Relative efficacy of different types of exercises in the treatment of knee and hip osteoarthritis: A network meta-analysis of randomised controlled trials

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Abstract

Background: The need for exercise in osteoarthritis (OA) has been long-recognised, leading international guidelines and experts to universally endorse exercise as a core treatment for OA. However, currently there is no consensus on which type of exercise is most beneficial, and there is clear differentiation of exercise effects across different OA outcomes.

Objective: The primary objective was to estimate the relative efficacy of different exercises for pain, function, physical performance and quality of life (QoL) outcomes in people with knee and hip OA. This research aim was also accompanied by an update of the evidence in overall exercise versus usual care in conservatively managed OA and in those who had undergone joint replacement surgery. The primary time point was at, or nearest to, eight weeks. However, for analysis of post-joint replacements, the primary time point was three months.

Method: A literature search was performed in nine electronic databases and hand searches without limitation in publication date or language. Exercises were classified into aerobic,

strengthening, flexibility/skills (flex/skills), mind-body and mixed. Inclusion criteria to be fulfilled were: i) randomised controlled trials (RCTs) of knee OA or hip OA or mixed knee and hip OA, including postoperative participants; ii) RCTs comparing one type of exercise with another type, or other non-exercise interventions; and iii) provision of outcomes for pain, function, performance or QoL. The first search was performed in December 2015 and a final update was conducted in December 2017. Upon completion of screening, the most widely used non-exercise control group was identified to perform NMA. Effect size (ES) of exercise benefits was measured as standardised mean difference between groups and was reported along with 95% confidence intervals (CIs) for conventional meta-analysis (performed using frequentist approach), and with 95% credible interval (CrI) for network meta-analysis (performed using Bayesian approach).

Results: In the first search, 13672 citations were identified from electronic databases and hand searches. After removal of duplicates and full texts screening, 199 citations (185 trials) met the inclusion criteria. After the update in December 2017 40 more eligible citations (32 trials) were added, giving a total of 239 citations (217 trials). However, only 106 trials were deemed eligible for analysis in this thesis because the focus

was on the single most common non-exercise comparator used – usual care. In the conventional meta-analysis which was performed to examine the overall effect of exercise versus usual care, 77 trials (n=6472) contributed to the analysis. In the network meta-analysis that was performed to compare the relative efficacy of different exercises, 103 trials (n=9134) were included. Finally, in the meta-analysis of exercise versus usual care on postoperative outcomes, only nine trials (n=467) were eligible.

Compared to usual care, exercise conferred higher ES for pain (ES 0.56; 95%CI 0.44, 0.68), function (ES 0.51; 95%CI 0.38-0.63) and performance (ES 0.46; 95%CI 0.35, 0.57) compared to QoL (ES 0.21; 95%CI 0.11, 0.31) at eight weeks. Single component exercise, particularly aerobic exercise, was most likely to be the most effective for improving OA outcomes. For many outcomes, the differences between different exercises were not statistically significant, except for pain where aerobic or mind–body exercise were significantly better than mixed exercise. These results were generally driven by studies on knee OA, and by strengthening and mixed exercises. Overall evidence indicates that exercise therapy had better benefits in people with knee OA, in people not on the waiting-list for surgery, and in trials with younger

participants (mean age <60-years old). Peak benefits were demonstrated at 2-3 months after commencement of exercise and were likely to remain significantly better than usual care beyond this point for another three months.

There were insufficient trials on subsets of hip OA and mixed OA, and OA awaiting surgery (mainly total joint replacement) to permit extensive analyses. The number of trials investigating postoperative outcomes was also small but were sufficient to be pooled for exploratory analysis. The results at three months after surgery suggest that there were no differences between groups given pre-operative exercise and groups given usual care. Although differences between groups were in favour of exercise for pain (ES 0.13), function (ES 0.25) and performance (ES 0.03), none were statistically significant.

Conclusion: Exercise significantly improves pain, function and performance for knee and hip OA, with single component exercises (particularly aerobic exercise) being consistently better than mixed exercise. However, due to the small number of studies, the results for particular OA subsets (i.e. hip and mixed OA, OA awaiting total joint replacement and postoperative OA) were uncertain. This indirectly reflects the

gap in the evidence and the need for future confirmatory studies.

Declaration

I confirm that this thesis presented for examination is mainly composed by me. Data acquisition, analysis, interpretation and presentation were mainly performed by me, having received assistance in validation of data from peers (Dr. Monica SM Persson, Dr. Joanne Stocks and Dr. Yunfei Hou) and advice on Bayesian analysis from Dr. Jie Wei (Central South University, China) and Prof Nicky J Welton (University of Bristol, UK). Revision and editing of the text, flow and content of this thesis were undertaken based on feedback from my supervisors (Prof Weiya Zhang, Prof Michael Doherty and Dr Michelle Hall).

I also declare that this work is original and the use of copyright material is duly acknowledged. This thesis has not been submitted or accepted for any other degree.

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Glossary of abbreviations

ACR	American College of Rheumatology
ACSM	American College of Sports Medicine
ADL	activity of daily living
BMI	body mass index
CI	confidence interval
CrI	credible interval
DMOADs	disease modifying osteoarthritic drugs
ES	effect size
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
ITT	intention-to-treat
JR	joint replacement
KL	Kellgren-Lawrence grading
MA	conventional meta-analysis
MRI	magnetic resonance imaging
NICE	The National Institute for Health and Care Excellence
NMA	network meta-analysis
NSAIDs	non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OR	odds ratio
QoL	quality of life
RCT	randomised controlled trials
RF	rheumatoid factor
SD	standard deviation

SF	Short form
VAS	visual analogue scale
VO_{2max}	maximum oxygen uptake
WOMAC	Western Ontario & McMaster Universities Osteoarthirtis Index

1 Introduction

This chapter aims to introduce osteoarthritis (OA) with specific focus on knee and hip OA.

1.1 Osteoarthritis

OA is a common complex disorder affecting one or more synovial joints. Clinically, it is characterised by a variety of symptoms, with pain being the most prominent. Pathologically it is identified by irreversible focal articular cartilage loss and new bone formation (osteophytes) at joint margins. It is a condition largely attributed to biomechanical insults with some degree of inflammatory and biochemical involvement. Without effective disease modifying treatment, supportive therapies are the main strategy to limit the burden of OA.

The earliest evidence of OA in humans is from the knee and ankle of a Neanderthal man that lived at least 400,000 years ago (McLain, 1991). Being one the of most common abnormalities documented in excavated human skeletons, OA is as much a common 'ailment' in our ancestors as it is in modern society (Rogers et al., 1981, Dequeker and Luyten, 2008). Despite considerable evolution of its vertebrate hosts from dinosaurs (Rothschild and Tanke, 1992) to man and animals of modern day, certain morphological changes that

characterise OA such as formation of osteophytes – exuberant bone growth (shown in Fig. 1-1) – have remained remarkably unchanged.

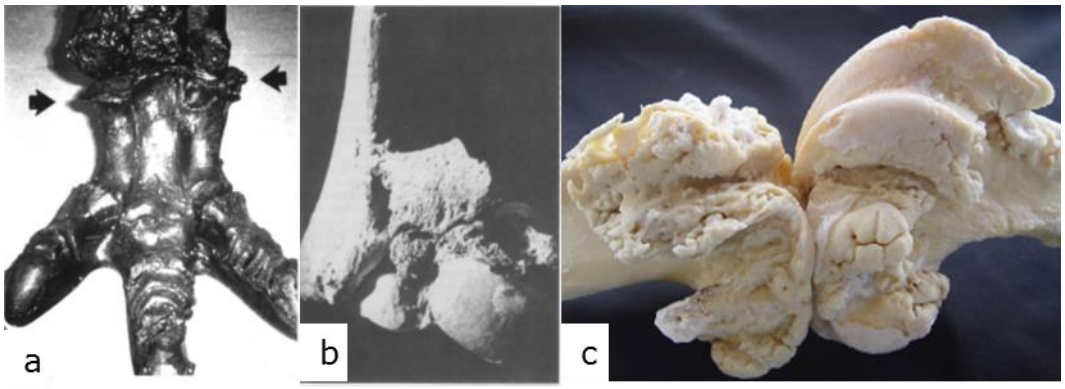


Fig. 1-1 Morphological evolution of osteophytes.
Osteophytes seen in (a) ankle of dinosaur, (b) ankle of Neanderthal man and (c) knee of modern day cow with severe joint deformity
Adapted from Rothschild and Tanke (1992), McLain (1991) and Barbosa et al. (2014)

1.1.1 **Nature of osteoarthritis**

Contrary to the connotation of inflammation from the post fix '-itis', inflammation is not generally considered a crucial component in OA. Instead, OA had been classically appreciated as a biomechanical disorder of the cartilage caused by 'wear and tear' from old age and excessive joint loading (Dequeker and Luyten, 2008, Felson, 2013).

OA is sometimes referred to as 'degenerative joint disease' because it is often found in association with deterioration of the meniscus, subchondral bone and other periarticular tissues (Joseph et al., 2012). However, this terminology is equally

misleading as it reflects OA as being a passive and inevitable process of aging/degeneration.

At the early stages of cartilage breakdown, there is characteristically an active and dynamic metabolic attempt to repair and to restore stability of the entire joint (Felson, 2013). As shown in Fig. 1-2, response to joint insults is not only confined to the articular cartilage but also involves many peri- and intra-articular tissues (e.g. synovium, capsule, bone, ligament and meniscus), albeit to varying degrees.

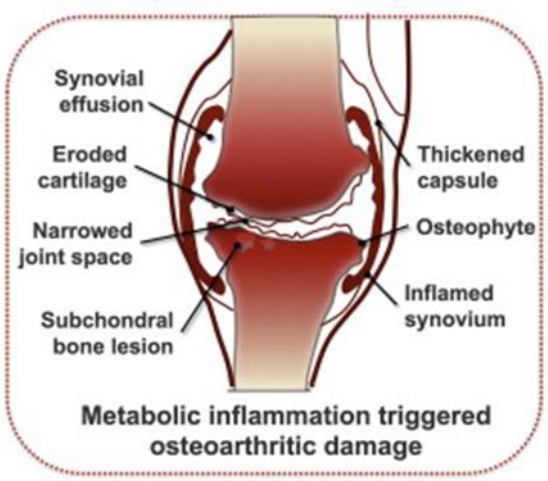


Fig. 1-2 Multi-tissue involvement in osteoarthritis.
Adapted from Wang et al. (2015)

Joints undergoing osteoarthritic changes tend to be asymptomatic in the majority of people when the joint insult does not overwhelm its inherent repair capability. As pathological insult continues, the homeostatic equilibrium

between tissue synthesis and degradation of the whole joint eventually fails, following which symptoms (e.g. pain and discomfort) are more likely to appear (Fig. 1-3).

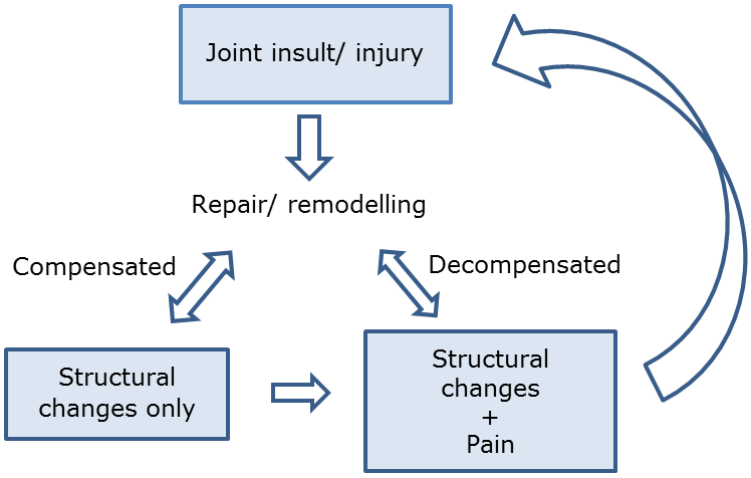


Fig. 1-3 Dynamic adaptive osteoarthritic process.
Source: Author's own

Today, the understanding of OA as a simple joint disorder is changing. OA is now considered a complex disorder exhibiting established links to various systemic dysfunctions and co-morbidities such as widespread pain (Kluzek et al., 2015) and metabolic abnormalities. Along with this is also the recognition that OA actually consists of distinctive aetiological (e.g. primary or secondary), clinical (e.g. single or multi-joint) and structural (e.g. uni-compartmental or tri-compartmental knee OA) subtypes which can manifest in a different manner in

different individuals (Waarsing et al., 2015, Herrero-Beaumont et al., 2009) .

1.1.2 **Definition**

There is no simple definition of OA. An example of this can be seen from the definition that was proposed in 1986 by an OA working group. The definition encompassed clinical, pathological, biochemical and biomechanical features to embody the complex nature of OA (Flores and Hochberg, 2003). Although the American College of Rheumatology (ACR) used a more concise and unifying definition, the definition is still reflective of the complex nature of clinical OA (Altman et al., 1986). These definitions are summarized in Fig. 1-4.

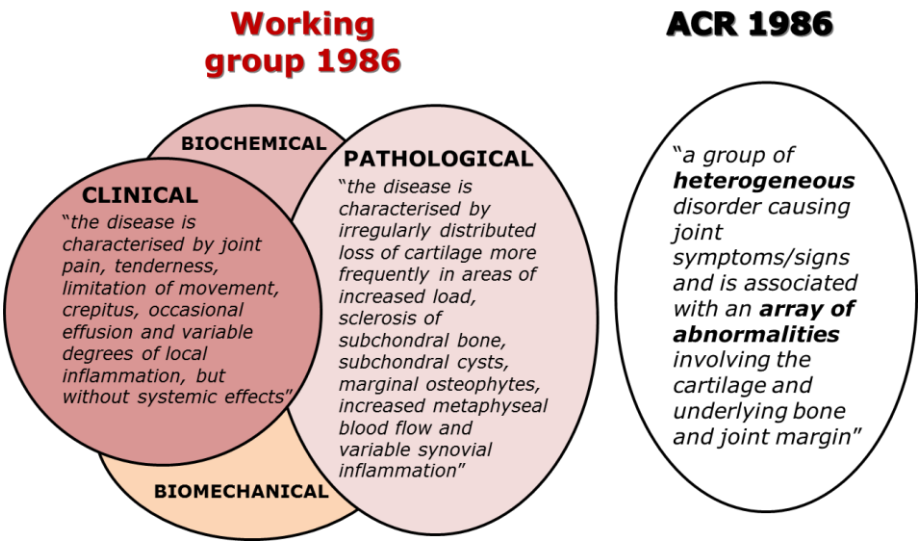


Fig. 1-4 Multidimensional concept in definitions of osteoarthritis by osteoarthritis working group 1986 and American College of Rheumatology (ACR).
Adapted from Flores and Hochberg (2003), Altman et al. (1986)

Other than clinical classification of painful OA, working groups concerned with clinical trials and research have also flagged the importance of a definition for asymptomatic OA (Kraus et al., 2015, Lane et al., 2011). This subset of OA – who are with structural abnormalities but without symptoms – are generally regarded to be of considerable importance to be studied alongside clinical OA (established OA) in order to understand the whole OA spectrum.

1.1.3 **Clinical and radiographic classification**

Depending on the purpose of a study, case definition and classification of OA is typically achieved either through clinical assessment, radiographic assessment, or both.

Symptomatic or clinical OA, is often determined based on ACR criteria. Presence of positive history and signs, with or without negative laboratory investigations for inflammatory arthritis (erythrocyte sedimentation rate and rheumatoid factor), is sufficient for definitive case identification in knee and hip OA (Table 1-1). Radiographic features are not mandatory. The diagnostic performance of ACR criteria has been formally validated with clinically diagnosed patients (Altman et al., 1986, Altman et al., 1991).

Table 1-1 American College of Rheumatology (ACR) definition of OA by clinical ± laboratory criteria

Knee	**Hip**
Knee pain + At least 5 of 9: • >50 years old • Joint stiffness <30 minutes • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth • RF ,1:40 • ESR< 40mm/hr • Synovial fluid – clear, white blood cell count <2000/mm3	Hip pain + • Hip internal rotation <15 + • ESR ≤45mm/hr (or hip flexion ≤ 115) OR • Hip internal rotation ≥15 + • Pain on hip internal rotation + • Morning stiffness ≤60 minutes + • >50 years old

RF= Rheumatoid factor; ESR= erythrocyte sedimentation rate
Adapted from Altman et al. (1986), Altman et al. (1991)

However, there are some limitations in the use of ACR classification due to the lack of standardised definition/description for pain and a tendency to miss mild or early OA. Within a primary care population, only 41% of those with symptomatic OA fulfilled the ACR clinical classification (Peat et al., 2006).

OA classification is also often performed radiographically. X-ray imaging of the joints is easily acquired and radiographic grading system such as the Kellgren and Lawrence (KL) grading system (Kellgren and Lawrence, 1957) offers a simple

cut-off composite score to establish presence of radiographic OA. This is often taken as grade 2 and above, even grade 2 signifies definite presence of osteophyte alone, without joint space loss. Fig. 1-5 illustrates the KL grading.

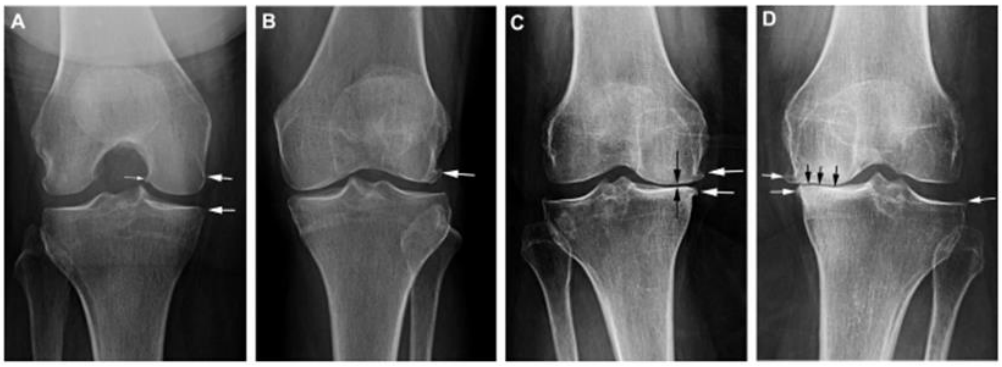


Fig. 1-5 Kellgren-Lawrence grading.
A: Grade 1-Minimal osteophytes; B: Grade 2-Definitive osteophyte; C: Grade 3-Definitive osteophytes and joint space narrowing; D: Grade 4 – Obliteration of joint space.
Adapted from Hayashi et al. (2016)

Although magnetic resonance imaging (MRI) provides better visualization of changes in joint structures including abnormalities in soft tissues (e.g. synovial hypertrophy, joint effusion), cartilage and bone marrow oedema, conventional imaging using X-rays is still widely preferred for diagnosis in clinical trials because it is relatively inexpensive, easily available and easily assessed. Other than cost concern, MRI cannot provide clear cut-off criteria to indicate the presence or absence of radiographic OA (Hunter et al., 2015). There is no

established scoring for MRI diagnosis because the images on MRI varies widely with the image sequencing and specification of the machine used (as shown in Fig. 1-6). Furthermore, the specificity of MRI signals are also questionable as a large proportion (88%) of pain-free knees have been reported to show at least one MRI change consistent with OA (Guermazi et al., 2012).

