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Benjamin Waller

The Effect of Aquatic Exercise on Symptoms, Function, Body Composition and Cartilage in Knee Osteoarthritis

JYVÄSKYLÄN YLIOPISTO

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ABSTRACT

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Knee osteoarthritis (OA) is the most common joint disease associated with pain and loss of functional capacity. The management of knee OA is multifaceted and covers the whole OA continuum from injury prevention to the end stage of the disease. Recently, specific focus has been on preventing the progression of cartilage degeneration and avoiding loss of function in the early phase of the disease via the provision of exercise interventions. Aquatic exercise is a popular but under-researched exercise option. Therefore, the purpose of this dissertation was to investigate the role of aquatic exercise in the management of knee OA, focusing especially the effect it evokes on both functional capacity and biochemical composition of knee cartilage.

Two systematic reviews with meta-analysis were performed. The first investigated the effect of therapeutic aquatic exercise on pain and functional capacity, compared to controls, in individuals with lower limb OA; it included 11 studies. The second review evaluated the effects of aquatic exercise on different aspects of functional capacity, e.g. muscle strength, agility and walking ability, compared to control and land-based exercise, in healthy older adults and included 28 studies. Data from a 4-month randomised controlled trial with a 12-months' follow-up period was used to investigate the effect of a progressive aquatic resistance training program on walking ability, cardiovascular fitness, muscle strength, symptoms and body composition in 87 postmenopausal women with mild knee OA. Furthermore, the effect of the intervention on the biochemical composition of tibiofemoral cartilage was investigated using T2 relaxation time (T2) mapping and delayed gadolinium-enhanced magnetic resonance imaging (dGEMRIC index).

The results of this dissertation revealed that therapeutic aquatic exercise produced a small sized but statistically significant decrease in pain and improvement in walking ability and joint flexibility in individuals with lower limb OA. Compared to control interventions, aquatic exercise significantly improved muscle strength, agility, flexibility, walking speed and aerobic fitness in healthy older adults. Aquatic exercise was at least as effective as land-based exercise at improving functional capacity in healthy older adults. Following 4-months of aquatic resistance training, there was a significant increase in walking speed, improved cardiovascular fitness and a decrease in fat mass. Only improvements in walking speed were maintained at the 12-months' follow-up. Additionally, a small effect in the biochemical composition of the tibiofemoral cartilage was detected post-intervention in both T2 and dGEMRIC index. To conclude, aquatic exercise exerts a positive effect on different aspects of functional capacity in both healthy adults and individuals with knee OA. The effect of aquatic exercise on the composition of cartilage needs to be clarified.

Keywords: osteoarthritis, aquatic exercise, qMRI, cartilage, walking ability

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Dedicated to my girls Hilma, Saimi, Isla and my beautiful wife, Katja.
Love you forever.

"Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it"

Plato

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Jyväskylä 10.11.2016
Benjamin Waller

FIGURES

TABLES

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals. Additionally, some unpublished data are included in the dissertation.

I Waller B, Ogonowska-Słodownik A, Vitor M, Lambeck J, Daly D, Kujala UM, Heinonen A. The effect of therapeutic aquatic exercise on symptoms and function associated with lower limb osteoarthritis. A systematic review with meta-analysis. Physical Therapy 2014; 94(10):1383-95.

II Waller B, Ogonowska-Słodownik A, Vitor M, Rodionova K, Lambeck J, Heinonen A, Daly D. The effect of aquatic exercise on physical functioning in the older adult: A systematic review with meta-analysis. Age and Ageing 2016; 45(5):593-601.

III Waller B, Munukka M, Multanen J, Rantalainen T, Pöyhönen T, Nieminen M, Kiviranta I, Kautiainen H, Selänne H, Dekker J, Sipilä S, Kujala U, Häkkinen A, Heinonen A. Effects of a progressive aquatic resistance exercise program on the biochemical composition and morphology of cartilage in women with mild knee osteoarthritis: protocol for a randomised controlled trial. BMC Musculoskeletal Disorders 2013; 14:82.

IV Waller B, Munukka M, Rantalainen T, Lammentausta E, Nieminen M, Kiviranta I, Kautiainen H, Kujala U, Häkkinen A, Heinonen A. The effects of high intensity aquatic resistance training on body composition and walking speed in postmenopausal women with mild knee osteoarthritis: a 4-month RCT with 12-month follow-up. Submitted for publication 2016

V Munukka M*, Waller B*, Rantalainen T, Häkkinen A, Nieminen MT, Lammentausta E, Kujala U, Paloneva J, Sipilä S, Peuna A, Kautiainen H, Selänne H, Kiviranta I, Heinonen A. Efficacy of Progressive Aquatic Resistance Training on Articular Cartilage: A Randomised Controlled Trial. Osteoarthritis and Cartilage 2016; 24(10):1708-17.
* Equal contribution

ABBREVIATIONS

ACSM	American College of Sports Medicine
ACR	American College of Rheumatology
ADL	Activities of daily living
AE	Aquatic exercise
AGS	American Geriatrics Society
ANCOVA	Analysis of covariance
AQUAREHAB	Research project investigating the effect of aquatic exercise in postmenopausal women with early knee osteoarthritis
BMI	Body mass index
Con	Control
CI	Confidence interval
CSA	Cross-sectional area
CV_{RMS}	Coefficient of variation of the root-mean-square deviation
dGEMRIC	Delayed gadolinium-enhanced magnetic resonance imaging of cartilage
DXA	Dual-energy *X*-ray absorptiometry
ECM	Extra-cellular matrix
ES	Effect size
GAG	Glycosaminoglycan
Gd-DTPA2-	Gadolinium embedded diethylene triaminopentaacetic acid
ICC	Intra-class correlation coefficient
K/L	Kellgren and Lawrence
KOOS	Knee injury and osteoarthritis outcome score
LE	Land-based exercise
LTPA	Leisure time physical activity
mmol/L	Millimoles per litre
METh	Metabolic equivalent task hour
mL	Millilitre
MRI	Magnetic resonance imaging
ms	Millisecond
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PG	Proteoglycan
PCM	Pericellular matrix
qMRI	Quantitative magnetic resonance imaging
QoL	Quality of life
ROI	Region of interest
ROM	Range of motion

RPE	Rating of perceived exertion
RCT	Randomised controlled trial
SD	Standard deviation
SMD	Standardized mean difference
UKK	Urho Kekkonen Centre for Health Promotion Research
$VO2_{max}$	Maximal oxygen uptake
WHO	World Health Organization
WOMAC	Western Ontario and McMaster University Osteoarthritis index

CONTENTS

1 INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of pain and activity limitations for the individual sufferer (Allen & Golightly 2015) and a major factor in the health care budgets i.e. the financial burden of OA on the US economy is equal to 1% of total gross domestic product (Yelin et al. 2007). The development of knee OA progresses slowly over years, often as a result of trauma, but there is a substantial increase in the incidence of symptomatic knee OA in people over 55 years of age (Roos 2005). In the early phase of OA, changes are seen in the biochemical composition of the extra cellular matrix (ECM) of the cartilage. As cartilage degeneration progresses, the biomechanical properties of the cartilage are altered, reducing its ability to resist and distribute tensile, shear and compressive forces, causing further degradation and ultimately joint failure. Development of pain and loss of functional capacity in association with cartilage changes are common but not inevitable (Lawrence, Bremner & Bier 1966). However, some cartilage defects do not progress indicating an ability of cartilage to regenerate (Wang et al. 2006). While cartilage loss is a common characteristic of knee OA, it is best regarded as a whole organ disease, affecting both intra- and extra-articular structures (Goldring & Goldring 2010).

There is currently no known cure or treatment that prevents or reverses the biochemical changes in the cartilage associated with OA. Therefore, the current management focuses on non-pharmacological, pharmacological and surgical treatments (Zhang et al. 2010, McAlindon et al. 2014). Roos and Arden (2016) devised the continuum of knee OA which illustrates the development of knee OA from the inciting event, i.e. trauma at a young age and gradual progression of OA through early OA to end-stage OA (Roos & Arden 2016). The management and prevention of knee OA progression focuses on the known risk factors for the progression of knee OA (Roos & Arden 2016). These risk factors, which are also targets for treatment, include pain, muscle weakness, decreased walking ability, gender, decreased physical activity, excess weight and obesity, and age (van Dijk et al. 2010, Pisters et al. 2012, Holla et al. 2015). Land-based exercise, irrespective of type (strength or aerobic), has been shown to be effective at decreasing pain and reducing body mass as well as improving

functional capacity and lower limb biomechanics (Messier et al. 2013, Bennell et al. 2014, Juhl et al. 2014, Fransen et al. 2015). Additionally, exercise and regular physical activity have been shown to impact on the biochemical composition of tibiofemoral cartilage in healthy people (Van Ginckel et al. 2010, Teichtahl et al. 2009) as well as in individuals at risk of OA development (Roos & Dahlberg 2005, Hawezi et al. 2015) and in post-menopausal women with mild knee OA (Koli et al. 2015). However, pain-modulated avoidance of activities, resulting in decreased functional capacity, has been reported in individuals with knee OA, making land-based exercise sometimes impossible or unlikely to be undertaken (Holla et al. 2014).

Water is a facilitating environment in which persons with knee OA can safely and comfortably exercise, utilising a full joint range of motions, even at higher training intensities not possible or normally recruited on land (Bressel et al. 2014). Land-based neuromuscular training has been shown to prevent knee injuries and improved function in people at risk of knee OA (Gagnier, Morgenstern & Chess 2013, Ageberg & Roos 2015), however, no such evidence exists for aquatic exercise. There is low level evidence that aquatic exercise can improve the functional capacity in healthy older adults (Bergamin et al. 2012). Bartels et al. (2016), in their recent systematic review, claimed that aquatic exercise exerted a similar effect on pain and self-reported functioning as its land-based counterpart in people with hip and knee OA (Fransen et al. 2015, Bartels et al. 2016). Batterham et al. (2011) demonstrated that aquatic and land-based exercises have similar effects on pain, self-reported functioning and mobility (Batterham, Heywood & Keating 2011). Further, there is no systematic evidence that aquatic exercise can improve functional capacity as assessed with performance-based measures in people with hip and knee OA (Dobson et al. 2013). Additionally, there are no studies evaluating the efficacy of aquatic exercise for pain and function nor are there any reports on the biochemical composition of tibiofemoral cartilage in people with mild knee OA. There is some evidence suggesting that land-based exercise can exert a long term effect on people with hip and/or knee OA (Fransen et al. 2015) but limited evidence suggest limited long term benefits from aquatic exercise (Cochrane, Davey & Matthes Edwards 2005, Lund et al. 2008), possibly due variations in the content and intensity of the interventions. One option is the use of resistance boots to progressively increase the training intensity (Pöyhönen et al. 2001a, Pöyhönen et al. 2001b). Aquatic resistance training three times-a-week has been shown to improve significantly physical functioning in healthy older adults (Pöyhönen et al. 2002) as well as in subjects who have undergone knee arthroplasty (Valtonen et al. 2010). Since it is possible to perform high repetition of low compression and shear force movements, highly intensive aquatic resistance training may also have benefits for cartilage health as well as improving the functional capacity in people with knee OA.

The main purpose of this doctoral dissertation was to investigate the effects of 4-months' aquatic resistance training on physical performance, body composition and biochemical composition of femoral cartilage in

postmenopausal women with mild knee OA. A second goal was to determine if these changes would be maintained after 12-months' follow-up. This dissertation also investigated what effect aquatic exercise has on known risk factors for knee OA as well as its progression in healthy older adults, with a specific emphasis on the risk-factors associated with functional capacity. Lastly, aquatic exercise has only been shown to improve certain self-reported outcomes such as pain and functioning, therefore this dissertation investigated the effect of aquatic exercise on physical performance measures in patients with lower limb OA. It is hoped the data collected in this dissertation will encourage physicians to recommend aquatic exercise during the earlier development phases of knee OA.

2 REVIEW OF THE LITERATURE

2.1 The knee joint

The knee is a tri-articular synovial joint consisting of the medial and lateral tibiofemoral joints and the patellofemoral joint. The knee allows motion in two planes; flexion and extension in the sagittal plane and internal and external rotation in the horizontal plane. The knee joint, along with its associated muscles, plays an important role in allowing functional movements such as stair climbing, rising from a chair, walking and running as well as shock absorption and transfer of forces between the tibia and femur. Due to the shape of the articulating bone, i.e. the curved femoral condyles on the distal femur and the flat proximal tibia, the stability and function of the knee relies greatly on the joint's soft tissue (muscle, tendons and ligaments) and its articular structure, i.e. articular cartilage and menisci (Neumann 2002, Threlkeld 2002).

The location and anatomy of the knee expose it to a high risk of damage, either as a direct result of injury or a stress injury due to excessive forces from altered lower limb biomechanics. The cartilage of the knee is a specialised structure that can suffer from both types of injury and due to its aneural and avascular structure with its low cellular turnover, this tissue is slow to repair (Arokoski et al. 2000). Failure to repair adequately, irrespective of the cause, results in the progression to a global joint disease, which is known as osteoarthritis (OA).

2.1.1 Articular cartilage

The bony surfaces of the distal femur and proximal tibia are covered with articular cartilage, which is an aneural and avascular tissue (Threlkeld 2002). The role of articular cartilage is to provide a friction-free surface to allow smooth joint movements and to resist and distribute joint loading forces (compressive, tensile and shear) from one bone to another (Threlkeld 2002). Cartilage is composed of chondrocytes (1-5% of cartilage volume) surrounded

by the extra-cellular matrix (ECM), which only the chondrocytes secrete and maintain (Goldring 2012a, Chen et al. 2013). The ECM is made up of collagen fibres (10-20%) of which 90-95% are type II, large proteoglycans (PG) (10-20%), and water (65-80%) (Bhosale & Richardson 2008). Cartilage is divided in to distinct layers/zones which have their own unique function due to the collagen fibre orientation, chondrocyte distribution and shape and cartilage hydration (Figure 1) (Threlkeld 2002, Goldring 2012a).

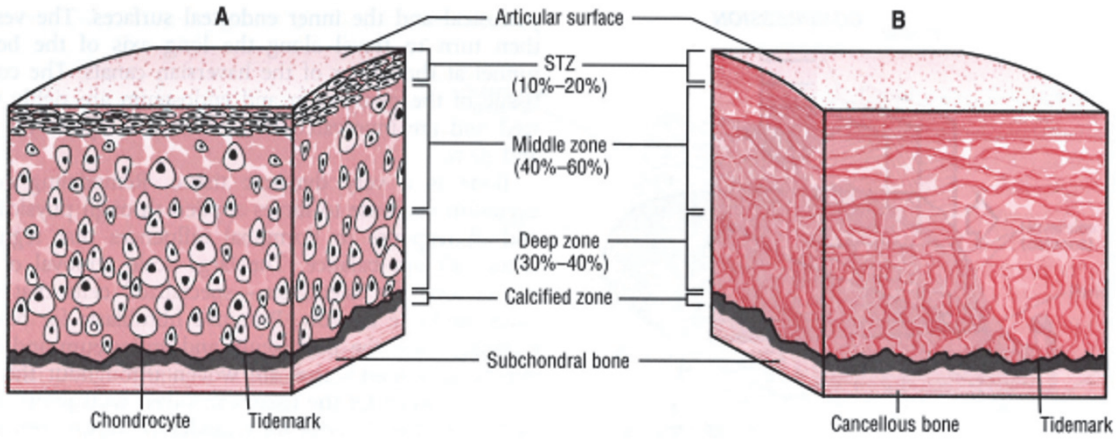

FIGURE 1 Cross-section view of the structure of articular cartilage. Organisation of chondrocytes is shown in part **A** and organisation of the collagen fibres in part **B**. Reproduced with permission (Threlkeld 2002).

The superficial (tangential) zone, which is the thinnest zone, is composed of collagen II fibres orientated in parallel to the cartilage surface; it provides resistance to high tensile and shear forces. The collagen fibres are densely packed, which results in ellipsoid shaped chondrocytes which primarily synthesise collagen. The superficial zone is covered in synovial fluid, secreted by the synoviocytes in the synovium, and contains a high concentration of hyaluronan (hyaluronic acid) which allows for friction-free gliding of the joint surfaces (Smith 2011, de Sousa et al. 2014). The superficial zone also acts as a filter, allowing movement of nutrients between the cartilage and synovial fluid but preventing the infiltration of larger macromolecules, e.g. from the immune system present in the synovial tissue (Bhosale & Richardson 2008, Smith 2011). The highest concentration of water is found in the superficial zone with its concentration decreasing with cartilage depth (Threlkeld 2002). The thicker collagen fibres in the intermediate (transitional) zone are irregularly arranged, it is in this region that the large rounded chondrocytes are found. The cells in this zone have high metabolic activity and produce larger amounts of PGs than the cells in the superficial zone. This zone resists primarily compressive forces (Arokoski et al. 2000). In the deep zone the collagen fibres are orientated perpendicularly to the subchondral bone surface and have the largest diameter of all collagen fibres in cartilage. The chondrocytes in this zone are spherical in shape, produce the highest concentration of PGs, and are significantly fewer in number than those in the higher zones. The final layer is the calcified layer

where the collagen fibres of the deep zone are anchored into the subchondral bone, creating a wavy basophilic line called the tidemark; this separates the calcified region from the deep zone. The chondrocytes in this zone are smaller in size and fewer in number. This zone resists shear forces and provides shock absorption for the less resilient subchondral bone (Arokoski et al. 2000, Bhosale & Richardson 2008). The calcified zone differs from the three other zones with respect the mineralization of its extracellular matrix and by the presence of blood vessels and nerve fibres that originate from the subchondral bone (Goldring & Goldring 2010, Houard, Goldring & Berenbaum 2013).

Biomechanical properties of cartilage

Articular cartilage has evolved to withstand the shear, compression and tension forces and it has developed specific biphasic (i.e. it can deform its solid matrix and adjust the internal hydrostatic pressure) biomechanical properties. This is achieved by the specialized structure of the ECM, which is composed of fluid (containing water and dissolved ions), the solid collagen and the PG containing matrix. The chondrocytes are protected from direct contact with the ECM by the surrounding layer of PGs and type VI collagen, the pericellular matrix (PCM), which together with the chondrocyte form the chondron (Chen et al. 2013). The forces dissipated by the ECM are transferred to the chondrocytes through the PCM (Madry, Luyten & Facchini 2012, Chen et al. 2013). Additionally, the PCM acts as a transducer of biochemical signals, e.g. growth factors and cytokines (Wilusz, Sanchez-Adams & Guilak 2014). These two pathways are the primary mechanisms through which the chondrocyte is stimulated to produce the components vital to the homeostasis of the ECM (Chen et al. 2013, Houard, Goldring & Berenbaum 2013, Wilusz, Sanchez-Adams & Guilak 2014).

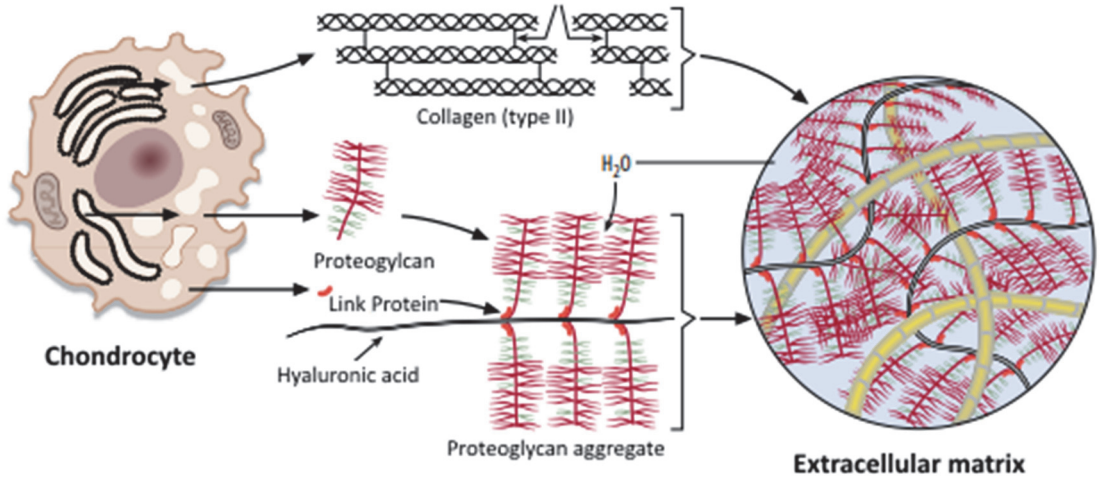

FIGURE 2 Production and structure of the collagen, proteoglycans (PG) and glycoaminoglycans (GAG). Adapted (Buckwalter & Martin 1995).

The biochemical composition of the extracellular matrix (ECM) is composed of PGs attached to chains of hyaluronic acid to which the hydrophilic glycosaminoglycan (GAG) molecules bind via linking proteins (Figure 2) (Buckwalter & Martin 1995). The cation charge of the PGs creates an osmotic difference, attracting water molecules into the cartilage which bind to the PGs, causing swelling. This swelling is restrained by the collagen matrix, creating an initial swelling pressure. When a compressive load is applied to the cartilage, the interstitial tissue flows into adjacent regions of the cartilage, minimizing pressure gradients within the cartilage. Release of the compression results in the restoration of the pressure gradient equilibrium through PG swelling. Regular cyclic movements improve cartilage nutrition and removal of catabolites from the cartilage and maintain synovial fluid health through stimulation of the synoviocytes (Scanzello & Goldring 2012, Wang et al. 2013). This provides an optimal environment under which the chondrocyte can synthesise the components of the ECM, thus maintaining the biomechanical properties of cartilage (Arokoski et al. 2000, Wang et al. 2013). Under normal physiological loading, the chondrocytes maintain homeostasis through a balance between anabolic and catabolic processes (Madry, Luyten & Facchini 2012). However, if there is abnormal loading or following a traumatic event, the balance between these processes can be disrupted (Chen et al. 2013, Houard, Goldring & Berenbaum 2013). In this situation, there is an increased loss of the ECM and this induces the degeneration of cartilage and a loss of its biomechanical properties and ultimately leads to the loss of cartilage, which is a characteristic of osteoarthritis (Arokoski et al. 2000).

2.2 Knee Osteoarthritis

The knee is the most common location for symptomatic OA (Allen & Golightly 2015). Knee OA, more commonly encountered in the medial tibiofemoral joint (Ledingham et al. 1993, Duncan et al. 2006), is characterised by the progressive loss of the cartilage surface, narrowing of the joint space and development of osteophytes leading to pain and loss of functional capacity (Altman et al. 1986). Previously, OA was considered to be a wear-and-tear disease, characterised by loss of cartilage from the bony surfaces of an articular joint (Loeser et al. 2012). Advances in our understanding of OA pathophysiology have changed this perception and knee OA is now considered a whole joint disease that affects the entire articular joint and the surrounding tissues.

The OARSI (Osteoarthritis research Society International) group recently defined OA as:

"Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness (Kraus et al. 2015)."

2.2.1 Pathophysiology of knee OA

Changes in cartilage homeostasis are considered to be a response mounted by the chondrocyte to an abnormal stress or injury, i.e. a reparative response (Martin et al. 2004, Goldring & Goldring 2007, Houard, Goldring & Berenbaum 2013). This reparative response could be triggered by a sudden trauma, abnormal loading over a longer period of time or changes in the chemical environment of the chondrocytes. The earliest phase of cartilage degeneration is characterised by a loss of PG and disruption of the collagen matrix, which results in an increase in the water content of the cartilage and unrestrained swelling of the cartilage. This leads to an initial upregulation of chondrocyte activity involving both anabolic and catabolic processes and cell proliferation (Martin et al. 2004, Houard, Goldring & Berenbaum 2013). The tissue is striving to achieve the desired outcome i.e. matrix remodelling (Loeser et al. 2012), and in some cases, the pathology never progresses further, suggesting that during the early stages of OA progression, there is a possibility to prevent progression (Ding et al. 2006, Wang et al. 2006). This early phase can last for many years (10-15 years) before the clinical presentation of OA occurs; this is represented as the first part "susceptible individuals" in Figure 3 and phase II in Figure 4 (Roos & Arden 2016). While knee OA is common, not everyone suffers from the disease and thus OA is not, as once thought, an inevitable consequence of aging, suggesting that cartilage health can be maintained throughout the life course (Martin & Buckwalter 2002, Goldring & Goldring 2007, Loeser 2009).

FIGURE 3 The progression of knee OA from inciting event to end-stage knee OA which can take 10-15 years. Reproduced and adapted with permission (Roos & Arden 2016)

Since the catabolic processes are amplified through increased production of inflammatory mediators and these are accompanied by a decrease in the anabolic processes, the end result is chondrocyte senescence (Martin et al. 2004, Madry, Luyten & Facchini 2012). The further loss of PG leads to a decline in the ability of cartilage to withstand compressive forces, and in combination with fibrillation of the collagen in the cartilage surface, cartilage loses its resilience to withstand shear forces. As OA progresses, fibrillation of the cartilage continues down from the surface along the collagen fibre and ultimately leads to a decrease in cartilage thickness and later to complete, non-reversible cartilage loss. A representation of the early loss of GAG and collagen from the surface of the cartilage is represented as stage III in Figure 4.

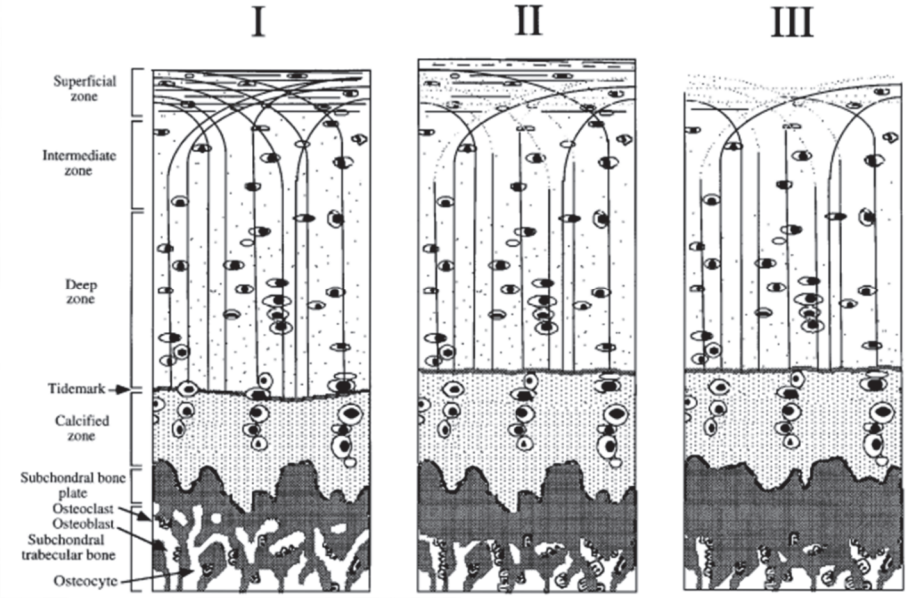

FIGURE 4 Representation of the gradual progression of OA in a beagle dog model with oval chondrocytes, GA represented as dots and collagen as a curved line. Panel I shows normal cartilage. Panel II illustrates a decrease in the GAG concentration within the superficial and intermediate zones with disorganization of the superficial collagen fibres with simultaneous thickening of the calcified cartilage and subchondral bone. In panel III, there has been a further loss of the cartilage surface and a progression of subchondral bone changes. Reproduced with permission (Arokoski et al. 2000).

OA is not just a disease of the cartilage; there are also changes in the subchondral bone, menisci, synovium, ligaments and muscles (Figure 5). Early changes in the subchondral bone include thickening of the subchondral plate, the barrier between the trabecular bone and the cartilage, as well as the development of osteophytes. The development of osteophytes increases the contact surfaces and therefore provides more stability to joint but also restricts the joint's range of motion (ROM). Although not evident in early OA, as cartilage degeneration progresses, there are vascular infiltration and the formation of subchondral lesions or bone cysts (Taljanovic et al. 2008). The subchondral bone is highly innervated and it has been proposed that it is a

source of OA pain (Taljanovic et al. 2008, Glyn-Jones et al. 2015). Some evidence suggests that changes in the subchondral bone precede the cartilage changes and that they are a precursor to cartilage degeneration (Bijlsma, Berenbaum & Lafeber 2011), but this remains a topic of debate (Madry, Luyten & Facchini 2012, Glyn-Jones et al. 2015). Osteoblasts, like chondrocytes, respond to mechanical loading via the production of inflammatory cytokines; these agents diffuse through the subchondral bone into the cartilage, stimulating or maintaining the catabolic response (Goldring 2012b, Madry, Luyten & Facchini 2012).

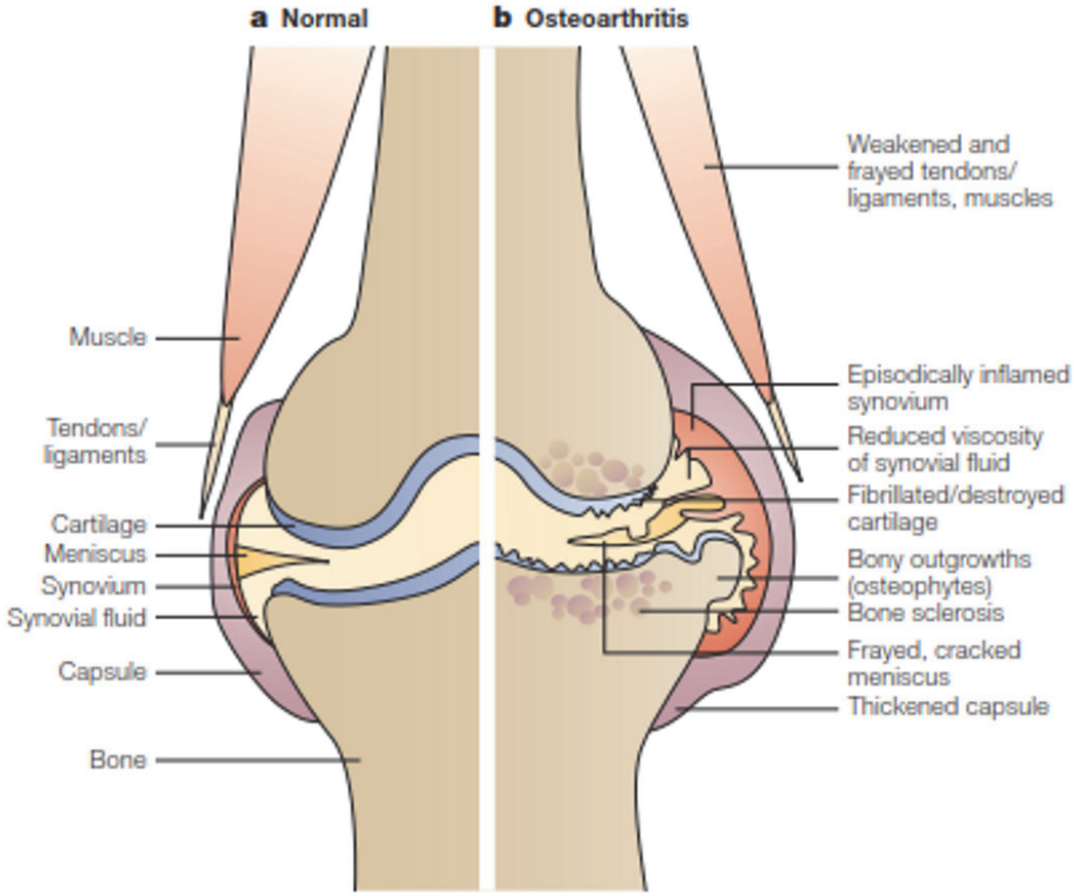

FIGURE 5 Normal synovial joint versus a synovial joint with osteoarthritis. Reproduced with permission (Wieland et al. 2005).

The role of the meniscus is to reduce the compressive stress in the tibiofemoral joints, as well as ensuring joint stabilisation and joint lubrication (Neumann 2002). The loss of meniscal integrity, as a result of injury or as part of the overall joint degeneration process, displays a strong association with cartilage degeneration and the onset of OA (Englund, Guermazi & Lohmander 2009, Madry, Luyten & Facchini 2012). It is still unknown if the degeneration of the menisci is a cause or a consequence of OA (Englund, Guermazi & Lohmander 2009). Inflammation of the synovium (synovitis), a common feature of early OA, is thought to be initiated by the diffusion of inflammatory markers from the cartilage and loose cartilage fragments becoming attached to the synovium

(Scanzello & Goldring 2012). Synoviocytes, similar to chondrocytes and osteoblasts, release inflammatory agents and degrading enzymes, further driving cartilage degeneration and OA progression (Krasnokutsky et al. 2011, Scanzello & Goldring 2012). Chronic swelling, a symptom of knee OA, constantly stretches the joint capsule, e.g. the formation of a Baker's cyst, indicating loss of strength of the capsule and ligaments resulting in passive instability of the joint (Knoop et al. 2011). The joint capsule thickens due to fibrosis, resulting in decreased ROM and pain. Inflammation, swelling, joint laxity and proprioception receptor damage are all associated with arthrogenic muscle inhibition mediated through spinal and supraspinal pathways (Rice & McNair 2010). Changes in the structure and function of the muscles crossing the knee joint are commonly encountered in people with knee OA (Ikeda, Tsumura & Torisu 2005, Fink et al. 2007, Bennell et al. 2013). Although these changes could be solely related to aging, they are thought to be secondarily accelerated as a consequence of the disuse caused by pain and the subsequent associated sedentary behaviour (Sions et al. 2012, Strollo et al. 2015). There are several morphological changes, including loss and reduced size of type II muscle fibres, grouping of muscle fibres, increased intermuscular fat infiltration and increase fibrosis and formation of contractures (Ikeda, Tsumura & Torisu 2005, Fink et al. 2007). Additionally, there is evidence of accelerated denervation, re-innervation associated neurogenic muscular atrophy and altered afferent nerve function (Ikeda, Tsumura & Torisu 2005, Rice & McNair 2010, Pietrosimone et al. 2011).

2.2.2 Clinical diagnosis of knee OA

It appears that early stage OA and chondral injuries are amenable to early prevention and treatment i.e. not all individuals with chondral injury or early changes progress to end-stage clinical OA with its severe pain and activity limitations requiring joint replacement (Wang et al. 2006, Ding, Cicuttini & Jones 2007, Roos & Arden 2016). Therefore, it would be most advantageous if it were possible to identify those individuals with early OA.

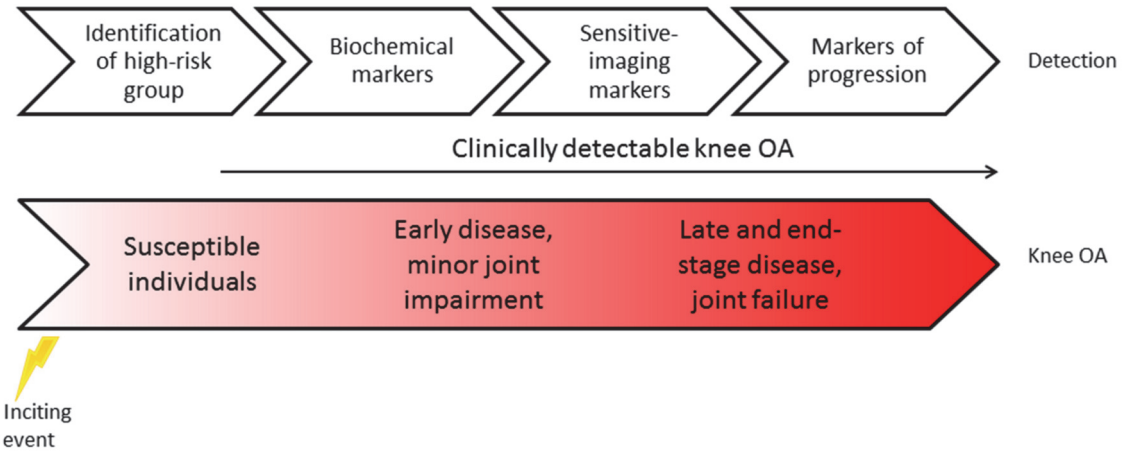

FIGURE 6 The progression of knee OA from inciting event to end-stage knee OA. Reproduced and adapted with permission (Roos & Arden 2016).

The diagnosis of knee OA has been traditionally based on clinical finding with or without radiological imaging. However, recent advancements in imaging, e.g. quantitative magnetic resonance imaging (qMRI) and understanding of the pathophysiology have made it possible to identify knee OA at an earlier stage (Figure 6). Pain present during activity which eases with rest is the most common reason for first seeking medical help in OA (Hawker et al. 2008). Joint stiffness appearing in the morning, evening and after periods of inactivity, that is relieved after 30 minutes of activity, is also typically present (Bijlsma, Berenbaum & Lafeber 2011). Table 1 shows the American College of Rheumatology (ACR) clinical and radiological criteria for the classification of osteoarthritis of the knee (Bijlsma, Berenbaum & Lafeber 2011).

TABLE 1 American College of Rheumatology clinical and radiological criteria for osteoarthritis of the knee and hip (Bijlsma, Berenbaum & Lafeber 2011).

Clinical diagnosis of knee OA	
Osteoarthritis if 1,2,3,4 or 1,2,5, or 1,4,5 are present	
1	Knee pain for most days of previous month
2	Crepitus on active joint motion
3	Morning stiffness last 30 minutes or less
4	Age 38 years or older
5	Bony enlargements of the knee on examination
Clinical and radiographic diagnosis of knee OA	
Osteoarthritis if 1,2 or 1,3,5,6 or 1,4,5,6 are present	
1	Knee pain for most days of previous month
2	Osteophytes at joint margins on radiographs
3	Synovial fluid typical of osteoarthritis (laboratory)
4	Age 40 years or older
5	Crepitus on active joint motion
6	Morning stiffness lasting 30 minutes or less

The classification of knee OA has traditionally been performed using the Kellgren-Lawrence (K/L) grading system (Kellgren & Lawrence 1957) which classifies OA into five categories (0-V) according to findings in weight-bearing radiographs (Table 2). However, the ACR system does not contain criteria for the diagnosis of early knee OA i.e. knee OA in the ACR criteria is considered as K/L ≥ II (Bijlsma, Berenbaum & Lafeber 2011). In some studies, K/L I and II have been considered as early radiographic OA and K/L ≥2 as radiologically confirmed OA changes (Kellgren & Lawrence 1957, Altman et al. 1986). However, there is known to be a poor relationship between clinical presentation and K/L grading and as such, the K/L classification system is not able to monitor changes occurring over short periods of time (under two years) (Cicuttini & Wluka 2014, Favero et al. 2015). Histologically, the OARSI staging system has classified early OA as grades 1-4 in which there are no signs of erosion of the articular cartilage i.e. no evidence of OA can be seen in plain film radiographs (Pritzker et al. 2006, Madry, Luyten & Facchini 2012). K/L I has been suggested for a patient in whom the is possible radiographic evidence of early OA, however due to the poor intra- and interrater reproducibility

(Schiphof et al. 2011) and a lack of identification of active processes in other tissues, this approach has limited use on its own.

TABLE 2 Classification of radiographic OA according to the Kellgren-Lawrence grading system (Kellgren & Lawrence 1957).

Grade	Description
0	No changes
I	Doubtful narrowing of the joint space and possible osteophytic lipping
II	Definite osteophytes and possible narrowing of the joint space
III	Moderate multiple osteophytes. Definite narrowing of the joint space, and some sclerosis, and possible deformity of the bone ends
IV	Large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends

Advances in magnetic resonance imaging (MRI) have improved the possibility diagnosing and measuring the tissue changes taking place in the early phase of OA development, where traditional radiography has been of limited use. Some semi-quantitative scoring systems of the joint changes in early knee OA have been devised e.g. the Whole Organ Magnetic Resonance Imaging Score (WORMS) (Peterfy et al. 2004) and the Boston Leeds Osteoarthritis knee Score (BLOKS) (Hunter et al. 2008). Luyten et al. (Luyten et al. 2012) proposed that the following criteria should be included in an MRI or arthroscopy-based classification of early knee OA:

1. Pain in the knee
2. Standard radiographs K/L 0 or I or II (osteophytes only)
3. At least one of the following:
    a. Arthroscopic findings of cartilage lesions.
    b. MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration, and/or subchondral bone

Innovative qMRI techniques based on the relaxation time of interstitial water provide indirect information on the macromolecular composition and structure of cartilage. T2 relaxation time (T2) mapping is sensitive to the loss of tissue collagen and also to the orientation of collagen fibres in the extracellular matrix (Nieminen et al. 2000, Mosher et al. 2004). The delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) technique utilizes a paramagnetic contrast agent, gadolinium, to detect a reduction in the amount of GAG in the ECM, a phenomenon considered to represent the onset of the cartilage degenerative process (Burstein & Gray 2003). However, these methods are too time consuming for clinical application and due to natural variations in cartilage composition, no classification for healthy and osteoarthritic cartilage has been devised. Furthermore, there is no association between the K/L ratings of 0/I/II and values for either T2 or the dGEMRIC index (Multanen et al. 2015).

The limitations in accuracy and cost involved in the above classifications and diagnostic tools mean that there are currently no accepted diagnostic

criteria for detecting early OA (Luyten et al. 2012, Roos & Arden 2016). Furthermore, radiography or MRI findings alone are not effective ways of diagnosing symptomatic knee OA. Not all people with findings of radiographic knee OA, as measured with the K/L or degeneration of joint structure through MRI investigations, experience pain. Conversely, people with symptoms associated with knee pain may not exhibit radiographic or MRI findings associated with knee OA (Lawrence, Bremner & Bier 1966). The lack of a clear definition for what represents early OA as well as the difficulty in its diagnosis have serious consequences, i.e. often the disease has already advanced to late stage OA with significant changes in joint structures before the sufferer seeks help. Thus, there is an urgent need to improve the diagnosis and classification of early OA in order to identify at risk patients at as early stage as possible (Luyten et al. 2012, Kraus et al. 2015).

2.2.3 Risk factors for development of knee OA

The known risk factors for predisposing a person to joint damage and therefore knee OA are shown in Table 3. While these are risk factors, they do not alone predict the onset of knee OA nor do they predict the severity of symptoms associated with knee OA (Roos & Arden 2016). Many of these risk factors are modifiable, e.g. the use of correct warm-up with exercise aimed at improving neuromuscular functioning has been noted to be able to reduce the number of knee injuries (Gagnier, Morgenstern & Chess 2013) and diet control combined with sufficient physical activity can control weight gain (Waters, Ward & Villareal 2013). However, it is not fully understood how these risk factors interact with each other and lead to knee OA, nor is it know whether they differ between specific populations (Dekker 2014, Roos & Arden 2016). While molecular changes may be present, they do not always result in symptoms. Roos and Arden (2016) claimed that these risk factors interact with other comorbidities, pain processing, spinal sensitisation, depression and anxiety to produce symptomatic OA (Roos & Arden 2016). However, once progression has occurred, the pathological changes in the knee have many similarities and ultimately terminate in the same end point.

TABLE 3 Risk factors for knee OA adapted with permission (Dekker 2014, Silverwood et al. 2015).

Systemic risk factors	Local mechanical risk factors
Age	Previous Injury
Gender	Physical activity
Genetic Predisposition	Occupational risks
Depression	Muscle weakness
Hand OA	Malalignment
Co-morbidity	
Race and Ethnicity	
Excess Weight and Obesity	

2.2.4 Risk factors for progression of early to late stage knee OA

There are numerous risk factors associated with the progression of hip and knee OA (Figure 7) and there ultimately interact with each other through processes associated with aging, metabolic changes and altered joint biomechanics and loading (Dekker 2014). It would be advantageous to identify these risk factors in individuals at risk or with early stage knee OA in order to implement interventions intended to prevent the progression of knee OA with respect to both degeneration of cartilage and the clinical symptoms, i.e. pain and decreased functional capacity. This dissertation will focus on the following risk factors; pain, muscle weakness, poor walking ability, excess weight and obesity, age and physical inactivity.

Pain

OA related knee pain is the main reason for seeking medical treatment (Dieppe & Lohmander 2005). Knee OA is also one of the most common causes of chronic pain (Schaible 2012) as well as activity limitations in adults (Dekker 2014). Cartilage is aneural and therefore not considered a direct source of nociceptive pain (Schaible 2012). However, a change in chondrocyte homeostasis through injury or abnormal mechanical loading and subsequent cartilage destruction does lead to the presentation of pain (Houard, Goldring & Berenbaum 2013). Knee OA related pain commonly originates from inflammation of the synovium (synovitis) and bone lesions, which are both common findings in early and late stage knee OA (Taljanovic et al. 2008, Scanzello & Goldring 2012). Osteophyte formation, a phenomenon associated with later stage OA, may impinge on soft tissues, evoking pain (Sofat, Ejindu & Kiely 2011). In early OA, pain is typically nociceptive in its origin; it is caused by inflammatory chemicals including prostaglandins and cytokines produced by the chondrocytes and synovium (Goldring & Otero 2011, Houard, Goldring & Berenbaum 2013). During the course of disease progression, the constant mechanical stimulation of joint afferents results in the sensitisation of the primary joint nociceptors (allodynia and hyperalgesia) and the central sensitisation of nerve pathways, resulting in

OA related chronic pain (Sofat, Ejindu & Kiely 2011, Schaible 2012). This, in part, explains the findings of severe pain in the absence of radiographically diagnosed knee OA (K/LII-IV) as these processes can begin without significant cartilage loss detectable in radiographs (Luyten et al. 2012, Madry, Luyten & Facchini 2012).

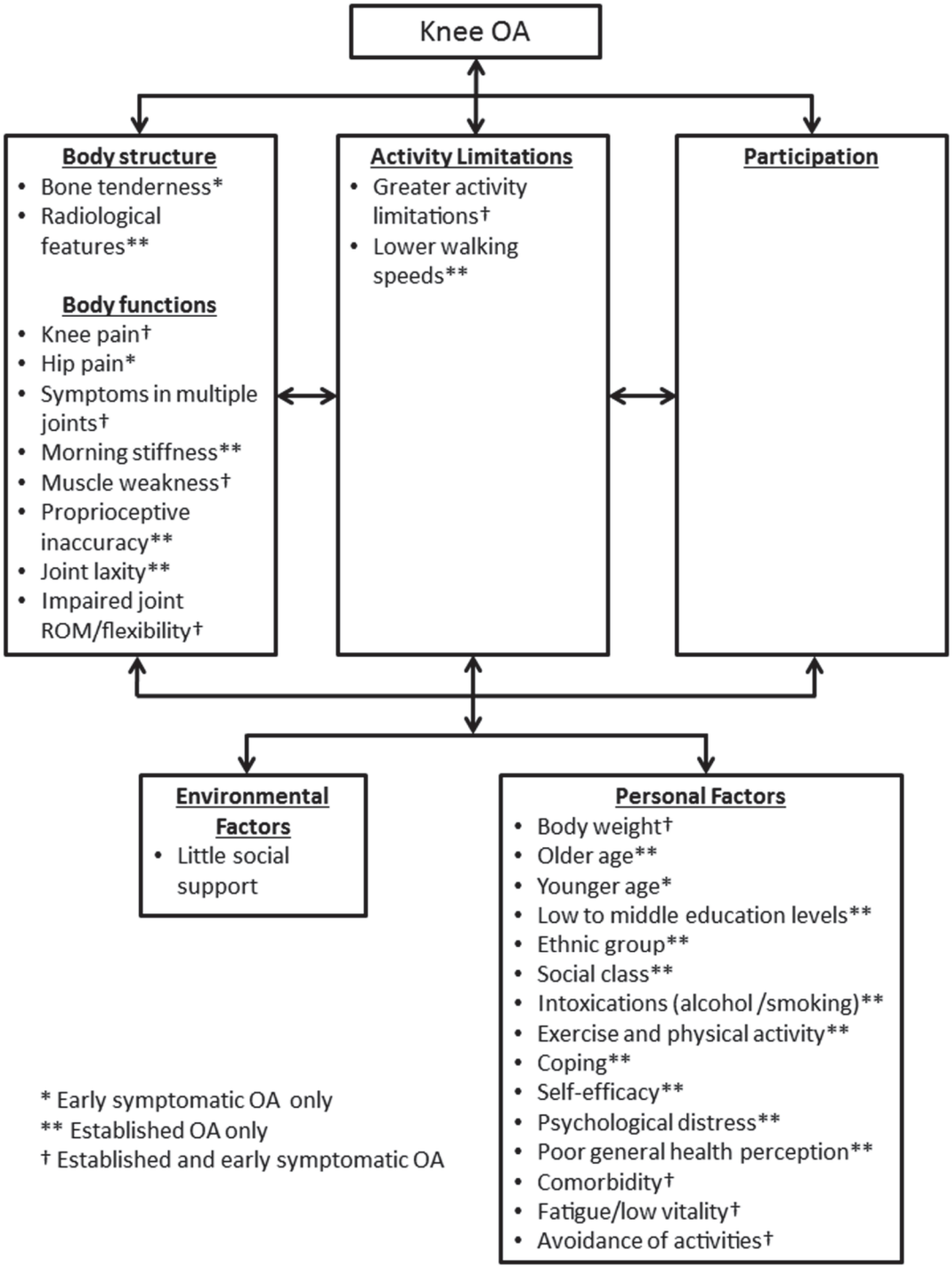

FIGURE 7 Risk factors for progression of activity limitations in early OA Adapted with permission (Dekker 2014, Holla 2014).

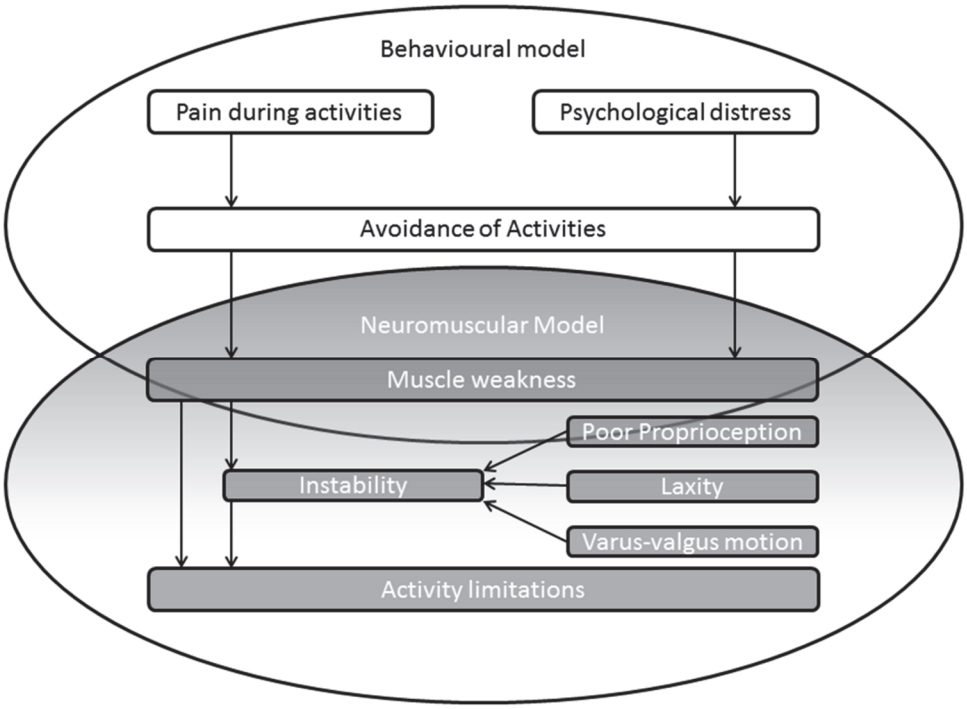

FIGURE 8 The integrated behavioural and neuromuscular explanation of activity limitations in OA. Reproduced with permission (Holla 2014, Dekker 2014).

Even though pain in early knee OA is intermittent, it can cause significant changes in behaviour through activity avoidance, which in turn can lead to a decrease in muscle function, increased joint instability and limitations in functional capacity. Hawker et al. (2008) suggested that as pain increases, so too does the prevalence of depression and decreased mood, which amplifies the avoidance of activities as well as increasing the sensitivity to pain, thus ultimately leading to more pain (Hawker et al. 2008). Pain at baseline predicted an increase in activity avoidance over a 5-year follow-up in people with early knee OA, and it also predicted an increase in activity limitations (Holla et al. 2015). Subsequently, a behavioural model for increased activity limitations has been presented (Holla et al. 2014). Dekker et al. (2014) developed this further into an integrated behavioural and neuromuscular model for explaining the progression of activity limitations in OA which could explain the role of pain in the progression of activity limitations in knee OA (Figure 8); this model integrates both behavioural and neuromuscular risks of activity limitations through muscle weakness (Dekker 2014).

Muscle weakness

Muscle weakness predicts the functional decline and OA progression (van Dijk et al. 2010, Pisters et al. 2012, van der Esch et al. 2014, Oiestad et al. 2015). Muscle weakness can be either directly modulated through arthrogenic muscle

inhibition caused by swelling, the presence of inflammatory mediators, joint laxity and damage to joint afferents (Rice & McNair 2010) or due to atrophy through disuse as a result of pain and psychological distress (Figure 8) (Dekker 2014, Petterson et al. 2008). It remains unclear if muscle weakness is a cause of or a consequence of OA related processes (Baker et al. 2004, Bennell et al. 2013, Oiestad et al. 2015). However, Ikeda et al. (2005) observed atrophy of the quadriceps in asymptomatic women with knee OA K/L grade II, pointing to an interaction between cartilage degeneration and muscle function at an early stage of OA (Ikeda, Tsumura & Torisu 2005). The role of the quadriceps in normal knee biomechanics is to act as shock absorbers and joint stabilisers (Neumann 2002). Quadriceps weakness, results in increased loading on the cartilage of the tibiofemoral joints through reduced active absorption force. Weakness in the quadriceps muscles may change gait biomechanics. For example, just before the point of heel strike, the quadriceps should contract strongly, moving and absorbing the force of impact away from the tibiofemoral joint, however, this role of quadriceps diminish in the presence of knee OA; a similar phenomenon can also be seen after artificially induced arthrogenic muscle inhibition in healthy individuals (Torry et al. 2000). The relationship between muscle weakness and changes in knee biomechanics is however more complex. The combination of afferent feedback and muscle co-activation appears to be more important in maintaining normal knee function than muscle strength alone (Knoop et al. 2011). Additionally, weaknesses in the other lower limb muscles have a role to play in the disturbed biomechanics of the knee during gait and the alterations in activities of daily living (ADL) which involve hip abductors, abductors and extensors (Chang et al. 2005, Bennell et al. 2013), as well as ankle plantar-flexors (Kulmala et al. 2014).

Walking ability

Walking is the most common form of locomotion; since each step is responsible for a load which is 2-3 times the body weight; thus loading of knee cartilage is unavoidable. Slower walking speeds result in a decrease in impulse through the knee at heel strike and thus the size of the forces acting on the knee joint (Henriksen et al. 2014). A decrease in walking speed commonly occurs in people with knee OA and is a prognostic factor for increased activity limitations and decreased functional capacity (van Dijk et al. 2010, Pisters et al. 2012). Knee pain is a strong modulator of the changes in physical activity, but in addition, kinematic changes in gait have been found in people with moderate knee OA (Mills, Hunt & Ferber 2013). Moreover, individuals with knee OA have been shown to alter their gait in order to protect the knee from excessive loading, in particular to attempt to decrease the loading on the medial compartment. Furthermore, changes in gait kinematics with the aim of reducing joint loading are common in people with knee OA (Mills, Hunt & Ferber 2013). These changes do not ensure optimal gait efficiency and furthermore, they do not invariably protect the knee from abnormal loading and possible OA progression (Mills et al. 2013a).

Excess weight and obesity

OA and obesity are intrinsically linked through both inflammatory mechanisms and sub-optimal biomechanical loading of the cartilage (Vincent et al. 2012, Messier et al. 2013, Vuolteenaho, Koskinen & Moilanen 2014). Being overweight or obese is associated with an increased risk of suffering from osteoarthritis as well as a more rapid progression of the disease (Vincent et al. 2012). Obese people with knee OA tend to alter their gait as a result of several factors i.e. their lower relative strength, the presence of pain and fat mass e.g. thigh fat (Nebel et al. 2009, Messier et al. 2013, Messier et al. 2014). Kinesiophobia due to pain, which is magnified in obese individuals, decreases physical activity, which in turn facilitates weight gain (Somers et al. 2009, Vincent et al. 2012). The presence of excessive intramuscular fat compromises muscle quality; this not only affects muscle function and the associated reduced physical functioning but also is associated with systemic and local inflammation (Vincent et al. 2012). A systemic low grade inflammation is a feature of obesity; it is mediated through adipokines such as leptin, a compound which stimulates the production of metalloproteinases and pro-inflammatory mediators in chondrocytes (Vuolteenaho, Koskinen & Moilanen 2014). The elevated levels of cytokines increase ECM loss by stimulation of catabolic processes and inhibition of anabolic activities in the chondrocytes (Loeser et al. 2012).

Aging

OA has long, and incorrectly, been considered as a consequence of aging with this assumption arising from the increasing prevalence of OA with advancing age (Allen & Golightly 2015). However, although by the age of 60 years, as many as 80% of the population exhibit radiological findings associated with knee OA (Lawrence, Bremner & Bier 1966), not all older adults suffer from symptomatic knee OA (Loeser 2009). Normal, non-symptomatic, aging related changes in cartilage include articular surface fibrillation, browning of the cartilage surface and a decrease in cartilage hydration (Loeser 2009). The ability of chondrocytes to synthesise the constituents of the ECM and their resistance to anabolic cytokines decreases with increased age (Martin & Buckwalter 2002). Thus, the chondrocyte have a reduced ability to preserve cartilage homeostasis and to respond to a new injury or maintain the balance between anabolic and catabolic processes from a previous knee injury (Martin & Buckwalter 2002). Chondrocyte senescence, i.e. the cells' inability to replicate, may be accelerated by extrinsic stresses including excessive mechanical loading and/or prolonged stimulation from the cytokines involved in chronic inflammation (Loeser 2009, Greene & Loeser 2015).

Aging is associated with a decrease in muscle strength (Brady & Straight 2014) and power (Sayers et al. 2005, Strollo et al. 2015) as well as with changes in gait biomechanics (Kulmala et al. 2014), which, as previously discussed, expose the cartilage to abnormal loading. Furthermore, a sedentary lifestyle is common in older populations; this is a major contributing risk factor for weight gain, higher fat mass, lower fat free mass, decrease in muscle mass and strength

and increased risk of co-morbidities (Vincent, Raiser & Vincent 2012, Westerterp 2013). An age-related pro-inflammatory mechanism has recently been proposed as the link between age and osteoarthritis, however, further research will be needed to clarify this phenomenon (Greene & Loeser 2015). Therefore, although age is a strong risk factor for the development and progression of knee OA, it is clear that there are multifactorial age-related mechanisms involved in the progression of knee OA, including chondrocyte senescence, loss of functional capacity and metabolic changes.

Gender

Women are at greater risk of suffering from OA than men (Allen & Golightly 2015). A more precipitous loss of cartilage is seen in females than males in both healthy (Hanna et al. 2009) and OA affected joints (Ding et al. 2007). Hormonal changes after the menopause i.e. a decline in the level of oestrogen in the circulation, are thought to be related to an acute loss of cartilage and also to be associated with the increase in concentrations of pro-inflammatory cytokines (Martin-Millan & Castaneda 2013). However, this association remains to be fully clarified and further research is required in this area (Roman-Blas et al. 2009). Older women tend to have lower amounts of total skeletal muscle mass in comparison with older men (Valentine et al. 2009). After the menopause, women experience an accelerated loss of muscle mass with subsequent impaired muscle performance, resulting in a decline in functional capacity (Sipilä & Poutamo 2003). This exposes females to a greater risk of abnormal joint loading and consequently to OA progression. Taken together, accelerated loss of cartilage and muscle as well as hormonal changes appears to put women at a higher risk of suffering OA.

Physical activity

While participation in sports increases the risk of injury resulting in knee OA later on in life (Roos 2005), a low level of physical activity (PA) is also associated with a progression of knee OA (Dunlop et al. 2011). A decrease in physical activity can lead to the development of obesity, loss of muscle mass and function and increased risk of the appearance of co-morbidities (Misic et al. 2007, Manini 2011). The reduction in PA has been associated with increased age, pain, disease, obesity, a decline in functional capacity and decreased muscle strength. Moreover, the combination of increased age with one or more diseases has been shown to be strongly associated with limitations in physical activity. The combined contributions of osteoarthritis and cardiovascular disease account for up to 80% of the activity limitations in adults over 65 years old (Manini 2011). Therefore, these diseases must be target in interventions intended to decrease physical activity limitations.

2.2.5 Summary of risk factors for knee OA

While knee pain is the main reason for initially seeking medical assistance, it is now appreciated that there should be an equal focus on activity limitations at the early phase of OA development (van Dijk et al. 2010, Holla et al. 2015). Both pain and decreased functional capacity are known risk factors for progression of knee OA and are valid targets for therapeutic interventions. In addition, these risk factors display both mechanical and metabolic interactions, as shown in Figure 9 (Manini 2011). Following the ICF model, there are clear interactions between disease, aging, body functions and body structures, activities and environmental and personal factors. As the limitations with in each domain, e.g. body function, increase, so too do the activity limitations, resulting in knee OA progression. However, each individual will be affected differently by each domain, making it impossible to devise a "one-size-fits all" generic intervention for knee OA. Therefore, inventions implemented to manage and prevent knee OA progression need to be impact on the main risk factor or factors specific to the individual. However, as early changes are often asymptomatic, the emphasis should be placed on changing modifiable risk factors for activity limitations, such as age related physiological changes and sedentary lifestyle related muscle weakness and decreased neuromuscular function and poor walking ability in asymptomatic populations.

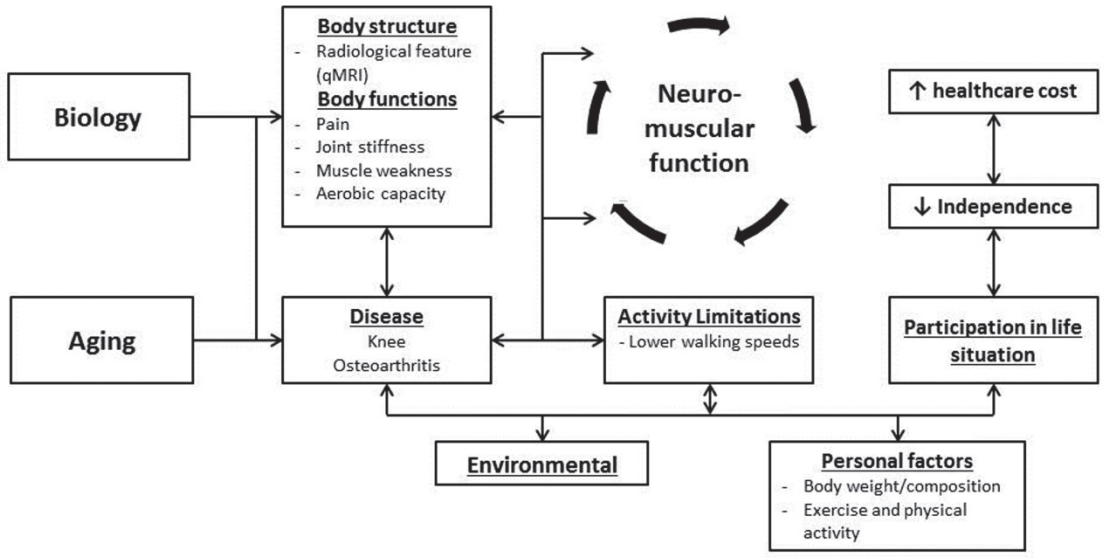

FIGURE 9 Interaction between disease, body structures and function and neuromuscular function and activity limitations. Adapted (Manini 2011).

2.3 Management of knee OA

Prevention is better than cure, so they say. However, to date, no treatments have been developed that prevent the progression of early to late stage OA, nor is it currently possible to reverse structural changes associated with OA. Treatment of knee OA has traditionally focused on pain management and improving functional capacity through non-pharmaceutical (e.g. exercise), pharmaceutical (e.g. NSAIDs and paracetamol) and surgical (e.g. arthroscopy) means (Zhang et al. 2010, Hochberg et al. 2012, McAlindon et al. 2014). Ultimately, joint replacement surgery (arthroplasty) has been the final option for joint failure. While effective at reducing pain, arthroplasty has several drawbacks; 1) the prosthesis has a limited life period and will often require revision, 2) the risk of side effects and 3) often does not fully restore functional capacity of the patient (Valtonen et al. 2009). Recently, due to the advances in diagnostic tools, our understanding of the progression of knee OA has improved and this has opened new avenues for treatment and prevention. The OA continuum has emphasized how OA develops with time, often slowly over many years, each with its own corresponding stages of prevention (Figure 10) (Roos & Arden 2016). Primary prevention, specifically for knee OA, involves management of the known risk factors associated with the onset of OA related changes (Table 3). The secondary phase includes management and possible reversal of the early changes in joint structure and impairments associated with early knee OA as well as preventing disease progression to late stage knee OA (Figure 10). The final stage of knee OA management involves the continued tertiary prevention and management of pain, combatting the decreased functional capacity and reduced quality of life in order to avoid the need for joint replacement surgery (Roos & Arden 2016).

