: The researchers stated that the heterogeneous nature of the interventions prevented them from conducting a meta-analysis and their conclusions were general without differentiating between studies with or without exercise. McVeigh concluded that there was strong evidence for the effectiveness of hydrotherapy in the treatment of FM with improvement in pain, health status, and tenderness even though the authors stated that "most studies failed to report or include an ITT analysis or conceal treatment allocation" pg 125. McVeighs' conclusion highlights the use of "hydrotherapy" and acknowledges the heterogeneous nature of the interventions reviewed which prevents the researchers from making specific recommendations. Although, the quality of individual studies was assessed they were not considered in stating these conclusions.

Mist's review [43]

Definition of the intervention: Exercise was defined as "planned, structured physical activity whose goal is to improve one or more of the major components of fitness – aerobic capacity, strength, flexibility, or balance" pg 248 Complementary and alternative medicine was defined as a "group of diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine" (pg 248).

Stratification: Mist presented four groups.

Qigong: In the first group, six Qigong intervention studies were combined including a mixed of Qigong and mindfulness, internal and external, a home program, Qigong by itself and combined with body awareness compared to control, daily activities or education. It should be noted that one study included children increasing the clinical heterogeneity of the sample.

Tai Chi: the second group investigated the effects of tai chi intervention and included five studies; two of which were RCTs with eight and 10 forms each vs education and control.

Yoga: yoga interventions were investigated next– only one RCT was included in this group of three; the study combined yoga with mindfulness vs a wait list control group.

Other: 3 studies were included with one RCT addressing a Pilates intervention vs a control home exercise program.

Conclusion: Mist included two study designs -- RCTs and time series trials designs, thereby introducing increased heterogeneity and made it problematic to understand the effects of the combined studies. In spite of the potential for heterogeneity, meta-analysis was performed for Qigong, tai chi, yoga and other interventions. Forest plots are presented for each exercise modality; however, we are uncertain what outcomes the authors have used to present their meta-analysis.

Mist has identified a number of potential interventions for the management of FM, however, caution is needed while considering Mist's results as part of the body of knowledge of FM and physical activity at the present time. There are important methodological issues in this review that need the authors' attention before we can entertain the idea of arriving at conclusions regarding the effectiveness of these interventions.

Ramel's review [40]

Definition of the intervention: Ramel's question led to the inclusion of RCTs that reported original data comparing exercise versus usual care, education and wait list controls and which measured a specific outcome (pain). Authors acknowledged the heterogeneity in treatment type and duration.

Stratification/subgroup analysis: none

Conclusions: Ramel concluded that six to 24 weeks of strength training, pool, and multi-component exercises may be helpful in the management of pain. Although this finding is

important, the heterogeneity of the included studies adds little to our understanding of what intervention is more likely to reduce pain in individuals with FM. Despite the methodological limitations, the quality of the studies was rated as moderate; their meta-analysis supports the evidence that physical activity may have a positive effect on pain relief in adults with FM in the short term. Assessed quality of individual studies was considered in stating these conclusions.

3.3.5 Overlap

A total of 60 RCTs were included in these nine reviews; 29 (48%) of them overlapped among reviewers and 31 (52%) were 'unique' or reviewed only by one author.

The overlap by review is presented bellow and also and also in Table 3.5:

- Bidonde [36] included 16 RCTs; nine overlapped with Hauser, three with Kelley, 14 with Lima, four with McVeigh; and two with Ramel.
- Busch [37] included five RCTs; one overlapped with Hauser and one with Ramel.
- Chan [38] included four RCTs, one of which overlapped with Hauser and three with Mist
- Hauser [41] included 35 RCTs; nine overlapped with Bidonde, one with Busch, one with Chan, six with Kelley, eight with Lima, two with McVeigh, and seven with Ramel.
- Kelley [42] included seven RCTs, three overlapped with Bidonde, six with Hauser, three with Lima, one with McVeigh, and two with Ramel.
- Lima [39] included 18 RCTs, 14 overlapped with Bidonde, eight with Hauser, three with Kelley, four with McVeigh, and two with Ramel.
- McVeigh [44] included 10 studies, only those RCTs that included exercise (n=4) were examined in this review: four overlapped with Bidonde, two with Hauser, one with Kelley, four with Lima, and two with Ramel.
- Mist [43] included 16 studies but only nine RCTs were considered in this review: three studies overlapped with Chan.

- Ramel [40] included 10 RCTs, two overlapped with Bidonde, one with Busch, seven with Hauser, two with Kelley, two with Lima, and two with McVeigh.

Table 3.5 Number of RCTs overlapped among reviews.

	Bidonde (in press)	Busch 2013	Chan 2012	Hauser 2010	Kelley 2010	Lima 2013	McVeigh 2008[a]	Mist 2013[b]	Ramel 2009
	n = 16	n = 5	n=4	n = 35	n = 7	n = 18	n = 4/10	n=9/16	n = 10
Bidonde (in press)		0	0	9	3	14	4	0	2
Busch 2013	0		0	1	0	0	0	0	1
Chan 2012	0	0		1	0	0	0	3	0
Hauser 2010	9	1	1		6	8	2	0	7
Kelley 2010	3	0	0	6		3	1	0	2
Lima 2013	14	0	0	8	3		4	0	2
McVeigh 2008[a]	4	0	0	2	1	4		0	2
Mist 20013[b]	0	0	3	0	0	0	0		0
Ramel 2009	2	1	0	7	2	2	2	0	

[a]McVeigh included 10 studies but only 4 RCTs with an exercise component were included in this review.
[b]Mist included 16 studies but only 9 RCTs were included in this review.
Bidonde [36], Busch [37], Chan [38], Hauser [41], Kelley [42], Lima [39], McVeigh [44], Mist [43], and Ramel [40]

3.3.6 Data synthesis

3.3.6.1 Main findings of RCTs on systematic reviews:

The effects of physical activity interventions (mean differences and SMD results reported for intervention vs control group only) were quantified as mean differences or SMDs with 95% confidence intervals (i.e., meta-analyzed) in seven reviews, reported in terms of significance testing in two reviews, and measured but unclearly reported in one review. Results are presented for pain, multidimensional function, physical function outcomes (Table 3.6) and attrition and adverse effects (Table 3.7 and 3.8).

Pain: Results of four meta-analyses show (significant and positive) effects on pain. The magnitude of the effects varied as follows: Hauser [41] included 21 RCTs in their analysis and found a small statistically significant effect for aerobic - mixed exercise interventions (SMD = -0.31 [-0.46,-0.16]); Ramel [40] included 10 RCTs of aquatic mixed, land mixed, strength, aerobic and composite interventions and also found a small statistically significant effect on pain

(SMD = 0.45 [0.09, 0.80]), Bidonde [36] found a moderate statistically significant effect for aquatics interventions vs control (SMD = -0.53 [-0.76,-0.31], seven RCTs), and Busch [37] reported non-statistically significant effect for resistance training vs control (SMD = -1.89 [-3.86, 0.07], two RCTs). The two reviews without meta-analysis [38;44] reported the effect on pain as being inconsistent for Qigong (three RCTs, Chan) and 'positive' for hydrotherapy (four RCTs with pool based exercise, N = 135). With the exception of Qigong and resistance, the evidence supports benefits of exercise training (of multiple kinds) for pain reduction.

Multidimensional Function: Four reviews meta-analyzed this outcome and one presented data for one study. Reviews reported effects favouring the intervention as the following: a small statistically significant effect for aerobic - mixed exercise (SMD = -0.40 [-0.60, -0.20], 24 RCTs, [41]); a small statistically significant effect for exercise of any type (SMD = -0.34 [-0.53,-0.14], five RCTs, [42]; and a moderate statistically significant effect for aquatic exercise (SMD = -0.55 [-0.83, -0.27], seven RCTs, [36]). Busch [37] and Lima [39] both reported large statistically significant effects; Busch [37] found only one RCT which evaluated exercise training on multidimensional function (SMD = -1.27 [-1.83, -0.72) and Lima [39] three RCTs (MD = -1.35 [-2.04, -0.67]). Chan [38] found inconsistent results for the effects of Qigong on multidimensional function (three RCTs); while McVeigh [44] reported 'positive effects' for hydrotherapy with exercise in three of four RCTs. Thus, with the exception of Qigong, seven reviews found positive results for physical activity interventions on multidimensional function for individuals with FM.

Physical Function: Four reviews presented a meta-analyses of the physical function outcome and reported the following effects: small statistically significant effect for aquatic exercise (SMD = -0.44 [-0.76, -0.11], five RCTs, self-reported physical function [36]), a moderate statistically significant effect for aerobic - mixed exercise (SMD = -0.52 [-0.66, -0.37], 15 studies, any measure of physical fitness,[41]), a moderate statistically significant effect for resistance exercise (SMD = -0.50 [-0.89,-0.11], three RCTs, self-reported physical function), and a large statistically significant effect for aquatic physical therapy (MD = 43.55 [3.83, 83.28], two RCTs, 6 minute walk test [39]). Chan [38] did not find any significant effect of Qigong on physical function (two RCTs) while McVeigh [44] reported 'significant effects' were found in physical function (three RCTs). Although there are limitations in how this outcome was

measured and reported, evidence on exercise interventions (i.e. aquatic, resistance, aerobic, mixed or new to FM) gives us confidence to express that there are benefits for individuals with FM with regards to physical function.

Attrition and Adverse effects

Attrition, or the reduction of the number of participants in research, occurs when cases are lost from a sample over time which consequently leads to loss of data and potential bias [56]. Reasons for withdrawal from the RCTs in these reviews are summarized in Table 3.7. Reporting of adverse effects in these reviews has not been described systematically and in a standardized way (see Table 3.8). Given that the reporting of adverse effects is so patchy in this body of literature, attrition or withdrawals (number of study participants who drop out and reasons) may temporarily serve as an indication for potential harms derived from the interventions until adverse effects get reported comprehensively.

Table 3.7 Results of analyses of attrition as reported in the included reviews.