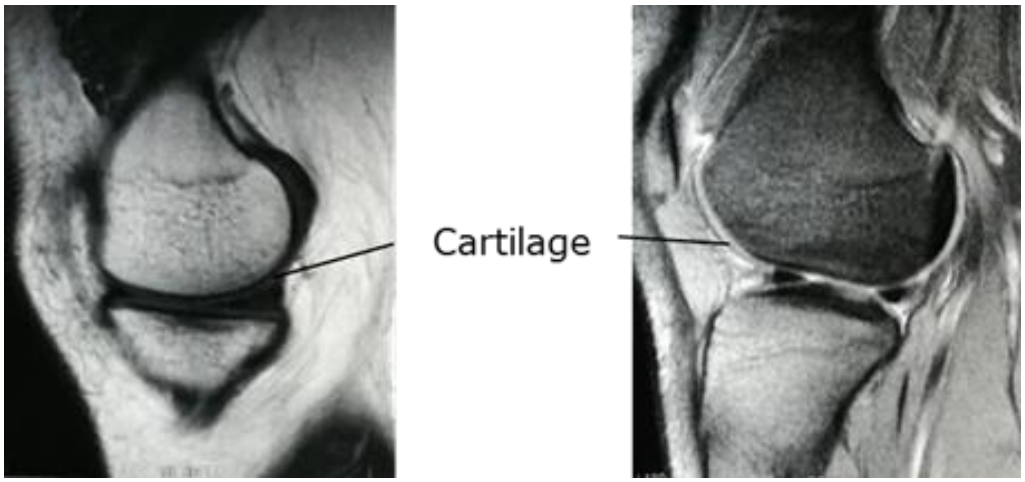


Fig. 1-6 Appearance of cartilage changes with different imaging techniques on magnetic resonance imaging (MRI). Source: Author's own

1.1.4 **Epidemiology**

Globally, the crude prevalence of the general population affected by OA in at least one joint ranges from 10% to 20% (Murphy and Helmick, 2012, March and Bagga, 2004, Plotnikoff et al., 2015, Islam et al., 2016). This figure increases with age. Before 40 years of age, prevalence of

lower limb OA is generally uncommon (<5%) (Sowers et al., 2000, van Saase et al., 1989), although it may be higher in young adults with joint injuries and congenital joint abnormalities (Lohmander et al., 2007). Between the ages of 40 to 50 years, a sharp rise in the prevalence of knee OA invariably occurs across different parts of the world (Woolf and Pfleger, 2003) (shown in Fig. 1-7). Beyond 50 years old, the prevalence of radiographic knee OA and hip OA can be as high as 67% and 45%, respectively in some population (Pereira et al., 2011).

Fig. 1. **Prevalence of osteoarthritis of the knee, by age group, sex, and region, 2000** (*16*). A regions = developed countries in North America, Western Europe, Japan, Australia, and New Zealand. AF = countries in sub-Saharan Africa. AM BD = developing countries in the Americas. EM = countries in the Eastern Mediterranean and North African regions. EU BC = developing countries in Europe. SEA = countries in South-east Asia. WP B = countries in the Western Pacific region

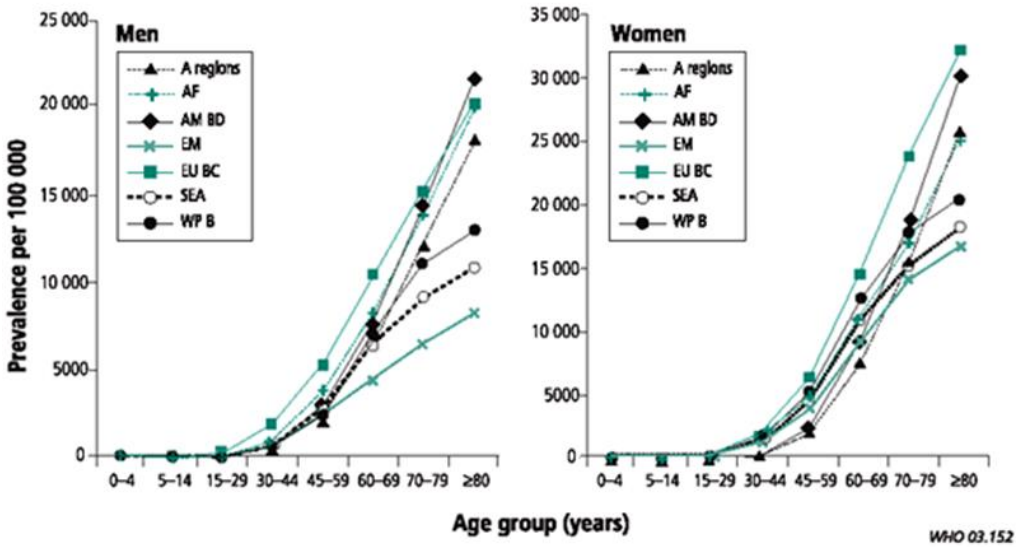


Fig. 1-7 Prevalence of knee OA by age and gender
Adapted from Woolf and Pfleger (2003).

Female preponderance is seen at most joint sites, more markedly in knee OA compared to hip OA especially after 50 years of age (van Saase et al., 1989, Yu et al., 2015, Prescott, 2007, Oliveria et al., 1995, Woolf and Pfleger, 2003). Peak female to male ratio for lower limb OA occurs at the 70-75 years age bracket (Prieto-Alhambra et al., 2013) but is generally not more than 2:1 (Oliveria et al., 1995).

Globally, knee OA seems to be more common than hip OA by 2-4.5 times (Cross et al., 2014). This is consistent with regional estimates of American and Europeans. In the Massachusetts population, the standardized incidence rate for hip OA (defined using clinical + radiographic criteria) was 88 per 100,000 person-years, while the corresponding estimate for knee OA was 2.5 times more - 240 per 100,000 person-years (Oliveria et al., 1995). Meanwhile, in the Europeans, population-based studies of different cohorts have estimated the new cases for knee OA to be 2-3% per year while those for hip OA is <1% per year (Ingham et al., 2011, Leyland et al., 2012, Grotle et al., 2008).

Radiographically defined OA is generally 3-6 fold in excess of symptomatic OA (Zhang et al., 2001, Kim et al., 2014), implying that a large proportion of radiographic OA has no pain. However, symptomatic OA still has a significant health

impact. Globally, OA accounts for 10% of years lived with disability (Vos et al., 2012). In the UK it is estimated that 10% of middle aged people with knee OA report some limitations in activities of daily living (ADL) (Peat et al., 2001). Approximately 80%-90% of hip and knee replacements in the US and UK were attributable to OA (Katz et al., 2001, Katz et al., 2004, Culliford et al., 2012).

1.1.5 **Risk factors**

There is no definitive cause or pathway in OA. As shown in Fig. 1-8, the development and progression of OA (radiographic and clinical OA) occur as a result of interplay between multiple systemic or local risk factors (Mikesky et al., 2006, Katz, 2006, Karlson et al., 2003, Srikanth et al., 2005, Knoop et al., 2011, Barr et al., 2012, Kerkhof et al., 2014). These risk factors mainly act through mechanical, biochemical and genetic pathways, exerting varying influence at different stages of OA (i.e. development or progression of OA) (Radin and Rose, 1986, Andriacchi et al., 2004) and at different joint sites (Arden and Nevitt, 2006, Litwic et al., 2013).

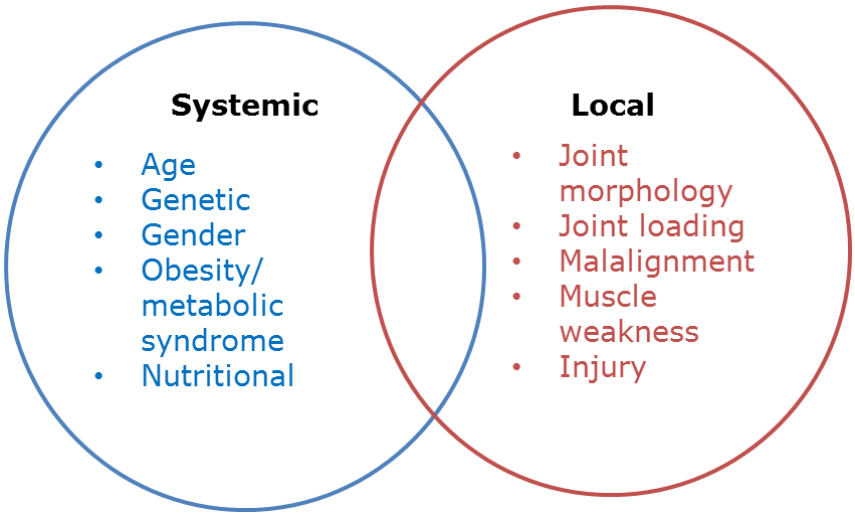


Fig. 1-8 Interplay between systemic and local risk factors that contributes to the development and progression of osteoarthritis.
Source: Author's own

Risk factors may be different between knee OA and hip OA. That is to say, risk factors can be joint specific. For example, male gender is a risk factor for hip OA but not for knee OA in some populations (Kim et al., 2014). Furthermore, the strength of association for risk factors can also vary by joint. This is demonstrated in the hereditability for OA where hip OA (60%) has higher genetic preponderance to knee OA (45%) (Spector and MacGregor, 2004). Similarly, with respect to the association between previous injury and OA, a stronger association occurs for hips (odds ratio (OR) 5.0; 95% CI 1.4, 18.2) than knees (OR 3.8; 95% CI 2.61, 5.70) (Richmond et al., 2013, Blagojevic et al., 2010).

Mechanical mechanisms are widely accepted as the primary pathology in OA. The mechanical theory is indisputable because of the strong association between trauma, injury and other joint-level biomechanical abnormalities and OA (e.g. varus malalignment, joint dysplasia/ incongruent joint surface) (Ganz et al., 2008, Heijink et al., 2012). In addition, almost all systemic risk factors (e.g. age, female, genetics) implicated in development of OA also appear capable of altering the mechanical environment in the joint, primarily through disruption of cellular function of bones and cartilages (Roman-Blas et al., 2009, Loeser, 2009). Although the presence of tissue inflammation is well documented in OA and pain, this is mainly thought to be the consequence of biomechanical derangement and attempted repair rather than a primary causative factor of OA (Felson, 2013).

1.1.5.1 Obesity

Of all risk factors, obesity/overweight which increases OA risk by 2-3 fold (Blagojevic et al., 2010) is an important factor to be acknowledged. Firstly, this is because obesity is modifiable – modest weight loss of 5kg over 10 years is shown to reduce risk of symptomatic knee OA by 50% (Felson et al., 2000). Secondly, the influence of obesity in the OA process is extensive. It not only predisposes a person to development of

OA but also to OA progression (Grotle et al., 2008, Reijman et al., 2007) and joint replacements (Wang et al., 2009, Lohmander et al., 2008). It may be apparent that the link between obesity and OA is mechanical especially when body mass index (BMI) is shown to affect OA in a dose-dependent manner (Cooper et al., 2000).

However, biomechanics alone cannot explain the link between obesity and non-weight bearing joints (Yusuf et al., 2010), neither can it explain why the association between excessive weight is stronger for knee OA than hip OA (Grotle et al., 2008, Lohmander et al., 2008). Although this discrepancy may be attributed to the presence of local factors in the knee (i.e. valgus/varus malalignment) (Sharma et al., 2000, Niu et al., 2009), theories implicating the role of systemic biochemical factors such as chronic inflammation and lipid metabolic abnormalities are emerging (Pottie et al., 2006, Griffin and Guilak, 2005). Fig. 1-9 illustrates both the biomechanical and biological mechanisms of obesity in OA.

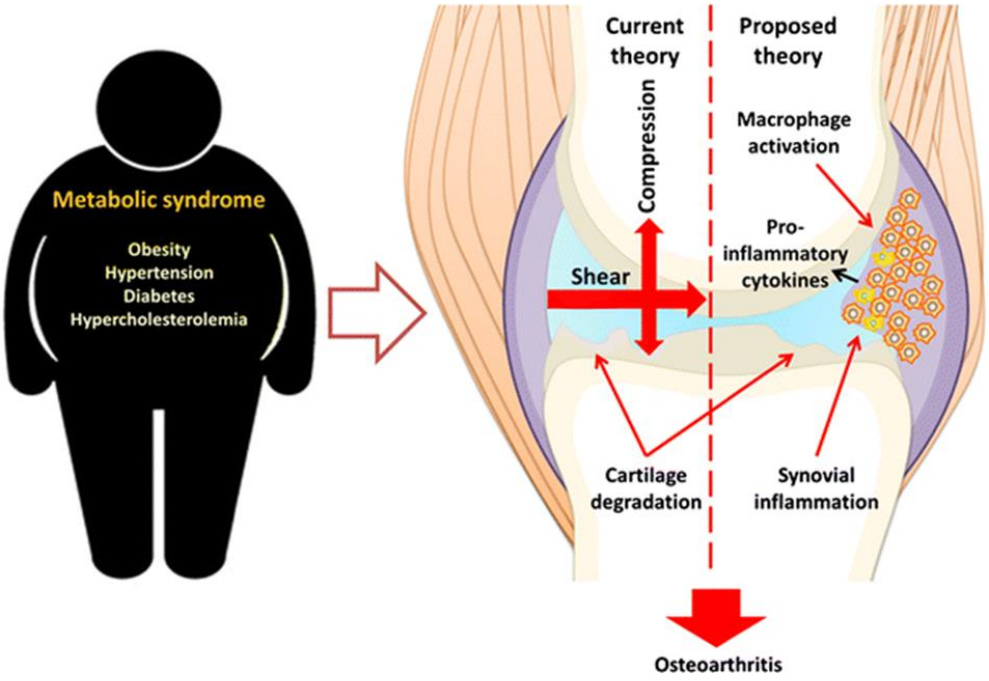


Fig. 1-9 Possible link between obesity and osteoarthritis.
Current mechanical theory attributes cartilage degradation to excessive force loading of the joint. Latest biochemical theory suggests elevated pro-inflammatory cytokines activity, which are commonly found in association with obesity and metabolic syndrome, are responsible for cartilage destruction
Adapted from Sun et al. (2016)

1.1.5.2 Physical activity

It is well recognised that when a joint is immobilized or refrained from loading, atrophy and abnormal structural changes can occur in various joint tissues (cartilage, bone and muscle) within days (Arokoski et al., 2000, Barak et al., 2011). In this regard, physical activity would seem to be chondro-protective and could mitigate the risk of OA.

However, a number of case-control and epidemiological surveys have shown that certain physical activities have

modest to strong correlation to OA onset. Physical activities that are implicated include weight-bearing sports (Spector et al., 1996), heavy intensity tasks (carrying heavy objects, brisk cycling, strenuous sports or gardening with heavy tools) (McAlindon et al., 1999). Some vocational activities related to farming, construction and those that require at least 30 minutes of squatting or kneeling have also been associated with higher OA risk (Croft et al., 1992, Cooper et al., 1994).

It has been estimated that healthy cartilage can tolerate physiological loading of daily activities (Haut, 1989) up to an acute impact equivalent to 3-6 times the load of running or jumping (25Mega pascal) (Vuori, 2001). The threshold is lower if the activities are repetitive and torsional in nature (Buckwalter, 2002), or in the presence of injury (Richmond et al., 2013). However, the intensity needed to induce cartilage damage is difficult to determine accurately. This is because the actual loading threshold is likely to vary in different regions within the joint, with joint position during impact (Haut, 1989, Spector et al., 1996), with the nature of activities that are being performed and with sensitivity and reliability of imaging methods used to assess cartilage integrity (Silverwood et al., 2015).

1.1.5.3 Muscle weakness

Although weakness of muscles may occur after OA onset due to pain inhibition, muscle disuse and reduced physical activity, longitudinal studies have demonstrated that muscle weakness can also occur before OA development (Alnahdi et al., 2012). Oiestad et al. (2015) estimated that quadriceps weakness increases the odds of developing radiographic knee OA by 65% (OR 1.65 95% CI 1.23, 2.21) in their meta-analysis of studies with at least two years follow-up.

However, a critical evaluation of existing evidence is warranted to confirm the causal relationship between muscle weakness and OA. This is because conclusions can differ based on the test protocols used for muscle strength testing (e.g. which muscle was tested, differences in gender, joint alignment and duration of follow up)(Takagi et al., 2017, Slemenda et al., 1998, Sharma et al., 2003).

Furthermore, there is also some evidence indicating that having stronger muscles is not necessarily protective (Litwic et al., 2013). Limited evidence suggests that stronger muscles may increase the risk of OA progression, especially in mal-aligned and unstable knees (Sharma et al., 2003). Nevertheless, from a biomechanical perspective it is very likely that muscle weakness contributes in some way to the

pathogenesis of OA. This is because stronger muscles help to maintain joint stability, to attenuate/absorb excessive loading forces (Dufek and Bates, 1990) and to protect the joint against injuries.

1.1.5.4 Malalignment

Joint alignment modifies load transmission across the knee in laboratory studies. In dynamic and static loading conditions, varus and valgus alignment consistently increases the stress on the medial and lateral compartment of the knees, respectively (Fukuda et al., 2000). Radiographically, this manifests as greater progression of joint space narrowing in the corresponding joint compartment (Sharma et al., 2010). Biomechanically, increased compressive loading in the medial joint compartment may become evident as increased external knee adduction moment (KAM) (Baliunas et al., 2002) (shown in Fig. 1-10).

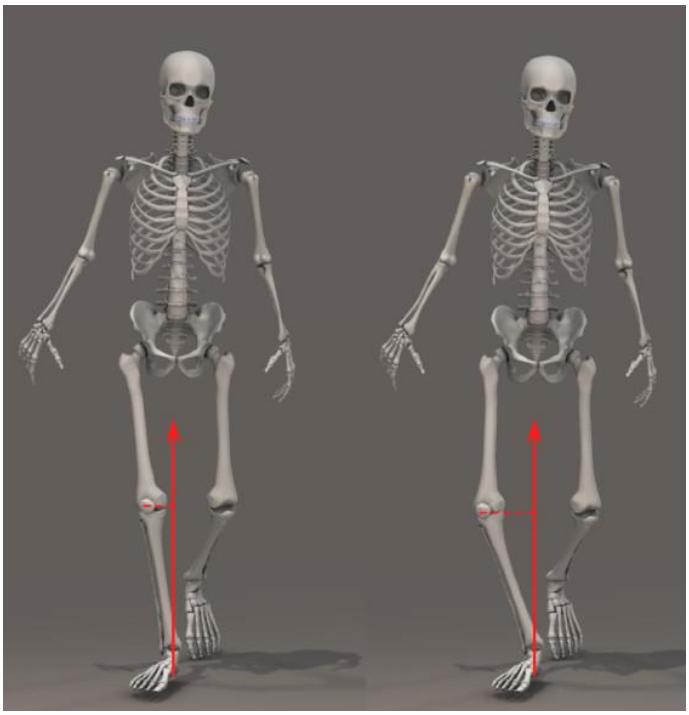


Fig. 1-10 Effect of knee alignment on adduction moment. Varus knee alignment increases loading on the medial knee compartment during walking and may manifest biomechanically as increased knee adduction moment (broken red line). Adapted from Levinger et al. (2013)

1.1.6 **Clinical features and clinical course**

Once established, symptoms may progress insidiously or rapidly depending on OA subtypes. In general, OA symptoms tend to be chronic and may remain stable up to six years (Collins et al., 2014). Clinically, OA can be diagnosed based on a range of clinical findings as shown in Table 1-1. Of these, localised pain and short-lasting early morning stiffness are dominant features. In the early stages, pain in OA is usually during activity. In the later stages, pain may occur even at rest.