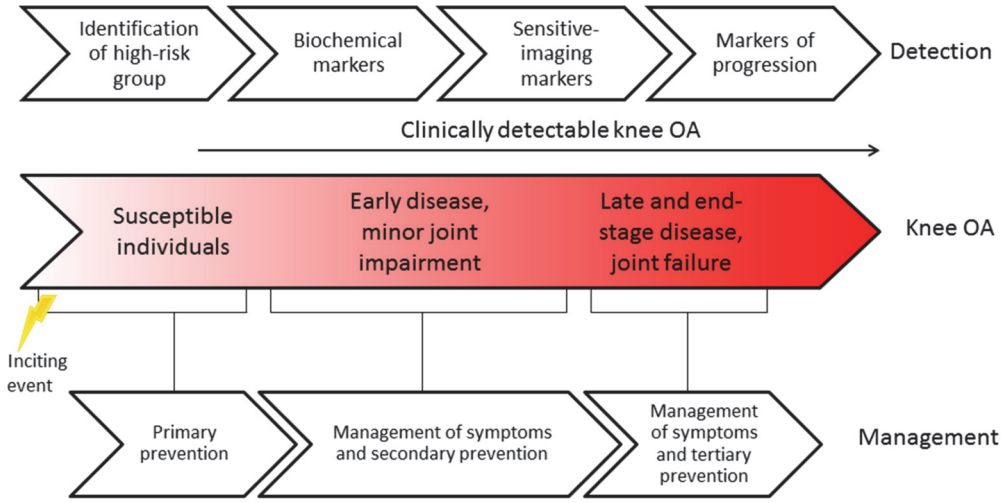

FIGURE 10 The continuum of OA development with detection and prevention/management of different stages of knee OA. Reproduced and adapted with permission (Roos & Arden 2016).

Non-pharmaceutical Management Options

The current OARSI guidelines for the non-surgical management of knee osteoarthritis list land-based exercise, weight management, strength training, water-based exercise and self-management as well as education as the core treatments for all individuals (McAlindon et al. 2014). Additional therapies such as orthotics and physical therapy treatments are also recommended but not as strongly as previously. Therefore, this dissertation will focus on exercise interventions. Exercise has long had a central role in the management of knee OA related symptoms as a way of combatting the reduced functional capacity (Bennell, Hall & Hinman 2016). While there is good evidence that land-based exercise can decrease pain and improve self-reported functioning, there is no current evidence that one type of land-based training is superior to any other (Juhl et al. 2014, Fransen et al. 2015). Exercise, irrespective of the type or intensity (Lange, Vanwanseele & Fiatarone Singh 2008), neuromuscular (Ageberg, Link & Roos 2010, Ageberg & Roos 2015) or aerobic (Roddy, Zhang & Doherty 2005), has been shown to be effective at decreasing pain and improving functional capacity in people with knee OA. Further, neuromuscular exercises have improved the functional capacity in young people at risk of knee OA (Roos & Dahlberg 2005) and high-impact exercises in postmenopausal women with mild knee OA (Multanen et al. 2014). Exercise interventions have been claimed to evoke both morphological and neurological changes in the musculature, including improved muscle strength and power, voluntary muscle activation and better proprioception as well as facilitating muscle atrophy and reducing the inter-muscular fat content (Sipila et al. 1997, Bennell et al. 2013, Knoop et al. 2013, Ageberg & Roos 2015). Moreover, an active life style with physical exercise has been shown to be beneficial for the maintenance of the biochemical properties of cartilage in animals (Kiviranta et al. 1988, Kiviranta et al. 1992) and humans, i.e. chondro-facilitative (Teichtahl et al. 2009, Cotofana et al. 2010, Van Ginckel et al. 2010, Murray, Benke & Mandelbaum 2016). Further, exercise has been demonstrated to be able to reverse the experimental cartilage atrophy present after disuse and immobilisation studies (Kiviranta et al. 1994, Souza et al. 2012) and slow down progression of OA in animals, i.e. it is chondro-protective (Brismar et al. 2003, Murray, Benke & Mandelbaum 2016). Therefore, exercise appears to be an effective way to maintain cartilage health, in addition to its beneficial effect to relieve pain and improve functional capacity. Age in itself is not a modifiable risk factor but age related changes can be modified by exercise. The maintenance of physical activity and participation in exercise has been linked to fending off cellular and molecular damage and delaying illness, thus combatting disabilities to ensure the organism functions optimally for the longest period of time (Manini 2011).

Exercise has been suggested as the primary non-pharmaceutical treatment in the management of early OA (Filardo et al. 2016), as it has the potential to be chondro-protective and chondro-facilitative (Murray, Benke & Mandelbaum 2016). However, there are several studies investigating the effect of exercise interventions on healthy and degenerated human cartilage but all have

involved land-based interventions (Roos & Dahlberg 2005, Van Ginckel et al. 2010, Multanen et al. 2014, Koli et al. 2015). Only two previous studies have examined the effects of land-based exercise on the biochemical composition of cartilage in postmenopausal women with mild knee OA, i.e. Kellgren-Lawrence grades I/II with knee pain (Multanen et al. 2014, Koli et al. 2015). These studies, from the same research group detected an improvement in the collagen matrix in the patella cartilage, reflected by a decrease in T2, of postmenopausal women with mild knee OA. The intervention lasted for one-year, and involved three times a week, high-impact exercise (Koli et al. 2015). In contrast, the same study observed no worsening or improvement in the collagen matrix (T2) or in the GAG concentration (dGEMRIC index) of the tibiofemoral (Multanen et al. 2014). These results suggest that the moderate shear and compression forces produced at the patellofemoral joint were more effective at improving collagen orientation and cartilage hydration than the high compressive forces exerted on the tibiofemoral joint. Moreover, Roos and Dahlberg (2005), found an increase in the T1 relaxation time in the presence of contrast agent after a 4-month neuromuscular training programme in young people at risk of developing knee OA following meniscectomy (Roos & Dahlberg 2005). The results of their study suggest that a neuromuscular programme, i.e. a protocol involving low impacts, can increase the GAG content, possibly through changes in lower limb biomechanics (Roos & Dahlberg 2005). These trials indicate that exercise is an appropriate intervention not only for people at risk of knee OA but also in those individuals with early signs of the disease, i.e. people in the first half of the OA continuum shown in Figure 10 (Roos & Arden 2016).

In conjunction with exercise, weight management is another cornerstone of the non-pharmaceutical management of knee OA (Zhang et al. 2010, Hochberg et al. 2012, McAlindon et al. 2014). For every 5kg weight gain, there is a 35% increased risk for developing OA (Lementowski & Zelicof 2008) and a higher BMI has been associated with increased joint pain as well as with the severity of other symptoms (Andersen et al. 2003). Non-pharmaceutical interventions for weight management are primarily exercise and diet (Vincent et al. 2012), with exercise and diet in combination being more effective than exercise or diet alone (Messier et al. 2013).

Pharmaceutical and Surgical Management Options

Pharmacologic modalities commonly recommended for the initial management of patients with knee OA have included paracetamol and oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) as the most common drugs (Hochberg et al. 2012) with paracetamol recommended as the first-line option for analgesia (Zhang et al. 2010). Both paracetamol and NSAIDs have similar efficacies on pain and function as land-based and water-based exercise (Zhang et al. 2010, McAlindon et al. 2014). The perceived risk scores for paracetamol and NSAIDS are higher than for exercise or water based-exercise (Hochberg et al. 2012, McAlindon et al. 2014); and with NSAIDs there is a risk of gastrointestinal and renal side effects whereas paracetamol is a known liver

toxin (Zhang et al. 2010). The use of slow-acting drugs such as glucosamine and chondroitin sulphate remains controversial, even though a small, short term beneficial effect with few side effects was reported in a recent Cochrane review (Singh et al. 2015). However, long term use of these supplements is not currently recommended (Zhang et al. 2010).

Surgical options for early knee OA include osteochondral autografts, cell-free implants and chondrocyte transplantation (Angele et al. 2016). Osteotomy and arthroplasty are the main stay of surgical management for end-stage knee OA (Zhang et al. 2010). However, these also carry a high risk of harms and prosthesis revision is often required. These interventions require rehabilitation and changes to leisure time physical activity to optimize post-surgical functional capacity (Valtonen et al. 2009). Moreover, while pain is often relieved, an improvement in functional capacity is often only seen in patient-reported measures of physical functioning, e.g. Western Ontario and McMaster University Osteoarthritis Index (WOMAC) physical function domain; in contrast it is not detected in performance-based measures of functional capacity (Stratford & Kennedy 2004, Stratford, Kennedy & Woodhouse 2006).

2.3.1 Aquatic exercise for knee OA

Aquatic exercise is often recommended to people with hip and/or knee OA (Zhang et al. 2010, Hochberg et al. 2012, McAlindon et al. 2014). Water is a facilitating environment in which individuals with knee OA can safely and comfortably exercise at possibly higher intensities than on land, while utilising a full joint range of motions not possible or normally recruited out of the water. The physical properties of water are buoyancy, hydrostatic pressure, temperature, viscosity, flow and turbulence. An in-depth description of these factors is available elsewhere (Gulick & Geigle 2009, Becker 2011) and is beyond the scope of this literature review but reference to specific aspects will be made, as necessary. Below is a summary of the literature investigating the effects evokes by aquatic exercise.

Pain

Pain is a major modulator for activity avoidance in patients with OA (Holla et al. 2014). In a very recent systematic review (2016), the effect of aquatic exercise on pain was (standardised mean difference, SMD) -0.31 (95% confidence interval (CI) -0.47 to -0.15), which is slightly smaller than achieved with land-based exercise -0.49 (-0.59 to -0.39) (Fransen et al. 2015, Bartels et al. 2016). Exercise has many effects on OA related pain involving many physiological factors including increased leg strength, improvements in ROM with reduced extension impairments and improvements in proprioception (Runhaar et al. 2015). Several studies investigating the acute response to high intensity underwater treadmill and land treadmill walking in patients with lower limb OA have shown a significant acute decrease in pain immediately after aquatic treadmill walking but pain was worsened after land treadmill walking at an

equivalent intensity (Denning, Bressel & Dolny 2010, Roper, Bressel & Tillman 2013). A more recent study confirmed this finding, with an acute decrease in pain following one aquatic exercise session of different intensities and modalities (Fisken et al. 2014). Therefore, it is unclear if the mechanism behind the pain relief in knee OA is the unloading effect from immersion the water (Hall et al. 2008), or the effect of the exercise itself, irrespective of its intensity (Runhaar et al. 2015).

Compared to land interventions, aquatic exercise has reduced swelling, thus relieving the pressure on nerve endings in patients after anterior cruciate ligament reconstruction (Tovin et al. 1994, Zamarioli et al. 2008), however, the role of effusion in muscle weakness and changes in gait have remained unclear (Bennell et al. 2013). The relief of pain improves maximal voluntary contraction in subjects with knee OA. The pain relief experienced during aquatic exercise could improve the voluntary contraction of the muscles as well as prevent the pain-induced sub-optimal muscle activation patterns, although this proposal has yet to be tested. The mechanisms behind the pain-relieving effects include a short term de-loading effect from buoyancy which could influence nociceptors in the synovium, ligaments and tendons that are subjected to constant abnormal loading on land. Immersion in warm water causes improvements in the peripheral circulation and this could lead to the removal of cytokines and other molecules responsible for activation of nociceptors (Hall et al. 2008, Runhaar et al. 2015). Furthermore, after an initial increase, there is evidence of a decrease in spinal and peripheral neural excitation following immersion (Pöyhönen & Avela 2002, Cronin et al. 2016), which could modulate pain signals at the spinal level. Central sensitisation is commonly encountered in knee OA suffers (Hochman et al. 2010, Hochman et al. 2011), and aquatic exercise may modulate the perceived risk of experiencing pain while performing the exercise (Butler & Moseley 2013).

Physical functioning

While it seems likely that aquatic exercise can improve patient-reported physical functioning, there is conflicting evidence on its ability to impact performance-based measures of functional capacity and related risk factors for the progression of knee OA. All of the above mechanisms mediating pain relief are of short duration (Fisken et al. 2014), and there is limited evidence for any long term effect of aquatic exercise on pain relief in individuals with knee and/or hip OA (Bartels et al. 2016). In the recent Cochrane review, the effect of aquatic exercise on functional capacity was assessed using patient-reported outcomes, which, are thought to display a high correlation with pain levels (Stratford & Kennedy 2004, Stratford, Kennedy & Woodhouse 2006, Dobson et al. 2013). Unfortunately, self-reported measures of functional capacity have a high risk of bias due to the lack of subject blinding to the intervention and its measurement (Higgins, Altman & Sterne 2011, Hansen et al. 2014). Batterham et al. (2011) reported that aquatic exercise had a similar sized effect on walking ability and static balance as land based exercise but that study included not

only patients with OA but also those with rheumatoid arthritis (RA) (Batterham, Heywood & Keating 2011).

There is conflicting evidence on whether aquatic therapy can improve lower limb muscle strength, i.e. there are reports of either no effect (Cochrane, Davey & Matthes Edwards 2005, Hinman, Heywood & Day 2007) or a very small effect (Foley et al. 2003, Wang et al. 2007). A similar pattern emerges when one examines walking ability, with several studies reporting improvements (Foley et al. 2003, Fransen et al. 2007, Wang et al. 2007, Wang et al. 2011) but others detecting no effect (Cochrane, Davey & Matthes Edwards 2005, Hinman, Heywood & Day 2007) from aquatic exercise. To date, no RCT has been conducted to discover if aquatic exercise could produce changes in gait speed or in the kinematics associated with early or late knee OA (Hamai et al. 2009). Roper et al. (2013) demonstrated an improvement in knee flexion during gait in knee OA subjects following just 3 sessions of high intensity underwater treadmill training (Roper, Bressel & Tillman 2013). Additional research is needed in this area. Moreover, there is no systematic review which would have investigated the impact of aquatic exercise on the previously described risk factors for knee OA progression assessing muscle strength or walking ability in early knee OA.

Aquatic exercise may also be an effective modality to prevent knee OA in pre-clinical populations. Bergamin et al. (2012), in their recent systematic review of the impact of aquatic exercise in healthy older people, indicated that aquatic exercise could improve measures of physical performance (Bergamin et al. 2012). This study population could represent those at risk of decreased neuromuscular function, low physical activity, increased body mass and chondrocyte senescence, i.e. individuals with an increased risk of knee OA. The systematic review conducted by Bergamin et al. (2012), suffered from methodological limitations, e.g. incomplete search, limited inclusion criteria and furthermore it did not include a meta-analysis estimating the size of the putative effects on different aspects of physical functioning (Bergamin et al. 2013). Nonetheless, the review concluded that there is some evidence that aquatic exercise can improve muscle strength, walking ability, agility and aerobic fitness in healthy older people. Numerous studies have investigated the impact of aquatic exercise on functional capacity in healthy older people but the study populations have been small and the trials have been subject to methodological shortcomings. Therefore, a systemic review with meta-analysis is needed to pool all the studies together in order to discover the effect of aquatic exercise on functional capacity in healthy older adults.

Aquatic exercise for weight loss

Aquatic exercise is recommended for overweight and obese people for whom land-based exercise is not beneficial due to musculoskeletal injury and pain, difficulty in reaching the sufficient exercise intensity or simply because the individual lacks motivation to perform this kind of exercise. Aquatic exercise has been demonstrated to be effective at decreasing body mass in middle aged

men and women (Greene et al. 2009), healthy older adults (Cox et al. 2010, Bergamin et al. 2013) and in individuals with lower limb osteoarthritis (Lim, Tchai & Jang 2010, Kim et al. 2012). However, the changes in body mass have been small, 0.76 to 1.3kg, although no worse than studies investigating the impact of land-based exercise alone for weight loss in individuals with knee OA (Messier et al. 2013). There is nothing known about the effects of aquatic exercise on body composition in people with early, symptomatic, knee OA.

Aquatic exercise for cartilage health

Land-based exercise has been shown to exert an effect on cartilage health but until now, there has been no research conducted on the effect of aquatic exercise on cartilage health. There is a common perception that aquatic exercise is low intensity plus low impact and therefore it does not provide a sufficient stimulus to cause either chondro-protective (maintain cartilage health) or chondro-facilitative effects (improve cartilage health) (Murray, Benke & Mandelbaum 2016). The possible mechanism behind the effects of aquatic exercise on cartilage could be different from compression and instead may be related to its properties as a unique and distinctive training modality. Water provides an opportunity to expose the cartilage to low shear and compression forces at a higher frequency than is possible on land. Therefore, high volume movements performed during aquatic exercise may represent a sufficient mechanical stimulus to increase or modify chondrocyte activity. This hypothesis is in agreement with the previous work of Koli et al. (2015) where moderate loads compared to compression appeared beneficial for collagen orientation and hydration (Koli et al. 2015). In addition, there may be changes in peripheral blood flow following immersion, possibly improving nutrient delivery and waste product removal from the joint via the synovium (Becker 2011). In line with the concept of the importance of continuous passive movements after surgery for improving cartilage health and synovial fluid composition after cartilage surgery, it could be hypothesized that high volume, low impact aquatic exercise might confer benefits for cartilage health (Knapik et al. 2013). Decreased activity and synovitis negatively affects the contents of hyaluronic acid and cytokines in the synovial fluid (Smith 2011, Scanzello & Goldring 2012). Therefore, high volume full ROM movements may improve the synovial fluid content and subsequently achieve a possible improvement in cartilage homeostasis (Wang et al. 2013).

While little is known on the impact of aquatic exercise on cartilage, an assessment of bone health especially that of subchondral bone, may give some indication of the possible indirect effect being mediated through the communication between the osteocytes and chondrocytes (Goldring 2012b). One of the main advantages of aquatic exercise is the reduction in impacts i.e. aquatic jumping is associated with a 45% reduction in landing impact forces compared to dry-land jumping and this may have an osteogenic effect if there is high repetition (Triplett et al. 2009). While impact and fast movements have been shown to be osteogenic, and improve bone traits in healthy and

osteoporotic adults, there are conflicting findings on the effect of aquatic exercise on bone traits, i.e. aquatic exercise has been shown to have no effect (Pernambuco et al. 2013), to maintain (Bravo et al. 1997) or even to slightly improve (Rotstein, Harush & Vaisman 2008) certain bone traits. These studies are of low methodological quality with a high risk of bias, differing in both their intervention content and duration. Therefore, further research is needed to clarify whether non-impact aquatic exercise can improve specific bone traits. It does seem that there is sufficient data to propose there may be benefits for cartilage health associated with aquatic exercise. The previously discussed improvements in functional capacity may improve neuromuscular function of the lower limb, thus possibly impacting on cartilage homeostasis and health (Roos & Dahlberg 2005).

2.3.2 Guidelines for prescription of aquatic exercise for knee OA

The OARSI guidelines state *"we separated the exercise programs into land-based exercise, strength and water-based exercise for more specificity"*, this seems to indicate that aquatic exercise is a single modality (McAlindon et al. 2014). It is recognized that land-based exercise can be broken up into different modalities including strength and aerobic training, neuromuscular exercise and other forms including Tai chi (Bennell & Hinman 2011, Bennell et al. 2014). Similarly aquatic exercise can be divided into different categories based on the differences in exercise physiology, i.e. muscle strength and power (e.g. aquatic resistance training), aerobic training (aquatic treadmill walking, deep water running, swimming, and aqua-aerobics), balance (e.g. Ai Chi, under-water obstacle course) and neuromuscular (e.g. reduced weight-bearing closed-chain exercises). Land-based exercise for individuals with OA follows the guidelines for exercise in healthy older adults (Nelson et al. 2007) or American Geriatric Society (AGS Clinical Practice Committee 2001, Bennell & Hinman 2011). Currently, there are no specific guidelines describing what kind of individuals with lower limb OA would benefit most from aquatic exercise. Moreover, there is no consensus on what is the optimal aquatic exercise for people with knee OA. The heterogeneity in findings noted in the recent systematic review was suggested to be due to difficulties in controlling training intensity as well as in measuring the work done during aquatic exercise (Bartels et al. 2016).

Often aquatic exercise is directly compared with land-based training with studies trying to directly replicate the same type of exercise in both environments; however, this type of comparison is rarely valid and needs to be assessed with caution. Aquatic exercise should be considered as a different form of exercise because of the impact of immersion on the cardiovascular, endocrine and neuromuscular systems and direct comparison to land-based exercise should be avoided (Hall et al. 2008, Becker 2011). Therefore, consideration of the different physiological responses to exercise in water should be taken into account when designing an aquatic therapy program for a specific therapeutic effect. Aquatic exercise designed for aerobic and strength training should follow established recommendations.

Aerobic aquatic training

When aerobic exercise is prescribed for an OA patient, its intensity may be assessed by using a rating of perceived exertion (RPE) or a percentage of $V0_2$max or heart rate maximum which has been previously measured on land. Moderate intensity is described as RPE 5-6/10 (40-60% of $V0_2$ max/HR max) and 7-8/10 (60-80% of $V0_2$ max/HR max) for vigorous (AGS Clinical Practice Committee 2001, Nelson et al. 2007). Heart rate and $V0_2$max vary extensively between different aquatic exercise modalities and individuals (Denning et al. 2012). Immersion in water evokes significant changes in the cardiovascular system, including a shift of about 700mL of fluid from the lower extremities into the thoracic cavity, which increases stroke volume. Therefore, in combination with the decrease in peripheral resistance, a decrease in heart rate of 5-15% is often seen during aquatic exercise (Becker 2011, Denning et al. 2012). Most studies comparing the different responses to aquatic exercise have used a underwater treadmill and deep or shallow water running and the subjects have been healthy young individuals. In contrast, studies looking at the effects of aquatic exercise in individuals with lower limb OA have tended to apply callisthenic-type exercises, therefore direct comparisons are difficult. Furthermore, as far as I am aware, no studies investigating the maximal aerobic responses to aquatic exercise in this patient population have been published. Irrespective of the aquatic exercise modality, similar RPE values are associated with lower heart rates and $V0_2$ levels compared to land based exercise (Denning et al. 2012). Recently, three protocols for measuring aerobic capacity during deep-water running and shallow water walking have been developed and validated. The results of these tests provide the basis for accurately monitoring the intensity of an individualised aquatic training programme (Cuesta-Vargas & Heywood 2011, Benelli et al. 2014).

Aquatic strength training

The recommendation for prescription of resistance training is based on the application of a percentage of the individuals 1 repetition maximum (1RM). Low intensity strength training involves 10-15 repetitions (reps) at 40% 1RM, moderate is 6-10 reps at 40-60% 1 RM and 6-8 reps at >60% of 1RM high (AGS Clinical Practice Committee 2001, Nelson et al. 2007). Prescribing resistance training in water is much more difficult as there are currently no methods to externally control the work done by the muscles. When immersed, the body is exposed to different forces than on land, since buoyancy supports the body and unloads the joints. However, this does not seem to affect the muscles ability to produce force. Pöyhönen et al. (2001) showed that isometric force production for knee extensors was similar in water and land although when measured by electromyography (EMG), the EMG amplitude seemed to decrease by 11-25%, depending on which muscle was being measured (Pöyhönen et al. 2001a, Pöyhönen et al. 2001b). At low speeds, buoyancy supports movement of the limbs, leading to low EMG amplitude values e.g. this phenomenon was seen during slow shoulder movements, which increase as the angular velocity of the

movement increases (Kelly et al. 2000). It is attributed to the drag created as the object moves through the water and is a consequence of fluid viscosity (internal friction) and turbulent flow (Gulick & Geigle 2009, Becker 2011). As an object moves through water, the water molecules start moving, creating turbulent water and frictional resistance to movement (Pöyhönen et al. 2000). Additionally, as a body moves through water, positive pressure builds up in the front and negative pressure behind the object, thus pulling the object back. The magnitude of drag will depend on the velocity, size and shape of the object as shown in the equation below (Equation [1]):

$$F_d = \frac{1}{2}\,\rho\,A\,v^2\,C_d \qquad [1]$$

Drag force production during underwater movement (F_d = Drag force, ρ = Density of water, A = surface area v = Angular velocity C_d = Coefficient of drag)

One method for controlling resistance during aquatic resistance training is the use of equipment that increases the surface area (A) and shape (C_d is affected by shape and streaming and Reynolds number) of the limb (Pöyhönen et al. 2000). The addition of a large resistance boot to the lower limb significantly increases drag forces during under water movement, even though there is a reduction in angular velocity (Pöyhönen et al. 2001a). In healthy women, drag forces produced during knee flexion and extension exercises in water with large resistance boots were 145N ± 30 compared to barefoot conditions of 45N ± 13 during knee extension; during knee flexion, the corresponding values were 145N ± 30 and 55N ± 13 (Pöyhönen et al. 2001a). This highlights the importance of utilising equipment to provide additional resistance to progress and optimise aquatic resistance training. Interestingly, Uthman et al. (2013) ranked aquatic exercise as high for probably improving both function and pain in lower limb OA. However, they also classified all but one of the top five ranking aquatic exercise programs as containing strength type aquatic exercises (Uthman et al. 2013). However, none of these trials actually used additional resistance aids, suggesting that their use of the term aquatic strength training may not be truly accurate.

2.3.3 Aquatic resistance training for knee OA

One possible aquatic training modality for knee OA would be progressive aquatic resistance training. Significant benefits have been observed with a progressive aquatic resistance training programme for physical functioning in healthy women (Pöyhönen et al. 2002) and following knee arthroplasty (Valtonen et al. 2010). Pöyhönen et al. (2002) reported that after a ten-week, 2-3 times a week aquatic resistance training programme, there was a significant improvement in isometric and isokinetic knee flexion and extension force as well as an increase in cross-sectional area of the thigh (CSA) (Pöyhönen et al. 2002). A similar, 12-week, aquatic resistance programme designed for knee arthroplasty patients revealed improvements in isokinetic knee flexion and

extension forces, improved walking speed, stair climbing ability, better performance in the sit-to-stand test and increased thigh CSA (Valtonen et al. 2010). Only the improvements in isokinetic force production for knee extensors and flexors were maintained at the 12-months' follow-up (Valtonen et al. 2011). The improvements in neuromuscular function suggest that this exercise modality could be used to treat the pain and decreased functional capacity in people with knee OA. This specific aquatic resistance training programme utilises the full range of knee and hip motion and therefore ensures optimal movement of synovial fluid and exposure of the whole cartilage to the low compressive and gliding forces created during the muscle contraction and movement. Therefore, aquatic resistance exercises involving a full range of motion, if performed at a high enough frequency and intensity, may confer benefits for cartilage health. To date, no studies have been performed on individuals with either early or later-stage knee OA however, there appears to be great potential for this training modality.

2.4 Current literature for aquatic exercise in the management of knee OA

Osteoarthritis (OA) is the leading cause of pain and activity limitations placing a burden on the economy equal to 1% of total gross domestic product (Yelin et al. 2007). There is an urgent need to develop interventions that can manage symptoms and reduce the impairment in functional capacity as well as preventing the progression and possibly improving cartilage health in the early phase of cartilage degeneration. Exercise appears to be a possible intervention option e.g. there is evidence that land-based exercise exerts a diverse impact on people with knee OA, including a decrease in pain and improvements in physical functioning (Multanen et al. 2014, Fransen et al. 2015, Koli et al. 2015) and even a possible modification of the biochemical composition of cartilage (Roos & Dahlberg 2005, Koli et al. 2015). However, land-based exercise programs are not always feasible or popular in individuals with OA related knee pain. Knee pain evoked kinesiophobia, results in avoidance of activity which is a major modulator of decreased physical activity and decreased functional capacity in subjects with early knee OA (Holla et al. 2014). Aquatic exercise is a popular exercise option for both healthy older adults and people with knee OA (Bergamin et al. 2012, Bartels et al. 2016). Water is a particularly attractive medium as a facilitator of exercise, allowing the person to train at sufficient intensities required to achieve improvements in physical capacity which may not be possible on land (Hall et al. 2008). In a recent systematic review which incorporated a meta-analysis (2016), aquatic exercise was shown to have a short term positive effect on pain and symptoms as well as achieving an improvement in patients-reported functioning and quality of life (Bartels et al. 2016). Batterham et al. (2011) showed that aquatic exercise was equally

effective as land-based training in patients-reported outcomes (Batterham, Heywood & Keating 2011). However, to date there has been no systematic review with a meta-analysis investigating the effects of aquatic exercise on performance-based measures of functional capacity. A summary of the current literature for land-based and aquatic exercise in the management of knee OA across the OA continuum from inciting event to end stage is shown in Figure 11 (Ageberg & Roos 2015, Roos & Arden 2016). While, there is evidence suggesting that neuromuscular exercises can reduce the incidence of knee injuries, there is no data to demonstrate whether exercise can prevent the progression of knee OA and therefore the focus has been placed on management of knee OA.

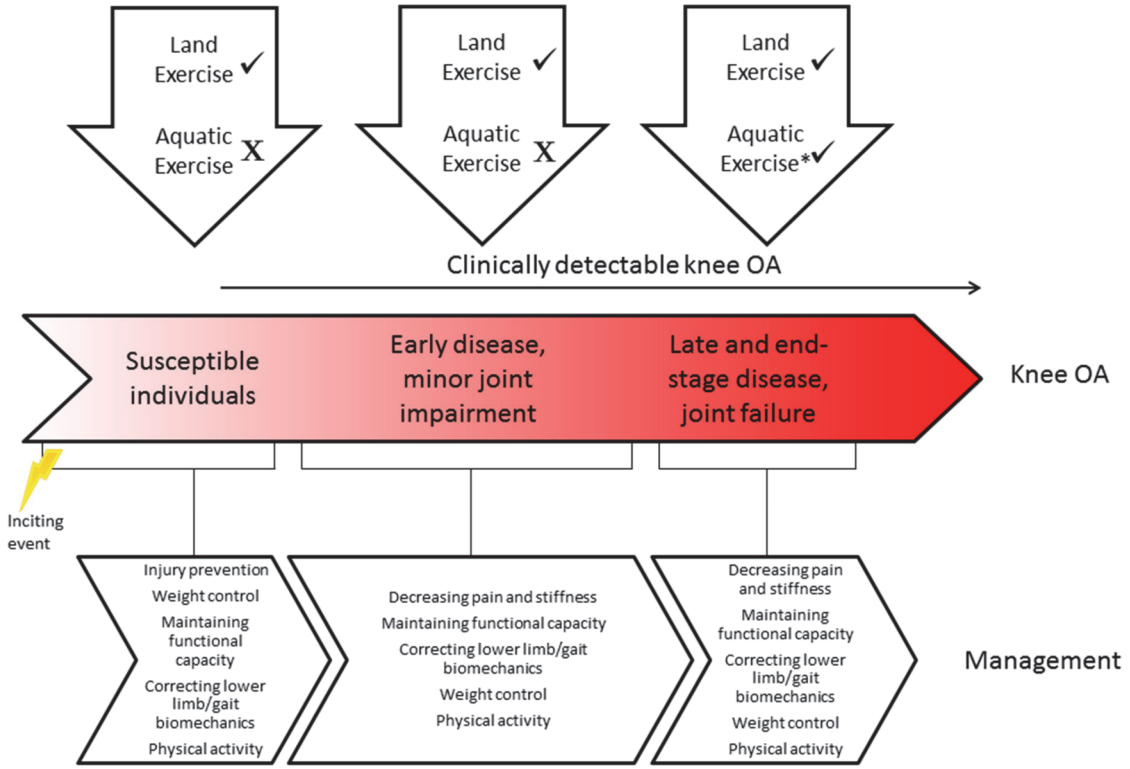

FIGURE 11 Role of aquatic exercise, based on current evidence, compared to land-based in the management of knee OA across the OA continuum. X = insufficient data to recommend, ✓= sufficient data to recommend. * only self-reported symptoms and physical function. Reproduced and adapted with permission (Ageberg & Roos 2015, Roos & Arden 2016).

Pain, decreased functional capacity and increased weight are risk factor for OA progression and worsening of pain and activity limitations As far as I am aware, no study has been conducted on the effects of aquatic exercise on early knee OA. This is primarily because a clear classification and diagnosis of early knee OA remains a topic of current research and only recently have advances in qMRI techniques made it possible to detect the biochemical and morphological changes occurring in cartilage in early OA and this make it possible to conduct these kinds of intervention studies (Nieminen et al. 2001, Lammentausta et al. 2006). These approaches have not been used widely in intervention studies and

their use will require further validation. As cartilage changes are seen in both asymptomatic and symptomatic individuals, it seems plausible to hypothesize that aquatic exercise may maintain functional capacity and prevent the progression to symptomatic knee OA. The role of aquatic exercise in the primary or early secondary prevention phase could be investigated with asymptomatic healthy people. Maintaining physical capacity in older adults may confer protection against some of the known risk factors for OA progression. While many small studies have been performed investigating the effect of aquatic exercise on functional capacity of healthy older adults, no systematic review with a meta-analysis has been conducted evaluating the effect of aquatic exercise on different aspects of functional capacity in this population.

Therefore, this study will investigate the effects of aquatic exercise on pain, functional capacity i.e. muscle strength, walking speed and aerobic fitness, levels of physical activity, body composition and the biochemical composition of cartilage at different stages of the knee OA .

3 PURPOSE OF THE STUDY

Knee OA is a common joint disease that leads to pain and loss of functional capacity. Current research indicates that land-based exercise is effective at decreasing pain and increasing functional capacity as well as exerting an impact on cartilage health in people at risk of developing OA as well as in those individuals actually suffering from early to late stage knee OA. Aquatic exercise is a very popular modality for people with knee OA, especially because of the reduction in the amount of pain experienced during training. However, there is minimal data supporting its implementation in this population, particularly in the earlier stages of the disease's development. Therefore, the purpose of this dissertation was to investigate the efficacy of aquatic exercise for persons in different stages of knee OA. In order to achieve this goal, the dissertation consists of two systematic reviews with meta-analyses and one 4-month randomised controlled trial with a 12-month follow-up.

The specific research questions were:

1. Based on the current published literature, can therapeutic aquatic exercise improve pain and physical functioning, as compared to usual care, in persons with lower limb and specifically knee OA? (Study I)

2. Based on the current published literature, what aspects of physical functioning can be improved by aquatic exercise as compared to usual care or land-based exercise, in healthy older adults? (Study II)

3. Does a 4-month intensive aquatic resistance training program have an effect on symptoms, physical functioning, body composition and biochemical composition of tibiofemoral cartilage in post-menopausal women with mild knee OA, and furthermore, are the results maintained during a 12-month follow-up period? (Studies III, IV and V)

4 RESEARCH METHODS

4.1 Study designs implemented in the dissertation

In order to fulfil the purpose of this dissertation, two different study designs were implemented (Table 4). The first design was a systematic review with a meta-analysis. Two systematic literature reviews, collecting the data from previously published randomised controlled trials (RCT) evaluated the effect of therapeutic aquatic exercise on symptoms and function in people with lower limb OA (Study I) and the effect of aquatic exercise on function in healthy older adults (Study II). A distinction was made between therapeutic aquatic exercise and aquatic exercise because the interventions for people with lower limb OA generally were designed to have a specific therapeutic effect, i.e. pain relief, whereas the aquatic exercise intervention was designed to have a specific effect on performance-based measures of functional capacity. The data for Study I used results from RCT studies published before 1st December 2013 and Study II used data from RCT studies published before 31st December 2015.

The second study design was a registered randomised controlled trial (AQUAREHAB study, ISRCTN65346593). This randomised clinical trial investigated the efficacy of intensive aquatic resistance training program in postmenopausal women with early knee OA. The AQUAREHAB-study, had a 4-month intervention period with a 12-month follow-up period after the intervention. We classified mild knee OA as the situation where the participant experienced knee pain on most days and there were radiographic changes in tibiofemoral joints K/L I (possible osteophytes) or II (definite osteophytes and possible joint space narrowing) (Kellgren & Lawrence 1957). The data for AQUAREHAB was collected in Jyväskylä, Finland between January 2012 and July 2014. The published protocol for the RCT project was Study III. Studies IV and V, used the data collected from the pre-, post- intervention and the 12 months' follow-up measurements.

TABLE 4 Description of the study designs, participants and outcomes included in this dissertation.

Study	Study Design	Participants	Intervention	Comparison group	Duration of intervention and follow-up	Primary outcome measures	Secondary outcome measures
I	**Systematic Review** with meta-analysis	Adults with diagnosed lower limb osteoarthritis	Therapeutic aquatic exercise	Control (usual care)	ANY	Pain, symptoms, self-reported functioning and performance-based measures of function, quality of life	N/A
II	**Systematic Review** with meta-Analysis	Healthy older adults aged >50	Any aquatic exercise	Control (usual care) and/or land-based exercise	ANY	Self-reported functioning and performance-based measures of function	N/A
III	**Protocol study** (AQUAREHAB)	Women aged 60-68 years with mild tibiofemoral osteoarthritis	Progressive aquatic resistance training	Control (usual care)	INT: 4 months FU: 12 months	qMRI, bone traits and body composition	Muscle strength, muscle power, agility, postural stability, walking ability, gait quality self-reported questionnaires (pain, symptoms, functioning, quality of life)
IV	**Experimental** Randomised controlled trial with 1 year follow-up	Women aged 60-68 years with mild tibiofemoral osteoarthritis	Progressive aquatic resistance training	Control (usual care)	INT: 4 months FU: 12 months	Body composition, walking speed	Knee extension and flexion isometric strength, pain, symptoms, self-reported functioning, quality of life
V	**Experimental** Randomised controlled trial	Women aged 60-68 years with mild tibiofemoral osteoarthritis	Progressive aquatic resistance training	Control (usual care)	INT: 4 months	qMRI (T2-relaxation, dGEMRIC)	Estimated cardiovascular fitness, knee extension and flexion isometric strength, pain, symptoms, self-reported functioning, quality of life

INT = intervention period, FU = Follow-Up period, N/A = Not applicable, qMRI = quantitative magnetic resonance imaging

4.2 Systematic review and meta-analysis (Studies I and II)

Both systematic reviews were conducted in line with the Preferred Reporting Items for Systematic Reviews (PRISMA) (Moher et al. 2009).

4.2.1 Eligibility criteria, study selection and search strategy

Trials included into the systematic reviews had to have utilized a randomised RCT design and fulfil the stated criteria according to the PICOS system (Population, Intervention, Comparison, Outcome and Study design) (Rios, Ye & Thabane 2010). Eligibility criteria are described in Table 5. A broad search using Medline, Cinahl, SPORTDiscus, PEDro and Embase databases for both studies (I and II) was performed, with the addition of PubMed for Study I and Web of Science and Cochrane library for Study II. For both reviews, an example of the comprehensive combination of keywords can be found in the appendix of each respective study.

TABLE 5 Study inclusion criteria for Study I and II.

	Study I	Study II
Search Terms	"hydrotherapy" or "water exercise" or "aquatic exercise" or "aquatic therapy" or "water rehabilitation" or "aquatic physical therapy" or "aquatic rehabilitation" or "aquatics" AND "osteoarthritis" or "OA" or "arthritis"	"aquatic therapy" or "aquatic exercise" or "water therapy" or "hydrotherapy" or "aquatic physiotherapy" or "water exercise" or "aquatic rehabilitation" or "pool exercise" or "water rehabilitation" o "aquatic physical therapy" or "aquatics" or "swimming intervention" AND "elderly" or "older people" OR "older population" or "older adults" or "aging" "senior"
Date of search	December 1st, 2013	December 31st, 2015
PICOS **P**opulation, **I**ntervention, **C**omparison, **O**utcome measure and **S**tudy design	**P:** clinically diagnosed lower limb osteoarthritis (ACR or radiographic) **I:** Therapeutic aquatic exercise (any) with full immersion **C:** Control **O:** Pain, Function, Quality of life **S:** Randomised controlled trial	**P:** Older adults, average age >55 years with no medical diagnosis of disease e.g. OA. Frail healthy included **I:** Aquatic exercise (any) with full immersion **C:** Control and/or land based-exercise **O:** Performance-based measures of and/or self-reported functioning **S:** Randomised controlled trial
Limitations	English PEDro score of ≤5	Lower age limit 50 years, presence of comorbidity e.g. osteoarthritis, cardiac disease

A hand search of references, grey literature and guidelines was performed in both studies. Duplicates were removed using Endnote© (Endnote X7, Thomson Reuters, USA). Based on the title, animal trials and non-relevant studies were excluded. The abstracts were then read and non-clinical trials or non-intervention trials were excluded. Inclusion was based on the assessment of two independent reviewers and full agreement was required. Full text manuscripts for the remaining trails were retrieved and read by each reviewer and the final selection made. If needed, disagreements were resolved through discussion and assistance from a third reviewer.

4.2.2 Data extraction

For the qualitative synthesis intervention description, inclusion/exclusion criteria, baseline data and values for all outcomes at baseline, post and longer follow-up (3-6 months) was extracted by two reviewers and checked for accuracy by a third reviewer. Where possible, intention-to-treat data was extracted for follow-up measurements, otherwise per protocol data was utilized. When data was not presented in the publication as mean and standard deviation (SD) or was described in a form which prevented calculation of mean and SD, the original author was contacted and original data requested. In all cases, a researcher-devised excel form was used for the data handling.

Outcome measure selection

All outcomes with appropriately reported data were extracted and included in the qualitative and quantitative synthesis. Outcome measures were grouped according to their construct and design. Self-reported pain (Juni, Reichenbach & Dieppe 2006), physical functioning (Veenhof et al. 2006) and quality of life were extracted according to the *a priori* ranking list (Table 6). The results from Study I, published in this dissertation, differ from the original published manuscript. In this dissertation agility and walking ability were separated whereas they had been combined in the original manuscript under the title physical functioning tests (activities) (Study I).

TABLE 6 Ranking order for self-reported questionnaires (Study I and II).

Pain	Physical Functioning	Quality of life
1) Global pain score	1) WOMAC VA3.0 or numerical	1) KOOS QoL
2) Pain on walking	2) WOMAC LK or VA3.0 modified,	2) SF36 MCS or SF12 MCS
3) WOMAC osteoarthritis index pain subscore	3) HOOS or KOOS or Lesquesne modified	3) SF36 General health
4) Composite pain scores other than WOMAC	4) SF-36 (composite scores)	4) SF36 role mental health
5) Pain on activities other than walking	5) Health assessment questionnaire	5) Other algofunctional composite scores
6) WOMAC global score	6) Arthritis Impact Measurement Scales 2-Short Form (AIMS2-SF)	
7) Lesquesne osteoarthritis index global score	7) SF-36 physical function or physical role functioning	
8) Other algofunctional composite scores	8) Activities and balance confidence scale	
9) Patient's global assessment		
10) Physicians global assessment		

Performance-based measures of functional capacity were also extracted using pre-planned selection criteria based on construct i.e. muscle strength, muscle power, muscle endurance, respiratory muscle function, agility, postural stability, walking ability, flexibility/ROM, aerobic fitness and self-assessed functioning (Rikli & Jones 1999). *A priori* ranking lists for all performance-based measures of functional capacity are shown in Table 7. Ranking order for performance-based measures of functional capacity, i.e. activity or agility were selected based on the proposals of Dobson et al. (Dobson et al. 2013). Forced inspiration (more active in water) was ranked higher than expiration.

TABLE 7 Ranking order for performance-based for measures of function.

Muscle group/movement	Activities/Agility	Walking ability	Flexibility
1) Knee extension	1) Timed up and go (TUG)/8ft up and go	1) 40-80m walk test (fast-paced)	1) Sit and reach
2) Full lower limb extension e.g. leg press	2) Chair stand (30 sec)	2) 50ft walk test (fast-paced)	2) Trunk flexion
3) Knee flexion	3) Ascending stairs	3) 6 minute walking test (6MWT)	3) Trunk extension
4) Hip extension	4) Descending stairs	4) 8ft walk test	4) Back scratch
5) Grip strength			
6) Chest press			
7) Shoulder pull down			
8) Shoulder press			

4.2.3 Statistical synthesis and Meta-analysis

The meta-analysis was performed using Review Manager (RevMan, Version 5.3. Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2014). In all cases, the size of the effect was calculated as the standardised mean difference (SMD). In these studies (I and II), a SMD of 0.2-0.5 was considered as small, 0.5-0.8 as medium and ≥0.8 as a large effect. The Cochrane software calculates SMD using Hedges' g [Equation [2]) which is similar to Cohen's *d* except that it uses a pooled standard deviation s* (Equation [3]) (Deeks et al. 2011).

$$Hedges'\ g = \frac{\bar{x}_1 - \bar{x}_2}{s^*} \quad [2]$$

$$s^* = \sqrt{\frac{(n_1-1)s_1^2 + (n_2-1)s_2^2}{n_1 + n_2 - 2}} \quad [3]$$

In all analyses, we used an inverse-variance weighted random-effects model that incorporates heterogeneity into the model. High heterogeneity as measured with I^2 was expected, due to the combination of different outcome measures (Higgins et al. 2003). In all cases, the effect size is presented as SMD and 95% confidence intervals. Three quantitative syntheses were performed; one for therapeutic aquatic exercise versus control for people with lower limb OA. A second synthesis compared aquatic exercise versus control and the third compared aquatic exercise to land-based exercise, both in healthy older adults. When not reported, standard deviation was calculated from 95% confidence intervals using the RevMan's built in calculator (Equation [4]). In cases where median and interquartile ranges were reported, median was taken as best estimated mean and interquartile ranges were divided by 1.35 (Hozo, Djulbegovic & Hozo 2005, Batterham, Heywood & Keating 2011).

$$\begin{aligned} &\mathrm{CI} = \mathrm{mean} \pm 1.96 \times \mathrm{SE} \\ &\mathrm{mean} \pm \mathrm{CI} = \mathrm{Ci}\alpha \\ &\mathrm{CI}\alpha \div 1.96 = \mathrm{SE} \\ &\mathrm{SD} = \mathrm{SE} \times \sqrt{\mathrm{n}} \end{aligned} \quad [4]$$

Additional sensitivity analyses

Additional sensitivity analyses conducted in Study I investigated the effects of therapeutic aquatic exercise on people with knee OA only, and trials including subjects with either/or knee and hip OA. Sensitivity tests for Study II, performed in both meta-analyses, investigated the impact of the drop-out rate (<15% and ≥15%), methodological quality (removal of low Delphi <4), age (68< and ≥68 years old), training frequency (<3 or ≥3 times a week) and effects at different levels according to the International Classification of Functioning, Disability and Health (ICF), i.e. body structure and function or activities and

participation. The percentage (%) of drop-outs was calculated in both studies (I and II) using baseline sample size and the number of participants who did not attend the post-intervention measurement or whose post-intervention data was not reported.

4.2.4 Methodological quality, risk of bias and publication bias assessments

Methodological quality for Study I was assessed using the 11 point PEDro scale (Sherrington et al. 2000) which has been shown to be a reliable (Maher et al. 2003) and valid assessment tool (de Morton 2009). The PEDro scale is based on the 9 point Delphi scale developed by Verhagen et al. (1998) and is used specifically with RCT's in physiotherapy (Verhagen et al. 1998). Methodological quality, for Study II was assessed using the 9 point Delphi scale.

The 9 similar quality assessment criteria of the Delphi and PEDro scale are: eligibility criteria, random allocation, allocation concealment, baseline similarity, participant blinding, therapist blinding, assessor blinding, adequate follow-up, intention-to-treat analysis, between group comparisons and point and variability measures given. The additional category in the PEDro scale is whether the main outcome is achieved from 85% of subjects. Each criterion is scored 1 = yes and 0 = no, don't know/unclear. In the PEDro scale, the first criterion (eligibility) is not included in the final score which ranges from 0-10 while the Delphi scale ranges from 0-9. The maximum score that an exercise intervention trial can generally be awarded is 9 and 8 for Pedro and Delphi respectively because of the difficulties in blinding the subjects and therapist to the intervention in exercise trial (van Tulder et al. 2003). A trial with a score of ≥7 (PEDro) and ≥6 (Delphi) is considered to have high methodological quality, while trials scoring ≤5 and <4 are considered as low quality for the PEDro and Delphi respectively (Maher et al. 2003).

The risk of bias was assessed using the Cochrane Risk of Bias assessment (Higgins, Altman & Sterne 2011). This consists of 8 bias domains referring to selection bias (sequence generation and allocation concealment), performance bias (blinding of participants and care provider), blinding of outcome assessment for self-reported outcomes and physical performance measures, attrition bias (incomplete outcome data), selective outcome reporting and other bias. Each domain is scored as low risk, high risk or unclear. An overall score for risk of bias was awarded to each trial, based on seven of these domains (blinding of participants excluded) (Higgins, Altman & Sterne 2011). The other possible risks of bias were considered as trial size, power analysis and centre status, these were extracted to give additional information on possible risk of bias (Hansen et al. 2014). Small study effect was assessed through interpretation of funnel plot asymmetry (Sterne et al. 2011).

Assessment of methodological quality and risk of bias were performed independently by at least two of four reviewers (BW, AO, VM and DD) and compared. In case of disagreement, consensus was found by consulting another reviewer (JL).

4.3 AQUAREHAB (Studies III-V)

The AQUAREHAB study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) (Moher et al. 2012).

4.3.1 Eligibility criteria and subject recruitment

Volunteer postmenopausal women, between the ages of 60-68 years old, were recruited through a series of local newspaper advertisements; they were living in the county of Central Finland which has a population of approximately 275,000. Inclusion eligibility was initially assessed using a structured telephone interview. The telephone questionnaire included questions concerning degree of knee pain, previous diagnosis of OA, current level of physical activity and past medical history. Suitable participants underwent weight bearing radiographic imaging of both knees. An experienced radiologist and orthopaedic physician assessed the images by grading the degree of OA in the tibiofemoral and patellofemoral joints using the Kellgren-Lawrence grading (K/L 0-IV) (Kellgren & Lawrence 1957). Those participants who had a KL score of I (possible osteophytes) or II (definite osteophytes, possible joint space narrowing), were included in the next stage of the eligibility assessment where they underwent a medical and physiotherapy screening. At this point, any possible physical or medical limitations to full participation in the intervention were assessed e.g. severely restricted joint range of movement (ROM), excessive laxity of knee joint, possible physical disabilities and abnormalities found from resting echocardiogram. All of those participants fulfilling all the inclusion criteria were included into the study and underwent the baseline measurements (Table 8).

TABLE 8 Inclusion and exclusion criteria for AQUAREHAB.

Inclusion criteria	Exclusion criteria
- Female aged 60-68 year old - Radiographically confirmed changes in tibiofemoral joint K/L grade I and II - Mild to moderate knee pain during on most days the last 12 months - No illness that would prevent or limit participation in an active exercise program - Ability to voluntarily sign consent form - Willingness to participate in all tests and be randomly allocated in to intervention or control group - Appropriate kidney function for efficient removal of contrast agent (Krea)	- Complete T2 datasets (pre- and post) - BMI > 34 - Knee pain > 50/100mm VAS pain - Kellgren-Lawrence grades of 0 or III-IV - Intra-articular steroid injections in past 3 months - Knee surgery of any kind within the last 12 months. - Knee instability, musculoskeletal injury or other disease that would prevent full participation in training - Loose particles in knee joint - Femoral neck bone mineral density (BMD, g/cm^2) lower than -2.5 or undergoing treatment for osteoporosis - Contra-indications to MRI scans e.g. metallic implants, tattoos, claustrophobia - History of cancer or radiotherapy

4.3.2 Randomisation and blinding

After baseline measurements, all participants were randomly allocated a three digit identification number (ID) to blind researchers to the intervention allocation and provision. A blinded statistician, only provided with ID and K/L grade, performed a computer generated block randomisation of size of 10, stratified according to K/L grade I or II. The MRI scans were performed by external radiologists blinded to intervention allocation. Dual-energy X-ray absorptiometry (DXA) measurements were performed by the principle investigator (BW), but segmentation and analysis were done using the built-in software without modification. Due to practical limitations, the physical therapists providing the intervention also performed the performance-based outcome measures, but the principal investigator was blinded.

4.3.3 Ethics

The AQUAREHAB research project was given ethical consent on 30th November 2011 Dnro 19U/2011 from the Ethics Committee of the Central Finland Health Care District. The study was conducted according to good clinical and scientific guidelines and the Declaration of Helsinki (2000). Written informed consent was obtained from all subjects before their participation in the study. All subjects were informed that they had the right to withdraw from the study at any time, without needing to provide a reason for withdrawal.

4.3.4 Exercise intervention

Those subjects randomised into the intervention group participated in one hour of aquatic resistance training, three times a week for four months, i.e. a total of 48 training sessions. The intervention protocol implemented in this study was adapted from a programme previously used and shown to be effective in healthy women (Pöyhönen et al. 2002) and for individuals who had undergone post knee arthroplasty (Valtonen et al. 2010). Each one hour long session consisted of a 15 minute warm up, a 30 minute intensive aquatic resistance exercise programme and a 10-15 minute cool down. The intervention was completed in small groups of 6-8 subjects in a pool heated to 32 degrees with depths 1.3-1.5m. Aquatic steps were used to ensure that all subjects were able to complete the standing exercises at a depth level approximately to their xiphoid bone ±5cm ensuring weight bearing on the supporting leg amounting to 25-50% of their own body weight (Harrison, Hillman & Bulstrode 1992). All sessions were supervised by 2 experienced physiotherapists, who had been trained to instruct these aquatic programs and were accredited for life-saving before the trial began.

Warm-up

The warm up consisted of a circuit of 10 different exercises followed by a 2-4 minute session of aerobic exercise to gradually increase heart rate. The full structure and movements are shown in detail in the supplemental material of Study V.

Lower limb resistance training program

The intensive aquatic resistance program consisted of 5 lower-limb aquatic resistance exercises (Figure 12). Progression of the exercise program was ensured by using resistance boots of different sizes and by varying the duration of the sets. Table 9 shows the different durations of each set and targeted amount of repetitions per set for each stage of the intervention. The intensity of the training sessions was set at "as hard and fast as possible" to ensure maximal muscle contraction. Pöyhönen et al. discovered that during maximal knee flexion and extension exercises in water with large resistance boots, the drag forces produced up to 80-85% (145 ± 30 N) of maximal isokinetic movements (Pöyhönen et al. 2001a). Whereas, barefoot aquatic knee flexion and extension movements produced approximately 28% drag force resistance compared to land measured maximum isokinetic testing. Training with the large boots evoked approximately three times greater drag force resistance compared to the value when performed barefoot (Pöyhönen et al. 2001a). Three progressions levels were used in this project: barefoot, small fins and large boots. The small fins had a frontal area of 0.0181m^2 (Theraband products, The Hygienic Corp., Akron, OH 44310 USA) and large boots 0.075m^2 (Hydro-Tone hydro-boots, Hydro-Tone Fitness Systems, Inc. Orange, CA 92865-2760, USA).

TABLE 9 Intensity and progression of each phase of the aquatic resistance training.

Weeks	Resistance type	Sets	Repetitions per set	Time (sec)	Recovery (sec)	Target RPE*	Total time (mins)	Total No. reps per session
1-2	Barefoot	3	25-30	45	30	14-15	30	750-900
3-5 alternating	Small	3	20-25	45	30	15-16	30	600-750
	Small	3	12 to 15	30	45	16-17	26	288-360
6-8, 12 alternating	Small/ Large	3	14-20	45	30	16-17	30	420-600
9-11, 13-16 alternating	Large	3	14-20	45	30	16-18	30	420-600
	Large	3	12 to 15	30	45	16-18	26	288-360

* RPE = Rate of Perceived Exertion (BORG 6-20)

FIGURE 12 Exercises included in the aquatic resistance training. A) Knee flexion/extension in sitting, B) Kickback, C) Knee flexion/extension in standing, D) Hip abduction/ adduction, E) Hip flexion/extension with knee extended.

Full knee joint range of motion was strictly controlled to ensure optimal movement of synovial fluid and exposure of the whole cartilage to the low compressive and gliding forces created by the muscle contraction and movement. There were two instructors present during every training session with one providing instruction on timings and the other supervising technique and giving individual instructions as necessary. This ensured the high intensity of the training with good quality, full range of motion movements. The planned daily training programs and progressions are shown in detail in the supplemental material of Study V. The exercises were completed in the form of a circuit with each subject completing all three sets of each movement before moving on to the next one. Variety was also ensured by altering the order of the movements and with which leg the training was started. An additional 60 seconds between movements was provided to allow safe transition between stations and give a small amount of additional rest.

Cool down

The cool down consisted of a 4-5 minute of active light aerobic movements to gradually reduce heart rate followed by 5-8 minutes of light static stretching.

Monitoring and controlling training intensity

Intensity of training of every session was monitored using Polar heart rate monitors (F6 or RCX5, Polar Oy, Finland) and rating of perceived exertion (RPE, BORG 6-20) (Borg 1982). Target training zone was 60-80% of maximum heart rate according to the Karvonen formula e.g. 60% training limit = (220 – age) x 0.6 and 80% training limit = (220 – age) x 0.8 with no adjustments made for the possible effects of immersion (Becker 2011). Psychological wellbeing during the training session experienced by the participant was also measured for every session using a 1-5 scale (1=Poor, 2=Tolerable, 3= Satisfactory, 4=Good 5=Excellent).

To ensure there was true progression between the three resistance levels, several additional measurements were taken. Blood lactate levels were measured to obtain quantitative measures of training intensity and to ensure that all training groups were training at similar intensities. Samples were taken during week 12 (Session 34-36), before training after 15 minutes of rest and 3 minutes after the cessation of main strength training session. These were recorded for each different intensity level of training (barefoot, small and large resistance boots, 45 seconds work per leg). Fingertip blood samples were taken using a safety lancet, normal 21G with penetration depth 1.8mm (Sarstedt AG & co, Germany) and collected into 20 µL capillary tubes which were placed in 1-mL hemolyzing solution. Care was taken to clean the skin to avoid contamination from chlorinated pool water. The samples were analysed using an automatic system (EKF diagnostic, Biosen, Germany) after training. During these three sessions, the number of repetitions achieved per movement was also measured.

Assessment of side effects

Adverse effects or health problems attributable to the testing protocol or intervention exercise protocol were documented and reported. Following each individual measurement and training session, self-reported knee pain was assessed on a visual analogue scale (VAS 0-100mm) as well as any other physical symptoms such as pain elsewhere than the knee, stiffness and general fatigue. All subjects had medical insurance and access to the attending medical physician free of charge throughout the 4 month intervention and 12 month follow up period.

Control group

The controls were asked to maintain their usual activities and they were offered the possibility of participating in two sham contact sessions consisting of 1 hour of light stretching and relaxation during the 4-month intervention period.

4.3.5 Outcome measures

The outcomes measures for the AQUAREHAB project have been categorized using the International Classification of Functioning, Disability and Health (ICF) (Figure 13).

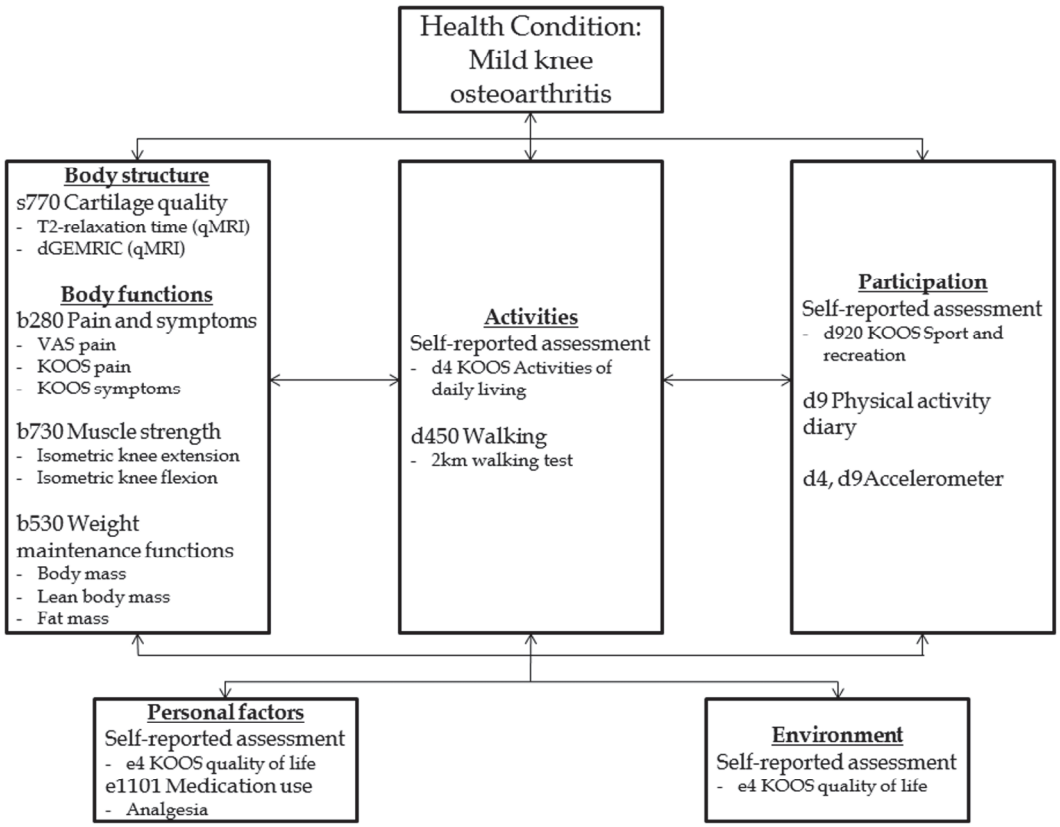

FIGURE 13 Measurements utilized in the AQUAREHAB study presented according to the ICF model.

Walking speed and estimated cardiorespiratory function

Maximal aerobic power (VO_{2max}, ml/kg/min) was estimated using the UKK 2km walk test (UKK Institute, Tampere, Finland). This test required the subject to walk 2km, around a 200m running track, as quickly as possible with a target of 80% maximal heart rate (Laukkanen et al. 1993a). VO_2 max was estimated using walking time, body mass index (BMI), age and heart rate at the end of the test (Equation [5]. The heart rate was measured by a portable heart-rate monitor (Polar F6, Polar Electro Ltd, Kempele, Finland). This is a convenient approach for estimating V02 max (Laukkanen et al. 1992b) and sensitive to changes (KukkonenHarjula et al. 1998). Its validity has also been tested with a correlation coefficient of 0.69-0.77 (Laukkanen et al. 1992a). Aerobic capacity or V02 peak were estimated from the results of the UKK 2km walk test, calculated according to the formula below and expressed in units of mL/(kg·min):

$$116.2 - 2.98 \times (\text{time, min}) - 0.11 \times (\text{heart rate}) - 0.14 \times (\text{age}) - 0.39 \times (\text{body mass index}) \quad [5]$$

Additionally walking time for completing the 2km walk test was recorded in seconds. Walking speed in meters per second (unit m/s) was calculated using the following equation [6]:

$$\textit{2000/time taken to complete test in seconds} \quad [6]$$

Muscle strength

Maximal isometric knee flexion and extension strength of both legs were measured using an adjustable dynamometer chair (Good strength, Metitur Ltd, Jyväskylä, Finland). The best result from 3 contractions was used and recorded in Newtons (N). In our laboratory, the precision of the test is 6% for knee extension and 9 % for knee flexion (Sipilä et al. 1996).

Biochemical composition of cartilage

Two qMRI techniques were used to quantify the biochemical composition of cartilage; T2 relaxation time (milliseconds, ms) and the dGEMRIC index (ms) measured using a Siemens Magnetom Symphony Quantum 1.5-Tesla scanner (Siemens AG, Medical Solutions, Erlangen, Germany). Single slice images from the centre of the medial and lateral femoral condyles were taken for both T2 relaxation time and dGEMRIC measurements from the affected knee with the highest K/L grade. In case of identical grading bilaterally, the right knee was imaged. Accurate repositioning was ensured by using a specially designed inflatable pillow, this also prevented movement during the imaging. A full description of the MRI methodology can be found from the protocol of the study (Study III) and appendix of the study (V).

T2-Relaxation time

Arrangement of collagen and hydration state of the cartilage was measured using T2 relaxation time mapping (T2). The T2 method has been histologically validated in vitro (David-Vaudey et al. 2004), and it has been applied in several human studies to assess chondral repair (Kurkijärvi et al. 2007, Trattnig et al. 2007b, Welsch et al. 2008, Welsch et al. 2009, Oneto, Ellermann & LaPrade 2010). The repeatability (CV_{RMS}) of T2 relaxation time in a healthy knee subject with a 1.5 Tesla clinical scanner is 3.2-5.4% (Hannila et al. 2015). A decrease in T2 values is indicative of an improved integrity and orientation of the collagen fibres and a decrease in the hydration of articular cartilage (Nieminen et al. 2001, Lammentausta et al. 2006).

dGEMRIC index

Delayed gadolinium-enhance magnetic resonance imaging of cartilage (dGEMRIC), a technique which is sensitive to the distribution of GAG, was used to evaluate the biochemical composition of cartilage. T1 images were taken 90 minutes after intravenous injection of 0.4mL/kg (double dose) of Gd-DTPA2- (Magnevist, Schering, Berlin). The dGEMRIC method has been

validated in several *in vitro* studies (Allen, Burstein & Gray 1999, Bashir et al. 1999, Nieminen et al. 2002) and it has been utilized in many *in vivo* studies (Bashir et al. 1997, Gillis et al. 2001, Tiderius et al. 2001, Burstein & Gray 2003, Tiderius et al. 2003, Tiderius et al. 2004, Vasara et al. 2005, Kurkijärvi et al. 2007, Trattnig et al. 2007a, Trattnig et al. 2008). The reproducibility of dGEMRIC (CV_{RMS}) of dGEMRIC in asymptomatic subjects is 7% for full-thickness ROIs and 5% for bulk cartilage (Multanen et al. 2009). The intraclass correlation coefficient (ICC) for bulk cartilage is 0.95 (95% CI 0.85-0.99) and 0.87 (0.61 – 0.96) for femur and tibia respectively (Multanen et al. 2009). The GAG concentration is directly related to the dGEMRIC index values and a lower dGEMRIC index is associated with a lower GAG content (Bashir et al. 1999, Nissi et al. 2004).

Segmentation

Single sagittal slices at the centre of the medial and lateral femoral condyles were manually segmented using an in-house MATLAB application with built-in motion correction for dGEMRIC (Mathworks, Inc. Natick, MA, USA). In this study we focused on the full thickness central and posterior ROIs of the femoral condyles and the central ROI of the tibial plateaus (Figure 14). T2 images were segmented with a relaxation time limit of 0-120 ms and dGEMRIC images using an in-house designed motion correction. Particular care was taken on interpretation and drawing of the lines for the bone-cartilage and cartilage surface. dGEMRIC indices were corrected for BMI (Tiderius et al. 2006). In our laboratory, the inter-observer error (CV_{RMS}) for T2 full-thickness ROIs is 1.3% to 3.3% and 2.8% to 4.0% for dGEMRIC.