Bidonde (in press)	"All cause attrition rates were not higher for aquatic exercise training intervention than for comparators."
Busch 2013	"Based on evidence across all included studies…attrition rates are not higher for resistance intervention than for comparators. There were no statistically significant differences between attrition rates between the interventions"
Chan 2012	"…details of dropouts and withdrawals were described in all included RCTs. In two RCTs ITT analysis was planned but was not performed due to high dropout rates…" (pg 645)
Hauser 2010	16 studies reported attrition rates, with a median of 67% (range 27 to 90%) (pg 6)
Kelley 2010	"the percentage of dropouts ranged from 5.6% to 46.7% in the exercise groups and 0% to 63% in the control group"(pg 5)
Lima 2013	Not reported
McVeigh 2008	Three studies failed to specify if all participants completed the study and two studies had dropout rates of 22.7% and 21.8%
Mist 2013	"…832 participants were enrolled in 16 studies and 81% completed the studies without differential attrition by study arm or exercise modality"
Ramel 2009	High dropout rates may be an important issue as a couple of trials with high dropouts found insignificant changes to pain (pg 192)

Bidonde [36], Busch [37], Chan [38], Hauser [41], Kelley [42], Lima [39], McVeigh [44], Mist [43], and Ramel [40]

Table 3.8 Results of analyses of adverse effects as reported in the included reviews

Chan 2012 Kelley 2010 & Ramel 2009	No comment or reports on adverse effects
Bidonde (in press)	"When considering the evidence of adverse effects and attrition rates in the 16 included studies, individuals with FM were able to perform supervised aquatic exercise training safely. However, given the low number of studies and the lack of detail provided by authors on adverse effects, the evidence should be taken with caution."
Busch 2013	In general, adverse effects were poorly recorded, but no serious adverse effects were reported. "Only two of the three studies provided information on adverse effects of resistance training. Valkeinen 2004 reported "after the initial phase of training, the patients did not complain of any unusual exercise-induced pain or muscle soreness" (p 227). Kayo 2011 reported that no instances of attrition due to adverse effects were observed during the study. Hakkinen 2001 did not report on adverse effects. Bircan 2008 stated, "no patient experienced musculoskeletal injury...during the intervention" (p.529). Jones indicated there were "no adverse events or injuries during the intervention" (p. 1045). However, Jones 2002 further stated "six participants (3 per group) experienced a worsening of one or more of the following pain measures: FIQ VAS for pain, total myalgic score, and number of tender points"
Hauser 2010	"11 studies reported on side effects. Five studies reported that no side effects occurred, and six studies reported an increase of symptoms leading to a drop out in some cases. Only 6 patients assigned to aerobic were designated to have an adverse events possibly related to exercise (metatarsal stress fracture, plantar fasciitis, ischialgia, transient knee pain) pg 6. Side effects were inconsistently reported. No definitive statement on the safety of aerobic in FM is therefore possible.
Lima 2013	"adverse events/reactions or side effects related *to the use of the pool* were mentioned in some studies as: muscle pain, tinea pedis, chlorine hypersensitivity, and exacerbation of the concomitant illnesses" (page 901)
McVeigh 2008	" two (studies) reported no side effects and three reported adverse effects including mild and transient rash, sunburn and mild gastroenteritis and a deterioration in shoulder function" (page 125).
Mist 2013	"..only one study reported negative side effects (increased shoulder pain and plantar fasciitis) in two study participants (Lynch). All studies reported that there were no serious adverse events" (pg257)

Bidonde [36], Busch [37], Chan [38], Hauser [41], Kelley [42], Lima [39], McVeigh [44], Mist [43], and Ramel [40].

Table 3.6. Results of meta-analyses of intervention vs control on pain, multidimensional function and physical function as reported in the included reviews.

Author	Intervention	**Pain.** SMD [95% CI], effect size descriptor[a] (number of studies, number of participants)	**Multidimensional Function.** SMD /MD [95% CI], effect size descriptor[a] (number of studies, number of participants)	**Physical Function.** SMD /MD [95% CI], effect size descriptor[a] (number of studies, number of participants, test)
Reviews having Meta-analysis				
Bidonde (in press)	Aquatics Exercise	SMD -0.53 [-0.76,-0.31], moderate effect favouring the aquatic exercise (7, 382)	SMD -0.55 [-0.83,-0.27], moderate effect favouring the aquatic exercise (7, 367)	SMD -0.44 [-0.76,-0.11], small effect favouring the aquatic exercise (5, 285, self-reported physical function)
Busch 2013	Resistance Exercise	SMD -1.89 [-3.86, 0.07], large effect favouring RET (2, 81)	SMD -1.27 [-1.83,-0.72], large effect favouring RET (1, 60)	SMD -0.5 [-0.89,-0.11], moderate effect favouring RET - (3 studies, N =107, SRPF)
Hauser 2010	Aerobic and Mixed	SMD -0.31 [-0.46,-0.16], small effect favoring exercise (21, 484)	SMD -0.40 [-0.60, -0.20], small effect favouring the exercise (24, 587)	SMD -0.52 [-0.66, -0.37], moderate favouring the intervention (15, 429, any measure of physical fitness)
Kelley 2010	Exercise (any mode)	n/a	SMD -0.34 [-0.53,-0.14], small effect favouring exercise (5, 332)	n/a
Lima 2013	Aquatic Exercise	Outcome measured but data not provided	MD -1.35 [-2.04,-0.67], large effect favouring aquatic intervention (3, 118)	MD 44.55 [3.83, 83.28], favouring the intervention (2, 88, 6MWT)
Mist 2013	Mode newly applied to FM	Outcome measured – unclear reporting	Outcome measured – unclear reporting	Outcome measured – unclear reporting
Ramel 2009	Exercise (any mode)	SMD 0.45 [0.09,0.80], small effect favoring exercise (10, 513)	n/a	n/a
Reviews having qualitative synthesis only				
Chan 2012	Qigong	Inconsistent findings in 2 studies: not significant in one study (SF36 bodily pain with N= 128), and significant improvement in one study (VNS with N = 57)	Inconsistent findings in 3 studies: not significant in two studies (FIQ with N= 128, SF36 with N = 36), and significant improvement in one study (QOL with N = 57)	Non-significant findings in two studies (6 MWT N = 128, Chair test N = 36)
McVeigh 2008[b]	Hydrotherapy	Positive effects in two studies: (VAS with N = 35, FIQ VAS with N = 69)	Positive effects in 3 studies (FIQ with N = 46, FIQ with N = 69, EQ-5D with N = 35), and not significant in one (FIQ with N = 44)	Positive effects in 3 studies (6 MWT with N = 46 and N = 69, Isokinetic strength with N = 35, and grip strength with N = 44)

[a] Cohen's categories [31][b] only four primary studies considered.
6MWT: 6 minute walk test; AE: aerobic; AQ: aquatic; CI: confidence interval; EQ-5D: health status questionnaire; FIQ: fibromyalgia impact questionnaire; HRQOL/QOL health related quality of life or quality of life; n=number of

studies included; N=number of participants included; RET resistance exercise training; SF-36: short form 36 (test); SMD: standardized mean difference; SRPF: self-reported physical function; VAS: visual analogue scale
Authors: Bidonde [36], Busch [37], Chan [38], Hauser [41], Kelley [42], Lima [39], McVeigh [44], Mist [43], and Ramel [40]

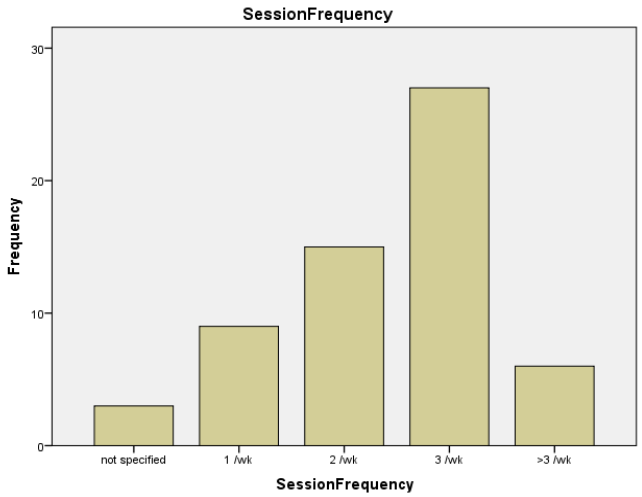
3.3.6.2 Parameters: Frequency, Intensity, and Duration

The research evidence to date supports the effectiveness of exercise in the management of FM. However, it is unclear what are most appropriate parameters supporting these interventions. This has led to uncertainty when prescribing and recommending exercises for individuals with FM in clinical practice. The following section presents important information for clinicians regarding exercise prescription for FM: first, a synthesis (including 60 RCTs) of commonly known exercise parameters such as frequency, intensity, time (length in weeks or minutes) that respond to questions like how often, how long, how hard the exercise should be performed. Second, we present sub-group comparisons carried out by three review authors highlighting effects of the interventions in this umbrella review outcomes of interest.

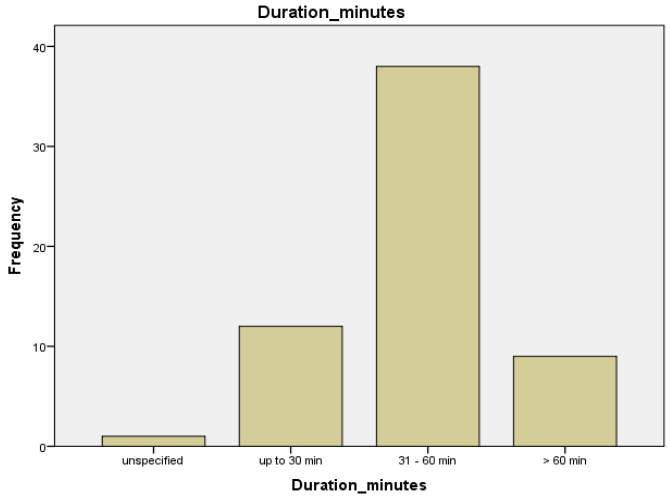
A detailed look at exercise parameters of interventions for all included studies showed that majority were performed three times a week, at a moderate intensity, between 31 to 60 minutes for a period between seven to 12 weeks. The break down descriptive information for each parameter is summarized below (Table 3.9).

Frequency of exercise (sessions per week) of the 60 RCTs showed a clear pattern with majority exercising two (n=15) and three (n=27) times a week. Some authors did not specify how many times a week (n=3); while few exercised one time a week (n=9) or more than three times a week (n=6) (see Figure 3.2a).

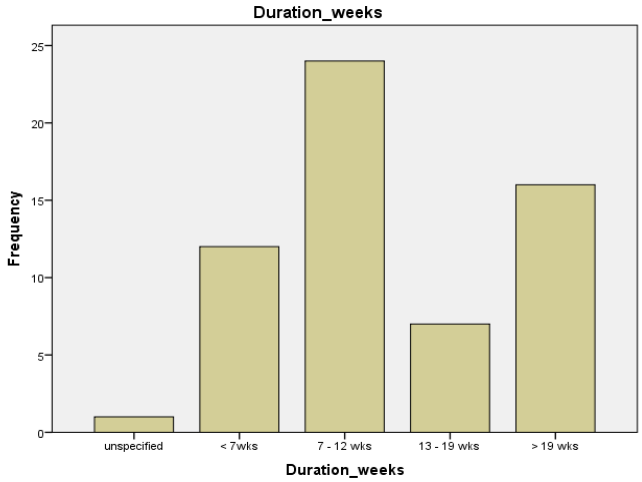
Intensity of exercise was classified following the ACSM percentage heart rate max (% HR_{max} - very light less than 57, light 57-63; moderate 64-76; vigorous 77-95) categories. If the intensity was given as either a numerical or written range (i.e. 60-75 % HR_{max}, low to moderate) we calculated the average number to place the study within a category. The intensity was unspecified in 12 studies, not applicable such as the use of Qigong in six studies, self-determined in six studies, very light in three studies, light in two studies, moderate in 25 studies, and vigorous in six studies.



a. Frequency of exercise (sessions per week)



b. Session duration (time in minutes of exercise per session)



c. Length of the intervention (in weeks)

Figure 3.2. Exercise parameters in the RCTs included in the nine reviews.

Session duration (time in minutes of exercise per session) was unspecified in one study; less than 30 minutes in 12 studies; between 31 and 60 minutes in 38 studies, and lasting more than 60 minutes (sometimes combined with other modalities) in nine studies (see Figure 3.2b).