Bony changes around the joint could manifest as joint deformity and abnormal joint alignment such as valgus (knocked knees) or varus alignment (bowed knees). Another sign seemingly synonymous with lower limb OA is quadriceps weakness. It is not only common in knee OA but also hip OA (Bennell et al., 2011). In some patients with advanced OA, limitation of joint motion may develop secondary to muscle contracture, capsular fibrosis, altered joint surface congruence, osteophytes and occasionally intra-articular loose bodies.

The clinical progression of OA is variable and depends on multiple factors. While symptoms are usually stable and some may even experience improvement (Nicholls et al., 2014), those who are obese, depressed and suffer from medical comorbidities tend to report an unfavourable pain trajectory over six years (Collins et al., 2014).

Progression of radiographic OA, on the other hand, appears to be relatively higher than symptomatic progression. Population estimate suggests that the cumulative rate of radiographic knee OA progression ranges from 32% over eight years (Felson et al., 1995) to 40% over 15 years (Leyland et al., 2012). As for the hip, amongst those with pre-disposing structural abnormality in the hip, only a small proportion

(20%) eventually demonstrate OA changes over an 18 year period (Hartofilakidis et al., 2011).

There is a paucity of prospective epidemiological studies that investigate progression to joint replacements. However, longitudinal multicentre studies indirectly suggest that the number of affected individuals undergoing joint replacement is possibly more than 5% per year among Europeans (i.e. 17% at 3 year endpoint) (Conaghan et al., 2010) and nearly 4% per year among Americans (26% over 7 years) (Skou et al., 2016). The corresponding rate in hip OA is not well described.

1.1.7 **Pathophysiology**

Although modern technology has tremendously improved the visualisation/demonstration of pathological changes in diverse tissues of the joint, the precise sequence of pathological events occurring in the joints is still poorly elucidated.

1.1.7.1 Articular cartilage breakdown

The model of OA that considers articular cartilage breakdown as the initial event is very popular. The hyaline articular cartilage is a viscoelastic connective tissue of 1-3 mm in thickness (in the knee). Its highly organized extracellular matrix is designed to cushion compressive force and it reduces friction of articulating surfaces (Faber et al., 2001). Of the total volume of the matrix, 65-80% is composed of

pressurised interstitial water, 20-35% load bearing macromolecules (mainly type II collagen and aggrecan proteoglycan) and <2% chondrocytes (Sophia Fox et al., 2009). Chondrocytes – the only resident cell in the cartilage – is responsible for maintaining the extracellular matrix. As there are no vascular or lymphatic tissues in the cartilage, the viability of chondrocytes relies on diffusion of oxygen and nutrients from the synovial fluid, and from blood in the underlying subchondral bone (Hunziker et al., 2002). For this reason, joint mobilization (which improves diffusion of nutrients to cartilage) is beneficial for the joint (Eckstein et al., 1999).

Disruption of the proteoglycan network, the scaffold of cartilage, is known to occur before any other sign of OA (Goldring and Goldring, 2010) – causing increased water retention and increase cartilage volume in the early stages. Upregulation of anabolic activities is observed initially when the repair response is initiated. However, as the insult continues, anabolic activity is gradually replaced by catabolic activities – leading to loss of chondrocytes and proteoglycan. The hydraulic permeability, crucial in maintaining cartilage integrity by 'regulating' the water content of the matrix, is also disrupted as OA progresses. These changes then progress to

cartilage ‘softening’, fraying and fissuring of the cartilage (Buckwalter, 2002) eventually leading to cartilage loss (shown in Fig. 1-11).

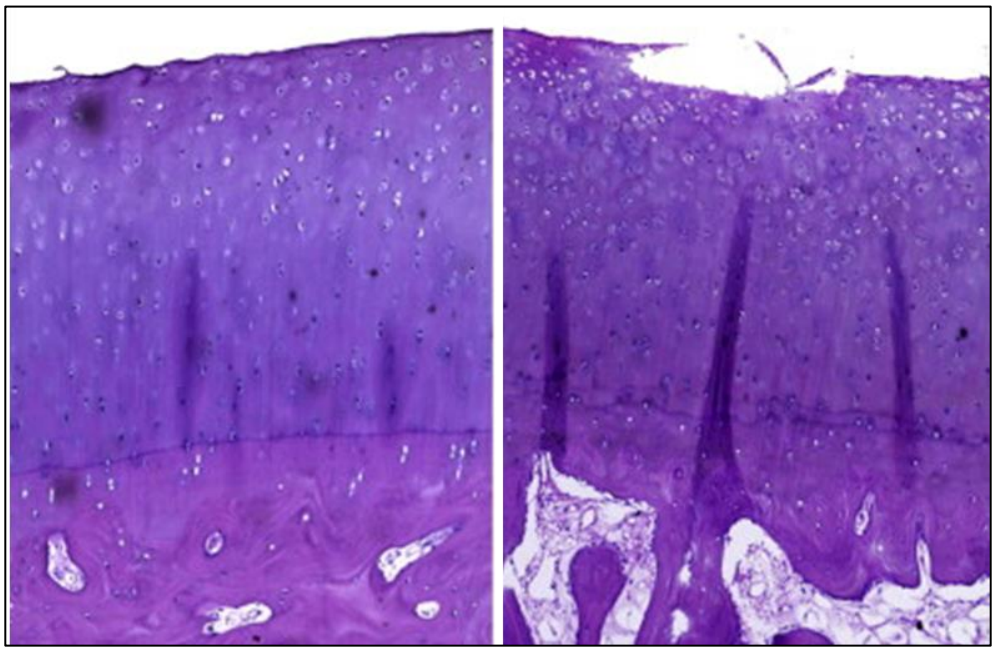


Fig. 1-11 The smooth cartilage surface of normal joint (left) is loss in osteoarthritic joint (right).
Adapted from Elmesiry et al. (2014)

Due to the limitations of its natural repair process, hyaline cartilage breakdown is almost always irreversible. Even when repair occurs, the fibrocartilaginous repair tissue that consist mainly of type I collagen is not as resilient as the native hyaline cartilage that contains type II collagen (Mainil-Varlet et al., 2003). The mechanically less competent scar tissue could lead to exacerbation of joint insult.

1.1.7.2 Bone alteration

Bony abnormalities most often seen in radiographic imaging include marginal osteophytes, subchondral sclerosis/ thickening and subchondral cysts (shown in Fig. 1-12). Osteophytes are osteochondral nodules that are comprised of new bone and fibro-cartilage that arise from periosteal cells at the joint margin where cartilage, synovium and periosteum converge (Sandell and Aigner, 2001). It can be regarded as reactive cartilage formation which occurs in response to abnormal mechanical loading to regain/maintain joint stability (Pottenger et al., 1990). Exuberant growth of osteophytes however, could be undesirable as it may lead to restriction of normal joint movement, joint deformity and malalignment.

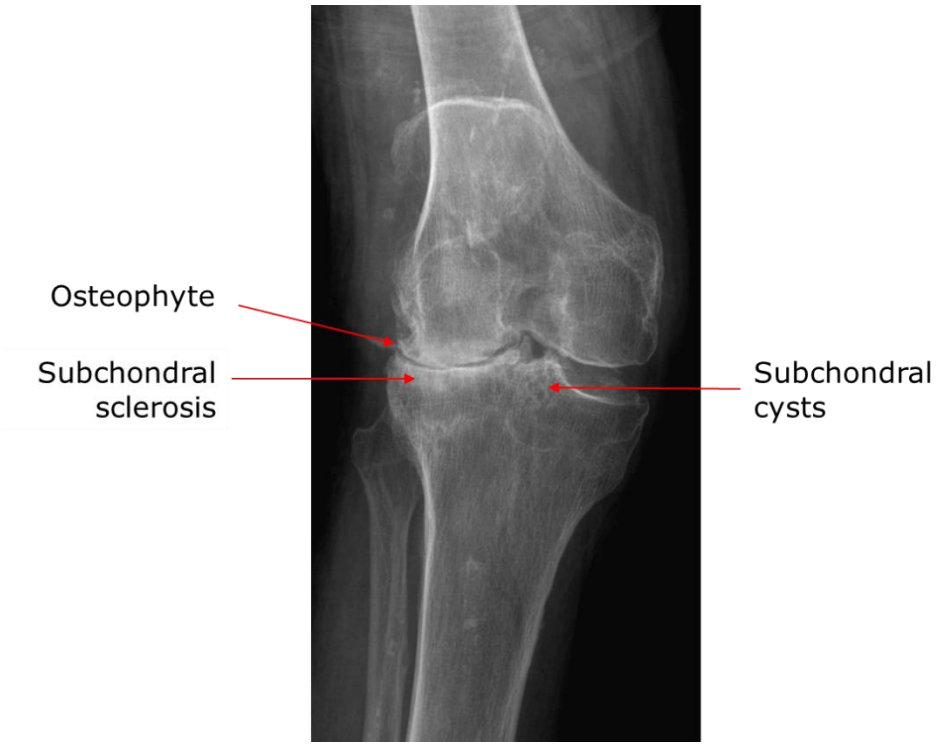


Fig. 1-12 Typical bony changes in osteoarthritic joint
Adapted from Altman and Gold (2007)

Degradation of cartilage is widely thought to precede subchondral changes. Following the mechanical failure of overlying cartilage, subchondral sclerosis is thought to occur as a result of remodelling of micro-fractures in the subchondral bone. However, an alternative view has been proposed and argues that changes in the stiffness of the underlying subchondral bone occurs first. This then alters the cushioning mechanics of the cartilage, leaving the cartilage vulnerable to injury (Radin and Rose, 1986). To date, the causality is still difficult to determine because pathology in both tissues usually co-exist.

Similarly, the cause of subchondral cysts is also controversial. One hypothesis regards subchondral cyst as a passive event caused by synovial fluid intrusion into the underlying bone through fissured cartilage (Landells, 1953). The other hypothesis suggests that cavitation is formed by resorption of necrotic and contused bony tissue (Rhaney and Lamb, 1955).

1.1.7.3 Bone marrow oedema

This is a common MRI finding in subchondral bone of OA joints. On MRI, it is appreciated as an area of increased signal intensity on fluid-sensitive imaging sequences (e.g. bright signals on T2-weighted images) with ill-defined margins (Fig. 1-13). On histological examination, it shows mixed pathology of bone marrow fibrosis and necrosis, and trabecular micro fractures at different stages of healing. However, contrary to the MRI signals that suggest oedema, there is no significant fluid accumulation on direct examination (Taljanovic et al., 2008, Xu et al., 2012).

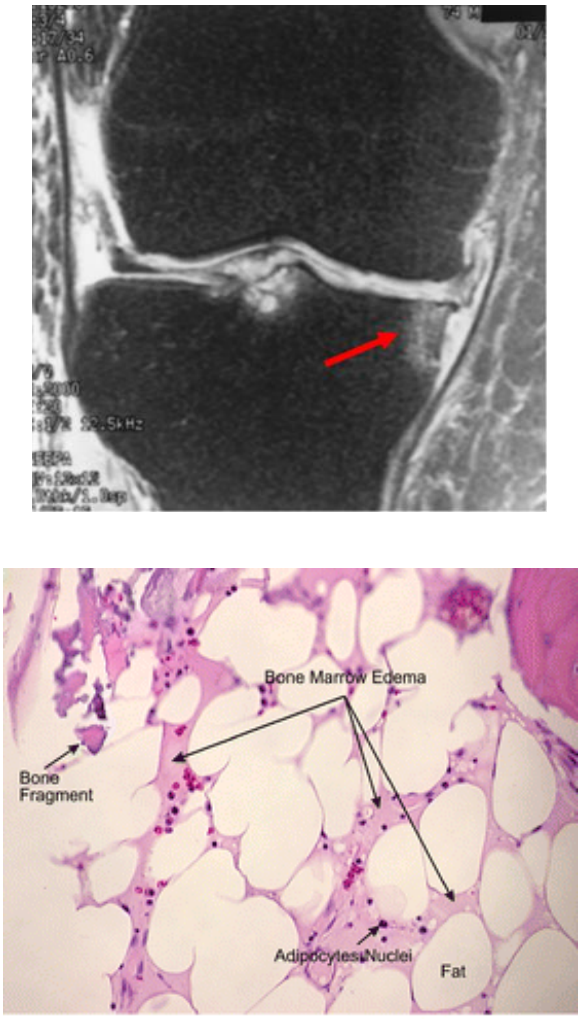


Fig. 1-13 Appearance of bone marrow lesion on magnetic resonance imaging of the knee (top) and on histological examination (bottom).
Adapted from Felson et al. (2001) and Taljanovic et al. (2008)

1.1.7.4 Synovial inflammation

Synovial inflammation is a well-documented feature in OA (de Lange-Brokaar et al., 2012), along with other evidence of increased inflammatory markers in plasma and synovial fluid (Sokolove and Lepus, 2013). However, the synovial inflammation in OA is not as prominent as that found in

classical inflammatory rheumatoid arthritis. It is reflected clinically as joint effusion, swelling and stiffness. At present, the role of synovial inflammation in OA is still unclear. Some hypothesise that synovial inflammation is merely a response to cartilage breakdown. In contrast, others argue that synovial inflammation precedes OA and could logically be a cause and not a consequence of cartilage breakdown (Pelletier et al., 2001).

1.1.7.5 Pain- structure relationship

Since not all painful joints have abnormal x-rays and conversely not all joints with abnormal x-rays are painful, there is a notion that structural changes and symptoms are discordant. The proportion of overlap may range between 15-80% (refer Fig. 1-14) (Bedson and Croft, 2008). With improved understanding and advanced imaging modalites, the discrepancy between structure and pain is narrowing.

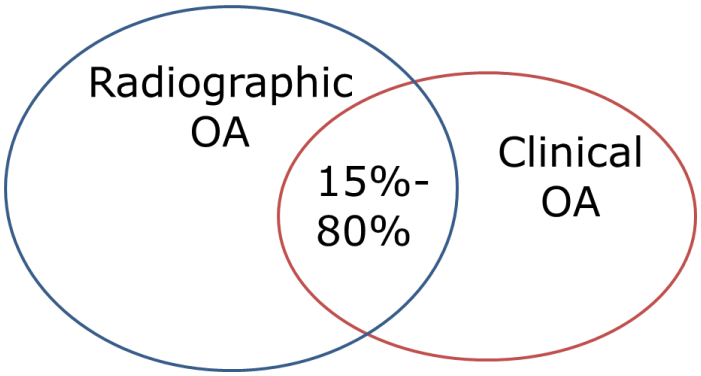


Fig. 1-14 Partial overlap between radiographic and clinical osteoarthritis (OA).
15-80% with radiographic OA would fulfil clinical criteria, and vice versa. Adapted from Bedson and Croft (2008)

Other than bone, soft tissues such as synovium, ligaments, muscles and menisci which are not visible on X-rays are also potential sources of pain in OA (Hill et al., 2007, Xu et al., 2012). Using modern imaging methods we are now able to confirm the association between pain and soft tissue changes around the joint (Yusuf et al., 2011). Furthermore, the cartilage that is normally aneural has been shown to be capable of emanating pain as inflammatory mediators induce abnormal nervous and vascular growth in the deeper layer of cartilage (Walsh et al., 2010). The newly innervated cartilage could now become sensitised to insults such as hypoxia or excessive mechanical loading (Bonnet and Walsh, 2005).

This could explain the presence of pain despite normal X-rays. Numerous epidemiological studies also supports pain-structure

relationship by demonstrating the presence of a graded relationship between pain and KL grading severity (Lethbridge-Çejku et al., 1995, Muraki et al., 2009). However, in some OA subgroups (e.g. widespread and multi-joint OA), pain can be disproportionately problematic in comparison to the structural damage. In this subgroup, contribution from disturbances in nociceptive signal processing (pain sensitisation) or neuropathic-like pain is more prominent than tissue damage itself. That is to say the neurophysiological disturbance causes pain to arise at a lower threshold and also increase the likelihood for pain to be experienced at sites away from the affected joints. This reflects a state of augmentation of pain perception or decrease tolerance to pain (Finan et al., 2013).

The mechanisms responsible are related to increased neuronal hyper-excitability (increased response to stimuli), impaired inhibition of the pain pathways, formation of pain memory (neuroplasticity), or generation of ectopic foci of impulses in the peripheral and central nervous system (Phillips and Clauw, 2013, Hunter et al., 2008, Dimitroulas et al., 2014, Schaible, 2012).

By contrast, some radiographic abnormalities are not always associated with pain. The weak association may be better explained by the biopsychosocial framework of pain. That is to

say, pain perception and processing is not solely determined by the degree of tissue injuries or biological derangements but also influenced by psychosocial factors (Fig. 1-15). Poor coping, anxiety depression, bad pain experience and low self-efficacy are examples of psychosocial risk factors for pain (Rayahin et al., 2014, Youngcharoen et al., 2016). These between subject psychosocial confounders (difference in pain experience, self-efficacy) are difficult to address satisfactorily in clinical trials. However, when these factors can be successfully controlled for (i.e. within the same individual), correlation between pain and structural abnormality has indeed been found (Neogi et al., 2009).

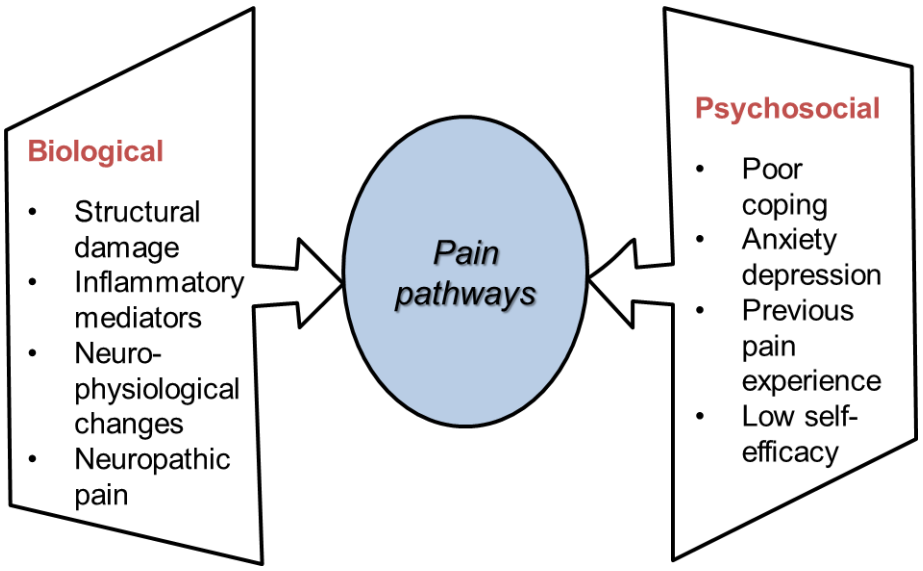


Fig. 1-15 Biopsychosocial factors associated with greater severity of pain.
Source: Author's own

1.1.7.6 Impaired proprioception and joint range of motion

Proprioception is the ability of joint to perceive/sense spatial movement (consciously or unconsciously). It contributes to postural and joint stability through protective reflexes (Roos et al., 2011). Proprioceptive acuity decreases with age but in OA, the deterioration is augmented as the structures providing sensory feedback such as the ligaments, capsule and muscles. are all further compromised by OA (Alexander, 1994, Roos et al., 2011). Proprioceptive and balance impairment can cause difficulties with mobility.

In healthy joints, the capsule and muscle together contribute >80% of joint 'innate resistance' to movement (Johns and Wright, 1962). In OA, limited joint motion can be additionally contributed to by inflammation (causing fibrosis of joint capsule and synovium) and physical inactivity (causing disuse contractures of tissues and muscles around the joint). In the presence of pain, joint motion can be further compromised by reflex and voluntary contractions of muscle around the joint.