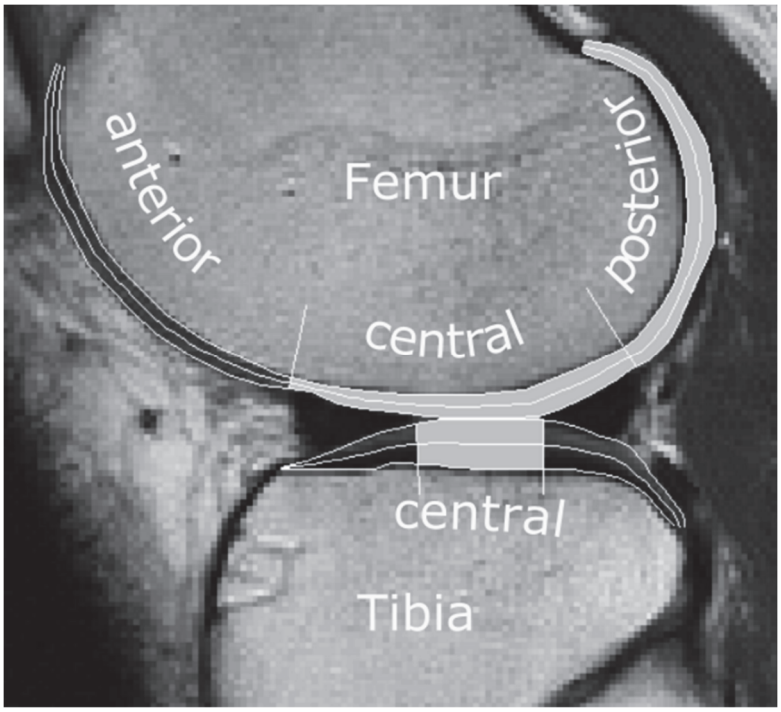

FIGURE 14 Regions of interest (ROI) for the segmentation of femoral and tibial cartilage. The highlight area shows the regions of interest (ROI) for this dissertation

Dual-energy X-ray absorptiometry (DXA)

Dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy; GE Lunar Healthcare, Madison, WI, USA) was used to assess body composition (total body fat and lean body mass (kg)). Analyses were carried out using enCORE software (ENcore 2011, version 13.60.033) following the manufacturer's protocols without modification. The *in vivo* precision of these measurements has been reported to be CV 1.3-2.2% (Uusi-Rasi et al. 2010).

Self-reported pain, symptoms, physical functioning and Quality of life

A Likert version of the knee injury and osteoarthritis outcome score (KOOS) was used to measure 5 different domains: pain (9 questions), other symptoms (7 questions), activities of daily living (16 questions), sport and recreation (5 questions) and knee related quality of life (4 questions). Each response was scored on a scale of 0-4. Scores for domains were transformed into a score 0-100 with a score of 0 indicating extreme knee problems and 100 representing no knee problems. The internal consistency for the KOOS is 0.86-0.96 and test-rest (ICC) is 0.67-0.95 (Bekkers et al. 2009). The reliability of the Finnish language version of the KOOS has been shown to be similar to that of the English version (Koli et al. 2011).

Health status

General health and habitual physical activity at baseline were assessed by a questionnaire devised by the research group. This health questionnaire addressed medical conditions, current medications, years of menopausal hormone therapy, history of fractures and current daily physical activity. Pre-study physical activity levels were converted into metabolic equivalent task hours (METh) per week (Ainsworth et al. 2011).

Analgesic use

Throughout the entire 12-month follow-up period all subjects were asked to keep a record of their daily amount of analgesics taken to manage their knee pain. Space was provided in the physical activity diary for ease of recording.

VAS pain

Pain in both knees a baseline was measured using the visual analogue scale (VAS) 0-100mm where 0 = no pain and 100 = worse pain imaginable.

4.3.6 Physical activity

Physical activity diary

During both the intervention period and the one year follow up period, daily physical activity of every subject (excluding pool training) was recorded using a leisure time physical activity diary. The diary was completed daily and each activity, duration and intensity (1 = low, 2 = moderate or 3 = hard) was recorded. From this data METh per week and per month were calculated (Ainsworth et al. 2011).

Accelerometer

In week 13 of the intervention period, the daily physical activity (excluding intervention) was measured on 3 consecutive days including one weekend day using an accelerometer (Hookie AM 20, Traxmeet Finland). Mean amplitude deviation (MAD) of the obtained acceleration signal for each 5-sec epoch was calculated and categorized according to Vähä-Ypyä et al. (Vähä-Ypyä et al. 2015)

4.3.7 Statistical analysis

Baseline results are presented as mean and standard deviation (SD) unless otherwise stated. Possible statistical differences in between-group baseline demographics were tested using a bootstrap type t-test (3500 repetitions) and Chi-squared.

Treatment effects

All main outcome variables were analysed according to the intention-to-treat analysis principle. Changes in main outcomes are reported in the text as mean difference (95% confidence interval, p-value). Repeated measures for walking speed, cardiovascular fitness, body composition, muscle strength and all domains of the KOOS were analysed using generalised linear mixed-models with an unstructured correlation structure. Fixed effects were group, time and group-time interaction. Quantitative MRI for pre- and post- intervention were analysed using the bootstrap type analysis of covariance (ANCOVA); the confidence interval was obtained by bias-corrected bootstrapping (5000 replications) due to violation of distributions assumptions. T2 was adjusted for baseline value, height and weight and the dGEMRIC index was adjusted for baseline value only. Repeated ANOVA was used to compare the differences between the three training intensities (barefoot, small fins and large boots).

Standardised beta coefficient (β), adjusted for baseline values, was calculated for effect size post-intervention and at the 12-months' follow-up. Cohen's standards for beta values above 0.10, 0.30 and 0.50 represent small, moderate and large effects respectively. Effect size for the impacts of daily physical activity on the primary outcome measures, was calculated using Cohen's f^2, where 0.02, 0.15 and 0.35 indicate a small, moderate and large effect, respectively (Cohen 1988). These analyses were performed using commercial statistical software (Stata, 13.1, StataCorp, College Station, Tx, USA).

Power Calculations

A target sample size of 70 (35 per research arm) was required for the AQUARAHAB study to ensure that the trial would have power of at least 80% to detect a difference of 40ms in dGEMRIC values between the groups at two-side α=0.05. Since it was anticipated that there would be a dropout rate of about 10%, we aimed to recruit at least 80 participants at baseline into the study.

5 RESULTS

5.1 Study selection and participants

5.1.1 Systematic reviews (Studies I and II)

A total of eleven (1092 participants) and twenty-eight (1456 participants) RCT trials met the inclusion criteria for Study I and II, respectively, and were included into their respective systematic reviews. The screening process for both Studies is shown in Figure 15. Mean age ranged from 62-76 and 55-82 years old, BMI range was 26.6-32.9 and 23.1-30.0 and women made up approximately 73% of the participants in Study I and 89% of those in Study II. A summary of the populations included is shown in Tables 10 and 11. There were some differences in population demographics (except for the diagnosis of lower limb OA) and exercise intervention frequency and duration between the trials included in Studies I and II. Two trials investigating the effect of therapeutic aquatic exercise on people with lower limb OA had longer follow-up periods. One trial carried out measurements at three months' (Lund et al. 2008) and one at 6 months' follow-up (Cochrane, Davey & Matthes Edwards 2005) (Study I). Only one of the studies for healthy older adults (Study II) had a longer follow-up period, preventing a meta-analysis (Bocalini et al. 2010).

Scores for methodological quality (Pedro and Delphi) for their respective studies are shown in Tables 10 and 11. Scoring for each individual criterion is presented in the supplemental material for each respective article. Risk of bias was either unclear or high for all trials included in both systematic review and no trial was classified as having a low risk of bias. In Study I, only one trial was scored as having a high risk of bias (Lim, Tchai & Jang 2010) while only six from Study II could be rated as having unclear risk of bias (Taunton et al. 1996, Tsourlou et al. 2006, Cox et al. 2008, Bergamin et al. 2013, Elbar et al. 2013, Martínez et al. 2015) All trials had been conducted as single centre interventions. Five trials had accessible protocols (Fransen et al. 2007, Hale, Waters & Herbison 2012, Elbar et al. 2013, Moreira et al. 2013, de Oliveira et al. 2014).

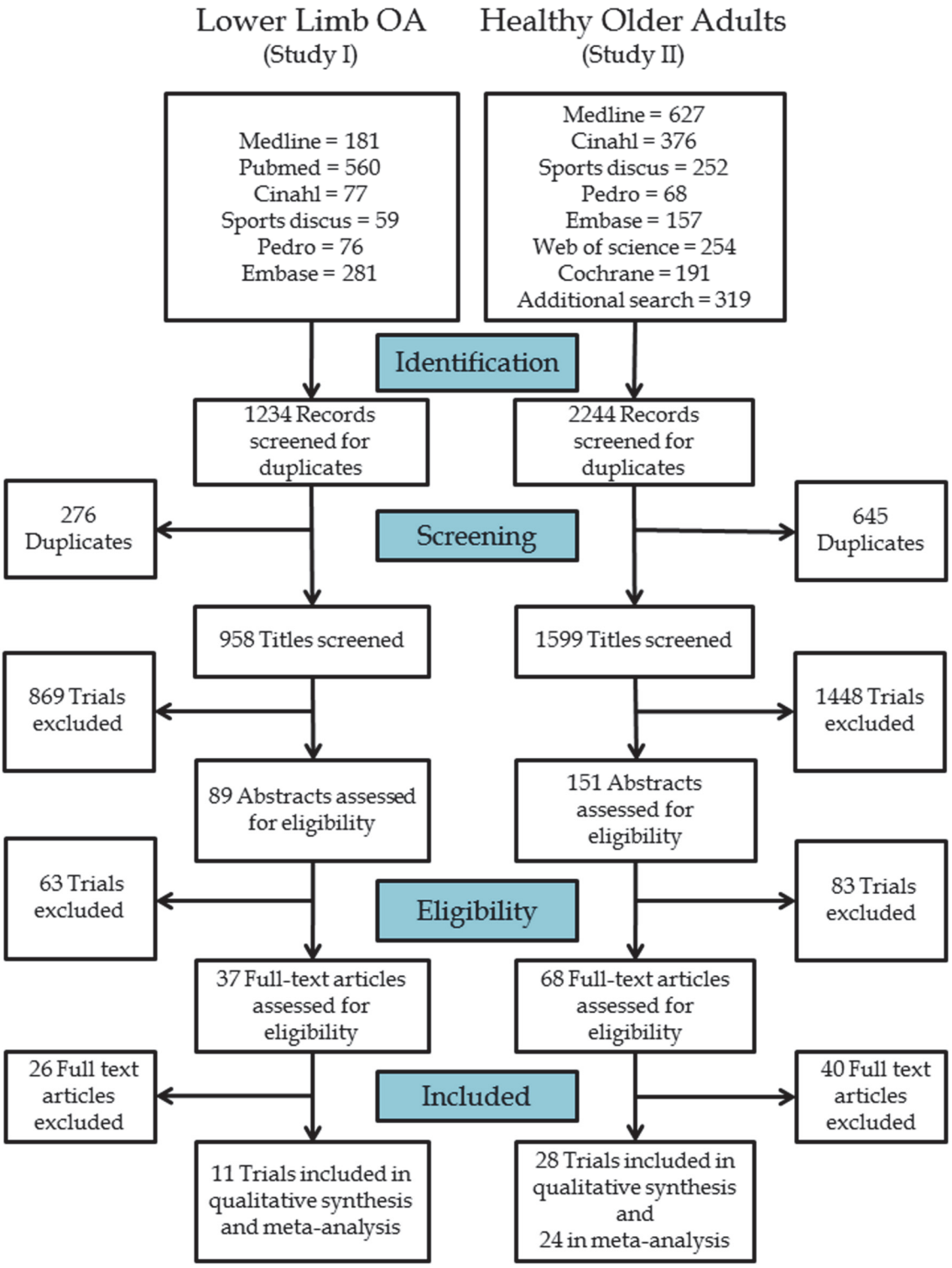

FIGURE 15 Flow chart showing search results and selection process for the systematic reviews (Studies I and II).

TABLE 10 Description of trial participants, interventions and outcome measures utilised in the meta-analysis investigating the effect of therapeutic aquatic exercise in individuals with lower limb OA (Study I).

Trial	Location of OA	PEDro Score /10	Sample size (Dropouts)	Age (years)†	Gender (Female)	Primary outcome	Intervention	Intensity	Dose per protocol*	Outcome measures for meta-analysis
Patrick 2001 (Patrick et al. 2001)	Lower limb	6	**TAE:** 125(21) **C:** 124 (3)	65.7 66.1	86% 87%	Pain and function‡	45-60 min of upper- and lower flexibility, ROM and strength exercises	Gentle	20/40/52/2080	HAQ pain (0-3)[1], Perceived QoL scale (0-10)[2], HAQ disability (0-3)[13]
Foley 2003 (Foley et al. 2003)	Hip/knee (51/126)	8	**TAE:** 35(1) **C:** 35(3)	73.0(8.2) 69.8(9.0)	43% 57%	Muscle strength	Warm-up, lower limb strength exercises, cool down	3 sets x 10-15 reps. progression addition of gaiters	6/18/30/540	WOMAC Pain[1] and stiffness[2], SF12 MCS[3], *isometric knee extension[4], 6 min walk test[11],* WOMAC Function[13]
Cochrane 2005 (Cochrane, Davey & Matthes Edwards 2005)	Hip/knee (mixed)	7	**TAE:** 153(48) **C:** 159(21)	69.9(6.8) 69.6(6.3)	63% 62%	Pain and function‡	1 hour of strength, ROM, endurance, stretches, balance and co-ordination exercises	Increase speed and resistance, progressed every 6-8 weeks.	52/104/60/6240	WOMAC Pain[1] and stiffness[2], SF36 mental health[3], isometric knee extensio[4] stair climb ascending[8], 8-ft walk test[11] , WOMAC Function[13]
Wang 2007 (Wang et al. 2007)	Hip/knee	6	**TAE :** 21(1) **C:** 21(3)	69.3(13.3) 62.7(10.7)	80% 89%	Function	AFAP - flexibility, strength and 10 min aerobic training	10-15 reps for strength. Borg (CR10) 3-4 for aerobic training.	12/36/60/1800	VAS pain[1] 6 min walk test[11], isometric knee extension[4], ROM knee[10], HAQ[13]
Fransen 2007 (Fransen et al. 2007)	Hip/knee (mixed)	8	**TAE:** 55(3) **C:** 41(0)	70.0(6.3) 69.6 (6.1)	73% 83%	Pain and function	Strength, lower limb, mobility, trunk work and balance	10-20 reps	12/24/60/1440	WOMAC Pain[1], SF 36 MCS[3], , timed-up-and-go[8], 50-ft walk test[11], WOMAC Function[13],
Hinman 2007 (Hinman, Heywood & Day 2007)	Hip/knee (16/55)	8	**TAE:** 36(1) **C:** 35(4)	63.3(9.5) 61.5(7.8)	69% 69%	Pain and function	Warm up. leg strength exercises, 6-10 min walking cool down	2-5 sets x 10 reps, individual progression	6/12/52/624	VAS pain[1], KOOS symptoms[2], assessment of Quality of life scale[3], isokinetic knee extension[4], KOOS ADL[13]

Lund 2008 (Lund et al. 2008)	Knee	8	**TAE:** 27(1) **C:** 27(2)	65(12.6) 70(9.9)	81% 67%	Pain	10 min warm up, 20 min strength and endurance exercises. 20 min balance, stretching and cool down	3.5 minutes per exercise, 30 sec stretch per muscle group	8/16/50/800	VAS pain[1], KOOS symptoms[2] and QoL[3], isokinetic knee extension[4], KOOS ADL[13]
Lim 2010 (Lim, Tchai & Jang 2010)	Knee	7	**TAE:** 26(2) **C:** 24(4)	65.7(8.9) 63.3(5.3)	88% 88%	Function	5 min warm up, 30 min, 5 min cool down	65% HR max	8/24/40/960	Bodily pain mean (0-10)[1], SF 36 MCS[3] Isokinetic knee extension[4], WOMAC Global[13]
Arnold 2010 (Arnold & Faulkner 2010)	Hip	6	**TAE:** 28(5) **C:** 25(6)	74.4(7.5) 75.8(6.2)	77% 59%	Balance /falls	Warm-up, lower and upper limb, trunk strengthening exercises, cool down	Not stated	11/22/45/990	30 sec chair stand[6], TUG $_{(cog)}$[8], 6 min walk test[11], activities and balance confidence Scale[13]
Wang 2011 (Wang et al. 2011)	Knee	7	**TAE:** 28(2) **C:** 28(2)	66.7(5.6) 67.9(5.9)	85% 85%	Pain	AFAP - flexibility, strength and 10 min aerobic training	10-15 reps for strength. Borg (CR10) - 3-4 for aerobic.	12/36/60/2160	KOOS pain[1], symptoms[2] QoL[3], ROM knee extension[10], 6 min walk test[11], KOOS ADL[13]
Hale 2012 (Hale, Waters & Herbison 2012)	Hip/knee	8	**TAE:** 23(3) **C:** 16(1)	73.6(1.5) 75.7(1.1)	74% 75%	Balance /falls	Warm-up (walking stretching), balance exercises, cool down (walking, stretching)	Week 1-3 1 min per exercise. Week 4-6 1.5 min per exercise, week 7-12 2 min per exercise	12/24/50/1200	WOMAC Pain[1] and stiffness[2], isometric knee extension strength[4], timed-up-and-go[8], WOMAC Function (0-68)[13]

NR = Not reported, HR max = heart rate maximum, †mean and standard deviation, TAE = Therapeutic aquatic exercise, C = Control, *Dose: weeks/sessions per weeks/duration of training/total number of training minutes ǂTrue primary was Cost effectiveness based on outcomes for pain and function, *Italics* = Insufficient data for outcome reported, AFAP= Arthritic Foundation Aquatic Program, WOMAC = Western Ontario and McMaster University Arthritis Index, KOOS = Knee Injury and Osteoarthritis Outcome Score, SF 12/36 MCS = Short Form Mental Health Component, HAQ = Health Assessment Questionnaire, QoL = Quality of Life

Designated construct for outcome measures: 1 = Pain, 2 = Symptoms, 3 = Quality of Life, 4= Maximum strength, 5 = Muscular power, 6 = Muscular endurance, 7 = Respiratory muscle function, 8 = Agility, 9 = Postural stability, 10 = Flexibility, 11 = Walking ability, 12 = Aerobic power, 13 = Self-reported functioning

TABLE 11 Description of Trial participants, interventions and outcome measures utilised in the meta-analysis investigating the effect of aquatic exercise in healthy older adults (Study II).

Trial	Delphi score	Sample size (Drop outs)	Age (Years)†	Gender (female)	Aquatic Intervention	Primary outcome	Comparison	Intensity	Dose per protocol*	Outcome measures for meta-analysis
Avelar 2010 (Avelar et al. 2010)	**5**	**AE:** 14(2) **LE:** 15(1) **C:** 17(7)	68(5.7) 69(5.6) 71(3.9)	61%	Lower limb stretching and muscle endurance exercises	Balance /falls	**Land:** Corresponding land exercise **Control:** usual care	Stretch: 30 seconds Muscle: 3 sets of 20 repetitions	6/2/NR/ -	*Berg Balance scale, Tandem gait test, Gait speed*
Bento 2012 (Bento et al. 2012**)**	**4**	**AE:** 27(3) **C:** 20(6)	65.6(4.2) 65.6(4.4)	67%	Lower limb aerobic and strength exercises	Strength	**Control:** usual care	Aerobic: RPE 12-16 40-60% HRR Strength RPE 12-16	12/3/60/2160	Isometric knee extension strength[4], 30s chair stand (reps)[6], 8ft up and go[8], Sit and reach (cm)[10]
Bergamin 2013 (Bergamin et al. 2013)	**4**	**AE:** 20(3) **LE:** 20(3) **C:** 19(0)	71.2(5.4)	51%	Upper and lower limb exercises	Function	**Land:** corresponding land exercises **Control:** NR	60% HR max (range 55%–65%) RPE 13-16	24/2/60/ 2880	Isometric knee extension strength[4], 8ft up and go[8], Sit and reach (cm)[10]
Bocalini 2008 (Bocalini et al. 2008)	**4**	**AE:** 27(2) **LE:** 25(10)	64(1) 64(1)	100%	Upper and lower limb exercises with resistance devices	Function	**Land:** supervised walking	10–15 reps at intensity of 70% age-predicted HR max	**AE:** 12/3/60/2160 **LE:**12/5/60/3600	30s chair stand (reps)[6], 8ft up and go[8], Sit and reach (cm)[7], maximum aerobic power[12]
Bocalini 2010 (Bocalini et al. 2010)	**4**	**AE:** 30(3) **C:** 20(2)	>62	100%	Upper and lower limb exercises with resistance devices	Function	**Control:** sedentary, usual care	10–15 reps at intensity of 70% age-predicted HR max	12/3/60/2160	30s chair stand (reps)[6], 8ft up and go[8], Sit and reach (cm)[10] *800m walk test, VO2max*
Broman 2006 (Broman et al. 2006)	**4**	**AE:** 18(3) **C:** 11(2)	69.0(4.0) 69.8(3.5)	100%	Deep water running with vest	Cardio-vascular fitness	**Control:** NR	75% HR max	8/2/48/768	Peak aerobic power (cycle ergometer)[12]
Candeloro 2007 (Candeloro & Caromano 2007)	**3**	**AE:** 16(6) **C:** 15(0)	65-70	100%	Stretching and strengthening exercise	Strength	**Control:** 32 Classes about general health care	NR	16/2/60/1920	*Isometric knee extension strength, sit-and-reach-test*
Carrasco 2012 (Carrasco & Vaquero 2012)	**3**	**AE:** 34 **SWIM:** 29 **C:** 30 (34 in total)	55.4(6.5) 58.8(6.5) 56.6(6.4)	100%	AE: Upper and lower limb exercises with resistance devices SWIM: Swimming	Strength	**Control:** Usual care	RPE 10-15	52/2/45/4680	Isometric knee extension[4], *Counter movement jump,* Upper-limb power (swim bench)[5]
Cox 2008 (Cox et al. 2008)	**6**	**SWIM:**56(8) **LE:** 60(8)	55.8(4.5) 55.2(4.8)	100%	Swimming	Cardio-vascular fitness	**Land:** supervised walking	60–70% of heart rate reserve	24/3/60/4320	1.6 km walk time (min)[11]

Elbar 2013 (Elbar et al. 2013)	**6**	**AE:** 18(1) **C:** 18(0)	69.6(5.2) 69.6(4.5)	NR	Balance training	Balance /falls	**Control:** NR	Progressions were made when the individuals have reached adaptation.	12/2/40/960	Step initiation phase (ms) during step execution test[8], Sway area (two-legged eyes open)[9], *get-up-and-go*
Graef 2010 (Graef et al. 2010)	**4**	**AE1:** 10(0) AE2:10(0) **C:** 7(0)	68.4(6.7) 64.1(3.5) 67.6(4.7)	100%	AE1: Aerobic general exercise. resisted UL exercises AE2. Same no resistance	Strength	**Control:** Usual care	Aerobic: 11-13RPE; Strength: 4-5 sets 8-15 repetitions	12/2/50/1200	Dynamic 1RM horizontal shoulder flexion strength[4]
Ide 2005 (Ide, Belini & Caromano 2005)	**4**	**AE:** 27(8) **LE:** 27(8) **C:** 27(6)	62.2	NR	Resisted upper limb and trunk exercises	Strength	**Land group:** Resisted upper limb and trunk exercises. **Control:** lectures and activities	Gradual increases in intensity in accordance with the ability of each participant.	10/3/60/1800	Inspiratory maximal pressure[7]
Kim 2013 (Kim & O'Sullivan 2013)	**2**	**AE:** 10(2) **C:**10(3)	70.9(5.0) 72.6(5.1)	100%	Adapted swimming, lower an upper limb strengthening	Balance /falls	**Control:** NR	RPE 7-13	12/3/60/2160	Isokinetic knee extension (strength 60°/sec)[4], power 180°/sec[2])[5], 8ft up and go[8], chair sit-and-reach[10]
Kovách 2013 (Kovách et al. 2013)	**3**	**AE:** 17(0) **LE:** 22(0) **C:** 15(0)	67.9(6.9) 66.6(5.5) 64.6(6.2)	76%	AE: NR	Function	**Land:** Pilates exercise **Control:** NR	NR	24/3/60/4320	Chair stand[6], 8 ft up-and-go[8], sit-and-reach[10], 6 minute walk[11]
Martínez 2015 (Martínez et al. 2015)	**3**	**AE:** 16(0) **C:** 10(0)	67.5(5.4) 67.4(4.7)	100%	Water exercise	Function	**Control:** Usual care	40-60% Heart rate reserve	12/5/50/3000	getting up from a chair and moving around house[8], putting on and taking shirt[10], 10m walk test[11]
Moreira 2013 (Moreira et al. 2013)	**6**	**AE:** 64(5) **C:** 44(3)	58.6(6.7) 59.3(6.1)	100%	Lower and upper limb strength exercises	Balance /falls‡	**Control:** no regular exercise	Progressive 2-5 sets of 30-10 seconds	24/3/55/3960	*Isometric knee extension strength, stance test, sit-and-reach, Timed-up-and-go*
Oh 2015 (Oh et al. 2015)	**6**	**AE:** 40(6) **LE:** 40(8)	74.7(2.9) 68.2(4.4)	NR	Flexibility, strength and endurance exercise	Balance /falls	**Land: g**eneral exercises combined with smooth movements	4 RPE (10 points scale)	10/3/60/1800	Isometric hip extension strength[4], timed up-and-go[8], chair sit-and-reach[10], SF-36 physical functioning[13]
de Oliveira 2014 (de Oliveira et al. 2014)	**7**	**AE:** 28(8) **LE:** 23(5)	69(3) 69(4)	100%	Balance, strength, endurance, aerobic and flexibility exercises	Balance /falls	**Land:** floor gymnastics group	4 set s of 10 to 20 repetitions,	12/2/60/1440	Area of centre of pressure (two-legged eyes open)[9]
Pernambuco 2013 (Pernambuco et al. 2013)	**5**	**AE:** 42(6) **C:** 42(11)	66.8(4.2) 66.9(3.2)	100%	Lower and upper limb aerobic exercises	Function‡	**Control:** no regular exercise	7 minutes of each movement type	32/2/50/3200	*10m walk test, putting on and taking shirt, getting up from a chair and moving around house*

Rhodes 1995 (Rhodes et al. 1995)	**4**	**AE:** 27(4) **LE:** 26(6) **C:** 23(9)	70(3.2)	100%	Aerobic, strength, endurance, flexibility and balance	Cardio-vascular fitness	**Land:** similar to AE **Control:** educational sessions	60-65% HR max	12/3/50/1800	Grip strength[1], trunk flexion[10], VO2max (walking test)[12]
Ruoti 1994 (Ruoti, Troup & Berger 1994)	**3**	**AE:** 22(10) **C:** 22(8)	56.0(6.8) 65.2(5.3)	75%	lower and upper limb endurance exercises	Cardio-vascular fitness	**Control:** usual care	Target 80% HR max	12/3/60/2160	Shoulder abduction/adduction[6], VO2max (mod. Balke and Ware, walk)[12]
Sato 2007 (Sato et al. 2007)	**5**	**AE1:** 10(0) **AE2:** 12(1) **C:** 8(0)	79.2(5.1) 75.3(6.0) 77.6(6.8)	NR	AE1/2: Gait, ADL exercise, flexibility and strength	Function/ QoL	**Control:** group socialising, watching TV	RPE 11	**1:** 24/1/60/1440 **2:** 24/2/60/2880	SF-36 Physical component score[13]
Shibata 2012 (Shibata et al. 2012)	**4**	**AE:** 15(0) **C:** 15(3)	66.1(9.3) 68.8(5.3)	83%	Walking exercises	Function	**Control:** NR	RPE 11-13	10/1/45/450	10 times-sit-to-stand[6], SF8 Physical component score[13]
Simmons 1996 (Simmons & Hansen 1996)	**4**	**AE:** 13(3) **LE:** 13(1) **C:** 13(3)	82.0(5.4) 78.2(5.8) 81.3(6.5)	81%	Gait and lower limb exercises	Balance /falls	**Land:** gait and lower limb exercises **Control:** cards playing	Participant tolerance with rest periods as needed	5/2/45/450	Functional reach[8]
Takeshima 2002 (Takeshima et al. 2002)	**4**	**AE:** 15(0) **C:** 15(0)	69.3(4.5) 69.3(3.3)	100%	Lower and upper limb endurance and strength exercises	Function	**Control:** Usual physical activity	Light to moderate intensity measured with heart rate and RPE	12/3/70/2520	Dynamic knee extension strength[4], vertical jump[5], Force expiratory volume (FEV1)[7], Side steps (20 sec)[8], Trunk Flexion flexibility[10]
Tauton 1996 (Taunton et al. 1996)	**4**	**AE:** 23(4) **LE:** 18(2)	65-75	100%	Aerobic, flexibility, balance, strength and endurance	Cardio-vascular fitness	**Land:** match closely to aquatic program	60-65% HR max	12/3/50/1800	Grip strength[4], modified press-ups[6], sit-and-reach[10], peak aerobic power (Balke treadmill)[12]
Tavares 2009 (Tavares & Sacchelli 2009)	**4**	**AE:** 17(0) **LE:** 20(0)	72(4.6) 70(5.9)	81%	Stretching and strengthening exercises	Function	**Land:** Strengthening, stretching and balance exercises	1-2½ minutes per exercise	24/2/60/2880	Older Americans resources and services program (self-reported questionnaire)[13], *Brazilian Multidimensional Functional assessment questionnaire*
Tsourlou 2006 (Tsourlou et al. 2006)	**4**	**AE:** 12(2) **C:** 10(0)	69.3(1.9) 68.4(6.7)	100%	Aerobic and resistance exercises	Strength	**Control:** normal care	65%-80% HR max	24/3/60 4320	Knee extension isometric peak torque[4], Squat jump[5], Timed up and go[8], sit and reach[10]

NR = Not reported, HRmax = heart rate maximum, †mean and standard deviation, ǂprimary purpose was bone traits, *Dose: weeks/sessions per weeks/duration of training/total number of training minutes, AE = aquatic exercise, LE = land-based exercise, C = control, RPE = Rating of perceived exertion, QoL = Quality of Life, *Italics* = Insufficient data for outcome reported

Designated construct for outcome measures: 1 = Maximum strength, 2 = Muscular power 3 = Muscular endurance 4 = Respiratory muscle function 5 = Agility 6 = Postural stability 7 = Flexibility 8 = Walking ability 9 = Aerobic power 10 = Self-reported functioning

Feasibility of aquatic exercise interventions (Studies I and II)

The planned exercise dose for people with lower limb OA (Study I) had varied from 100 min/week to 180 min/week, with the trials lasting from 6 weeks to 52 weeks (in total from 9 to 107 hours), frequency of treatment was either twice or three times a week (twice a week was the most popular n=7) (Table 10). Overall, 50% (n=7) reported adherence to the training which ranged from 81-100%. The interventions had specific therapeutic goals and therefore will be referred to as therapeutic aquatic exercises. The aquatic intervention utilised in the management of lower limb OA would have been impossible to reproduce in all but four trials (Fransen et al. 2007, Hinman, Heywood & Day 2007, Wang et al. 2007, Wang et al. 2011) based on information given or referred to in the text. Repetition amount was most common form of setting the training intensity with five trials using 10-15 repetitions (Foley et al. 2003, Fransen et al. 2007, Hinman, Heywood & Day 2007, Wang et al. 2007, Wang et al. 2011) with two additionally setting an RPE of 3-4 (Borg 0–10), i.e. light to moderate intensity, two trials used time (Lund et al. 2008, Hale, Waters & Herbison 2012), one used 65% maximum heartrate (Lim, Tchai & Jang 2010) and three did not provide sufficient information (Patrick et al. 2001, Cochrane, Davey & Matthes Edwards 2005, Arnold & Faulkner 2010). Further, only one out of 11 trials referred to recommended exercise guidelines. Drop-outs in the OA trials ranged from 3-31% and 0-22% in the therapeutic aquatic exercise and control groups respectively (Table 10).

The planned exercise dose for healthy older adults (Study II) varied from 80 min/week to 210 min/week for 5 weeks to 24 weeks, the frequency of treatment was either twice or three times a week (three times a week was most popular n = 9) (Table 11). The intensity of interventions for healthy older adults was set using the rating of RPE (Borg 0-10 or 6-20) or heart rate (HR) in all studies except one (Simmons & Hansen 1996) with only five trials referring to specific exercise guidelines (Tsourlou et al. 2006, Bocalini et al. 2008, Bocalini et al. 2010, Bento et al. 2012, Bergamin et al. 2013). The intensity of aerobic training ranged between 40-70% of heart rate reserve, 60-80% of heart rate maximum or 11-16 of perceived rate of exertion (Borg 6-20 scale) and 4-9 (Borg 0-10 scale) i.e. moderate to hard training (Borg 1982). Actual intensity achieved during the interventions was reported in only one study (Broman et al. 2006). Training intensity was individualised, based on results from land-based aerobic fitness testing in three trials (Ruoti, Troup & Berger 1994, Rhodes et al. 1995, Broman et al. 2006). Drop-outs ranged from 0-45%, 0-36% and 0-41% for the aquatic exercise, land-based exercise and control groups respectively (Table 11).

Control groups in both studies (I and II) were mainly usual care, i.e. continuing usual care for symptoms associated with OA (Study I) and maintaining a similar level of physical activity as before initiation (Study II). One OA trial organized a computer class in which the control group could participate (Hale, Waters & Herbison 2012) while five control groups from Study II participated in group activities, e.g. playing cards, with no physical activity involved (Rhodes et al. 1995, Simmons & Hansen 1996, Ide, Belini &

Caromano 2005, Candeloro & Caromano 2007, Sato et al. 2007). In Study II, the intensity of land-based exercise was reportedly always set at the same level as the aquatic counterpart, however, they were not always truly comparable. For example, in two trials, land-based training consisted of walking alone (Bocalini et al. 2008, Cox et al. 2008), one trial had a poorly described land-based exercise program (Oh et al. 2015), one trial utilised similar exercises as in the aquatic exercise but performed on the floor (de Oliveira et al. 2014), one used the same exercises as in the aquatic exercise program, but performed standing while holding onto the back of a chair (Simmons & Hansen 1996), one performed the same exercise as the aquatic exercises but without resistance (Bergamin et al. 2013) and one used Pilates (Kovách et al. 2013).

5.1.2 Randomised controlled trial AQUAREHAB (Studies III-V)

A total of 87 participants met the inclusion criteria (aquatic exercise group n=43 and control group n=44). Baseline characteristics, shown in Table 12, were similar between the groups. After the intervention, 84 participants agreed to continue to the 12-month follow-up period, of these 77 participants actually completed all of the follow-up measurements. Recruitment of subjects for Study I and II is shown in Figure 16.

TABLE 12 Baseline demographics and clinical characters of subjects included into the AQUAREHAB study (Studies III, IV and V).

	Exercise group (n=43)	Control group (n=44)
Age (years)	63.8 (2.4)	63.9 (2.4)
Height (cm)	161.7 (5)	161.6 (5)
Body mass (kg)	69.6 (10.3)	71.0 (11.2)
Body mass index (kg/m^2)	26.6 (3.8)	27.1 (3.5)
Time from menopause (years)	14 (6)	14 (6)
Affected leg (right/left)	36/7	34/10
K/L grade, n (%)		
Grade 1	23 (53.5)	24 (54.5)
Grade 2	20 (46.5)	20 (45.5)
Knee pain during last week, (VAS, mm)*		
Affected knee	28 (25)	24 (19)
Non-affected leg	24 (19)	23 (18)
Analgesia (knee), n (%)	11 (47)	9 (48)
Glucosamine use (occasionally, n (%))	12 (28)	8 (18)
(METh/week)	29 (31)	36 (33)
Smoker		
Never	17	13
Current	3	3
Previous	23	28
Blood pressure		
Normal	23	14
Elevated	9	11
Medical management	11	19
Walking speed (m/sec)	1.74 (0.15)	1.73 (0.17)

Values are means (SD) or n (%) unless otherwise noted. METh = metabolic equivalent task hour.*Visual Analogue Scale range 0-100mm

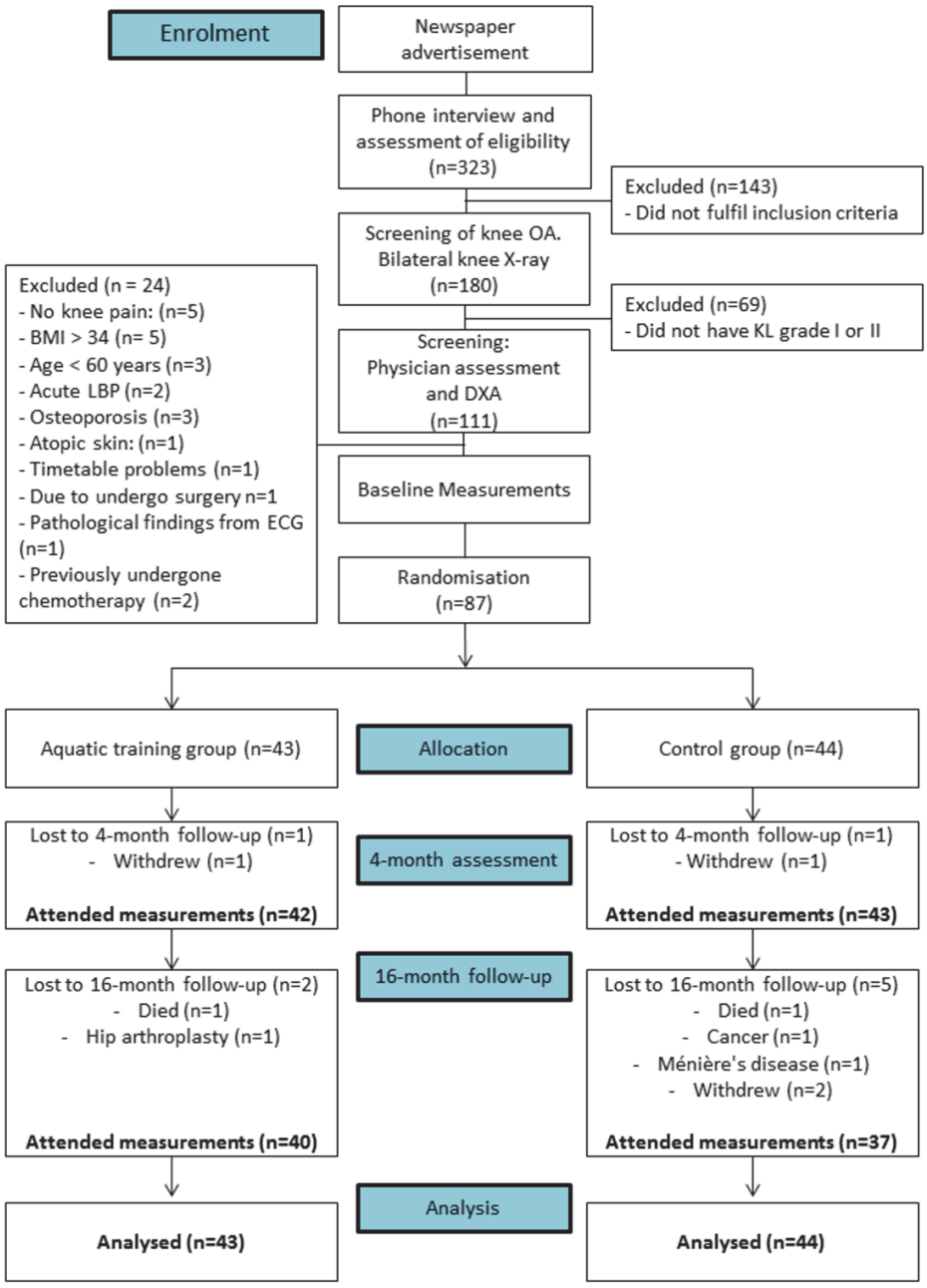

FIGURE 16 Flow chart showing subject recruitment and retention for the AQUAREHAB study (Studies III, IV and V).

Feasibility of intensive aquatic resistance training (Studies III-V)

Two subjects did not attend the follow-up measurements (1 control and 1 intervention and a further seven (5 control and 2 intervention) did not attend the 12-months' follow-up. Reasons for drop-outs are shown in Figure 16. Adherence to the aquatic training program was high (88%), with only three subjects attending less than 70% of sessions. The drop-out rate for each group was 2.3% (n=1 per group). Training frequency was mean 2.6 (SD 0.5) per week (including dropouts).

Training intensity

Actual training intensity recorded from each completed training session and the 30 minute resistance training only are summarised in Table 13. The results indicate that in general there was a gradual increase in RPE when progressing from barefoot to large resistance boots, whereas no significant changes in heart rates were recorded. The training intensity appeared to slightly decrease over the last 4 weeks of training (weeks 13-16) (Figure 17). The total number of repetitions completed in one session significantly decreased between each intensity level. For example, 70.5% of these repetitions involved full knee active flexion and extension and mean ROM was approximately 134 (SD 6) degrees (affected knee) as measured during baseline assessment. Blood lactate levels measured immediately after cessation of the training decreased as resistance increased (Table 13). During the first three weeks, there was a gradual increase in training intensity (RPE) with a decrease reported in the frequency of knee pain (during training) (Figure 17). Mean (SD) intensity of knee pain reported was low for all three training intensities 12.7 (15.7) 11.2 (5.5) and 15.3 (20.6) for barefoot, small fins and large boots respectively.

TABLE 13 Measured training intensities for whole sessions and individual intensity for aquatic resistance training (30 minutes) set only.

	Barefoot	Small Fins	Large boots	P-Value**
No. of Sessions	8	14	26	-
Repetitions	481 (66)	408 (71)	376 (65)	0.000
RPE*				
Whole session	13.7 (1.0)	14.9 (1.3)	15.0 (1.5)†	0.000
Resistance program*	16.0 (1.9)	16.2 (1.6)	15.8 (1.8)	0.551
Average HR (bpm)				
Whole session	100 (132)	102.7 (8.9)	102.5 (9.9)	0.565
Resistance program*	106 (15)	106 (14)	110 (12)†	0.276
Average HR (%)				
Whole session	61 (5.9)	61 (5.3)	61 (6.3)	0.947
Resistance program*	68 (10)	68 (9)	71 (8)†	0.276
Max HR (bpm)				
Whole session	140 (16.8)	141 (16.5)	142 (13.3)	0.875
Resistance program*	147 (23)	151 (28)	163 (30)†	0.101
Max HR (%)				
Whole session	85 (7.8)	84 (8.9)	84 (8.0)	0.679
Resistance program*	94 (15)	97 (19)	105 (19)†	0.102
Psychological wellbeing				
Whole session	4.2 (0.33)	4.2 (0.36)	4.3 (0.4)	0.283
Resistance program*	4.4 (0.57)	4.3 (0.52)	4.36 (0.54)	0.548
Blood Lactate (mmol/L)	4.9 (2.1)	4.5 (1.9)	4.0 (1.8)†	0.282

Mean and (SD) unless otherwise stated. ** repeated ANOVA, †Bare vs Large ($p < 0.05$)
* Resistance program = 30 minutes of aquatic resistance training only sessions 34, 35, and 36.
RPE = Rating of perceived exertion (BORG 6-20) bpm = beats per minute

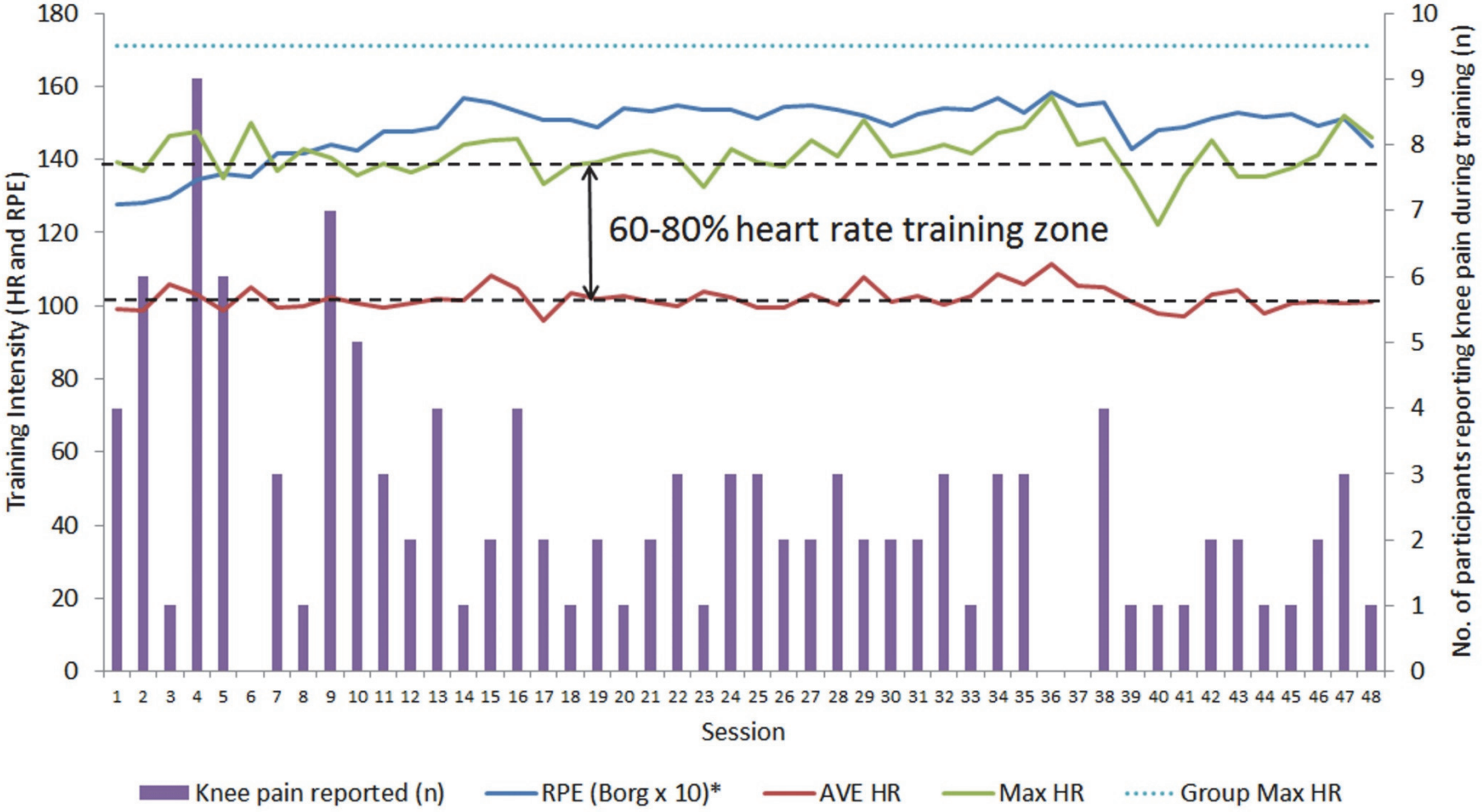

FIGURE 17 Description of average training intensities and frequency of pain in affected knee during each training session for all subjects (Studies IV and V)(HR = heart rate, * RPE = Rating of perceived exertion multiplied by ten to estimate heart rate, AVE = Average, Max = Maximum).

5.2 Effects of aquatic exercise

The effect of therapeutic aquatic exercise on functional capacity in people with lower limb OA (Study I) and the effect aquatic exercise in healthy older adults (Study II), presented as standardised mean difference (SMD, Hedges' g with 95% confidence intervals (CI)) are shown in Figure 18. The results of the sensitivity tests are presented in Figure 19. Full results for the meta-analyses including the number of studies, sample sizes, heterogeneity and size of effect with 95% CI as well as forest plots for each analysis can be found in the original publications (Studies I and II).

The overall effects of aquatic resistance training in women with mild knee OA (AQUAREHAB), displayed as standardised beta coefficient (Beta (β) with 95% CI), for performance-based measures of function, self-reported symptoms and function and body composition are presented in Figure 20 (Studies IV and V). Mean, SD and p-values are shown in Table 14. The effects of aquatic resistance training on the biochemical composition of tibiofemoral cartilage post-intervention are presented in Table 15 (Study V).

5.2.1 Pain, symptoms and quality of life in people with lower limb OA (Study I) and women with mild knee OA (Studies IV and V)

All but one trial investigating the effect of therapeutic aquatic exercise on lower limb OA measured pain and symptoms; of these, six reported pain as the primary outcome (Study I). VAS pain (n=5) and WOMAC pain (n=4) were the two most commonly utilised outcome measures. Eight trials measured quality of life (QoL) with a range of outcome measures used (Table 10). The results of the systematic review (Study I) indicated that therapeutic aquatic exercise had a small but statistically significant effect on pain SMD 0.26 (95% CI 0.11 to 0.41), stiffness/symptoms 0.20 (0.03 to 0.36) and QoL 0.24 (0.04 to 0.45). There was no significant effect of therapeutic aquatic exercise on pain, symptoms and QoL in subjects with knee OA (Figure 16). There was no effect of aquatic resistance training on pain, symptoms or quality of life in women with early knee OA (Figure 18) (Studies IV and V).

5.2.2 Functional capacity in people with lower limb OA (Study I) and healthy older adults (Study II)

There was a small but statistically significant effect of therapeutic aquatic exercise (Study I) on overall (pooled) physical functioning in people with lower limb OA 0.23 (0.14 to 0.32) (Figure 18). The effect of therapeutic aquatic exercise on both self-reported 0.30 (0.18 to 0.43) and performance-based measures 0.17 (0.04 to 0.30) of function in participants with lower limb OA was small but statistically significant (Figure 18). In the two studies with longer follow-up

times (Cochrane, Davey & Matthes Edwards 2005, Lund et al. 2008), the effect of therapeutic aquatic exercise had been lost (not pooled together). In healthy older adults (Study II), aquatic exercise had a moderate effect on overall pooled physical functioning 0.70 (0.48 to 0.92) compared to controls (Figure 18). Therapeutic aquatic exercise and aquatic exercise were found to improve flexibility, walking ability and self-reported functioning in both individuals with lower limb OA (Study I) and healthy older adults (Study II) when compared to control interventions (Figure 18). Aquatic exercise seemed to exert a moderate sized effect on muscle strength in healthy older adults but in contrast therapeutic aquatic exercise had no effect on muscle strength in individuals with lower limb OA. Aquatic exercise appeared to have a large effect on aerobic power compared to controls (Figure 18). However, baseline differences explain a major portion of this large change. Aquatic exercise appears to have a small but significant advantage over land-based exercise in improving overall (pooled values from all trails and outcomes) physical functioning 0.39 (0.39 to 0.66) (Figure 18). However, the comparison group (walking) in Bocalini *et al.* (2008) was deemed a non-comparable intervention (Bocalini et al. 2008). Removal of this trial resulted in a non-significant benefit 0.17 (-0.03 to 0.36) of aquatic exercise over land-based exercise. Moreover, only the improvements in self-reported functioning favoured aquatic exercise over its land-based counterpart.

Three trials (Lund et al. 2008, Lim, Tchai & Jang 2010, Wang et al. 2011) investigated the effect of therapeutic aquatic exercise on knee OA (Study I) with no significant effect seen on pain 0.25(-0.08 to 0.57), a small effect on self-reported functioning 0.32 (0.00 to 0.64) and no effect on physical performance tests 0.16 (0-0.40 to 0.71) (Figure 19). In both systematic reviews, several trials (Rhodes et al. 1995, Carrasco & Vaquero 2012, Kim et al. 2012, Bergamin et al. 2013) excluded subjects from the final analysis for low adherence to exercise and in all cases counted them as drop-outs and therefore did not report their data (incomplete data bias) with true intention-to-treat analysis used in only two trials (Cox et al. 2008, de Oliveira et al. 2014). Although the drop-out rate did not affect the overall result, the heterogeneity (I2) for both analyses revealed much smaller and non-significant values, 19% and 6% respectively, indicating smaller variance between the trials with low drop-out rates. In both comparisons, i.e. aquatic exercise versus control and aquatic versus land-based, exercise younger participants (<68 years) seemed to benefit more from aquatic exercise. Training frequency did not seem to have any effect on the overall effect. Aquatic exercise appeared to have a similar sized effect on outcomes measuring constructs of body structure and function and activity and participation (Figure 19).

Effect of Aquatic Exercise on Functional Capacity (Studies I and II)

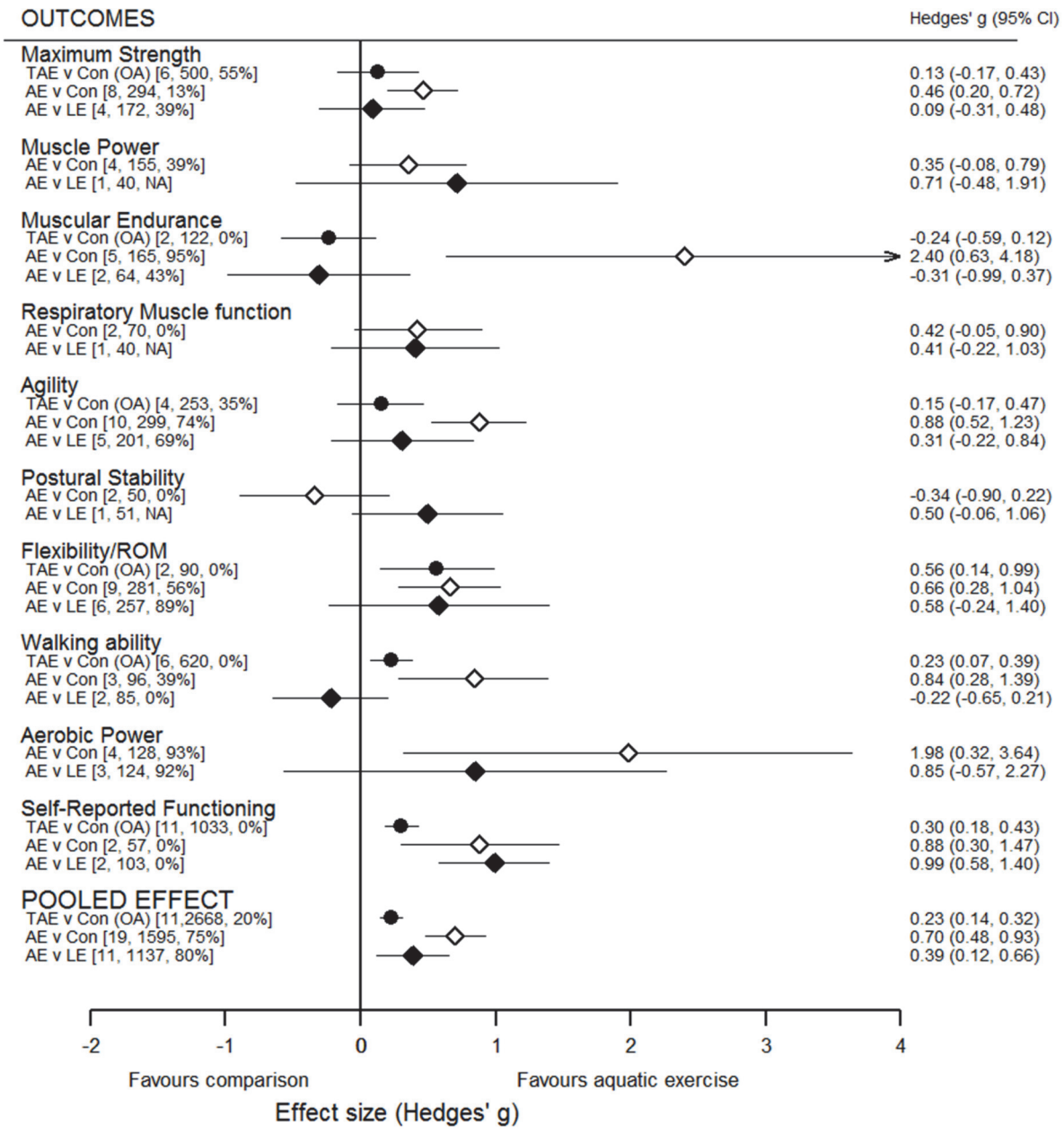

FIGURE 18 Size of effect of aquatic exercise on different domains of physical functioning in subjects with lower limb OA. TAE = therapeutic aquatic exercise, AE = aquatic exercise, Con = Control, LE = land-based exercise. ● = TAE v Con in people with lower limb OA (Study I), ◇ = AE v Con in healthy older adults (Study II), ◆ =AE v LE in healthy older adults (Study II).

Sensitivity Testing (Studies I and II)

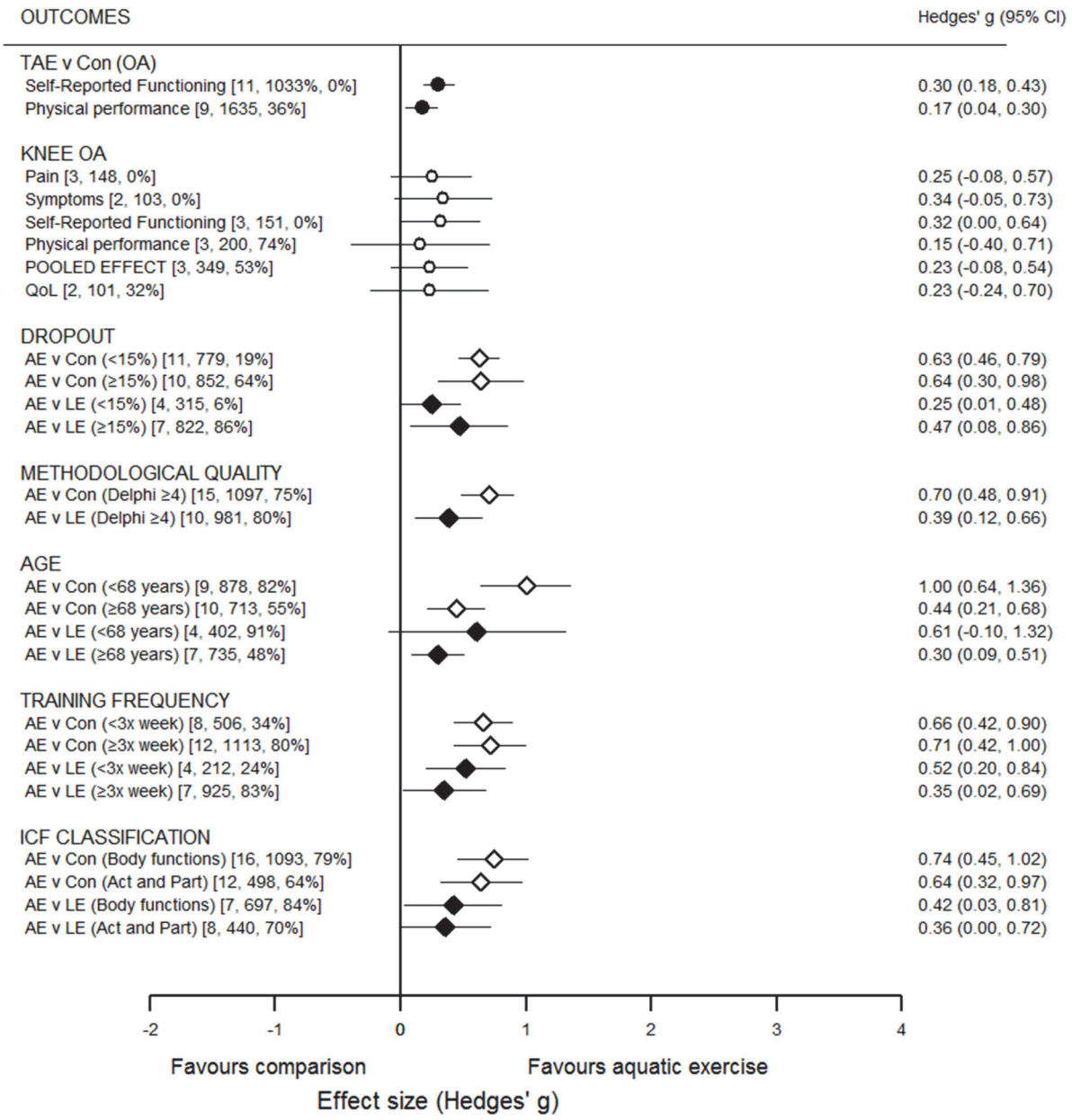

FIGURE 19 Sensitivity testing for the effect of TAE and AE (Studies I and II). TAE = therapeutic aquatic exercise, AE = aquatic exercise, Con = Control, LE = land-based exercise. ● = TAE v Con in people with lower limb OA (Study I), ○ = TAE v Con in subjects with knee OA (Study I), ◇ = AE v Con in healthy older adults (Study II), ◆ =AE v LE in healthy older adults (Study II).

5.2.3 Effects of aquatic resistance training on women with mild knee OA (Studies IV and V)

The effects of aquatic resistance training on functional capacity, symptoms and body composition are shown as Beta values and (95% CI) in Figure 20. Walking speed in women with early knee OA increased significantly in the aquatic resistance training group in comparison to the control group. Interestingly, the significant increase in walking speed (mean difference) -0.052m/sec (95% CI -0.018 to 0.086, p=0.002) was maintained at the 12-months' follow-up -0.046m/sec (95% CI 0.008 to 0.084, p=0.032), (Figure 20). There was a significant increase in estimated $V0_{2\ peak}$ 1.23 (0.30 to 2.15, p=0.009) after the intervention in favour of the aquatic resistance training group which was not maintained at 12-months' follow-up (Figure 20). There was no effect of aquatic resistance training on muscle strength, pain, symptoms or self-reported functioning. After 4-months of aquatic resistance, there was a significant decrease in fat mass -1.17kg (95% CI -2.00 to -0.43, p=0.002), in favour of the intervention group. These improvements in fat mass were lost at the 12-months' follow-up measurements. There was no change in lean mass at neither post-intervention nor 12-month follow-up measurements (Figure 20). In a more in-depth analysis, there was a significant decrease in fat mass in both legs -0.47kg (-0.74 to -0.20, p=0.000) or a loss of 4.5% fat mass in the training group compared to a 1.1% increase in the control group and the trunk lost -0.63kg (-1.1 to -0.17, P=0.007) or a loss of -3.1% compared to an increase 1.0% in the control group. Both significant findings were lost at the 12-months' follow-up. No localised change in lean mass was seen at any time point. A significant decreased in body weight post-intervention of -1.11kg (-1.85 to -0.42, p=0.004) in favour of the training group was seen with no significant between-group difference remaining at the 12-months' follow-up -0.39kg (-1.51 to 0.64, p=0.543).

Effect of Aquatic Resistance Training (Studies IV and V)

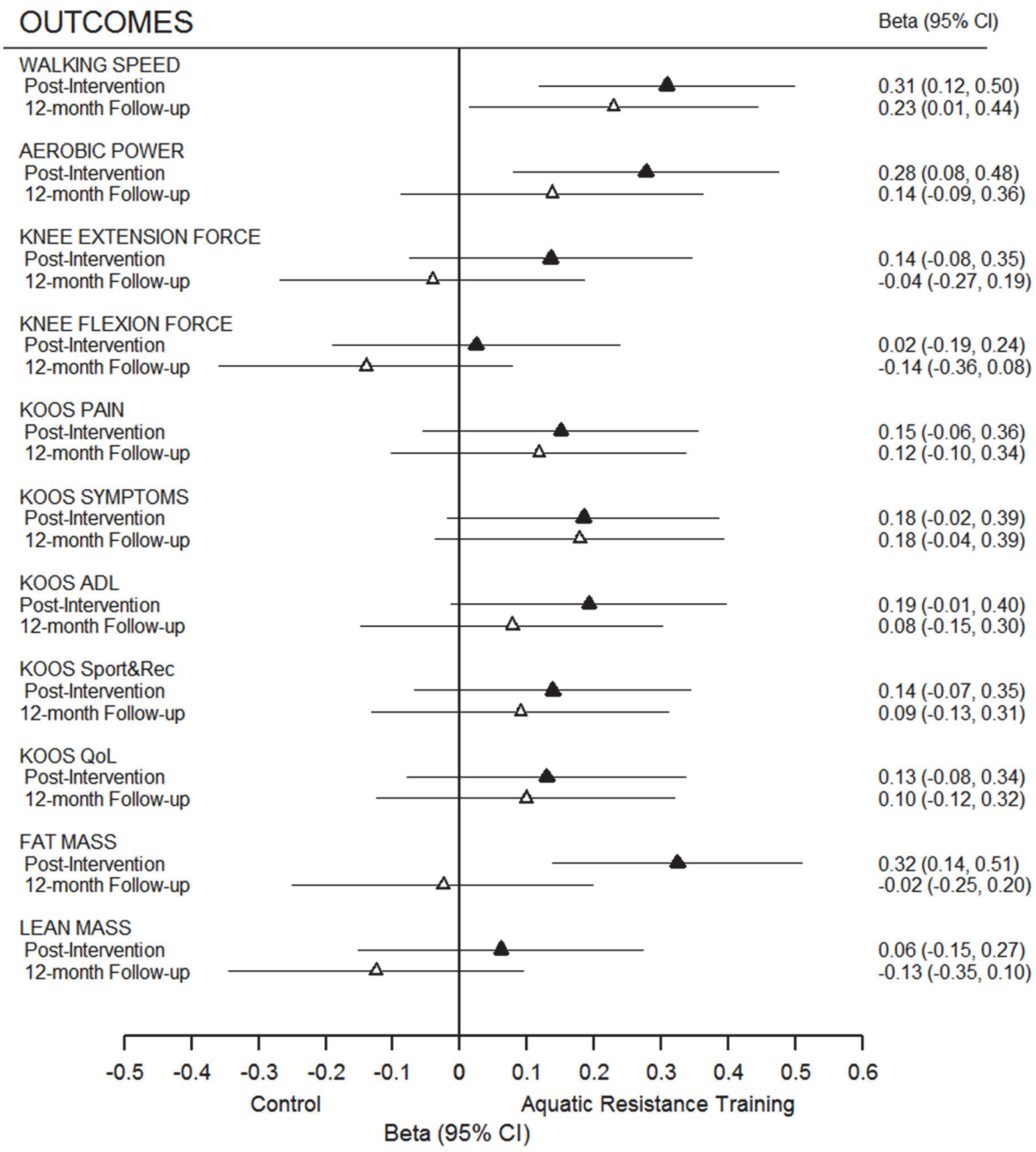

FIGURE 20 Standardised beta coefficients (β, 95% CI) of aquatic resistance training on walking speed, aerobic power, KOOS and body composition. ▲ = baseline to 4-months (post-intervention, ▲ = baseline to 16-month follow-up (Studies IV and V)

TABLE 14 Effect of aquatic resistance training on function, pain and body composition after 4-month intervention and 12-month follow up (Studies IV and V).