Length of the intervention (in weeks): The median number of weeks for the 60 RCTs was 12 weeks (range: 3 to 34); 12 RCTs exercised individuals less than seven weeks; 24 RCTs between 7 and 12 weeks; seven RCTs between 13 and 19 weeks and 16 RCTs' length was higher than 20 weeks (see Figure 3.2c).

Table 3.9. Exercise parameters of included RCTs.

RCT Author/year	Review(s)	N	Exercise Frequency (x/week)	Int. Length (minutes)	Intensity %HR_{max}	Duration (weeks)	Follow up	Pool Temp
Alentorn-Geli, 2008 [57]	Hauser	24	2	90	unspecified	6		
Altan 2004 [58]	Bidonde, Hauser, Lima	50	3	35	67.5	12	12 weeks	37 C
Altan 2009 [59]	Mist	50	3	60	n/a	12	24 weeks	
Arcos Carmona 2011 [60]	Bidonde	53	2	60	40	10		28 C
Assis 2006 [52]	Hauser, Lima Bidonde	60	3	60	67.5	15		28-31C
Astin 2003[61]	Chan, Mist	128	1	60	unspecified	8	16 & 24 weeks	
Bircan 2008 [62]	Busch, Hauser	30	3	40	unspecified	8		
Buckelew 1998 [63]	Hauser	119	1	135	65	6	12 weeks, 1 year & 2 years	
Calandre 2009[64]	Bidonde, Lima	81	3	60	individual need	6	10 & 18 weeks	36 C
Carson 2010-12*[65;66]	Mist	53	6	35	n/a	8	12 weeks	
Cedraschi 2004 [67]	Lima	164	2	90	self-determined	6	24 weeks	34 C
Da Costa 2005 [68]	Ramel, Kelley, Hauser	79	unspecified	90	58	12	36 weeks	
De Andrade 2008 [69]	Bidonde, Lima	46	3	60	68	12		28-33C outdoor
De Melo Vitorino 2006 [70]	Bidonde, Hauser, Lima	38	3	60	unspecified	3		unspecified
Etnier 2009 [71]	Hauser	16	3	60	60	18		
Evcick 2008 [72]	Bidonde, Hauser, Lima	63	3	60	unspecified	5	19 weeks	33 C
Fontaine 2007 [73]	Hauser	48	6	20	68	12		
Gowans 1999 [74]	Lima, McVeigh	45	2	30	65	6		warm pool

RCT Author/year	Review(s)	N	Exercise Frequency (x/week)	Int. Length (minutes)	Intensity %HR_{max}	Duration (weeks)	Follow up	Pool Temp
Gowans 2001-02-04 [49;75;76]	Kelly, Lima, Houser, Bidonde	51	3	30	67.5	23		unspecified
Gusi 2006 [77-80]	Ramel, Hauser, Lima, McVeigh, Bidonde	35	3	60	70	12	12 weeks	33 C
Haak 2008 [81]	Chan, Mist	57	1	75	n/a	7	16 weeks	
Hakkinen 2000-02 [82;83]	Ramel, Busch	21	2	not provided	n/a	21		
Hecker 2011 [84]	Bidonde, Lima	24	1	60	40	23		32-34 C
Ide 2008 [51]	Bidonde, Lima	40	4	60	unspecified	4		32 C
Jentoff 2001 [85]	Bidonde, Hauser, Lima, McVeigh	44	2	60	70	20	24 weeks	34 C
Jones 2002 [86]	Busch	68	2	60	n/a	12		
Jones 2008 [87]	Hauser	165	3	60	66.5	24		
Jones 2012 [88]	Mist	101	2	90	n/a	12		
Kayo 2011 [89]	Busch	60	3	60	55	16	12 weeks	
King 2002 [90]	Kelley, Hauser	152	3	25	66.5	12	12 weeks	
Kingsley 2005 [54]	Kelley	29	2	30	79.5	12		
Lemstra 2005 [91]	Ramel	79	unspecified	12.5	70	6	60 weeks	
Liu 2012 [92]	Mist	14	3	87.5	unspecified	6		
Lynch 2012* [93]	Mist	100	7	50	unspecified	8	16 & 24 weeks	
Mannerkorpi 2000[94]	Bidonde, Lima, McVeigh, Ramel	69	1	35	self-selected	24		unspecified
Mannerkorpi 2004[95]	Chan, Mist	36	1	20	unspecified	12		
Mannerkorpi 2009 [50]	Bidonde	166	1	45	70	20	48 weeks	33 C
Martin 1996 [96]	Hauser	60	3	60	76	6		
McCain 1988 [97]	Hauser	42	3	50	86	20		
Mengshoel 1992 [98]	Ramel, Hauser	35	2	60	79.5	20		

RCT Author/year	Review(s)	N	Exercise Frequency (x/week)	Int. Length (minutes)	Intensity %HR_{max}	Duration (weeks)	Follow up	Pool Temp
Meyer 2000 [99]	Hauser	21	3	21	76	24		
Munguia Izquierdo 2007/08 [100;101]	Kelley, Hauser, Lima, Bidonde	60	3	26.5	65	16		32 C
Nichols 1994 [102]	Hauser	24	3	20	66.5	8		
Noregaard 1997 [103]	Hauser	38	3	40	70	12		
Ramsay 2000 [104]	Hauser	74	1	60	unspecified	12		
Richards 2002 [105]	Hauser	136	2	60	70	12	1 year	
Rivera Redondo 2004 [106]	Hauser, Lima	40	5	45	76	8	24 weeks and 1 year	
Rooks 2007 [107]	Ramel, Hauser	135	2	60	self-determined	16		
Schachter 2003 [108]	Ramel, Kelley, Hauser	143	4	17.5	79.5	16		
Sencan 2004 [109]	Hauser	60	3	40	unspecified	6	6 weeks	
Silva 2008 [110]	Lima	10	unspecified	50	unspecified	unspecified		
Stephens 2008 [53]	Hauser, Chan	30	3	30	70	12		
Tomas-Carus 2007-08 -09 [111-114]	Hauser, Lima, Kelley, Bidonde	30	3	60	62.5	34		33 C
Valim 2003 [115]	Hauser	76	3	45	70	20		
Valkeinen 2004-05 [116;117]	Busch	26	2	75	76	21		
Valkeinen 2008 [118]	Ramel, Hauser	26	1	45	76	21		
VanSanten 2002 [119]	Hauser	129	3	50	self-selected	24		
Van Santen2002b [120]	Hauser	37	3	50	86	23		
Wang 2010 [121]	Mist	66	2	60	n/a	12	24 weeks	
Wigers 1996 [122]	Ramel, Hauser	60	3	45	66.5	14	4.5 year	

N=number of individuals randomized in the study; n/a = not applicable; HR_{max} = Heart rate maximum; x/week = times per week;
Reviewed by: Bidonde [36], Busch [37], Chan [38], Hauser [41], Kelley [42], Lima [39], McVeigh [44], Mist [43], and Ramel [40]

3.3.6.3 Findings: Sub-Group comparisons on exercise parameters

Three reviews (Bidonde [36], Hauser [41] and Lima [39]) presented subgroup comparisons on exercise parameters (frequency, intensity, accumulated time of the intervention and length of the interventions) with SMDs and confidence intervals. Bidonde and colleagues [36] presented additional sub-group analysis by age, duration of FM disorder, impact of the disease at baseline, and baseline pain. These sub-group analyses are not presented here. Sub-group analysis was conducted for the aquatic vs control group in Lima [39] and Bidonde's review [36], and was not specified in Hauser's review [41]. Although these results are very promising, they are often based on a small number of studies and need to be interpreted with caution.

Analysis of the frequency of the interventions (see Table 3.10) showed that the more days exercising the more benefits were gained by individuals; exercising three times/ week showed significant results in all three outcomes (MDF, PF and pain) moderate effects were reported in Bidonde's [36] outcomes (MDF, PF, and pain) and a small effect for pain in Hauser's analysis [41]. However, one and two times/week also showed significant results with small and moderate effects for MDF and pain. Assuming these individuals were deconditioned at baseline, it is not surprising that adding a day or two of physical activity will produce changes in symptoms. There were no studies exercising more than three times/week in Bidonde's review [36] and no significant results were found by Hauser (results not shown) [41].

Table 3.10. Sub-group analysis: Effect of frequency of training on pain, multidimensional function and physical function in Hauser [41] and Bidonde [36]. Values presented in SMD [95% CI] (number of studies included in the analysis).

	Outcome	**No studies**	**1time/week[a]**	**2time/week[a]**	**3time/week[a]**
Bidonde	MDF	2,0,5,0	-0.34[-0.65, -0.03]	N/A	-0.64[-0.93, -0.35
Bidonde	PF (ST)	1,0,3,0	NS	N/A	0.74 [0.31, 1.16]
Bidonde	Pain	1,1,4,0	-0.39[-0.65, -0.12]	-0.59[-1.14, -0.04]	-0.63[-1.08, -0.17]
Hauser[b]	Pain	1,2,8,2	NS	-0.69[-0.95, -0.27]	-0.35[-0.62, -0.09]

MDF: multidimensional function; PF: physical function; ST: strength; NS = not significant N/A = not applicable
[a]Values expressed as positive/negative following the direction of the measurement tool. In the case of MDF and pain lower values means improvement, in the PF (ST) higher values means improvement.
[b]Hauser presents study arms; we have estimated the number of studies by dividing that number by half.

Intensity of the intervention (Table 3.11) was reported by Bidonde [36] and Hauser [41] using the same units of measurement (%HR_{max} and self-selection) but applying a different division. While Hauser [41] divisions were self-selected, very low intensity (i.e. less than 50% HR_{max}) and low to moderate intensity (i.e. 50 to 80% HR_{max} or what he called more than 50% HR_{max}), Bidonde [36] used self-selected and the ACSM's criteria (i.e. very light less than 57%, light 57-63%, etc.).

Overall, when the intensity of exercise was self-selected, a small effect for pain with similar values (and number of studies) was found in Hauser [41] and Bidonde [36]; no significant results for MDF and PF were reported by Bidonde [36]. Hauser [41] reported no significant effects for pain when the intensity was set to less than 50% HR_{max}, and small effects for pain when the intensity was set more than 50% HR_{max}; Bidonde [36], however, reported a moderate effect for pain when the intensity was set very light (less than 57% HR_{max}) and a large effect for both moderate (64-76% HR_{max}) and light to vigorous intensities (57-95% HR_{max}). Bidonde [36] reported a large effect on MDF when the intensity was from light to moderate (57-76% HR_{max}) and no significant results for intensities set from light to vigorous (57-95% HR_{max}) and moderate (64-76% HR_{max}) (results not shown). In the physical function outcome (strength), Bidonde [36] reported a large effect when the intensity was set from light to moderate (57- 63% HR_{max}) and a moderate effect for moderate intensity (64-76% HR_{max}).

It should be noted that while interpreting and presenting results regarding intensity, intensity is typically set in ranges (i.e. from 60 to 80 % HR_{max}). In this case, we shall assume participants started at 60% and progressed to 80% through the course of the intervention, but authors seldom report details of the intensity progression, monitoring results of HR, and/or whether the participants reached the target intensity.

Table 3.11. Sub-group analysis: Effects of exercise intensity on pain, multidimensional function and physical function in Hauser [41] and Bidonde [36]. Values presented in SMD [95% CI] (number of studies included in the analysis).