1.1.8 **Co-morbidities in OA**

According to a survey of 60 general practices in the UK, people with OA are at higher risk of experiencing additional musculoskeletal and non-musculoskeletal comorbidities (OR 2.35; 95%CI 2.16, 2.55) (Kadam et al., 2004) than those

without OA. Anxiety-depression disorder affects two out of five people with lower limb OA seeking GP consultation (Axford et al., 2010). Sleep disorders can be 25%-35% more prevalent in painful OA than in a non-symptomatic cohort (Allen et al., 2008). Some disorders such as widespread musculoskeletal pain appear to be more common when there is bilateral joint pain or with higher severity of joint pain (Carlesso et al., 2017).

More importantly, OA has a strong association with complications related to analgesics. For example, non-steroidal anti-inflammatory drugs (NSAIDs) predispose patients to cardiovascular, renal and gastrointestinal complications (Pelletier et al., 2016) and prescribed opioids (Rolita et al., 2013) increase falls and fractures risks. This may in part explain the higher mortality among symptomatic OA compared to asymptomatic OA (Liu et al., 2015).

Furthermore, a number of factors implicated in the pathophysiology of metabolic syndrome and cardiovascular disease are also shared by OA (Findlay, 2007, Engström et al., 2009), explaining the strong relationship between OA and these disorders (Rahman et al., 2013). It is therefore not surprising that people with OA have higher all-cause mortality compared to the general population (Nüesch et al., 2011,

Barbour et al., 2015), challenging the traditional view that OA is a non-fatal joint condition.

1.2 **Management of OA**

There is currently no treatment shown to reverse structural changes of OA. Therefore, alleviating symptoms, preventing progression of OA and maintaining/improving physical function are the primary goals. Management for OA has to be holistic in order to meet the multidimensional (physical, psychological and social) and individual needs of patients. The recommended practice is for all people with OA to be offered a range of non-pharmacological interventions first (McAlindon et al., 2014). Some with more severe symptoms would be considered for additional pharmacological therapies and fewer with intractable symptoms would be offered surgical intervention.

1.2.1 **Non-pharmacological**

Non-pharmacological treatment is a universal first line treatment for all stages of OA. Patient education, weight loss for the overweight and obese, and physical activity/exercise are core non-pharmacological approaches advocated by The National Institute for Health and Care Excellence (NICE)

(NICE.org.uk., 2014) and other guidelines (Nelson et al., 2014).

Patient education may take many forms such as education on lifestyle modification, coping behaviours, self-management strategies and on understanding of the OA process itself. While education intervention has no direct effect on pain, physical function or structural progression, it is recommended for its role in alleviating anxiety, improving patient self-confidence, ensuring treatment adherence and correcting maladaptive behaviours and beliefs (Buszewicz et al., 2006).

Physical activity/exercise and weight loss for those who are overweight/obese, are widely advocated not only to improve OA outcomes but also for general well-being and for reducing risk factors for metabolic syndrome and other co-morbidities related to sedentary lifestyle. It is also important to recommend physical activity even to patients who may be too frail/disabled to meet the minimum recommendation. This group of individuals can still gain health benefits by minimising sedentary activities and staying as active as possible (Minor et al., 1989, Chodzko-Zajko et al., 2009).

Other non-pharmacologic therapies approved by NICE include orthotic aids and electrotherapeutic modalities (NICE.org.uk.,

2014). Orthotic aids primarily function to correct abnormal biomechanics (as illustrated in Fig. 1-16) while electrotherapeutic modalities provide pain relief.

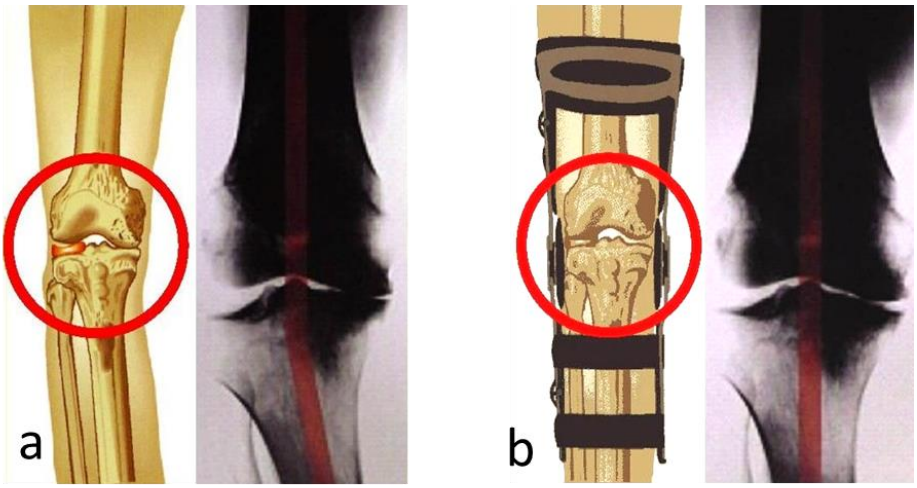


Fig. 1-16 Medial unloader brace.
Loading on medial knee is relieved after correction of knee malalignment. Pictures are courtesy of DJO Global.

1.2.2 **Pharmacological and neutraceutical**

1.2.2.1 Analgesics

A great number of drugs and formulations are used today to control pain in OA, including the 'gastro-sparing' cyclo-oxygenase-2 inhibitors within the NSAID family. NSAIDs are available in both topical and oral formulations. Another popular topical drug is capsaicin. Pharmacological agents for systemic use include paracetamol, NSAIDs and opioids, and for intra-articular administration corticosteroids and hyaluronic

acid. Table 1-2 lists the common types of pharmacologic agents and administrative routes.

Table 1-2 Examples of prescriptive and non-prescriptive analgesics

Topical	**Oral**	**Intra-articular injection**
NSAIDs	Paracetamol	Corticosteroid
Capsaicin	NSAIDs	
Rubefacients	Opioids	

NSAIDs= non-steroidal anti-inflammatory drugs

Topical treatments are popular for its ease of accessibility and for being a safer option compared to systemic therapies. Topical options are the first line analgesics especially for peripheral joint OA with no widespread pain. As a group, topical NSAIDs were reported to be efficacious only within the first 2 weeks of application when compared to placebo (Lin et al., 2004). However, when a more recent meta-analysis examined topical diclofenac on its own, it was shown that the effect of diclofenac could persist longer – i.e. up to 12 weeks (Deng et al., 2016).

Paracetamol, on the other hand, is the first line oral analgesic. NSAIDs should only be considered when regular paracetamol is ineffective. For those in whom oral NSAIDs are deemed

unsafe, intra-articular corticosteroids may be used instead. It has been shown that this option is as effective as oral NSAIDs for pain relief up to 3 months (Bannuru et al., 2014).

1.2.2.2 Disease modifying OA drugs (DMOADs)

While analgesic may be important to control the symptoms of OA, it does not alter the outcome of OA. Preventing, arresting or even reversing the changes of OA would be the function of a group of drugs known as disease or structure modifying OA drugs (DMOADs). Some supplements (e.g., glucosamine, chondroitin) and drugs that target specific enzymatic activities (involved in the production of biochemical mediators, cartilage and bone turnover) are being actively investigated for their putative potential to treat OA (Martel-Pelletier et al., 2012). However, results from clinical evaluation of all potential DMOADs have not been conclusive (Wandel et al., 2010). One of the leading challenges faced in the development of DMOADs is the lack of recruitment criteria for pre-clinical OA when changes are still confined to the cellular level – a stage during which the opportunity for disease modification may be greatest (Ryd et al., 2015). At present, OA identified through traditional radiographic and clinical recruitment methods are characteristically 'established' with limited potential for reversibility (Mobasheri, 2013). Moreover, there is also an

absence of reliable/sensitive measure of OA progression and lack of long study follow up (considering the stable nature of OA) that further complicate efforts to identify DMOADs.

1.2.2.3 Nutraceuticals

Other than glucosamine and chondroitin sulphate, some food supplements such as vitamins C, D, E and K, and avocado and soybean unsaponifiable fractions have also been explored for chondro-protective capability (Thomas et al., 2018). If effective, these nutraceuticals would be expected to alleviate pain, improve function and retard OA progression (Hung et al., 2017). However, no definitive clinical indication has been found to date (Gallagher et al., 2015). Even though avocado and soybean unsaponifiable fractions appear to be promising in general (Christiansen et al., 2014), it has not been widely supported by guidelines (Nelson et al., 2014).

1.2.3 **Cellular therapy**

Preliminary evidence supporting the regenerative potential of stem cells and other cellular derivatives makes cellular-based therapy an attractive alternative for people with OA who are deemed unsuitable for joint replacements. Active research is ongoing and at present, its clinical benefit and safety is still uncertain owing to non-standardised study protocols including harvesting and processing methods (Chahla et al., 2016).

1.2.4 **Surgery**

For patients who do not obtain satisfactory relief from conservative management, surgery may be offered for palliative or 'curative' purpose. The arthroscopic debridement and lavage procedure for palliative purpose is not supported by clinical study and recent NICE guidelines unless there is evidence of true locking by loose bodies (NICE.org.uk., 2014, Moseley et al., 2002). In some cases, osteotomies may be performed to correct malalignment and it may be combined with joint replacement surgery – which could be partial or total.

Short term outcome after total joint replacements is promising. A majority of knee OA and hip OA patients (80-90%) experienced improved function and symptoms after surgery (Katz, 2006). A relatively small portion (~10-30%) continued to experience symptoms when reviewed at 3month – 5 years after knee and hip replacements (Beswick et al., 2012). Although joint replacement is widely regarded as 'curative', there is an increased risk for revision surgery in patients of younger age (Santaguida et al., 2008) or if they have multiple co-morbidities (Bozic et al., 2014).

2 Exercise for OA

The importance of exercise in OA management has already been recognised for at least 50 years (Golding, 1969). Today, it forms one of the core therapy in OA to not only control symptoms (McAlindon et al., 2014), but also to potentially slow the clinical progression of OA (Bastick et al., 2015, de Rooij et al., 2016).

2.1 Terminologies: Physical activity and exercise

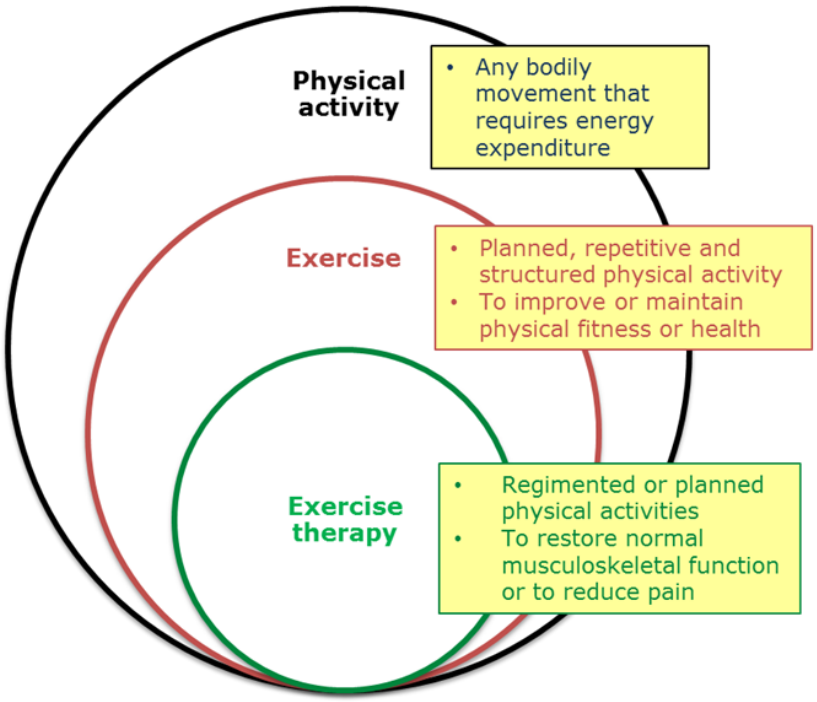


Fig. 2-1 Relationship between exercise and physical activity. Adapted from Chodzko-Zajko et al. (2009), Ageberg and Roos (2015)

The term ‘exercise’ is sometimes used interchangeably with ‘physical activity’. However, although these terminologies are related, they are different with regards to concept and purpose (Fig. 2-1). The American College of Sports Medicine (ACSM) regard e*xercise* as ‘movements that are planned, repetitive and structured to improve or maintain physical fitness of health’ while the term *physical activity* has a more general connotation that lacks specific purpose – it encompasses any bodily movement that requires energy expenditure (Chodzko-Zajko et al., 2009). Further to this, the term *exercise therapy* may be preferred by some to discriminate exercise explicitly done for therapeutic purpose (i.e. overcoming musculoskeletal disability or pain), from exercise done to improve general health (Ageberg and Roos, 2015) .

For most purposes exercise may be simply regarded as a form of organized/purposeful physical activity. It is often structured around a basic framework consisting of few elements, collectively known as the FITT principle: **f**requency (how many times), **i**ntensity (how hard), **t**ime (how long) and **t**ype (what exercise) (Deschenes and Garber, 2013).

2.2 Goals and principle

Exercise is strongly advocated in the general aging population for the generic purpose of encouraging physical activity, which is itself an independent predictor of many morbidities (e.g. obesity and metabolic diseases) (Chodzko-Zajko et al., 2009). Whereas in the OA population, the specific aims of exercise therapy are to control pain symptoms, improve or maintain physical function/QoL and to limit progression of OA whenever possible. Both the generic and specific aims should not be considered mutually exclusive especially when there is substantial evidence to suggest that morbidity count influences long term functional outcomes in OA (Holla et al., 2010, van Dijk et al., 2010) (shown in Fig. 2-2).

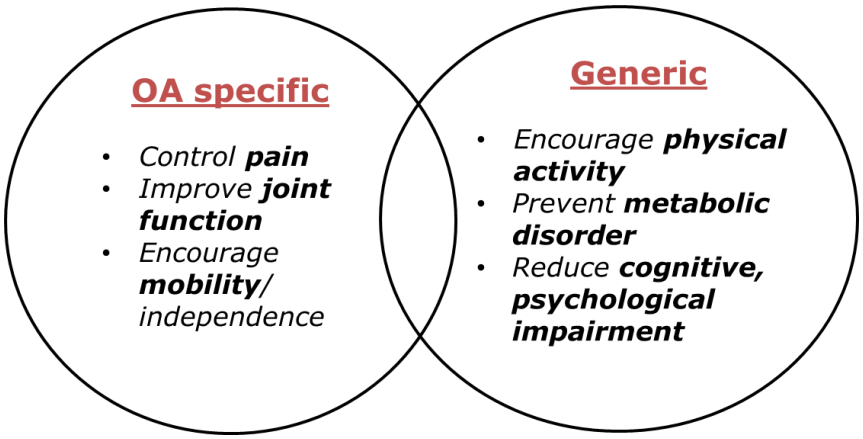


Fig. 2-2 Osteoarthritic (OA) specific and generic goals of exercise therapy are not mutually exclusive.
Source: Author's own

The therapeutic targets in exercise are multiple and involve both biological and psychosocial targets. Biological targets encompass reduction of weight in the obese, preserve joint motion, improve muscle strength and balance to ensure joint stability, and improve fitness to encourage mobility/ independence. Psychosocial targets of treatment on the other hand are potentially more challenging to overcome. These include management of mood disorder, activity avoidance behaviour, and poor coping or self-management strategies.

In order for exercise programs to effectively address physical deficits, it is important to adhere to some training principles (refer Fig. 2-3). One important consideration is the principle of **progressive overload** which dictates that improvements can only be gained when the given physical stimulus is beyond the intensity/volume that the body is accustomed to (Paterson and Warburton, 2010). Additional benefits gained from this point onwards would then be subjected to the positive dose response relationship (Haskell et al., 2007). As the body adapts to continuous stimulus, the minimum threshold required to induce improvement will need to be increased.

Other principles include the principle of **specificity** (specific exercise type for specific performance), and **reversibility** (exercise benefits are not permanent) (American College of

Sports Medicine, 2013). Also important is the principle of **individuality** that indicates exercise should be tailored to individual needs and abilities.

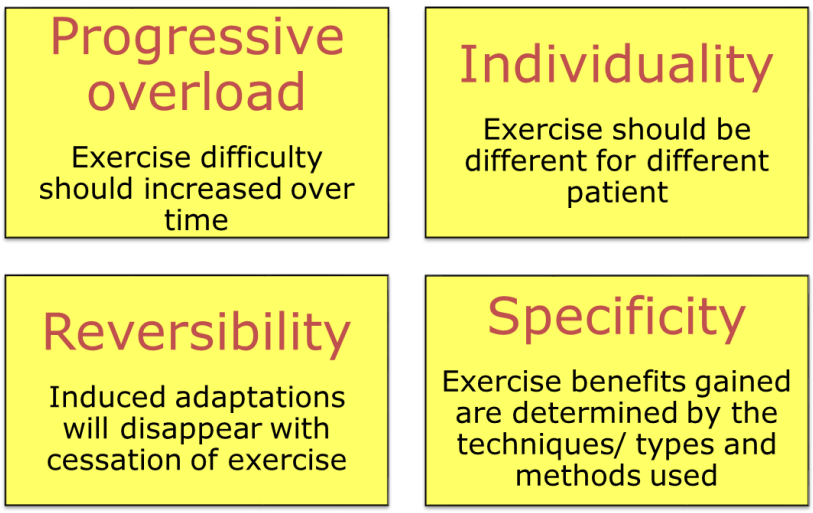


Fig. 2-3 Principles of training.
Adapted from American College of Sports Medicine (2013)

2.3 Individualising exercise programs

Many different aspects of exercise delivery have to be considered when designing an individualised exercise program. The fundamentals of individualising exercise is often guided by the framework of FITT introduced in section 2.1. At the core of designing an individualised exercise program is identifying the physical treatment target – i.e. which component of health is impaired. This will then determine the type of exercise to be prescribed.

Another component of individualising exercise involves determining how frequent the exercise should be performed

(e.g. programs to be initiated at higher frequency in those who are active and lower frequency for those who are sedentary) and the level of exercise intensity (e.g. high intensity in those with no co-morbid and low intensity in those with multiple co-morbid). In prescribing exercise for individuals it is also important to include details of exercise duration (i.e. period for which the exercise should be maintained), the rate at which training should be increased, the setting (e.g. hospital based for those requiring close supervision), the medium of exercise (e.g. water or land), and other clinical considerations to ensure patient safety and efficacy of the exercise programs.

2.3.1 **By health component**

According to ACSM, component of physical health can be sub grouped into few domains such as muscle strength, cardiorespiratory fitness, joint range of motion or muscle flexibility and balance (American College of Sports Medicine, 2013). Each of these health components can be individually targeted by different exercise programs with distinctive movement patterns or training methods (see Table 2-1).

Table 2-1 Characteristics of exercise that targets different component of physical health

Components	Type and characteristics of exercise
Muscle strength	Strengthening exercise:
	Focus on lifting weights or resistance
Cardiorespiratory fitness	Aerobic/ endurance exercise:
	Focus on sustained and repetitive movement of large muscle groups e.g. arms, legs
Joint range of motion	Flexibility/ stretching exercise:
	Focus on keeping the muscles/joints in stretched position within prescribed range of motion
Balance	Proprioceptive/ neuromuscular skills training:
	Focus on maintaining postural control and stability while standing or moving

The property of specificity in exercise was well demonstrated by a three arm (strength training, proprioception training and non-exercise) randomised controlled trials (RCT) with over 100 participants by Lin et al. (2009). Both groups that were given exercises showed significant improvements over non-exercise group in pain and function outcome. However, both exercise groups had different physical gains. The most evident change shown by strength training group was in knee extension strength whilst proprioception training group showed most improvement in walking performance on spongy surface.