Variable	Aquatic Training		Control		p-value[a]	AT	Control	p-value[a]
	BL (n=43)	FU (n=42)	BL (n=44)	FU (n=43)		12m-FU (n=40)	12m-FU (n=37)	
WALKING ABILITY								
Walking speed (m/s)	1.74 (0.15)	1.83 (0.16)	1.73 (0.17)	1.76 (0.17)	0.002	1.82 (0.14)	1.77 (0.13)	0.03
AEROBIC POWER (ml/kg/min)								
$VO_{2\ max}$	25.3 (5.5)	27.6 (5.5)	25.3 (4.8)	26.3 (4.6)	0.01	26.9 (5.4)	25.6 (4.4)	0.19
FORCE (N)								
Aff ext	333 (64)	355 (69)	346 (72)	352 (63)	0.17	348 (66)	370 (62)	0.77
Aff flex	164 (51)	184 (47)	169 (42)	182 (36)	0.50	187 (47)	183 (40)	0.45
KOOS (0-100)								
Pain	80. 6 (10.4)	84.3 (10.5)	82.1 (11.8)	83.3 (11.7)	0.18	86.8 (10.5)	85.1 (12.4)	0.19
Symptoms	74.4 (12.9)	80.9 (12.1)	74.8 (14.1)	77.5 (14.9)	0.09	81.4 (11.4)	77.9 (14.5)	0.12
ADL	84.5 (10.4)	87.7 (9.7)	85.2 (11.0)	86.0 (14.6)	0.11	89.2 (11.2)	88.3 (11.0)	0.40
Sport&Rec	63.6 (20.5)	70.6 (21.7)	64.8 (22.2)	67.6 (26.5)	0.22	71.0 (20.7)	68.7 (24.6)	0.40
QoL	66.0 (17.5)	72.6 (18.1)	70.6 (20.1)	74.1 (23.1)	0.25	75.0 (18.2)	76.4 (24.4)	0.31
BODY COMPOSITION								
Body mass (Kg)	69.2 (10.3)	68.2 (10.4)	70.8 (11.2)	70.9 (11.3)	0.004	68.6 (10.6)	70.8 (11.5)	0.54
BMI	26.6 (3.8)	26.2 (3.9)	27.1 (3.5)	27.1 (3.6)	0.001	26.4 (4.0)	26.9 (3.7)	0.89
Lean mass (kg)	40.3 (3.9)	40.6 (3.9)	41.4 (4.4)	41.7 (4.4)	0.59	40.1 (4.0)	41.9 (4.2)	0.41
Fat mass (Kg)	26.0 (8.6)	24.8 (8.8)	26.5 (8.0)	26.4 (8.1)	0.002	25.7 (8.8)	26.1 (8.5)	0.70

All results presented as mean and (standard deviation), Aff ext = Affected side knee extension, Aff flex = Affected side knee flexion, ADL = Activities of daily living, QoL = Quality of life, BMI = Body mass index, BL= Baseline, FU= post-intervention follow-up, 12-FU = 12-months' follow-up, [a]Mixed model analysis

Biochemical composition of Cartilage

Values of the T2 relaxation times and dGEMRIC index baseline values and post 4-month intervention are given in Table 15. After adjustments, there was a significant decrease in both T2 relaxation time (p=0.021), mean difference -1.2ms (-2.2 to -0.2) and in the dGEMRIC index (p=0.022) -23ms (-43 to -3) in the training group compared to controls in the full thickness posterior ROI of the medial femoral cartilage (Table 15).

TABLE 15 The effect of 4-months of aquatic resistance training on the biochemical composition of tibiofemoral cartilage (Study V).

Variable		Aquatic training (AT)		Control		p-value
		BL (n=42)	FU (n=42)	BL (n=42)	FU (n=42)	
T2, ms						
FEMUR	**Lateral condyle**					
	Central	52.6 (4.9)	52.4 84.9)	53.4 (4.1)	53.4 (3.5)	0.58[b]
	Posterior	49.6 (4.6)	49.4 (3.9)	48.8 (3.6)	49.6 (3.6)	0.30[b]
	Medial condyle					
	Central	52.8 (4.5)	52.6 (4.9)	52.0 (4.4)	52.5 (5.3)	0.47[b]
	Posterior	52.0 (4.7)	50.8 (4.2)	51.9 (4.5)	52.1 (4.5)	0.021[b]
TIBIA	**Lateral condyle**					
	Central	41.0 (8.3)	40.3 (8.2)	42.9 (8.1)	42.9 (8.1)	0.30[b]
	Medial condyle					
	Central	44.5 (5.0)	44.5 (4.6)	42.7 (4.2)	42.7 (4.3)	0.41[b]
dGEMRIC, ms						
FEMUR	**Lateral condyle[d]**					
	Central	433 (70)	428 (65)	424 (44)	428 (45)	0.93[c]
	Posterior	422 (60)	423 (78)	428 (57)	433 (60)	0.71[c]
	Medial condyle[e]					
	Central	411 (61)	396 (63)	410 (65)	405 (56)	0.13[c]
	Posterior	453 (60)	471 (76)	448 (61)	490 (77)	0.022[c]
TIBIA	**Lateral plateau**					
	Central	424 (76)	418 (85)	419 (82)	421 (84)	0.91[c]
	Medial plateau					
	Central	382 (75)	367 (59)	386 (50)	382 (62)	0.19[c]

T2 = transverse relaxation time; [b] ANCOVA Adjusted for baseline value, height and weight.
dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; [c] ANCOVA Adjusted for baseline value.
Missing data for dGEMRIC [d] n=16, [e] n=12

5.3 Effects of daily physical activity on walking speed and body composition (Study IV)

Between-groups differences in daily physical activity can be seen in Figure 21. The total mean (SD) MET-hours (METh) per week, including the intervention, were 40 (13) and 26 (16) in the training and control group, respectively ($p<0.001$). No between-group differences were seen in METh activity once the METh from the aquatic resistance training was removed from the subjects in the intervention group ($p=0.112$). There was no statistically significant difference between the groups in the physical activity as measured with accelerometers, excluding the time of the actual intervention. Sedentary behaviour accounted for 80% (5.0) or 13,903 (869) MADs of daily activity. The remaining physical activity (in MADs) was divided into slow walking 3166 (821), normal walking 198 (175) and brisk walking, jogging and running combined in total 1.7 (1.4) MADs. There was a significant ($p<0.001$) between-group difference in average monthly METh during the intervention period 160(53) versus 104(63) METh for intervention and control groups respectively. This difference was immediately lost following the cessation of the aquatic training $p=0.56$. After combining the groups, the results of the mixed models analysis indicated that there was a significant time interaction between physical daily activity (METh) and changes in fat mass ($p=0.007$) with a small sized effect (Cohen's f^2) of $f^2=0.05$. There was no effect ($p=0.52$) on lean mass, $f^2=0.002$ and a small $f^2=0.02$ but non-significant ($p=0.25$) effect on walking speed.

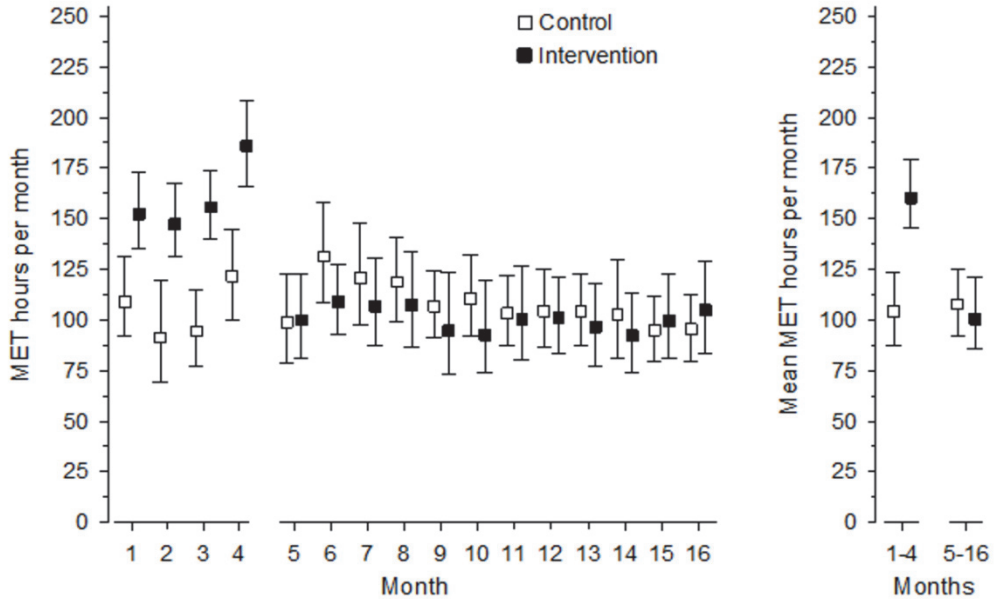

FIGURE 21 Monthly physical activity METh during the 4-month intervention and 12-months' follow-up period (Studies IV and V).

5.4 Adverse effects

Systematic reviews (Studies I and II)

Adverse effects in the OA populations were documented in all of the trials with five reporting some form of adverse effect as a direct result of participation in the therapeutic aquatic exercise protocol including an increase in pain (Foley et al. 2003, Hale, Waters & Herbison 2012). In three trials (Foley et al. 2003, Arnold & Faulkner 2010, Hale, Waters & Herbison 2012), only 4 (1%) subjects dropped out from the therapeutic aquatic exercise intervention groups as a direct result of the adverse effects from the programme (Table 10). In Study II, harms were reported in five trials (Taunton et al. 1996, Broman et al. 2006, Cox et al. 2008, Bocalini et al. 2010, Moreira et al. 2013) with n=8 and n=6 as a direct result of the aquatic and land-based exercise respectively.

Aquatic resistance training (Studies IV and V)

One subject stopped the intervention following pain experienced after the first use of the large resistance boot (session 16). Although symptoms were short lasting (2 days), this subject chose not to persist with the intervention but participated in all of the follow-up measurements. One subject complained of breathlessness during training; following the assessment by a physician, the cause of the symptoms were related to abnormal breathing patterns and after suitable guidance, the participant was able to complete the intervention and attend the follow-up measurements. The results of both participants are included as per intention-to-treat analysis.

6 DISCUSSION

The results of this dissertation indicate that aquatic exercise can exert a positive effect on symptoms, functional capacity and body composition, and may have an impact on cartilage health in individuals with knee OA. Further, aquatic exercise is effective at improving functional capacity in healthy older adults. Aquatic exercise can preserve different aspects of functional capacity in healthy older adults, many of which are known risk factors for developing knee OA as well as promoting its progression (Study II). This dissertation is the first study to show that 4-months of aquatic resistance training significantly improves walking speed and cardiovascular fitness and decreases fat mass in postmenopausal women with mild knee OA (Studies III-V). The improvements in walking speed were maintained after 12-months' follow-up, evidence of a long term benefit of aquatic resistance training on functional capacity. Additionally, aquatic resistance training produced significant changes in the biochemical composition of tibiofemoral cartilage in women with mild knee OA, suggesting that aquatic resistance training could be used to modulate cartilage health. Therapeutic aquatic exercise can also decrease pain and improve patient-reported function in individuals with lower limb OA (Study I). However, the effects of aquatic exercise on performance-based measures of function remain unclear with significant effects only seen on walking ability and knee range of motion with no effect on muscle strength and agility. It seems that there is a tendency to prescribe aquatic exercise more cautiously to people with lower limb OA. However, based on current literature and the results of the AQUAREHAB-study, this may be not only unnecessary but possibly prevent these patients from benefitting from the improvements in functional capacity conferred by this type of exercise. Therefore, the results of this dissertation indicate that aquatic exercise should be exploited more extensively in the management of knee OA due to its potential chondro-protective and chondro-facilitative properties, leading to improvements in functional capacity, perhaps via a direct effect on chondrocyte activity.

6.1 Effect of aquatic exercise

6.1.1 Pain and symptoms

Pain is the most common reason why a person with lower limb OA initially seeks medical assistance; it is a predictor for worsening of pain and progression of knee OA (van Dijk et al. 2010, Pisters et al. 2012, Holla et al. 2015). Inability or lack of willpower to train on land due to pain is a common reason for avoidance of physical activity and an indication for recommending aquatic exercise. Study I found that therapeutic aquatic exercise can evoke a small but statistically significant effect on pain over control interventions, a finding which has been confirmed in the very recent Cochrane review (Bartels et al. 2016). The effects of therapeutic aquatic exercise on pain and self-reported function are comparable to those achieved from land-based exercise or the use of paracetamol and NSAIDs (Roddy, Zhang & Doherty 2005, Zhang et al. 2010, McAlindon et al. 2014, Fransen et al. 2015). Although there was no significant change in pain level detected in the AQUAREHAB study, it must be remembered that these subjects only had mild knee OA with very low pain scores at baseline. Knee pain in the early phase of OA progression is intermittent and this could have affected the ability to detect changes in this population (Roos & Arden 2016).

Interestingly, during intensive aquatic resistance training, one-in-four of the subjects reported knee pain during the initial period of training, this frequency dropped quickly to under one-in-twenty, evidence of an adaptation to the training and increased exercise tolerance, even when the training intensity was increased (Figure 17). Roper et al. (2013) indicated that subjects with lower limb OA could train at equally high intensities, with significantly less pain during on an underwater treadmill compared to the pain experienced on a land treadmill (Roper, Bressel & Tillman 2013). Moreover, Fisken et al. (2014) and Denning et al. (2010) both observed acute decreases in pain following one aquatic exercise session, with the size the of decrease in pain being similar irrespective of training intensity, i.e. light to hard (Denning, Bressel & Dolny 2010, Fisken et al. 2014). Therefore, pain is decreased during aquatic exercise irrespective of the modality, thus the primary goal of aquatic exercise should be to gain patient specific improvements in functional capacity rather than striving only for pain relief.

6.1.2 Effects of aquatic exercise on functional capacity

Lower levels of functional capacity, i.e. weaker muscles, slower walking speeds, and increased activity limitations are risk factors for progression and worsening of OA related activity limitations and pain (van Dijk et al. 2010, Pisters et al. 2012, Holla et al. 2015, Oiestad et al. 2015). As the severity of OA worsens, functional capacity decreases and there is an increase in activity limitations which results in an increased burden on the healthcare services (McAlindon et al. 2014) and a decrease in quality of life through limitations in participation

(Manini 2011). The results of this dissertation show that aquatic exercise can have a positive effect on many different aspects of functional capacity in healthy older adults, postmenopausal women with mild knee OA and in patients with lower limb OA. These improvements in functional capacity may protect the cartilage from abnormal or excessive loading, i.e. aquatic exercise may have a chondro-protective effect.

Muscle strength

Muscle weakness is a risk factor for acquiring OA and also for the progression of early OA with muscle weakness often observed in individuals with knee OA (van Dijk et al. 2010, Pisters et al. 2012, van der Esch et al. 2014, Oiestad et al. 2015). Muscle strength, power and mass are all associated with functional capacity in older adults (Brady & Straight 2014). It is well known that muscle function and functional capacity decrease with increasing age and that resistance training on land has been capable of halting, even reversing this process (Brady & Straight 2014). This dissertation indicates that only healthy older adults can gain a significant improvement in muscle strength from aquatic exercise. There was no significant effect on muscle strength in either women with mild OA or subjects with lower limb OA. While this could be due to the lower training intensities of the training used in the OA RCT's (Study I), it does not explain why there was no effect on muscle strength in the women with mild knee OA (Studies IV and V). Moreover, this was surprising, considering the fact that in two published studies, Pöyhönen et al. (2002) and Valtonen et al. (2010) an equivalent aquatic resistance training intervention was utilized, although with different populations and both reported improvements in muscle force production (Pöyhönen et al. 2002, Valtonen et al. 2010). The aforementioned trials used isokinetic force measures to measure peak muscle power production which mimics closer the true muscle work performed during aquatic resistance training and could explain the differences (Valtonen et al. 2010, Pöyhönen et al. 2002). The high number of full ROM repetitions completed at high speeds in the AQUAREHAB study would have logically improved muscle power and power-endurance more than maximal isometric strength. Moreover, 4 out of 6 trials measuring the effect of aquatic exercise on knee extension strength in people with lower limb OA, also used isometric strength testing (Study I). One additional explanation could be that the resistance and resulting muscle activation in aquatic exercise may not be sufficient to overcome the effect of arthrogenic muscle inhibition (Rice & McNair 2010). The addition of lower limb resistance boots has been shown to increase resistance and therefore, to elevate muscle activity (electromyographically measured) during lower limb aquatic exercises (Pöyhönen et al. 2001a, Pöyhönen et al. 2001b). However, only one OA trial (Cochrane, Davey & Matthes Edwards 2005) out of the 6 trials (Study I) measuring muscle strength utilised additional resistance equipment, although this has been shown to be necessary if one wishes to attain maximal muscle activation during aquatic exercise (Pöyhönen et al. 2001a, Pöyhönen et al.

2001b). Additionally, type II muscle fibres (fast twitch) are lost more quickly and furthermore the de-innervation of motor neurones increases with age, leading to activity avoidance; these processes may not have been sufficiently affected by the stimulus and tension created during aquatic exercise (Marcell 2003, Pietrosimone et al. 2011, Sions et al. 2012). Furthermore, the intramuscular tension developed during the aquatic resistance exercises may not have been sufficiently high to stimulate muscle hypertrophy (Pöyhönen et al. 2001a).

The depth of the pool may have played a role in limiting the effectiveness of the aquatic resistance training to achieve maximal muscle contraction and consequently to optimise the effect on muscle strength. Our pool depth was 20-30 cm deeper than the pool utilised in previous studies, i.e. 130-150 cm (Pöyhönen et al. 2002, Valtonen et al. 2010). A shallow depth is important to optimise the ability of the participant to maximally recruit all motor units within the exercising muscle, i.e. a depth above T11 is considered to be buoyancy dependant. Thus stability of the standing position may have been compromised at the increased depth, and this is an effect of immersion which has been shown to affect muscle activation (Tarnanen et al. 2012). Although aquatic steps were used to lift the participant further out of the water, they were not beneficial in all the subjects. Aquatic plyometric training is another possible modality to improve muscle strength and power that could be utilised if the primary outcome is to increase muscle strength or power. The effects of aquatic plyometric programs have been shown to improve sprint time, agility, strength and vertical jump with reduced impacts on landing and less muscle soreness than in comparable land training in both athletes and non-athletes (Robinson et al. 2004, Gulick et al. 2007, Stemm & Jacobson 2007, Ploeg et al. 2010). The multi-joint movements and large force production during the take-off phase when combined with the low impact make aquatic plyometric training a potential approach in people with knee OA (Triplett et al. 2009). Furthermore, by giving the participant a task to perform, e.g. clearing an obstacle or reaching a specific height might have been beneficial as it would provide an external goal to the training, that was lacking from the aquatic resistance training programme. The efficacy of such a programme has not yet been investigated in patients with lower limb OA.

Walking ability

An improvement in walking ability was detected in all studies, in all three different populations studied. There was some heterogeneity between outcomes used between each study e.g. 8ft, 50ft, 6MWT, 2km walking test, but all measured walking ability as a factor of distance covered in a certain time, i.e. walking speed. A slower walking speed is a common finding in older adults (Bohannon 1997) and subjects with knee OA (Zeni & Higginson 2009, Mills et al. 2013b). While the changes encountered in older adults are attributed to the biological effects of ageing (Sipilä & Poutamo 2003), the changes in people with early and late-stage OA are also due to pain avoidance, kinesiophobia and unloading of the more frequently affected medial compartment (Zeni & Higginson 2009, Mills et al. 2013a, Holla et al. 2014).

There has long been a debate about the specificity of aquatic exercise, i.e. can exercise performed in water, i.e. eliminating gravity and with different kinetics, kinematics and muscle activations achieve, the same kinds of positive therapeutic effects as exercise performed on land (Heywood et al. 2016)? The results of this dissertation appear to support the use of aquatic exercise to improve land-based functional capacity. Efficient gait requires co-ordination between agonist and antagonist muscles and strength alone is not a marker of improved gait biomechanics (Zeni & Higginson 2009, Mills et al. 2013a, Mills et al. 2013b). However, people with knee OA have increased co-activation of the knee extensors and flexors, resulting in an increase in joint loading (Zeni & Higginson 2009). A decrease in weight-bearing, as a result of immersion, decreases nociceptor stimulation and afferent feedback, e.g. decrease in muscle spindle activation (Cronin et al. 2016, Pöyhönen & Avela 2002) and reduces the sensation of pain (Hall et al. 2008, Denning, Bressel & Dolny 2010, Roper, Bressel & Tillman 2013, Fisken et al. 2014). These conditions may inhibit hyperalgesia, creating more optimal training conditions for improving neuromuscular function and decreasing co-activation of the agonist and antagonist muscles during aquatic exercise. Further, although the drag resistance during this type of exercise was not maximal, the peak EMG signal during underwater knee extension and flexion is either the same or higher than the corresponding EMG measured during land-based maximal isokinetic knee extension and flexion (Pöyhönen et al. 2001a). In addition, the muscle recruitment patterns appear to be different during aquatic exercise compared to those developed on land (Pöyhönen et al. 2001a). The effect of this physiologically different type of training appears to transfer directly to land-based gait, even if the aquatic exercise is not performed in a standing position as in Cox et al. (2008), where swimming alone produced improvements in walking ability (Cox et al. 2008). This hypothesis is further strengthened from the fact that aquatic exercise can improve walking ability in persons with lower limb OA even with low training intensity. However, only Roper et al. (2013) have investigated the effects of aquatic exercise on the kinematics and kinetic of gait in subjects with lower limb OA (Roper, Bressel & Tillman 2013), although similar findings have been seen during underwater walking performed soon after knee and hip arthroplasty (Giaquinto et al. 2010a, Giaquinto et al. 2010b).

People with knee OA decrease their walking speed in order to decrease the size of the impulse passing through the knee joint at the point of heel strike. The decreases in body weight and fat mass were relatively small and insufficient to have significantly altered the impact force during gait (Messier et al. 2013). Therefore, an increase in walking speed may in fact accelerate OA progression and cause a worsening of activity limitations. Improvement in walking speed, following 4 months of aquatic resistance training, was maintained at the 12-months' follow-up, indicating that this may expose the joint to excessive loading and further OA progression (Tanaka et al. 2016). Since there was no acute worsening of clinical findings, i.e. changes in any domains of the KOOS detected at the 12-month follow-up measurements, this suggests

there was no significant acute worsening of knee OA. However, as the participants returned to similar levels of physical activity after the intervention period, it is reasonable to assume they did not utilise this improved walking ability during activities of daily living. In addition, a 12-months' follow-up period is fairly short in terms of knee OA progression and a longer follow-up period may have been needed to detect an effect, either beneficial or detrimental. Walking speed was calculated from the UKK 2km walking test (Laukkanen et al. 1993b) and it is reasonable to assume that the maintenance in walking speed may not just be caused by an improvement in neuromuscular performance but also a learning effect from the intervention. The intervention was of high intensity and the subjects experienced, many for the first time, the sensation of intense physical exertion. This could have taught the participants that it was safe to exert themselves at a higher intensity than they previously thought reasonable. It is possible to speculate that this learning effect was retained at one year after the termination of the intervention. Alternatively, it is possible that the participants in the aquatic resistance training group scored their daily physical activity at lower intensities than the control group, hiding a true difference in their daily physical activity. Objective measures of physical activity before and after the intervention, e.g. with an accelerometer, would have been required to confirm or reject this hypothesis.

Aerobic fitness

Aerobic fitness was not directly measured in any of the OA trials included in Study I. Aquatic exercise can significantly improve aerobic fitness in healthy older adults as compared to controls and also has equivalent effects as land-based exercise, if one excludes the report of Bocalini et al. (Bocalini et al. 2008). The large effect from Ruoti et al. (1994) was partially due to a decrease in aerobic fitness in the control group as well as possible due to the difference in the ages of the two research groups (65 years old in aquatic exercise and 56 in control group) and possible bias in the measurements (lack of assessor blinding). However, it is important to note that the training intensity in this trial was set at 80% heartrate max as measured from a land-based pre-intervention VO_2 testing, i.e. individualised and of high intensity (Ruoti, Troup & Berger 1994). The intensity utilized by Rhodes et al. was set at only 60-65% of heartrate max and Broman et al. (2006) used 75% acquired during land-based testing (Rhodes et al. 1995, Broman et al. 2006). Finally, the trial Tauton et al. (1996) showing no effect of the training on aerobic fitness, did not set training intensity based on individual results of aerobic fitness testing (Taunton et al. 1996). The conclusion from there trials is that it is essential that the training intensity during aerobic aquatic exercise should be adapted to each individual if one wishes to achieve an optimal effect.

Following 4-months of aquatic resistance training, there was a significant increase in aerobic fitness in the training group compared to controls. This is as expected, as the aquatic resistance training did appear to have contained a considerable aerobic element and it should have improved aerobic fitness. If a

10% decrease in maximum heart rate during aquatic exercise is expected (Becker 2011, Denning et al. 2012), our data indicate that the participants trained at a level of approximately 65-70% of their estimated maximum heart rate, which follows the ACSM guidelines for aerobic training (Nelson et al. 2007). Moreover, Edvardsen et al. (2013) found that during maximal treadmill exercise in women age 60-69, maximal heart rate was 163.0 (14.2) and RPE (BORG 6-20) was 17.8 (1.1) (Table 13), indicating that the subjects in our study were training regularly at a high intensity (Edvardsen et al. 2013). Additionally, the blood lactate levels were at or above the anaerobic threshold (4 mmol/L). However, this improvement in aerobic fitness was lost at the 12-months' follow-up, even though the improvement in walking speed, part of the equation for calculating aerobic fitness with the 2km walk test (Equation [5]), was maintained. Body weight and heart rate at the end of the test, both of which had returned to baseline at 12-month follow-up, are part components of the equation (Equation [5]) and this may explain the result. Therefore the improvements in cardiovascular fitness, which incorporates many factors, should be interpreted with caution, as it is possible that improvements in walking efficiency and changes in body weight may, in part, explain the changes.

Self-reported versus performance-based measures of function

There was a clear difference in the use of patient reported and objective measures of physical performance between the studied populations. All of the 11 trials investigating the effect of therapeutic aquatic exercise on patients with lower limb OA used a self-reported questionnaire for measuring change in functional capacity (Study I). However, only four out of 28 trials investigating the effect of aquatic exercise on function in healthy older adults utilised patient-reported outcome measures, while all but one trial utilized objective measures of physical functioning (Sato et al. 2007, Tavares & Sacchelli 2009, Shibata et al. 2012, Oh et al. 2015). The result may be explained, in part, by the differing purpose of the trails included in the two systematic reviews (Study I and II). Further, the size of the effect was larger in both studies (Study I and II) for the self-reported outcomes compared to performance based measures, indicating that even though the participants perceived they had attained a better functional capacity, the objective performance-based measures indicated this may represent an over-estimation of the true improvements in function.

The most common questionnaire, utilised in the trails investigating the effect of aquatic exercise on patients with lower limb OA, was the WOMAC questionnaire (Study I). Although widely used in OA studies, it has been shown to overestimate true improvements in physical functioning in the presence of decreased pain (Stratford & Kennedy 2004, Stratford, Kennedy & Woodhouse 2006), as well as suffering from a measurement bias when used in these kinds of aquatic exercise intervention studies (Higgins, Altman & Sterne 2011). The acute changes in pain experienced by people with lower limb OA after therapeutic aquatic exercise may also result from an over-estimation of functional capacity with self-reported questionnaires alone. To conclude, the

effect of exercise on function in individuals with OA should be measured using both self-reported questionnaires and physical performance measures (Stratford, Kennedy & Woodhouse 2006).

6.1.3 Effects of aquatic exercise on body composition

Weight loss and exercise are considered as the cornerstones of non-pharmacological management of osteoarthritis and it would be beneficial if different methods of exercising for this population, including aquatic exercise, could be validated for both early and late-stage knee OA. The results from Study IV detected greater improvement in body composition compared with other studies investigating the effects of aquatic exercise on weight and body composition in persons with OA. Lim et al. (2010) found a significant decrease in body fat percentage (1.1%), however the decrease in fat mass was not significant (-0.7kg) (Lim, Tchai & Jang 2010). Kim et al. (2012) observed a significant reduction in weight (-0.76kg) (Kim et al. 2012). Therefore, the decrease in body mass of 1.2kg seen in Study IV is almost double that previously reported in aquatic exercise trials. In both of the aforementioned published trials, the participants trained in the pool 3 times a week for 12 weeks compared to the present work's 16 weeks, which may partially explain the difference.

Messier et al. (Messier et al. 2013) showed that an 18 month, 3 x week land-based exercise program produced a similar loss in total body weight, an overall loss of 1.8kg. Exercise alone conducted for 18-months produced a mean decrease in weight of -1.8kg. However, the decrease in fat mass was only 1% (0.4 kg) and a 2.6kg loss of lean mass was seen in this group with a much larger loss in the diet only and diet with exercise groups. The aquatic resistance training programme evoked no change in lean mass and muscle strength. A decrease in lean mass is a common negative side effect of weight loss in this population (Messier et al. 2013, Heymsfield et al. 2014). This is interpreted to mean that while the exercise was intensive enough to cause significant decreases in fat mass, it was also sufficient to maintain strength and lean mass, which is opposite to the observation in the exercise-only group in the study of Messiers et al. (Messier et al. 2013). Decreased quadriceps muscle strength has been associated with the development and faster progression of knee OA (van der Esch et al. 2014, Oiestad et al. 2015), and muscle strength has been associated with muscle mass in individuals with knee OA (Slemenda et al. 1998, Conroy et al. 2012). Pöyhönen et al. (2002) and Valtonen et al. (2010) both reported an increase in cross-sectional area of the thigh musculature, as measured with quantitative CT, following a similar aquatic exercise program as applied here (Pöyhönen et al. 2002, Valtonen et al. 2010). One limitation of our study was the lack of CT imaging of the thigh musculature. DXA imaging only allows measurement of overall fat and lean mass body content but it is not able to determine whether the change in fat mass was inter- or intra-muscular or if there was a change in the structure of the muscles.

Increased fat mass has been linked to knee OA through low-grade inflammation (Vincent et al. 2012), with higher levels of cytokines and adipokines associated with an increased risk of developing knee OA as well as faster progression of the disease (Houard, Goldring & Berenbaum 2013, Vuolteenaho, Koskinen & Moilanen 2014, Beavers et al. 2015). Beavers et al. (2015) and Messier et al. (2013) reported that exercise alone was not sufficient to reduce the levels of two inflammatory markers, IL-6 and CRP, over an 18-month period (Beavers et al. 2015, Messier et al. 2013). In contrast, diet alone and diet with exercise, which both caused significant reductions in fat mass, were associated with a decrease in the concentrations of both markers (Messier et al. 2013, Beavers et al. 2015). The intervention in their study was of low intensity and 12 out 18 months were unsupervised, possibly reducing its impact on levels of inflammatory markers in the blood. The fat mass loss in our study was achieved globally, which has been suggested to be more effective at reducing the levels of inflammatory markers in individuals with knee OA (Beavers et al. 2015). Moreover, it has been postulated that the acute inflammatory response to high intensity training could reduce low grade inflammation. Our study did not measure inflammatory markers and therefore this hypothesis of possible additional beneficial mechanisms from high intensity aquatic resistance training has to remain speculative (Leggate et al. 2010).

The importance of the role of physical activity in the weight control in individuals with knee OA was confirmed in this dissertation. After removal of group assignment, those participants who had higher monthly METh's lost more fat mass than those with lower monthly METh's. After cessation of aquatic resistance training, it did seem as if the participants returned to their previous levels of physical activity, which is in line a previous aquatic resistance training study (Valtonen et al. 2011). Education on life-style changes has been proposed as a vital part of management of both early and late-stage OA (Filardo et al. 2016). Moreover, Messiers et al. (2013) claimed that exercise with diet would be superior to exercise alone for weight loss in overweight and obese people with knee OA (Messier et al. 2013). After the intervention, the participants were only instructed to exercise spontaneously and not directly given any advice that other forms of physical activity would be suitable for people with mild knee OA. The implementation of a life-style education program, including dietary and advice, may have maintained or even continued the improvements achieved in body composition at the end of the intervention.

6.1.4 Effects of aquatic exercise on the biochemical composition of cartilage

It has been stated that the best interventions would maintain cartilage health and inhibit or even reverse the degenerative changes in cartilage and other structures; exercise is one potential intervention option (Filardo et al. 2016, Roos & Arden 2016). Little research has been conducted into clarifying the effects of exercise on the biochemical composition of cartilage in a joint showing OA

related degeneration (Multanen et al. 2014, Koli et al. 2015). This is the first study which has investigated the effects of aquatic exercise on the biochemical composition of tibiofemoral cartilage and the first exercise based study (land or water based) to demonstrate concurrent changes in both T2 relaxation time and the dGEMRIC index. After 4-months of aquatic resistance training, both T2 relaxation time and dGEMRIC index in the posterior region of the medial femoral condyle significantly decreased, with no change in the central femur and tibia regions. Therefore, these results suggest that the posterior cartilage in individuals with mild knee OA might be responsive to the high repetition, low compression and shear cyclic forces associated with aquatic resistance training. In contrast, the chondrocytes in the central region of the femur and tibia cartilage may require a higher or atypical load before they trigger an adaptive response. However, care must be taken when interpreting these results, as the size of changes observed with both techniques falls within or is close to the measurements errors (Multanen et al. 2009, Hannila et al. 2015). Further, due to lack of data on the responsiveness with both the T2 and dGEMRIC techniques, the power calculation was based on the data from the work by Roos and Dahlberg which means there is a possibility that this study was of under-powered in this respect (Roos & Dahlberg 2005).

All chondrocytes, including cells extracted from OA cartilage, have a latent loading adaptation capacity to proliferate and regenerate the ECM, e.g. to synthesize collagen and GAGs, when exposed to a sufficient stimulus and suitable environment (Teichtahl et al. 2009, Van Ginckel et al. 2010, Gahunia & Pritzker 2012, Jeon et al. 2012). Cartilage, adapts to the forces to which it is exposed (Teichtahl et al. 2009, Van Ginckel et al. 2010), conversely the tissue undergoes atrophy when the load is removed (Kiviranta et al. 1994, Vanwanseele et al. 2002, Vanwanseele et al. 2003, Souza et al. 2012). Regular, cyclic, full ROM movements of the joint could have improved cartilage nutrition and promoted the removal of catabolites from the cartilage, thus stimulating chondrocyte activity (Arokoski et al. 2000, Wang et al. 2013). Furthermore, the response was limited to the medial femoral cartilage, possibly as a result of its anatomical characteristics. The medial tibial plateau is concave compared to the convex surface of the lateral side, thus on the medial tibiofemoral joint, there is greater contact between the cartilage surfaces and this may make possible a greater effect from aquatic resistance training (Neumann 2002). Additionally, although the medial condyle is more often affected by OA (Ledingham et al. 1993, Duncan et al. 2006), it may have a greater potential for repair. This remains speculation due to the inability of either MRI technique to differentiate healthy cartilage from cartilage displaying the early OA changes (Multanen et al. 2015).

A decrease in T2 values is indicative of an improved integrity and orientation of the collagen fibres and a decrease in the hydration of articular cartilage (Nieminen et al. 2001, Lammentausta et al. 2006). This response is similar to that seen in our previous study, which observed a decrease in T2 relaxation time in mildly osteoarthritic patella cartilage following a one year

exercise intervention (Koli et al. 2015). While the exercise modality was different, the mechanical forces impacting on the patella cartilage during the progressive impact exercise were gliding in their nature with moderate compression in the patellofemoral joint. This is similar to the forces to which the tibiofemoral cartilage was exposed during aquatic resistance training. Therefore, our findings support the concept that tibiofemoral cartilage in knees showing early OA related changes can respond to exercise and may require shear forces, not simply compression, to stimulate a response within the cartilage.

A corresponding significant decrease in the dGEMRIC index was seen in the posterior region of medial femoral cartilage. A lower dGEMRIC index is associated with a lower GAG concentration, thus, a decrease in dGEMRIC index may be a relection of degeneration of cartilage (Bashir, Gray & Burstein 1996, Nissi et al. 2004). There are three ways to interpret these results; 1) aquatic resistance training may have produced a decrease in GAG concentration within the cartilage matrix, 2) there may have been faster contrast agent diffusion into the cartilage through increased permeability of the cartilage surface or 3) improved transport of the contrast agent into the joint space (Li et al. 2010). The first two are both characteristics of OA progression (Arokoski et al. 2000). These results disagree with the findings of Roos and Dahlberg (2005) who found an increase in the dGEMRIC index following a 4-month neuromuscular training intervention (Roos & Dahlberg 2005). However, they measured only one small region of the medial femoral cartilage and their dGEMRIC values were not corrected for the BMI of their participants. Further, their population was younger individuals at a high risk of developing knee OA following surgery for meniscal injury. An alternative explanation emerges from a previous cross-sectional study which observed similar associations, i.e. lower T2 and dGEMRIC index in the central ROI of the patella cartilage in young people with repetitive patella dislocation (Bengtsson Moström et al. 2014). This finding was speculated to be due to a reparative process within the cartilage. Additionally, there may have been faster diffusion of the contrast agent into the medial tibiofemoral cartilage after intravenous injection (i.e. improved contrast agent delivery) as a result of vascular changes, i.e. increased blood flow in the subchondral bone and synovium. Furthermore, possible improvements in lower limb biomechanics may exert an influence on contrast agent delivery to the knee joint. In addition, the improved diffusion of the contrast agent could be explained by a decrease in cartilage thickness, i.e. reversal of the cartilage swelling which is a characteristic of early OA (Luyten et al. 2012, Madry, Luyten & Facchini 2012). Cartilage thickness was not measured here, leaving this issue open to speculation and a topic for further investigation. Therefore, one can only conclude that while the results indicate that the integrity of the collagen-interstitial water environment may be responsive to the types of shear/compressive forces generated during aquatic exercise, further research will be required to clarifty the exact nature of the acute responses of cartilage to this type of loading, in particular, do they cause changes in the GAG contentrations and the content of the interstitual fluid.

6.2 Methodological considerations

The conclusions of this dissertation are based on the findings from three separate projects utilising two different study designs. Two systematic reviews with meta-analyses and a 4-month randomised controlled trial with 12-month follow-up were performed (Studies I and II). Each study had different populations representing different stages of the OA continuum, i.e. healthy older adults, women with mild knee OA and people with lower limb OA and therefore they complement each other. The systematic reviews were conducted in line with the PRISMA statement and represent the current highest level of evidence on the effect of aquatic exercise on pain and function in subjects with lower limb OA as well as evaluating function in healthy older adults (Moher et al. 2009). While not all the participants in Study I had knee only OA and not the all healthy adults in Study II will develop knee OA, the results give a good impression of the impact of aquatic exercise on risk factors for OA progression and common goals in OA management. The AQUAREHAB-study, an efficacy study, was conducted in line with the CONSORT guidelines for conducting a randomised controlled trial (Moher et al. 2012). In order to control for the confounding factors associated with OA progression, i.e. obesity, gender, age and co-morbidities, the inclusion criteria for the AQUAREHAB study were very stringent, limiting its generalisation to the entire population. Furthermore, the participants included in this dissertation were mainly female (Study I 73%, Study II 89% and Studies III-V 100% women) and thus the results cannot be extrapolated to males. Although exercise interventions have been shown to reduce pain and improve functional capacity in individuals with lower limb OA, the result of this study cannot be used to claim that aquatic exercise can prevent knee OA progression. The overall results of this dissertation indicate that aquatic exercise can be an effective exercise modality in the management knee OA, however, the limitations of each study design need to considered.

6.2.1 Strengths and limitation of the systematic reviews (Studies I and II)

Strengths of the methods used in both systematic reviews include the use of *a priori* inclusion criteria for the outcome measures based on previous work (Rikli & Jones 1999, Juni, Reichenbach & Dieppe 2006, Veenhof et al. 2006, Dobson et al. 2013) and the application of standardised mean difference to express the overall size of effect of aquatic exercise on functional capacity, making it possible to combine of results from different RCT studies, measured with a variety of outcomes. However, this method does hinder the direct interpretation of the results for clinical application. The overall effect of aquatic exercise on functional capacity was assessed by combining different outcome measurements (as SMDs) into the same meta-analysis; this was necessary as the wide range of different outcomes measured in the included studies prevented the use of the more clinically interpretable mean-difference. Nonetheless, in both studies (I and II), the high heterogeneity should be taken into account,

although its impact was partially controlled for by applying a weighted random-effect model. However, in many of the analyses, the heterogeneity (I^2) remained high. Therefore, interpretation of the meta-analyses should also include an interpretation of the results from each individual construct (sub-group) analyses. This strength in the design of our systematic meta-analysis is that it allows for a more specific analysis of the effect of aquatic exercise on different ICF constructs, i.e. body functions and activities. Unfortunately, the results of both systematic reviews do not provide a clear indication of which populations would benefit most from aquatic exercise and whether one type of aquatic exercise would be more beneficial over another. Additionally, we are unable to define the optimal intervention dose, type of exercise and training intensity for these population groups. Most studies had low power to detect a true change as a result of small sample sizes, validating the necessity for the systematic reviews but this also opens the results to problems in their interpretation. There was insufficient data to perform a meta-analysis investigating the long-term effects of aquatic exercise in individuals with lower limb OA or in older adults, due to lack of measurements taken after a long-term follow-up. None of the trials in either study (Study I and II) measured the physical activity of the participants outside the intervention, making it difficult to attribute all the effects directly to the exercise interventions alone. It is nearly impossible to blind participants from allocation in these types of trials unless Zelen type designs are used, leading to the potential for bias in favour of the aquatic training in all studies (Zelen 1990). The trials investigating the effect of aquatic exercise on lower limb OA had higher Pedro scores than trials investigating its effect on healthy older adults.

In an attempt to control for methodological bias, Study I only included trials all with moderate to high methodological quality according to the PEDro scoring system (Sherrington et al. 2000), however, this also introduces its own form of bias within the systematic review. Two out of three trials investigating the effect of aquatic exercise on knee only OA had failed to recruit sufficient subjects to meet their own power calculation (Lund et al. 2008, Hale, Waters & Herbison 2012); this could explain the results for the knee OA only analysis. By including different affected joints into the review (Study I), and thus more trials and participants, it was possible to have greater confidence in the findings, but at the same time, it prevents one from drawing definitive conclusions on the effects of aquatic exercise for specific affected joints.

6.2.2 Strengths and limitations of the AQUAREHAB study (Studies III, IV and V)

The strengths of this AQUAREHAB study include the high adherence to a very intensive aquatic resistance training program. The high adherence to the intervention and the small number of drop-outs highlight the confidence in the treatment response and emphasize the participants' good motivation to persist with this aquatic resistance training intervention. This is the first study to monitor leisure time physical activity, in addition to the exercise taken during

the aquatic exercise intervention study. Therefore, this study controls for an important confounding factor and demonstrates a true effect from aquatic exercise. This study fulfilled all the important quality criteria of an RCT, except for blinding the participants to exercise therapy, which is almost impossible to achieve in exercise therapy studies (Furlan et al. 2009). The main limitation of this study was the use of strict inclusion criteria which resulted in a homogeneous sample. This limits direct application of our results to individuals with more severe knee OA. Nonetheless, it is reasonable to assume that this programme, after minor adaptation, would prove suitable for improving functional capacity and decreasing the body weight in subjects with more severe knee OA. However, this study only confirms that this programme is suitable for women with mild knee OA and further studies will be needed to confirm its efficacy in subjects with hip OA. This study had multiple endpoints. All p-values and confidence intervals are quoted, rather than introducing the problems and potential errors associated with formal adjustments for potential multiplicity issues. Although training intensity was closely monitored through heart rates and RPE, we could not control for the exact work done by the muscles of the lower limb, unlike in land-based training.

Strict imaging procedure and segmentation rules ensured good stability and repeatability of the T2 and dGEMRIC indices. This limits, but does not rule out, the possibility that the results of this study are affected by the magic angle (particularly T2) and partial volume effects (Hannila et al. 2015, Wang & Regatte 2015). The long imaging time in dGEMRIC mapping might have introduced motion artefact but this was controlled for in our study by applying the motion correction technique in the in-house software, as well as strict inclusion/exclusion criteria for image quality. Nonetheless, the size of changes is within or close to the measurement error and therefore the possibility these findings are attributable to a measurement error, cannot be ruled out (Multanen et al. 2009, Hannila et al. 2015).

MRI imaging was performed with a 1.5 Tesla scanner, whereas a 3.0 Tesla scanner would have produced better spatial resolution and higher signal-to-noise ratio. In some cases, occasionally too thin and deteriorated cartilage and movement or pulsating artery artefact prevented reliable segmentation of cartilage, resulting in lost data. In addition, a single-slice segmenting method was used to assess articular cartilage, whereas a multi-slice method might have produced more a comprehensive view of the knee cartilage. The MRI analysis application automatically divided cartilage into deep and superficial compartments (50%/50%) and since only a 1.5 tesla scanner was available, the segmented cartilage thickness ranged from two to five voxels, reducing the spatial accuracy and therefore care should be taken when interpreting these results. Pre-contrast T1 imaging was not used in this study however its importance has been questioned and it is felt that its omission did not affect our conclusions (Li et al. 2009, Hawezi et al. 2011). Classification of OA severity was performed using Kellgren-Lawrence classification (weight-bearing) and therefore it was not possible to differentiate between healthy and

biomechanically altered cartilage between ROIs (Multanen et al. 2015). It is still unknown if an aquatic training programme lasting longer than 4 months would have created a global response throughout the cartilage. It is plausible to hypothesise that as cartilage health in one ROI improves, it may trigger a positive response in adjacent ROI's. Finally, the relevance of the different qMRI parameters and their response to acute biochemical changes are not yet fully understood and further investigations about the interaction between exercise and these parameters are warranted.

Dietary intake was not measured or controlled. Inclusion in a study has been shown to affect participants' dietary habits as well as their physical activity. Therefore we cannot directly attribute all the changes as a pure effect of the intervention. However, it is unlikely that diet alone would have maintained the lean body mass alone without exercise (Heymsfield et al. 2014). Nonetheless, one could speculate that an increase in lean mass and a more profound decrease in fat mass could have occurred if the intervention had been combined with an appropriate diet. (Thomas et al. 2012) A lack of access to this intensive aquatic exercise program and education, i.e. the failure of the participants to identify appropriate land based exercise possibilities for maintaining benefits achieved during the intervention may have led them to return to their previous level of physical (in)activity (Pisters et al. 2010). This is supported by follow-up feedback from the participants who expressed frustration that these kinds of intensive aquatic exercise programs were not available at their local leisure facilities.

6.3 Practical application of aquatic exercise interventions for knee OA

This study combined the data from a total of 2642 subjects in two systematic reviews and one RCT investigating the effect of aquatic exercise (1099 lower limb OA, 1456 in healthy older adults, 87 postmenopausal women with mild knee OA). Very few harms were experienced in the aquatic exercise groups, 15 in total (lower limb OA n = 5 (Study I), healthy older adults n = 8 (Study II), mild knee OA n = 2 Studies III-V). Aquatic resistance training prescribed at very high intensities, was found to be responsible for only 2 harms reported from 1816 training hours. Aquatic exercise could be a treatment option when there is a contra-indication to land based exercise, i.e. severe pain, kinesiophobia, low functional capacity and low exercise motivation and compliance. Further, patient choice should be taken into account when selecting the training modality. The results of this dissertation suggest that aquatic exercise could be used as a training modality to improve functional capacity and in this respect; it has the potential to be chondro-protective. Due to the high compliance and high levels of vitality experienced by the participants during this high intensity aquatic resistance training programme as well as the very

low incidence of any harms described in 39 published aquatic exercise trials, aquatic exercise could be used to convince the patient that exercise is not harmful and can in fact feel good. Furthermore the benefits are not obtained in the pool, they may be transferred to land based exercise and daily physical activity.

6.3.1 Modalities of aquatic exercise for knee OA

In the current guidelines, unlike the situation for land-based exercise, aquatic exercise is not differentiated into different modalities and there are no specific guidelines when it should be recommend to individuals lower limb OA. Juhl et al. (2014) indicated that in order to achieve the best results, exercise programs for knee OA should only have one aim whereas the majority of the aquatic interventions have included a mixture of strength, aerobic and flexibility exercises (Juhl et al. 2014). Uthman et al. (2014) showed that aquatic exercise interventions with mixed training methods had a high ranking of probably achieving benefits in terms of pain and function (Uthman et al. 2013). However, these results were based on self-reported outcomes and according to the findings of this dissertation; these over-estimate the improvements in functional capacity. Nonetheless, it is likely that a well-planned aquatic exercise program focusing on a specific physiological response would have optimal effect on both of these parameters. An aquatic exercise program should have specific goals that can be measured with performance-based measures of function and not just self-reported outcomes measures (Figure 22).

Low repetition, high effort, aquatic resistance training should be considered when the treatment goal is to improve muscle strength. The exercise should be designed to ensure maximum velocity, i.e. the greatest effort from the participant, made progressive by the addition of resistance devices and care should be taken to ensure that water depth is not excessive. Aerobic aquatic exercise, including deep water running, high repetition aquatic resistance training, aqua-aerobics and swimming appear to improve aerobic fitness in healthy older people and women with mild knee OA. Individually tailored training intensity, following aquatic fitness testing e.g. during deep water or shallow water running, will ensure the optimal physiological response from the prescribed aquatic exercise programme (Cuesta-Vargas & Heywood 2011, Benelli et al. 2014). The AQUAREHAB study measured heart rate and perceived rate of exertion, both of which are recommended as methods for prescribing exercise intensity, from every session in every participant and these both appeared to be appropriate methods of measuring intensity of aquatic exercise. Neuromuscular training is recommended in individuals with knee OA but the appearance of pain can affect the proprioceptive feedback during exercise (Knoop et al. 2011). The aquatic exercise programme devised by Hinman et al. (2007), integrates many common aspects of land-based neuromuscular training, while using the body weight supporting effect of buoyancy to assist the movement (Hinman, Heywood & Day 2007). This type of program may be useful initially, with a gradual decrease in water depth to increase weight-

bearing as a way to increase exercise tolerance. Muscle spindle activity, and the resulting sensory feedback, decreases during immersion; therefore the use of live underwater video recording may enhance the effectiveness of aquatic neuromuscular training (Cronin et al. 2016). Training balance in water allows the participant to reach further out of their usual base of support, reduces the fear of falling and allows active responses to losses of balance due to the slower movements. In fact, improving balance, as well as decreasing the risk of falling was a primary treatment goal in two of the OA trials (Arnold & Faulkner 2010, Hale, Waters & Herbison 2012). However, in these trials, there was no effect on any performance-based measures of function. Exercising in water allows the recruitment of full joint ROM, which is not always possible on land. Aquatic exercise, irrespective of mobility, appears to improve joint ROM and flexibility and it would be worthwhile to undertake further research to clarify whether the effects are mediated through neural or non-neural mechanisms or a combination of both. The results of Study V, indicate that the low shear forces produced during high volume aquatic resistance exercise could have a chondro-facilitative effect on cartilage, and thus on those chondrocytes, in regions not adapted to exposure to regular high force loads. By improving the cartilage health and environment in one region of the cartilage, it may be possible to trigger an improvement in neighbouring regions, i.e. mechanotransduction (Khan & Scott 2009, Leong et al. 2011). Further, these results suggest that aquatic exercise may have a role as a rehabilitation modality to improve or maintain function as well as aiding recovery by gradually loading the cartilage following a cartilage injury or after cartilage surgery. However, this is speculation which can only be confirmed by further research. Figure 22 presents a summary of the different aquatic training modalities and possible specific effects investigated in this dissertation.

6.3.2 Frequency and duration

In contrast to the systematic review of Bergamin et al. (2012) who stated that aquatic exercise three times a week was an optimal frequency, we found no difference between training twice and three times a week. The difference between these outcomes may result from our more comprehensive search and inclusion criteria, which identified 28 studies for inclusion compared to 9 in the review by Bergamin et al. (2012) (Bergamin et al. 2012). Long term adherence to physical activity is important in individuals with knee OA and although adherence to a high intensity aquatic resistance training three times a week was high, it is unknown if training at such a high intensity could be sustained over a longer period. The overall level of physical activity, including aquatic exercise, should be taken into account, especially if weight control is a treatment outcome. Aquatic exercise of high intensity and too frequent sessions may affect physical activity outside of the intervention.

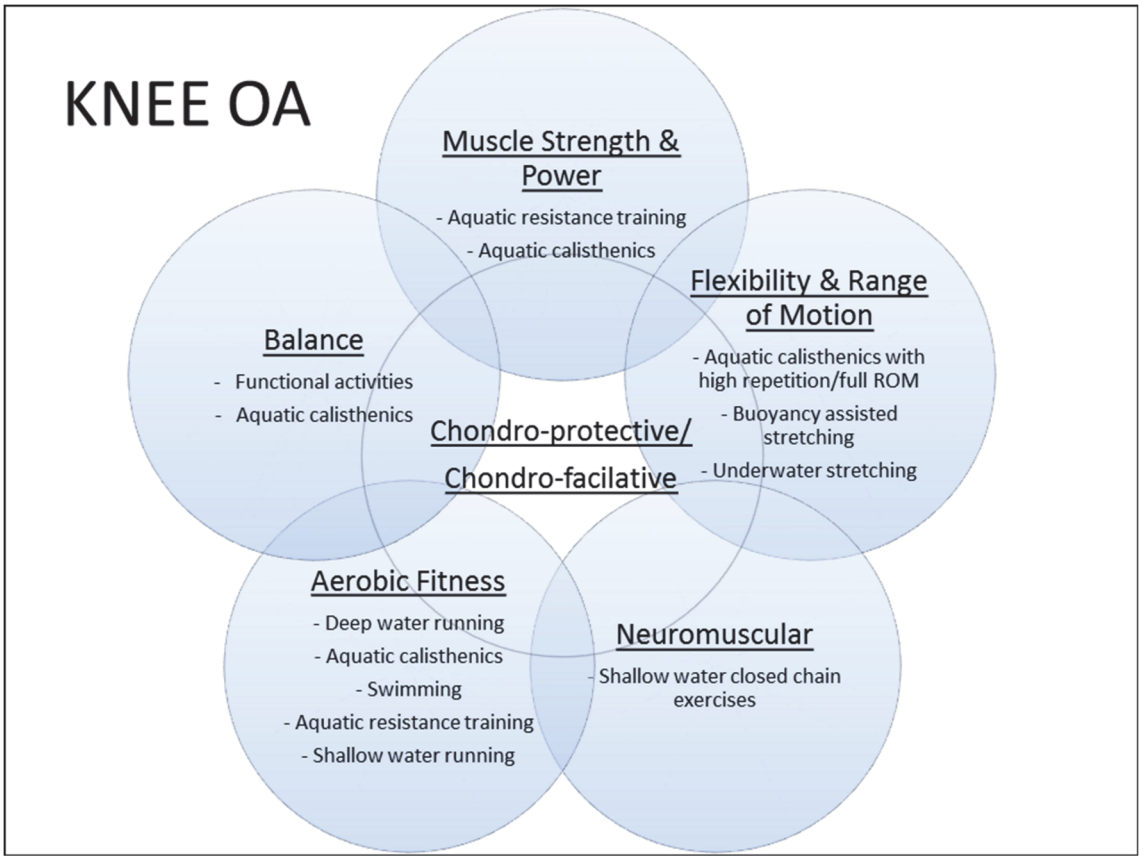

FIGURE 22 Evidence-based aquatic exercise modalities for the management of knee OA.

6.3.3 Intensity of aquatic exercise

The benefits of the aquatic environment should not be overlooked; they can facilitate an optimal training stimulus, however, often the intensity of this stimulus has not been utilized or has not been accurately described in the literature investigating the efficacy of aquatic exercise in individuals with knee OA. In this dissertation, our high intensity aquatic exercise intervention was stringently planned and extremely closely monitored. It was determined that high intensity aquatic training was safe in this population of women with mild knee OA. For this reason, the focus of exercise prescription should be on achieving high level training intensities and maximal strength repetitions as recommended in the current guidelines e.g. ASCM or AGS (AGS Clinical Practice Committee 2001, Nelson et al. 2007, Bennell & Hinman 2011).

6.4 Suggestions for future research

This study presents data that supports the use of aquatic exercise in the management of knee OA in all stages of the disease progression. It was particularly interesting that aquatic exercise exerted positive effects on walking ability in all three populations studied, irrespective of improvements in muscle strength and training modality and intensity. Walking is the most common form of leisure-time physical activity and furthermore, it allows participation in social activities, thus maintaining independence. Future research should be conducted into the biomechanical changes in gait after aquatic exercise and clarify the potential mechanisms behind this property i.e. reduction in muscular co-contraction. Underwater treadmill walking appears to be a promising new method of aquatic exercise which has been claimed to exert a positive impact on pain, walking ability and strength in individuals with lower limb OA (Denning, Bressel & Dolny 2010, Roper, Bressel & Tillman 2013, Bressel et al. 2014). It also allows for accurate control of intensity via external factors such as flow and speed which is one limitation inherent in aquatic resistance training (Bressel et al. 2012). Further research is needed to evaluate the true efficacy for this innovative aquatic intervention.

This is the first study to reveal that high repetition aquatic resistance training can have an impact on cartilage health. The results of this study and previous work (Multanen et al. 2014, Koli et al. 2015), suggest that knee cartilage responds regionally to different stimuli, depending on its loading history. However, the results from the T2 and dGEMRIC imaging were somewhat contradictory. While the results of this dissertation indicate good stability and repeatability of the T2 and dGEMRIC indices, the limitations of the dGEMRIC methods, which are based on the administration of contrast agents, have significant implication. The implementation of new qMRI methods, which are more sensitive to changes in the biochemical composition of cartilage, e.g. T1rho and T2rho, will be necessary to confirm the hypothesis that non-impact aquatic resistance training can influence cartilage health (Rautiainen et al. 2014a, Rautiainen et al. 2014b). These methods may even reveal changes in the central regions, where the changes may have been too small to be identified by the T2 or dGEMRIC methods.

The AQUAREHAB study included a very homogenous group of otherwise healthy post-menopausal women with mild knee OA. Future research should investigate the effect of intensive aquatic resistance training on patients with severe knee OA, hip OA and male patients as well as individuals who with, in addition to suffering from OA, have other co-morbidities e.g. cardiovascular disease and/or obesity. Moreover, the lack of impacts during aquatic resistance training make it a suitable intervention for people with post-traumatic cartilage lesions or post-chondral graft surgery as a way of maintaining functional capacity while facilitating cartilage healing by improving nutrition supply while still supplying low mechanical loading

(Howard et al. 2010, Hirschmuller et al. 2011, Vanlauwe et al. 2012). Recent advances in surgical techniques, when combined with the aforementioned qMRI procedures, represent an exciting combination which will no doubt be exploited in future investigations.

Future research should investigate the type of mechanical stimulus required to achieve a specific effect on the different regions of cartilage. There are regions of cartilage that are not exposed to constant compression forces, i.e. posterior region or patella cartilage which may benefit from the present type of aquatic exercise. In contrast, the central femoral and tibial cartilage regions may require interventions that restore normal joint mechanics and loading during ADLs (Roos & Dahlberg 2005). It is possible that the inclusion of aquatic plyometric exercise, i.e. higher joint compression at take-off and low impact (Triplett et al. 2009) or Ai Chi (Tai Chi in water), i.e. a more sustained but low load compression type of aquatic exercise, may have produced different changes in the cartilage and functional ability. Therefore, the response of cartilage to different types of aquatic exercise should be investigated.

Aquatic exercise is often considered expensive and not cost effective. However, one can gain specific benefits from using aquatic exercise in the management of knee OA. Future studies should examine the cost effectiveness of shorter, highly intensive, aquatic exercise interventions, e.g. of 4-6 weeks' duration, followed by the provision of a land-based exercise program that is based on the exercise pedagogy as part of the aquatic exercise. Increasing daily physical activity in this patient group may maintain or even enhance the positive effects of the intervention. This could be achieved by providing of top-up booster sessions, exercise education or monitoring of physical activity after the intervention has finished with physical activity diaries or exploitation of modern technology such as text messaging or e-mails (Pisters et al. 2007). It is evident that the transition between water- and land based exercise require innovative approaches.

The results of this study not only revealed that intensive aquatic exercise is effective, they also demonstrate that little harm was associated from training at a high intensity while in water. Therefore, clinicians should use water as a facilitating medium to maximise physiological adaptions and to achieve the best possible benefits for improving function. However, physicians still find it difficult to know when to recommend aquatic exercise. Furthermore, monitoring of the actual intensity achieved during aquatic exercise is even more challenging. Better methods to monitor training intensities during aquatic exercise are needed for both the prescriber and the participant.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings of this study are as follows:

1. Aquatic exercise decreases pain and symptoms while improving self-reported functional capacity, quality of life and measured walking speed in people with lower limb OA.

2. Aquatic exercise is effective at improving functional capacity in healthy older adults compared to control and is at least equally effective as land-based exercise.

3. A progressive 4-month aquatic resistance training program of high intensity improves walking ability and decreases fat mass in post-menopausal women with mild knee OA, however, only the improvements in walking ability were maintained at the 12-months' follow-up. Additionally, this kind of aquatic resistance training programme led to regional adaptation in tibiofemoral cartilage in postmenopausal women with mild knee OA.

In conclusion, the results of this study indicate that aquatic exercise is an effective exercise modality in the management of knee OA as well as maintaining functional capacity in healthy older adults. A high intensity aquatic resistance training programme can improve walking speed and decrease fat mass in women with mild knee OA. Furthermore, the regional changes seen in the biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee OA lend support to the proposal that cartilage can respond to aquatic resistance training. Aquatic exercise is not a single entity, instead it should be considered as consisting of many different training modalities, each with their own specific purpose and outcomes. The effects of aquatic exercise on functional capacity should be measured using both self-reported and performance-based measures of function.

FINNISH SUMMARY

Vesiharjoittelun vaikutukset oireisiin, toimintakykyyn, kehon koostumukseen ja nivelrustoon polven nivelrikkoa sairastavilla

Polven nivelrikko on maailman yleisin nivelsairaus, joka pitkälle edetessään aiheuttaa kipua sekä heikentää toiminta- ja liikkumiskykyä. Nivelrikon hoito on monialainen kokonaisuus joka pitää sisällään kaikki taudinkuvaan kuuluvat vaiheet vammojen ennaltaehkäisystä taudin lopulliseen vaiheeseen, tekonivelleikkaukseen. Nivelrikon hoidossa on viime vuosina keskitytty nivelruston rappeutumisen sekä heikentyneen toiminta- ja liikuntakyvyn etenemisen ehkäisyyn taudin aikaisissa vaiheissa. Polven nivelrikon etenemiseen liittyviä riskitekijöitä ovat polvikipu, heikentynyt toimintakyky (esimerkiksi alentunut lihasvoima, aerobinen suorituskyky ja kävelynopeus), ylipaino ja ikääntyminen. On olemassa tieteellistä näyttöä, että näihin riskitekijöihin voidaan positiivisesti vaikuttaa liikuntainterventioiden avulla. Näin ollen liikuntainterventiot voivat suojata polven nivelruston rappeutumista.

Alkavan polven nivelrikon yleisin oire on paikallinen kipu. Tutkimukset ovat osoittaneet polvikivun aiheuttavan liikkumisen pelkoa ja vähentävän päivittäistä fyysistä aktiivisuutta. Vähentynyt fyysinen aktiivisuus puolestaan alentaa toimintakykyä. Lisäksi liikkumattomuus lisää ylipainon riskiä ja siihen liittyviä kehon koostumuksen muutoksia, kuten lisääntynyttä kehon rasvamassaa. Terapeuttisen vesiharjoittelun, kuten fysioterapeutin ohjaaman liikeharjoittelun, on todettu olevan tehokas harjoittelumuoto polven nivelrikon hoidossa. Vesi harjoitteluympäristönä vähentää polviniveleen kohdistuvia kuormia verrattuna kuivalla maalla suoritettuun harjoitteluun. Lisäksi vesi mahdollistaa tehokkaamman harjoittelun vähemmällä kivulla. Vesiliikunta, kuten vesijuoksu ja vesijumppa, ovat suosittuja liikuntamuotoja terveiden ikääntyneiden keskuudessa. Vesiliikunnan on todettu ylläpitävän yleiskuntoa ja toimintakykyä mikä voi suojella polvea epäsuotuisilta muutoksilta. Vaikka nivelrikko on yleinen tutkimusaihe, niin terapeuttisen vesiharjoittelun vaikutuksia lievää polven nivelrikkoa sairastavilla ei ole tutkittu. Lisäksi systemaattista kirjallisuuskatsausta meta-analyysillä, joka tutkii vesiharjoittelun vaikutuksia toimintakykyyn sekä polven nivelrikosta kärsivillä että terveillä ikääntyneillä, ei ole aiemmin ollut. Tämän väitöskirjatutkimuksen tavoitteena oli selvittää tämänhetkinen tieteellinen näyttö terapeuttisen vesiharjoittelun vaikutuksista kipuun, toimintakykyyn ja elämänlaatuun alaraajan nivelrikosta kärsivillä aikuisilla. Myös tieteellinen näyttö vesiliikunnan vaikutuksista toimintakyvyn eri osa-alueisiin terveillä nivelrikkoriskin alaisilla henkilöillä selvitettiin. Lisäksi selvitettiin progressiivisen vesivastusharjoittelun välittömiä ja pitkäaikaisvaikutuksia polven kipuun, lihasvoimaan, kävelynopeuteen, kehon koostumukseen ja polven nivelruston biokemialliseen koostumukseen vaihdevuosi-iän ohittaneilla naisilla, joilla oli todettu lievä polven nivelrikko.