				Very light[b]	**Light[b]**	**Moderate[b]**	**Vigorous[b]**
	Outcome	**No studies**	**Self-Selected[b]**	**<57 HR_{max}**	**57-63 HR_{max}**	**64-76 HR_{max}**	**77-95 HR_{max}**
Bidonde	MDF	2, 0, 2	NS	N/A	-0.89 [-1.40, -0.38]		
	MDF	1			NS		
	MDF	2				NS	
Bidonde	PF (ST)	1,2	NS		1.17 [0.39, 1.96]		
	PF (ST)	2				0.56[0.05, 1.06]	
Bidonde	Pain	2,1,0, 1	-0.41 [-0.72, -0.10]	-0.59 [-1.14, -0.04]		-0.82 [-1.53, -0.12]	
	Pain	2			NS		
	Pain	1			-1.12 [-1.71, -0.54]		
Hauser[a]	Pain	2,1,10	-0.42 [-0.77, -0.07]	NS	>50% -0.26 [-0.42, -0.11]		

MDF= multidimensional function, PF=physical function, ST = strength, NS = no significant; N/A = not applicable
[a]Hauser: study presents study arms; we have estimated the number of studies by dividing that number in half.
[b]Values expressed as positive/negative following the direction of the measurement tool. In the case of MDF and pain lower values means improvement, in the Physical Function (ST) higher values means improvement.

Bidonde [36] and Hauser [41] carried out subgroup analyses on the effects of exercise duration (<1000 minutes, 1000 to 2000 minutes, > 3000 minutes) and found that longer intervention (more than 2000 minutes) yielded the best results in terms of MDF, physical function and pain (Table 3.12).

Three systematic reviews (Bidonde [36], Hauser [41] and Lima [39]) analyzed the effects of the intervention by length in weeks (Table 3.13). Hauser [41] and Bidonde [36] had the same divisions (less than seven weeks, seven to 12 weeks, and more than 12 weeks) while Lima's [39] subgroups were set at 4 to 8 weeks, 9 to 20, and more than 20 weeks. Lima's results [39] were presented in mean differences; we transformed the data presented in the reviews to standardized mean differences using RevMan computer software [123] for ease of comparison. Table 3.13 presents the standard mean differences and its magnitude (interpretation) by length of intervention in weeks.

Table 3.12. Sub-group analysis: Effect of total duration in minutes of exercise (session/week x weeks) in minutes on pain, multidimensional function and physical function in Hauser [41] and Bidonde [36]. Values presented in SMD [95% CI] (number of studies included in the analysis).

	Outcome	Number of studies[a]	<1000 minutes	1000 to 2000 minutes	> 2000 minutes
Bidonde	MDF	2,2,3	-0.48[-0.91, -0.05]	-0.33[-0.64, -0.01]	-0.75[-1.12, -0.38]
Bidonde	PF (ST)	2,0,2	NS	N/A	1.04[0.51, 1.57]
Bidonde	Pain	2,2,3	-0.52[-0.90, -0.13]	-0.32[-0.64, -0.00]	-0.82[-1.24, -0.41]
Hauser[a]	Pain	5,4,4	-0.47[-0.86,-0.08]	-0.36[-0.59,-0.13]	NS

MDF = multidimensional function; NS = not statistically significant; N/A = not applicable, PF = physical function; ST = strength.

[a]Values expressed as positive/negative following the direction of the measurement tool. In the case of MDF and pain lower values means improvement, in the PF (ST) higher values means improvement.

[b] The unit of analysis in Hauser was "study arm". To estimate the number of studies for Hauser, we have assumed there were two arms in each study.

Table 3.13. Sub-group analysis: Effect of duration in weeks on multidimensional function, physical function, and pain in Bidonde [36], Hauser [41], and Lima [39].

Duration	Multidimensional Function	Physical Function	Pain
Short			
4 - 8 wks	--	L: NS	L: NS
< 7 wks	B: NS	B: NS	H: large, -1.16 [-1.86, -0.48] (1)
Medium			
7 - 12 wks	B: large, -0.82 [-1.28,-0.36] (2)	B:large, 0.93 [0.22, 1.64] (2)	H: small, -0.24 [-050, -0.02] (6) B: small, -0.49 [-0.84, -0.14] (3)
9 - 20 wks	L: NS	--	L: NS
Long			
12+ wks	B: moderate, -0.52 [-0.90, -0.14] (4)	B: moderate, 0.63 [0.20, 1.06] (3)	H: small, -0.24 [-0.40, -0.08] (6) B: moderate, -0.54 [-0.80, -0.29] (4)
20+ wks	L:moderate, -0.77 [-1.15,-0.39] (3)	L: small, 0.46 [0.04, 0.89] (2)	L: NS

Values presented in SMD [95% CI] (number of studies included in the analysis). NS = not statistically significant; B=Bidonde [36], H=Hauser [41] L=Lima [39]

[a]Values expressed as positive/negative following the direction of the measurement tool. In the case of multidimensional function and pain lower values means improvement, for strength higher values means improvement

[b]Hauser presents study arms; we have estimated the number of studies by dividing that number in half.
[c] Cohen's categories on magnitude of effect <.2 no effect, .2 to .49 small effect, .5 to .79 moderate effect, ≥ .8 large effect.

Pain was analyzed by the three authors. Hauser [41] was the only one reporting a large effect for the short period (one study). Bidonde [36] and Hauser [41] reported small effects for the seven to12 week period and Lima's results were not significant in the 8-20 period. While Hauser [41] has a small effect for those interventions larger than 12 weeks (six studies), Bidonde [36] reported a moderate effect (four studies) and Lima [39] found no significant results (three studies). This is quite surprising given that Bidonde [36] and Lima [39] overlap in 14 studies.

As promising as the above sub-group analysis might appear to be, we should be aware that the analyses were conducted differently and therefore what is presented contains intrinsic differences. For example, Bidonde [36] indicated the use of change score values in the meta-analysis; Hauser [41] did not specify what was used by stating that "standardized mean differences were calculated by means and standard deviations or change scores for each intervention (pg 3)" and Lima [39] did not specify what was used in their analysis. Despite the overlap in the number of studies among these three authors, this can explain some of the discrepancies in the results.

Looking at the classification and grouping of interventions in these reviews, it may be reasonable to think that by reducing clinical heterogeneity and combining interventions of similar characteristics, as well as standardizing reporting and outcomes a more defined and specific knowledge associated to the outcomes under investigation may emerge. Despite the disparity and variance in the results of the included studies, most findings stress the merits of exercise training in the management of FM.

3.4 Discussion

To our knowledge this is the first umbrella systematic review in the area of physical activity and FM. This umbrella systematic review identified 13 reviews of physical activity for adults with FM. Of these, nine systematic reviews (including 60 RCTs and 3816 participants) met the selection criteria and were included in the synthesis of best evidence. Given the clinical and methodological heterogeneity of the reviews, we decided it was inappropriate to combine

them statistically. Nevertheless, the main finding of our synthesis shows there is substantial and convincing evidence that exercise training of diverse modes (i.e., aquatic, resistance, aerobic, mixed physical activity interventions) improves pain, multidimensional and physical function outcomes for individuals with FM. Conversely, the evidence is inconclusive for new (to FM) modalities of exercise interventions for FM (i.e. yoga, Pilates, TaiChi) due to paucity of research in the area and methodological flaws.

Failure to include operational definitions, a weakness of some of these nine reviews, creates ambiguity regarding the 'effectiveness' of the 'intervention'. Given this weakness and other methodological limitations (i.e. lack of a priori design, scientific quality used in formulating conclusions, provision of included and excluded studies), conclusions remain tentative; there is need for a common classification and description of the interventions. The evidence suggests that exercising in 'moderation' may yield benefits for people with fibromyalgia. Most interventions had a frequency of three times a week, lasted 31 to 60 minutes, were performed at an intensity of light to moderate, and had a duration of more than seven weeks. Sub-group analyses were performed in three reviews with a small number of included studies. These analyses are very promising as this type of information advances our knowledge about the specific details of the interventions. Exercise performed with a light to moderate (57 to 76% HR_{max}) intensity is effective for multidimensional function, physical function and pain. Very light intensity as well as self-selected intensity had smaller effect sizes but were also effective. A frequency of three times a week was effective for all outcomes (MDF, PF and pain); this was true for 2 times a week for pain and one time a week including MDF for interventions. A pool temperature of 33 to 36 was effective for MDF, PF, and pain. Pain also improved when exercise was done in water temperatures between 27 and 32 degrees Celsius.

Adverse event reporting is a critical element of RCTs publications as this helps guide the implementation of new therapeutic approaches in clinical practice. Poor reporting of adverse events can cause overestimation or underestimation of the effect of an exercise intervention leading to incomplete or erroneous messages to individuals with FM and their care providers. Adverse events' reporting in the FM and exercise area is still weak; the reporting is often suboptimal and unstandardized. Meanwhile, attrition rates should help to uncover adverse events. Withdrawals can occur due to life events (e.g. lack of childcare, work related reasons),

intervention-related events (e.g. injury) or disease specific events (e.g. exacerbations of symptoms). Important information on adverse events can be gleaned from participants' withdrawals and reasons often reported by authors. It would be expected that both the control and intervention group would have withdrawals due to life event and disease-related reasons; however, the intervention group will also sustain withdrawals for intervention specific reasons. Thus, the differences between the attrition rates in the control and the intervention groups can be seen as an indicator or be attributed to adverse events. If this assumption is valid, the differences between attrition rates could be used as an indication for adverse events. While some authors reported no differences in attrition between training intervention and comparators [36], others presented the information in percentages that ranged from 6% to 90% [41-44]. We encourage researchers (and journals) to adopt a standardized adverse reporting system and apply it to publications related to exercise interventions for individuals with FM. Adverse event reporting standards should be established to ensure consistency and provide critical information for clinicians and decision making professionals to monitor the symptoms and safety of the interventions.

3.4.1 Methodological Concerns

These nine reviews were published relatively close in time, so predictably we found there was 48% RCTs overlap among them which means researchers are accessing the same pool of articles. There were, however, 52% 'unique' (or reviewed only by one author) RCTs of which a great percentage corresponds new (to FM) modalities (i.e. yoga, Pilates, TaiChi). While overlap can occur at any of the PICO levels (i.e. population, intervention, comparators, outcome) this review only explored how often a publication was reviewed by authors.

The degree of overlap in the separate reviews is a function of the overlap in the review questions. Indeed, if two reviews were to have identical questions, one would expect a complete overlap and lack of congruence would point to flaws in the search and selection process. The ability to replicate results strengthens our confidence in the results; therefore, one could argue that in these reviews there is a degree of replication of reviews (represented by the overlap), despite different methods of critique and analysis. Although each author contributed to the overall understanding of the field, these overlap shows emerging issues of construct and internal

validity. Whilst an overlap may be unavoidable, this might raise the question of whether systematic reviews can be relied upon to reflect the state of the evidence. Also, such discordance might cause difficulties for decision makers (including clinicians, policymakers, researchers, and individuals with FM) and loss of trust on systematic reviews. More concerning than the issue of overlap is that some reviews "double counted" individual studies or failed to distinguish between the primary publication (the one that reports the results of the primary outcomes) and secondary publications (where other aspects of randomized trial's findings are published). We found evidence for this error in four reviews. In some reviews, a study was double counted thus distorting the results of the synthesis of results (count of subjects, meta-analysis).