Apart from these conventional exercises that addresses physical health, there is another exercise – mind-body exercise – which is receiving increasing attention purportedly for having additional mental health benefits beyond those conferred by conventional exercises (Brosseau et al., 2017). The role of psychological and mental health is well recognise in the context of OA management. Mind-body exercise (e.g. Tai-chi and Yoga) which has additional element of mindfulness and relaxation to the physical routine is believed to be beneficial especially for those who have features suggestive of abnormalities in central pain mechanisms such as widespread pain. This is because mind-body exercise could potentially affect pain perception through brain, mind, body and behavioural interaction (National Center for Complementary and Integrative Health).

In the context of this present work and unless otherwise specified, exercise types would refer to the classification of exercise according to its target of health component (i.e. strengthening, aerobic, flexibility, skills and mind-body). This classification is used because it is the core consideration when individualising exercise. It is distinct from exercise types which are determined based on the medium or setting of exercise deliveries – which are usually the next consideration after

specific exercise to target the physical impairment(s) has been identified (American College of Sports Medicine, 2013).

2.3.2 **By medium of exercise delivery**

Almost all of these exercises (i.e. strengthening, aerobic, flexibility and skills) may be delivered exclusively in water, on land, or in combination. The main clinical consideration for this decision is based on whether loading of the joint is desired or whether it should be avoided. For example, if aerobic exercise is required by a patient whose pain is aggravated by weight-bearing (e.g. standing or running), a feasible alternative would be water-based aerobic exercise such as aqua jogging or cycling.

2.3.3 **By setting of exercise delivery**

These exercises may also be delivered in groups or individually depending on feasibility and preference of the patients and therapists. Exercises can be performed either at home for logistics constraints, or at a health facility for safety concerns (e.g. fall risk, poorly controlled hypertension or diabetes). Another reason for exercise to be performed in health facility is to encourage adherence (Fransen and McConnell, 2008) and familiarity to the exercise program.

2.4 **Indications for exercise in OA**

Indications for exercise in OA mainly pertains either to prevent the development or progression of OA, or to address the associated symptoms and co-morbidities. In clinical practice, exercise is preponderantly used to reduce pain and address functional disability (NICE.org.uk., 2014, The Royal Australian College of General Practitioners, 2018).

2.4.1 **Pain**

Pain is a complex manifestation from the interaction between various biopsychosocial dimensions classically described as sensory-discriminative dimension (refers to sensation of pain), affective-motivational dimension (refers to negative feelings association with the pain) and cognitive-evaluative dimension (refers to the thought process in evaluating the pain)(Schneider and Karoly, 1983). Pain is reported to be one of the primary reason people with OA seek consultation from GPs (Paskins et al., 2013).

However, prospective and cross sectional estimates indicated that only half of the population with joint pain (which is likely attributable to OA) would seek GP consultation within one to three years following the onset of pain (Sheikh et al., 2014, Mitchell et al., 2006). In their cross sectional study, Mitchell et al. (2006) further determined that those who seek

consultation were likely to have more severe pain, more disability and greater concern about their condition than those who preferred to self-manage their pain. Although the causal relationship could not be established in this cross sectional study, it did demonstrate a relationship between cognitive/ behavioural factors and pain experience.

In OA, the source of pain is unclear. It may originate from any, if not all, of the structures involved in and around of joint (as explained in Chapter 1). Some clinical features have been associated with worse pain outcome. The examples are the presence of synovitis/effusion (OR range: 3.2 to 10), bone marrow lesion (OR range: 2-5) (Yusuf et al., 2011), and certain psychological traits (e.g. pain experience, pain catastrophizing) (Fu et al., 2017). Although there is lack of direct evidence to link obesity and pain in OA, the association can be inferred from clinical evidence that demonstrated significant pain reduction after weight loss (Riddle and Stratford, 2013, Richette et al., 2011). Exercise is one of the means to achieve weight loss.

2.4.2 **Functional disability**

Functional or mobility difficulty is another common reason for health care utilization among people with chronic hip and knee pain (Thorstensson et al., 2009, Paskins et al., 2013).

In a 3-year study, questionnaire was sent to all 8995 individuals aged 50 years and above from three GPs to ascertain the effects of new onset knee pain on functional status (Jinks et al., 2007). Of the 43% (3907) of the original cohort who had remained in the study at the final follow-up, there were 501 individuals who reported developing new onset of knee pain. In this group of new knee pain, their average physical functioning score (measured with Short-Form-36) markedly declined by 10 points from baseline. The functional status of those who were already with knee pain at the commencement of study, on the other hand, had remained relatively unchanged throughout the study period even when they no longer experience pain.

Although the respondents of this study had no confirmed diagnosis of knee OA, the findings could still be applicable to population with knee OA because knee pain in those aged ≥50 are usually attributable to OA (Thomas et al., 2002). In view of this finding, it may be prudent to introduce rehabilitative measures/ education for people with OA once they have been clinically diagnosed.

2.4.3 **Impaired physiological function**

2.4.3.1 Muscle function

Typical manifestations of muscle dysfunction are shown in Table 2-2. The most prominent feature is loss of muscle strength. In both knee and hip OA, muscle weakness is not only confined to quadriceps (knee extensors) but also affects hip extensors and knee flexors (Loureiro et al., 2013, Alnahdi et al., 2012).

Table 2-2 Clinical and biomechanical manifestation of muscle deconditioning

Clinical	**Biomechanical**
• Atrophy	• Reduced muscle strength/power
• Instability	• Increase postural sway
• Fatigue/Tiredness	• Altered muscle activation pattern
• Joint or muscle soreness	• Reduced walking speed/ altered gait

Weak muscles can be of normal appearance (Gur and Caklin, 2003) because muscle strength is not solely determined by the cross sectional area of muscles. The ability of muscle to generate force may be impaired in the presence of pain (Felson, 2006) or effusion (Torry et al., 2000), high fat to muscle ratio (Lexell et al., 1988) and poor neural control

(Sale, 1988). Sometimes, the cause of weakness can be unclear (Fitzgerald et al., 2004b).

Other domains of muscle function such as power (rate of force development, Δforce/Δtime), fatigability or endurance (Mau-Moeller et al., 2017) and activation pattern (Petterson et al., 2008) can be impaired as well, some to a greater extent than others. In knee OA for example, there is greater reduction in power than in strength itself (Suetta et al., 2007). This can be explained by the preferential loss of type II muscle fibres, which are fast contracting in comparison to the slower contracting type I fibres (O'Reilly et al., 1997, Nilwik et al., 2013).

Loss of muscle strength appears to be associated with higher risk of falls (de Zwart et al., 2015), poorer self-reported function (Hall et al., 2017), greater self-reported joint instability (Felson et al., 2007) and more fatigue (Hodges et al., 2016). The impact of muscle strength on function is not related in a linear manner and is likely to be apparent only when it crosses a threshold (Ruhdorfer et al., 2015, Edelaar et al., 2017). For some people with OA, this relationship can be additionally modified by other factors such as pain severity (Ruhdorfer et al., 2015, O'Reilly et al., 1998).

In addition to motor function, the muscle also has specialised sensory function. Specialised neuro-sensory receptors (Golgi tendon organ, muscle spindles) assist the muscles in regulating its firing and activation patterns (Proske and Allen, 2019). In deconditioned muscles, these functions are also impaired (Roos et al., 2011). As the coping ability of muscle gradually reduces over time, normal physical loading then becomes increasingly demanding, paving the way for manifestations of chronic musculoskeletal disorder.

2.4.3.2 Joint motion

The function of a joint is to permit movement between adjacent bony structures. Due to disuse and the adverse impact of OA, the muscles and other periarticular tissues become 'tight' and limit normal range of joint motion (Page, 2012). Regaining joint range of motion is important to correct muscle imbalance and to maintain function.

Full range of knee and hip movements is especially important in societies whose cultures involve kneeling, seating cross-legged and squatting (Hemmerich et al., 2006). Although these activities are not common in western cultures, a knee flexion of up to 110° is still crucial for daily activities (Rowe et al., 2000). Irrespective of the difference in the demand of joint flexibility, mobilising the joint throughout its full physiological

range is important. This ensures that tissues (e.g. muscles, capsule and ligaments) that span across the joint, are consistently 'worked out' to prevent tightness or contractures.

The impairment of joint motion is not often perceived and is easily masked by pain and muscle weakness (Pua et al., 2009). However, the consequences from joint motion limitation are not 'negligible' or 'benign'. Joints with restricted movement not only experience compromised diffusion of nutrients into cartilage, but also subjected to more pain. Tight capsular structures increase tensile stress in the joint which causes pain and reduced efficiency in muscle performance (e.g. increasing muscle effort) (Bennell et al., 2011).

Additionally, as much as 25% of the variability in clinical outcomes with respect to self-reported function and observed disability for people with knee OA and hip OA have been attributed to restricted joint mobility (Steultjens et al., 2000). Restriction of flexion at the hip and knee could slow down walking (Escalante et al., 1999) and limit abilities in some activities such as climbing stairs, sitting down and rising up from a seated position (Odding et al., 1996).

2.4.3.3 Proprioception and balance

Stability of the joint, and in some way postural stability, is maintained by static and dynamic stabilisers. Static stabilising forces are conferred by the bones, ligaments and capsule while muscles provide dynamic stability (Goldman et al., 2016). In order for muscles to execute quick and appropriate corrective forces at times of compromised stability (e.g. impending fall, misstep), the neuro-motor system coordinating these responses has to be sensitive to changes in posture and balance (Röijezon et al., 2015).

As shown in Fig. 2-4, proprioceptive sensory signal (i.e. signal related to joint position sense) may originate peripherally from muscles and many other tissues in and around the joint (e.g. ligament, tendon, menisci). These peripheral signals are processed along with additional central information (from vestibular and visual signals) to protect the joint from excessive movement, reducing risk of pain progression (Knoop et al., 2011).

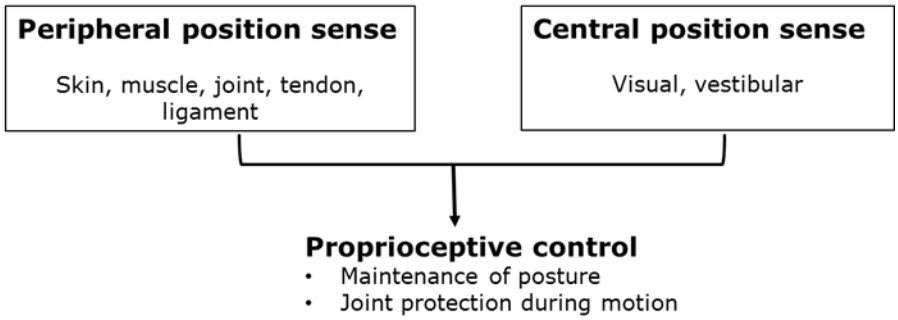


Fig. 2-4 Postural and stability control depends on neuronal inputs from both peripherally and centrally located sensory organs.
Adapted from Roos et al. (2011)

Due to the detrimental effects of aging and OA on proprioceptive function, more than half of people with knee OA (63%) report instability with ADL (Fitzgerald et al., 2004a). Such self-reported instability is evident biomechanically as increased knee motion variability (Gustafson et al., 2015) and altered joint contact mechanics (Farrokhi et al., 2014).

OA-induced proprioceptive dysfunction is potentially extensive, and contralateral asymptomatic joints have also been shown to demonstrate diminished function (Sharma et al., 1997). This can easily explain the higher risk of falls (relative risk 1.22; 95%CI 1.03, 1.46) reported in elderly people with lower limb arthritis compared to those without (Sturnieks et al., 2004) and the higher prevalence of self-reported instability

(34.5%) among those with radiographic knee OA compared to those without (19.4%) (Nguyen et al., 2014).

Theoretically, proprioception is essential for functional performance. However, cross-sectional studies have not been able to demonstrate a consistent relationship between proprioception and function in people with established knee OA (Bennell et al., 2003, Pai et al., 1997). This is most probably because the moderating effect of various factors such as pain and muscle weakness (van der Esch et al., 2007) is not always adjusted for in the analyses. Nevertheless, for those who are at risk of knee OA, one prospective study has suggested that poor proprioception may lead to poorer pain and disability outcomes at 30 months (Felson et al., 2009).

2.4.3.4 General fitness

General fitness – sometimes known as endurance or aerobic fitness – implies the ability to perform reasonably intense physical activity for prolonged period with aerobic metabolism. The capacity of the cardiorespiratory and musculoskeletal systems to perform aerobic metabolism (use oxygen efficiently) can delay accumulation of lactic acid that contributes to fatigue (Cairns, 2006). However, as with most physiological function, aging also compromises

cardiorespiratory reserve such that its ability to perform intense work is diminished (Milanović et al., 2013).

By 80 years of age, the left ventricular contractility would have reduced by 60% and heart rate by 25% compared to those attained at 20 years of age (Strait and Lakatta, 2012). This age-related decline in general fitness can be exaggerated by physical inactivity (Dunlop et al., 2011). The disparity of aerobic fitness between OA and healthy controls can be as high as 70% (Philbin et al., 1995).

It is estimated that a minimum aerobic capacity (typically quantified as maximum oxygen uptake – VO_{2max}) of 18ml/kg/min is needed for older adults to perform ADL independently (Fleg, 2012). Although no formal estimate is available, judging from baseline VO_{2max} values reported by some RCTs, there is some indirect indications of the gravity of poor fitness among OA (Coriolano et al., 2015, Philbin et al., 1995). It stands to reason that many people with OA experience breathlessness and fatigue with simple ADL. The implication of this for the elderly, including those with OA, is reduced mobility and physical independence in activities of self-care.

A further important aspect of physical fitness is its role as a predictor and prognostic marker for mortality and morbidity. This link is recognised in the general population (Lee et al., 2010), among people with high BMI (Fogelholm, 2010), in the subgroup of people with OA and obesity (Sutbeyaz et al., 2007) and even for subgroups of OA following joint replacements (Xue, 2011, McIsaac et al., 2016). The mechanism is unclear but is proposed to relate to its inverse relationship with various cardiovascular risk factors such as dyslipidaemia, blood pressure and cigarette smoking (Grundy et al., 2012, Erez et al., 2015).

2.4.4 **Physical inactivity**

2.4.4.1 Prevalence

More than a decade ago, a population survey indicated that only 25% of adult Americans with self-reported arthritis, irrespective of joints affected, meet the recommended level of physical activity needed to maintain or improve physical fitness (Hootman et al., 2003). With objective activity monitoring, a recent meta-analysis estimated that the corresponding number for knee and hip OA who meets the weekly physical activity of at least 150 minutes is probably higher at 40-60% (Wallis et al., 2013) and that this level can

change according to social cultural practices (Song et al., 2013).

People with OA are observed to be consistently less active than age-matched healthy controls irrespective of regional variability in physical activity level (Herbolsheimer et al., 2016). The activity level is even lower among people with OA who are obese (de Groot et al., 2008). In knee OA, inactivity and body weight demonstrates a dose response relationship whereby the odds of inactivity is four times higher among those who are obese (OR 3.9; 95% CI 2.6, 5.7) than those who are overweight (OR 1.8; 95%CI 1.2, 2.5) (Lee et al., 2013).

The sedentary behaviour among people with OA may not be entirely contributed by joint pain as suggested by an ancillary study of Osteoarthritis Initiative (Kahn and Schwarzkopf, 2015). In this study, despite better pain and functional status, patients who had undergone knee replacement were not recording higher accelerometer activity when compared to those awaiting for joint replacement.

2.4.4.2 Reciprocal relationship of physical inactivity and physical impairments

The presence of painful joints can prevent affected individuals from engaging in physical activities, potentiating age-related

decline in general and joint health, and obesity (Hunter and Eckstein, 2009). These can in turn lead to unfavourable OA outcomes such as pain and disability (Roos and Arden, 2016). Thus people with OA are prone to fall into a perpetual cycle of physical inactivity and physical disability, unless active intervention is given to break the cycle (shown in Fig. 2-5).

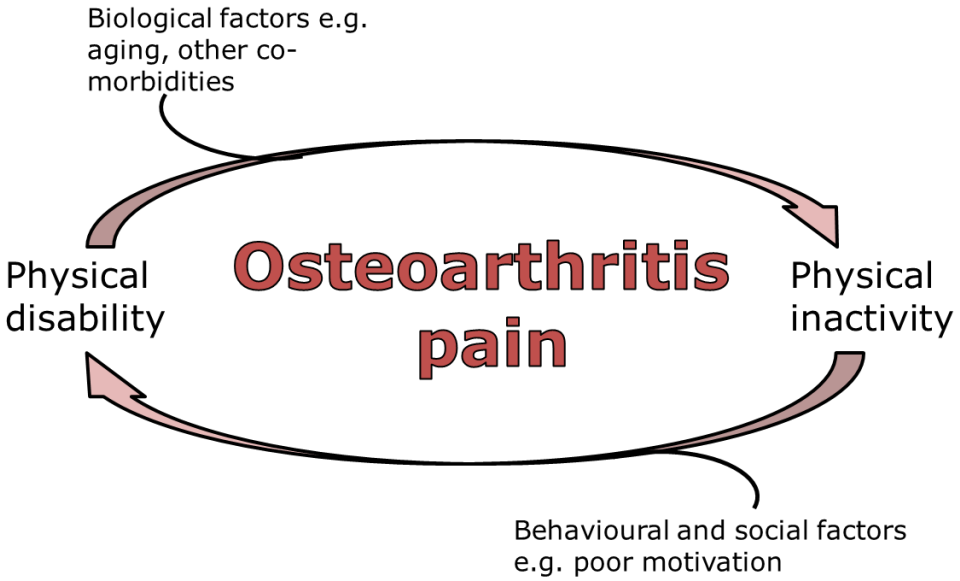


Fig. 2-5 Vicious cycle of physical impairment and inactivity due to osteoarthritis pain.
The problem can be compounded by various biological and behavioural or social factors.
Source: Author's own

Implementing exercise therapy is one crucial strategy to break the cycle and to arrest spiralling decline in health. While doing so, it is also equally important to acknowledge further barriers (e.g. lack of proactive facilitation from caregivers, aversion of

physical activity from fear of pain and injury, scepticism over the benefits of exercise) (Hurley et al., 2010, Dobson et al., 2016) that can compromise the efficacy of exercise intervention.

2.4.5 **Psychological impairment**

Psychological well-being consists of few positive cognitive attributes such as self-acceptance, capacity to identify purpose in life, personal growth and positive relationships (Ryff, 1989). In OA, many of these attributes are lacking and are instead replaced by a sense of helplessness, ill health beliefs, depression, poor social support and poor coping (Hurley et al., 2003).

Depression-anxiety disorder, a common psychological disorder in those with chronic joint pain affects one in five people with OA of any joint (Stubbs et al., 2016), and one in three people with OA of the lower limb (Axford et al., 2010). The cause of anxiety-depression in OA is multifactorial. It is correlated with many factors at the individual level (e.g. fatigue, life event, female gender), societal level (e.g. social isolation, low education level) and disease level (e.g. severity of pain, level of physical limitation) (Yohannes and Caton, 2010). Pain and physical disability/fatigue are possibly the more important

correlates of depression in OA (Hawker et al., 2011, Gerrits et al., 2015).