Tämä väitöskirjatutkimus koostui kahdesta laajasta projektista, joista ensimmäinen sisälsi kaksi systemaattista kirjallisuuskatsausta ja meta-analyysin.

Toinen projekti koostui satunnaistetusta ja kontrolloidusta liikuntainterventiosta sekä seurantatutkimuksesta intervention jälkeen. Ensimmäinen systemaattinen katsaus ja meta-analyysi selvitti terapeuttisen vesiharjoittelun vaikutuksia kipuun sekä toimintakykyyn ihmisillä, joilla oli todettu alaraajanivelrikko. Harjoittelun vaikuttavuutta verrattiin kontrolliryhmään. Katsaus sisälsi 11 satunnaistettua ja kontrolloitua vesiharjoittelututkimusta. Toinen systemaattinen katsaus ja meta-analyysi selvitti vesiliikunnan vaikutuksia fyysiseen toimintakykyyn terveillä yli 55-vuotiailla aikuisilla. Harjoittelun vaikuttavuutta verrattiin kontrolliryhmään ja maalla suoritettuun liikuntaan, analyysi sisälsi 28 vesiharjoittelututkimusta. Satunnaistettuun kontrolloituun liikuntatutkimukseen osallistui 87 lievää polven nivelrikkoa sairastavaa 60–68 –vuotiasta naista. Neljä kuukautta kestäneestä progressiivisesta vesivastusharjoittelusta tutkittiin sen välittömiä ja pitkäaikaisvaikutuksia liikkumiskykyyn, aerobiseen kuntoon, alaraajojen lihasvoimaan, itsearvioituihin oireisiin sekä kehon koostumukseen. Lisäksi vesivastusharjoittelun vaikutuksia polvinivelen (reisiluu-sääriluuliitos) rustoon mitattiin kvantitatiivisen magneettikuvantamisen T2 relaksaatioaika ja dGEMRIC –menetelmillä.

Tämän väitöskirjatutkimuksen tulokset osoittavat, että terapeuttinen vesiharjoittelu vähentää nivelrikkoon liittyvää kipua ja niveljäykkyyttä sekä parantaa itsearvioitua ja objektiivisesti mitattua toimintakykyä alaraajan nivelrikosta kärsivillä. Vesiliikunnan todettiin lisäävän lihasvoimaa ja lihaskestävyyttä, parantavan ketteryyttä, kehon liikkuvuutta, kävelykykyä, aerobista kuntoa ja itsearvioitua toimintakykyä verrattuna kontrolli-interventioihin terveillä yli 55-vuotiailla aikuisilla. Lisäksi vesiliikunnan todettiin parantavan toimintakykyä yhtä tehokkaasti kuin kuivalla maalla suoritettu harjoittelu. Neljä kuukautta kestänyt vesivastusharjoittelu lisäsi merkitsevästi harjoitteluryhmän kävelynopeutta ja aerobista kuntoa sekä alensi kehon rasvamassaa verrattuna kontrolliryhmään. Vuoden seurantatutkimuksessa ainoastaan kävelynopeuden todettiin pysyneen liikuntaintervention jälkeisellä tasolla. Vesivastusharjoittelun jälkeen polviruston biokemiallisessa koostumuksessa havaittiin positiivisia muutoksia reisiluun nivelnastan mediaalipuolen ruston posteriorisessa osassa sekä T2 relaksaatioaika että dGEMRIC –menetelmillä kuvattuna.

Johtopäätöksenä on, että vesiharjoittelu vaikuttaa positiivisesti fyysiseen toiminta- ja liikkumiskykyyn kaikissa nivelrikon taudinkuvaan kuuluvissa vaiheissa. Vesivastusharjoittelu edistää liikkumiskykyä ja aerobista kuntoa sekä alentaa kehon rasvamassaa lievää polven nivelrikkoa sairastavilla naisilla. Vesivastusharjoittelun vaikutukset polviruston biokemialliseen koostumukseen vaativat lisätutkimusta.

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ORIGINAL PUBLICATIONS

I

EFFECT OF THERAPEUTIC AQUATIC EXERCISE ON SYMPTOMS AND FUNCTION ASSOCIATED WITH LOWER LIMB OSTEOARTHRITIS: A SYSTEMATIC REVIEW WITH META-ANALYSIS

by

Waller B, Ogonowska-Słodownik A, Vitor M, Lambeck J, Daly D, Kujala UM, Heinonen A. 2014

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Research Report

Effect of Therapeutic Aquatic Exercise on Symptoms and Function Associated With Lower Limb Osteoarthritis: Systematic Review With Meta-Analysis

Benjamin Waller, Anna Ogonowska-Slodownik, Manuel Vitor, Johan Lambeck, Daniel Daly, Urho M. Kujala, Ari Heinonen

Background. Current management of osteoarthritis (OA) focuses on pain control and maintaining physical function through pharmacological, nonpharmacological, and surgical treatments. Exercise, including therapeutic aquatic exercise (TAE), is considered one of the most important management options. Nevertheless, there is no up-to-date systematic review describing the effect of TAE on symptoms and function associated with lower limb OA.

Purpose. The purpose of this study was to conduct a systematic review with meta-analysis to determine the effect of TAE on symptoms and function associated with lower limb OA.

Data Sources. The data sources used in this study were: MEDLINE, PubMed, EMBASE, CINAHL, PEDro, and SPORTDiscus.

Study Selection. All studies selected for review were randomized controlled trials with an aquatic exercise group and a nontreatment control group. In total, 11 studies fulfilled the inclusion criteria and were included in the synthesis and meta-analysis.

Data Extraction. Data were extracted and checked for accuracy by 3 independent reviewers.

Data Synthesis. Standardized mean difference (SMD) with 95% confidence interval (95% CI) was calculated for all outcomes. The meta-analysis showed a significant TAE effect on pain (SMD=0.26 [95% CI=0.11, 0.41]), self-reported function (SMD=0.30 [95% CI=0.18, 0.43]), and physical functioning (SMD=0.22 [95% CI=0.07, 0.38]). Additionally, a significant effect was seen on stiffness (SMD=0.20 [95% CI=0.03, 0.36]) and quality of life (SMD=0.24 [95% CI=0.04, 0.45]).

Limitations. Heterogeneity of outcome measures and small sample sizes for many of the included trials imply that conclusions based on these results should be made with caution.

Conclusions. The results indicate that TAE is effective in managing symptoms associated with lower limb OA.

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Osteoarthritis (OA) is the most common form of arthritis,[1] with the knee, hand, hip, and spine being the most common symptomatic body parts affected.[2] People with OA of the lower limb are affected by symptoms in all levels of the *International Classification of Functioning, Disability and Health* (ICF).[3] There is currently no known cure for OA, and management focuses on nonpharmacological (eg, exercise, education, physical therapy, weight loss), pharmacological (eg, nonsteroidal anti-inflammatory drugs, acetaminophen, glucosamine, chondroitin), and surgical (eg, arthroplasty, osteotomy) treatments.[4–6]

Exercise in the form of land-based strengthening and aerobic conditioning or therapeutic aquatic exercise (TAE) and weight loss are considered the most central elements in the current nonpharmacological recommendations in the management of OA.[4,6] There is high-quality evidence supporting the prescription of land-based exercise for people with lower limb OA. Land-based strength and aerobic training has been shown to have a small to moderate effect size (ES) in pain (range=0.32–0.52) and functioning (range=0.32–0.46),[7–10] with no clear superiority between the 2 exercise regimens. Therapeutic aquatic exercise is recommended to people with lower limb OA because of the reduced loading on the joint as a result of buoyancy.[11] Although unproven,[12] the reduced loading is thought to protect the joints from further damage and allows more efficacious training for people who are unable to train effectively on land. However, like land-based training,[13] there is no consensus on what type of TAE is most effective in the management of lower limb OA.

To date, 2 systematic reviews have been published investigating the effect of TAE on OA: a Cochrane review[14] and a systematic review with meta-analysis.[15] The Cochrane review was limited to studies published up to May 2006 and included 6 studies, 5 of which had a control-comparison group. This review[14] indicated that TAE has a small effect on pain (ES=0.19 [95% confidence interval (95% CI)=0.04, 0.35]), function (ES=0.26 [95% CI=0.11, 0.42]), walking ability (ES=0.18 [95% CI=−0.03, 0.39]), and quality of life (ES=0.32 [95% CI=0.03, 0.61]) compared with controls. The systematic review by Batterham et al[15] demonstrated that TAE and land-based exercise have similar effects on self-reported functioning and mobility. The authors concluded that neither approach appeared to be superior to the other. This review was based on studies published up to July 2010, including participants with OA or rheumatoid arthritis, or both.

Nevertheless, in recent years, there has been an increased number of randomized controlled trials (RCTs) investigating the effect of TAE on people with lower limb OA not yet integrated into a systematic review or meta-analysis. Therefore, the aim of this review was to investigate, through a systematic review and meta-analysis of RCTs, the effect of therapeutic aquatic exercise on symptoms and function in people with lower limb OA.

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- eAppendix 1: Example of PubMed Search
- eAppendix 2: Quality and Risk of Bias Assessment (PEDro)
- eAppendix 3: Hierarchy of Outcome Measures
- eAppendix 4: Meta-Analysis for the Effect of Therapeutic Aquatic Exercise (TAE) on Knee Osteoarthritis
- eAppendix 5: Meta-Analysis for the Effect of Therapeutic Aquatic Exercise (TAE) on Hip and Knee Osteoarthritis

Method

Search Strategy and Study Selection

For this systematic review and meta-analysis, we performed a broad search of 6 databases (MEDLINE, PubMed, CINAHL, SPORTDiscus, PEDro, and EMBASE) using a comprehensive combination of key words: "hydrotherapy" or "water exercise" or "aquatic exercise" or "aquatic therapy" or "water rehabilitation" or "aquatic physical therapy" or "aquatic rehabilitation" or "aquatics" AND "osteoarthritis" or "OA" or "arthritis." The search included publications, in English, appearing before December 1, 2013 (eAppendix 1, available at ptjournal.apta.org). Additionally, a hand search of references was performed. Inclusion was based on assessment by 2 independent reviewers (B.W. and J.L.), and full agreement was required. Based on titles and abstracts, duplicates and nonaquatic exercise studies were excluded. Following this search, full-text manuscripts for the remaining studies were retrieved and read by each reviewer, and final selection was made. If needed, disagreements were resolved through discussion with and assistance from a third reviewer (D.D).

Studies included in our review had to have an RCT design, be published in English, and fulfill the following criteria according to the PICOS (Population, Intervention, Comparison, Outcome, and Study) system.[16] The study population included people with clinically diagnosed OA (as assessed with radiography[17,18] or according to American College of Rheumatology guidelines[19]) in one or more joints of the lower limb, with no age or sex restrictions. We

included all interventions that could be classified as therapeutic aquatic exercise where there was full immersion of the body. No limitation was placed on the type of exercise (aerobic, range of motion [ROM], strength) or outcome measures used. Studies were excluded if the comparison group participated in an exercise intervention (land or water based) with or without an additional intervention (eg, home exercises, education). Furthermore, studies with a PEDro score of ≤5, indicating low methodological quality and a high risk of bias,[20] were excluded. The studies had to have a control-comparison group who continued usual care or participated in a sham intervention. Outcome data had to be reported for at least one outcome at baseline and postintervention.

Quality Assessment

Methodological quality or risk of bias was assessed using the 11-point PEDro scale,[21] which has been shown to be a reliable[20] and valid[22] assessment tool. The PEDro scale is based on the 9-point Delphi scale developed by Verhagen et al[23] and is used specifically with RCTs in physical therapy. The 11 quality assessment criteria are: eligibility criteria, random allocation, allocation concealment, baseline similarity, participant blinding, therapist blinding, assessor blinding, adequate follow-up, intention-to-treat analysis, between-group comparisons, and point and variability measures given. In the PEDro scale, the first criterion (eligibility) is not included in the final score, which ranges from 0 to 10. Each criterion is scored 1 ("yes") or 0 ("no, don't know/unclear"). Generally, the maximum a TAE study can be scored is 8 because of the difficulties in blinding the participants and therapist from the intervention in exercise studies.[24] A study with a score of ≥7 is considered to have high methodological quality, and studies scoring ≤5 have considered to have low methodological quality.[20] Assessment of methodological quality was performed independently by 2 reviewers (B.W. and A.O-S.) and compared. In case of disagreement, consensus was obtained by consulting a third reviewer (J.L.).

Data Extraction

Intervention description, inclusion and exclusion criteria, baseline data, and values for all outcomes at baseline, postintervention, and longer follow-up (3–6 months) were extracted by 2 reviewers (A.O-S. and M.V.) and checked for accuracy by a third reviewer (B.W.). Where possible, intention-to-treat data were extracted for follow-up measurements; otherwise, per protocol data were extracted. When data were not presented in the study as mean and standard deviation or were presented in a form that prevented calculation of mean and standard deviation, the original authors were contacted, and original data were requested. Standard deviation was calculated from 95% CI values for the study by Hale et al[25] and from standard error values for the study by Lund et al.[26] Mean and standard deviation were estimated from median values and interquartile ranges for all outcomes from the study by Foley et al.[27] In these cases, the median value was taken as best estimated mean, and interquartile ranges were divided by 1.35.[15,28] The original authors provided aggregate data for lower limb muscle strength measurements.[26] Postintervention scores for the Six-Minute Walk Test and isometric strength from the study by Foley et al[27] were requested, but no reply was received. Outcomes were divided into 5 groups: pain, stiffness, self-reported functioning, physical performance measures, and quality of life. In all cases, the ES between TAE and control groups was calculated as the standardized mean difference (SMD). Data were corrected so that effects in favor of TAE are described as positive ES values. In this study, an ES (SMD) of 0.2 to 0.5 was considered as small, 0.5 to 0.8 as medium, and ≥0.8 as a large effect.[29] For all analyses, we used an inverse-variance weighted random-effects model that incorporates heterogeneity into the model, and ES is presented as SMD (95% CI).

Results

In total, 1,234 potential studies were found; no additional studies where found by hand searching of references. Based on title and abstract content, 1,197 of these studies were excluded. The full texts of the remaining 37 studies were read, and a further 26 studies were excluded, resulting in 11 studies being retained in the qualitative and quantitative synthesis of this review (Fig. 1).

Methodological Quality and Risk of Bias of Included Studies

Methodological quality of the included studies is shown in Table 1, and scoring for each criterion is presented in eAppendix 2 (available at ptjournal.apta.org). Five studies achieved PEDro scores of 8/10.[25–27,30,31]

Participants

In total, data were extracted for 1,092 participants. Mean age ranged from 62 to 76 years, with an average body mass index range of 26.6 to 32.9 kg/m^2. Women comprised approximately 73% of the participants. Six studies included knee and hip OA,[25,27,30–33] 3 studies included only knee OA,[26,34,35] 1 study included hip OA only,[36] and 1 study included any lower limb OA.[37] The study by Patrick et al[37] has previously been classified as a knee/hip OA study, but on consultation with the authors, it was reclassified as any lower limb OA. A summary of the populations included is shown in Table 1.

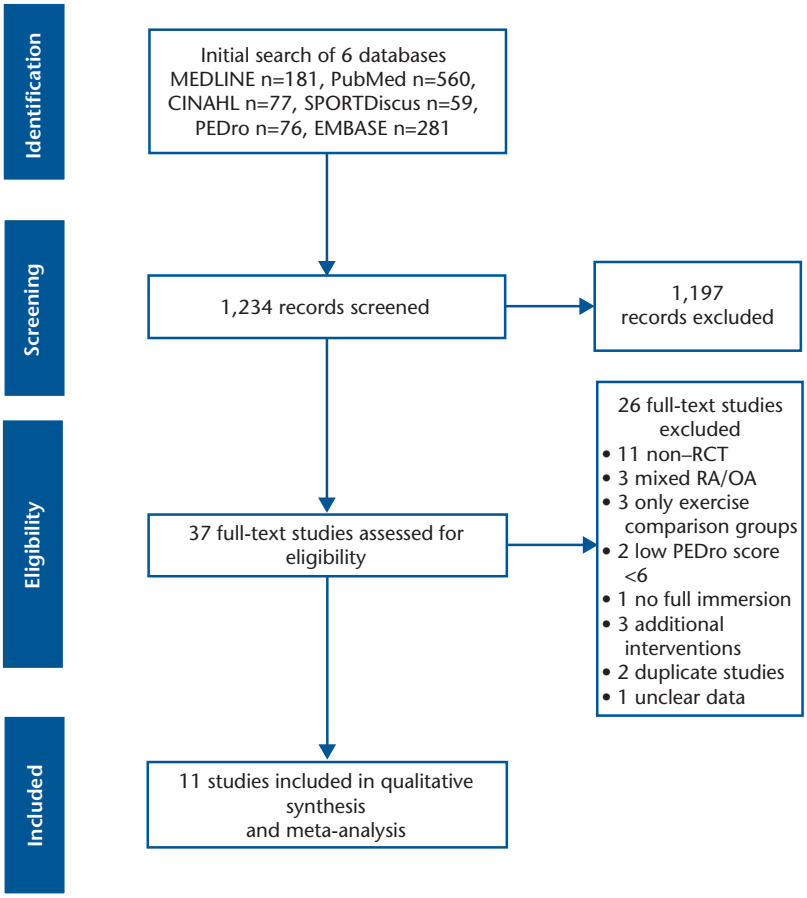


Figure 1.
Flow diagram showing screening process and search results. RCT=randomized controlled trial, RA=rheumatoid arthritis, OA=osteoarthritis.

Therapeutic Aquatic Exercise Interventions

Intervention duration, frequency, dose, intensity, exercise selection, and adherence were different among studies. The interventions, intensity, and dose for each study are described in Table 2. Planned exercise dose varied from 100 minutes per week to 180 minutes per week for 6 weeks to 52 weeks (in total, from 9 to 107 hours). Frequency of treatment was either 2 or 3 times a week (2 times a week was most popular, n=7). Additionally, for all but 4 studies,[30,31,33,35] it would have been impossible to accurately reproduce the intervention based on information given in or referenced in the text (Tab. 2).

Outcome Measurements

All outcomes with appropriately reported data were extracted and included in the qualitative and quantitative synthesis. Outcome measures were grouped according to their construct and design (Tab. 2). In cases where more than one outcome was used to measure a single construct in a single study, outcome selection was based on a predescribed hierarchy with the highest ranked outcome measure being included. Suitable recommendations were found to base selection for the constructs of pain[38] and self-reported functioning and quality of life[39] (eAppendix 3, available at ptjournal.apta.org). The mental component summary of the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36) and the 12-Item Short-Form Health Survey (SF-12) was ranked higher than other scales for quality of life[39]; for the study by Cochrane et al,[32] we selected the data for SF-36 mental health over SF-36 role mental health. No selection for stiffness was required. Due to the wide variety of constructs covered by the physical functioning tests, we decided to first divide the constructs into activities, muscle strength, and joint ROM. Selection of outcome measure for activities, when possible, was based on the suggestions of Dobson et al.[40] In cases of disagreement, we selected the outcome that best covered different constructs related to activity (Timed "Up & Go" Test/stairs selected before walking ability). When isokinetic strength was measured (in newton-meters) using different angular velocities, the results for 60°/s were used. Unless data for both affected and unaffected sides were reported, measurements for the right side only were included here. Table 2 shows the full list of outcomes used in each study; outcomes in bold type indicate those used in the quantitative synthesis.[41]

Overall Effect of TAE on Lower Limb OA

Directly after intervention, TAE had a small but significant effect on pain (SMD=0.26 [95% CI=0.11, 0.41]) and stiffness (SMD=0.20 [95% CI=0.03, 0.36]) (Fig. 2). The effect of TAE on both self-reported and objectively measured physical functioning also was small but significant (SMD=0.30 [95% CI=0.18, 0.43] and SMD=0.22 [95% CI=0.07, 0.38], respectively). Therapeutic aquatic exercise had a small but significant effect on physical functioning at

Table 1.
Description of Included Studies, Population, Adverse Effects, and Dropouts[a]

Study	Location of OA	PEDro Score (/10)	Sample Size and Comparison	Age (y)	Male/ Female	Participant Recruitment	Pain	Self-reported Function	Adverse Effects	Dropouts (%)[b]
Patrick et al,[37] 2001	Lower limb	6	TAE group (n=125) Control group (n=124)	65.7 66.1	18/107 16/108	Advertisement from local area	1.53 (0.60) 1.44 (0.61)	5.74 (1.62) 5.20 (1.73)	None reported	21 (17) 3 (2)
Foley et al,[27] 2003	Hip/knee (51/126)	8	TAE group (n=35) Control group (n=35)	73.0 (8.2) 69.8 (9.0)	20/15 15/20	Advertisement from local health services	10.0 (3.0)[c] 10.0 (4.0)	34.0 (16.0)[c] 37.0 (17.0)	2 reported increased pain	1 (3) 3 (9)
Cochrane et al,[32] 2005	Hip/knee (mixed)	7	TAE group (n=153) Control group (n=159)	69.9 (6.8) 69.6 (6.3)	56/97 60/99	Advertisement in health services	8.72 (3.62) 9.10 (3.14)	30.1 (13.1) 31.1 (11.2)	None reported	48 (31) 33 (21)
Wang et al,[33] 2007	Hip/knee	6	TAE group (n=21) Control group (n=21)	69.3 (13.3) 62.7 (10.7)	4/16 2/16	Advertisement in community sources	52.2 (23.8) 55.3 (24.6)	0.90 (0.4) 0.95 (0.5)	None reported	1 (5) 3 (14)
Fransen et al,[30] 2007	Hip/knee (mixed)	8	TAE group (n=55) Control group (n=41)	70.0 (6.3) 69.6 (6.1)	15/40 7/34	Advertisement in newspapers and community and physician referral	38.2 (17.4) 44.4 (17.0)	46.3 (20.4) 50.8 (19.3)	None reported	3 (5) 0 (0)
Hinman et al,[31] 2007	Hip/knee (16/55)	8	TAE group (n=36) Control group (n=35)	63.3 (9.5) 61.5 (7.8)	12/24 11/24	Advertisement	6 (2) 5 (2)	757 (327) 630 (315)	Only minor, no dropouts	1 (3) 4 (11)
Lund et al,[26] 2008	Knee	8	TAE group (n=27) Control group (n=27)	65 (12.6) 70 (9.9)	5/22 9/18	Recruited from outpatient and GPs and advertisement	59.8 (18.4) 48.5 (31.9)	44.7 (18.1) 39.6 (13.2)	None affecting participation	1 (4) 2 (7)
Lim et al,[34] 2010	Knee	7	TAE group (n=26) Control group (n=24)	65.7 (8.9) 63.3 (5.3)	3/23 3/21	Recruited from patients registered at hospital	4.41 (1.44) 4.12 (2.08)	35.1 (11.3) 30.40 (19.1)	None in TAE group	2 (8) 4 (17)
Arnold and Faulkner,[36] 2010	Hip	6	TAE group (n=28) Control group (n=25)	74.4 (7.5) 75.8 (6.2)	6/20 9/16	Advertisements and posters in clinics, recreational facilities	Not reported	70.4 (21.9) 65.3 (18.1)	1 fall, minor increased pain	5 (18) 6 (22)
Wang et al,[35] 2011	Knee	7	TAE group (n=28) Control group (n=28)	66.7 (5.6) 67.9 (5.9)	4/22 4/22	Advertisements in sports and community centers	61 (20) 66 (18)	73 (20) 70 (19)	1 reported dizziness	2 (7) 2 (7)
Hale et al,[25] 2012	Hip/knee	8	TAE group (n=23) Control group (n=16)	73.6 (1.5) 75.7 (1.1)	6/17 4/12	Volunteers recruited by advertisement	7.2 (5.81–8.62) 7.5 (6.67–8.39)	24.7 (21.0–28.5)[d] 27.8 (24.7–31.0)	1 in TAE group, increased leg pain	3 (13) 1 (6)

[a] OA=osteoarthritis, TAE=therapeutic aquatic exercise, GPs=general practitioners. Values presented as mean (SD) unless otherwise stated.
[b] Directly after intervention.
[c] Median and interquartile range.
[d] Mean and 95% confidence interval.

activity level (SMD=0.22 [95% CI=0.01, 0.42]) and ROM (SMD=0.56 [95% CI=0.14, 0.99]) and no significant effect on muscle strength (Fig. 3). Therapeutic aquatic exercise had a small but significant effect on quality of life (SMD=0.24 [95% CI=0.04, 0.45]).

Effect of TAE at 3- and 6-Month Follow-ups

One study carried out follow-up measurements at 3 months,[26] and one study performed a follow-up at 6 months after cessation of intervention.[32] Thus, pooling was not possible due to lack of data. In these studies, the effect of TAE had been lost at both follow-up measurement points.

Effect of TAE on Specific Joint OA

Three studies[26,34,35] investigated the effect of TAE on knee OA, with no significant effect demonstrated (eAppendix 4, available at ptjournal.apta.org). One study included only hip OA[36]; therefore, no comparisons can be made. Six studies[25,27,30–33] included participants with either hip or knee joint OA, with effect of TAE reported in eAppendix 5 (available at ptjournal.apta.org).

Adverse Effects

Adverse effects were documented in all of the studies, with 5 studies reporting some form of adverse effect as a direct result of participation in the TAE intervention, including increase in pain.[25,27] In total, only 4 participants from 3 studies,[25,27,36]

Table 2.

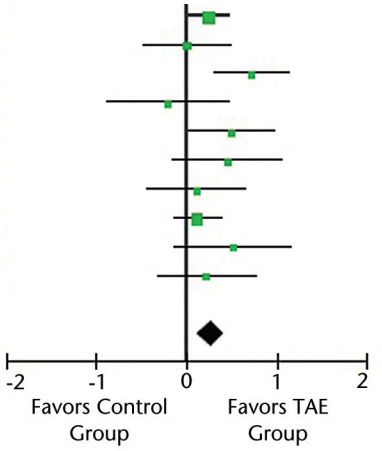
Description of Interventions and Outcome Measures Used in Included Studies[a]

Study	Aquatic Intervention	Intensity	Pool (Depth/ Temperature)	Dose per Protocol[b]	Adherence	Outcome Measures			
						Pain and Stiffness	Self-reported Function	Physical Performance Measures	QoL
Patrick et al,[37] 2001	AFAP, 45–60 min of upper and lower limb flexibility, ROM, and strength exercises	Gentle exercises for flexibility; no other intensity stated	85°–92°F	20/40/52/2,080		**HAQ pain (0–3)**	**HAQ disability (0–3)**		**Perceived QoL scale (0–10)**, current health desirability rating CES-D (0–10), Quality of Well-being Scale
Foley et al,[27] 2003	Warm-up, lower limb strength exercises, cool-down	3 sets × 10–15 reps, progression with addition of gaiters		6/18/30/540	84%	**WOMAC pain (0–20) and stiffness (0–8)**	**WOMAC function (0–68)**, SF-12 PCS	6MWT, isometric knee extension strength	**SF-12 MCS (25–70)**, arthritis self-efficacy (symptoms, satisfaction)
Cochrane et al,[32] 2005	1 h of strength, ROM, endurance, stretches, balance, and coordination exercises	Increase speed and resistance, progressed every 6–8 wk	3 different pools	52/104/60/6,240		**WOMAC pain (0–20) and stiffness (0–8)**, SF-36 pain	**WOMAC function (0–68)**, SF-36 social functioning, physical function	8-ft walk test, **isometric knee extension (N)**/ flexion strength, **stair climb ascending (s)**/descending	**SF-36 mental health (0–100)**, role mental health, vitality, general health, EuroQol-VAS
Wang et al,[33] 2007	AFAP flexibility, strength, and aerobic training	10–15 reps for strength, Borg (CR-10) 3–4 for aerobic training	30°–32°C	12/36/60/1,800	81.7%	**VAS pain (0–100)**	**HAQ (14 question) (0–3)**	**6MWT (m), isometric knee extension (kg)**/ flexion strength, **ROM knee (degrees)** and hip	
Fransen et al,[30] 2007	Strength, lower limb, mobility, trunk work, and balance	10–20 reps		12/24/60/1,440		**WOMAC pain (0–100)**	**WOMAC function (0–100)**, SF 36 PCS	**TUG (s)**, 50-ft walk test, stair climb ascending	**SF-36 MCS (0–100)**, DASS-21
Hinman et al,[31] 2007	Warm-up, leg strength exercises, 6- to 10-min walking, cool-down	2–5 sets × 10 reps, individual progression	34°C	6/12/52/624	99%	**VAS pain (0–10)**, WOMAC pain	**WOMAC function (0–1,700)**	**TUG (s), isometric knee extension strength (kg)**, 6MWT, step test	**Assessment of Quality of Life Scale (range=−4 to 100)**
Lund et al,[26] 2008	10-min warm-up, 20-min strength and endurance exercises, 20-min balance, stretching, and cool-down	3.5 min per exercise, 30-s stretch per muscle group	33.5°C	8/16/50/800	92%	**VAS pain (0–100)** and rest, **KOOS symptoms (0–100)** and pain	**KOOS ADL (0–100)** and sports recreation	**Isokinetic knee extension (60°/s, N·m)**/flexion	**KOOS QoL (0–100)**
Lim et al,[34] 2010	5-min warm-up, 30-min strength and endurance exercises, 5-min cool-down	65% maximum heart rate	1.15 m/34°C	8/24/40/960	>67%	**Bodily pain mean (VAS 0–10)**/pain interference	**WOMAC global (0–96)**, SF-36 PCS	**Isokinetic knee extension (N·m)**/ flexion	**SF-36 MCS (0–100)**
Arnold and Faulkner,[36] 2010	Warm-up, lower and upper limbs, trunk strengthening exercises, cool-down	Not stated	Variable depth/30°C	11/22/45/990	65%		**Activities and Balance Confidence Scale (0–100)**	Berg Balance Scale, 6MWT, **30-s chair stand**, $TUG_{cognitive}$	
Wang et al,[35] 2011	AFAP flexibility, and aerobic training	10–15 reps for strength, Borg (CR-10) 3–4 for aerobic training	30°C	12/36/60/2,160	86.4%	**KOOS pain (0–100)**	**KOOS ADL and sports recreation (0–100)**	**6MWT, ROM knee extension** and flexion	**KOOS QoL (0–100)**
Hale et al,[25] 2012	Warm-up (walking, stretching), balance exercises, cool-down (walking, stretching)	Weeks 1–3: 1 min per exercise Weeks 4–6: 1.5 min per exercise Weeks 7–12: 2 min per exercise	0.94–1.3 m/28°C	12/24/50/1,200	20%–100%	**WOMAC pain (0–20) and stiffness (0–8)**	**WOMAC function (0–68)**, AIMS-2, Activities and Balance Confidence Scale	**TUG (s), isometric knee extension strength (kg)**, step test, fall risk ratio	

[a] Bold type indicates measures included in meta-analysis, with scale range shown in parentheses. QoL=quality of life, ROM=range of motion, HAQ=Health Assessment Questionnaire, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index, KOOS=Knee Injury and Osteoarthritis Outcome Score, ADL=activities of daily living, SF-12=12-Item Short-Form Health Survey, SF-36=36-Item Short-Form Health Survey, PCS=physical component summary, MCS=mental component summary, DASS-21=Depression Anxiety Stress Scale, CES-D=Center for Epidemiological Studies Depression Scale, AIMS-2=Arthritis Impact Measurement Scales-2, AFAP=Arthritis Foundation Aquatic Program, CR-10=category ratio 1–10, 6MWT=Six-Minute Walk Test, TUG=Timed "Up & Go" Test, reps=repetitions.
[b] Duration (weeks)/number of sessions/session duration (minutes)/total dose per protocol (minutes).

Pain

Study or Subgroup	TAE Group $\bar{X}$	TAE Group SD	TAE Group Total	Control Group $\bar{X}$	Control Group SD	Control Group Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)
Cochrane et al,[32] 2005	−8.46	3.74	153	−9.35	3.54	158	25.4	0.24 (0.02, 0.47)
Foley et al,[27] 2003	−10	2.963	34	−10	2.963	32	8.1	0.00 (−0.48, 0.48)
Fransen et al,[30] 2007	−27.3	18.7	55	−40	16.2	41	10.3	0.71 (0.30, 1.13)
Hale et al,[25] 2012	−7.8	3.925	20	−7.1	1.917	15	4.4	−0.21 (−0.88, 0.46)
Hinman et al,[31] 2007	−4	2	36	−5	2	35	8.4	0.49 (0.02, 0.97)
Lim et al,[34] 2010	−3.27	1.67	24	−4.12	2.08	20	5.4	0.45 (−0.15, 1.05)
Lund et al,[26] 2008	−55.8	21	27	−58.1	20	25	6.5	0.11 (−0.43, 0.65)
Patrick et al,[37] 2001	−1.382	0.737	98	−1.462	0.619	117	20.1	0.12 (−0.15, 0.39)
Wang et al,[33] 2007	−43.5	18.6	20	−54.9	25.2	18	4.8	0.51 (−0.14, 1.16)
Wang et al,[35] 2011	72	18	26	68	18	26	6.5	0.22 (−0.33, 0.76)
Total (95% CI)			493			487	100	0.26 (0.11, 0.41)
Heterogeneity: tau^2=0.01, χ^2=10.81, *df*=9 (*P*=.29), I^2=17%								
Test for overall effect: *z*=3.48 (*P*=.0005)								



Stiffness

Study or Subgroup	TAE Group $\bar{X}$	TAE Group SD	TAE Group Total	Control Group $\bar{X}$	Control Group SD	Control Group Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)
Cochrane et al,[32] 2005	−3.88	1.67	152	−4.15	1.48	158	53.3	0.17 (−0.05, 0.39)
Foley et al,[27] 2003	−4	2.222	34	−4	2.222	32	11.4	0.00 (−0.48, 0.48)
Hale et al,[25] 2012	−3.7	1.392	20	−3.4	1.502	15	5.9	−0.20 (−0.87, 0.47)
Hinman et al,[31] 2007	−73	45	36	−95	44	35	11.9	0.49 (0.02, 0.96)
Lund et al,[26] 2008	64.6	12	26	61.4	12	25	8.7	0.26 (−0.29, 0.81)
Wang et al,[35] 2011	69	20	26	61	17	26	8.8	0.42 (−0.13, 0.97)
Total (95% CI)			294			291	100	0.20 (0.03, 0.36)
Heterogeneity: tau^2=0.00, χ^2=4.24, *df*=5 (*P*=.52), I^2=0%								
Test for overall effect: *z*=2.37 (*P*=.02)								

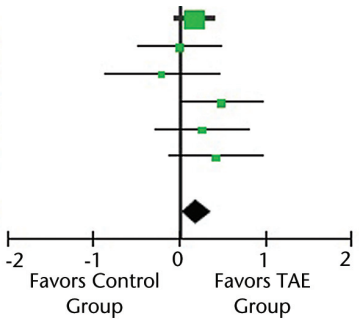


Figure 2.
Forest plots showing the effect of therapeutic aquatic exercise (TAE) on pain and stiffness. 95% CI=95% confidence interval.

Self-reported functioning

Study or Subgroup	TAE Group $\bar{X}$	TAE Group SD	TAE Group Total	Control Group $\bar{X}$	Control Group SD	Control Group Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)
Arnold and Faulkner,[36] 2010	69.6	24.4	26	62.9	20.8	25	5.0	0.29 (−0.26, 0.84)
Cochrane et al,[32] 2005	−29.26	14.48	149	−32.42	13.25	156	29.9	0.23 (0.00, 0.45)
Foley et al,[27] 2003	−33	12.593	34	−37	9.63	32	6.4	0.35 (−0.14, 0.84)
Fransen et al,[30] 2007	−34.8	23.7	55	−49.9	19	41	8.7	0.69 (0.27, 1.10)
Hale et al,[25] 2012	−24	8.899	20	−24.9	7.015	15	3.4	0.11 (−0.56, 0.78)
Hinman et al,[31] 2007	−598	316	36	−656	373	35	7.0	0.17 (−0.30, 0.63)
Lim et al,[34] 2010	−20.9	9.9	24	−27.6	18.3	21	4.3	0.46 (−0.14, 1.05)
Lund et al,[26] 2008	62.7	12	27	61.1	11	25	5.1	0.14 (−0.41, 0.68)
Patrick et al,[37] 2001	−0.933	0.55	101	−1.127	0.671	121	21.5	0.31 (0.05, 0.58)
Wang et al,[33] 2007	−0.9	0.4	20	−1	0.5	18	3.7	0.22 (−0.42, 0.86)
Wang et al,[35] 2011	76	16	26	69	18	26	5.0	0.40 (−0.14, 0.95)
Total (95% CI)			518			515	100	0.30 (0.18, 0.43)
Heterogeneity: tau^2=0.00, χ^2=5.21, *df*=10 (*P*=.88), I^2=0%								
Test for overall effect: *z*=4.81 (*P*<.00001)								

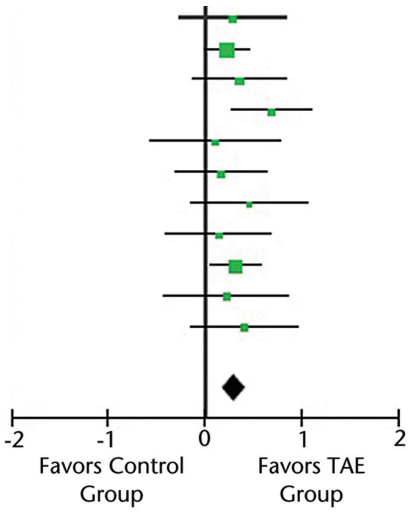


Figure 3.
Forest plots showing the effect of therapeutic aquatic exercise (TAE) on physical functioning. 95% CI=95% confidence interval.

Physical functioning tests									
	TAE Group			Control Group			Weight	Standardized Mean Difference IV,	Standardized Mean Difference IV,
Study or Subgroup	$\bar{X}$	SD	Total	$\bar{X}$	SD	Total	(%)	Random (95% CI)	Random (95% CI)
Physical functioning tests (activities)									
Arnold et al,[36] 2010	7.5	3.9	26	8.1	2.6	25	5.7	−0.18 (−0.73, 0.37)	
Cochrane et al,[32] 2005	−3.24	1.93	153	−3.78	2.72	159	14.1	0.23 (0.01, 0.45)	
Fransen et al,[30] 2007	−8.2	1.7	55	−9.2	2.2	41	8.3	0.51 (0.10, 0.93)	
Hale et al,[25] 2012	−10.1	2.9	20	−10.7	6.8	15	4.2	0.12 (−0.55, 0.79)	
Hinman et al,[31] 2007	−10.32	1.94	36	−10.3	2.78	35	7.1	−0.01 (−0.47, 0.46)	
Wang et al,[33] 2007	388.4	80.3	20	390.7	88.6	18	4.6	−0.03 (−0.66, 0.61)	
Wang et al,[35] 2011	386	75.8	26	329.1	82.3	26	5.5	0.71 (0.15, 1.27)	
Subtotal (95% CI)			336			319	49.6	0.22 (0.01, 0.42)	
Heterogeneity: tau^2=0.02, χ^2=8.47, *df*=6 (*P*=.21), I^2=29% Test for overall effect: *z*=2.10 (*P*=.04)									
Physical functioning tests (muscle strength)									
Cochrane et al,[32] 2005	166.02	108.92	152	145.92	99.82	158	14.0	0.19 (−0.03, 0.42)	
Hale et al,[25] 2012	18.8	8.465	20	19	12.528	15	4.2	−0.02 (−0.69, 0.65)	
Hinman et al,[31] 2007	29.9	12.5	36	24.7	9.5	35	7.0	0.46 (−0.01, 0.93)	
Lim et al,[34] 2010	50.4	19.3	24	63.1	24.1	21	5.0	−0.58 (−1.17, 0.02)	
Lund et al,[26] 2008	73.22	25.86	26	75.08	33.5	25	5.7	−0.06 (−0.61, 0.49)	
Wang et al,[33] 2007	16	4.5	20	12.9	3.8	18	4.3	0.73 (0.07, 1.39)	
Subtotal (95% CI)			278			272	40.4	0.13 (−0.17, 0.43)	
Heterogeneity: tau^2=0.07, χ^2=11.18, *df*=5 (*P*=.05), I^2=55% Test for overall effect: *z*=0.88 (*P*=.38)									
Physical functioning tests (joint range of motion)									
Wang et al,[33] 2007	−1.2	2.6	20	−3.2	3.5	18	4.4	0.64 (−0.01, 1.29)	
Wang et al,[35] 2011	−2.4	2.2	26	−3.3	1.1	26	5.7	0.51 (−0.04, 1.06)	
Subtotal (95% CI)			46			44	10.0	0.56 (0.14, 0.99)	
Heterogeneity: tau^2=0.00, χ^2=0.09, *df*=1 (*P*=.77), I^2=0% Test for overall effect: *z*=2.62 (*P*=.009)									
Total (95% CI)			660			635	100	0.22 (0.07, 0.38)	
Heterogeneity: tau^2=0.03, χ^2=22.72, *df*=14 (*P*=.06), I^2=38% Test for overall effect: *z*=2.79 (*P*=.005) Test for subgroup differences: χ^2=2.78, *df*=2 (*P*=.25), I^2=28.1%									

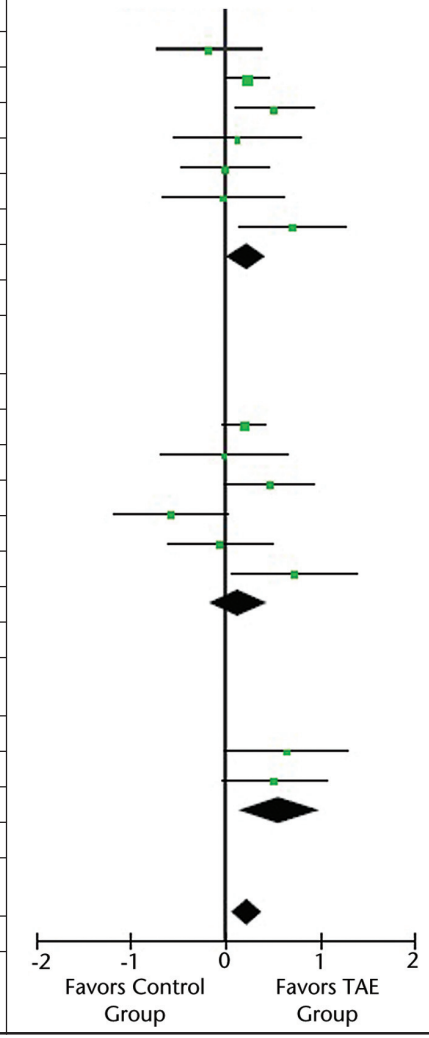


Figure 3.
Continued

Quality of Life									
	TAE Group			Control Group			Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Study or Subgroup	$\bar{X}$	SD	Total	$\bar{X}$	SD	Total			
Cochrane et al,[32] 2005	62.55	18.61	150	60.68	17.39	157	20.3	0.10 (−0.12, 0.33)	
Foley et al,[27] 2003	53.3	11.481	34	50.5	10.37	32	10.7	0.25 (−0.23, 0.74)	
Fransen et al,[30] 2007	54.6	8.9	55	48	11.4	41	12.8	0.65 (0.24, 1.07)	
Hinman et al,[31] 2007	0.43	0.2	36	0.5	0.2	35	11.2	−0.35 (−0.82, 0.12)	
Lim et al,[34] 2010	54.8	8.8	24	48.4	14.3	21	8.2	0.54 (−0.06, 1.14)	
Lund et al,[26] 2008	43	12.47	27	43.1	11.18	25	9.3	−0.01 (−0.55, 0.54)	
Patrick et al,[37] 2001	6.396	1.697	101	5.79	1.752	121	18.4	0.35 (0.08, 0.62)	
Wang et al,[35] 2011	73	12	26	67	13	26	9.1	0.47 (−0.08, 1.02)	
Total (95% CI)			453			458	100	0.24 (0.04, 0.45)	
Heterogeneity: $tau^2=0.04$, $\chi^2=14.28$, $df=7$ ($P=.05$), $I^2=51\%$									
Test for overall effect: $z=2.33$ ($P=.02$)									

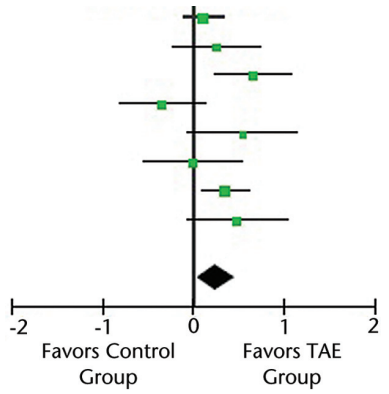


Figure 4.
Forest plots showing the effect of therapeutic aquatic exercise (TAE) on quality of life. 95% CI=95% confidence interval.

dropped out as a direct result of the adverse effect caused by the TAE program (Tab. 2).

Discussion

Our meta-analysis indicates that TAE is an effective treatment option for the management of symptoms and functional deficits as a result of lower limb OA compared with no treatment. The previous meta-analysis[14] contained 5 studies with a control-comparison group and included 661 participants, whereas our meta-analysis contains 11 high-quality studies with 1,092 participants, thus supporting the need for this update. The effects of TAE on pain and self-reported function were comparable to those achieved from land-based exercise or the use of acetaminophen and nonsteroidal anti-inflammatory drugs.[4,7–10] This finding, in combination with the high adherence to intervention, low dropout rate, and frequency of severe adverse effects, confirms that TAE should be considered a potentially effective treatment option for people with lower limb OA.

Pain is the most common reason for a person with lower limb OA to initially seek medical assistance, and a common belief is that water is a suitable environment for people who are unable or unwilling to train effectively on land due to pain. Our study demonstrated that TAE can have a small but significant effect on pain, thus strengthening findings from the earlier Cochrane review.[14] Although pain in OA has typically been considered nociceptive, there is growing evidence showing that 28% to 34% of people with hip or knee OA have neuropathic centralized pain.[42,43] The included outcome measures (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC], Knee Injury and Osteoarthritis Outcome Score [KOOS], and visual analog scale for pain) may not truly capture the pain experienced by people with lower limb OA.[26,31] There is currently a lack of data identifying types of pain and patients who might benefit more from TAE over land-based exercises.

A small but significant ES for both self-reported functioning and physical functioning was demonstrated. The previous reviews[14,15] did not find any effect on physical function, whereas our study is the first to show TAE can have a small but significant effect on physical functioning at activity level. No significant effect of TAE, however, was seen for muscle strength. Care must be taken in interpreting these results, as only left-side and right-side results were reported here, without consideration of affected and unaffected sides. Based on the information provided in the manuscripts, only 1 of the 11 included studies[34] made reference to established exercise prescription guidelines in their intervention planning. Lund et al[26] suggested that the intensity of the aquatic intervention in their study could have been too low to stimulate positive changes. If the interventions were not of sufficient intensity or duration to cause physiological changes at the level of muscle structure and function, it could partially explain why the effects of TAE were lost even at short-term follow-up. One possible advantage of the aquatic environment is that this population may be able to train at higher intensities than on land.[44,45] Nevertheless, due to limited reporting of actual intensities used and limited use of exercise guidelines in the intervention design, it is difficult to confirm the hypothesis. Moreover, Juhl et al[46] indicated that, for best results, the exercise programs for knee OA should have one aim alone, whereas the TAE interventions included a mixture of strength, aerobic, and flexibility exercises. Furthermore, the ES for self-report functioning was similar to the ES of pain and could explain the differences between perceived functional ability and actual functional ability as measured with physical performance tests.

The small effect of TAE on quality of life was of equivalent size to that seen in the previous review investigating the effect of TAE on lower limb OA[14] and is in line with the findings from other studies investigating the effects of exercise on quality of life.[47] The small ES could be explained by the limited improvements in physical functioning found in our review. Small changes in quality-of-life measures have been reported in association with small or nonsignificant changes in physical functioning.[48] Moreover, interpretation of the results has to be done with caution, as the outcome measures used may not accurately represent the true changes in quality of life within this population. Only 2 studies[26,37] used an OA-specific measure (KOOS quality of life). Commonly used generic instruments, such as the SF-36, which was used in 4 studies,[27,30,32,34] tend to be less responsive than OA-specific measures.[49–51]

This review has both strengths and weaknesses. Strengths include selection of studies, all with moderate to high methodological quality of the PEDro score,[21] and in combining studies with small sample sizes, we provided the most accurate effect of TAE. The advantage of using SMD to report ES is that it allows the synthesis of different outcome measures, but the disadvantage is that it is difficult to apply in a clinical situation. Furthermore, the use of minimal clinically important difference (MCID) and responder criteria has been suggested and recommendations made for this population group[51,52]; however, only one study[30] reported the number of participants reaching MCID. Although we controlled for methodological quality, we did not

exclude studies that failed to recruit sufficient participants to meet their power calculation.[25,26] Removal of these studies from the overall analysis did not affect overall outcome for the main synthesis but could explain the results for the knee OA-only analysis. Our study did not demonstrate a significant effect of TAE on populations containing individuals with only knee OA or hip OA.[36] It is our view that the lack of significant effect in these analyses was a result of a lack of internal validity (eg, sample size and differences at baseline) in addition to insufficient intervention intensity. Moreover, it is recognized that the symptoms and treatments associated with hip OA are different from those of knee OA. However, we can support the pooling of studies from diverse populations because exercise performed in water generally affects the musculoskeletal system globally and not only locally at one particular joint. All but one outcome measure (KOOS) found in this review can be appropriately used with both hip and knee OA. Our results and other aquatic-based studies in general do not provide a clear indication of which OA patient populations would benefit more from TAE over a land-based intervention, but these data might permit more optimal prescription of what is often a limited and high-cost treatment. Additionally, our review was unable to demonstrate the optimal intervention dose, type of exercise, and training intensity for this population group.

In conclusion, this meta-analysis confirmed that TAE is an effective treatment option for people with lower limb OA and should be considered a frontline management option. Researchers planning an aquatic intervention study should ensure that all aspects of the disease, not just pain and self-reported functioning, are taken into consideration. The diverse outcome measures used suggest there is a need for researchers to refer to current recommendations when designing new projects to facilitate more specific between-study comparisons. Future research should identify the patient groups that would benefit the most from TAE and the effects of aquatic exercise on cartilage and examine methods to maintain the training effect and increase physical activity following the treatment period. Nevertheless, investigation of the effect that TAE has on this population in clinical situations is needed using pragmatic study designs and large sample sizes.

Mr Waller, Mr Lambeck, Professor Daly, Professor Kujala, and Professor Heinonen provided concept/idea/research design and writing. Mr Waller, Mrs Ogonowska-Slodownik, Mr Vitor, and Mr Lambeck provided data collection. Mr Waller, Mrs Ogonowska-Slodownik, Professor Daly, Professor Kujala, and Professor Heinonen provided data analysis. Professor Heinonen provided project management, facilities/equipment, and institutional liaisons. Mrs Ogonowska-Slodownik, Professor Kujala, and Professor Heinonen provided consultation (including review of the manuscript before submission).

This research was presented as part of an oral presentation at the World Aquatic Health Conference; October 2013; Indianapolis, Indiana, and as an e-poster at the 2nd World Congress on Controversies, Debates and Consensus in Bone, Muscle and Joint Diseases (BMJD); November 21–24, 2013; Brussels, Belgium.

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eAppendix 1.

Example of PubMed Search

((((“osteoarthritis”[MeSH Terms] OR “osteoarthritis”[All Fields]) AND “humans”[MeSH Terms]) OR (OA[All Fields] AND “humans”[MeSH Terms])) OR ((“arthritis”[MeSH Terms] OR “arthritis”[All Fields]) AND “humans”[MeSH Terms]) AND “humans”[MeSH Terms]) AND ((((((aquatics[All Fields] OR (aquatic[All Fields] AND (“rehabilitation” [Subheading] OR “rehabilitation”[All Fields] OR “rehabilitation”[MeSH Terms]))) OR (aquatic[All Fields] AND (“physical therapy modalities”[MeSH Terms] OR (“physical”[All Fields] AND “therapy”[All Fields] AND “modalities” [All Fields]) OR “physical therapy modalities”[All Fields] OR (“physical”[All Fields] AND “therapy”[All Fields]) OR “physical therapy”[All Fields]))) OR ((“water”[MeSH Terms] OR “water”[All Fields] OR “drinking water”[MeSH Terms] OR (“drinking”[All Fields] AND “water”[All Fields]) OR “drinking water”[All Fields]) AND (“rehabilitation” [Subheading] OR “rehabilitation”[All Fields] OR “rehabilitation”[MeSH Terms]))) OR (aquatic[All Fields] AND (“therapy”[Subheading] OR “therapy”[All Fields] OR “therapeutics”[MeSH Terms] OR “therapeutics”[All Fields]))) OR (aquatic[All Fields] AND (“exercise”[MeSH Terms] OR “exercise”[All Fields]))) OR (“hydrotherapy”[MeSH Terms] OR “hydrotherapy”[All Fields]) AND “humans”[MeSH Terms]) AND “humans”[MeSH Terms] AND (“0001/ 01/01”[PDAT] : “2013/11/30”[PDAT])

eAppendix 2.

Quality and Risk of Bias Assessment (PEDro)

Study	Random Allocation	Allocation Concealment	Baseline Similarity	Participant Blinding	Therapist Blinding	Assessor Blinding	Adequate Follow-up	Intention-to-Treat Analysis	Between Group Comparisons	Point & Variability Measures	Final PEDro Score (/10)
Patrick et al,[37] 2001	1	0	1	0	0	0	1	1	1	1	6
Foley et al,[27] 2003	1	1	1	0	0	1	1	1	1	1	8
Cochrane et al,[32] 2005	1	1	1	0	0	1	0	1	1	1	7
Wang et al,[33] 2007	1	0	1	0	0	0	1	1	1	1	6
Fransen et al,[30] 2007	1	1	1	0	0	1	1	1	1	1	8
Hinman et al,[31] 2007	1	1	1	0	0	1	1	1	1	1	8
Lund et al,[26] 2008	1	1	1	0	0	1	1	1	1	1	8
Lim et al,[34] 2010	1	0	1	0	0	1	1	1	1	1	7
Arnold and Faulkner,[36] 2010	1	0	1	0	0	1	0	1	1	1	6
Wang et al,[35] 2011	1	1	1	0	0	1	1	0	1	1	7
Hale et al,[25] 2012	1	1	1	0	0	1	1	1	1	1	8

eAppendix 3.

Hierarchy of Outcome Measures

Hierarchy of continuous pain-related outcomes[38]	
Ranking	**Outcome**
1	Global pain score
2	Pain on walking
3	WOMAC pain subscore
4	Composite pain scores other than WOMAC
5	Pain on activities other than walking
6	WOMAC global score
7	Lesquesne osteoarthritis index global score
8	Other algofunctional composite scores
9	Patient's global assessment
10	Physician's global assessment
Hierarchy of continuous self-reported functioning and quality-of-life outcomes (Adapted From the Findings of Veenhof et al[39])	
Ranking	**Outcome**
1	WOMAC VAS, version 3.0, or numerical scale
2	WOMAC Likert scale or VAS, version 3.0, modified
3	HOOS or KOOS or Lesquesne modified
4	SF-36 (component summary)
5	Health Assessment Questionnaire
6	Arthritis Impact Measurement Scales-2 Short Form (AIMS-2-SF)
7	SF-36 physical function or role–physical
8	Activities and Balance Confidence Scale

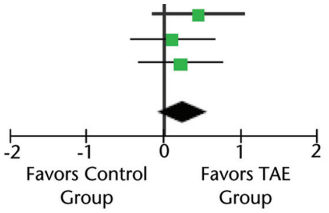
[a] WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index, VAS=visual analog scale, HOOS=Hip Injury and Osteoarthritis Outcome Score, KOOS=Knee Injury and Osteoarthritis Outcome Score, SF-36=36-Item Short-Form Health Survey, AIMS-2=Arthritis Impact Measurement Scales-2 Short Form.

eAppendix 4.

Meta-Analysis for the Effect of Therapeutic Aquatic Exercise (TAE) on Knee Osteoarthritis[a]

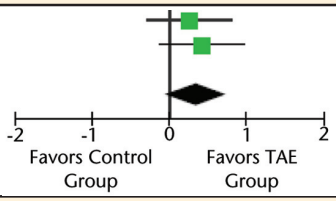
Pain

Study or Subgroup	TAE Group $\bar{X}$	TAE Group SD	TAE Group Total	Control Group $\bar{X}$	Control Group SD	Control Group Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Lim et al,[34] 2010	−3.27	1.67	24	−4.12	2.08	20	29.1	0.45 (−0.15, 1.05)	
Lund et al,[26] 2008	−55.8	21	27	−58.1	20	25	35.5	0.11 (−0.43, 0.65)	
Wang et al,[35] 2011	72	18	26	68	18	26	35.4	0.22 (−0.33, 0.78)	
Total (95% CI)			77			71	100	0.25 (−0.08, 0.57)	
Heterogeneity: tau^2=0.00, χ^2=0.68, *df*=2 (*P*=.71), I^2=0%									
Test for overall effect: *z*=1.49 (*P*=0.14)									



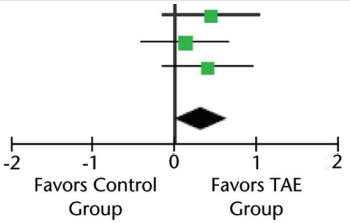
Stiffness

Study or Subgroup	TAE Group $\bar{X}$	TAE Group SD	TAE Group Total	Control Group $\bar{X}$	Control Group SD	Control Group Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Lund et al,[26] 2008	64.6	12	26	61.4	12	25	49.9	0.26 (−0.29, 0.81)	
Wang et al,[35] 2011	69	20	26	61	17	26	50.1	0.42 (−0.13, 0.97)	
Total (95% CI)			52			51	100	0.34 (−0.05, 0.73)	
Heterogeneity: tau^2=0.00, χ^2=0.17, *df*=1 (*P*=.68), I^2=0%									
Test for overall effect: *z*=1.73 (*P*=.08)									



Self-reported functioning

Study or Subgroup	TAE Group $\bar{X}$	TAE Group SD	TAE Group Total	Control Group $\bar{X}$	Control Group SD	Control Group Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Lim et al,[34] 2010	−20.9	9.9	24	−27.6	18.3	21	29.4	0.46 (−0.14, 1.05)	
Lund et al,[26] 2008	62.7	12	27	61.1	11	27	36.3	0.14 (−0.40, 0.67)	
Wang et al,[35] 2011	76	16	26	69	18	26	34.3	0.40 (−0.14, 0.95)	
Total (95% CI)			77			74	100	0.32 (0.00, 0.64)	
Heterogeneity: tau^2=0.00, χ^2=0.74, *df*=2 (*P*=.69), I^2=0%									
Test for overall effect: *z*=1.96 (*P*=.05)									



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eAppendix 4.
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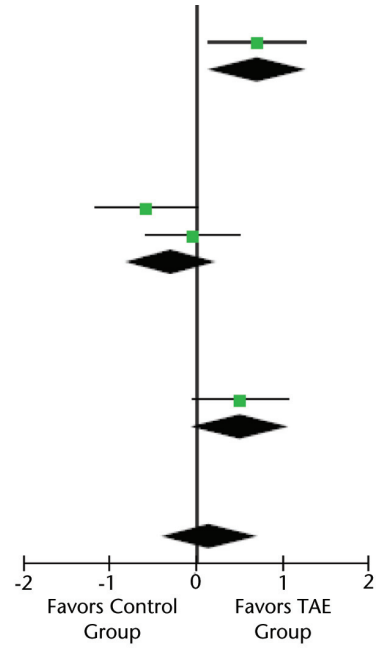
Physical functioning tests									
Study or Subgroup	TAE Group $\bar{X}$	TAE Group SD	TAE Group Total	Control Group $\bar{X}$	Control Group SD	Control Group Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Physical functioning tests (activities)									
Wang et al,[35] 2011	386	75.8	26	329.1	82.3	26	25.1	0.71 (0.15, 1.27)	
Subtotal (95% CI)			26			26	25.1	0.71 (0.15, 1.27)	
Heterogeneity: Not applicable									
Test for overall effect: z=2.47 (P=.01)									
Physical functioning tests (muscle strength)									
Lim et al,[34] 2010	50.4	19.3	24	63.1	24.1	21	24.2	−0.58 (−1.17, 0.02)	
Lund et al,[26] 2008	39.17	15.61	26	39.94	19.25	25	25.4	−0.04 (−0.59, 0.51)	
Subtotal (95% CI)			50			46	49.6	−0.30 (−0.82, 0.23)	
Heterogeneity: tau^2=0.06, χ^2=1.65, df=1 (P=.20), I^2=39%									
Test for overall effect: z=1.11 (P=.27)									
Physical functioning tests (joint range of motion)									
Wang et al,[35] 2011	−2.4	2.2	26	−3.3	1.1	26	25.3	0.51 (−0.04, 1.06)	
Subtotal (95% CI)			26			26	25.3	0.51 (−0.04, 1.06)	
Heterogeneity: not applicable									
Test for overall effect: z=1.81 (P=.07)									
Total (95% CI)			102			98	100	0.16 (−0.40, 0.71)	
Heterogeneity: tau^2=0.24, χ^2=11.52, df=3 (P=.009), I^2=74%									
Test for overall effect: z=0.55 (P=.58)									
Test for subgroup differences: χ^2=7.58, df=2 (P=.02), I^2=73.6%									



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eAppendix 4.

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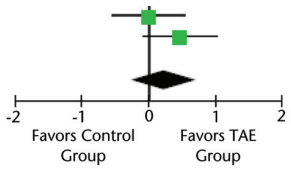
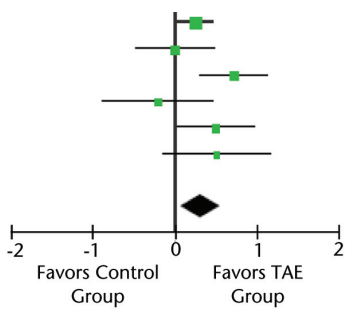
Quality of Life									
Study or Subgroup	TAE			Control Group			Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
	$\bar{X}$	SD	Total	$\bar{X}$	SD	Total			
Lund et al,[26] 2008	43	12.47	27	43.1	11.18	25	50.5	−0.01 (−0.55, 0.54)	
Wang et al,[35] 2011	73	12	26	67	13	26	49.5	0.47 (−0.08, 1.02)	
Total (95% CI)			53			51	100	0.23 (−0.24, 0.70)	
Heterogeneity: tau^2=0.04, χ^2=1.48, *df*=1 (*P*=.22), I^2=32%									
Test for overall effect: *z*=0.96 (*P*=.34)									

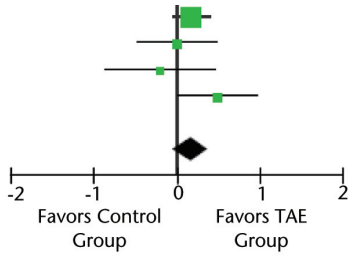
[a] 95% CI=95% confidence interval.

eAppendix 5.

Meta-Analysis for the Effect of Therapeutic Aquatic Exercise (TAE) on Hip and Knee Osteoarthritis[a]

Study or Subgroup	TAE $\bar{X}$	TAE SD	TAE Total	Control Group $\bar{X}$	Control Group SD	Control Group Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Knee and Hip									
Pain									
Cochrane et al,[32] 2005	−8.46	3.74	153	−9.35	3.54	158	30.3	0.24 (0.02, 0.47)	
Foley et al,[27] 2003	−10	2.222	34	−10	2.963	32	15.4	0.00 (−0.48, 0.48)	
Fransen et al,[30] 2007	−27.3	18.7	55	−40	16.2	41	18.3	0.71 (0.30, 1.13)	
Hale et al,[25] 2012	−7.8	3.925	20	−7.1	1.917	15	9.7	−0.21 (−0.88, 0.46)	
Hinman et al,[31] 2007	−4	2	36	−5	2	35	15.8	0.49 (0.02, 0.97)	
Wang et al,[33] 2007	−43.5	18.6	20	−54.9	25.2	18	10.3	0.51 (−0.14, 1.16)	
Total (95% CI)			318			299	100	0.31 (0.07, 0.55)	
Heterogeneity: tau^2=0.04, χ^2=8.76, *df*=5 (*P*=.12), I^2=43%									
Test for overall effect: *z*=2.57 (*P*=.01)									
Stiffness									
Cochrane et al,[32] 2005	−3.88	1.67	152	−4.15	1.48	158	57.3	0.17 (−0.05, 0.39)	
Foley et al,[27] 2003	−4	2.222	34	−4	2.222	32	16.6	0.00 (−0.48, 0.48)	
Hale et al,[25] 2012	−3.7	1.392	20	−3.4	1.502	15	9.0	−0.20 (−0.87, 0.47)	
Hinman et al,[31] 2007	−73	45	36	−95	44	35	17.2	0.49 (0.02, 0.96)	
Total (95% CI)			242			240	100	0.16 (−0.04, 0.37)	
Heterogeneity: tau^2=0.01, χ^2=3.41, *df*=3 (*P*=.33), I^2=12%									
Test for overall effect: *z*=1.55 (*P*=.12)									





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eAppendix 5.