Due to methodological limitations of these reviews and their intrinsic differences we decided that it was inappropriate to combine the information statistically. Undertaking a meta-analysis would only be appropriate if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure answers are clinically meaningful. Some of the included reviews did not follow or did not present clear and sound principles of combining data in a meta-analysis. In our view, this reduces the validity, credibility and precision of the cumulative knowledge on FM and physical activity interventions based on methodologically different reviews. Transparent and clear review conduct and reporting will result in higher quality reviews that might facilitate statistically combination of data in the future.

3.4.2 Evidence Based Practice

An important observation refers to confidence in results presented in systematic reviews, their direct applicability to clinical settings, and their potential to influence evidence based practice. In 2003, Van Tulder, a member of the editorial board of the Cochrane Back Review Group, stated, "systematic reviews represent one of the key advances in medical science in the past 10 years and offer the real opportunity to lead to changes in medical practice worldwide." The classification of levels of evidence which are generally accepted designate results of systematic reviews at the top of the hierarchy of evidence [124]. This umbrella systematic review found that there has been an increase number of RCTs publications for aquatics, aerobics and mixed exercise interventions, and new forms of exercise interventions for FM like Qigong, tai chi, Pilates, etc. Due to the growing number of reviews in this area we were able to confirm

that there is a need, to synthesise the information in the physical activity and FM field. We find this growth in reviews to be both timely and logical given the number of RCTs published in the last decades. Yet, according to our findings, a number of review articles in the area were medium to low quality. In agreement with Moher [16] we found inconsistency in the quality the reviews and a significant difference between "Cochrane reviews and non-Cochrane reviews in the quality of reporting several characteristics." This is a concern given the preferential status and degree of influence that SRs have on evidence based decisions in health care. As the number of individual studies are gathered and presented in review articles, we believe that it is critical for those who produce systematic reviews to strive for the highest standard of quality; we fear, otherwise, is type of evidence are a disservice as they will mislead clinicians, clinical guidelines developers, granting agencies, people with FM, and other relevant decision makers.

Integrating the results from the quality of the evidence to results from the quantitative/descriptive analysis strengthens the conclusions and recommendations of reviews. All reviews evaluated and documented the quality of the included studies but only two [36;37] reminded readers of the quality of the included studies in formulating conclusions. Seven reviews [38-44] failed to account for sources of potential biases, imprecision, or other methodological dangers in their conclusions. Furthermore, the use of generic call to action from researchers in some of the included reviews is problematic. This is represented mostly by an end phrase such as "future large, long-term, rigorous…studies are needed…" [40] "more studies of longer duration and better quality are needed…." [42], "further rigorously designed RCTs are required …" [38]. Reporting related of areas that need to be addressed will help the research on FM and physical activity to move forward; clearer and specific directions from researchers/reviewers are required.

3.4.3 Strengths and Limitations of the study

There are several strengths of this umbrella systematic review. First, we used a comprehensive search strategy, developed and implemented by a health science librarian as part of a larger project examining the effectiveness of physical activity interventions for individuals with FM. Second, duplicate screening and quality assessments were conducted. Third, a validated instrument (AMSTAR) was used to assess the methodological quality of included reviews. Fourth, we retrieved data from the reviews as well as primary studies to obtain a broad

view of the field. Although we only found a small number of systematic reviews (9), we were able to identify and extract detailed descriptions of interventions from 60 RCTs included in the reviews.

Clinicians, and individuals with FM, would like to know the optimal features of an exercise program; unfortunately, given the nature of the research available, we were unable to make specific recommendations. However, results of sub-group comparisons are promising and begin to shed some light on exercise parameters (i.e. types, intensities, frequencies of diverse exercise training modalities) and their relative effectiveness. The number of studies included in the sub-group analysis is small, so it is possible results do not represent all people with FM and may need revision as further research accumulates.

When it comes to exercise preferences, we know that one size does not fit all so it is important to understand effects of different modes of exercise, as well as the effect of the intervention across sub-groups within those with FM. Factors such as severity of disorder, co-morbid conditions, and age, as well as variable levels of access to facilities, equipment and/or instruction in various types of exercise modality may influence the adoption and planning of exercise interventions. We have provided detailed descriptions of the interventions in this body of literature. By scrutinizing the details provided and the results of sub-group analyses the development and provision of more meaningful recommendations for exercise will be possible. Conclusions could not be made on the basis of statistically significant changes and clinical differences, which serve as important foundations of evidence base practice. Thus, our lack of statistical results warrants further reviews carefully considering the interventions (homogeneity of trials and similarity of interventions) combined in this area.

The main weakness of this umbrella systematic review is that the quality of the data upon which it relies was not strong. This umbrella review presented information of all eligible reviews regardless of its quality as assessed using AMSTAR. The pre-existence of high quality reviews with sufficient uniformity of methods and quality of the evidence is needed for an umbrella review to be truly useful in making health care treatment and delivery decisions. Although we believe the information presented is useful, we found, there was insufficient high quality (reviews) evidence regarding physical activity interventions for adults with FM to be confident in their estimates. A difficulty in this umbrella review was to present information of

all eligible systematic reviews regardless of the quality derived from the AMSTAR scores. The AMSTAR tool used in this review, served to evaluate the quality of the reviews but not without its challenges. Further development of this or other tools is necessary.

The potential for biases (reviewer bias, information bias) was present in this review. Every possible effort was made to minimize biases and ensure the validity of our findings. For example, collaboration with the last two authors (BB & SM) bring objectivity and reliability to the information provided, an external reviewer was invited to assess first two authors reviews, last two authors were delegated the task of describing first two authors reviews' interventions. Our goal was to present information and results that accurately represent in the effects of exercise interventions in the target population. It is conceivable that numerous other factors account for variability in the response to exercise (e.g., baseline physical activity, medications, motivation, socio-demographics, culture); however, the ability to discriminate what and how other factors account for the response to exercise was beyond the scope of this project and is potentially an area for future research.

Although we performed a comprehensive literature search, the selection of reviews was limited to the past five years and three languages. The databases searched covered non-English language sources; however the inclusion of further non-English language databases might have helped to identify additional reviews. There was a review published in German that was not included, since none of the authors could translate it. Considering the substantial number of new trials published in this topic over the past few years, it is possible that there are reviews we have not included. Even though reviews should be updated regularly, new studies are constantly published, and most reviews are seldom or never updated. Another issue is that all types of interventions may not be covered by a review, and thus important primary studies/interventions might be overlooked.

3.4.4 Implications for Research

We have used the EPICOT approach to describing implications for future research [125]. We anticipate that results from this umbrella systematic review will inform researchers, guide groups and policymakers on the evidence of the effectiveness of physical activity interventions

in the management of FM. This umbrella review provided the opportunity to inspect not only the reviews but the studies upon which they were conducted. The recommendations below, therefore, deal with not only the conduct of reviews but the provisions of exercise interventions.

Evidence: There were limitations regarding the homogeneity of the reviews that prevented us to meta-analyse the effects of interventions on our outcomes of interest. A better description of research procedures and training protocols of individual RCTs, is needed in future research to address all aspects of potential bias more adequately. Reviewers need to be more explicit about how data has been handled (i.e. SMDs, MDs, change scores, means) and analyzed to allow comparisons among reviews possible.

Population: The nine reviews included mainly middle-aged women living in developed countries, which make findings difficult to generalize to other populations and settings while at the same time brings awareness of the need for studies coming from other parts of the world. If systematic reviews aim to help policy makers, and practitioners to make informed decisions, greater focus should be placed on making the sample representative of the population.

Intervention: More detail and standardization in reporting exercise frequency, duration, intensity, and mode is needed to identify exercise volume more precisely and to determine if the prescribed exercise protocols meet current recommendations as per ACSM guidelines. Researchers undertaking exercise interventions are encouraged to describe physical activity and exercise parameters (i.e. type, intensity, duration) and characteristics of individuals recruited. In other words the assumptions of homogeneity and similarity of interventions have to be considered when combining studies to ensure results are valid and clinically relevant.

Comparators: In this review, several comparators were used and sometimes review authors unintentionally have misguided the readers in their comparisons. Standardization of what constitute a ‘control’ group or ‘head to head’ comparison, etc. is advised. Clarifying the particulars about the comparators will increase the potential for valid findings in the area.

Outcomes: As researchers, we must improve documentation of adverse effects (injuries, exacerbations of fibromyalgia, and other associated adverse effects). Assessment of adherence to frequency and intensity of exercise should be an integral part of the results section of all RCTs

and review articles studying effects of exercise interventions. Further research should aim to elucidate a dose-response relationship. Formal follow-up periods are needed to assess stability of responses, as well as consideration to whether people are exercising and at what volume during follow up. In addition, further work to validate a set of outcome measures for fibromyalgia research, such as has been initiated by OMERACT, is desirable to allow comparisons across studies and elucidation of the more effective interventions. Determination of the minimum clinically important difference and responsiveness of the core measures is also necessary. Finally, the long term effects of exercise training warrants further consideration.

3.4.5 Implications for practice

The interventions reviewed and combined in the included reviews were oftentimes clinically diverse. If future systematic reviews are more precise in evaluating clinical heterogeneity (e.g. specific details of the population and interventions) this may help elucidate the principles of how and what makes physical activity beneficial for individuals with FM and better inform clinical practice. Follow ups (post interventions evaluation) of physical activity on FM were uncommonly found (21/60 studies). The lack of evidence on long term effects of physical activity warrants further investigation.

Any causal relationship between physical activity interventions and adverse effects is not substantiated by current evidence. Adverse events have been loosely reported and the message about harm derived from physical activity for individuals with FM is vague. In agreement with Hauser [41], we believe the creation of a standardized method of reporting adverse effects is necessary. Unfavourable events, increase of FM symptoms, or other signs associated with the use of a particular physical activity intervention need to be systematically documented and reported.

3.5 Conclusion

In conclusion, this umbrella systematic review identified and summarized information from nine systematic reviews and found positive results for diverse exercise interventions on pain, multidimensional function, and self-reported physical function and no evidence of positive results for alternative and complementary physical activity interventions at this point. Adverse effects reported suggested there was no serious harm performing physical activity for individuals

with FM. There are however, methodological weaknesses in some of these reviews which reduce applicability of the research to clinical practice.

Although it appears there are benefits, the lack of specificity prevents us to answer simple questions that health professionals and individuals with FM may ask regarding which particular elements and modes of exercise, as well as doses and frequency of delivery can improve the outcomes of interest.

Finally, the number of review articles is proliferating and thus researchers and reviewers need to consider the rigor and quality of the information being reviewed. As well, consumers of these reviews (i.e. clinicians, individuals with FM) should not rely on the findings and recommendations uncritically.

Conflict of Interest

We confirm that there is no present or past affiliation or other involvement in any organisation or entity with an interest in the Physical Activity and FM Umbrella Systematic Review which might lead me/us to have a real or perceived conflict of interest.