As shown in Fig. 2-6, anxiety-depression in OA has considerable impact on the societal and personal burden such as increased health service use (Sharma et al., 2016), potentially reduced adherence to treatments (Sumlin et al., 2014) and restriction in leisure activities (Machado et al., 2008). It can possibly lead to higher requirement for analgesics as the relationship between anxiety-depression and pain is reciprocal. Pain is usually more severe in people with anxiety-depression disorder (de Heer et al., 2014), and tends to be more progressive in the presence of depression (Scott et al., 2016).

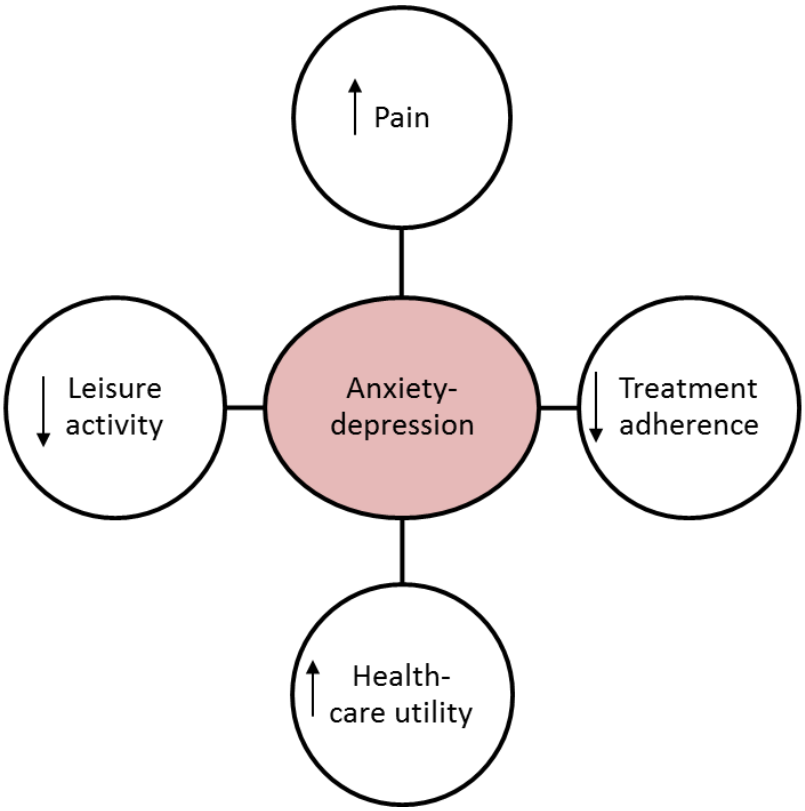


Fig. 2-6 Impact of anxiety-depression disorder.
Source: Author's own

2.5 **Mechanisms of exercise**

The primary goals for the use of exercise in OA is to reduce pain and function disability. Although consistent relationship between these two (pain and functional disability) has not been demonstrated, it is reasonable to expect the changes are reciprocal whereby better pain control would result in improved function (Henriksen et al., 2011) and vice versa.

A number of explanation on the mechanisms underpinning the post intervention changes in pain and function have been proposed. Mechanisms believed to be responsible for the

beneficial effects of exercise are not confined to the joint or musculoskeletal system (refer Fig. 2-7). Instead, exercise effects are the results of an integrated response from multiple systems, treating OA as a 'whole-person' and not merely a joint condition. At the peripheral joint level, for example, evidence exists to indicate that exercise alters a range of mechanical factors (including reducing excessive body weight) which can potentially lead to optimization of joint function, joint stability and minimizing harmful insult or joint loading (Hunter and Eckstein, 2009).

At the central level, exercise could potentially improve pain and functional capacity of people with OA via psychosocial and cognitive pathways such as enhancing the feeling of general well-being, decreasing depression, and promoting positive behavioural cognitive changes and coping strategies (Beckwée et al., 2013). Therefore, exercise plays an important therapeutic role in OA because it is a treatment modality that is able to meet almost all the biopsychosocial needs widely found in people with chronic painful conditions (Bevers et al., 2016).

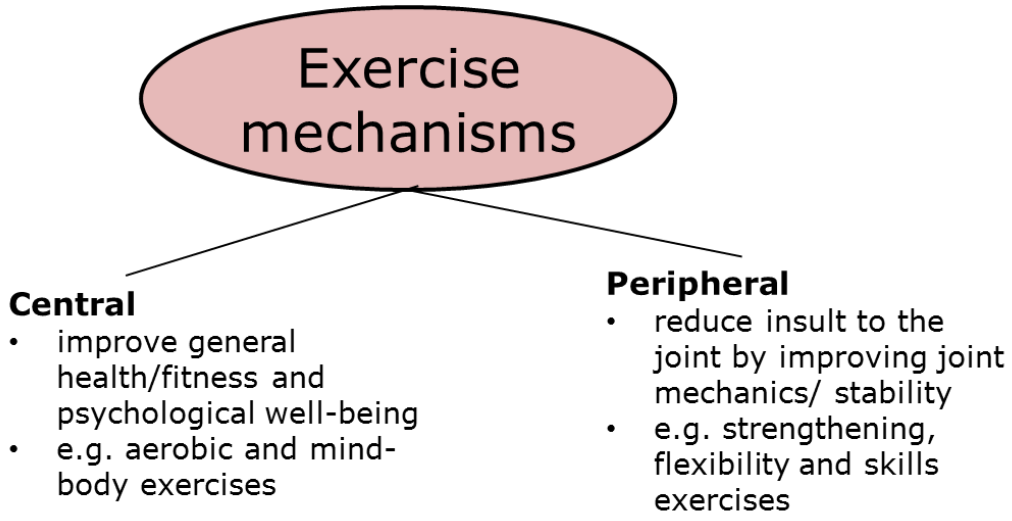


Fig. 2-7 Mechanisms of action for exercise

2.5.1 **Effects on pain**

As pain is multidimensional and has significant psychosocial or contextual component, it may partially explain why pharmacological agents (e.g. NSAIDs) has met with limited success in managing OA pain (Conaghan et al., 2015). In this regard, exercise may be more effective than pharmacological therapy. Not only exercise has shown potential to modify pain via biological mechanisms but also through contextual pathways. Contextual pathways are related to a range of psychosocial factors (e.g. anxiety-depression, self-efficacy) which can influence pain experience (Beckwée et al., 2013).

As a trade-off for the lack of specificity in its action, there is no reliable means to determine exactly how exercise alters pain for any given population group. In strengthening exercise for

example, whilst improvement in pain is often attributed to gains in strength, it is not uncommon for the change in pain and strength to occur independent of each other (Svege et al., 2016, Foroughi et al., 2011). Furthermore, there is no valid method to evaluate if the improvement in pain is achieved entirely via modification of local factor, or via contextual pathways including altered psychological state (i.e. general sense of well-being, decrease depression), or via modification of both physical and psychological factors.

Irrespective of the dominant mechanisms, knee and hip OA have been consistently proven to experience significant pain relief from all exercise types (land/water or home-/ facility-based or strength/ aerobic) with the magnitude of effect ranging from small (0.2-0.5) to large (>0.8) (Cohen, 1992) (see Appendix 1). However, there is no clear clinical evidence to indicate whether pain relief can be maximised if exercise is to be customised according to pain phenotypes. Nevertheless, based on current understanding, it is reasonable to hypothesise that exercises that act at the joint level would preferentially target patients with nociceptive/ somatic pain via mechanical pathway. Patients with neuropathic and non-somatic pain, on the other hand, would probably respond best to exercises with more systemic effects that act via

biochemical and neurophysiological pathways. Details of how each different exercise induces local or systemic changes are discussed in the following sections.

2.5.2 **Effects on self-reported function**

Similar to pain, functional outcomes in OA are commonly based on validated questionnaires which may be disease specific e.g. Western Ontario & McMaster Universities Osteoarthirtis Index (WOMAC) or non-disease specific e.g. Short Form -36 (SF-36). Irrespective of the tool used, functional outcomes following exercise generally demonstrated significant improvements and these improvements often corresponded in magnitude to the pain reduction reported (Lauche et al., 2013, Fransen et al., 2014). This is expected as patients are known to avoid activity for fear that the pain would be aggravated. An excessive form of fear of movement is known as kinesiophobia (Larsson et al., 2016).

In some studies, however, the magnitude of improvement appeared to be disproportionate. In Tanaka et al. (2013b) effect size (ES) for pain was 0.77 (95%CI 0.28, 1.24) and for function was 0.37 (95%CI 0.24, 0.50) while in Lu et al. (2015) pain was 1.16 (95%CI -0.71, 3.03) and function was 0.55 (95%CI 0.16, 0.94). These studies suggested the presence of additional modifiers of self-reported function. The potential

modifiers are likely to include physical factors (such as reduced strength, restricted joint range of movement or impaired balance control) and psychological factors (inadequate coping strategies, poor health beliefs or confidence) (Heuts et al., 2004) (Somers et al., 2009).

At present, there is no evidence to clearly indicate if the role of exercise in functional improvement is primarily direct (i.e. by correcting the physical impairments), indirect (i.e. by improving pain) or combination of the two pathways

2.5.3 **Effects at joint-level**

At the joint level, exercise mainly acts via biomechanical and neuromuscular mechanisms to impart desirable joint environment which could potentially prevent symptoms progression or even improve disabilities in OA (Hunter and Eckstein, 2009, Runhaar et al., 2015).

2.5.3.1 Strengthening exercise

Strengthening exercise has been the central component of exercise therapy for knee and hip OA (Brosseau et al., 2015, McAlindon et al., 2014) specifically to reverse muscle weakness and maintain muscle strength. Compared to other muscles in the lower limb, quadriceps muscle is probably the single most studied due to its prognostic value in OA risk and progression (Bennell et al., 2014c, Huang et al., 2017).

Strengthening exercise can be characterised as static (which encompasses isometric contraction such as leg press against a wall) or dynamic (which encompasses isotonic contraction such as lifting a dumbbell, and isokinetic contractions).

Significant improvement in physical performances (e.g. strength, power, maximal load lifted) have been consistently shown in the general aging population and in people with OA after performing strengthening exercises (Ivey et al., 2000, Latham and Liu, 2010). The gains in strength are often attributed to adaptive responses in the local neuromuscular tissue, leading to increased muscle mass and better muscle activation pattern (Hurley and Roth, 2000). These collective responses in the muscle will presumably act to restore joint stability, limit injurious forces acting on the joint and subsequently prevent aggravation of joint damage (Hunter and Eckstein, 2009).

This model of biological response to strengthening exercise does not fully explain how strengthening exercise actually influences changes in pain and function. If this model is solely responsible for the changes in pain and function outcomes, there should be consistent correlation between strength parameter(s) and these outcomes. However, pain has been found to improve without changes in strength and vice versa

(McQuade and de Oliveira, 2011, Farrokhi et al., 2013). Despite unclear mechanisms of action, large body of good evidence exists to support the use of strengthening exercise to improve pain and function (Vincent and Vincent, 2012).

2.5.3.2 Flexibility exercise

Unlike strengthening exercise, the impact of isolated flexibility or stretching exercise in OA has received relatively less attention even though it is often included in multicomponent exercise programs purportedly as warm-up routines. Flexibility exercise is characteristically prescribed to overcome 'tightness' of soft tissues (i.e. muscles-tendon unit and other non-contractile tissues) spanning the joints in order to promote joint mobility, restore muscle imbalance (Zakas et al., 2005) (Weppler and Magnusson, 2010) and other problems associated with restricted joint motion (previously described in 2.4.3.2). Its role in prevention of injury is controversial in healthy population (Behm et al., 2015, Lauersen et al., 2014) and is under-investigated in OA.

When no adaptive changes in the soft tissue were detected following improvement of joint mobility, alternative theory was proposed suggesting that flexibility exercise works by altering the stretch tolerance at sensory level instead (Law et al., 2009). The actual mechanism may in fact be complex because

its association with various effect modifiers – stretching techniques (static or dynamic), different population, and duration of exercise – could not be fully explained by either theories (Behm and Chaouachi, 2011).

A systematic review of 35 RCTs that examined the use of stretches for prevention of contractures in people at risk concluded that there is limited value in prescribing flexibility exercises in the short and long term (Katalinic et al., 2010). There is no evidence of equivalent quality to support the efficacy of isolated flexibility exercise on joint mobility in OA. Based on the few available clinical studies on OA, joint range of motion may increase by 9% on average after 2 months, or longer, if participants perform knee mobility/stretching exercises exclusively (Aoki et al., 2009, Weng et al., 2009). Some trials suggest that the benefits of stretching exercise may be enhanced by incorporating other types of exercises (Petrella and Bartha, 2000). In programs where stretching/flexibility exercise is not the dominant component, improvement in joint range of motion is still achievable but it may require a period longer than 2 months (Cheing and Hui-Chan, 2004, Hiyama et al., 2012).

2.5.3.1 Skills/proprioceptive exercise

The aim of skills/ proprioceptive exercise is to promote/ maintain postural control and stability while standing or moving, without which movements may seemed clumsy and increases fall risk. Since the presence of pain and muscle weakness cannot fully account for the self-reported instability in people with OA, it is hypothesized that there are additional elements (i.e. neuro-motor control) responsible for controlling balance and thus contribute towards functional stability (van der Esch et al., 2012). There is no established clinical means to assess the integrity of neuro-motor control in isolation as it may be masked by deficiencies in other physical domains such as muscle weakness. Instead, many different balance and proprioceptive indicators (e.g. reposition sense, single leg stance, laboratory measurements) had been used as surrogate parameters across different studies (Jan et al., 2009, Liao et al., 2015, Duman et al., 2012).

Irrespective of the methods of assessment, it appears that exercise (irrespective of form) has beneficial effect on neuro-motor skills – especially if it is weight-bearing or close kinetic chain in nature (Jan et al., 2009). Positive effects had been demonstrated in people with advanced knee OA (Duman et al., 2012) and following knee replacement (Liao et al., 2015). An

additive effect on stability does not always occur when exercise that targets balancing abilities is combined with other types of exercise (Fitzgerald et al., 2011, Rogers et al., 2011).

2.5.4 **Effects at systemic-level**

To improve pain and function, exercises such as aerobic and mind-body exercises act predominantly at systemic/central level in contrast to strengthening and flexibility exercises which target predominantly peripheral impairments to improve the bio-mechanic environment of the joint. At the systemic level, the analgesic effects of aerobic and mind-body exercises are possibly brought about by numerous pathways.

Potential pathways to reduce pain include i)biochemical pathway – exercise has been associated with reduction of systemic inflammatory markers (Simao et al., 2012) and induction of endorphin release (Koltyn, 2000); ii) neurophysiological pathways – exercise improves delta sleep (Buguet et al., 1980) and increases descending pain inhibition (Nijs et al., 2012); and, iii) psychosocial pathways – exercise participation promotes positive health beliefs, encourages learning of coping strategies and self-efficacy (Hurley et al., 2003).

In addition to its analgesic effects, aerobic and mind-body exercises should also be used with the intention of improving

general well-being of people with OA. General health – as measured with a number of parameters such as cardiovascular fitness, body mass index, physical activity level and mental-affective state – not only independently predicts all-cause mortality and morbidity, but also OA outcomes (Barry et al., 2014, Scopaz et al., 2009, Butnoriene et al., 2015).

2.5.4.1 Aerobic exercise

The standard measurement of cardiorespiratory fitness is expressed as the maximum volume of oxygen used per minute per kilogram of body weight during maximum exertion – VO_{2max}. However, maximal testing to estimate this parameter is rarely performed in OA trials. Instead, other less rigorous but more convenient submaximal tests such as the 6 minute walk test (measuring the distance walked within a specified time) (Escalante et al., 2011) and other self-reported methods (e.g. scale of perceived exertions/ perceived tiredness) are preferred.

Nevertheless, the positive effect of exercise (or even regular physical activity) on the fitness of the older population is still well demonstrated. Healthy older women have achieved 10% improvement in VO_{2max} following eight weeks of intensive aquatic training program (Broman et al., 2006). This illustrates that, even though age-related decline in fitness is not

completely reversible, it can be attenuated or even improved by exercise/physical activity.

The able-bodied older adults are recommended to accrue a minimum of 150 minutes per week of moderate aerobic just to maintain their fitness level (Buchner et al., 1997). In more sedentary people with OA, however, a less strenuous activity level can still confer significant benefits. When prescribed a walking program of 120 minutes/week, not only did a group of sedentary people with OA maintained their fitness but they managed to show improvement in fitness of 18% after three months (Buchner et al., 1997). This is consistent with most evidence that frailty should be an indication, and not a contraindication, to exercise (Marzetti et al., 2017). The 2018 European League Against Rheumatism (EULAR) recommendations further reinforce the benefits of exercise in people with OA as it calls for physical activity promotion to form an integral component of standard care in arthritides (Rausch Osthoff et al., 2018).

Other than cardiorespiratory fitness, weight management is also another indication for the use of aerobic exercise. In a RCT involving subgroup of knee OA who were obese, weight loss of 6.1kg (95%CI 4.7-7.6kg) was associated with significant symptom and functional improvements

(Christensen et al., 2007). A more recent and larger multicentre study involving 1400 cohorts at risk of OA was also conducted to establish the effect of weight loss on pain (Riddle and Stratford, 2013). This study did not only confirm the findings of the previous RCT but also further suggested that pain would improve in a dose-dependent manner when the weight reduction achieved at least 10%.

To achieve weight reduction, a person has to exercise twice the amount required to maintain general and cardiovascular health (Fig. 2-8) (Haskell et al., 2007).

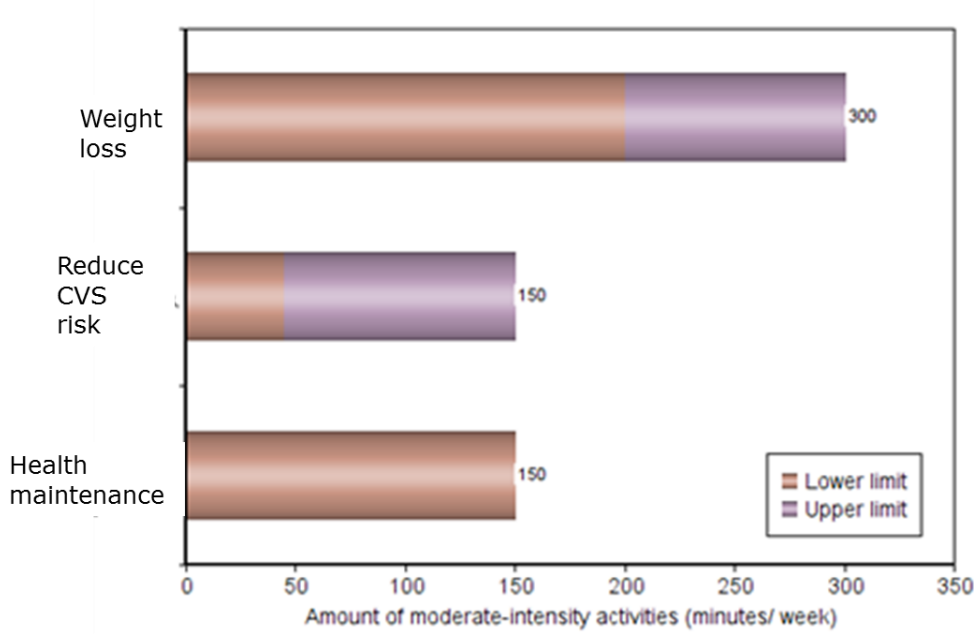


Fig. 2-8 Activity level required to lose weight is double the amount needed to maintain health and reduce cardiovascular risk.
Adapted from (Haskell et al., 2007)

With aerobic exercise alone, overweight/obese adults may loss 1.6-1.7kg over 6-12 months – a reduction of 300g/month at best (Thorogood et al., 2011). With concurrent attention to dietary intake (i.e. ensuring that the exercising group maintain their normal dietary intake) a higher rate of weight loss in excess of 2kg/month can be attained – 7.5kg over three months (Ross et al., 2000).