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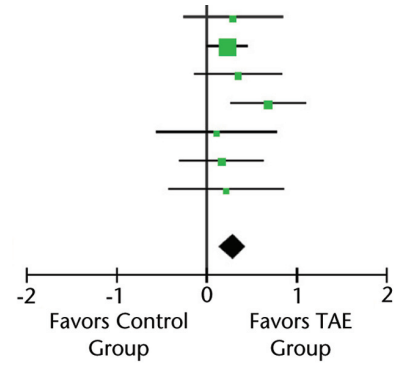
Self-reported functioning									
	TAE Group			Control Group			Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Study or Subgroup	$\bar{X}$	SD	Total	$\bar{X}$	SD	Total			
Arnold and Faulkner,[36] 2010	69.6	24.4	26	62.9	20.8	25	7.8	0.29 (−0.26, 0.84)	
Cochrane et al,[32] 2005	−29.26	14.48	149	−32.42	13.25	156	46.6	0.23 (0.00, 0.45)	
Foley et al,[27] 2003	−33	12.593	34	−37	9.63	32	10.0	0.35 (−0.14, 0.84)	
Fransen et al,[30] 2007	−34.8	23.7	55	−49.9	19	41	13.6	0.69 (0.27, 1.10)	
Hale et al,[25] 2012	−24	8.899	20	−24.9	7.015	15	5.3	0.11 (−0.56, 0.78)	
Hinman et al,[31] 2007	−598	316	36	−656	373	35	10.9	0.17 (−0.30, 0.63)	
Wang et al,[33] 2007	−0.9	0.4	20	−1	0.5	18	5.8	0.22 (−0.42, 0.86)	
Total (95% CI)			340			322	100	0.29 (0.14, 0.45)	
Heterogeneity: tau^2=0.00, χ^2=4.44, df=6 (P=.62), I^2=0%									
Test for overall effect: z=3.74 (P=.0002)									



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eAppendix 5.
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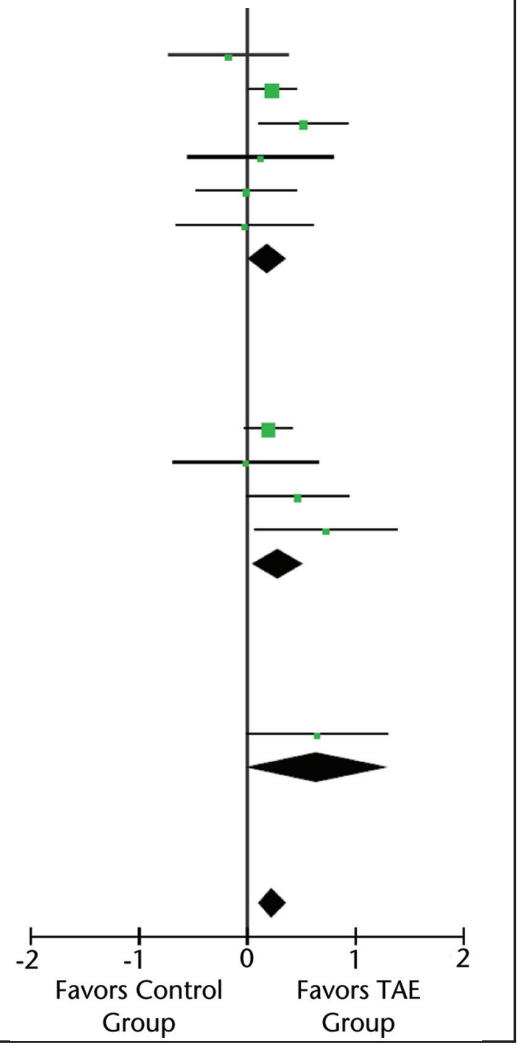
Physical functioning tests									
	TAE Group			Control Group			Weight	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Study or Subgroup	$\bar{X}$	SD	Total	$\bar{X}$	SD	Total	(%)		
Physical functioning tests (activities)									
Arnold et al,[36] 2010	7.5	3.9	26	8.1	2.6	25	5.4	−0.18 (−0.73, 0.37)	
Cochrane et al,[32] 2005	−3.24	1.93	153	−3.78	2.72	159	26.0	0.23 (0.01, 0.45)	
Fransen et al,[30] 2007	−8.2	1.7	55	−9.2	2.2	41	9.2	0.51 (0.10, 0.93)	
Hale et al,[25] 2012	−10.1	2.9	20	−10.7	6.8	15	3.7	0.12 (−0.55, 0.79)	
Hinman et al,[31] 2007	−10.32	1.94	36	−10.3	2.78	35	7.4	−0.01 (−0.47, 0.46)	
Wang et al,[33] 2007	388.4	80.3	20	390.7	88.6	18	4.1	−0.03 (−0.66, 0.61)	
Subtotal (95% CI)			310			293	55.6	0.18 (0.01, 0.35)	
Heterogeneity: tau^2=0.00, χ^2=5.40, *df*=5 (*P*=.37), I^2=7%									
Test for overall effect: *z*=2.02 (*P*=.04)									
Physical functioning tests (muscle strength)									
Cochrane et al,[32] 2005	166.02	108.92	152	145.92	99.82	158	25.9	0.19 (−0.03, 0.42)	
Hale et al,[25] 2012	18.8	8.465	20	19	12.528	15	3.7	−0.02 (−0.69, 0.65)	
Hinman et al,[31] 2007	29.9	12.5	36	24.7	9.5	35	7.2	0.46 (−0.01, 0.93)	
Wang et al,[33] 2007	16	4.5	20	12.9	3.8	18	3.8	0.73 (0.07, 1.39)	
Subtotal (95% CI)			228			226	40.5	0.28 (0.05, 0.52)	
Heterogeneity: tau^2=0.01, χ^2=3.64, *df*=3 (*P*=.30), I^2=18%									
Test for overall effect: *z*=2.39 (*P*=.02)									
Physical functioning tests (joint range of motion)									
Wang et al,[33] 2007	−1.2	2.6	20	−3.2	3.5	18	3.8	0.64 (−0.01, 1.29)	
Subtotal (95% CI)			20			18	3.8	0.64 (−0.01, 1.29)	
Heterogeneity: not applicable									
Test for overall effect: *z*=1.92 (*P*=.06)									
Total (95% CI)			558			537	100	0.23 (0.10, 0.36)	
Heterogeneity: tau=0.00, χ^2=10.93, *df*=10 (*P*=.36), I^2=9%									
Test for overall effect: *z*=3.51 (*P*=.0006)									
Test for subgroup differences: χ^2=2.03, *df*=2 (*P*=.36), I^2=1.4%									



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eAppendix 5.
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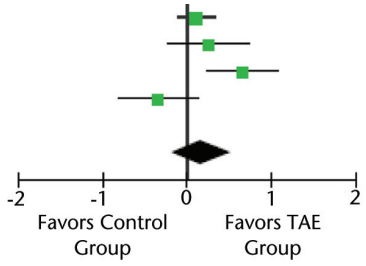
Quality of life									
	TAE Group			Control Group					
Study or Subgroup	$\bar{X}$	SD	Total	$\bar{X}$	SD	Total	Weight (%)	Standardized Mean Difference IV, Random (95% CI)	Standardized Mean Difference IV, Random (95% CI)
Cochrane et al,[32] 2005	62.55	18.61	150	60.68	17.39	157	31.8	0.10 (−0.12, 0.33)	
Foley et al,[27] 2003	53.3	11.481	34	50.5	10.37	32	21.7	0.25 (−0.23, 0.74)	
Fransen et al,[30] 2007	54.6	8.9	55	48	11.4	41	24.3	0.65 (0.24, 1.07)	
Hinman et al,[31] 2007	0.43	0.2	36	0.5	0.2	35	22.3	−0.35 (−0.82, 0.12)	
Total (95% CI)			275			265	100	0.17 (−0.19, 0.52)	
Heterogeneity: tau^2=0.01, χ^2=10.25, *df*=3 (*P*=.02), I^2=71%									
Test for overall effect: *z*=0.93 (*P*=.35)									



[a] 95% CI=95% confidence interval.

II

THE EFFECT OF AQUATIC EXERCISE ON PHYSICAL FUNCTIONING IN THE OLDER ADULT: A SYSTEMATIC REVIEW WITH META-ANALYSIS

by

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SYSTEMATIC REVIEW

The effect of aquatic exercise on physical functioning in the older adult: a systematic review with meta-analysis

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Abstract

Background: ageing and sedentary behaviour cause negative changes in the neuromuscular systems of healthy older adults resulting in a decrease in physical functioning. Exercising in water (aquatic exercise, AE) has been shown to be effective at improving physical functioning in this population; however, no systematic review with meta-analysis has been published.
Purpose: to investigate the effect of AE on physical functioning in healthy older adults compared to control or land-based exercise (LE) through a systematic review with meta-analysis of randomised controlled trials.
Data sources: Medline, Embase, Cinahl, PEDro, SPORTDiscus, Web of Science, Cochrane Library, published before 31st December 2015.
Study selection: in total, 28 studies met the inclusion criteria and were included in the systematic review; 24 studies with 1,456 subjects (89% female) and with mean age 66.4 years were included in the meta-analysis.
Data extraction: data were extracted and checked for accuracy by three independent reviewers.
Data synthesis: size of treatment effect was measured using the standardised mean difference with 95% confidence intervals (CIs).
Results: compared to control interventions, AE had a moderate positive effect on physical functioning 0.70 [95% CI 0.48 to 0.92]. Compared to LE, AE had a small positive effect on physical functioning 0.39 [0.12 to 0.66].
Limitations: there is a high risk of bias and low methodological quality in the studies particularly when comparing AE to LE with possible over estimation of the benefit of AE.
Conclusions: AE may improve physical functioning in healthy older people and is at least as effective as LE.

Keywords: *aquatic exercise, older adults, systematic review, physical functioning, activity limitations*

Introduction

The improvements in healthcare and life style have enhanced life expectancy and thus active life years are increasing. After early adulthood, there is an association between increased age and decreased physical functioning which has led to increased financial demands on healthcare services [1]. Finding methods to slow or reverse the decrease in physical functioning has therefore become a major focus for research.

Physical activity through the life course has long been recommended to limit the decline in physical functioning. An increase in daily physical activity can slow or partially

reverse the negative effect of ageing on function and prevent the progression of chronic and disabling conditions [2]. Many different modes of physical activity have been recommended to maintain or improve physical functioning including strength training, aerobics, walking and aquatic exercise (AE). AE is a popular exercising method for a wide range of populations including healthy older adults.

To our knowledge, only one systematic review has been published investigating the effect of AE on physical fitness in healthy older adults. This review [3] indicated that AE three times per week significantly improves physical function. However, this study included both randomised and non-randomised clinical trials and lacked a meta-analysis. Therefore, the purpose of this study was to investigate the effect of AE on physical functioning in healthy older adults compared to no intervention (control) and land-based exercise (LE) through a systematic review with meta-analysis of randomised controlled trials (RCTs).

Methods

Eligibility criteria

Studies included into our review fulfilled the following criteria according to the PICOS system (Population, Intervention, Comparison, Outcome and Study design) [4]. Population included participants with a mean age ≥ 55 year old with a lower age limit of 50 years, male or female and no diagnosis of disease. Frail older adults were included but only if there was a medical screening excluding the presence of another diagnosis, e.g. osteoarthritis, cardiac disease, osteoporosis/osteopenia or neurological insult. We included all interventions that could be classified as exercise in an aquatic environment (AE) with no limitation on the type of exercise. Studies were included if they had either a control group (C) and/or LE comparison group. Outcomes used in the study had to measure physical functioning and the study had to be of RCT design.

Search strategy and study selection

For this systematic review and meta-analysis, we performed a broad search of seven databases (Medline, EMbase (excluding Medline), Cinahl, Pedro, SPORTDiscus, Web of Science, Cochrane library (clinical trials)) using a comprehensive combination of keywords. The keywords used were elderly OR older people OR older population OR older adults OR ageing OR senior AND aquatic therapy OR aquatic exercise OR water therapy OR hydrotherapy OR aquatic physiotherapy OR water exercise OR aquatic rehabilitation OR pool exercise OR water rehabilitation OR aquatic physical therapy OR aquatics OR swimming intervention. The search was performed by two persons independently and included publications appearing before 31st December 2015 with no language limitations. An example of the search parameters, for Medline, can be found in Appendix 1 (see the supplementary data on the journal website http://www.ageing.oxfordjournals.org). Additionally, all assessed full texts, systematic reviews and guidelines found were searched by hand for possible additional studies. Thesis titles were searched through Proquest. A search of registered and published protocols (ISRCTN registry, ClinicalTrials.gov, Australian New Zealand Clinical trials registry (ANZCTR) and Brazilian registration of clinical trials) was also performed.

Duplicates were removed using Endnote© (Endnote X7, Thomson Reuters, USA). Based on title, animal studies and non-relevant studies were excluded. Following this, abstracts were read and non-clinical trials or intervention studies were excluded. At each stage, agreement on inclusion/exclusion between two reviewers (BW and DD was required before next stage was initiated. Full text articles for the remaining studies were retrieved and read by three independent reviewers (BW, OA and KR) and a fourth reviewer (DD) was consulted as necessary.

Data extraction

Intervention description, inclusion/exclusion criteria, baseline data and post intervention values for all outcomes were extracted by two reviewers (OA and VM) and checked for accuracy by a third reviewer (BW). Where possible, intention-to-treat data were extracted for follow-up measurements otherwise per protocol data were extracted.

Outcome measure selection

The data for all outcomes measuring different constructs of physical function, in line with Rikli and Jones [5], were extracted and included in the qualitative and quantitative synthesis. The various functional traits of muscle were described using four distinct sub-groups; maximum strength, muscle power, muscle endurance and respiratory muscle function. The remaining outcomes were divided into distinct sub-groups; agility, postural stability, walking ability, flexibility, aerobic power and self-reported functioning. In cases where multiple muscle groups were tested, the results for only one muscle group or one or more suitable outcome measure was used in the same study we followed *a priori* ranking list with highest ranked outcome measure taken in preference [6] (Ranking lists can be found from Appendix 4 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org).

Statistical synthesis

The meta-analysis was performed using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The size of effect was calculated as the standardised mean difference (SMD) and 95% confidence intervals (CIs). In this study, a SMD of 0.2–0.5 was considered as small, 0.5–0.8 medium and ≥0.8 a large effect. For all analyses, we used an inverse-variance weighted random-effects model that incorporates heterogeneity into the model. High heterogeneity, as measured with I^2, was expected due to the combination of different outcome measures [7]. Two meta-analyses were

performed one comparing AE to C and the second comparing AE to LE. Standard deviation was calculated from standard error. When two different aquatic interventions had been investigated and included in the meta-analysis, the size of the control group was divided by two [8]. Where necessary, data were multiplied by −1, therefore a positive effect indicates a result in favour of AE [9].

Additional analysis

Post hoc sensitivity tests were performed investigating the effects of dropout rate (<15% and ≥15%), methodological quality (Delphi ≥4), age (<68 and ≥68 years old), training frequency (<3 or ≥3 times a week) and effects of AE at different International classification of function, health and disability (ICF) levels (body structure and function or activities and participation). Percentage (%) of dropouts was calculated using baseline sample size and number of participants who did not attend post intervention measurement.

Methodological quality, risk of bias and publication bias assessments

Methodological quality was assessed using the 9-point Delphi scale [10]. The maximum an exercise intervention study can generally score is 7 because of the difficulties in blinding the participants and therapist from the intervention. Scores of <4 and ≥6 are considered to have low and high methodological quality, respectively. Risk of bias was assessed using the Cochrane Risk of Bias assessment [11]. Additionally, trial size, power analysis and centre status were extracted to give additional information on possible risk of bias [12]. Assessment of methodological quality and risk of bias were performed independently by at least two of three reviewers (BW, OA and JL) and compared. In case of disagreement, consensus was found by consulting a fourth reviewer (DD). Small study effect was assessed through interpretation of funnel plot asymmetry [13].

Results

In total, 2,244 relevant titles were found, 67 articles were accessed for eligibility and 28 studies [14–26, 28-36, 41–46] were retained in the qualitative and 24 [14–19, 21–26, 28–35, 42, 44–46] in the quantitative synthesis of this review (Figure 1). In total 16 studies compared AE to a control intervention (three compared two different aquatic interventions), 6 compared aquatic to LE and 6 compared aquatic with a land-based and a control intervention.

Participants

In total, data were extracted for 1,456 (AE n = 724, LE n = 309 and C n = 423) participants of which 89% were female with a mean age range of 55.4–82.0 years and mean age of 66.4 years (Appendix Table 1). Self-reported pre-study physical activity was mostly described as sedentary or not participating in regular intensive exercise. Nevertheless,

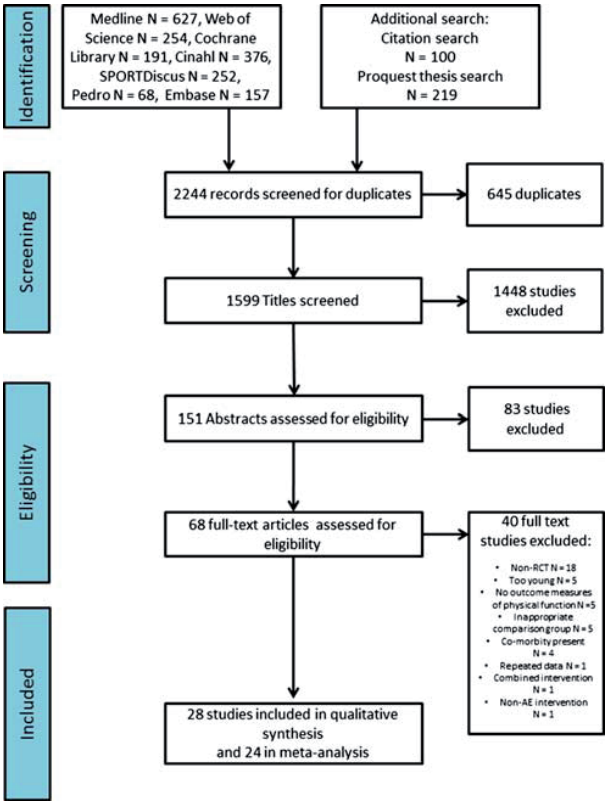

Figure 1. Flow diagram showing the study screening process and search results.

Bento *et al.* [14] stated that 77% reported themselves as either very active or active and Graef *et al.* [15] reported that exercise participants had been exercising in water for several months prior to recruitment. Additional leisure time physical activity during the intervention period was not measured in any of the included studies.

Methodological quality risk of bias and small study bias of included studies

Methodological quality is shown in Appendix Table 1 and eight studies could be considered as having high quality [16–20]. Risk of bias was either unclear or high for all studies. Scoring for each individual criterion of the Delphi scale and risk of bias as well as funnel plots for each meta-analysis are shown in Appendices 3, 5 and 6, respectively (see the supplementary data on the journal website http://www.ageing.oxfordjournals.org). Power analysis was conducted in six studies [15–18, 20, 21], *a priori* sample size was calculated in three [16, 18, 20] with sufficient recruitment met in one [18]. All studies were conducted as single centre interventions. Two studies had accessible protocols [19, 20]. Only five studies directly reported performing the outcome measures before randomisation [16, 22–25]. While 17 studies reported performing the outcome measures after the training period, only three [15, 22, 23] reported their exact timing (less than 1 week).

Aquatic exercise interventions

A summary description of the interventions, intensity and dose for each study can be found in Appendix Table 1. Types of AE utilised in the studies were mainly a mixture of strength, endurance and flexibility exercises for the upper and lower limbs. One study utilised deep water running [26] and one swimming [16]. Planned exercise dose varied from 80 to 250 min/week for 5–32 weeks, frequency of treatment was either once (n = 1), twice (n = 12), three (n = 14) or five (n = 1) times a week. Intensity of aerobic training ranged between 40–70% of heart rate reserve, 60–80% of heart rate maximum or 11–16 of perceived rate of exertion (Borg 6–20 scale) and 4–9 (Borg 10 scale), i.e. moderate to high intensity [27]. Actual training intensity achieved during the intervention was reported in only one study [26]. Harms were reported in five studies [16, 20, 26, 28–30] with a total of n = 8 and n = 6 participants reporting a harm as a direct result of the AE and LE, respectively.

Comparison interventions

Intensity of land-based training was reportedly always set at the same level as the aquatic training; however, they were not always comparable. In two studies, land-based training consisted of walking alone [16, 31], one study had a poorly described LE programme [18], one study utilised similar exercises to the AE but performed on the floor [19], one used the same exercises as in AE but performed standing while holding on to the back of a chair [32], one performed the same AE exercises but without resistance [22] and one used Pilates [33].

Effect of aquatic exercise physical functioning

Data from four studies could not be synthesised into the meta-analysis due to insufficient reporting and no data were provided from authors. Incomplete data reporting for relevant outcomes have been denoted with italics within Appendix Table 1. Further, the control group from Bocalini *et al.* (2008) [11] was not involved in the randomisation process and therefore excluded. For Elbar *et al.* [17] which was of a randomised crossover design, only data from the first phase were included.

Aquatic exercise compared to control

AE compared to C had a moderate effect on physical functioning 0.70 [95% CI 0.48 to 0.92] in favour of AE (Figure 2). Impact of the results from Bocalini *et al.* (2010) [28] (publication bias), Kim *et al.* [34] (significant baseline differences) and Ruoti *et al.* [35] (baseline difference and unexplained loss from baseline to post intervention in control group) on the overall effect sizes appears disproportionate. Removal of these study results only slightly decreases the effect on physical functioning 0.61 [0.46 to 0.75] in favour of AE. Heterogeneity (I^2) was 32%.

Aquatic exercise compared to land-based exercise

AE appears to have a small and significant advantage over LE in improving physical functioning 0.39 [0.39 to 0.66] (Figure 3). However, the comparison group (walking) in Bocalini *et al.* [31] was a non-comparable intervention. Removal of this study resulted in no significant benefit (0.17 [−0.03 to 0.36]) of aquatic over LE. Heterogeneity (I^2) for this analysis was 75%.

Sensitivity analyses

Results for all sensitivity tests can be found from Appendix 7 (see the supplementary data on the journal website http://www.ageing.oxfordjournals.org).

Dropout rates

Study dropouts ranged from 0% to 45%, 0% to 36% and 0% to 41% for the AE, LE and control groups, respectively (Appendix Table 1). Several studies [22, 31, 33, 36] excluded subjects from the final analysis for low adherence to exercise and in all cases counted them as dropouts and therefore did not report their data (incomplete data bias) with true intention-to-treat analysis used in only two studies [16, 19]. When including only studies with a low dropout rate (<15%), the effect of AE compared to C was similar to the main analysis. The comparison of AE to LE was smaller, although still significant, compared to the main analysis (Appendix 7). However, the heterogeneity (I^2) for both analyses showed much smaller and non-significant values, 19% and 6%, respectively, indicating smaller variance between the studies with low dropout rates.

Age

Younger participants <68 years may benefit more from AE. In the comparison of AE to C, the effect of AE was larger in the group aged <68 years compared to ≥68 years. A similar trend was seen in the comparison of AE to LE (Appendix 7).

Training frequency

Training frequency did not seem to have an effect. When comparing AE to C and AE to LE, AE had a similar sized effect on those who trained <3 times a week compared to ≥3 times a week (Appendix 7).

Methodological quality

Excluding studies with low methodological quality <4 Delphi did not affect the overall result for either comparison of AE to C or AE to LE (Appendix 7).

ICF classification of outcomes

AE appeared to have a similar sized effect on outcomes measuring constructs of body structure and function and

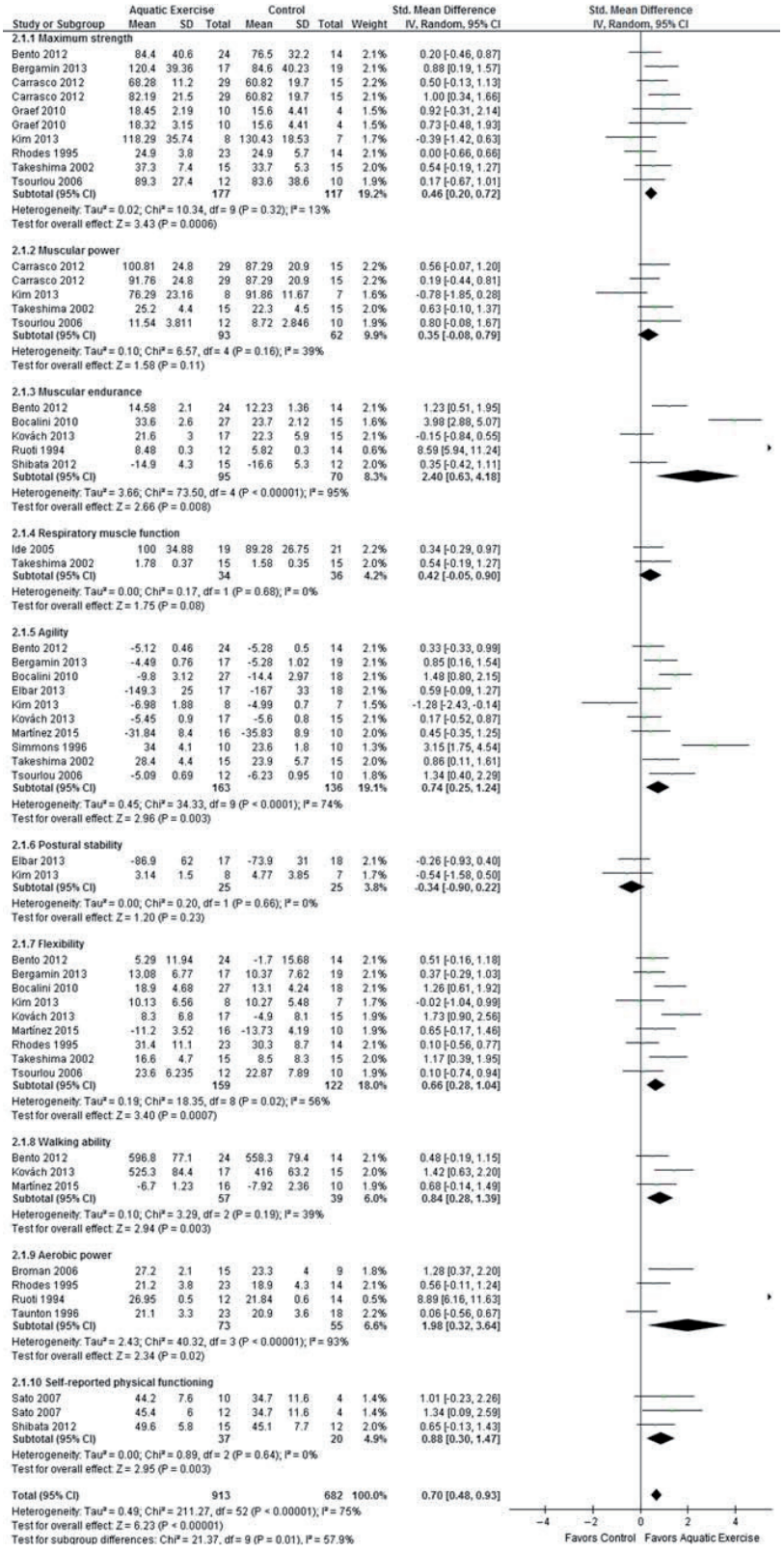

Figure 2. Forest plots showing the effect of AE on physical functioning when compared to control interventions.

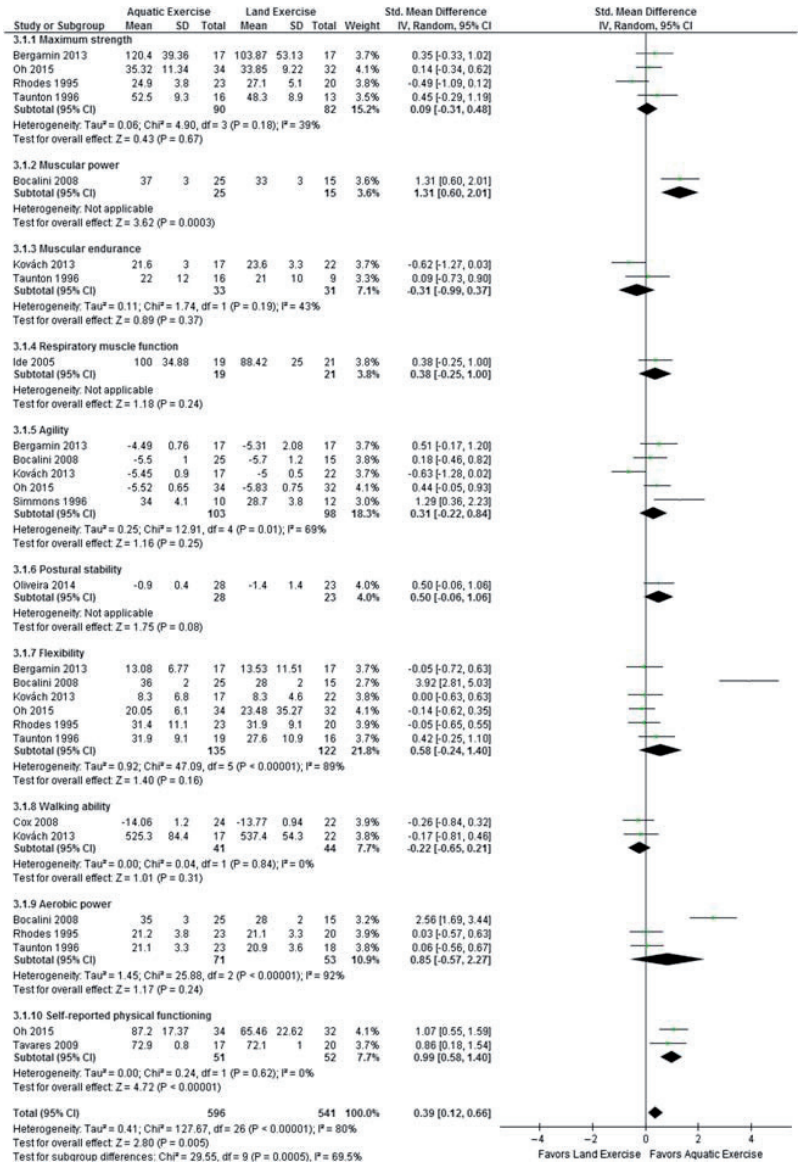

Figure 3. Forest plots showing the effect of AE on physical functioning when compared to LE.

activity and participation. This was seen equally in both AE compared to C and AE compared to LE (Appendix 7).

Discussion

This study is the first systematic review, investigating the effects of AE for healthy older adults, to include a meta-analysis. Our results indicate that exercise in water at moderate to high intensities irrespective of modality may have moderate sized positive effects on physical functioning in healthy older adults when compared to a no training, i.e. a control group. Further, when the comparison group participated in LE, our results suggest that AE may be slightly more effective at improving physical function. However, due to high risk of bias, high heterogeneity and low methodological quality, these results have to be interpreted with care. Nevertheless, AE appears to be at least as effective at improving function as LE. We are unable to show longer term effects of AE due to lack of data.

Optimal physical functioning in older adults can be measured using different constructs [37]. Our results show that AE may have a moderate overall positive effect on constructs at different levels of the ICF, i.e. muscle power and flexibility (body function) and agility and walking ability (activities). Further, when compared to LE, AE had a similar effect on both body function and structures and activities (Figures 2 and 3, Appendix 7). In contrast to the systematic review of Bergamin *et al.* [3] who stated that AE three times a week was an optimal frequency, we found no difference between training twice and three times a week. The difference between conclusions may

result from our more comprehensive search and inclusion criteria which identified 28 studies for inclusion compared to 9 in the Bergamin *et al.* study [3]. Further, our study used a meta-analysis on which the conclusion is based. While adults under the age of 68 years old appeared to benefit more from AE, these results should be considered in light of the slightly higher intensity training utilised in these studies and the high heterogeneity in the meta-analysis (82–91%).

Muscle strength, power and mass are all associated with functional capacity [2] and although resistance training on land has been shown to improve maximal muscle force in older adults, this improvement does not always result in improvements in function [38]. In contrast, the findings of this review show similar effect sizes in both muscle capacity and physical functioning suggesting a carryover effect from AE (Figures 2 and 3) [2]. The aquatic environment provides situations of instability by using the effects of turbulence which could promote greater improvements in body balance reactions [39]. The LE interventions were in general more static in nature and would not have challenged the neuromuscular systems as much as the AE interventions. Further, it is worth noting that only Bocalini *et al.* (2010) [28] reported baseline times of ≥13.5 s for the timed-or 8 ft up-and-go test (utilised in 9 out of the 13 studies measuring agility). While this study also reported the largest ES for the effect of AE on agility, the study of Bento *et al.* [14] reported no effect of AE however the participants in this study were already active or very active. Therefore, AE could be more beneficial for those older adults with lower levels of physical functioning.

The present study has a number of strengths, including the use of *a priori* inclusion criteria for the outcome measures based on previous work [5, 6] and using SMD to express the overall size of effect of AE on physical functioning allowing combination of results measured with other outcomes. However, this method does hinder the direct interpretation of the results for clinical application. The comprehensive search with no language or quality limitations reduced the possibility of omitting appropriate studies. The sensitivity analysis assessed the impact of different methodological and reporting biases, however, no change in conclusions resulted from these analyses. Few studies reported harm resulting from the interventions indicating AE is safe for this population. However, the results of this study are still open to significant bias due to limitations in the methodology, small study bias and high or unclear risk of bias in the included studies. In particular, the choice of type of LE overestimated the effectiveness of AE over LE. While the combining of different outcome measurements (as SMDs) into the same meta-analysis presents the effect of AE on physical functioning as a whole, there is a risk of studies with higher numbers of outcomes to bias the results. Interpretation of the meta-analyses should also include an interpretation of the results from each individual construct (sub-group) analyses. The percentage of women in analysed studies was 89% and was an inclusion criterion for 16 of these, limiting the applicability of the results to male populations. Further, even though 24 of the studies were published after the first CONSORT statement in 2001 [40], reporting of methods, dropouts and results were often incomplete. In particular, the randomisation process was not completely reported. Only 9 of these 28 studies had a flow chart showing participant recruitment and effect of high attrition rate was often ignored in the statistical analyses. Additionally, the sample size of the included studies was often small and even though a random-effects model was utilised, the impact of this bias was not always controlled for. Moreover, only six studies performed a power analysis and three performed a sample size calculation *a priori*. There was insufficient data to perform a meta-analysis investigating the long-term effects of AE on older adults due to lack of follow-up measurements. No studies measured the leisure time physical activity of the participants during the intervention period thus making it difficult to attribute all the effects directly to the exercise interventions alone. While the protocol for the systematic review was not registered, creating a potential source of bias, a full protocol is available from the first author. This openly documents the original protocol and changes made during the revision process. Future studies should address the methodological weaknesses described in this review to ensure that AE is appropriately utilised in the community. Additionally they should focus on the long-term adherence to different exercise modalities.

Conclusion

Based on the results from our systematic review with meta-analysis, we can conclude that AE appears to be effective at maintaining and improving physical function in healthy older adults. When compared to LE, AE appears to be at least as effective and could be used as an alternative training modality when LE is not feasible or desired.

Key points

- AE may have a moderate effect on physical functioning in older healthy adults.
- AE is at least as effective at improving function as LE.
- Further high quality research is required to investigate the optimal type of AE for this population.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Conflicts of interest

None declared.

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Supplementary Data

Appendix Table 1: Qualitative analysis and description of included studies

Article	Country	Delphi score	Sample size (Drop outs)	Age Mean (SD)	Male/ female (%)	Aquatic Intervention	Comparison	Intensity	Dose per protocol*	Outcome measures for meta-analysis
Avelar 2010[26]	**Brazil**	**5**	**AE:** 14(2) **LE:** 15(1) **C:** 17(7)	68(5.7) 69(5.6) 71(3.9)	39/61	Lower limb stretching and muscle endurance exercises	**Land:** Corresponding land exercise **Control:** usual care	Stretch: 30 seconds Muscle: 3 sets of 20 repetitions	6/2/NR/ -	*Berg Balance scale, Tandem gait test, Gait speed*
Bento 2012[14]	**Brazil**	**4**	**AE:** 27(3) **C:** 20(6)	65.6(4.2) 65.6(4.4)	33/67	Lower limb aerobic and strength exercises	**Control:** usual care	Aerobic: RPE 12-16 40-60% HRR Strength RPE 12-16	12/3/60/2160	Isometric knee extension strength[1], 30s chair stand (reps)[3], 8ft up and go[5], Sit and reach (cm)[7]
Bergamin 2013[22]	**Italy**	**4**	**AE:** 20(3) **LE:** 20(3) **C:** 19(0)	71.2(5.4)	49/51	Upper and lower limb exercises	**Land:** corresponding land exercises **Control:** NR	60% maximum HR (range 55%–65%) RPE 13-16	24/2/60/ 2880	Isometric knee extension strength[1], 8ft up and go[5], Sit and reach (cm)[7]
Bocalini 2008[27]	**Brazil**	**4**	**AE:** 27(2) **LE:** 25(10)	64(1) 64(1)	0/100	Upper and lower limb exercises with resistance devices	**Land:** supervised walking	10–15 reps at intensity of 70% age-predicted HRmax	**AE:** 12/3/60/2160 **LE:**12/5/60/3600	30s chair stand (reps)[3], 8ft up and go[5], Sit and reach (cm)[7], maximum aerobic power[9]
Bocalini 2010[28]	**Brazil**	**4**	**AE:** 30(3) **C:** 20(2)	>62	0/100	Upper and lower limb exercises with resistance devices	**Control:** sedentary, usual care	10–15 reps at intensity of 70% age-predicted HRmax	12/3/60/2160	30s chair stand (reps)[3], 8ft up and go[5], Sit and reach (cm)[7] *800m walk test, VO2max*
Broman 2006[29]	**Sweden**	**4**	**AE: 18**(3) **C: 11**(2)	69.0(4.0) 69.8(3.5)	0/100	Deep water running with vest	**Control:** NR	75% HRmax	8/2/48/768	Peak aerobic power (cycle ergometer)[9]
Candeloro 2007[30]	**Brazil**	**3**	**AE: 16(6)** **C: 15(0)**	65-70	0/100	Stretching and strengthening exercise	**Control:** 32 Classes about general health care	NR	16/2/60/1920	*Isometric knee extension strength, sit-and-reach-test*
Carrasco 2012[31]	**Spain**	**3**	**AE:** 34 **SWIM:** 29 **C:** 30 (34 in total)	55.4(6.5) 58.8(6.5) 56.6(6.4)	0/100	AE: Upper and lower limb exercises with resistance devices SWIM: Swimming	**Control:** Usual care	RPE 10-15	52/2/45/4680	Isometric knee extension[1], *Counter movement jump*, Upper-limb power (swim bench)[2]
Cox 2008[16]	**Australia**	**6**	**SWIM:**56(8) **LE:** 60(8)	55.8(4.5) 55.2(4.8)	0/100	Swimming	**Land:** supervised walking	60–70% of heart rate reserve	24/3/60/4320	1.6 km walk time (min)[8]
Elbar 2013[17]	**Israel**	**6**	**AE:** 18(1) **C:** 18(0)	69.6(5.2) 69.6(4.5)	NR	Balance training	**Control:** NR	Progressions were made when the individuals have reached adaptation.	12/2/40/960	Step initiation phase (ms) during step execution test[5], Sway area (two-legged eyes open)[6], *get-up-and-go*
Graef 2010[15]	**Brazil**	**4**	**AE1:** 10(0) AE2:10(0)	68.4(6.7) 64.1(3.5)	0/100	AE1: Aerobic general exercise.	**Control:** Usual care	Aerobic: 11-13RPE; Strength: 4-5 sets 8-15	12/2/50/1200	Dynamic 1RM horizontal shoulder flexion strength[1]

			C: 7(0)	67.6(4.7)		resisted UL exercises AE2. Same no resistance		repetitions		
Ide 2005[32]	**Brazil**	**4**	**AE:** 27(8) **LE:** 27(8) **C:** 27(6)	62.2	NR	Resisted upper limb and trunk exercises	**Land group:** Resisted upper limb and trunk exercises. **Control:** lectures and activities	Gradual increases in intensity in accordance with the ability of each participant.	10/3/60/1800	Inspiratory maximal pressure[4]
Kim 2013[33]	**Republic of Korea**	**2**	**AE:** 10(2) **C:**10(3)	70.9(5.0) 72.6(5.1)	0/100	Adapted swimming, lower an upper limb strengthening	**Control:** NR	RPE 7-13	12/3/60/2160	Isokinetic knee extension (strength 60°/sec[1], power 180°/sec[2]), 8ft up and go[5], chair sit-and-reach[7]
Kovách 2013[34]	**Hungary**	**3**	**AE:** 17(0) **LE:** 22(0) **C:** 15(0)	67.9(6.9) 66.6(5.5) 64.6(6.2)	24/76	AE: NR	**Land:** Pilates exercise **Control:** NR	NR	24/3/60/4320	Chair stand[3], 8 ft up-and-go[5]sit-and-reach[7], 6 minute walk[8]
Martínez 2015[23]	**Mexico**	**3**	**AE:** 16(0) **C:** 10(0)	67.5(5.4) 67.4(4.7)	0/100	Water exercise	**Control:** Usual care	40-60% Heart rate reserve	12/5/50/3000	getting up from a chair and moving around house[5], putting on and taking shirt[7], 10m walk test[8]
Moreira 2013[20]	**Brazil**	**6**	**AE:** 64(5) **C:** 44(3)	58.6(6.7) 59.3(6.1)	0/100	Upper and lower limb strength exercises	**Control:** no regular exercise	Progressive 2-5 sets of 30-10 seconds	24/3/55/3960	*Isometric knee extension strength, stance test, sit-and-reach, Timed-up-and-go*
Oh 2015[18]	**Republic of Korea**	**6**	**AE:** 40(6) **LE:** 40(8)	74.7(2.9) 68.2(4.4)	NR	Flexibility, strength and endurance exercise	**Land: g**eneral exercises combined with smooth movements	4 RPE (10points scale)	10/3/60/1800	Isometric hip extension strength[1], timed up-and-go[5], chair sit-and-reach[7], SF-36 physical functioning[10]
de Oliveira 2014[19]	**Brazil**	**7**	**AE:** 28(8) **LE:** 23(5)	69(3) 69(4)	0/100	Balance, strength, endurance, aerobic and flexibility exercises	**Land:** floor gymnastics group	4 set s of 10 to 20 repetitions,	12/2/60/1440	Area of centre of pressure (two-legged eyes open)[6]
Pernambuco 2013[35]	**Brazil**	**5**	**AE:** 42(6) **C:** 42(11)	66.8(4.2) 66.9(3.2)	0/100	Lower limb aerobic exercises	**Control:** no regular exercise	7 minutes of each movement type	32/2/50/3200	*10m walk test, putting on and taking shirt, getting up from a chair and moving around house*
Rhodes 1995[36]	**Canada**	**4**	**AE:** 27(4) **LE:** 26(6) **C:** 23(9)	70(3.2)	0/100	Aerobic, strength, endurance, flexibility and balance	**Land:** similar to AE **Control:** educational sessions	60-65% HRmax	12/3/50/1800	Grip strength[1], trunk flexion[7], VO2max (walking test)[9]
Ruoti 1994[37]	**United States of America**	**3**	**AE:** 22(10) **C:** 22(8)	56.0(6.8) 65.2(5.3)	25/75	lower and upper limb endurance exercises	**Control:** usual care	Target 80% HRmax	12/3/60/2160	Shoulder abduction/adduction[3], VO2max (mod. Balke and Ware, walk)[9]
Sato 2007[21]	**Japan**	**5**	**AE1:** 10(0) **AE2:** 12(1) **C:** 8(0)	79.2(5.1) 75.3(6.0) 77.6(6.8)	NR	AE1/2: Gait, ADL exercise, flexibility and strength	**Control:** group socialising, watching TV	RPE 11	**1:** 24/1/60/1440 **2:** 24/2/60/2880	SF-36 Physical component score[10]
Shibata 2012[38]	**Japan**	**4**	**AE:** 15(0) **C:** 15(3)	66.1(9.3) 68.8(5.3)	17/83	Walking exercises	**Control:** NR	RPE 11-13	10/1/45/450	10 times-sit-to-stand[3], SF8 Physical component score[10]
Simmons 1996[39]	**United States of**	**4**	**AE:** 13(3) **LE:** 13(1)	82.0(5.4) 78.2(5.8)	9/81	Gait and lower limb exercises	**Land:** gait and lower limb exercises	Participant tolerance with rest periods as	5/2/45/450	Functional reach[5]

	America		**C:** 13(3)	81.3(6.5)			**Control:** cards playing	needed		
Takeshima 2002[24]	**Japan**	**4**	**AE:** 15(0) **C:** 15(0)	69.3(4.5) 69.3(3.3)	0/100	Lower and upper limb endurance and strength exercises	**Control:** Usual physical activity	light to moderate intensity measured with heart rate and RPE	12/3/70/2520	Dynamic knee extension strength[1], vertical jump[2], Force expiratory volume (FEV1)[4], Side steps (20 sec)[5], Trunk Flexion flexibility[7]
Tauton 1996[40]	**Canada**	**4**	**AE:** 23(4) **LE:** 18(2)	65-75	0/100	Aerobic, flexibility, balance, strength and endurance	**Land:** match closely to aquatic program	60-65% HRmax	12/3/50/1800	Grip strength[1], modified press-ups[3], sit-and-reach[7], peak aerobic power (Balke treadmill)[9]
Tavares 2009[41]	**Brazil**	**4**	**AE:** 17(0) **LE:** 20(0)	72(4.6) 70(5.9)	19/81	stretching and strengthening exercises	**Land:** Strengthening, stretching and balance exercises	1-2½ minutes per exercise	24/2/60/2880	Older Americans resources and services program (self-reported questionnaire)[10], *Brazilian Multidimensional Functional assessment questionnaire*
Tsourlou 2006[25]	**Greece**	**4**	**AE:** 12(2) **C:** 10(0)	69.3(1.9) 68.4(6.7)	0/100	Aerobic and resistance exercises	**Control:** normal care	65%-80% HRmax	24/3/60 4320	Maximum knee extension isometric peak torque[1], Squat jump[2], Timed up and go[5], sit and reach[7]

NR = Not reported HRmax = heart rate maximum *Dose: weeks/sessions per weeks/duration of training/total number of training minutes *Italics* = Insufficient data for outcome reported

Designated construct for outcome measures: 1 = Maximum strength, 2 = Muscular power 3 = Muscular endurance 4 = Respiratory muscle function 5 = Agility 6 = Postural stability 7 = Flexibility 8 = Walking ability 9 = Aerobic power 10 = Self-reported functioning

Appendix 1 Summary of search strategy for Medline (Ovid).

Resources: Ovid MEDLINE(R) 1946 to December Week 5 2015

1. "Aged, 80 and over"/ or exp Aged/ or Middle Aged/

2. elderly.mp.

3. older people.mp.

4. older population.mp.

5. older adult*.mp.

6. aging.mp.

7. senior*.mp.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. aquatic therapy.mp.

10. aquatic exercise*.mp.

11. water therap*.mp.

12. Hydrotherapy/ or hydrotherap*.mp.

13. aquatic physiotherapy.mp.

14. aquatic physical therapy.mp.

15. water exercise*.mp.

16. aquatic rehabilitation.mp.

17. pool exercise*.mp.

18. water rehabilitation.mp.

19. aquatics.mp.

20. swimming intervention.mp.

21. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 8 and 21

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Appendix 3 Methodological quality (Delphi)

	Random-isation	Concealed allocation	Equal at baseline	Eligibility specified	Blind assessor	Blind care providers	Blind participants	Point estimates and variability	Intention-to-treat	Delphi score /9
Avelar 2010	Yes	dnk	Yes	Yes	Yes	dnk	No	Yes	dnk	5
Bento 2012	Yes	dnk	Yes	Yes	dnk	dnk	dnk	Yes	No	4
Bergamin 2013	Yes	dnk	dnk	Yes	dnk	Yes	dnk	Yes	dnk	4
Bocalini 2008	Yes	dnk	Yes	Yes	dnk	dnk	dnk	Yes	No	4
Bocalini 2010	Yes	dnk	Yes	Yes	dnk	dnk	dnk	Yes	No	4
Broman 2006	yes	dnk	Yes	Yes	dnk	dnk	dnk	Yes	No	4
Candeloro 2007	Yes	dnk	dnk	Yes	dnk	dnk	dnk	Yes	No	3
Carrasco 2012	Yes	dnk	dnk	Yes	dnk	dnk	dnk	Yes	No	3
Cox 2008	Yes	Yes	Yes	Yes	No	dnk	No	Yes	Yes	6
Elbar 2013	Yes	yes	Yes	Yes	Yes	dnk	dnk	Yes	dnk	6
Graef 2010	Yes	dnk	Yes	Yes	dnk	dnk	dnk	Yes	No	4
Ide 2005	Yes	dnk	Yes	Yes	dnk	No	No	Yes	dnk	4
Kim 2013	Yes	dnk	No	No	dnk	dnk	dnk	Yes	No	2
Kovách 2013	Yes	dnk	Yes	No	dnk	dnk	dnk	Yes	dnk	3
Martínez 2015	Yes	dnk	dnk	Yes	dnk	dnk	No	Yes	No	3
Moreira 2013	Yes	Yes	Yes	Yes	Yes	dnk	dnk	Yes	dnk	6
Oh 2015	Yes	Yes	Yes	Yes	Yes	No	No	Yes	dnk	6
Oliveira 2014	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Pernambuco 2013	Yes	dnk	Yes	Yes	Yes	dnk	dnk	Yes	dnk	5
Rhodes 1995	Yes	dnk	Yes	Yes	dnk	dnk	dnk	Yes	No	4
Ruoti 1994	Yes	dnk	No	Yes	dnk	dnk	dnk	Yes	No	3
Sato 2007	Yes	dnk	Yes	Yes	No	No	yes	Yes	No	5
Shibata 2012	Yes	Yes	No	No	dnk	dnk	dnk	Yes	Yes	4
Simmons 1996	Yes	dnk	Yes	Yes	No	No	No	Yes	No	4
Takeshima 2002	Yes	dnk	Yes	Yes	No	dnk	No	Yes	dnk	4
Taunton 1996	Yes	dnk	Yes	Yes	dnk	dnk	dnk	Yes	dnk	4
Taveres 2009	Yes	dnk	Yes	Yes	dnk	dnk	dnk	Yes	No	4
Tsourlou 2006	Yes	dnk	Yes	Yes	dnk	No	No	Yes	dnk	4

dnk = do not know

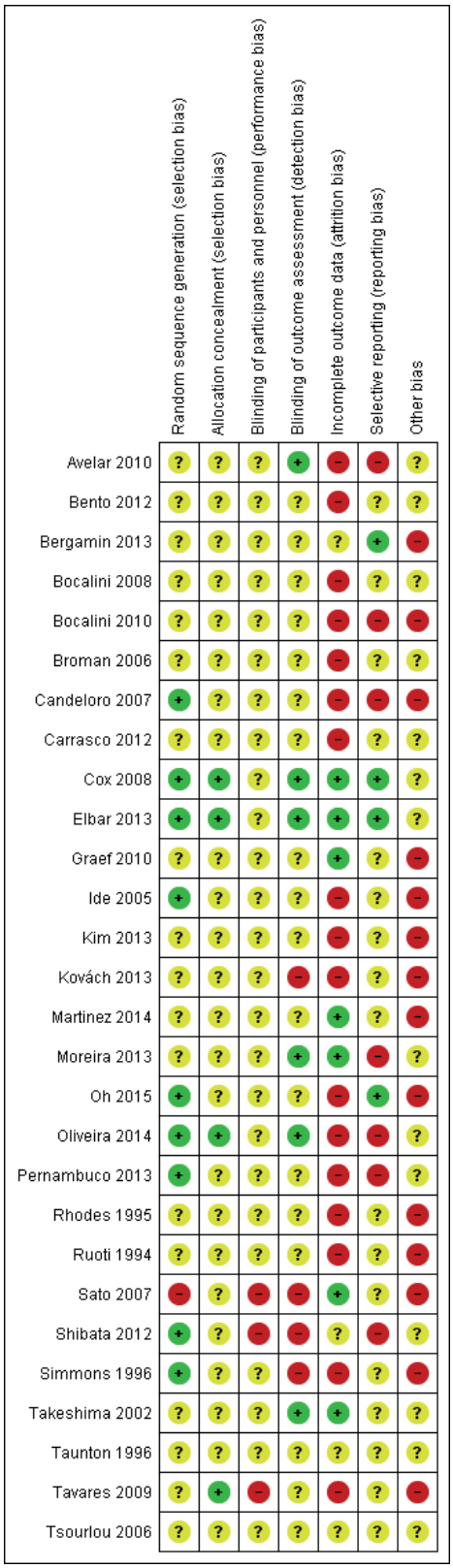
Appendix 4 Ranking order for outcome measures

When required the highest ranked outcome measure was chosen.

Muscle group/movement*	Activities/Agility	Walking ability	Flexibility	Self-reported Physical functioning
1) Knee extension	1) Timed up and go (TUG)/8ft up and go	1) 40-80m walk test (fast-paced)	1) Sit and reach	1) SF-36 (PCS)
2) Full lower limb extension e.g. leg press	2) Chair stand (30 sec)	2) 50ft walk test (fast-paced)	2) Trunk flexion	2) SF-36 physical function
3) Knee flexion	3) Ascending stairs	3) 6 minute walking test (6MWT)	3) Trunk extension	3) SF-36 Role physical
4) Hip Extension	4) Descending stairs	4) 8ft walk test	4) Back scratch	4) Other algofunctional composite score
5) Grip strength				
6) Chest press				
7) Shoulder pull down				
8) Shoulder press				

*****In cases were both isometric 1RM and isokinetic muscle strength were measured, results for isometric strength testing were included in the meta-analysis.

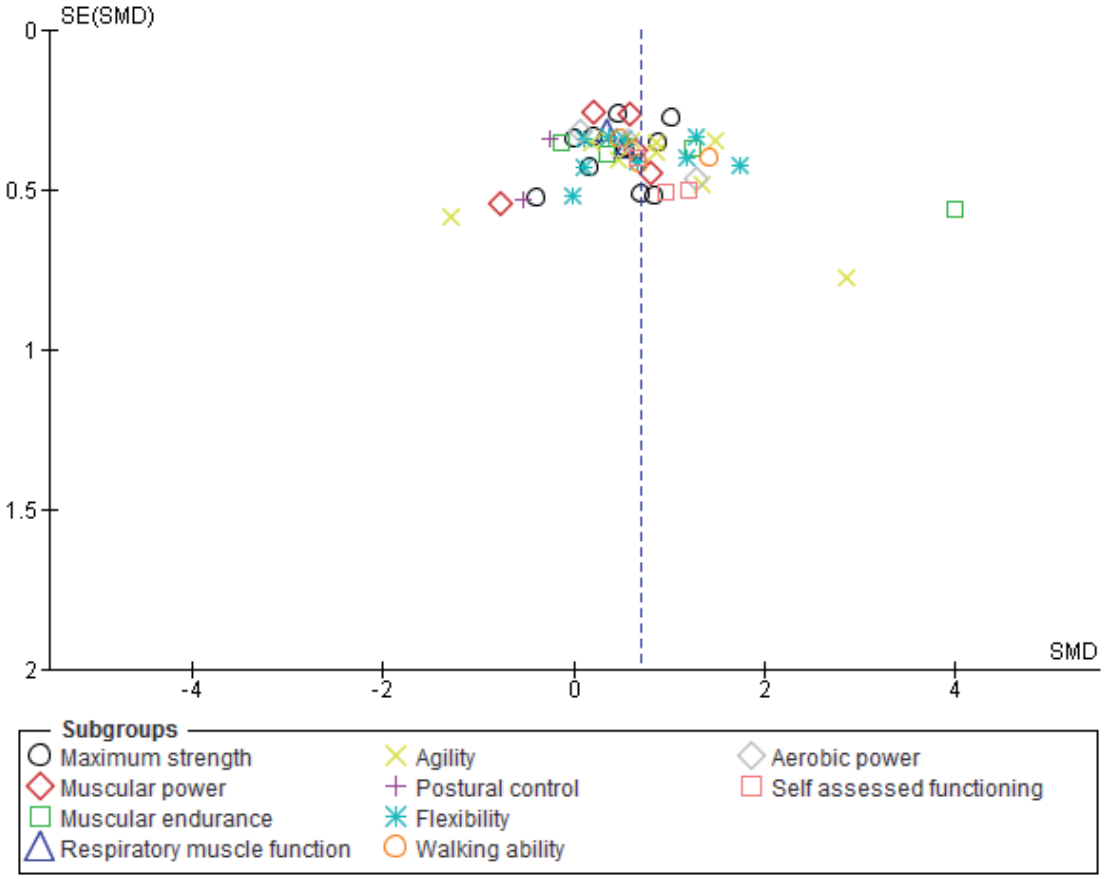
Appendix 5 Risk of bias for included studies



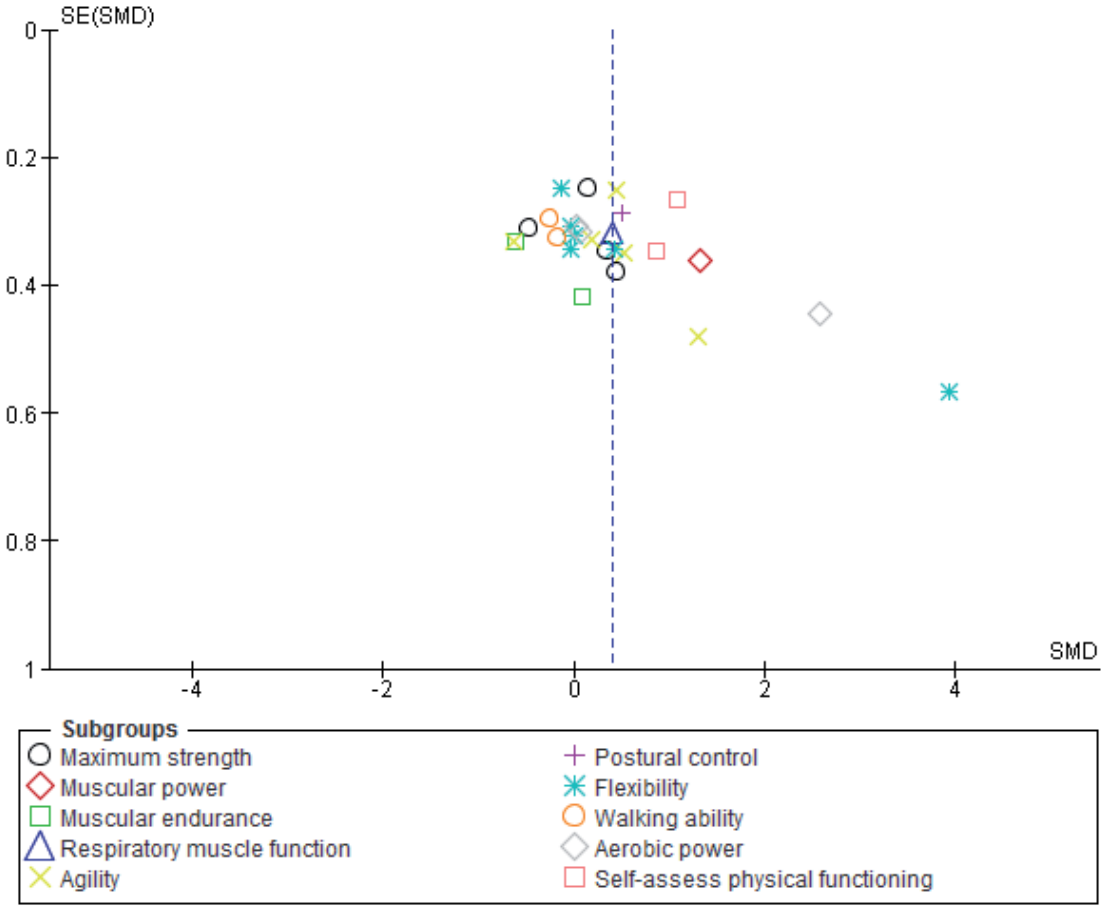
= Low risk of bias
= Unclear risk of bias
= High risk of bias

Appendix 6 Funnel plots for meta-analysis

Aquatic exercise versus Control



Aquatic exercise versus Land exercise



Appendix 7 Sensitivity testing

Sensitivity analysis		Comparison	Number of Studies	No. Participants		I^2	Overall Effect (p-value)	Standardised mean difference IV Random (95% CI)*
				Aquatic Exercise	Comparison			
drop out	<15%	AE v Con	9	445	354	19%	<0.000001	0.63 (0.46 to 0.79)
	≥15%		10	505	347	80%	0.001	0.64 (0.30 to 0.98)
	<15%	AE v LE	4	166	149	6%	0.04	0.25 (0.01 to 0.48)
	≥15%		7	430	392	86%	0.02	0.47 (0.08 to 0.86)
Methodological quality	Delphi ≥4	AE v Con	13	528	453	79%	<0.00001	0.70 (0.48 to 0.91
	Delphi ≥4	AE v LE	10	625	472	80%	0.001	0.39 (0.12 to 0.66)
Age	< 68	AE v Con	9	526	352	82%	<0.000001	1.00 (0.64 to 1.36)
	≥ 68		10	387	326	55%	0.0003	0.44 (0.21 to 0.68
	< 68	AE v LE	4	211	191	91%	0.09	0.61 (-0.10 to 1.32)
	≥ 68		6	385	350	48%	0.005	0.30 (0.09 to 0.51)
Training frequency	<3 times a week	AE v Con	8	298	208	34%	<0.00001	0.66 (0.42 to 0.90)
	≥3 times a week		11	635	478	80%	<0.00001	0.71 (0.42 to 1.00)
	<3 times a week	AE v LE	4	106	106	24%	0.001	0.52 (0.20 to 0.84)
	≥3 times a week		8	490	435	83%	0.04	0.35 (0.02 to 0.69)
ICF classification	Body structure and function	AE v Con	14	631	462	79%	<0.00001	0.74 (0.45 to 1.02)
	Activity and participation		12	282	216	64%	0.0001	0.64 (0.32 to 0.97)
	Body structure and function	AE v LE	7	373	324	84%	0.03	0.42 (0.03 to 0.81)
	Activity and participation		8	223	217	70%	0.05	0.36 (0.00 to 0.72)

*Positive results is in favour of aquatic exercise.

AE = Aquatic Exercise, Con = Control, LE = Land exercise

IV = inverse-variance, CI = confidence interval, ICF = International classification of Functioning, disability and health

III

EFFECTS OF A PROGRESSIVE AQUATIC RESISTANCE EXERCISE PROGRAM ON THE BIOCHEMICAL COMPOSITION AND MORPHOLOGY OF CARTILAGE IN WOMEN WITH MILD KNEE OSTEOARTHRITIS: PROTOCOL FOR A RANDMOISED CONTROLLED TRIAL

by

Waller B, Munukka M, Multanen J, Rantalainen T, Pöyhönen T, Nieminen M, Kiviranta I, Kautiainen H, Selänne H, Dekker J, Sipilä S, Kujala U, Häkkinen A, Heinonen A. 2013

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STUDY PROTOCOL Open Access

Effects of a progressive aquatic resistance exercise program on the biochemical composition and morphology of cartilage in women with mild knee osteoarthritis: protocol for a randomised controlled trial

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Abstract

Background: Symptoms associated with osteoarthritis of the knee result in decreased function, loss of working capacity and extensive social and medical costs. There is a need to investigate and develop effective interventions to minimise the impact of and even prevent the progression of osteoarthritis. Aquatic exercise has been shown to be effective at reducing the impact of osteoarthritis. The purpose of this article is to describe the rationale, design and intervention of a study investigating the effect of an aquatic resistance exercise intervention on cartilage in postmenopausal women with mild knee osteoarthritis.

Methods: A minimum of 80 volunteers who meet the inclusion criteria will be recruited from the local population through newspaper advertisements. Following initial assessment volunteers will be randomised into two groups. The intervention group will participate in a progressive aquatic resistance exercise program of 1-hour duration 3 times a week for four months. The control group will be asked to maintain normal care during this period. Primary outcome measure for this study is the biochemical composition of knee cartilage measured using quantitative magnetic resonance imaging; T2 relaxation time and delayed gadolinium-enhanced magnetic resonance imaging techniques. In addition, knee cartilage morphology as regional cartilage thickness will be studied. Secondary outcomes include measures of body composition and bone traits using dual energy x-ray absorptiometry and peripheral quantitative computed tomography, pain, function using questionnaires and physical performance tests and quality of life. Measurements will be performed at baseline, after the 4-month intervention period and at one year follow up.

Discussion: This randomised controlled trial will investigate the effect a progressive aquatic resistance exercise program has on the biochemical composition of cartilage in post-menopausal women with mild knee osteoarthritis. This is the first study to investigate what impact aquatic exercise has on human articular cartilage. In addition it will investigate the effect aquatic exercise has on physical function, pain, bone and body composition and quality of life. The results of this study will help optimise the prescription of aquatic exercise to persons with mild knee osteoarthritis.

Trial registration: ISRCTN65346593.

Keywords: Osteoarthritis, Quantitative MRI, T2 relaxation time, dGEMRIC, Bone, Aquatic exercise

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Background

Osteoarthritis (OA) of the lower limb is a leading cause of decreased function and quality of life [1]. It has been estimated that the prevalence of symptomatic OA of the knee is between 7-33% with an increase in prevalence with age and is the most common site of symptomatic OA [2-6]. Early signs of OA in articular cartilage, which is constituent for the initiation and progression of OA, are characterised with loss of proteoglycans, breakdown of the collagen matrix and increased water content [7]. As the disease progresses there is fibrillation of the cartilage, changes in the subchondral bone, formation of osteophytes and thickening of the synovium [8-11] and as such OA is considered a whole joint disease. These modifications within the joint lead to the gradual development of clinical symptoms such as stiffness, decreased range of motion and pain [12] which cause a decrease in joint proprioception [13] and inhibits muscle activation [14,15] leading to a decrease in activity. This disuse results in a lowering of aerobic capacity, muscle strength and muscle mass and ultimately a decrease in functional capacity and increased dependence [16,17]. Additionally, reduced muscle strength is a risk factor for future pain [17], self-reported knee instability [18] and increased risk of falling [19]. These in combination cause the extensive social and medical costs to society as a direct or indirect result of OA.