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APPENDICES

Table of Appendices

APPENDIX 1

Search Strategy Results

Database and Coverage	Search Date	Number of references Retrieved	Number of references after Deduplication
Cochrane Library	August 15, 2012		
Cochrane Reviews	Jan 2012 – March 2013	87	83
DARE		21	21
Trials		88	88
Methods Studies		1	1
Technology Assessments		0	0
Economic Evaluations		1	1
Issue 8, 2012			
Ovid Medline(R**)** 2007-2013	August 15, 2012 Jan 2012 – March 2013	151	5
Embase Classic + Embase 2007-2013	August 15, 2012 Jan 2012 – March 2013	126	50
CINAHL 2007-2013	August 15, 2012 Jan 2012 – March 2013	22	21
Web of Knowledge 2007-2013	August 15, 2012 Jan 2012 – March 2013	63	54
PubMed 2007-2013	August 15, 2012 Jan 2012 – March 2013	46	46
Trip database 2007-2013 (www.tripdatabase.com)	August 15, 2012 Jan 2012 – March 2013	29	28
AMED (ovid) 2007-2013	August 15, 2012 Jan 2012 – March 2013	8	8
PEDro 2008 – 2013		4	4
Dissertation Abstracts (ProQuest)		7	0
WHO International Clinical Trials Registry Platform		11	0
	Totals	**665**	**410**

APPENDIX 2

Primary (P) and Companion (C) studies

Author	P/C	Publication Title (English)
Hakkinen 2001 [82]	P	Strength training induced adaptations in neuromuscular function of premenopausal women with fibromyalgia: comparison with healthy women.
Hakkinen 2002 [83]	C	Effects of strength training on muscle strength, cross-sectional area, maximal electromyographic activity, and serum hormones in premenopausal women with fibromyalgia.
Gowans 2001 [49]	P	Effect of a randomized, controlled trial of exercise on mood and physical function in individuals with fibromyalgia.
Gowans 2002 [75]	C	Measuring exercise induced mood changes in fibromyalgia: a comparison of several measures.
Gowans 2004 [76]	C	Six month and one-year follow-up of 23 weeks of aerobic exercise for individuals with fibromyalgia
Gusi 2006 [77]	P	Exercise in waist-high warm water decreases pain and improves health-related quality of life and strength in the lower extremities in women with FM
Tomas-Carus 2007 [79]	C	Aquatic training and detraining on fitness and quality of life in FM
Tomas-Carus 2007 [78]	C	The fibromyalgia treatment with physical exercise in warm water reduces the impact of the disease (Spanish)
Tomas-Carus 2007 [80]	C	Effects of aquatic training and subsequent detraining on the perception and intensity of pain and number of sensitive points in women with FM (Spanish)
Munguia Izquierdo 2007 [100]	P	Exercise in warm water decreases pain and improves cognitive function in middle-aged women with fibromyalgia.
Munguia Izquierdo 2008 [101]	C	Assessment of the effects of aquatic therapy on global symptomatology in patients with fibromyalgia syndrome: A randomized controlled trial.
Tomas-Carus 2007 [112]	P	Exercise in warm water decreases pain but not the number of tender points in women with FM - an RCT (Spanish)
Gusi 2008 [111]	C	Cost-utility of an 8-month aquatic training for women with FM: a randomized controlled trial
Tomas-Carus 2008 [113]	C	Eight Months of Physical training in warm water improves physical and mental health in women with FM: a randomized controlled trial
Tomas-Carus 2009 [114]	C	Improvements of muscle strength predicted benefits in HRQOL and postural balance in women with fibromyalgia: an 8-month randomized controlled trial

APPENDIX 3

Exercise interventions pooled and/or compared by review author

1. Bidonde review [36]: 16 RCTs, three comparison groups

Included Studies	Group 1	Group 2
AQ vs Control		
Altan 2004 [58]	AQ MX (AE+FX+Relax)	Bal
Arcos Carmona 2011 [60]	AQ+Land MX (AE + Relax in land)	Control (placebo Magnet therapy)
Gowans 2001-02-04 [49;75;76]	AQ AE+Land AE	Control (TAU)
Gusi 2006 [77-80]	AQ MX (AE+ST)	Control
Mannerkorpi 2000 [94]	AQ MX (AE+FX)	ED
Mannerkorpi 2009[50]	AQ MX (AE+ FX +Coord) + ED	ED
Munguia Izquierdo 2007 -08 [100;101]	AQ MX (AE+ST)	Control (FM)
Tomas -Carus 2007 [111-114]	AQ MX (AE+ST)	Control
AQ vs Land		
de Melo Vitorino 2006 [70]	AQ Mx (AE +ST+ Relax)	MX (AE+Relax)
Evcick 2008 [72]	AQ MX (AE+FX+Relax)	MX (AE+ ST+ FX+ Relax)
Hecker 2011 [84]	AQ MX (AE+ FX+ROM)	MX (AE+ FX+ ROM)
Jentoff 2001[85]	AQ MX (AE+FX+ST)	MX (AE+ST+FX)
AQ vs AQ		
Calandre 2009 [64]	AiChi (Tai Chi in water)	AQ FX
de Andrade 2008 [69]	AQ AE	AQ (AE) SPA

2. **Busch's review [37]:** five RCTs, three comparison groups

Included Studies	Group 1	Group 2	Group 3
RET vs Control			
Hakkinen 2001-02 [82;83]	RET Fibromyalgia	RET Healthy	Control
Valkainen 2004 - 05 [116;117]	RET Fibromyalgia	RET Healthy	Control
Kayo 2011 [89]	RET	AE	Control
RET vs AE			
Bircan 2008 [62]	RET	AE	
Kayo 2011 [89]	RET	AE	Control
RET vs FX			
Jones 2002 [86]	RET	FX	

3. **Chan's review [38]:** four RCTs included, data not combined statistically

Included Studies	Group 1	Group 2
Astin 2003 [61]	Qigong and mindfulness meditation	Education/support
Haak 2008 [81]	Qigong (Internal and External)	Control (waiting list)
Mannerkorpi 2004 [95]	Qigong plus body awareness	Daily Activities
Stephens 2008 (not adults) [53]	Qigong	AE

4. **Hauser review [41]** : 35 RCTs included, three comparisons presented in this review

Included Studies	Group 1	Group 2	Group3	Group 4
AE vs Control (pain)				
Alentorn 2008 [57]	MX (AE+ FX+ Relax)	Comp (Vib+ MX (AE+ FX+ Relax))	Control	
Altan 2004 [58]	AQ MX (AE+FX+ Relax)	Bal		
Bircan 2008 [62]	AE	ST		
Buckelew 1998 [63]	MX (AE+ST+FX+ Posture +Biomechanics)	Comp (Biof+ Relax+MX (AE+ST+FX, Posture+ Biomechanics))	Biof+Relax	Control (ED/ Attention)
Fontaine 2007 [73]	LPA (likely mostly aerobic)	ED		
Gusi 2006 [77-80]	AQ MX (AE+ ST)	Control		
Jones 2008 [87]	Comp Meds+MX (AE+ ST+FX+Relax)	Meds+Placebo (Diet recall)	Placebo med+MX (AE+ST+FX+Relax)	Control: Placebo Med + placebo Diet recall
McCain 1988 [97]	AE	FX		
Mengshoel 1992 [98]	AE Dance	Control		
Munguia Izquierdo 2007 - 08 [100;101]	AQ MX (AE+ST)	Control (FM)	Control (Healthy)	
Nichols 1994 [102]	AE	Control		
Noregard 1997 [103]	AE	MX (AE+ FX+ ST)	Thermotherapy	
Ramsay 2000 [104]	AE home program	AE weekly supervised		
Rivera Redondo 2004 [106]	AQ+Land MX (AE+ST+FX)	CBT		
Rooks 2007 [107]	MX (AE+FX)	MX (AE+ST+FX)	FSHC	FSHC+MX(ST+ AE+FX)
Schachter 2003[108]	AE long bout	AE short bout	Control (TAU)	
Sencan 2004 [109]	AE	Meds	Control	
Tomas- Carus 2007[111-114]	AQ MX (AE+ST)	Control		
Valim 2003 [115]	AE	FX		
Van Santen 2002 [119]	MX (AE+FX+ST)	Biof	Control	
Wigers 1996 [122]	AE	SMT	Control (TAU)	
AE vs Control (multidimensional function)				
Alentorn 2008 [57]	MX (AE+FX+Relax)	Comp (Vib+MX (AE+FX+Relax)	Control	
Altan 2004 [58]	AQ MX (AE+FX+Relax)	Bal		

Da Costa 2005[68]	AQ+LD MX (AQ AE+ Land AE+ST)	Control (TAU)		
Etnier 2009 [71]	MX (AE+ST+FX)	Control -Delayed entry		
Fontaine 2007 [73]	LPA (likely mostly aerobic)	ED		
Gowans 2001-02-04 [49;75;76]	AQ AE+Land AE	Control (TAU)		
Gusi 2006 [77-80]	AQ MX (AE+ST)	Control		
Ide 2008 [51]	AQ Comp (AE+Relax)	Control (Supervised ~PA Recreational Activities)		
Jones 2008 [87]	Comp Meds+MX (AE+ ST+FX+Relax)	Meds+Placebo (Diet recall)	Placebo med+MX (AE+ST+FX+Relax)	Control: Placebo Med + placebo Diet recall
King 2002 [90]	AE (AQ +/or Land)	Comp AE (AQ +/or Land)+ED	ED	Control
Mannerkorpi 2000 [94]	AQ MX (AE+FX)	ED		
Martin 1996 [96]	MX (AE+ST+FX)	Relax		
Munguia Izquierdo 2007-08 [100;101]	AQ MX (ST+AE)	Control (FM)	Control (Healthy)	
Nichols 1994 [102]	AE	Control		
Noregard 1997 [103]	AE	MX (AE+FX+ST)	Thermotherapy	
Richards 2002 [105]	AE	MX (Relax+ FX)		
Rivera Redondo 2004 [106]	AQ+Land MX (AE+ ST+ FX)	CBT		
Rooks 2007[107]	MX (AE+FX)	MX (AE+ST+FX)	FSHC	FSHC+MX(ST+ AE+FX)
Schachter 2003[108]	AE long bout	AE short bout	Control (TAU)	
Stephens 2008 (~Adults) [53]	AE	Qigong		
Tomas -Carus 2007 [111-114]	AQ MX (AE+ST)	Control		
Valim 2003 [115]	AE	FX		
Valkainen 2008 [118]	MX (AE+ST)	C (AAU)		
van Santen 2002 [119]	MX (AE+FX+ST)	Biofeedback	Control	
AE vs Control (physical fitness)				
Bircan 2008 [62]	AE	ST		
Fontaine 2007 [73]	LPA (likely mostly aerobic)	ED		
Gowans 2001-02-04 [49;75;76]	AQ AE+Land AE	Control (TAU)		
Jones 2008 [87]	Comp Meds+MX (AE+ST+FX+Relax)	Placebo med MX (AE+ST+FX+Relax)	Meds+Placebo (Diet recall)	Control: Placebo Med + placebo Diet recall