2.5.4.2 Mind-body exercise

With greater understanding of the interaction between OA and cognitive-affective factors, mind-body exercise is beginning to look more promising than physical-only exercises. Since mind-body exercise has additional emphasis on mind or mental state during physical training, it could theoretically offer more holistic benefits over conventional physical-only exercises for OA. Although there is still paucity of studies on the use of mind-body exercise in OA, some inferences of its potential may be drawn from studies of other chronic conditions including conditions that are age-related (Mansky et al., 2006, Jahnke et al., 2010)

In a one-year RCT, a group of older persons at risk of cognitive decline was assigned to either Tai-chi or stretching exercise. Those in the Tai-chi intervention group experienced significant improvement in cognitive function (i.e. delay recall)

and lower risk of dementia (OR 0.21; 95%CI 0.05, 0.92) compared to participants in the stretching exercise group (Lam et al., 2012). In another similar but shorter RCT (12-week intervention and 24-week follow-up) involving participants with fibromyalgia, significant improvement in the SF-36 mental component was also seen in Tai-chi group in comparison to stretching group throughout the study period (Wang et al., 2010).

Systematic reviews on few conditions: multiple sclerosis (Senders et al., 2012), Parkinson's disease (Song et al., 2017) generally concur that mind-body exercise is likely to be beneficial in the short term for multiple physical and psychosocial domains but further studies are still needed as current evidence is mostly limited to smaller studies with short term follow-up (≤6 months). Given that the conventional forms of exercise are already with proven benefits, future mind-body exercise studies have to incorporate active interventions or other forms of exercise as controls to justify its use over existing conventional exercises.

2.5.5 **Effects on articular health**

Experimental OA models provided evidence that joint loading plays an important role in cartilage morphology and biosynthesis (Buschmann et al., 1999). Availability of modern

imaging techniques such as MRI not only provided the opportunity for us to confirm these findings in vivo (Sun, 2010) but also to further elicit that the relationship between mechanical loading and joint morphology is non-linear. While moderate level of activity is protective, overuse and disuse or immobilization appear to retard biosynthesis of cartilage (Bricca et al., 2017, Eckstein et al., 2006).

The vulnerability of cartilage to loading varies from joint to joint and also from one region to another within the same joint (Lin et al., 2013). This relationship is applicable to both healthy and injured cartilage, although the latter would be vulnerable at lower loading force (Galois et al., 2004, Iijima et al., 2017). Considering that MRI images of cartilage in women with early knee OA remained unchanged one year after being subjected to regular high impact aerobic exercise (Multanen et al., 2014), it appears that injured cartilage might still be fairly resilient to high mechanical stress in the early stages of OA.

2.5.6 **Effects on OA progression**

OA progression is often indicated by progression of symptoms or radiographic/structural severity. Several hypothesis on the possible mechanisms through which exercise may modify the course of OA include improvement of cartilage quality, correction of abnormal joint forces (e.g. adduction moment)

and attenuating local and systemic inflammatory activities (Bricca et al., 2017, Yumi et al., 2015, Rojas-Ortega et al., 2015).

Due to the lack of long term prospective studies, most of these hypotheses supporting the potential for exercise to be a disease-modifier cannot be confirmed. By using hip replacement surgery as a clinical surrogate of OA progression, there is some evidence to support disease-modifying potential for mixed exercise as it could delay hip replacement by two years in a cohort of people with painful radiographic OA (Svege et al., 2013). Similarly, when a 12-week multimodal program which included neuromuscular exercise training were delivered to a group of patients who were eligible for knee replacement, ¾ of them were found to have deferred surgery at one year follow-up (Skou et al., 2015)

Especially when obesity has been suggested to be a risk factor for joint replacements, exercise may also play an important role in delaying OA progression, either through weight reduction and/or through prevention of future weight gain (Van Wye et al., 2007).

2.6 Exercise in advanced OA and pre-post joint replacements

In advanced OA, other than contributing towards pain control and delaying joint replacement surgery (Svege et al., 2013, Skou et al., 2015), exercise may have a role in optimising early postoperative outcomes (Rooks et al., 2006). However, the evidence supporting its use in pre-operative rehabilitation is very weak. Pre-operative rehabilitation may improve pain and functional outcomes in the early postoperative period, but the improvements experienced were not clinically significant compared to controls (Wang et al., 2016).

In contrast, in the postoperative phase there is a strong consensus that exercise should be an integral part of rehabilitation to restore pre-morbid function (Westby et al., 2014).

2.7 Clinical efficacy of exercise for pain, function and QoL

Appendix 1 lists few meta-analyses that were available up until 2016 summarizing the effect of exercise on pain, function and QoL. Pain and function are both obligatory outcome measures in OA trials identified by OMERACT III conference (Bellamy et al., 1997). One clear observation from this list is

that the magnitude of efficacy differs between joint sites, with ES being greater for knee OA than hip OA.

Within the subgroup of knee OA, benefits are better for pain and function, ranging from small effects to large effects (Juhl et al., 2014, Lu et al., 2015), whilst the effect on QoL is comparatively more modest (Fransen and McConnell, 2015, Lauche et al., 2013). The benefits of exercise on pain and functional outcomes of hip OA, on the other hand, is only moderate at best (Fransen et al., 2014, Hernández-Molina et al., 2008). Interpretation of systematic reviews on hip should be done with caution because the primary evidence relating to hip OA is scarce. Of the 61 RCTs on OA, published between April 2016 and May 2017, only about 10% investigated hip OA (Schiphof et al., 2018).

A recent meta-analysis which performed an indirect comparison between oral analgesic and exercise suggested that both interventions produced comparable pain relief for knee OA (oral analgesic ES 0.41; 95%CI 0.23, 0.59; exercise ES 0.46; 95%CI 0.34, 0.59) (Henriksen et al., 2016). Since exercise is generally less effective in hip than in knee OA, the results from Heriksen et al. could infer that oral analgesics might be more effective in hip OA compared to exercise – provided that oral analgesics produce similar pain relief for the

hip as the knee. However, there is currently no direct evidence to support or refute this inference.

Making further definitive conclusions based on existing evidence is challenging for many reasons. One of the main difficulty faced is the high degree of heterogeneity between studies with regards to the content of exercise programs, intervention length, follow-up time points and the types of control group used.

2.8 **Rationale for study**

Irrespective of methodological differences, it is clear that exercise of all types is more effective than non-exercise intervention. However, there is substantial variation in OA guidelines in respect to their consensus on exercise programs, including the exercise types that they emphasised (Nelson et al., 2014). EULAR and NICE guidelines specifically endorse aerobic exercises in addition to strengthening exercises (Fernandes et al., 2013, NICE.org.uk., 2014), while Osteoarthritis Research Society International (OARSI) recommends all forms of land-/water-based as well as strengthening exercise without specific consensus on aerobic exercise (McAlindon et al., 2014). Recently, the Ottawa panel has given specific focus to also evaluate the evidence for non-

traditional exercise i.e. Tai-chi (Brosseau et al., 2017) which neither EULAR nor OARSI had made extensive references to in their consensus.

The main reason for the inconsistency between guidelines is probably because there are substantial gaps in the evidence where a single coherent 'ranking' for all the competing exercise types is lacking. There is a great reliance on randomised controlled trials (RCTs) and on meta-analysis to synthesise evidence. However, both these research methods have limited utility when multiple interventions (i.e. three or more) are involved, especially during decision making. In RCTs, conventionally only a few active interventions are included for comparison against a standard or inert control (i.e. usual care or non-exercise controls). Similarly, in meta-analyses, only one pair of comparison can be performed in a single analysis. Comparisons between different exercise types are, therefore, relatively limited. In short, the comparative effectiveness between different types of exercise remain substantially unknown because the evidence available at present is piecemeal and is reliant mostly on naïve comparisons from separate RCTs or meta-analyses.

One problem with this naïve indirect approach is that there is no formal way to substantiate or test the robustness of the

conclusion. There are bound to be methodological differences between different pairs of exercise comparisons as these results are derived from separate RCTs and meta-analyses. Conclusions may be conflicting as a result of different study protocols. One way to obtain meaningful results is for all exercise types to be compared simultaneously in one RCT or in one meta-analysis. Undertaking such a RCT would be very costly and labour intensive while conventional meta-analytic technique is not capable of handling multiple interventions.

With the introduction of new technique known as network meta-analysis (NMA), we now have the means to perform simultaneous comparisons for all different exercises and generate a more coherent summary 'ranking' within a single analysis. Another strength of NMA is that it does not require all the comparisons of interest to have been investigated clinically. For comparisons that lack direct evidence or are without clinical trials, indirect estimation of their relative effects can be calculated as long as these exercises are linked in the network. For example, comparison between aerobic and strengthening exercise may not have been assessed clinically but it can still be estimated from NMA if there are presence of aerobic versus usual care studies and strengthening versus

usual care studies (Caldwell, 2014). In this example, 'usual care' creates a link between the interventions.

Such analysis has been extensively used to inform decisions in many areas of medicine (Greco et al., 2015) but little has been done in OA (Bannuru et al., 2015, Wandel et al., 2010), especially in relation to exercise (Uthman et al., 2014). Although Uthman et al. had performed an NMA on exercise in OA but their primary objective was to investigate if there is currently sufficient evidence to support the use of exercise in OA and not to investigate the relative efficacy of different exercises, hence the need for this NMA. Further explanation on NMA can be found in the next chapter.

2.9 **Study aims and objectives**

This study aimed to estimate the relative efficacy of different exercises for pain, function, physical performance and QoL outcomes in people with knee and hip OA, primarily in comparison to usual care. The question was investigated using two different meta-analytic techniques - conventional meta-analysis (MA) and NMA. In line with the recommendations for individualised therapy by EULAR (Fernandes et al., 2013) and OARSI guidelines (McAlindon et al., 2014), findings from this study will provide a means for healthcare providers to identify

the most appropriate exercise therapy based on treatment goals and patient preference.

The specific objectives are:

i. to examine the efficacy and determinants of response to exercise therapy for knee and hip OA;
ii. to examine relative efficacy between different exercise therapies in knee and hip OA for pain, function, performance and QoL; and
iii. to preliminarily examine the efficacy of pre-operative exercise for postoperative outcomes.

3 Method

This chapter contains the study protocol to conduct a broad search. The results from this broad search were used to guide the analyses plan of this thesis, which primarily aimed to evaluate the relative efficacy of different exercises. This protocol had been published in Systematic Reviews (Goh et al., 2016).

3.1 **Meta-analysis**

Two meta-analytical approaches, MA and NMA, were used for this project.

3.1.1 **Conventional meta-analysis (MA)**

Conventional MA is useful to compare directly two different interventions (e.g. strengthening exercise versus usual care or strengthening exercise versus aerobic exercise). The primary aim of the present conventional MA was to establish the overall effect of exercise therapy compared to usual care and to identify potential determinants of response to exercise therapy. The specific methodology relating to the use of conventional MA for the present work can be found in Chapter 5.

3.1.2 **Network meta-analysis (NMA)**

The second method, NMA, was used to examine specifically the relative efficacy of different exercise types. The advantage of using NMA is that it links different interventions together through a common comparator and forms a network that combines both direct and indirect evidence, leading to the synthesis of mixed evidence. This approach not only improves the precision of the estimated ES but also allows us to infer the effect between two interventions that have not been directly compared in clinical trials.

Assuming that A-C comparison has never been performed clinically, existing evidence from A-B and B-C comparisons can be used to estimate the relative efficacy between A and C indirectly (Fig. 3-1). On the other hand, if direct evidence on A-C is already available from clinical trials, the loop of indirect evidence formed by A-B and B-C comparisons is still useful in that it supplements the direct A-C evidence and reduces the width of CIs for the direct A-C estimates.

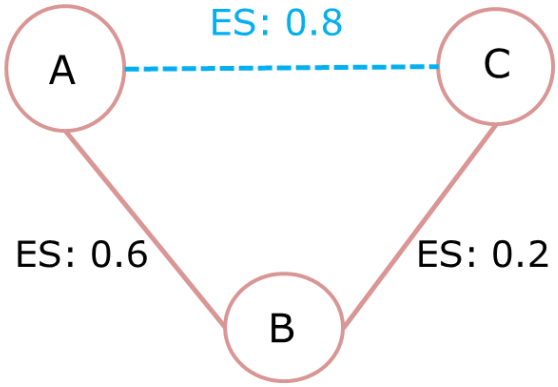


Fig. 3-1 Basic concept of network meta-analysis
A-B and B-C comparisons have been conducted in clinical trials (solid lines) with known effect size (ES) 0.6 and 0.2, respectively. However, A-C comparison (broken lines) has never been studied/ lacks evidence. With NMA, it is possible to derive an estimate of A-C (ES=0.8) through A-B and B-C studies.
Source: Author's own

There are a few assumptions that has to be met for NMA to be valid: i) similar to conventional meta-analysis, the distribution of effect modifiers in controlled and intervention groups are considerably homogeneous across all A-C trials (**similarity**), and across all A-C, A-B, and B-C trials that formed the network (**transitivity**) (Song et al., 2009, Cipriani et al., 2013); and, ii) the direct and indirect estimates from the evidence "loop" are in agreement with one another (**consistency**) (Caldwell, 2014). To simplify, *transitivity* may be regarded as clinical heterogeneity and *consistency* as statistical heterogeneity.

Ensuring similarity in effect modifiers (e.g. patient demographics, intervention duration, and disease severity)

across studies could be challenging because of incomplete reporting, or there may be too few homogenous studies available for pooling. Nevertheless, it is still possible to include non-homogenous trials as the differences in effect modifiers can be adjusted through regression analyses (Cipriani et al., 2013). Likewise, inconsistency may also be "resolved" statistically by applying models that relax the consistency assumption or with the use of inconsistency models (Cooper et al., 2009). When there is significant unexplained heterogeneity, however, researchers may have to resign to the inconsistency and not pool the studies for analyses (Cipriani et al., 2013).

In NMA, estimates from the shorter route are normally assigned more weight. This implies that direct evidence contributes more to the mixed ES compared to indirect evidence, and simple loop is given greater weightage over loop with multiple intermediates (Salanti et al., 2014).

3.2 **Eligibility of studies**

3.2.1 **Types of studies to be included**

Randomised controlled trials (RCTs) (including cross-over and cluster randomised trials) which examined the effects of exercise interventions in adults with knee or hip OA in all

settings were included. Studies were considered as an RCT if authors had explicitly stated that it was randomised (Higgins et al., 2011) or when randomisation could not be ruled out. Quasi-randomized trials were excluded. Reports of secondary analysis and post-hoc analysis were also excluded unless the information provided was of relevance.

3.2.2 **Participants**

People with symptomatic OA of the knee and hip, diagnosed clinically (e.g., ACR criteria), or radiographically (e.g., KL grading), or by use of other imaging (e.g., MRI) were included. There was no restriction on the severity or stage of OA. Hence, studies involving patients from early to 'end-stage' OA, including patients in community, on waiting-list for and after joint replacement, were all eligible.

Studies with mixed joint disorders from which the subgroup of OA cannot be separated, or studies which failed to explicitly specify the joint pain as OA (i.e. participants were not clinically or radiographically diagnosed) were excluded. Studies that examined the effects of postoperative exercise were only included if >80% of the participants underwent surgery for OA (Singh et al., 2015).

3.2.3 **Interventions**

Interventions that involved exercise prescribed in any form, such as strengthening exercise, aerobic exercise, or mind-body exercise (e.g. Tai-chi, yoga) were eligible for inclusion. In instances where the term 'exercise' was not used by the investigators, any physical training that fulfilled the basic characteristics of exercise (i.e., a structured programme which was repeated/practiced on a regular basis, e.g. 3 times a week) were also included. Exercise interventions might include adjunctive treatments and need not necessarily had to be exercise-only. However, for a complex multicomponent intervention, such studies were only considered if the exercise program was the dominant feature of the intervention. Table 3-1 shows what types of comparison would be eligible for inclusion.

Table 3-1 Determining eligibility of studies

Types of comparison		Study eligibility
Group 1	Group 2	
Exercise A	Exercise B	Yes
Exercise A	Non-exercise controls	Yes
Exercise A + Intervention B	Intervention B	Yes
Exercise A	Exercise A+ Intervention B	No
Exercise A	Doses of exercise A*	No

*Examples are different mode, intensity, delivery methods or setting of exercise A

Exercise was classified based on four core exercise types described by the ACSM (Deschenes and Garber, 2013) (strengthening, aerobic, flexibility, skills). Two more exercise categories: mind-body exercise and mixed exercise, were added in order to accommodate for exercise programs that would not fit into any of the categories considered under the ACSM convention. An intervention was classified as mixed exercise if the authors did not clearly identify the exercise element of interest, or included more than one category of exercise.

3.2.4 **Outcomes**

The primary outcome was pain. Secondary outcomes included self-reported function, objectively measured performance/physical tests and QoL. Except for outcomes based on physical testing, a hierarchical selection of measurement scale following Fransen (Fransen and McConnell, 2015) and Regnaux (Regnaux et al., 2015) was adopted if more than one scale was being used to measure the same outcome. However, a lower ranked scale was given priority over a higher ranked scale when the lower ranked score had more complete data. Details of the ranking used by Fransen (Fransen and McConnell, 2015) and Regnaux (Regnaux et al., 2015) for pain, function and QoL outcomes are listed below.

a) Primary outcome – pain

The hierarchical selection, in descending order of preference, was as follows:

- Pain overall
- Pain on walking
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale
- Pain on activities other than walking
- WOMAC global scale
- Lequesne OA index global score
- Other algo-functional scale

- Patient's global assessment
- Other outcomes

b) Secondary outcomes

i) Hierarchical selection for self-reported functional outcomes in descending order of preference was as follows:

- Global disability score
- Walking disability
- WOMAC disability sub-score
- Composite disability scores other than WOMAC
- Disability other than walking
- WOMAC global scale
- Lesquesne OA index global score
- Other functional scales

ii) For objective performance-based outcomes, no definite recommendation was available (Dobson et al., 2012). Hence, in order to standardise the performance measures, parameters that were reported in the most consistent manner were chosen. Examples are 6 minutes walking test, timed stair tasks and timed up and go. Joint

specific parameters such as strength, power, and range of motion were only used if walking parameters were not available. Strength parameters extracted, in descending order of preference, were knee extensors, knee flexors, hip abductors and others. When further uncertainty was found, the parameter of choice was occasionally made at random.

iii) Hierarchical selection for QoL measures was as follows:

- General health of Short Form (SF)- 36 or SF-12
- EuroQol (EQ)-5D
- World Health Organization Quality of Life
- Mental/physical Component Summary of Short Form (SF)-36
- Mental/physical Component Summary of SF-12
- Sickness Impact Profile
- Nottingham Health Profile
- Other quality of life scales

3.2.5 **Study time points**

Outcomes at different time points during the follow-up period were recorded and the commonest point across all trials was chosen as a primary outcome point. Additionally, outcome points during follow-up were grouped into intervals (e.g. <1 month, 1- month, 2- months, 3- months, 6- months, 9- months, 12- months and 18- months) for a secondary analysis for time-dependent effects.