Although there is no known cure for OA the disease-related factors such as impaired muscle function and reduced aerobic fitness can be improved and maintained with therapeutic exercise [20,21]. Previous systematic reviews have demonstrated that exercise has positive effects on pain and function for people with symptomatic OA of the knee [21-23] and is recommended as one of the primary non-pharmaceutical treatment modalities in current OA guidelines [24-29]. Exercising in water is also strongly recommended in these guidelines. There is evidence to suggest that therapeutic aquatic exercise has a short term positive effect on pain and function in persons with OA of knee and/or hip similar to that of land training [30,31]. There is good evidence to support the use of strength exercises in the management of symptoms resulting from OA [32] however, there is conflicting evidence that therapeutic aquatic exercises can improve strength of lower limb muscles in persons with OA [33-40]. It is thought that the benefits from aquatic exercise are primarily a result of the decreased effects of gravity. Buoyancy reduces compressive and shear forces on joints and thus offers a comfortable training medium for patients with OA [41].

Previously, one restriction in OA research was the lack of non-invasive *in vivo* techniques to quantify the structure and acute changes in cartilage. Advances in magnetic resonance imaging (MRI) have made mapping of the articular cartilage and loading related changes possible [42]. The "delayed Gadolinium Enhanced MRI of Cartilage" (dGEMRIC) technique utilizes a paramagnetic contrast agent gadolinium ($Gd\text{-}DTPA^{2-}$) to detect early reduction of glycosaminoglycan (GAG) from the matrix, a phenomenon considered to represent the onset of the degenerative process of cartilage [43]. Measurement of T2 relaxation time, sensitive to degeneration of tissue collagen and the orientation of collagen fibres in the extracellular matrix, has been developed to detect early degeneration or senescent changes of cartilage [44,45]. In addition, the assessment of morphological properties from three-dimensional MRI measurements enables assessment of tissue changes at a macroscopic scale [46] which have been found to be reliable, responsive and valid methods for mapping the volumetric data of articular cartilage [47-49].

There is still a lack of evidence that human cartilage can adapt to mechanical loading in a similar way to other tissues such as bone and muscle. Animal studies have suggested that physical exercise can improve tissue integrity by increasing the GAG content and indentation stiffness in load bearing cartilage [50,51]. In a cross-sectional study Tiderius et al. [52] concluded, based on dGEMRIC measurements, that GAG content was higher in regularly exercising individuals than in sedentary subjects. Additionally, observations by Teichtahl et al. [53] suggest that vigorous physical activity is associated with a reduced rate of patella cartilage volume loss in asymptomatic subjects. To date, only one randomised intervention study investigating the direct effect of exercise on biochemical composition of human cartilage [54] has been published. Roos et al. [54] reported a positive effect of a moderate four months exercise on the GAG content, measured with dGEMRIC in subjects with high risk of knee OA. Another study by Cotofana et al. [55] provides no evidence that a 3-month exercise intervention in untrained middle-aged women can significantly alter cartilage morphology in the knee joint. Furthermore, the optimal type or intensity of exercise for improvement in cartilage is not known and longitudinal effects of training are needed to determine the exercise response once OA is established. In particular, there are no studies investigating the effect non-impact training such as therapeutic aquatic exercise has on the structures related to and progression of OA in the knee joint.

Therefore we plan to investigate the effects of an intensive aquatic resistance exercise program on the biochemical composition and morphology of the knee cartilage as well as its effect on physical function in postmenopausal women with mild knee osteoarthritis. In addition, we plan to discover if the possible benefits of exercise on cartilage, symptoms and physical function can be maintained one year after training period.

The purpose of this article is to describe the rationale, design and intervention of a study investigating the effect an aquatic resistance exercise intervention has on the cartilage in postmenopausal women with mild knee osteoarthritis.

Methods and design

Study design

The design of this study will be a 4-month randomised controlled exercise intervention study (RCT) with a 16 - month follow up (Trial registration: ISRCTN65346593). After baseline measurements the voluntary participants will be randomly assigned into the two arms of the study, an aquatic resistance strength training group and a control group. All the outcome measurements will be performed at baseline, after the 4-month intervention and at follow up 12 months after cessation of training.

Participants and selection criteria

Volunteer postmenopausal women, between the ages of 60–68 year-old, will be recruited through a series of local newspaper advertisements and will be gathered from the county of Central Finland which has a population of approximately 275 000. Inclusion eligibility, (see below), will be initially assessed using a structured telephone interview. The telephone questionnaire includes questions concerning degree of knee pain, current level of physical activity and past medical history.

Suitable participants will be taken forward and they will undergo weight bearing x-ray imaging of both knees. An experienced radiologist and orthopaedic physician will assess the images grading the degree of OA in the tibiofemoral and patellofemoral joints using the Kellgren-Lawrence grading (K/L 0-IV) [56]. Those participants who have a KL score of I (possible osteophytes) or II (definite osteophytes, possible joint space narrowing), will be included in the next stage of eligibility assessment and undergo a medical and physiotherapy screening. At this point any possible physical or medical limitations to full participation in the intervention will be assessed e.g. severely restricted joint range of movement (ROM), excessive laxity of knee joint, possible physical disabilities and abnormalities found from resting echocardiogram.

Subjects will be excluded if they have at least one of the following criteria; BMI > 34, resting pain in knee VAS > 50/100, known loose particles in knee joint, acute inflammation in knee joint, knee intra-articular steroid injection in previous 3 months or oral steroid medication treatment in the previous 12 months, undergoing treatment for osteoporosis or T-score for femoral neck bone mineral density (BMD, g/cm^2) lower than −2.5 i.e. indicating osteoporosis as measured with DXA [57-59], previous cancer or radiotherapy, suffer from type I or II diabetes, cardiac disease, diagnosed rheumatic disease (other than OA), undergone surgical procedure to knee (excluding menisectomy or arthroscopy if over 12 months ago) or joint replacement surgery in lower limbs.

Additional exclusion criteria are problems that would prevent MRI imaging, including electronic or magnetic implants e.g. pace maker, metal within body e.g. internal bone fixations, artificial aortic heart valve, metal particles in eyes, large tattoos on lower limb, claustrophobia or possible allergy to the contrast medium. Further, fasting blood samples will be taken to analyse Krea to ensure kidney function for normal removal of contrast medium from the body. All those participants fulfilling all the inclusion criteria will be included into the study and undergo the baseline measurements. Figure 1 shows the flow chart describing the selection and measurement procedure for the whole study.

Sample size

The sample size and power calculations have been estimated for the primary end points of this study, i.e. the

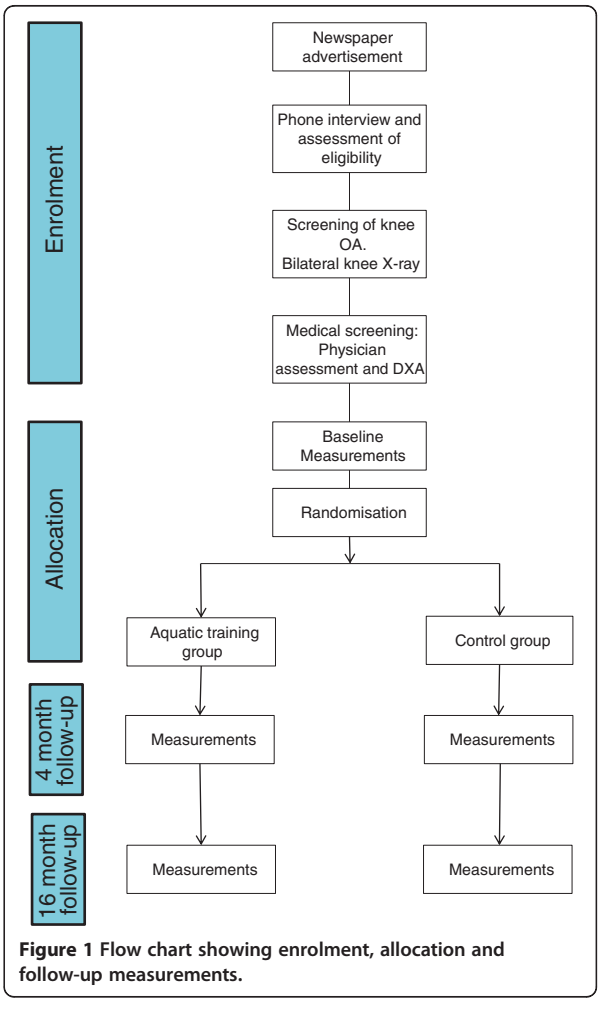

Figure 1 Flow chart showing enrolment, allocation and follow-up measurements.

dGEMRIC and T2 variables. Based on data from Roos et al. [54] and Tiderius et al. [55] it is estimated that 30 subjects are needed, at 80% power, to detect a mean ± SD difference of 40 ± 40 msec in the dGEMRIC between groups [54]. It is estimated that dropout rate will be about 20% at the 16 months follow up, consequently at least 70 subjects will need to be recruited.

Randomisation and blinding

The subjects will be randomly allocated into either of the two arms of the study by an external statistician blinded for the intervention and study participants and will only be provided with a randomisation number for each participant and severity of OA in knee according to x-ray classification. A computer generated block randomisation of size of ten, stratified according to Kellgren-Lawrence grading 1 and 2, will be used to ensure equal distribution of severity of OA within each group and equal group size.

As with all exercise intervention studies blinding of the subject from the intervention is not possible. Researchers (BW, MM, AH) will be blinded to the allocation of groups as well as blinded from the interventions and measurement except for pQCT (MM) and DXA (BW) measurements. Due to practical limitations the physical therapists providing the intervention will also be performing the physical performance measurements. All statistical analyses will be completed by a statistician (HK), who is blinded to the participants and measurements.

Primary outcomes

This research project will have two primary outcome measures. Delayed gadolinium-enhance magnetic resonance imaging of cartilage (dGEMRIC), sensitive to the distribution of GAG, will be used to evaluate the biochemical composition of cartilage. Arrangement of collagen and hydration state of the cartilage will be measured using T2 relaxation time mapping. Furthermore, knee cartilage morphology as a regional cartilage thickness will be analysed from the weight bearing area of tibiofemoral and patellofemoral cartilages. The dGEMRIC method has been validated in several *in vitro* studies [60-62] and it had been applied in several *in vivo* studies [43,52,63-71]. Also, T2 relaxation time method has been histologically validated *in vitro* [72], and it has been applied in several human studies to assess chondral repair [69,73-76].

MRI protocols

Prior to imaging, the subject will be advised to restrain from any strenuous physical activity during the 48 hours prior to the measurements to minimise possible transient changes in knee cartilage volume and composition. Subjects will be imaged at the same time of the day to avoid possible diurnal variation at the follow-up measurements. The participants will be imaged lying supine with knee to be imaged in slight flexion, stabilized in a leg holder and a custom made inflatable cushion. The cushion has been specifically designed to stabilize the patella without causing any compression of the patellofemoral joint. The imaging session will last in total 3 hours and will include initially a standard clinical MRI series and T2 relaxation time followed by a dGEMRIC series.

T2 mapping will be performed using a sagittal multi-slice multi-echo fast spin echo sequence (field of view (FOV) 140 mm, acquisition matrix 256 x 256, repetition time (TR) 2090 ms, eight echo times (TE) between 13 and 104 ms, echo train length (ETL) 8, slice thickness 3 mm). The slices will be positioned perpendicular to a line tangential to the posterior femoral condyles in the axial scout view. Two slices, each covering the central region of the medial and lateral condyles, will be analysed.

For the dGEMRIC series, immediately after the clinical and T2 imaging a double dose of Gd-DTPA^{2-} (Magnevist, Schering, Berlin) will be administered intravenously i.e., 0.4 ml/kg (0.2 mM/kg). At baseline, post intervention and 16 month follow up the amount of contrast administered will be corrected for body weight. It is felt this is appropriate because of the expected changes in body composition as a result of the intensive exercise intervention. In order to enhance the delivery of contrast agent into the knee cartilage, following administration of Gd-DTPA^{2-} the subject will be instructed to perform 5 minutes of flexion-extension exercises in a sitting position without resistance, 5 minutes of walking on a flat surface and 10 gentle deep squats. Exactly ninety minutes after the injection, T1 mapping in the presence of Gd-DTPA^{2-} (dGEMRIC) will be performed in the sagittal plane using a single slice inversion recovery fast-spin echo sequence (FOV = 14 cm, matrix 256 x 256, TR = 1800 ms, TE = 13 ms, six inversion times (TI) between 50 and 1600 ms, slice thickness 3 mm). The slice positioning will be copied from the T2 relaxation time mapping sequence, and the number of the slices in the correct orientation is reduced to one. The remaining slice is then positioned at the centre of the medial and lateral condyles as viewed on the axial scout image. The subject will be positioned into an identical position as for the first MRI imaging. For both the MRI images and pQCT measurements the knee with highest degree OA, as measured by the radiographic Kellgren-Lawrence scale, will be imaged. In the cases were both knee have identical KL score the right knee will be imaged.

Segmentation

Weight bearing cartilage regions of interest (ROIs) from single sagittal slices at the centre of the medial and

lateral tibial and femoral condyles will be segmented using a semi-automated in-house MATLAB application (Mathworks, Inc. Natick, MA, USA). dGEMRIC indices will be corrected for BMI [77]. In this research team the *in vivo* precision of dGEMRIC for full thickness cartilage in different ROIs ranges from 5% to 7% [78]. The inter-observer precision of T2 in different locations is on average 5% [79]. For quality assurance purposes, a set of phantom samples containing certain concentrations of agarose and nickel nitrate to modulate their T1 and T2 relaxation times will be imaged following the study protocol prior to baseline and follow-up measurement sessions to assess possible drift.

Secondary outcomes

Properties of bone and body composition

Peripheral quantitative computed tomography (pQCT) The bone properties of the distal radius and mid and distal tibia will be measured using a pQCT device (XCT-2000; Stratec Medizintechnik, Pforzhem, Germany). A 2-mm-thick single tomographic slice with pixel size 0.59 mm in plane resolution will be taken at 5% and 55% of the length of the tibia proximal to the distal end of the tibia. Lower leg length is defined as the distance between the medial condyle of tibia and medial malleolus. Selection of lower limb to be imaged will be based on the same principles as the MRI scan. The forearm slice will be taken at 4% of ulna length proximal to the distal endplate of ulna. Length of ulna is defined as the distance between olecranon process and the midline of lateral aspect of distal ulna. In all cases right upper limb will be scanned except when subjects had suffered from fracture of either right ulna or radius. The analysis of the pQCT images will be performed with the density distribution plug-in [80] of the BoneJ (http://bonej.org/densitydistribution) [81] ImageJ (http://rsbweb.nih.gov/ij/download.html) plug-in. Compressive bone strength index (BSI_d, g^2/cm^4), bone mineral content (BMC), total and trabecular density (ToD and TrD, mg/cm^3) and total and trabecular area (ToA and TrA, mm^2) will be analysed from the shaft slices. The pQCT device is calibrated daily using a standard phantom provided by the manufacturer and coefficient of variation (CV) for these protocols in our laboratory has been measured to range between 1.5-3.4% for the reported variables [82].

Dual-energy X-ray absorptiometry (DXA)

DXA (Lunar Prodigy; GE Lunar Healthcare, Madison, WI, USA) will be used to assess body composition and bone traits. Body composition analyses will be carried out using enCORE software (ENcore 2011, version 13.60.033). Using manufacturers software and protocols total body fat and lean body mass will be measured. *In vivo* precision of these measurements has been reported to be CV 1.3-2,2% [83]. Both proximal femur and Lumbar spine (L2-4) areal bone mineral density (aBMD, g/cm^2) and bone mineral content (BMC, g) will be scanned. Cross sectional geometry of the femoral neck will be analysed using advanced hip structure analysis (AHA) as per manufacturer's software. This will include femoral neck hip axis length (HAL, mm), cross sectional area (CSA, mm^2), cross sectional moment of inertia (CSMI, mm^4) and femoral neck strength index (FSI, mm^3) [84-86]. *In vivo* repeatability, CV, of these methods has been reported as 2.3% for CSA [87].

Questionnaires

Health status General health and habitual physical activity at baseline will be assessed by a questionnaire devised by the research group. This health questionnaire addresses medical conditions, current medications, years of menopausal hormone therapy, history of fractures and current leisure time physical activity. Throughout the entire follow up period all subjects will be asked to report their daily amount of analgesia taken to manage their knee pain. Space will be provided in the physical activity diary for ease of recording.

Impact of osteoarthritis of the knee

Self-assessed impact of osteoarthritis on functioning will be measured using two questionnaires, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [88] and the knee injury and osteoarthritis outcome score (KOOS) [89]. The visual analogue version (VAS) of the WOMAC (0-100 mm) will be used with a range of scores of 0–2400. This questionnaire has 24 questions and is divided into three domains; pain (score ranging from 0–500), stiffness (0–200) and function (0–1700). A higher score indicates more disability. The internal consistence (Cronbach's alpha) for the VAS version is 0.7-0.91 and test-retest (ICC) coefficient is 0.95 for pain, 0.90 for stiffness and 0.92 for function ([90]). A likert version of the KOOS will be used with each response being scored 0–4. The questionnaire has 5 domains: pain (9 questions), other symptoms (7 questions), activities of daily living (16 questions), sport and recreation (5 questions) and knee related quality of life (4 questions). Score for global and domains scores are transformed into a score 0–100 with a score of 0 indicating extreme knee problems and 100 no knee problems. The internal consistency for the KOOS is 0.86-0.96 and test-rest (ICC) is (0.67-0.95) [91]. Reliability of the Finnish language version of both WOMAC and KOOS has been shown to be similar to that of the English language version [92].

Quality of life

Self-assessed quality of life will be measured using the RAND-36-Item short form healthy survey instrument [93] this questionnaire is identical in wording to the short form 36 questionnaire (SF-36) but summation of final scores is different. It contains 8 domains: physical functioning (10 items), role limitations due to physical health problems (4 items), role limitations due to emotional problems (3 items), energy/fatigue (4 items), emotional well-being (5 items), social functioning (2 items), pain (2 items), and general health (5 items). Global and individual domains will be re-scored and given values of 0–100 with higher scores indicating a more favourable health state. The scores will also be divided into two summary measure: the physical component summary score (PCS) and the mental component summary score (MCS). The dimensions physical functioning, role limitation due to physical health problems, body pain and general health form the PCS and mental health, energy/fatigue, social functioning and role limitations due to emotional problems form the MCS. In a Finnish standardization population sample aged 18–79 years the homogeneity, i.e., the mean of the item intercorrelations of the Scale, was 0.63 and Cronbach alpha 0.94 [94].

Physical performance measures

Muscle strength Maximal isometric knee flexion and extension strength of both legs, as well as grip strength of dominant hand, will be measured using an adjustable dynamometer chair (Good strength; Metitur Ltd, Jyväskylä Finland). The best result from 3 contractions will be used and recorded in newtons (N). In our laboratory, the precision of the test is 6% for knee extension and 9% for knee flexion [95].

Muscle power

Single leg extension power will be measured using Nottingham power rig (University of Nottingham Medical School, Nottingham, UK) which has been tested for reliability and has a test retest co-efficient of variation (CV of 9.4%) [96] and in our laboratory the CV is 8% [97].

In addition lower limb power function will be determined by a maximal counter movement jump (CMJ) measured using a custom made force plate (University of Jyväskylä, Finland). This test is a measure of neuromuscular function. Jumping force, vertical ground reaction forces, power, impulse and jump height will be calculated. Data is collected at a sampling frequency of 500 Hz [98].

Aerobic fitness

Maximal aerobic power VO_2 max will be estimated using the UKK 2 km walk test (UKK Institute, Tampere, Finland). This test requires the subject to walk 2 km as quickly as possible with a target of 80% maximal heart rate [99]. VO_2 max is estimated using walking time, body mass index (BMI), age and heart rate at end of test. The heart rate will be measured by a portable heart-rate monitor (Polar F6, Polar Electro Ltd, Kempele, Finland). It is a feasible test for estimating V02 max [100] and sensitive to changes [101]. Its validity has also been tested with correlation coefficient of 0.69-0.77 [102].

Static balance

Static balance ability will be assessed using a force platform device (Goodbalance, Metitur Ltd, Jyväskylä Finland) which is validated and reliable method measuring body sway in different standing positions [103,104]. Balance will be measured in feet side-by-side eyes open and eyes closed and single leg stance [105].

Agility

Agility will be assessed with a standardised figure-of-eight running test consisting of two laps around two cones placed 10 meters apart in a figure of eight [106-108]. Time (in seconds) taken to complete the task will be measured using a photocell. This test has shown to be effective at detecting decreased motor performance (area under curve 0.86) additionally it has been shown to be a very sensitive (73.5%) and specific (86.1%) tool for measuring agility [109].

Gait

Spatial and temporal parameters of gait will be measured using the GAITRite® walkway (CIR systems, inc. Clifton, NJ 070872) [110]. This consists of a 577 cm long and 88.5 cm wide matt with 13,824 sensors placed on 1.27 cm in a grid. The collection frequency of the matt is 80Hz. The data is transferred by lead to a computer and is analysed using GAITRite 3.6b software. This technique has been validated with different populations [111,112] and found to be a reliable [112,113] instrument to measure spatial and temporal parameters of gait.

Daily physical activity

During both the intervention period (0–4 months) and the follow up period (5–16 months) daily physical activity of every subject (excluding pool training) will be recorded using a leisure time physical activity diary. The diary is completed daily and each activity, duration and intensity (1 = low, 2 = moderate or 3 = hard) is recorded. From this data MET-hours per week will be calculated [114,115]. In addition, during the intervention period

each subjects' daily activity will be measured for 3 days using a heart rate monitor (F6 Polar, Polar Oy, Finland), accelerometers (Hookie AM 20, Traxmeet, Finland) and hourly physical activity diaries.

Intervention

Those subjects randomised into the intervention group will participate in 1 hour of aquatic resistance training, three times a week for 4 months, totally 48 training sessions. The intervention will be completed in small groups of 6–8 subjects in a pool heated to 32 degrees with depths 1.3-1.5 m. Aquatic steps will be used to ensure that all subjects will complete the standing exercises at a depth level approximately to their xiphoid bone ±5 cm ensuring weight bearing on the supporting leg of 25-50% of own body weight [41].

Each training session will last approximately 1 hour. The session will consist of three distinct parts; the warm-up (15 minutes), lower limb strengthening program (35 - minutes) and cool down (10 minutes), a full description of exercises can be found from Table 1 and Figures 2, 3, 4, 5, 6. Warm up and cool down was planned by a physiotherapist with over 10 years of aquatic therapy experience with patients suffering from musculoskeletal problems (BW), the same therapist will ensure that quality of movement and intensity of the intervention is maintained throughout the training by reviewing the heart rate and perceived exertion by BORG 6–20 scale [116] which are collected after

Table 1 Description of exercises included in the intervention

Warm-up (10-15 minutes)	Strength training (35 minutes)	Cool down (10 minutes)
1. Standing hip flexion/extension	1. Standing hip flexion/extension (Figure 3): Standing side on to wall and stand on leg furthest away from wall. Swing leg nearest wall forwards and backwards as fast as possible using full range of motion. Keep knee of moving leg in full extension and ankle in dorsiflexion. Maintain spinal neutral at all times.	3-5 minutes of walking and supported cycling against wall
2. Standing hip abduction/Abduction	2. Hip adduction/abduction (Figure 2): Stand on right leg with knee fully extended. Keeping knee straight and ankle in dorsiflexion swing left leg from side to side as fast as possible using full range of motion. Left leg crosses over in front of right leg. Particular attention is paid to maintaining a neutral pelvic and spinal position.	Stretches, 30 seconds stretch for each side.
3. Seated bilateral knee flexion/extension.	3. Seated knee flexion/extension (Figure 5): Sitting on chair keeping back of legs fixed against seat, alternately flex and extend both knees as fast as possible using full range of motion.	1. Hip flexors (Iliopsoas)
4. Calf raises on edge of step (weeks 1-8 double leg, weeks 9-16 single leg)	4. Standing knee flexion/extension (Figure 4): Standing side on to wall and transfer weight on to leg furthest away from wall. Lift leg nearest wall straight up in front stopping just before any stretch sensation is felt in the posterior aspect of thigh. Keeping thigh still, flex and extend knee as fast as possible using full range of motion.	2. Gluteus maximus
5. Balance beam (EWAC, Netherlands) walking forwards and backwards (weeks 1-6 without arms, weeks 6-12 carry tray with ball on, 13-16 same eyes closed)	5. Kickback (reverse lunge) (Figure 6): Standing on edge of step board so that moving leg can be swung down next to it. Starting position is with supporting leg in full extend and other hip and knee is in flexion up near wall. Leg is explosively straightened down towards bottom of pool and then kicked backwards with leg straight as far as possible. During this movement supporting leg is flexed but plantar aspect of foot is kept firmly pressed against step.	3. Quadriceps
6. Standing abdominals (either pushing and pull frisbee, trunk rotation with frisbee or rowing with aquatic rolling pin), weeks 1-8 double leg stance, week 9-16 single leg).		4. Hamstrings
7. Abdominal with feet in frisbee against wall (figure of 8, circles 30 second each direction)		5. Iliotibial band
8. Hurdles (EWAC Netherlands), weeks 1-6 stepping over hurdles, weeks 6-12 double leg jumps forwards and backwards over 30 cm hurdle, 13-16 single leg jumps forwards over 30 cm high hurdle)		6. Adductors
9. Weeks 1-6 scissor jumps, weeks 6-12 jumping over 30 cm hurdle sideways, weeks, 13-16 single leg sideways jumping over 30 cm hurdle.		7. Gastrocnemius
10. Dynamic balance ½ of the group jog/run around other ½ of group who are trying to maintain balance.		

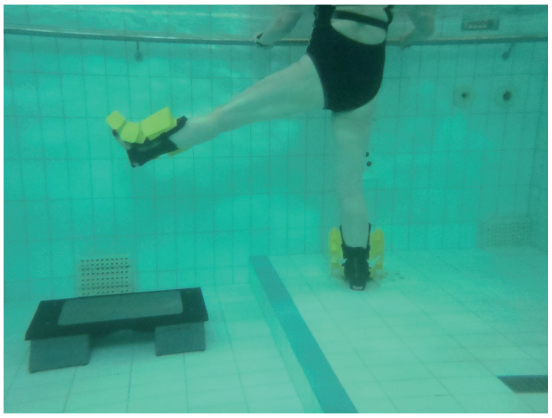

Figure 2 Hip abduction/adduction in standing.

Figure 4 Knee flexion/extension in standing.

every training session immediately after the main set before the cool down. All sessions will be supervised by 2 experienced physiotherapists, who had been trained to instruct these aquatic programmes and accredited for life-saving before the trial began.

The warm-up consists of 10 different movements to increase active ROM of all joints and enhance neuromuscular activation. Each movement will be completed for 1 minute (30 seconds per leg when alternating leg) with a 15 second rest period. Order of movements will be altered for each session randomly to maximise neuromuscular stimulation and prevent staleness as well as to maintain subjects' interest.

The strength training section consists of 5 exercises which have been thoroughly researched for both their effect on muscle activation [117,118] and effect on muscle strength and physical functioning [119-121]. Focus will be on performing each movement as fast as possible through full ROM. During all standing exercises emphasis will be made on maintaining the lumbar spine in a neutral position thus avoiding excessive loading on the spine and to encourage activation of trunk muscles during exercises. The progression of the exercise program will be ensured by using resistance boots of different sizes and by varying the duration of sets. Table 2 shows the different durations of each set and targeted amount of repetitions per set for each stage of the intervention. Each leg will be trained before resting e.g. 45 seconds left leg, 45 seconds right leg and 30 second rest.

Weeks 1–2 is an introductory period to allow subjects to become familiar with the movements with sets of 45 - seconds duration per leg per set with no resistance i.e. barefoot. Weeks 3–5 will consist of alternate trainings of 30 or 45 seconds with small fins (THERABAND PRODUCTS, The Hygienic Corporation, Akron, OH 44310 USA). Weeks 6–8 will be 3 week period with 45 seconds of work alternating sessions with small aquafins and large resistance boots (Hydro-Tone hydro-boots, Hydro-Tone Fitness Systems, Inc. Orange, CA 92865–2760, USA). Weeks 9–11 and 13–16 will consist of alternate trainings with

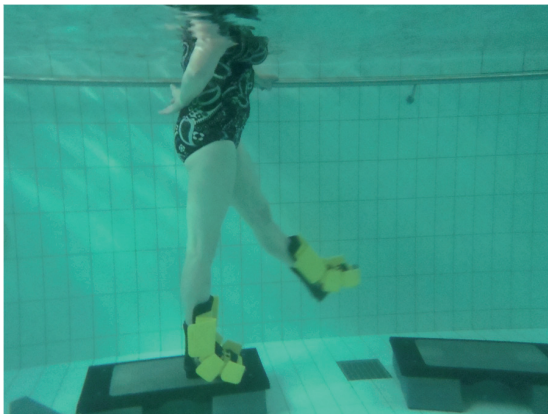

Figure 3 Hip flexion/extension in standing.

Figure 5 Knee flexion/extension in sitting.

Figure 6 Kickback (reverse lunge).

work of 30 and 45 seconds with large boots. Week 12 will consist of one session barefooted, one with small fins and one with large boots, work duration will be 45 seconds per set. The frontal area of aquafin resistance fins is 0.0181 m^2 and that of the large resistance boots 0.075 m^2. In a previous study the drag experienced during seated aquatic knee flexion/extension exercises in healthy women was triple with the large boots compared to the barefoot condition. Additionally, a significant increase in EMG activity was seen with the large boots compared to no boots [117,122].

Intensity of training of every session will be monitored using polar heart rate monitors (F6 or RCX5, Polar Oy, Finland) and perceived rate of exertion (BORG 6–20) [116]. Target training zone will be 60-80% of maximum heart rate according to the Karvonen formula e.g. 60% training limit = (220 − age) x 0.6 and 80% training limit = (220 − age) x 0.8.

Blood lactate levels will also be measured so as to obtain quantitative measures of training intensity and to ensure all training groups have trained at similar intensities. Samples will be taken during week 12, before training after 15 minutes of rest and 3 minutes after cessation of main strength training session. These will be recorded for each different intensity level of training (barefoot, small and large resistance boots, 45 seconds work per leg). Fingertip blood samples will be taken using safety lancet, normal 21 G with penetration depth 1.8 mm (Sarstedt AG & co, Germany) and collected into 20 μL capillary tubes which are placed in 1-mL hemolyzing solution. Care will be taken to clean skin to avoid contamination from chlorinated pool water. Samples will be analysed using an automatic system (EKF diagnostic, Biosen, Germany) after training.

Control group

The control group will be asked to maintain normal physical activity during the intervention period. They will be offered two sham contact sessions consisting of 1 hour of light stretching and relaxation during the 4 - month period.

Follow up period

After the post intervention measurements all participants will be advised to continue spontaneous physical activity, no other specific instruction will be given to the subject.

Ethical considerations

The study was given ethical consent on 30th November 2011 Dnro 19U/2011 from the Ethics Committee of the Central Finland Health Care District. Written informed consent will be obtained from all subjects before their participation in the study. All subjects included have the right to withdraw from the study whenever without needing to provide a reason for withdrawal. The study will be conducted according to good clinical and scientific guidelines and the declaration of Helsinki (2000).

Assessment of side effects

Adverse effects or health problems attributable to the testing protocol or interventions exercise protocol will be documented and reported. Following each individual measurement and training session self-reported knee pain will be assessed using a visual analogue scale (VAS 0-100 mm) along with any other physical symptoms such as pain elsewhere than knee, stiffness and general fatigue. All subjects will have medical insurance and have access to

Table 2 Intensity and progression of each program for phase's I-IV of aquatic exercises program

Weeks	Resistance type	Sets	Repetitions per set	Time (sec)	Recovery (sec)	Target PRE*	Total time (mins)	Total No. reps
1-2	Barefoot	3	25-30	45	30	14-15	30	750-900
3-5 (alternating)	Small	3	20-25	45	30	15-16	30	600-750
	Small	3	12 to 15	30	45	16-17	26	288-360
6-8 and 12	Small/Large	3	14-20	45	30	16-17	30	420-600
9-11 and 13–16 (alternating)	Large	3	14-20	45	30	16-18	30	420-600
	Large	3	12 to 15	30	45	16-18	26	288-360

*PRE = perceived rate of exertion (BORG 6–20).

the attending medical physician free of charge throughout the 4 month intervention and 12 month follow up period.

Statistical analysis

All analyses will be based on both intention-to-treat and dose related principles. Statistical analyses will be performed using statistical software (Stata, release 12.1, StataCorp, College Station, Texas and SPSS Version 19, IBM Corporation).

Discussion

This paper describes the rationale and design of a randomised control trial investigating the effect a progressive aquatic resistance training program will have on patellofemoral and tibiofemoral cartilage, properties of bone and body composition and physical function in post-menopausal women with mild knee osteoarthritis.

Exercise is one of the main non-pharmaceutical treatments recommended in the management of lower limb OA [24-26,28,29]. It is presumed that training in an aquatic environment has benefits for persons suffering from lower limb OA, however exact content and intensity of optimal training remain unclear [22]. For persons with knee and/or hip OA there is strong evidence to suggest aquatic exercise can cause a small but significant reduction in pain [30,33,34,36,38,123-127], improves self-assessed and measured function with a small to moderate effect size [33-36,38,123-125,127-130]. In addition, there is moderate evidence to show that aquatic exercise can cause a small but significant improvement in aerobic fitness [33,35,127,129,131]. Further there is limited data to suggest aquatic exercise can increase lower limb strength [33-39] and improve balance and decrease risk of falling [36,39,40]. Intensities of interventions in previously studies may not have been high enough to produce large changes in muscle strength and cardiovascular fitness but reporting of exercise programs used are in most cases incomplete. There are few studies investigating the effect of a progressive resistance program using specifically designed resistance equipment to manage symptoms associated with knee OA even though there is accumulating evidence to suggest it can be effective in improving neuromuscular function [117,118,120-122]. Also, there is some evidence to suggest water based exercise can either maintain [132] or slightly improve the properties of bone as measured with DXA [133]. However these are of low quality evidence and further research is required to validate the findings.

Both dGEMRIC [63,134] and T2 relaxation MRI [7,72,135] can distinguish between normal and OA cartilage. These techniques have been shown to be sensitive enough to demonstrate acute changes in human cartilage dGEMRIC [42,67] and T2-relaxation times [42,136]. These methods are therefore suitable for use in our study, and it is known that correct biomechanical loading of cartilage is important in maintaining cartilage health whereas obesity and trauma are risk factors for the development of OA [1]. Although there is evidence to show that biochemical characteristics of cartilage can be negatively affected with changes after periods of joint immobilization [137,138] and non-weight bearing [136]. No evidence exists to show the impact of an intensive non-impact exercise on cartilage.

As far as we know there have been no publications investigating the effect of aquatic exercise on cartilage and properties of bone in persons with knee OA. The aim of this study is to use repetitive aquatic resistance program with high intensity and repetition to discover what effects non-impact training has on knee cartilage, properties of bone and physical function. The information gained will help improve our understanding of the effects of exercise on the biochemical properties of cartilage and improve prescription of aquatic exercises in the management of OA.

Abbreviations

OA: Osteoarthritis; ROM: Range of Motion; pQCT: Peripheral quantitative computed tomography; DXA: Dual-energy X-ray absorption; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KOOS: Knees injury and Osteoarthritis Outcome Score; CV: Coefficient of Variation; VAS: Visual Analogue Scale; RPE: Rate of Perceived Exertion; MRI: Magnetic Resonance Imaging; dGEMRIC: Delayed Gadolinium-Enhance Magnetic Resonance Imaging of Cartilage; FOV: Field of View; TR: Repetition Time; TE: Echo Times; ETL: Echo Train Length; GAG: Glycosaminoglycan; BMD: Bone Mineral Density; BSI: Bone Strength Index; BMC: Bone Mineral Content; ToD: Total Density; TrD: Trabecular density; ToA: Total Area; TrA: Trabecular Area; aBMD: Areal Bone Mineral Density; BMC: Bone Mineral Content; AHA: Advance Hip structure Analysis; HAL: Hip Axis Length; CSA: Cross Sectional Area; CSMI: Cross Sectional Moment of Inertia (CSMI); FSI: Femoral neck Strength Index; BMI: Body Mass Index; CMJ: Counter Movement Jump; ECG: Echocardiogram.

Competing interests

All authors declare that they have no competing interests.

Authors' contributions

All authors were involved in the conception of the study plan and design as well as critically revising the draft manuscript for important intellectual content. All authors approved the final version to be published. BW, MM, JM and AHeinonen drafted the manuscript.

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IV

EFFECTS OF HIGH INTENSITY RESISTANCE AQUATIC TRAINING ON BODY COMPOSITION AND WALKING SPEED IN WOMEN WITH MILD KNEE OSTEOARTHRITIS: A 4-MONTH RANDOMISED CONTROLLED TRIAL WITH 12-MONTH FOLLOW-UP

by

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Effects of high intensity resistance aquatic training on body composition and walking speed in women with mild knee osteoarthritis: a 4-month RCT with 12-month follow-up

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Running title: Aquatic training reduces fat mass in knee OA

ABSTRACT

Objective: To investigate the effects of 4-months intensive aquatic resistance training on body composition in post-menopausal women with mild knee osteoarthritis. Additionally, the influence of leisure time physical activity (LTPA) was investigated.

Design: This randomised clinical trial assigned 87 volunteer postmenopausal women with mild knee OA into two study arms. The intervention group (n=43) participated in 48 supervised intensive aquatic resistance training sessions over 4-months while the control group (n=44) maintained normal physical activity. 84 participants continued into the 12-months' follow-up period. Body composition was measured with dual-energy X-ray absorptiometry. Additionally, walking speed over 2km and the knee injury and osteoarthritis outcome score (KOOS) were measured. Daily LTPA was recorded with self-reported questionnaires.

Results: After the 4-months intervention there was a significant decrease (p=0.002) in fat mass (mean change: -1.17kg; 95%CI: -2.00 to -0.43) and increase (p=0.002) in walking speed (0.052m/sec; 0.018 to 0.086) in favour of the intervention group. Improvement in body composition returned to baseline at 12-months' follow-up. In contrast, increased walking speed (p=0.032) was maintained (0.046m/sec; 0.006 to 0.086). No effect was seen in lean mass or KOOS. Overall LTPA had a small significant effect (p=0.007) on fat mass loss (f^2 =0.05) but no effect on walking speed.

Conclusions: Our findings show that a relatively short high intensity aquatic resistance training program decreases fat mass and improves walking speed in post-menopausal women with mild knee OA. Only improvements in walking speed were maintained at 12-months' follow-up. High levels of LTPA appeared important for controlling body composition.

Keywords: Osteoarthritis; Aquatic Exercise; body composition; walking speed

Trial registration number: ISRCTN6534659

INTRODUCTION

Knee osteoarthritis (OA) is a common cause of pain and activity limitations which create a significant burden on healthcare services[1]. While there is no known treatment that prevents or reverses OA, traditional management of OA has focused on reducing the symptoms, i.e. pain and joint stiffness and activity limitations, associated with the disease. Recently, focus has shifted from treatment of end-stage OA to preventing progression of the disease, especially in early knee OA[2]. Risk factors predicting worsening of symptoms and activity limitations include reduced functional capacity, being overweight or obese and decreased leisure time physical activity (LTPA)[3, 4]. Being over-weight or obese is associated with knee OA progression through sub-optimal biomechanical loading and low-grade systematic inflammation related to high body fat-mass as well as increasing risk of cardiovascular disease[2, 5]. There is an association between decreased physical activity and kinesiophobia in persons with knee OA[6], possibility facilitated by fear of additional knee pain[7]. This decrease in physical activity facilitates weight gain and decreased fitness, leading to further activity limitations[8].

Exercise, irrespective of modality, e.g. strength training and aerobic training, has been shown to evoke positive changes on symptoms and functional capacity as well as facilitating weight loss [9, 10]. Therefore exercise is strongly recommended in guidelines for the management of knee OA[1, 11], however, pain is a major modulator for activity avoidance in patients with OA and may limit compliance with land-based exercise interventions[7]. The aquatic environment, due to the effects of buoyancy, allows the individual to exercise with reduced weight bearing and impact on the affected joints[12]. Recent studies have shown that individuals with lower-limb OA experience significantly less pain during aquatic exercise compared to an increase in

pain experienced during land-based training of equivalent intensity[13, 14]. Our recent systematic reviews revealed that aquatic exercise evokes a small effect on physical functioning in people with lower limb OA[15] and a moderate to large effect on physical function in healthy older people[16]. The difference in effect size is thought, in part, to be due to the higher intensity of training implemented with the healthy older adults[17]. Further, lack of reporting of actual training intensities achieved in all the included aquatic exercise studies, limits interpretation of the results. In order to prevent knee OA progression, the exercise intervention aimed should be prescribed early in the disease progression[2]. To the authors knowledge only one previous study has investigated the effect evoked by aquatic exercise in the early stage of knee OA development[18]. Our study, a randomised controlled trial describing the efficacy of aquatic exercise on the tibiofemoral cartilage in postmenopausal women with mild knee OA, utilised a high intensity aquatic resistance training programme[18]. This previous report from our AQUAREHAB project indicated that 4-months of aquatic resistance training improved estimated cardiovascular fitness, had a high compliance and may have had an impact on tibiofemoral cartilage[18].

The aims of this study are to report the effect of 4-months intensive aquatic resistance training program on body composition, functional capacity and symptoms in postmenopausal women with mild knee OA. Additionally, to discover if possible changes are maintained after 12-months' follow-up. Further to report the training intensities achieved during the aquatic resistance training and impact of leisure time physical activity on the results.

MATERIALS AND METHODS

Study design

This study is reports primary and secondary outcome data collected from the registered AQUAREHAB research project (ISRCTN65346593), which is a randomised control trail consisting of a 4-month aquatic intervention with a 12-month follow-up period. Data was collected from January 2012 until April 2014. The full description of the protocol can be found from an open access manuscript[19], which was followed without changes and a full report of intervention recruitment can be found from our previous study[18]. This study has two experimental arms: 1) aquatic resistance training and 2) control. Included participants were women aged 60-68 years old with mild knee OA. In this study we classify mild knee OA as experiencing knee pain on most days, not exceeding 5/10 VAS, with radiographic changes in tibiofemoral joint grades I (possible osteophytes) or II (definite osteophytes, possible joint space narrowing) according to the Kellgren-Lawrence (K/L) classification[20]. Results for the quantitative magnetic resonance imaging (qMRI) have been previously reported[18], this study will report the results for body composition which was another primary outcome measure of the project[19]. This current study will also report secondary outcomes, i.e. walking speed and symptoms, for which only post intervention values for symptoms have been previously reported[18]. The study design and reporting follows the CONSORT[21] recommendations for the conducting and reporting of randomized controlled trials. The study protocol (Dnro 19U/2011) was approved by the Ethics Committee of the Central Finland Health Care District and conforms to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Subject recruitment

Participants were recruited from the county of Central Finland using newspaper advertisements and telephone recruitment methods. Eligibility criteria was female aged 60-68 years old, body mass index (BMI) <35, experiences knee pain almost daily, tibiofemoral joint K/L grade I or II and no medical reason preventing full participation in intensive exercise. Full eligibility criteria are described elsewhere[19].

Randomisation and blinding

The subjects were randomly allocated into either of the two arms of the study by an external statistician blinded for the study participants who was only provided with randomization number and severity of tibiofemoral OA according to X-ray classification. A computer-generated block randomization of size of ten, stratified according to K/L grading I and II, were used to ensure equal distribution of severity of OA within each group and equal group size. The first author performed the dual-energy X-ray absorptiometry imaging but analysis was performed using the manufactures' in-built software without modification. Further, physical therapists providing the intervention also performed the physical performance measures. Principal investigators were blinded to group allocation.

Interventions

Those participants in the intervention group participated in an aquatic resistance training sessions lasting 1 hour, 3 times a week for 16 weeks (48 sessions in total). Variable resistance equipment was used to progress training intensity with three resistance levels; barefoot, small

158 resistance fins (Theraband products, The Hygienic Corporation, Akron, OH 44310 USA) and
159 large resistance boots (Hydro-boots, Hydro-Tone Fitness Systems, Inc. Orange, CA 92865-
160 2760, USA). Training intensity was set at as "hard and fast as possible": A full description of
161 the training program, its progression and daily training program can be found elsewhere[18].
162 The control group maintained usual care and were asked to continue their usual leisure time
163 activities. They were offered the possibility of participating in two sessions consisting of 1
164 hour of light stretching, relaxation and social interaction during the 4-month intervention
165 period.
166
167 **Measures of exercise intensity and perceived exertion**
168
169 Maximum training intensity was ensured by measuring the maximum and average heart rates
170 using polar heart rate monitors (Polar Oy, Kemble. Finland), and rating of perceived exertion
171 (RPE, BORG 6-20) for every training session. Maximum heartrate was estimated using the
172 Karvonen formula (220–age=maxHR) with no adjustments made for the possible effects of
173 immersion. During the twelfth week, capillary blood lactates (methods described in full in
174 Appendix A) and repetitions for all three training situations for the main training set only, i.e.
175 excluding warm-up and cool-down, was measured. Self-reported emotional state felt during
176 training was measured with a 1-5 Likert scale (1-Poor, 2-Tolerable, 3-Satisfactory, 4-Good,
177 5-Excellent).
178
179 **Outcome measures**
180
181 Primary outcome, body composition (total body fat and lean body mass (kg)), was measured
182 with dual-energy X-ray absorptiometry (DXA, Lunar Prodigy; GE Lunar Healthcare,

Madison, WI, USA). Images were analysed as per manufacturers' protocols using enCORE software (enCORE 2011, version 13.60.033). In vivo precision of these measurements has been reported to be high (CV 1.3-2.2%)[22]. Additionally, walking speed in metres per second (m/sec) was calculated from the UKK 2km walking test, i.e. 2000/time taken to complete test, in seconds. This test requires the subject to walk 2km around a 200m flat track as quickly as possible without running[23]. This measurement describes walking ability and a surrogate for aerobic fitness. The calculation for the previously reported estimated cardiovascular fitness[18] can over-estimate improvements in presence of significant changes in BMI[24]. Additionally, self-report pain, symptoms (Sym), activities of daily living (ADL), sports and recreation (Sport&Rec) and quality of life (QoL) were measured using be the five domains of the Finnish version of the Knee Injury and Osteoarthritis Outcome Score (KOOS)[25]. For each domain, a score of 0 indicates extreme knee problems and 100 no knee problems[26].

Total daily physical activity

Daily leisure time physical activity (LTPA) for each participant was calculated for the whole 4-month intervention and 12-month follow-up period. LTPA was recorded using a leisure time physical activity diary, from which metabolic equivalent task hours (MET/h) per month was calculated[27]. The LTPA for the intervention group was calculated by combining the MET/h calculated from the aquatic resistance training and the physical activity diary.

Statistical Methods

Baseline results are displayed as mean and standard deviation (SD) unless otherwise stated and within group changes are reported as mean change and 95% confidence intervals (95%

CI). For the baseline demographics between group comparisons was performed using a bootstrap type t-test and Chi-squared. Repeated measures for walking speed, body composition and all domains of the KOOS were analysed using generalised linear mixed-models with unstructured correlation structure. Fixed effects were group, time and group-time interaction. Standardised beta coefficient (Beta (β)), adjusted for baseline values, was calculated for effect size post intervention and at 12-month follow-up. Cohen's standard for Beta values above 0.10, 0.30 and 0.50 represent small, moderate and large effects respectively[28]. Effect size for effects of total daily physical activity on the primary outcome measures, were calculated using Cohen's f^2, where 0.02, 0.15 and 0.35 indicate a small, moderate and large effect respectively[29]. Repeated ANOVA was used to compare the differences between the three training intensities (barefoot, small fins and large boots). Statistical analyses were performed using statistical software (Stata, release 13.1, StataCorp, College Station, Texas).

The target sample size (n=70, 35 per research arm) for this study was calculated based on the expected change in the magnetic resonance imaging outcomes for the AQUAREHAB project[18].

RESULTS

In total, 87 participants fulfilled the eligibility criteria and after attending baseline measurement were randomised into the two study arms. There were no significant differences between the groups in any descriptive variables at baseline (Table 1). 84 participants completed the intervention and agreed to participate in the 12-month follow-up. In total 76 participants attended 12-month follow-up measurement. The attendance for the control group sessions was 68%. Participant recruitment and reasons for loss to follow-up are shown in Figure 1.

Table 1 Baseline demographic and clinical characteristics

	Exercise group (n=43)	Control group (n=44)
Age (years)	63.8 (2.4)	63.9 (2.4)
Height (cm)	161.7 (5)	161.6 (5)
Body mass (kg)	69.6 (10.3)	71.0 (11.2)
Body mass index (kg/m^2)	26.6 (3.8)	27.1 (3.5)
Affected knee (right/left)	36/7	34/10
K/L grade, n (%)		
Grade 1	23 (53.5)	24 (54.5)
Grade 2	20 (46.5)	20 (45.5)
Analgesia (knee), n (%)	11 (47)	9 (48)
LTPA (METh/week)	29 (31)	36 (33)
Smoker		
Never	17	13
Current	3	3
Previous	23	28
Blood pressure, n(%)		
Normal	23	14
Elevated	9	11
Medical management	11	19

Values are means (SD) unless otherwise noted.
LTPA = leisure time physical activity, METh = metabolic equivalent task hour.

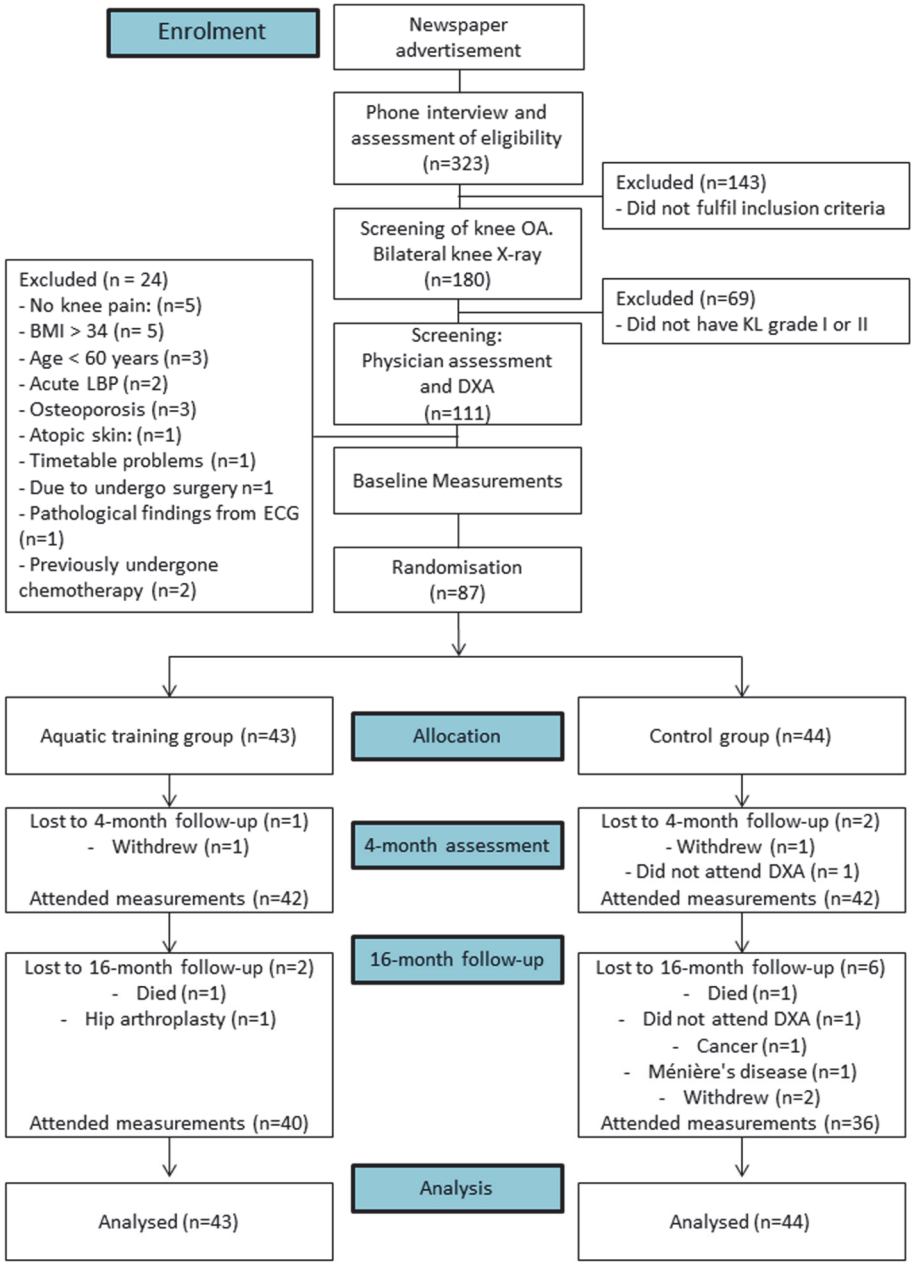

Figure 1 Flow chart showing participant recruitment, randomisation and retention

Training intensities achieved during aquatic resistance training

Adherence to the aquatic training program was high (88%), with only three subjects attending less than 70%. Training intensity recorded from each complete training session is shown in Table 2. There was a gradual increase in RPE when progressing from bare to large resistance

boots while no significant changes in heart rates were measured. Pain during aquatic resistance training in the affected knee was reported more frequently during the first month (37 times), followed by a gradual decrease in frequency as the training progressed, with a three-fold reduction in the frequency (12 times) by the fourth month. On average pain experienced in affected knee, measured with VAS pain scale 0 to 100, during the intervention was very mild mean 14 (SD 16). A full description of the daily training intensities measured and pain experienced during training can be found from the supplemental material Appendix A.

Table 2 Description of measured training intensities and psychological feelings experienced per progression

	Barefoot	Small Fins	Large boots
No. Sessions	8	14	26
RPE*	13.7 (1.0)	14.9 (1.3)	15.0 (1.5)†
Average HR (%)	61 (5.9)	61 (5.3)	61 (6.3)
Max HR (%)	85 (7.8)	84 (8.9)	84 (8.0)
Blood lactates (mmol/L)ǂ	4.9 (2.1)	4.5 (1.9)	4.0 (1.8)
Repetitions per session	481 (66)	408 (71)	376 (65)†
Self-reported emotional state	4.2 (0.33)	4.2 (0.36)	4.3 (0.40)

Mean and (SD) unless otherwise stated. *RPE = Rating of perceived exertion (BORG 6-20)
ǂ Measured directly after sessions 35-37,†Bare vs Large ($p<0.001$)

Treatment effects and maintenance at 12-months

Summaries of the treatment effects after 4-months and their maintenance at 12-months follow-up, as mean difference are presented in Figure 2 and Table 3. After 4-months aquatic resistance training there was a significant ($p=0.002$) and moderate decrease in fat mass (β: 0.32; 95% CI: 0.14 to 0.51) and over-all body weight ($p=0.004$) in favour of the intervention group (β: 0.34; 0.15 to 0.52). In deeper analysis, there was a significant ($p=0.000$) decrease in

fat mass in both legs -0.47kg (-0.74 to -0.20) or a loss of 4.5% fat mass in the training group compared to 1.1% increase in the control group and the trunk (p=0.007) -0.63kg (-1.1 to -0.17,) or a loss of -3.1% compared to an increase 1.0% in the control group. Both significant findings were lost a 12-months follow-up. No localised change in lean mass was seen at any time point.

After the intervention, a significant (p = 0.002) increase in walking speed was observed in favour of the intervention group (β: 0.3; 0.12 to 0.50). At 12-month follow-up walking speed in the intervention group remained significantly (p=0.032) faster compared to the control group (β: 0.2; 0.01 to 0.44). No other significant between group differences could be seen in any domain of the KOOS questionniare.

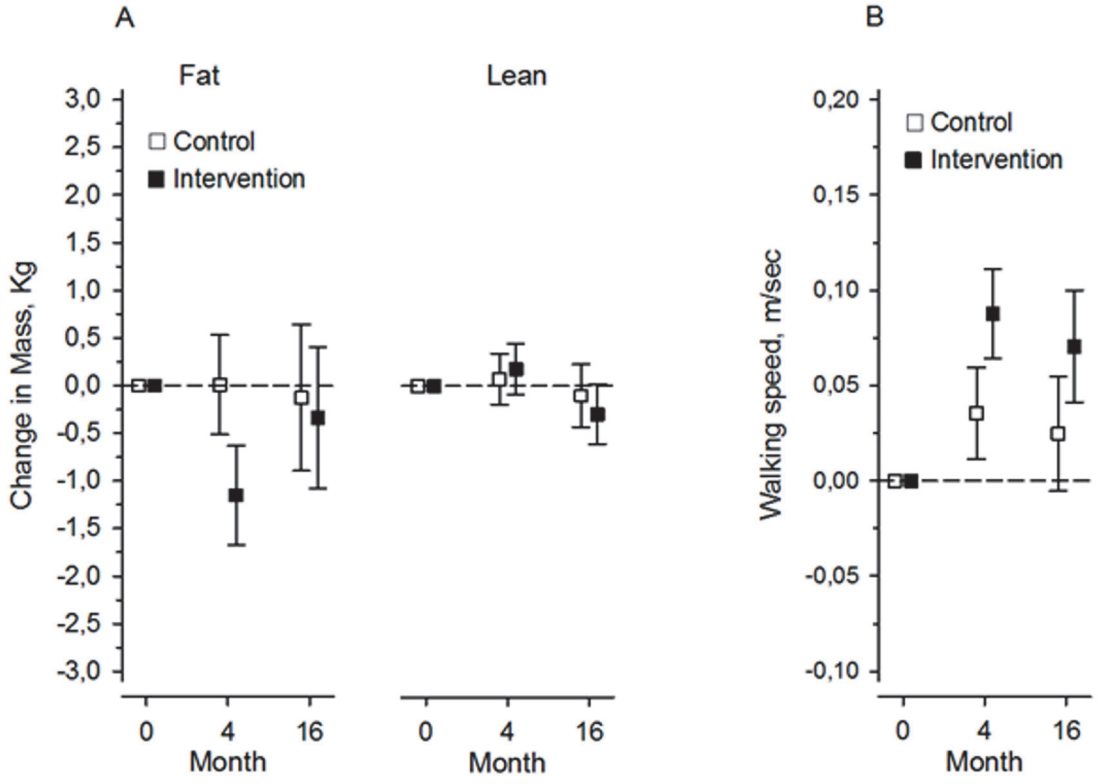

Figure 2 Changes in A) fat and lean mass (kg) and B) walking speed (m/sec) following a 4-months aquatic resistance training and 12-month follow-up period.

Table 3 Effect of aquatic resistance training on walking speed, body composition and clinical symptoms.

Variable	n	Aquatic training group		Control group		Mean Difference (95% CI)	p-value *	n	AT	Control	Mean Difference (95% CI)	p-value **
		BL mean (SD)	FU mean (SD)	BL mean (SD)	FU mean (SD)				12-FU mean (SD)	12-FU mean (SD)		
Walking time (sec)	87	1.74 (0.15)	1.83 (0.16)	1.73 (0.17)	1.76 (0.17)	0.052 (0.018 to 0.086)	0.002	73	1.82 (0.14)	1.77 (0.13)	0.046 (0.006 to 0.90)	0.032
Body Composition												
Body Mass (Kg)	87	69.2 (10.3)	68.2 (10.4)	70.8 (11.2)	70.9 (11.3)	-1.11 (-1.85 to -0.42)	0.004	76	68.6 (10.6)	70.8 (11.5)	-0.39 (-1.51 to 0.64)	0.543
BMI	87	26.6 (3.8)	26.2 (3.9)	(27.1 (3.5)	27.1 (3.6)	-0.46 (-0.74 to -0.19)	0.001	76	26.4 (4.0)	26.9 (3.7)	0.001 (-0.47 to 0.47)	0.892
Lean Mass (kg)	87	40.3 (3.9)	40.6 (3.9)	41.4 (4.4)	41.7 (4.4)	0.083 (-0.29 to 0.45)	0.590	76	40.1 (4.0)	41.9 (4.2)	-0.30 (-0.79 to 0.12)	0.410
Fat Mass (Kg)	87	26.0 (8.6)	24.8 (8.8)	26.5 (8.0)	26.4 (8.1)	-1.17 (-2.00 to -0.43)	0.002	76	25.7 (8.8)	26.1 (8.5)	-0.14 (-1.24 to 0.90)	0.700
KOOS (0-100)												
Pain	87	80. 6 (10.4)	84.3 (10.5)	82.1 (11.8)	83.3 (11.7)	2.3 (-1.93 to 6.31)	0.184	76	86.8 (10.5)	85.1 (12.4)	1.45 (-2.72 to 5.66)	0.187
Symptoms	87	74.4 (12.9)	80.9 (12.1)	74.8 (14.1)	77.5 (14.9)	4.07 (-0.43 to 8.54)	0.091	76	81.4 (11.4)	77.9 (14.5)	3.31 (-1.19 to 7.30)	0.119
ADL	87	84.5 (10.4)	87.7 (9.7)	85.2 (11.0)	86.0 (14.6)	3.36 (-0.38 to 7.118)	0.105	74	89.2 (11.2)	88.3 (11.0)	0.97 (-2.64 to 4.32)	0.397
Sport&Rec	87	63.6 (20.5)	70.6 (21.7)	64.8 (22.2)	67.6 (26.5)	4.81 (-3.00 to 12.61)	0.223	76	71.0 (20.7)	68.7 (24.6)	2.45 (-4.76 to 8.96)	0.396
QoL	87	66.0 (17.5)	72.6 (18.1)	70.6 (20.1)	74.1 (23.1)	2.76 (-3.51 to 8.66)	0.248	75	75.0 (18.2)	76.4 (24.4)	1.21 (-5.97 to 7.98)	0.308

BL = baseline, FU = post-intervention (4-months), 12-FU = 12-months follow-up, *post-intervention follow-up compared to baseline, **12-month follow-up compared to baseline

Effects of physical activity

There was a significant ($p<0.001$) between group difference in average monthly LTPA during the intervention period 160(53) versus 104(63) MET/h for intervention and control groups respectively. This difference was immediately lost following cessation of the aquatic training (Figure 3). There was a significant time interaction between increase in physical LTPA (MET/h) and decrease in fat mass ($p = 0.007$) with a small sized effect (Cohen's $f^2 = 0.05$), while, there was no effect ($p=0.52$) on lean mass ($f^2=0.002$) and a small but non-significant ($p=0.25$) effect on walking speed ($f^2=0.02$). While walking was the most popular form of LTPA (40.1%) there was no difference seen in exercise type or intensities between the control and intervention group.

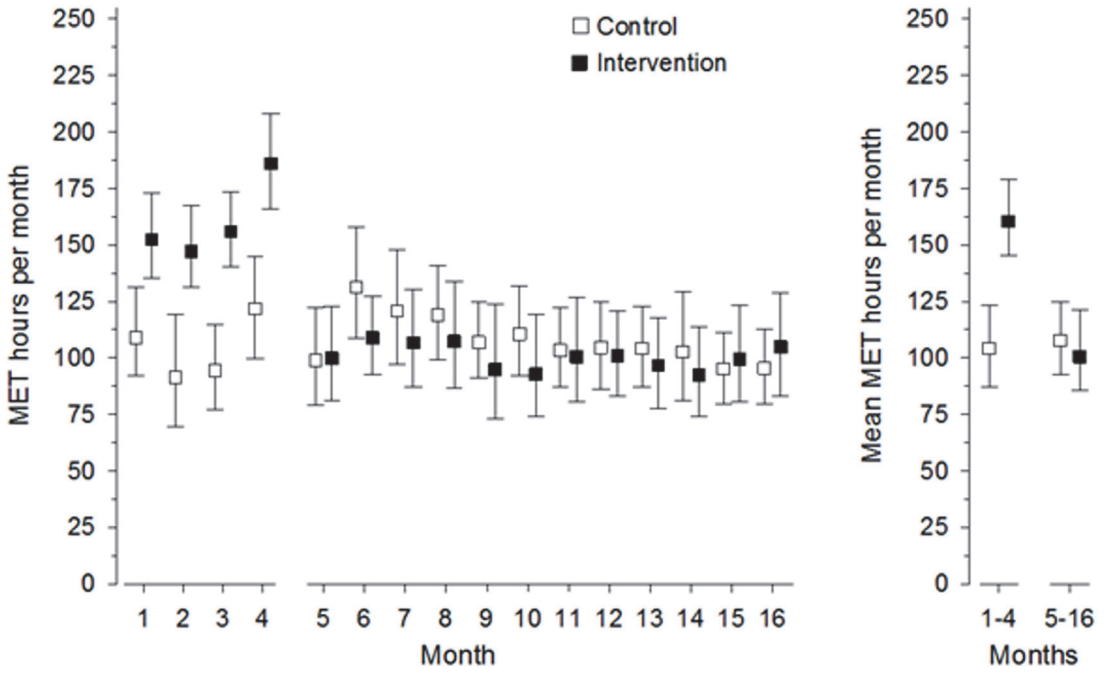

Figure 3 Monthly leisure time physical activity (METh)

Harms

As previously reported[18], one subject stopped the intervention following pain experienced after the first use of the large resistance boot (session 16). Although symptoms were short lasting (2 days) the subject chose not to continue the intervention but participated in all the follow-up measurements. One subject complained of dyspnoea; following physician assessment, the cause of the symptoms during training were related to breathing patterns adopted. After education training the participant was able to complete the intervention and attend follow-up measurements. The results of both participants are included as per intention-to-treat analysis.