King 2002 [90]	AE (AQ +/or Land)	Comp AE (AQ +/or Land)+ED	ED	Control
McCain 1988 [97]	AE	FX		
Noreegaard 1997 [103]	AE	MX (AE+FX+ST)	Thermotherapy	
Rivera Redondo 2004 [106]	AQ+Land MX (AE+ST+FX)	CBT		
Rooks 2007[107]	MX (AE+FX)	MX (AE+ST+FX)	FSHC	FSHC+MX(ST+ AE+FX)
Schachter 2003[108]	AE long bout	AE short bout	Control (TAU)	
Tomas- Carus 2007[111-114]	AQ MX (AE+ST)	Control		
Valim 2003 [115]	AE	FX		
Valkainen 2008[118]	MX (AE+ST)	Control (AAU)		
van Santen 2002 [119]	MX (AE+FX+ST)	Biof	Control	
Wigers 1996 [122]	AE	SMT	Control (TAU)	

5. Kelley's review [42]: seven RCTs included, one analysis

Included studies	**Group 1**	**Group 2**	**Group 3**	**Group 4**
Da Costa 2005 [68]	AQ+Land MX (AQ_AE+ Land_AE, ST)	Control (TAU)		
Gowans 2001-02-04 [49;75;76]	AQ AE+Land AE	Control (TAU)		
Gusi 2006 [77-80]	AQ MX (AE+ST)	Control		
King 2002 [90]	AE (AQ +/or Land)	ED	Comp AE (AQ +/or Land)+ED	Control
Kingsley 2005 [54]	ST	Control		
Munguia Izquierdo 2007 – 08 [100;101]	AQ MX (AE+ST)	Control (FM)	Control (Healthy)	
Schachter 2003[108]	AE long bout	AE short bout	Control (TAU)	

6. **Lima's review [39]:** 18 RCTs included, three comparison groups

Included Studies	Group 1	Group 2
AQ vs Control	4-8 weeks	
Gowans 1999 [74]	Comp (AQ AE+ED)	Control (Wait list)
Gowans 2001-02-04 [49;75;76]	AQ AE+Land AE	Control (TAU)
AQ vs Control	9-20 weeks	
Gowans 2001-02-04 [49;75;76]	AQ AE+Land AE	Control (TAU)
Gusi 2006 [77-80]	AQ MX (AE+ST)	Control
Munguia Izquierdo 2007 -08 [100;101]	AQ MX (AE+ST)	Control (FM)
Tomas -Carus 2008 [111-114]	AQ MX (AE+ST)	Control
AQ vs Control	20 weeks or more	
Gowans 2001-02-04 [49;75;76]	AQ AE+Land AE	Control (TAU)
Mannerkorpi 2000 [94]	AQ MX (AE+FX)	ED
Tomas- Carus 2007 [111-114]	AQ MX (AE+ST)	Control
AQ vs Control / Follow up		
Cedraschi 2004 [67]	Comp ((AQ-AE+Land-based unspec) +Relax +ED)	Control
Gusi 2006 [77-80]	AQ MX (AE+ST)	Control
AQ vs Land		
Assis 2006 [52]	AQ AE	AE
de Melo Vitorino 2006 [70]	AQ MX (AE+ST+Relax)	MX (AE+Relax)
Hecker 2011 [84]	AQ MX (AE+FX+ROM)	MX (AE+FX+ROM)
Jentoff 2001 [85]	AQ MX (AE+ST+FX)	MX (AE+ST+FX)
Evcick 2008 [72]	AQ MX (AE+FX+ Relax)	MX (AE+ST+FX+Relax)
AQ vs Other		
Altan 2004 [58]	AQ MX (AE+FX+Relax)	Bal
(de) Andrade 2008 [69]	AQ AE	AQ-AE SPA
Calandre 2009 [64]	Ai Chi (Tai Chi in water)	FX
Ide 2008 [51]	AQ Comp (AE+Relax)	Control (Supervised ~PA rec activities)
Rivera Redondo 2004 [106]	AQ+LD MX (AE+FX+ST)	CBT
Silva 2008 [110]	AQ MX (AE+FX)	TENS

7. **Veigh's review [44]:** four/10 RCTs with exercise included

Included Studies	Group 1	Group 2
Gowans 2001-02-04 [49;75;76]	AQ-AE+Land AE	Control (TAU)
Gusi 2006 [77-80]	AQ-MX (AE+ST)	Control
Jentoff 2001 [85]	AQ-(AE+ST+FX)	MX (AE+ST+FX)
Mannerkorpi 2000 [94]	AQ-MX (AE+FX)	ED

8. Mist's review [43]: nine RCTs/17 included studies, four comparison groups

Included studies	Group 1	Group 2
Qigon comparison		
Astin 2003 [61]	Qigong and mindfulness meditation	ED/support
Haak 2008 [81]	Qigong (Internal and External)	Control (waiting list)
Liu 2012 [92]	Qigong (home program)	Control (sham Qigong)
Lynch 2012 [93]	Qigong	Control (waiting list)
Mannerkorpi 2004 [95]	Qigong plus body awareness	Daily Activities
Yoga comparison		
Carson 2010-12 [65;66]	Yoga with mindfulness	wait list control
Tai Chi comparison		
Jones 2012 [88]	8-form Tai Chi	ED
Wang 2010 [121]	10 form Tai Chi	control
Other CAM exercises comparison		
Altan 2009 [59]	Pilates	Control (TAU) + home exercise program

9. Ramel's review [40]: 10 RCTs, one comparison

Included Studies	Group 1	Group 2	Group 3	Group 4
Da Costa 2005 [68]	AQ+Land MX (AQ_AE, Land_AE+ST)	Control (TAU)		
Gusi 2006, Tomas -Carus 2007,2007,2007 [77-80]	AQ MX (AE+ST)	Control		
Hakkinen 2001-02 [82;83]	ST (FM)	Control (FM)	ST (Healthy)	
Lemstra 2005 [91]	Comp (MX AE+FX+ST)+ED+ SMC, Massage)	Control		
Mannerkorpi 2000[94]	AQ MX (AE+FX)	ED		
Mengshoel 1992 [98]	AE Dance	Control		
Rooks 2007[107]	MX (AE+FX)	MX (AE+ST+FX)	FSHC	FSHC+MX (ST+AE+FX)
Schachter 2003[108]	AE long bout	AE short bout	Control (TAU)	
Valkainen 2008 [118]	MX (AE+ST)	Control (AAU)		
Wigers 1996 [122]	AE	SMT	Control (TAU)	

CHAPTER FOUR

DISCUSSION AND CONCLUSION

Discussion and Conclusions

4.1 Broad aim and specific objectives

The broad aim of this dissertation was to evaluate the effectiveness of physical activity interventions for individuals with FM with the aim to contribute to a more complete and individualized management of the disorder. Given the complexity of FM and the dearth of research in the area, the specific objectives of this work were formulated considering clinical and methodological issues of emerging research, as well as health delivery and policy implications. Many of these factors were reviewed in chapters one, two and three.

The personal suffering for those with FM and the societal burden of FM are evident. Therefore, the healthcare system has a duty to provide treatment according to the best efficacy data available to date. This dissertation represents an integrated approach to research that was developed as a partnership between the researcher, a team of collaborators (including clinicians) and consumers. Consumers in the team represented the voice, perspective, ideas, interest and values of patients and users of this information; their participation warranted changes that will meet other consumer's interests. Consumers have argued for this research to be relevant and helped in the dissemination of findings prompting the acceptance of it into non-academic settings. Thus, the needs and expectations of stakeholders involved in the creation of the knowledge needed to be considered when planning the objectives, methods and design of the research.

The objectives of this project were: To synthesize the evidence on the effectiveness of: a) Aquatic exercise interventions for adults with FM as reported in RCTs, and b) exercise interventions for adults with FM as reported in systematic reviews. Two approaches were used to achieve the aforementioned objectives: a (Cochrane) systematic review to address the first objective and an umbrella systematic review to address the second objective.

4. 2 Principal Findings

4.2.1 Effectiveness of Physical Activity Interventions for Individuals with FM (Chapter 2 & 3)

Chapter two presented results derived from a Cochrane systematic review aiming to evaluate the benefits and harms of aquatic exercise training in adults with FM. Sixteen RCTs (divided into three groups) examined aquatic interventions, with a total of 866 women and 15 men, and 24 outcomes. Meta-analyses, sensitivity analyses and sub-group analyses were conducted. The quality of the RCTs was evaluated following the Cochrane guidelines and incorporated into conclusion. Aquatic exercise training was compared to control (9 studies), to land exercise training (five studies), and two studies compared two types of aquatic interventions. Low to moderate quality evidence was found to suggest that aquatic exercise training is beneficial for improving wellness, symptoms and fitness and that no serious adverse effects result from the intervention. Very low to low quality evidence suggests that there are no differences in benefits between aquatic and land exercise training except in muscle strength (evidence favoring land) and sleep (one study favoring aquatic). No adverse effects were reported. The aquatic vs other aquatic group (sea vs pool and pool vs pool) yielded a small significant effect on sleep (one study), moderate effect on stiffness (one study) and large effect on depression (one study).

An evaluation and synthesis of systematic reviews of physical activity interventions for adults with fibromyalgia (FM) focussing on four outcomes: pain, multidimensional function (wellness or quality of life), physical function (self- physical function or physical fitness) and adverse effect were presented in Chapter 3. Nine systematic reviews (60 RCTs with 3816 participants) published from January 2007 to March 2013 were included. Meta-analysis was not conducted due to the heterogeneity of the sample, however evidence of positive results of diverse exercise interventions on pain, multidimensional function, and self-reported physical function were found. The evidence for new to FM interventions remains to be understood. Reported evidence on adverse effects showed there was no harm performing physical activity for individuals with FM. The uniqueness of the interventions themselves (the variability of the programs) in the reviews prevented us from answering important clinical questions to guide practical decisions about optimal modes and dosages (i.e. frequency, intensity, duration) of exercise. Finally, the number of review articles is proliferating and thus researchers and reviewers need to consider the rigor and quality of the information being reviewed and presented. As well, consumers of these reviews (i.e. clinicians, individuals with FM and policy makers) should not rely on them uncritically.

4.3 Overall Strength and Limitations

A strength of the work described in this dissertation relates to the comprehensive inclusion and analysis of RCTs and reviews, as well as the inclusion of outcomes of interest recommended by a group of experts in the field of FM formed by clinicians and consumers. This dissertation has made a contribution to the field of physical activity and FM as a result of sound design and strong argumentation supported by current and relevant literature. The findings of this dissertation have elucidated effective physical activity modalities and expand our knowledge of feasible interventions to include in the management of FM.

Another strength of the work is the researcher was able to conduct meta-analyses which permitted the inference of the aquatic exercise training intervention effectiveness compared to control (usual care, wait list, etc.) or a similar intervention carried out on land or water. Although numbers were small, clearer and more practical results regarding optimal features of exercise interventions are starting to emerge after conducting sub-group comparisons.

The first manuscript arose from a collaborative relationship with a highly regarded organization and is undergoing a meticulous peer review and editorial process and, thus, provides soundness and high quality evidence to consumers and health providers. Equally, the second manuscript has undergone detailed scrutiny and considered every possible path to avoid researcher related biases and will be submitted to a peer review journal/process. Consumer involvement in health care is widely recognized. Consumers (people with fibromyalgia) were actively involved in the first study and were consulted at all stages of the review and development of the manuscript. We believe their involvement complemented the perspective of the authors (clinicians and researchers) resulted in a review that is more relevant, readable and understandable to other consumers and certainly see their involvement as a strength of this work.

A weakness of this dissertation (or manuscripts) is the limited number of high quality RCTs and reviews with sufficient uniformity of methods to provide truly useful information and to produce high quality evidence in the area. Even though some of the conclusions could not be made on the basis of statistically significant changes or were not clinically significant, results from this dissertation serve as an important foundation for evidence based practice and warrant further research in the area. In addition to structured supervised physical activity, other factors

such as lifestyle, comorbidities, or baseline physical activity information, were not considered in this dissertation, but may help further the results.

Although physical activity interventions have been shown to have many benefits, the optimal training protocol for achieving benefits in wellness, symptoms and fitness has yet to be determined. It is not known if unsupervised individual or home based programs for individuals with FM would yield the same results as seen in these studies. Although a very comprehensive search strategy was carried out, most of the studies included in chapters two and three are European, North and South American in origin. This may represent a portion of the research in the area available worldwide. Participants in the manuscripts of this dissertation were mostly middle age women. Variables known to provide information about health inequalities (i.e. race, ethnicity, culture, religion, socioeconomic status, education) are not always provided, therefore were not extracted. Thus, our findings are not easily generalized beyond a middle age Caucasian female population. As health professionals aim towards achieving the highest level of health possible for all groups, broadening the spectrum of information in the physical activity and FM will help achieving a desired state of health equity among individuals with this disorder.

Clinical significance speaks of the practical importance of results to consumers (individuals with the disease) and health care providers. Although not many clinical significant results were found, this dissertation has set the groundwork for future studies. As well as, this work was able to point out at gaps in the research. Our results cannot be prescriptive at this point, but they are strong enough to encourage practitioners to continue recommending individuals with FM to exercise.

There are limitations in summarizing evidence. Even though reviews should be updated regularly, new studies are steadily been published, and most reviews are seldom or never updated. Another issue is that all types of interventions may not be covered by a review, and thus important primary studies/interventions might be overlooked.

Although this dissertation focused only on the effectiveness of exercise interventions for individuals with FM, the researcher only used RCTs which is only one type of evidence. To broaden our understanding, additional research designs should be given consideration; attention should be given to synthesis of observational studies and/or qualitative studies. This could

provide data on effectiveness of the interventions over time as well as bring the voice of the participants to light. Different research designs may be able to identify the individual influence of other interventions (pharmacologic, complementary) that occur concurrently in multifactorial complex disorders such as FM. Non-experimental designs such as an observational design might be able to track the onset and progression of adverse events and the incidence of these adverse events, as well as the effects of the intervention on major outcomes that affect individual's quality of life. Qualitative studies may highlight beliefs and worldviews, the insider experience of the disorder, understanding of barriers and facilitators of health behaviours such as the adoption of healthy lifestyle, awareness of access to healthcare and community interventions by vulnerable groups, insight from participants that will help us understand the reasoning behind data to date.

Although the most effective physical activity interventions for FM remains unknown, these nine reviews presented many physical activity options from aquatic, resistance, aerobic to new intervention modalities for individuals with FM. Although beyond the scope of this review, there is important information that can be linked to health care cost. From a health care cost perspective Spaeth [1] showed that a small increase in scores of measurements commonly used in assessing FM symptoms (i.e. FIQ score from 78.9 to 81.5 – while maximum score is 100 and higher values mean worsening of symptoms, one point in the Brief Pain Inventory) increases health care costs. Despite the variability in the results, there was consensus among these reviews that some of these interventions could lead to improvements in multidimensional function, pain and physical function, and, thus, considering the limitations of translating this into clinical practice, the value of physical activity in the management of FM as a cost-effective public health measure should not be unrecognised. Taking a broader view, based on an abundance of health science research reviewed to date clearly shows that regular physical activity promotes good health and helps prevent chronic diseases; these long term health outcomes were not examined in the reviews included in this umbrella review.

4.3 Implications and Future Directions

Several implications for further research arise from this dissertation. We have used the EPICOT approach to describing implications for future research [2].

Evidence: The main role of a non-pharmacological intervention such as physical activity is to help in the management of the disorder by alleviating or improving wellness, symptoms or function. Even though the number of studies described and evaluated in this work was relatively small, the findings of this dissertation will have implications for further research, practice and policy. The evidence of physical activity effectiveness is growing but not conclusive; further research is needed to more fully understand potential mechanisms by which improvements occurred and longer term impacts of the interventions in individuals with FM. As well there are other benefits associated with physical activity such as helping mental health and mood, promoting better sleep, controlling weight, helping or reducing risks of other health conditions, strengthening bones, muscles and preventing falls in older adults, and boost energy [3].

This dissertation presents the first umbrella review in the area of physical activity and FM, however, it is important to acknowledge that this manuscript has set the stage for future similar work and illustrates how to advance high quality work in the area. Furthermore, the Cochrane team with whom the researcher collaborated for the first manuscript is planning an overview of reviews similar to what is described in this work. As this is an ongoing area of research, access to high quality reviews with control or comparison groups that allow meta-analysis of the information is much more desirable. A similar publication to what is presented in this dissertation, with Cochrane reviews only, would provide much more robust evidence of the effectiveness of physical activity interventions for individuals with FM.

A major value of this dissertation is its contribution to FM management. The synthesis of evidence has taken clinician and consumers preferences into consideration, and supports the use of exercise interventions. If evidence from this dissertation ought to be translated into action knowledge needs have to be identified, the knowledge would need to be adapted to the local context, barriers and facilitators identified and also the intervention need to be tailored to specific barriers for change.

Population: Not surprisingly, most of the participants in this dissertation included women who were middle age, Caucasian, and living in developed countries. This limits generalization of

the findings. Other demographic characteristics (family status) settings (general population, clinical settings) socio-economic status, education, and race were not considered.

It is important to remember that individuals who participated in the studies reviewed in this dissertation RCTs did so voluntarily; they were self-selected volunteers. This type of research may attract individuals who believe in the benefits of a physical activity, are involved in community groups, are or have being involved in physical activities, and are emotionally and physically willing to go through interventions such as the ones described in this dissertation. These individuals may differ in important ways from people with FM in general. Last, the emergence of the new diagnosis criteria proposed by the ACR [4;5] may influence the demographic characteristics of individuals with FM participating in research in the future.

In Canada, a country with a universal health system, the management of FM is a key priority as well as the finding of evidence-based strategies to deal with the disorder. Canada, a country inhabited by individuals from diverse ethnic origins, is proud of its diversity. Findings from this dissertation invite improvements in research of diverse sub-populations. This will allow the identification and assessment of the burden of the disorder and lead to successful and meaningful initiatives for such subgroups.

Intervention: Even when is not possible to give specific parameters for exercise effectiveness today, it is essential to work towards a better understanding of factors that facilitate the achievement of desired outcomes among physical activity interventions. Thus, determining potential 'characteristics" (such as time living with the disorder or baseline pain levels) may help to alert clinicians and policy makers to plan optimal care choices that may ultimately yield the desired outcomes. Sub-group analysis has started to shed light on particular characteristics of the interventions that may allow sustainability of them. Determining these characteristics will likely be an important consideration in achieving expected outcomes of an intervention.

Given the limitations of the current research we were unable to present optimal physical activity intervention features for individuals with FM. Appropriate analysis and interpretation of information is only possible if the key attributes/information is described. Standardization of parameters of the interventions, for example, is one area where researchers could have a valuable contribution and role. Insight into the individual's achieved and target goals could help our

understanding of the area as a whole. Furthermore, the information described in this dissertation could be used as an initial point for the creation of standards or guidelines of the effectiveness of physical activity interventions for the management for FM. Physical activity includes activity that 'contract muscles' in a light to moderate intensity and is part of daily life like household (sweeping and cleaning), workplace (lifting boxes, walking or doing stairs), or lifestyle activities (gardening, carrying a basket of groceries or laundry). These activities are less predictable or performed routinely, and may not be sufficiently prolonged or intensive and are more difficult to study, but at a certain threshold, they may be effective in bringing health benefits. Perhaps the prevalence of FM may be reduced in more physically active groups. Exercise – a specific form of physical activity – is performed with the intention of acquiring or improving health benefits and fitness and can be accomplished through activities such as aerobics, strength, flexibility, etc. Although this dissertation focused on exercise training interventions (activities performed with a purpose) it will be interesting to understand how physical activity and exercise correlate in the life of individuals with FM. It may be feasible that by engaging in structured and regular exercise, day to day activities of daily living may improve. Even though this study does not present detailed answers to questions about exercise for FM, it does provide reassuring information for clinicians about effectiveness of some interventions on wellness, MDF, physical function and adverse events.

Outcomes: This dissertation utilized a series of outcomes recommended by OMERACT and individuals with FM [6], and designated some as major outcomes (being the most common) and other ones as minor. Yet the ways outcomes were measured was highly variable which creates difficulties for combining and reporting them. For example pain, it is commonly assessed by the visual analog scale (a scale 100mm or 10cm in length and anchored by the extremes of the characteristics being assessed) but other methods commonly used include short form McGill pain questionnaire [7], sub-scales of questionnaires like the SF-36 [8], FIQ [9] etc. Detailed descriptions of outcome measures used in research need to be included and ideally standardized to facilitate the pooling of the data and assessment of effectiveness of the intervention in a particular outcome of interest.

It is worth mentioning some of the OMERACT outcomes [6] are scarcely reported in the literature. Dyscognition was found only in one of the 16 studies included in the first manuscript

of this dissertation. This is a clear example of a discrepancy between what individuals with FM believe is significant and what researchers have measured in physical activity RCTs.

Adherence to an intervention is critical for its effectiveness. There is now some evidence about possible reasons for withdrawal; however, adherence and adverse effects understanding are important factors to investigate. As research furthers our knowledge about treatment effectiveness, adherence, withdrawal, and adverse effects need to be reported systematically. A clearer understanding of adverse effects and how to prevent them, will help us design interventions addressing specific barriers to achieve expected outcomes.

The researcher hopes findings of this dissertation will be translated and adopted into clinical practice. As health professionals and researchers, our goal is to provide individuals with the best care available. However, the (slow) translation of research findings into sustainable improvements in the clinical settings remains challenging and an obstacle to improving quality of care. A key to this process is the presence of partnerships or collaboration between the researcher, clinicians and consumers, as well as health care organizations in the future. These partnerships strengthen and facilitate discussions on methods, tools and outcomes for achieving the goal of advancing FM and physical activity clinical research translation and implementation. They have also helped to accelerate the impact of the research on health care practice by utilizing different strategies like disseminating knowledge to audiences including practitioners, individuals with FM, and policymakers through workshops, poster presentations, web announcements; identifying information important for health care delivery or supporting the development and refinement of strategies to translate findings of this dissertation into practice. In conclusion, in an era of health care reform, particularly in the area of primary care services, exploring and evaluating traditional and emerging physical activity interventions effectiveness can be of paramount importance for individuals with FM. Researchers must continue to identify factors associated with effectiveness of the interventions in order to better understand the needs of the individuals with FM. There has been much discussion in Canada about the need to engage individuals in physical activity. The results of this dissertation can serve to highlight aspects of how physical activity is key in the provision of a holistic management of FM.

4.4 Reference List

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