DISCUSSION

Our study indicates that an intensive aquatic resistance training program is effective at decreasing fat mass as well as improving walking speed in post-menopausal women with mild knee OA. This is the first randomised controlled study investigating the effects of aquatic resistance training on people with mild knee OA with a 12-month follow-up. While, our results show that the improvements in body composition are lost at 12-month follow-up, the improvements in walking speed were maintained. Importantly, changes in fat mass over the 16-month study period were significantly associated with overall total daily leisure-time physical activity. Further, this the first study to report the actual training intensities achieved by the subjects during an aquatic exercise intervention and the effect of LTPA during the intervention and follow-up period.

Increased fat mass is linked to knee OA through biomechanical[30] and low-grade inflammatory mechanisms[8] and is associated with an increased risk of suffering from knee OA as well as a more rapid progression of the disease[31, 32]. Our findings indicate a superior improvement in body composition compared with the two previous studies investigating the effects of aquatic exercise on body and fat mass in persons with OA[17, 33]. The -1.17kg decrease in fat mass evoked in our study is larger than the non-significant decrease in fat mass -(0.7kg) reported by Lim et al.[17], however, the duration of this program was three times a week for 8 weeks of aquatic exercise. Kim et al.[33] found a significant reduction in body mass (-0.76kg) following a twelve week (three times a week) aquatic exercise program compared to a -1.1kg decrease in body mass evoked in our study. One additional significant difference between these studies, other than duration, was the training intensities utilised in these two studies. Lim et al.[17] had an intensity set at 65% Max HR, while Kim et al.[33] with a

training intensity was set at RPE 12-13 (Borg 6-20), both equivalent to "somewhat hard" or approximately 60% Max HR[34]. During the interval training, average maximum heartrates were close to 85% with measured maximum HR up to 105%. Based on our finding we can demonstrate that water facilitates high intensity exercise which is well tolerated and appears to have similar effects as land-based exercise programs on body mass and fat mass. Messier et al.[10], for example, reported that an 18 month, 3 times a week land-based exercise-only program produced a slightly larger loss in total body weight (1.8kg) compared to our study. However, in their study the decrease in fat mass was only 1% (-0.4 kg) and loss of lean mass was -2.6kg in the exercise-only group. A loss of lean-mass is a common negative side effect of weight loss in this population[10, 35]. Previous literature has shown that decreased quadriceps muscle strength is associated with the development and faster progression of knee OA[36, 37], and muscle strength is associated with muscle mass in people with knee OA[38, 39], therefore preserving muscle mass during periods of weight loss is vital in this population. Our study showed no change in lean mass and muscle strength[18], indicating that it was intensive enough to cause significant decreases in fat mass it was also sufficient to maintain strength and lean mass.

Improvements in walking speed after 4-months aquatic resistance training, and its maintenance after a 12-month follow-up period, are in contrast to the results for body composition. Given the relatively small loss of body mass, our findings suggest that the effect on walking speed may have been caused by mechanisms other than weight loss. The results could indicate an improvement in cardiovascular fitness as previously reported[18], however, this was only estimated and open to error while the walking speed is a direct measure. While there were no improvements in muscle strength of the knee extensors and flexors, (previously reported[18]), we cannot rule out improvements in the un-measured ankle plantar flexors or hip

abductors which could improve gait biomechanics and efficiency[40]. Further, strength alone is not a marker of improved gait biomechanics and efficient gait requires co-ordination between agonist and antagonist muscles[41-43]. Immersion results in a decrease in nociceptor stimulation and afferent feedback[44, 45], and reduces the sensation of pain[13, 14, 46, 47]. These conditions may create a suitable training condition for improving gait biomechanics, which has been reported after on 3 sessions of underwater treadmill walking[14]. Alternatively, the intervention was of a high intensity and the subjects experienced, many for the first time, the sensation of high physical exertion. This could have taught the participants that it was safe for them to exert themselves at a higher intensity than previously thought. It is feasible to speculate that this exercise pedagogy was retained 12-months after intervention cessation. Thus, not only explaining the maintenance of walking speed but also indicates an added benefit of high over low intensity aquatic resistance training in this population.

Education on life-style changes has been suggested as a vital part of management of both early and late-stage OA, in order to sustain improved levels of physical activity following an intervention study[48]. Participants in the training did not have higher leisure time physical activity after the intervention than the control group therefore it is plausible to conclude that they returned back to pre-intervention level. Therefore, the increased walking speed may only describe improved functional capacity and may not be associated with increased walking speeds utilised in daily life. In combination with the possible exercise pedagogical effect of the high intensity exercise and implementation of a life-style education program, including dietary and advice, may have maintained or even continued the improvements body composition and walking speed. Importantly, our results showed that increasing LTPA had a positive effect on body composition irrespective of group allocation. However, while, LTPA did no change following the intervention, it was measured using self-reported questionnaires

386 and it is plausible to hypothesise that after the intervention the participants in the training
387 group perceived they functioned at lower levels than before the intervention. In our study, no
388 acute worsening of clinical findings, as measured with the KOOS, was seen at either time
389 point possibility a result of the lack of impairment at baseline, the fluctuating nature of OA
390 symptoms and the relatively short follow-up period[2].
391
392 The strengths of this study included the randomised control design. The high adherence to the
393 intervention and small number of drop-outs optimised the treatment response and shows
394 motivation to participate in such an aquatic resistance exercise intervention. This is the first
395 study to monitor leisure time physical activity, during an aquatic exercise intervention in
396 participants with knee OA[15] controlling an important confounding factor. The main limitation
397 of this study was the use of strict inclusion criteria which resulted in a homogeneous sample
398 limiting direct application of our results to other populations including men and persons with
399 more severe knee OA. However, it is conceivable to assume that adapted, this program would
400 be suitable for subjects with more severe knee OA. Further studies are needed to confirm its
401 efficacy in subjects with hip OA. The use of un-equal interventions i.e. only 2 sessions in the
402 control group, introduces bias in favour of the intervention. Therefore, these results only
403 indicate that aquatic resistance training is effective compared to no intervention and not more
404 effective than another intervention. The lack of assessor blinding to the intervention may
405 have resulted in bias however, assessors had no vested interest in the results of this study and
406 primary investigator was blinded throughout. Dietary intake was not measured or controlled
407 for, therefore we cannot directly attribute all the changes as a pure effect of the intervention
408 however diet alone would not have accounted for the maintenance of lean body mass[35].
409 Further, greater increases in lean mass and decrease in fat mass may have occurred with
410 appropriate diet[49]. It is not known if the mechanisms improving walking ability occurred

earlier during the intervention therefore, future studies could look at the effectiveness of a shorter intensive aquatic exercise intervention.

Conclusion

To conclude, our findings show that a 4-month intensive aquatic resistance training program can decrease fat mass and improve walking speed in post-menopausal women with mild knee OA. After 12-months' follow-up fat mass had returned to baseline, however, irrespective of group allocation, the highest levels leisure time physical activity had a positive effect one fat mass. In contrast the improvements in walking speed were maintained at 12-months follow-up, irrespective of levels of leisure time physical activity, however exact mechanisms remain unclear. Therefore, future research should investigate if lifestyle education following an intensive aquatic resistance training intervention optimises long term benefits on body composition. Additionally, to discover through which mechanism aquatic resistance training improves walking speed e.g. improved gait efficiency.

Author contributions

Waller, Benjamin: Analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding, collection and assembly of data.

Munukka, Matti: Analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding, collection and assembly of data.

Rantalainen, Timo: Analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support, collection and assembly of data.

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Nieminen, Miika : Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support.

Kiviranta, Ilkka: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Kautiainen, Hannu: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, statistical expertise, collection and assembly of data.

Häkkinen, Arja: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

Kujala, Urho: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

Heinonen, Ari: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding.

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Conflict of interest

There is no conflict of interest for any authors.

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614

SUPPLEMENTAL MATERIAL

These appendixes have been provided by the authors to give readers additional supporting information about their work.

Supplement to:, Benjamin Waller, Matti Munukka, Timo Rantalainen, Miika T. Nieminen, Eveliina Lammentausta, Ilkka Kiviranta, Arja Häkkinen Urho M. Kujala, Hannu Kautiainen, Ari Heinonen. *"High intensity aquatic exercise or daily physical activity for maintaining fat mass and walking ability for women with knee osteoarthritis?"*

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Appendix A: Daily training intensities and frequency of pain experienced during daily training

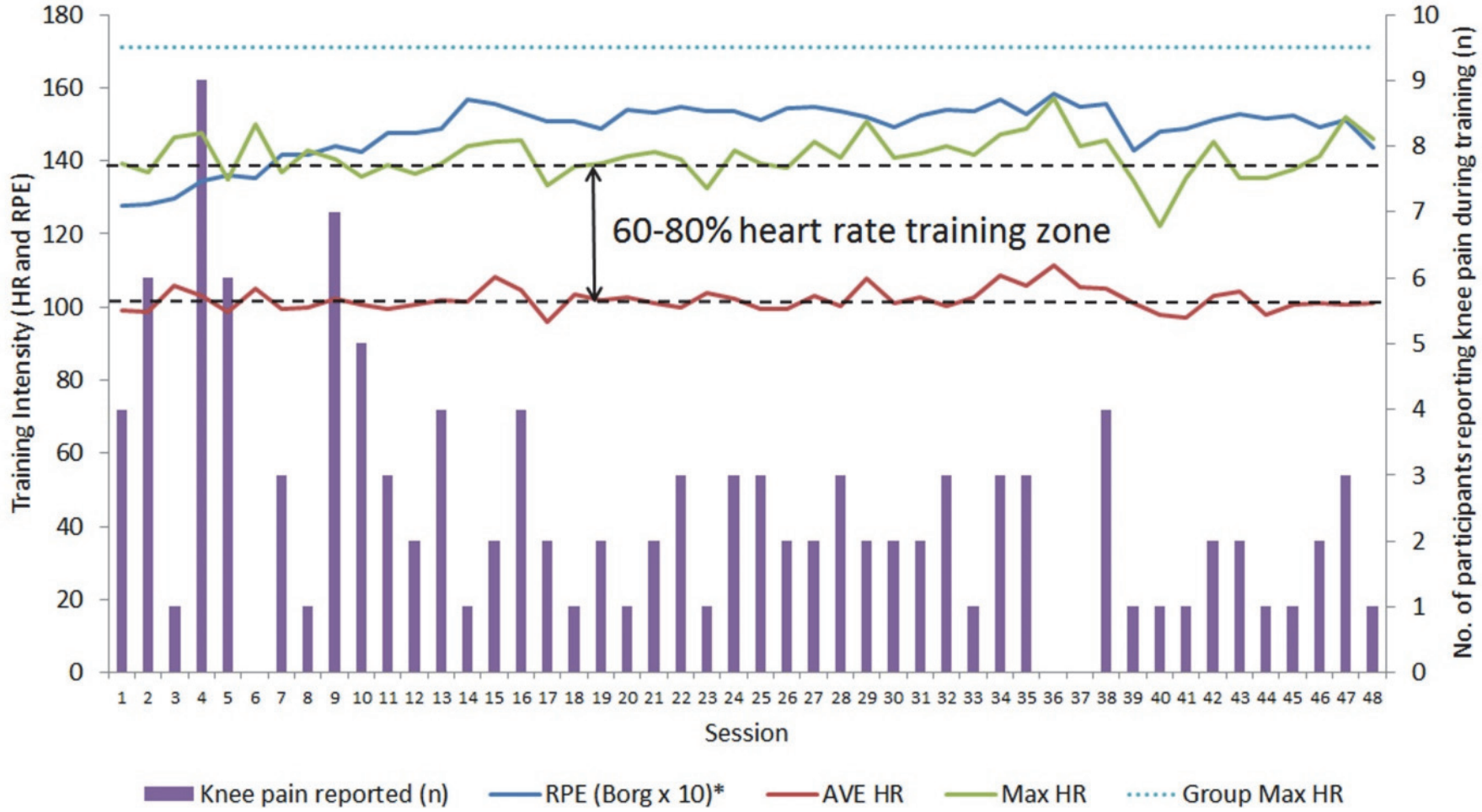

Figure 4 Description of average training intensities and frequency of pain in affected knee during each training session for all (HR = heart rate, * RPE = Rating of perceived exertion multiplied by ten to estimate heart rate, AVE = Average, Max = Maximum)

Physiological differences between resistance progressions

In total 34 subjects attended all three specific testing sessions (session 34-36) were measurements were taken from the 30 minutes of lower limb exercises only. Heartrates, rating of perceived exertion and psychological VIRE were measured in a similar way as reported in the manuscript. Additionally, blood lactate levels were measured so as to obtain quantitative measures of training intensity and to ensure all training groups have trained at similar intensities. Samples were taken during week 12, before training after 15 minutes of rest and 3 minutes after cessation of main strength training session. These were recorded for each different intensity level of training (barefoot, small and large resistance boots, 45 seconds work per leg). Fingertip blood samples were taken using safety lancet, normal 21G with penetration depth 1.8mm (Sarstedt AG & co, Germany) and collected into 20 µL capillary tubes which are placed in 1-mL hemolyzing solution. Care will be taken to clean skin to avoid contamination from chlorinated pool water. Samples will be analysed using an automatic system (EKF diagnostic, Biosen, Germany) after training.
Results are shown in table 3.

Training Session No.	34	35	36	P-Value**
Training resistance	Barefoot	Small Fins	Large Fins	
RPE*	16.0 (1.9)	16.2 (1.6)	15.8 (1.8)	0.551
Average HR (bpm)	106 (15)	106 (14)	110 (12)*	0.276
Average HR (%)	68 (10)	68 (9)	71 (8)*	0.276
Max HR (bpm)	147 (23)	151 (28)	163 (30)*	0.101
Max HR (%)	94 (15)	97 (19)	105 (19)*	0.102
Blood Lactates (mmol/L)	4.9 (2.1)	4.5 (1.9)	4.0 (1.8)*	
Knee Pain (Freq)	0	1	2	
Knee Pain severity (VAS 0-100mm)	0			
VIRE				

**repeated ANOVA *barefoot and large boots being statistically significant ($p < 0.05$)

V

EFFICACY OF PROGRESSIVE AQUATIC RESISTANCE TRAINING FOR TIBIOFEMORAL CARTILAGE IN POSTMENOPAUSAL WOMEN WITH MILD KNEE OSTEOARTHITIS: A RANDOMISED CONTROLLED TRIAL

by

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* Equal contribution

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Efficacy of progressive aquatic resistance training for tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis: a randomised controlled trial

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SUMMARY

Objective: To study the efficacy of aquatic resistance training on biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis (OA).
Design: Eighty seven volunteer postmenopausal women, aged 60–68 years, with mild knee OA (Kellgren–Lawrence grades I/II and knee pain) were recruited and randomly assigned to an intervention ($n = 43$) and control ($n = 44$) group. The intervention group participated in 48 supervised aquatic resistance training sessions over 16 weeks while the control group maintained usual level of physical activity. The biochemical composition of the medial and lateral tibiofemoral cartilage was estimated using single-slice transverse relaxation time (T2) mapping and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC index). Secondary outcomes were cardiorespiratory fitness, isometric knee extension and flexion force and knee injury and OA outcome (KOOS) questionnaire.
Results: After 4-months aquatic training, there was a significant decrease in both T2 −1.2 ms (95% confidence interval (CI): −2.3 to −0.1, $P = 0.021$) and dGEMRIC index −23 ms (−43 to −3, $P = 0.016$) in the training group compared to controls in the full thickness posterior region of interest (ROI) of the medial femoral cartilage. Cardiorespiratory fitness significantly improved in the intervention group by 9.8% ($P = 0.010$).

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Conclusions: Our results suggest that, in postmenopausal women with mild knee OA, the integrity of the collagen-interstitial water environment (T2) of the tibiofemoral cartilage may be responsive to low shear and compressive forces during aquatic resistance training. More research is required to understand the exact nature of acute responses in dGEMRIC index to this type of loading. Further, aquatic resistance training improves cardiorespiratory fitness.
Trial registration number: ISRCTN65346593.

Introduction

Knee osteoarthritis (OA) is a common cause of pain and limitations in physical function globally and represents a significant burden on healthcare costs[1]. The development of knee OA progresses slowly over years[2]. In the early phase of OA development, changes are seen in the biochemical composition of the cellular matrix of the cartilage. These include a decrease in glycosaminoglycan (GAG) content, responsible for hydrophilic properties of the collagen matrix, and loss of integrity of the collagen matrix, responsible for restraining hydrostatic pressure and maintaining cartilage stiffness[3]. As cartilage degeneration progresses its biomechanical properties are altered, reducing its ability to resist and distribute tensile, shear and compressive forces, causing further degradation and joint failure[4].

There is no known cure or treatment that prevents or reverses the biochemical changes in the cartilage, therefore, the current management of OA focuses on reducing the symptoms and decreased function associated with the disease[1]. Exercise, irrespective of modality (land or water) or type (strength or aerobic), has been shown to be effective in achieving these aims[5,6]. Moreover, an active life style with participation in exercise has been shown to be beneficial for maintenance of the biochemical properties of cartilage in both animals[7,8] and humans[9,10]. Further, exercise has been shown to reverse cartilage atrophy seen in disuse and immobilisation studies[11,12] and slow down progression of OA in animals[13]. Therefore, exercise could be an effective intervention for the maintenance of cartilage health. However, studies investigating the effect of exercise interventions on healthy and degenerated human cartilage are sparse[14–17]. Only two previous studies have investigated the effects of land based exercise on the biochemical composition of cartilage in postmenopausal women with mild knee OA, i.e., Kellgren–Lawrence grades I/II and knee pain[15,16]. We found an improvement in the collagen matrix in the patella cartilage of women with mild knee OA following a 1-year, three times a week, high-impact exercise intervention[15] while we did not see any worsening or improvement in the collagen matrix or GAG concentration of the tibiofemoral cartilage in the same study[16]. Therefore, there is sufficient evidence to show cartilage health is maintained by appropriate mechanical stimulus and environment[9,18].

Pain is a major modulator for activity avoidance in people with knee OA[19]. Water is a facilitating environment in which persons with lower limb OA can safely and comfortably exercise at high intensities utilising full joint range of motions[20]. Our recent systematic review showed that aquatic exercise has a similar effect on pain and self-reported functioning compared to land-based training[6]. Moreover, in our previous studies Pöyhönen *et al.*[21] and Valtonen *et al.*[22] both showed significant benefits of a progressive aquatic resistance training program for physical functioning in healthy women and following knee arthroplasty, respectively. Regular cyclic movements performed during aquatic exercise may provide sufficient mechanical stimulus and facilitate improved exchange of nutrients thus increasing chondrocyte activity[4,18]. Therefore, the aim of this study was to investigate if progressive, intensive and high volume aquatic resistance training affects the biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee OA.

Materials and methods

Study design

This study was a 4-month registered randomised controlled trial (ISRCTN65346593) with two experimental arms: (1) aquatic resistance training and (2) control. Recruitment and data collection took place between January 2012 and May 2013 and followed the published protocol without changes[23]. Included participants were women aged 60–68 years with mild knee OA. In this study we classify mild knee OA as radiographic changes in tibiofemoral joint grades I (possible osteophytes) or II (definite osteophytes, possible joint space narrowing) according to the Kellgren–Lawrence (K/L) classification and experiencing knee pain on most days[24]. The study protocol (Dnro 19U/2011) was approved by the Ethics Committee of the Central Finland Health Care District and conforms to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Subject recruitment

A multistage recruitment process was implemented (Fig. 1). Initially, postmenopausal women from the Jyväskylä region in Central Finland were voluntarily recruited through advertisements in local newspapers. Preliminary eligibility was assessed using a structured telephone interview ($n = 323$), followed by evaluation of OA severity in the tibiofemoral joint with radiographs ($n = 180$) and finally through medical screening ($n = 111$). Inclusion criteria were: postmenopausal woman aged 60–68 years, experiencing knee pain on most days, participates in intensive exercise ≤twice a week, radiographic changes in tibiofemoral joint K/L I or II, no previous cancer or chemotherapy, no medical contraindications or other limitations to full participation in an intensive aquatic training program and complete transverse relaxation time (T2) data. Exclusion criteria included a T-score <−2.5 (indicating osteoporosis)[25] measured from the femoral neck using dual-energy X-ray absorptiometry (DXA), resting knee pain visual analogue scale (VAS) >50/100, surgery of the knee due to trauma or knee instability, meniscectomy within the last 12 months, inflammatory joint disease, intra-articular steroid injections in the knee during the previous 12 months, contraindications to MRI and allergies to contrast agents or renal insufficiency. Due to confounding factors related to obesity, a body mass index (BMI) of >34 kg/m^2 was an exclusion criterion.

Randomisation and blinding

After baseline measurements, all participants were randomly allocated with a three digit identification number (ID) to blind

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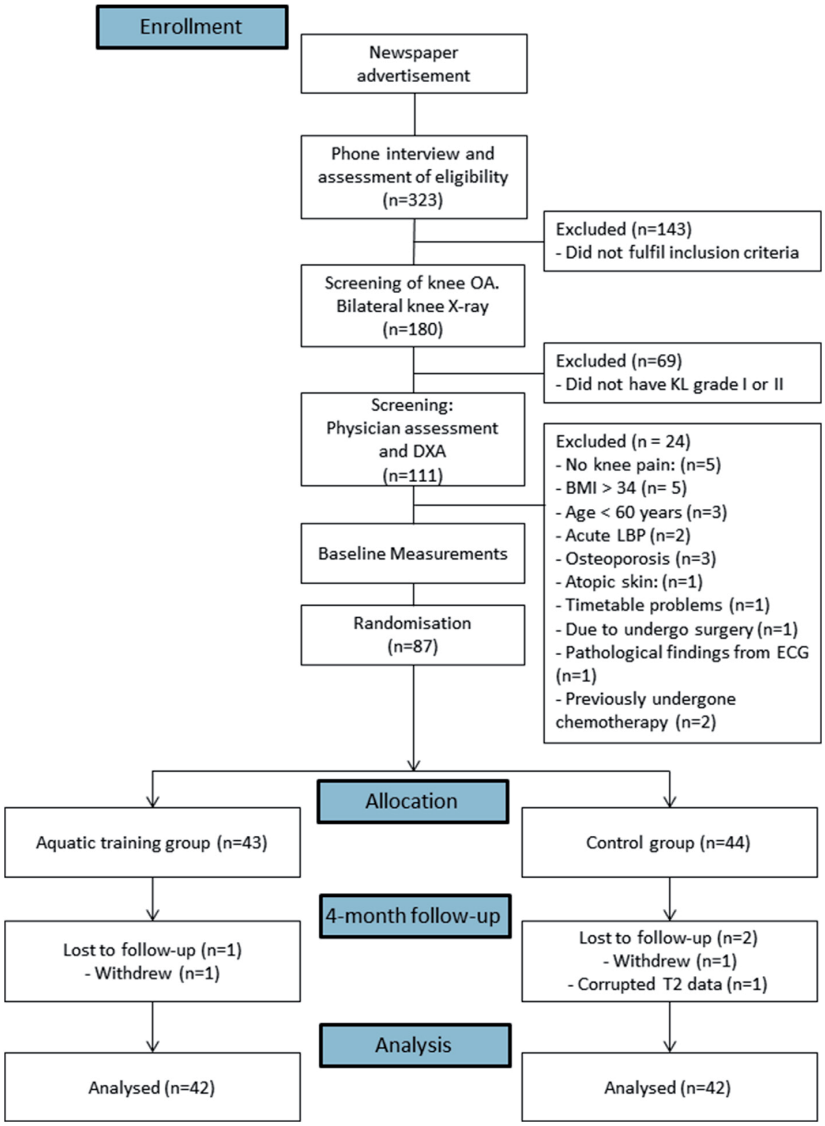

Fig. 1. Flow chart showing enrolment, allocation and 4 month end measurements.

researchers to intervention allocation and provision. A blinded statistician, only provided with ID and K/L grade, performed a computer generated block randomisation of size of 10, stratified according to K/L grade I or II. The MRIs were performed by external radiographers and segmentation was performed blinded to intervention allocation.

Health questionnaire

At baseline, a researcher-designed questionnaire was used to record physical activity levels, general health, medical conditions, current medications, menopausal status and hormone therapy. Leisure time physical activity levels, i.e., activity type (e.g., walking or golf), duration and intensity, prior to the study inclusion were converted into metabolic equivalent task (MET)-hours per week[26].

Primary outcome measures

Primary outcomes for this study were T2 relaxation time (T2) mapping (milliseconds, ms) and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC index, ms). Images were taken using a Siemens Magnetom Symphony Quantum 1.5-T scanner (Siemens AG, Medical Solutions, Erlangen, Germany). Single sagittal slice images from the centre of the medial and lateral femoral condyles were taken from the knee with the highest K/L grade (affected knee). In cases of identical grading bilaterally, the right knee was imaged. Images were manually segmented using an in-house MATLAB application with built-in motion correction for dGEMRIC (Mathworks, Inc. Natick, MA, USA). In this study we divided the femoral cartilage into three region of interests (ROIs); anterior, central and posterior (Fig. 2). dGEMRIC indices were corrected for BMI[27]. Precision, scan-rescan,

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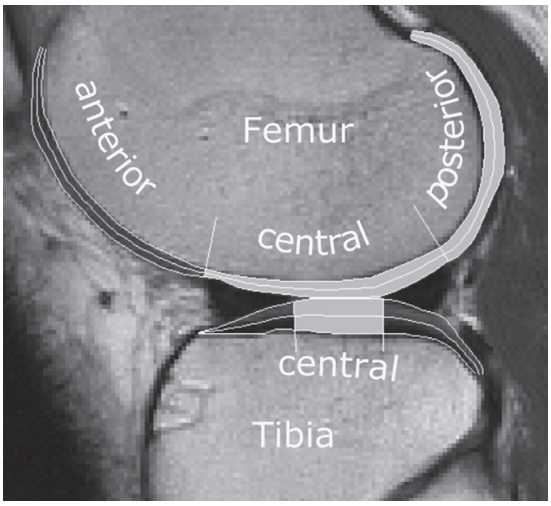

Fig. 2. Illustration of the ROIs in the full-thickness femoral and tibial cartilage. Midlines split both femoral and tibial cartilage into superficial and deep sections.

(CV_{RMS}) of dGEMRIC in asymptomatic subjects is 7% for full-thickness ROIs and 5% for bulk cartilage[28]. In our laboratory, the inter-observer error (CV_{RMS}) for T2 full-thickness ROIs was 1.3–3.3% and 2.8–4.0% for dGEMRIC index. The full MRI protocol and example images are provided in the online supplemental material.

Secondary outcomes

Cardiorespiratory fitness (VO_2 peak, ml/kg/min) was estimated using the UKK 2 km walking test (UKK Institute, Tampere, Finland)[29]. Isometric knee extension and flexion force (N) of the affected knee was measured using an adjustable dynamometer chair (Good strength; Metitur Ltd, Jyväskylä, Finland)[30].

Self-assessed impact of OA on pain, other symptoms, activities of daily living (ADL), sports and recreation (Sport) and knee related quality of life (QOL) were assessed using the validated Finnish[31] Likert version of the knee injury and osteoarthritis outcome score (KOOS) questionnaire[32]. Scores for each domain range between 0 and 100, with a score of 0 indicating extreme and 100 no knee problems.

Daily physical activity

Daily physical activity, for the whole intervention period, of each participant was recorded using a leisure time physical activity diary from which metabolic equivalent task (MET-hours) per week was calculated[26]. In week 13 of the intervention period the daily physical activity (excluding intervention) was measured for 3 consecutive days including one weekend day using an accelerometer (Hookie AM 20, Traxmeet Finland). Mean amplitude deviation (MAD) of the resultant acceleration signal for each 5-s epoch were calculated and categorized according to Vähä-Ypyä *et al.*[33].

Exercise protocol

The participants in the intervention group received 1 h of supervised lower limb aquatic resistance training three times a week for 16 weeks, for a total of 48 training sessions. Resistance of exercises was progressed with three different levels: barefoot, small fins and large resistance boots[21] and the training leg performed all the movements without contact with the pool walls or bottom i.e., non-weight bearing. The intervention was completed in small groups of 6–8 subjects in a pool heated to 30–32° with two instructors: one ensuring intensity and the other full range of movement. Intensity of the training sessions was set at "as hard and fast as possible" to ensure maximal muscle contraction. Pöyhönen *et al.*[34] discovered that during maximal knee flexion and extension exercises in water with large resistance boots the drag forces produced were 80–85% (145 ± 30 N) of maximal isokinetic movements. Full range of motion was strictly controlled for to ensure optimal movement of synovial fluid and exposure of the whole cartilage to the low compressive and shear forces created by the muscle contraction and movement. Training intensity was monitored using heart rate monitors (Polar Electro Ltd, Kempele, Finland), rate of perceived exertion (RPE) using the Borg 6–20 scale[35] and number of repetitions achieved per movement. Full description of exercises and training methodology can be found from the online supplemental material.

Control group

The control group maintained usual care and were asked to continue their usual leisure time activities. They were offered the possibility of participating in two sessions consisting of 1 h of light stretching and relaxation during the 4-month intervention period.

Statistical analyses

The main outcome variables were analysed according to the intention-to-treat analysis principle. Changes in all outcomes were analysed using the bootstrap type analysis of covariance (ANCOVA); confidence interval (CI) were obtained by bias-corrected bootstrapping (5000 replications) due to violation of distributions assumptions. T2 was adjusted for baseline value, height and weight and dGEMRIC index was adjusted for baseline value only. Secondary outcomes were adjusted for baseline value. There are multiple endpoints in this study, and results have to be viewed with certain provisos. All *P*-values and CIs are quoted, rather than introducing the problems and potential errors associated with formal adjustments for potential multiplicity issues. Between-group changes in all outcomes are reported in text as mean difference (95% CI, adjusted *P*-value). Effect size (d) was calculated by using the method of Cohen[36] where an effect size of 0.20 is considered small, 0.50 moderate, and 0.80 large. CIs for the effect sizes were obtained by bias-corrected bootstrapping (5000 replications). Statistical analyses were performed using statistical software (Stata, release 13.1, StataCorp, College Station, Texas).

Target sample size of 70 (35 per research arm) was required to ensure the power of at least 80% to detect a difference of 40 ms effect in dGEMRIC between the groups at two-side $\alpha = 0.05$. Predicting a dropout rate of about 10% we aimed to recruit at least 80 participants at baseline.

Results

In total 87 participants met the inclusion criteria and were randomised into the aquatic training group ($n = 43$) and control group ($n = 44$) (Fig. 1). The demographic and clinical characteristics of both groups were similar at baseline (Table I).

Program feasibility

Drop-out rate, during the 4-month intervention period, for each group was 2.3% ($n = 1$ per group) (Fig. 1). Training compliance was 88% and mean (SD) training frequency was 2.6 (0.5) times per week (including dropouts). The average intensity of each training session was RPE 15 (range, 12–17) and average (SD) maximum heart rate was 144 (12) beats per minute. The mean (SD) number of repetitions completed per session with the affected leg was 481 (67), 416

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Table I
Baseline demographic and clinical characteristics of the participants

	Exercise group ($n = 43$)	Control group ($n = 44$)
Age (years)	64 (2)	64 (2)
Height (cm)	162 (5)	162 (5)
Body mass (kg)	69.6 (10.3)	71.0 (11.3)
Body mass index (kg/m^2)	26.6 (3.8)	27.1 (3.5)
Time from menopause (years)	14 (6)	14 (6)
Pain killers for knee pain, *n* (%) of users	11 (25.6)	9 (20.5)
Glucosamine use occasionally, *n* (%)	12 (28)	8 (18)
Kellgren–Lawrence grade, *n* (%)		
Grade 1	23 (53.5)	24 (54.5)
Grade 2	20 (46.5)	20 (45.5)
Knee pain during last week, (VAS, mm)*		
• Affected leg	28 (25)	24 (19)
• Non-affected leg	24 (19)	23 (18)
Habitual physical activity (METh/week)	29 (31)	36 (33)

Values are means (SD) or *n* (%).
* Range, 0–100 mm.

(68) and 387 (58) for barefoot, small fins and large boots, respectively. 70.5% of these repetitions involved full knee active extension and flexion which was mean 134.4 (SD, 5.6) degrees (affected knee) as measured during baseline assessment.

Harms

There were two medical consultations (bilateral knee pain and dyspnoea) as a result of the aquatic training. One subject from the control group required a medical consultation for knee pain after the baseline physical performance measures. All three subjects continued their participation in the study and attended follow-up measurements.

Primary outcomes

To ensure accuracy, each MRI image was inspected for quality. One participant was excluded from the study due to corrupted data as a result of excessive movement artefact in T2 images (Fig. 1). One complete baseline dGEMRIC index data set was missing due to lost images (at time of imaging). Additionally, from the dGEMRIC index 11 medial compartments had movement artefact, while in the lateral compartment, 14 had artery-flow pulsating artefact, one had movement artefact and one inaccurate location of the slice compared to baseline image. In total 72 and 68 complete dGEMRIC data sets for medial and lateral femoral condyles respectively were available for quantitative analysis.

Table II
Effects of aquatic training on T2 relaxation time and dGEMRIC index in full-thickness ROIs

	Baseline, mean (SD)		Change to month 4, mean (95% CI)		Effect size (95% CI)	*P*-value	
	Training ($n = 42$)	Controls ($n = 42$)	Training ($n = 42$)	Controls ($n = 42$)		Crude	Adjusted
T2, ms							
Femur							
Lateral condyle							
Central	52.6 (4.9)	53.4 (4.1)	−0.18 (−1.05 to 0.59)	−0.03 (−0.95 to 0.91)	0.05 (−0.38 to 0.48)	0.81	0.58†
Posterior	49.6 (4.6)	48.8 (3.6)	−0.23 (−1.26 to 0.97)	0.74 (0.01 to 1.40)	0.31 (−0.12 to 0.74)	0.15	0.30†
Medial condyle							
Central	52.8 (4.5)	52.0 (4.4)	−0.20 (−1.17 to 0.83)	0.48 (−0.71 to 1.68)	0.18 (−0.25 to 0.61)	0.40	0.47†
Posterior	52.0 (4.7)	51.9 (4.5)	−1.16 (−1.85 to −0.50)	0.10 (−0.72 to 0.94)	0.48 (0.05 to 0.91)	0.028	0.021†
Tibia							
Lateral plateau							
Central	41.0 (8.3)	42.9 (8.1)	−0.66 (−1.86 to 0.45)	0.05 (−1.67 to 1.68)	0.15 (−0.28 to 0.58)	0.50	0.30†
Medial plateau							
Central	44.5 (5.0)	42.7 (4.2)	−0.02 (−1.45 to 1.41)	−0.02 (−0.85 to 0.79)	−0.00 (−0.43 to 0.43)	1.00	0.41†
dGEMRIC*, ms							
Femur							
Lateral condyle+							
Central	433 (70)	424 (44)	−4 (−16 to 7)	−1 (−11 to 8)	0.07 (−0.40 to 0.55)	0.77	0.93‡
Posterior	422 (60)	428 (57)	2 (−10 to 16)	6 (−8 to 22)	0.08 (−0.40 to 0.57)	0.72	0.71‡
Medial condyle§							
Central	411 (61)	410 (65)	−19 (−32 to −6)	−6 (−17 to 7)	0.34 (−0.12 to 0.80)	0.14	0.13‡
Posterior	453 (60)	448 (61)	−23 (−39 to −8)	1 (−14 to 16)	0.53 (0.06 to 0.99)	0.022	0.022‡
Tibia							
Lateral plateau							
Central	424 (76)	419 (82)	−1 (−20 to 17)	1 (−15 to 17)	0.03 (−0.46 to 0.52)	0.91	0.95‡
Medial plateau							
Central	382 (75)	386 (50)	−20 (−35 to −6)	−6 (−20 to 8)	0.32 (−0.15 to 0.78)	0.19	0.09‡

In T2 low values correspond to improved integrity and orientation of the collagen fibres and a decrease in hydration of articular cartilage. In dGEMRIC, high values correspond to high GAG concentration.
* Missing data for dGEMRIC +$n = 16$, §$n = 12$.
† ANCOVA: adjusted for baseline value, height and weight.
‡ ANCOVA: adjusted for baseline value.

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T2 and dGEMRIC index baseline values, changes, group differences and effect sizes (Cohen's *d*) at the end of the 4-month intervention are given in Table II. There was a significant decrease in both T2, mean difference −1.2 ms (95% CI: −2.2 to −0.2, $P = 0.021$) and dGEMRIC index −23 ms (−43 to −3, $P = 0.022$) in the training group compared to controls in the full thickness posterior ROI of the medial femoral cartilage. Further, significant decreases in the training group compared to controls were only seen in the deep posterior and not superficial ROI of the medial femoral cartilage, −1.6 ms (−3.0 to −0.3, $P = 0.016$), and −26 ms (−50 to −3, $P = 0.030$), for T2 and dGEMRIC index respectively (Fig. 3).Values for the deep and superficial posterior ROI (Fig. 3) can be found from the online supplemental material.

Secondary outcomes

Cardiorespiratory fitness VO_2 peak increased 9.8% in the training group and 4.4% in the control group ($d = 0.58$, $P = 0.010$). There were no between group differences in the knee extension or flexion muscle force or in any domains of KOOS (Table III).

Daily physical activity

The total mean (SD) MET-hours per week, including the intervention, were 40 (13) and 26 (16) in the training and control group respectively ($P < 0.001$). No between group differences were seen in MET activity once the intervention activity was removed ($P = 0.112$). There was no significant difference between the groups in physical activity as measured with accelerometers, excluding the intervention. Sedentary behaviour accounted for 80% (5.0) or 13,903 (869) MADs of daily activity. The remaining physical activity was divided into slow walking 3166 (821), normal walking 198 (175) and brisk walking jogging and running together 1.7 (1.4) MADs.

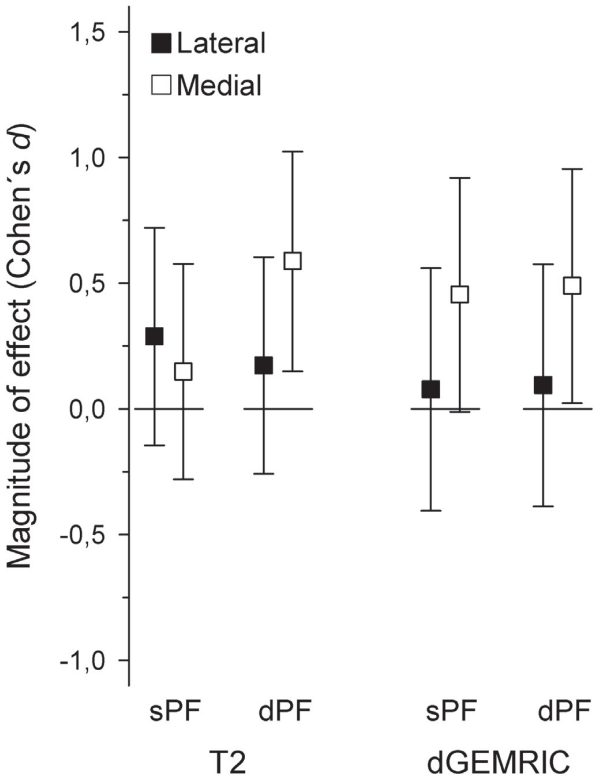

Fig. 3. Magnitude of effect (Cohen's *d* and 95% CI) at superficial and deep layers of T2 and dGEMRIC cartilage ROIs from medial and lateral condyles. sPF = superficial posterior femur; dPF = deep posterior femur.

Discussion

As far as we know, this is the first study to show a response in the biochemical composition of tibiofemoral cartilage following 4-months of progressive aquatic resistance training in postmenopausal women with mild knee OA. A small significant change was observed in the biochemical composition of the medial posterior femoral cartilage, which is less loaded during ADL[37]. Additionally, the training significantly improved cardiorespiratory capacity but had no significant effect on muscle force and self-reported symptoms.

This is the first study to show concurrent changes in both T2 and dGEMRIC index in an exercise intervention study. However, both MRI techniques have only been previously implemented once in the same study. In the study by Multanen *et al.*[16] we investigated the effects of a land-based impact intervention on the biochemical composition tibiofemoral cartilage in postmenopausal women with mild knee OA. No positive or negative effect was observed with either MRI technique, however, the posterior ROIs were not reported. In this previous study[16] the degree of knee motion during the land-based intervention was 0–65° and therefore the posterior ROI was not directly loaded. Knee flexion of over 90° is required to produce contact between the posterior ROI of the femur and central tibia[38] which was achieved with our intervention at high frequency. Therefore, our results suggest that the chondrocytes in the posterior region of the femoral cartilage in persons with mild knee OA may have a lower threshold for adaption compared to the central and might be more responsive to the high repetition low shear and compressive cyclic forces produced in the aquatic resistance training. In contrast, the chondrocytes in the central region of the femur and tibia cartilage may require a higher or atypical load to stimulate an adaptive response. Further, the response was limited to the medial femoral cartilage possibly due to anatomical differences. The medial tibial plateau is concave compared to the convex surface of the lateral side, thus on the medial tibiofemoral joint there is greater contact between the cartilage surfaces[39].

After 4-months of aquatic resistance training, T2 in the posterior region of the medial femoral condyle significantly decreased, with no change in the central femur and tibia regions. A decrease in T2 values is indicative of improved integrity and orientation of the collagen fibres and a decrease in hydration of articular cartilage[40,41]. In more detailed analysis we found that decrease in T2 occurred in deep posterior region of medial femoral cartilage which is in line with our previous study[15]. This study[15] showed a similar response in T2 in patella cartilage in women with mild knee OA following a 1 year intervention. While the intervention was different, the mechanical forces in the patella cartilage during the progressive impact exercises were shear with moderate compression in the patellofemoral joint i.e., forces were not directly compressive as in the tibiofemoral joint[16]. Therefore, our findings support the notion that the collagen-interstitial water environment in the tibiofemoral cartilage may respond to exercise.

We found a corresponding significant decrease in dGEMRIC index in the posterior region of medial femoral cartilage and again more specifically in its deep region. A lower dGEMRIC index is associated with a lower GAG concentration, thus, a decrease in dGEMRIC index may indicate degeneration of cartilage[42,43]. Our results suggest that the aquatic resistance training may have produced a decrease in GAG concentration within the cartilage matrix

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Table III
Effects of aquatic training on physical performance and clinical symptoms

	Baseline, mean (SD)		Change to month 4, mean (95% CI)		Effect size (95% CI)	*P*-value	
	Training ($n = 42$)	Controls ($n = 42$)	Training ($n = 42$)	Controls ($n = 42$)		Crude	Adjusted*
Cardiorespiratory fitness (ml/kg/min)							
Estimated VO_2 peak	24.6 (5.6)	24.9 (4.9)	2.4 (1.8 to 3.1)	1.1 (0.5 to 1.8)	0.58 (0.15 to 1.06)	0.006	0.010
Force (N)							
Extension	335 (64)	343 (70)	20 (8 to 33)	9 (−5 to 23)	0.27 (−0.17 to 0.70)	0.22	0.28
Flexion	164 (52)	165 (40)	20 (9 to 30)	17 (7 to 27)	0.07 (−0.36 to 0.51)	0.74	0.71
KOOS (0–100)							
Pain	80 (10)	82 (12)	4 (1 to 7)	1 (−2 to 4)	0.30 (−0.14 to 0.74)	0.17	0.25
Other symptoms	74 (13)	75 (14)	7 (3 to 10)	2 (−1 to 6)	0.37 (−0.07 to 0.81)	0.09	0.09
ADL	84 (10)	85 (11)	4 (1 to 7)	0 (−2 to 3)	0.39 (−0.03 to 0.78)	0.08	0.10
Sport	63 (20)	65 (22)	8 (2 to 14)	3 (−3 to 8)	0.27 (−0.16 to 0.73)	0.21	0.24
QOL	65 (17)	71 (20)	7 (3 to 11)	3 (−1 to 8)	0.26 (−0.18 to 0.71)	0.24	0.38

* ANCOVA: adjusted for baseline.

or faster contrast agent diffusion in to the cartilage through increased permeability of the cartilage surface[44], which are characteristics of OA progression[4]. These results conflict with the findings of Roos and Dahlberg[14] who found an increase in the T1 relaxation time in the presence of contrast agent following a 4-month neuromuscular training intervention. However, they measured only one ROI from the medial femoral cartilage and dGEMRIC values were not corrected for BMI, also their population was younger people at high risk of developing knee OA following surgery for meniscal injury. Alternatively, in a previous cross sectional study[45], similar associations i.e., lower T2 and dGEMRIC index was seen in the central ROI of the patella cartilage in young people with repetitive patella dislocation[45]. This finding was speculated to be due to a reparative process within the cartilage. Additionally, faster diffusion of the contrast agent into the medial tibiofemoral cartilage after intravenous injection may have been a combined result of improved contrast agent delivery through vascular changes i.e., increased blood flow in the subchondral bone and synovium with possible improvements in lower limb biomechanics. Further, an improved diffusion of the contrast agent could be explained by a decrease in cartilage thickness i.e., reversal of the cartilage swelling characterised in early OA[4,46]. Cartilage thickness was not measured in our study leaving this issue to speculation and open for further investigation in the future. Therefore, we could hypothesise that while our results indicate the integrity of the collagen-interstitial water environment may be responsive to shear/compressive forces during aquatic exercise, further research is required to understand the exact nature of acute responses in dGEMRIC index to this type of loading.

In line with the findings of our recent systematic review[6], we did not see a significant change in muscle force. However, we used isometric muscle testing whereas, the muscle contraction during isokinetic strength testing mimics closer the true muscle work performed during aquatic resistance training and could have been more sensitive to change. The improvements in cardiorespiratory fitness are in line with other studies investigating the effects of aquatic training[47]. An aquatic exercise program which also includes neuromuscular exercises e.g., partial weight bearing exercises might produce better improvements in neuromuscular performance and possibly stimulate GAG production[14] as it is possible to speculate that the loading mechanics in our study may have been ineffective for this purpose. There were no between group changes in any of the domains of the KOOS, this lack of significance is not a surprise given the high values reported at baseline. In combination with the results from the measures of physical performance and KOOS there is no indication that aquatic exercises had a harmful effect on clinical findings in this population. Therefore, aquatic resistance training of sufficient intensity to improve cardiorespiratory function is well tolerated, has high compliance and does not increase pain in women with mild knee OA. Further research should focus on the efficacy of aquatic resistance training for people with more severe stages of OA progression.

The strengths of this study include the high adherence to a highly intensive aquatic training program. This study fulfilled all the important quality criteria of an RCT, except for blinding the participants to exercise therapy, which is common in exercise therapy studies[48]. Strict imaging procedure and segmentation rules ensured good stability and repeatability of the T2 and dGEMRIC indices. This limits, but does not rule out, the possibility that the results of this study are affected by the magic angle (particularly T2) and partial volume effects. The long imaging time in dGEMRIC mapping might result in motion artefact which was controlled for in our study by using a motion correction technique built into the in-house software, as well as strict inclusion/exclusion criteria for image quality. Minor limitations include: MRI imaging performed with a 1.5 T scanner, whereas a 3.0 T scanner would have produced better spatial resolution and higher signal-to-noise ratio. The mean changes seen in T2 and dGEMRIC index fall within the upper limits of our measurement error for both techniques therefore we cannot exclude measurement error as a possible explanation for our findings. Further, this study had multiple endpoints and therefore results have to be viewed with caution. In some cases, occasionally thinned and deteriorated cartilage and movement or pulsating artery artefact prevented reliable segmentation of cartilage resulting in lost data. Also, we used single-slice segmenting method assessing articular cartilage, whereas multi-slice method might have produced a more comprehensive view of the knee cartilage. The MRI analysis application divided cartilage to deep and superficial compartments (50%/50%) and due to the 1.5T scanner used, segmented cartilage thickness was from two to five voxels reducing the spatial accuracy and therefore care should be taken when interpreting these results. Pre-contrast T1 imaging was not used in this study however its importance has been questioned and it is felt this omission does not affect our conclusions[46,49]. Classification of OA severity was performed using a combination of pain and Kellgren–Lawrence classification (weight-bearing) and therefore it was not possible to differentiate between healthy and biomechanically altered cartilage between ROIs and condyles[50]. It is still unknown if an aquatic training program of longer than 4-months would have created a global response throughout the cartilage. It is plausible to hypothesise that as cartilage health in one ROI improves it may cause a positive response in adjacent ROI's. Due to the strict inclusion criteria, our results cannot be directly applied to people with later stage OA, older or obese women and men. Finally, the authors acknowledge that the different qMRI parameters and their interactions are not yet fully understood and further investigations

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about the interaction between exercise and these parameters are warranted.

Our results suggest that, in postmenopausal women with mild knee OA, the integrity of the collagen-interstitial water environment (T2) of the tibiofemoral cartilage may be responsive to low shear and compressive forces during aquatic resistance training. Further research is required to understand the exact nature of acute responses in dGEMRIC index to this type of loading. Clinical relevance of our findings remains unclear but strongly warrants further research. Additionally, aquatic resistance training of sufficient intensity to improve cardiorespiratory function is well tolerated, has high compliance and low risk of harm amongst women with mild knee OA.

Author contributions

Munukka, Matti: Analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding, collection and assembly of data.

Waller, Benjamin: Analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding, collection and assembly of data.

Rantalainen, Timo: Analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support, collection and assembly of data.

Häkkinen, Arja: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

Nieminen, Miika: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support.

Lammentausta, Eveliina: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support.

Kujala, Urho: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

Paloneva, Juha: Analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Sipilä, Sarianna: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Peuna, Arttu: Analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support, collection and assembly of data.

Kautiainen, Hannu: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, statistical expertise, collection and assembly of data.

Selänne, Harri: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Kiviranta, Ilkka: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Heinonen, Ari: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding.

Conflict of interest

There is no conflict of interest for any authors.

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Supplementary data

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SUPPLEMENTAL MATERIAL

These appendixes have been provided by the authors to give readers additional supporting information about their work.

Supplement to: Matti Munukka, Benjamin Waller, Timo Rantalainen, Arja Häkkinen, Miika T. Nieminen, Eveliina Lammentausta, Urho M. Kujala, Juha Paloneva, Sarianna Sipilä, Arttu Peuna, Hannu Kautiainen, Harri Selänne, Ilkka Kiviranta, Ari Heinonen. Efficacy of Progressive Aquatic Resistance Training for Tibiofemoral Cartilage in Postmenopausal Women with Mild Knee Osteoarthritis: A Randomised Controlled Trial.

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Appendix A: MRI PROTOCOL

Prior to MRI imaging, the participant was advised to restrain from any strenuous physical activity during the 48 hours prior to the measurements to minimize possible transient changes in knee cartilage volume and composition. Participants were imaged at the same time of the day to avoid possible diurnal variation at the follow-up measurements.

The participants were imaged lying supine with imaged knee in slight flexion, stabilized in a leg holder and a custom made inflatable cushion. The cushion was specifically designed to stabilize the patella without causing any compression of the patellofemoral joint. The imaging session lasted 3 hours and included a standard clinical MRI series and T2 relaxation time followed by the dGEMRIC series.

T2 mapping was performed using a sagittal multi-slice multi-echo fast spin echo sequence (field of view (FOV) 140mm, acquisition matrix 256 x 256, repetition time (TR) 2090 ms, eight echo times (TE) between 13 and 104 ms, echo train length (ETL) 8, slice thickness 3 mm). The slices were positioned perpendicular to a line tangential to the posterior femoral condyles in the axial scout view. Two slices, each covering the central region of the medial and lateral condyles, were analysed.

For the dGEMRIC series, immediately after the clinical and T2 imaging, an intravenous injection of 0.4mL/kg (double dose) of Gd-DTPA^{2-} (Magnevist, Schering, Berlin) was administered. The amount of contrast agent administered was corrected for body weight at each measurement point. This was appropriate because of the expected changes in body composition as a result of the intensive exercise intervention. In order to enhance the delivery of contrast agent into the knee cartilage, following administration of Gd-DTPA^{2-}, the participants were instructed to perform 5 minutes of knee flexion-extension exercises in a sitting position without resistance, 5 minutes of walking on a flat surface and 10 gentle deep squats. Exactly ninety minutes after the injection, dGEMRIC mapping in the presence of Gd-DTPA^{2-} was performed in the sagittal plane using a single slice inversion recovery fast-spin echo sequence (FOV = 14 cm, matrix 256 x 256, TR = 1800 ms, TE 13 ms, six inversion times (TI) between 50 and 1600 ms, slice thickness 3 mm). The slice positioning was copied from the T2 relaxation time mapping sequence, and the number of the slice in the correct orientation is reduced to one. The remaining slice was then positioned at the centre of the medial and lateral condyles as viewed on the axial scout image. The participants were positioned into an identical position as for the first MRI imaging. Knee with highest degree of OA, as measured by the radiographic Kellgren-Lawrence (K/L) scale, was imaged. In the cases where both knee had identical K/L score the right knee was imaged.

For quality assurance purposes, a set of phantom samples containing certain concentrations of agarose and nickel nitrate to modulate their dGEMRIC and T2 relaxation times were imaged following the study protocol prior to baseline and follow-up measurement sessions, and no evidence of scanner drift was observed during the intervention.

Appendix B: EXERCISE PROTOCOL

The intervention protocol implemented in this study was adapted from previously used and shown to be effective in healthy women[1] and for people post knee arthroplasty[2]. Each one hour long session consisted of a 15 minute warm up, a 30 minute intensive aquatic resistance training program and a 10-15 minute cool down. Aquatic steps were used to ensure that all subjects were able to complete the standing exercises at a depth level approximately to their xiphoid bone ±5cm ensuring weight bearing on the supporting leg of 25-50% of own body weight. Intensity of the training sessions was set at "as hard and fast as possible (all out) using full range of motion and was monitored using heart rate monitors (Polar Electro Ltd, Kempele, Finland), rate of perceived exertion (RPE) Borg 6-20[3] and number of repetitions achieved was measured on three different occasions. The progression of the training was achieved by using resistance boots of different surface area to increase resistance[1] small fins with a frontal area of $0.0181m^2$ (THERABAND PRODUCTS, The Hygienic Corporation, Akron, OH 44310 USA) and large boots (Hydro-Tone hydro-boots, Hydro-Tone Fitness Systems, Inc. Orange, CA 92865-2760, USA) with a frontal area of $0.075m^2$.

Warm-up

The warm up consisted of a circuit of 10 different exercises followed by a 2-4 minute session of aerobic exercise to gradually increase heart rate (Table 1). Each exercise was performed at the required intensity for 2 minute with 15 seconds time for changing station. Subjects always started at different stations compared to the previous session. Variety was also ensured by altering the order of the movements.

Table 1. Warm up exercises and their progressions

	Exercise	Intensity
1	Standing hip flexion/extension	30 sec per leg RPE 10*
2	Standing hip abduction/adduction	30 sec per leg RPE 10*
3	Seated bilateral knee flexion/extension.	1 minute RPE 11-12*
4	Standing knee flexion7extension	30 sec per leg RPE 10*
5	Calf raises on edge of step (weeks 1-8 double leg, weeks 9-16 single leg)	30 sec per leg RPE 10*
6	Balance beam (EWAC, Netherlands) walking forwards and backwards (weeks 1-6 without arms, weeks 6-12 carry tray with ball on, 13-16 same eyes closed)	1 minute. Gradual increase in difficulty and was slightly different every session
7	Standing abdominals (either pushing and pull frisbee, trunk rotation with frisbee or rowing with aquatic rolling pin), weeks 1-8 double leg stance, week 9-16 single leg).	1 minute RPE 10*
8	Abdominal with feet in frisbee against wall (figure of 8, circles 30 second each direction)	1 minute RPE 10*
9	Hurdles (EWAC Medical Netherlands), weeks 1-6 stepping over hurdles, weeks 6-12 double leg jumps forwards and backwards over 30cm hurdle, 13-16 single leg jumps forwards over 30 cm high hurdle)	1 minute RPE 11-12*
10	Weeks 1-6 scissor jumps, weeks 6-12 jumping over 30cm hurdle sideways, weeks, 13-16 single leg sideways jumping over 30 cm hurdle.	1 minute RPE 11-12*
	Aerobic exercise	
	Dynamic balance ½ of the group jog/run around other ½ of group who are trying to maintain balance.	2-4 minutes RPE 12-14*

* BORG scale 6-20

Lower limb resistance training exercises and daily progressions

The intensive aquatic resistance program consisted of 5 lower-limb aquatic resistance exercises (Figures 1-5). The subjects were instructed to complete each movement as hard and as fast as possible in both directions. There were two instructors present for every training session with one providing instruction on timings and the other for technique and individual instruction as necessary. This ensured the high intensity of the training with good quality full range of motion movements. Use of long or short set duration and use of different sized resistance fins ensures variety and progression. Daily training programs and progressions are shown in detail in table 2. The exercises were completed in the form of a circuit with each subject completing all three sets of each movement before moving to the next one. An additional 45 seconds between movements was provided to allow safe transition between stations and give a small amount of addition rest.

Figure 1.Knee flexion/extension in sitting

Figure 2. Knee flexion/extension in standing

Figure 3. Kickback

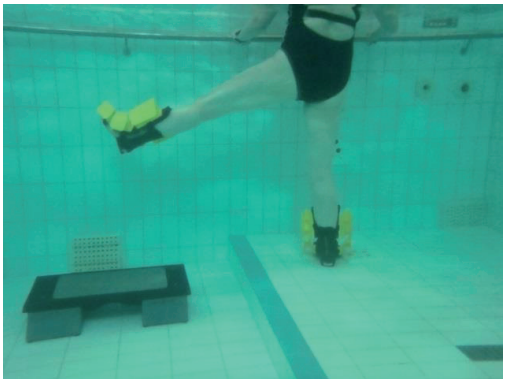

Figure 4. Hip abduction/adduction

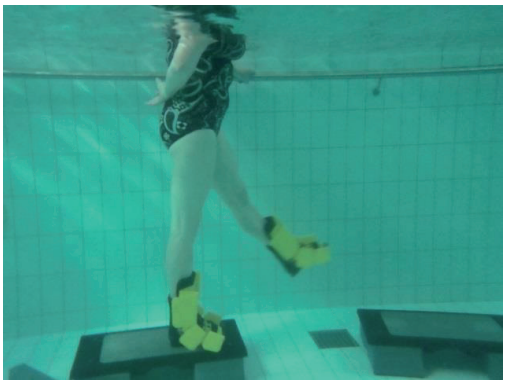

Figure 5. Hip flexion/extension with knee straight

Table 2. Daily progressions of the aquatic resistance training program

Week	Session No.	Resistance	Intensity RPE (6-20)	Sets x duration (sec) per leg	Recovery (sec)
1	1	Barefoot	12 - 14	2 x 30	30
	2			2 x 45	30
	3			3 x 45	30
2	4	Barefoot	12 - 14	3 x 45	30
	5			3 x 30	45
	6			3 x 45	30
3	7	Small fins	15 - 16	3 x 45	30
	8		16 - 17	3 x 30	45
	9		15 - 16	3 x 45	30
4	10	Small fins	16 - 17	3 x 30	45
	11		15 - 16	3 x 45	30
	12		16 - 17	3 x 30	45
5	13	Small fins	15 - 16	3 x 45	30
	14		15 - 16	3 x 45	30
	15		15 - 16	3 x 45	30
6	16	Small fins	16 - 17	3 x 45	30
	17	Large boots	16 - 17	3 x 45	30
	18	Small fins	15 - 16	3 x 45	30
7	19	Large boots	16 - 17	3 x 45	30
	20	Small fins	15 - 16	3 x 45	30
	21	Large boots	16 - 17	3 x 45	30
8	22	Large boots	16 - 17	3 x 45	30
	23	Small fins	15 - 16	3 x 45	30
	24	Large boots	16 - 17	3 x 45	30
9	25	Large boots	16 - 18	3 x 45	30
	26			3 x 30	45
	27			3 x 45	30
10	28	Large boots	16 - 18	3 x 30	45
	29			3 x 45	30
	30			3 x 30	45
11	31	Large boots	16 - 18	3 x 45	30
	32			3 x 45	30
	33			3 x 45	30
12	34	Barefoot	16 - 18	3 x 45	30
	35	Small		3 x 45	30
	36	Large boots		3 x 45	30
13	37	Large boots	16 - 18	3 x 45	30
	38			3 x 30	45
	39			3 x 45	30
14	40	Large boots	16 - 18	3 x 45	30
	41			3 x 30	45
	42			3 x 45	30
15	43	Large boots	16 - 18	3 x 45	30
	44			3 x 30	45
	45			3 x 45	30
16	46	Large boots	16 - 18	3 x 45	30
	47	Large boots		3 x 45	30
	48	Barefoot	15 - 16	3 x 30	45

Cool down

The cool down consisted of a 4-5 minute of active light aerobic movements to gradually reduce heart rate followed by 5-8 minutes of light static stretching.

Table 3. Cool down exercises

	Exercise	Intensity
	Walking and supported cycling against wall	4-5 minutes RPE 8-10
	Stretches	
1	Hip flexors (Iliopsoas)	15-20 sec per leg
2	Gluteus maximus	15-20 sec per leg
3	Quadriceps	15-20 sec per leg
4	Hamstrings	15-20 sec per leg
5	Iliotibial band	15-20 sec per leg
6	Hip adductors	15-20 sec per leg
7	Gastrocnemius	15-20 sec per leg
8	Soleus	15-20 sec per leg
9	Pectoralis major	15-20 sec per arm
10	Triceps	15-20 sec per arm
11	Trunk lateral flexion	15-20 sec per side

Appendix C: Deep and superficial posterior femoral ROIs for T2 and dGEMRIC values.

Table 4. Baseline and mean (95% CI) change to 4 month for T2 and dGEMRIC index in superficial and deep ROIs.

	Baseline, mean (SD)		Change to month 4, mean (95% CI)		Effect size (95% CI)	P-Value	
	Training (N=42)	Controls (N=42)	Training (N=42)	Controls (N=42)		Crude	Adjusted
T2, ms							
Femur							
Lateral condyle							
Posterior Superficial	54.0 (5.1)	53.3 (4.5)	-0.47 (-1.89 to 0.88)	0.67 (-0.26 to 1.61)	0.28 (-0.14 to 0.72)	0.184	0.274[a]
Posterior Deep	46.2 (5.1)	45.2 (3.6)	0.12 (-1.18 to 1.45)	0.75 (-0.11 to 1.57)	0.17 (-0.26 to 0.60)	0.420	0.767[a]
Medial condyle							
Posterior Superficial	54.1 (6.3)	55.1 (6.8)	-0.98 (-2.01 to 0.09)	-0.45 (-1.47 to 0.59)	0.15 (-0.28 to 0.58)	0.492	0.320[a]
Posterior Deep	50.3 (4.7)	49.3 (4.7)	-1.28 (-2.13 to -0.38)	0.64 (-0.38 to 1.75)	0.59 (0.15 to 1.02)	0.007	0.016[a]
dGEMRIC, ms							
Femur							
Lateral condyle							
Posterior Superficial	387 (50)	386 (43)	-7 (-18 to 5)	-4 (-17 to 12)	0.08 (-0.40 to 0.56)	0.742	0.756[b]
Posterior Deep	451 (72)	461 (75)	10 (-6 to 30)	15 (-3 to 35)	0.09 (-0.39 to 0.58)	0.689	0.675[b]
Medial condyle							
Posterior Superficial	408 (55)	398 (59)	-22 (-39 to -9)	1 (-16 to 18)	0.46 (-0.01 to 0.92)	0.052	0.065[b]
Posterior Deep	490 (70)	488 (70)	-24 (-43 to -5)	3 (-13 to 19)	0.49 (0.02 to 0.95)	0.033	0.030[b]

T2 = transverse relaxation time; [a]ANCOVA: adjusted for baseline value, height and weight.
dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; [b]ANCOVA: adjusted for baseline value.

Appendix D: Example of image segmentations

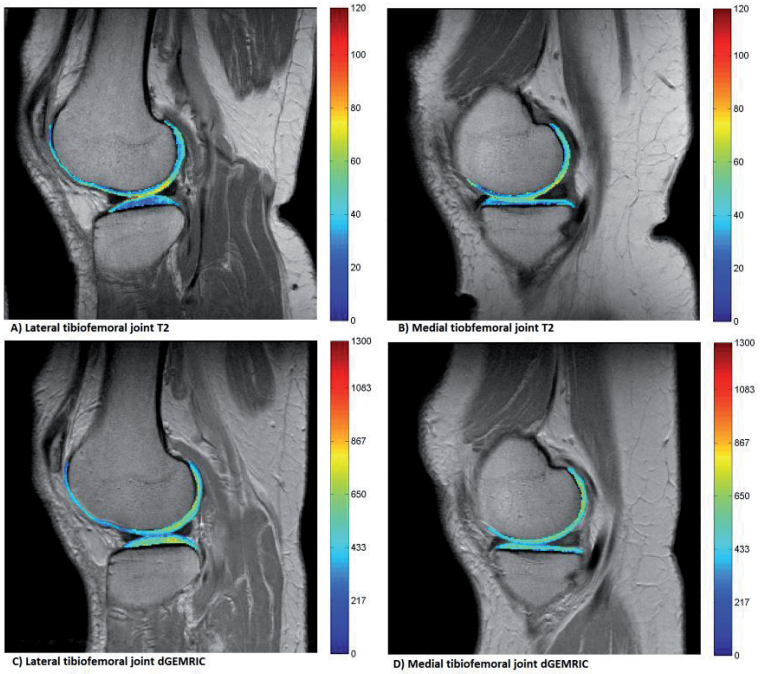

Figure 6 T2 and dGEMRIC images for medial and lateral tibiofemoral joints for one participant

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