3.3 **Search strategy**

The following electronic bibliographic databases were systematically searched from their dates of inception: Allied and Complementary Medicine Database (AMED), The Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), MEDLINE Ovid, Physiotherapy Evidence Database (PEDro), PubMed, SPORTDiscus and Google Scholar. There were no restrictions on languages. An example of a Medline search is shown in Appendix 2. The reference lists of systematic review protocols published in the Cochrane Library since 2014 were also searched as a supplement to the electronic database. Abstracts were not included.

3.4 Data collection

3.4.1 Study selection process

Following initial title and abstract screening, eligibility of studies were then confirmed by full text screening. Study selection was done by one reviewer (SLG) with advice from another reviewer (MH) – a trained physiotherapist whenever an exercise classification was unclear. Second reviewers (MP, JS and YFH) randomly validated 10% the study selection in 2 phases (i.e. one validation during the first half of screening and another during the second half of screening). A third reviewer (WZ) was only involved whenever discrepancies arose – i.e. if either one of the reviewers was unsure or could not agree with each other.

3.4.2 Data extraction and management

A structured database was created in Microsoft Access for data entry. In some situations, a study can provide two separate pairs of comparators, such as when knee or hip cohorts or male and female participants were presented separately. Conversely, studies that produced companion publications were combined, if possible, to maximise the yield of data without double counting. In studies where multiple treatment arms could not be satisfactorily paired, they were handled

differently, depending on the type of analysis (MA or NMA) that was being undertaken. The precise methods are detailed in the respective chapters (i.e. Chapter 5 for MA and Chapter 6 for NMA).

Study level data that were extracted are as follows:-

i. Study characteristics:
    - Study identification details (i.e. title, author, year of publication)
    - Number of study arms
    - Number of patients
    - Duration of study
    - Centre: hospital/healthcare centre, community
    - Study design: parallel, crossover

ii. Participant characteristics:
    - Demographic: mean age, gender
    - Associated risk factors: BMI, history of injury
    - Diagnostic criteria used for recruitment: ACR or radiographic
    - OA joint site: knee OA, hip OA or mixed group of knee and hip OA
    - Whether on waiting-list for joint replacement surgery or not, irrespective of whether it was partial or total replacement

iii. Intervention characteristics:

- Types of exercise: strengthening, aerobic, balance/skills, flexibility/range of motion, mind-body or mixed,
- Measurement of exercise adherence: log book or attendance record
- Form of delivery: group/class versus individual, hospital versus home-based
- Number of participants randomised
- Comparator types
- Baseline measurements
- Methods of adherence monitoring

iv. Outcome characteristics:

- Types of outcome and measurement tool used
- Intention to treat (ITT) analysis
- Number of patients analysed and attrition at various stages of the study
- Types of effect size and relevant statistics: standard deviation (SD), confidence interval (CI)
- Primary, and all measurement, time points

An abridged data extraction form (see Appendix 3) was used for data validation.

3.4.3 **Missing data**

If the required data could not be extrapolated from the published article, attempts were made to contact the authors for additional information. Where this was not possible, statistical imputations were used when appropriate.

As missing SD was one of the commonly encountered situations, common calculations for transforming other form of summary data to SD are listed in Appendix 4. In studies where insufficient information was provided for calculation, the SD was substituted with the widest SD obtained from other eligible studies (when the scale used was known), or substituted with the arithmetic mean of available SDs (when the scale used was unknown) (Fu, 2013). For example, when the SD for a 0-100mm pain scale was missing, the missing SD was replaced by the widest SD of eligible studies that also used 0-100mm scale. When the scale used could not be determined from the report (i.e. when it was unclear whether the pain scale was 0-100mm or 1-10cm) the arithmetic mean of all available SD (both 0-100mm and 1-10cm scale) was used.

3.5 **Analysis**

Microsoft Access was mainly used to develop the database. Processes of cleaning and formatting of dataset for analyses, and computation of the ES for MA were performed in Access, Excel and Stata. R was used to identify heterogeneous studies and WinBUGS to perform Bayesian analyses for NMA.

3.5.1 **Measures of treatment effect**

The ES of continuous data (pain, functional outcome and QoL) was calculated using standardised means difference, or Cohen *d*. Cohen *d* ES is a measurement of treatment effect in units of SD, and is operationally defined as small=0.2, medium=0.5 and large=0.8 (Cohen, 1992). Whenever possible the change score from baseline was used for calculation of ES. If this was not available, the end point (post-intervention) score or the between group difference reported by the authors was used instead. ITT and adjusted results were extracted whenever possible.

From Cohen *d*, a correction factor was used to obtain the unbiased ES (Hedges' *g*). Unless these ES calculations were already available by default in the statistical software, calculations were based on the equations listed in Appendix 4 (Higgins et al., 2011, Wan et al., 2014, Borenstein, 2009, Morris and DeShon, 2002). Point estimates of ES were

reported with its 95% confidence interval (CI) for MA, and 95% credible intervals (CrI) for NMA. ES was calculated based on the number of patients who were originally randomised when the number used for analysis was unclear. All analyses were based on random-effects model.

3.5.2 **Assessment of publication bias**

It is known that studies with non-significant findings tend to be unpublished. To detect publication bias, both Egger's test of publication bias and the visual inspection of asymmetric funnel plot were used. Egger's test is suggestive of publication bias if the p-value is less than 0.05 and this test was performed only when there were >10 studies, as recommended by Cochrane Handbook (Higgins JPT, 2011).

3.5.3 **Assessment of heterogeneity**

The I^2 statistic was used to quantify the impact of the heterogeneity on the pooled estimates. The value of I^2 indicates the magnitude of heterogeneity in the analysis and is interpreted as: 0%-40% - might not be important; 30%-60% - may represent moderate heterogeneity; 50%-90% - may represent substantial heterogeneity; and 75%-100% - considerable heterogeneity (Higgins JPT, 2011).

3.5.4 **Risk of bias assessment**

A modified Cochrane risk of bias assessment tool was used to assess the quality of studies (van Middelkoop et al., 2013). This is an assessment tool that considers the various sources of bias by examining the methods of randomisation, concealment, blinding and handling of missing data. Response for each criteria can either be yes, no or unclear following the pre-defined guidelines as outlined in Appendix 5.

- Was the randomisation procedure adequate?
- Were there more than 100 subjects in each treatment group?
- Was the treatment allocation adequately concealed?
- Were physicians blinded to the intervention?
- Were patients blinded to the intervention?
- Were outcome assessors blinded to the intervention?
- Was incomplete outcome data adequately assessed?
- Was ITT analysis used?
- Were the treatment and control groups similar at baseline?
- Were all pre-specified outcomes of interest reported in the pre-specified way?

Whenever a published protocol for the included study was available it was used as a supplementary source of information to enhance the quality assessment of the trial protocol. Criteria on the blinding of intervention for patients and physicians were generally considered to be unrealistic due to the nature of exercise intervention. Blinding of assessors was also regarded as impractical when the outcomes measures used (e.g. WOMAC, numerical rating score) were self-reported. The assessment was performed by one reviewer (SLG) with second reviewers (MSMP, JS, YFH) performing random validation in 10% of the included studies – again, in 2 phases (i.e. after the first 100 studies were extracted and another validation after the next 100 studies). Should disagreement between reviewers occur in over 5% of the total extracted variables, the whole set of the studies would be double extracted, otherwise the single extraction was used, i.e., a maximum 5% disagreement was allowed for data extraction.

3.5.5 **Subgroup analysis**

Extended subgroup analyses were performed based on the quality criteria of the study (e.g. sample size, ITT use), patient characteristics (e.g. mean age, mean BMI, gender), joint involvement, exercise and comparator types. These variable

were selected for their potential as effect modifiers of exercise response (e.g. joint site, mean age) or as sources of bias (e.g. adherence, ITT analysis, sample size).

As far as possible, categorisation of the continuous variables were based on accepted conventions (e.g. BMI) while categorical variables were analysed based on how the data was primarily extracted (e.g. ACR criteria). Some categories were aggregated for analyses when the number of studies for a particular group was deemed too small for meaningful analyses (e.g. extreme spectrum of the BMI classification). In the absence of established convention for continuous variable (e.g. percentage of female), judgement on classification was made so as the number of studies across the subcategories were of acceptable distribution while maintaining reasonable cut-offs values. Categorisation of age was done post-hoc when Baujat plot suggested that studies responsible for the high heterogeneity had participants with mean age younger than 60 years. Additional detail on Baujat plot can be found in section 5.2.

3.5.6 **Meta-regression**

Meta-regression was used to assess and quantify the association of various factors to the ESs. Specific covariates included in the model are specified in the relevant section 5.2.

3.5.7 **Sensitivity analysis**

Sensitivity analyses were performed to ascertain if the results were robust. Sensitivity analyses were undertaken when: (i) imputations of missing data had been employed; (ii) some arbitrary decisions had been made with respect to study selection, subgroup data aggregation/segregation; and (iii) outlying studies were suspected.

Small-study effect was specifically assessed because smaller studies tend to report larger ES and distort the summary estimates of meta-analyses (Nüesch et al., 2010). Not only do underpowered studies have low probability of finding true effects and low positive predictive value, they also tend to exaggerate the magnitude of true effects (Button et al., 2013).

3.6 **Deviation from published protocol**

The primary endpoint that was collected was revised to change score from baseline (i.e. endpoint score minus baseline score) instead of the endpoint score. Whilst data collection was ongoing, it was increasingly evident that a large number of trials may have unbalanced groups. Although the groups were generally comparable at baseline, the variability of their baseline characteristics were often considerably wide, especially in studies with <30 participants/arm. With such

small studies, homogeneity between groups is easily compromised when patients are lost to follow-up. Therefore, change in baseline score was deemed the more appropriate measure in the study level meta-analysis when the baseline covariates cannot be adjusted. The analysis was repeated by substituting change score with end-point score in order to assess if this deviation in protocol would change the findings.

3.7 **Difference between MA and NMA**

In MA, the unit of analysis was clear when a trial had only two arms. However, if it were a trial with 3 arms, appropriate measures as recommended by Cochrane handbook (Higgins JPT, 2011) were adopted to address potential correlation between comparisons that come from the same trial (e.g. by aggregating groups with common characteristics or by omitting one study arm). A detailed description of this is given in Chapter 5. In NMA on the other hand, all three arms can be included in the NMA because the correlation can be adjusted by the model. In addition to this primary difference between MA and NMA, detail differences between conventional MA and NMA in the context of the present work are illustrated in Table 3-2.

Table 3-2 Differences in conventional meta-analysis (MA) and network meta-analysis (NMA)

	MA (Direct comparison only)	NMA (Direct + indirect comparisons)
Types of comparison analysed	Exercise versus usual care	Exercise versus usual care; Exercise A versus Exercise B
Handling of studies with >2 exercise intervention	Aggregation of exercise groups was done whenever possible if they were of similar types. Otherwise, the exercise type that was generally under-evaluated was chosen	Aggregation of exercise groups was avoided unless they were of similar types; exercise of different types were all included
Model checking	Checking of model was by assessing magnitude of between study heterogeneity	Additional assessment of consistency between direct and indirect estimates was performed
Ranking of exercise	Ranking probability could *not* be performed	Ranking probability could be performed

Another difference between the conventional MA and NMA for the present work was that the data from MA was analysed based on frequentist statistics while data from NMA was enhanced with Bayesian analysis. Under the frequentist framework, investigators can only repeatedly test the null hypothesis ignoring what was already believed to be true. The Bayesian approach on the other hand, allows investigators to incorporate any prior information/knowledge into the analysis and reassess if the new data supports the belief or how the

new data enhances pre-existing evidence. Other differences between frequentist and Bayesian statistics are summarised in Table 3-3 (Schoot et al., 2014).

Table 3-3 Differences between frequentist and Bayesian statistics

	Frequentist	**Bayesian**
Reporting of estimates	Mean (95% confidence interval)	Mean (95% credible interval)
Confidence interpretation	Confidence interval interpretation: 95% of the studies if done over and over again, will contain the true population value	Credible interval interpretation: there is 95% probability that the true value is within the interval indicated
Sample size	Large sample size is considered more robust	Large sample not necessary
Prior information	Not incorporated into analysis	Prior information can be incorporated into the model and thus updating of earlier knowledge is possible
Parameter (e.g. population mean)	A population mean is unknown but has only one fixed true value.	A population mean is unknown but is not fixed. It has a distribution of random values

4 Characteristics of included studies

4.1 Screening flow

Electronic databases and hand searches performed up to December 2015 retrieved 13,672 citations. After removal of duplicates, a total of 7,635 citations were retained for title and abstract screening, following which 350 were shortlisted for full text screening. The number of citations found eligible for inclusion based on the criteria described in the preceding Chapter 3 were 199. These reports came from 185 separate trials.

Since then, two updates were carried out in September and December 2017 which increased the total of eligible citations to 239 and the number of representative trials to 217. Of these, only 106 trials were included in the analysis of this present work that focused on usual care as the non-exercise control group. Fig. 4-1 summarises the results. A detailed flow for the updates performed in 2017 is provided as Appendix 6. Disagreement for double extraction of data was within the acceptable limit, so predominantly single extraction was retained.

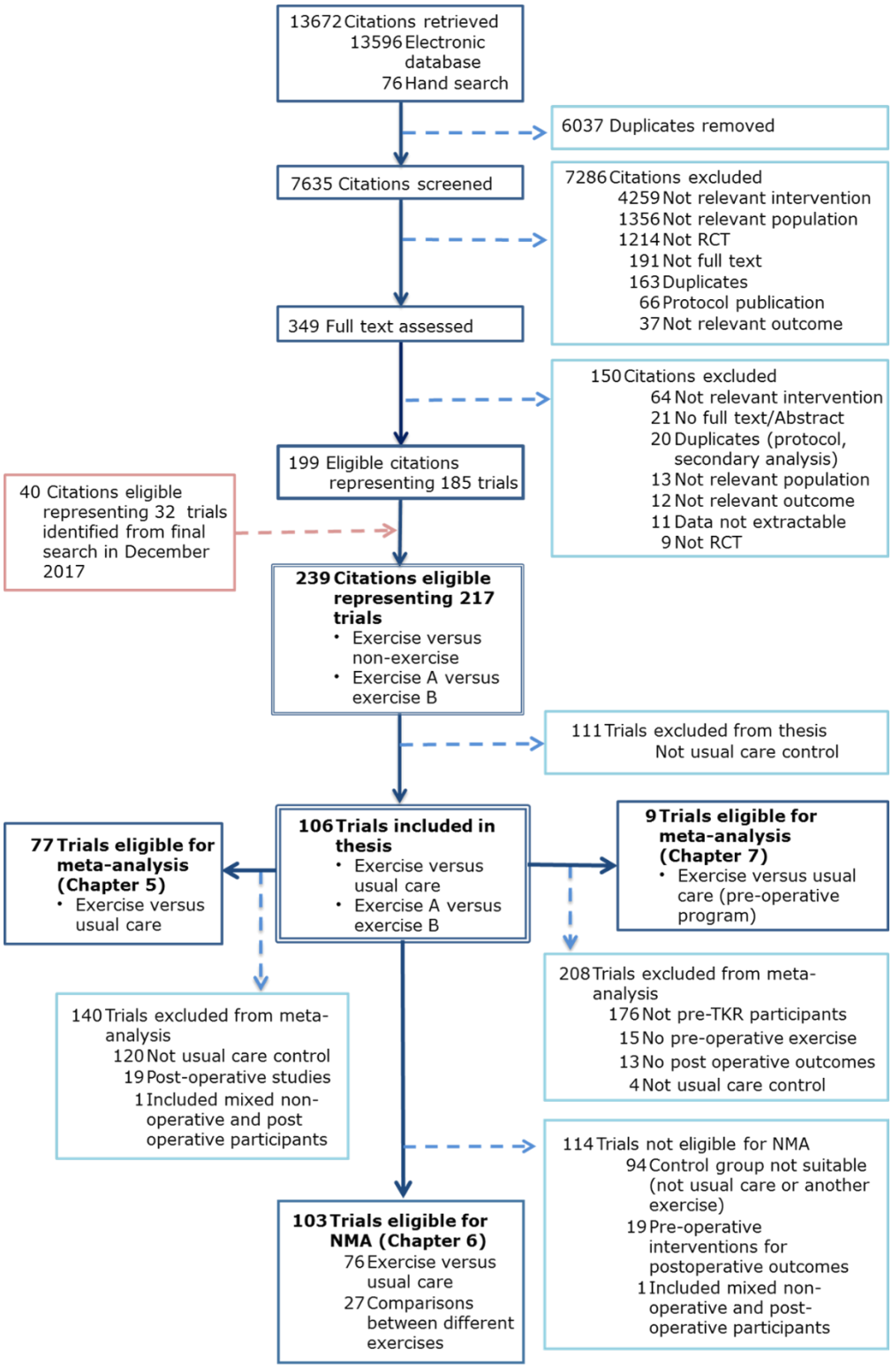


Fig. 4-1 Flow chart of study selection - Overall.
NMA= network meta-analysis; TKR=total joint replacement

4.2 Characteristics of intervention and control groups of eligible studies

These 217 trials consisted a total of 521 different group assignments: 151 groups from 2-arm studies; 45 from 3-arm studies; and 21 from 4-arm studies. There were 209 non-exercise groups and approximately 31% of these were assigned to usual care, making usual care the largest single non-exercise comparator group. Other categories of non-exercise control included usual physical activity (10%), education (10%), electrotherapeutic therapy (10%), pharmacotherapy (7%), waiting-list (6%), attention control/ sham therapy (5%), complementary medical therapy (3%), diet/ weight loss (3%), manual therapy (2%), self-management (1%) and the remainder of the non-exercise groups were given a combination of different treatments/interventions.

This finding was important in establishing the feasibility of using usual care group as the primary common comparator for trial connectivity in NMA. Both usual physical activity and waiting-list groups were integrated under usual care for analysis principally because these two groups were similar to usual care, whereby the intention was for the participants to carry on with their existing daily and treatment routines without interference. In this regard, the term ‘non-intervention

comparator' may be used occasionally in this thesis to reflect the 'passive' effects of usual care as oppose to other 'active' interventions used by researchers.

As for the exercise groups, standalone exercise programs were one of the commonest and was used in 60% of the 217 studies. Standalone exercise programs were exercise programs that were not being combined with other treatments. Considered together, this preliminary finding suggested that there are sufficient number of studies that used standalone exercise and usual care to perform NMA, without having to include studies with complex exercise programs. Therefore, after excluding studies using complex exercise programs and studies using other forms of active treatments as control groups, 106 studies (exercise alone versus usual care - 81 studies; exercise A alone versus exercise B alone - 25 studies) were finally utilised for the analyses in this thesis.

Appendix 7a lists the characteristics of each report/studies included in Chapters 5, 6 or 7. Appendix 7B provides detail description of exercise programs for each of the included study while Table 4-1 summarizes the frequency, intensity and other characteristics by different exercise groups. Nine groups were presribed exercise in water, 134 groups on land; 23 groups

were given group-based exercise, 25 groups individual-based exercise, and 15 groups given combination of individual and group exericse; exercises were home-based for 13 groups, centre-based for 62 groups, and mixed home- and centre-based 45 groups.

Table 4-1 Characteristics of different exercise groups

Exercise type	Frequency[#]	Intensity	Repetitions (reps)/ Duration of each session (minutes)	Supervision		Length of program in months[#]
				Groups with supervision (%)	No. of supervissed session over 8 weeks[#]	
Strength	3 (2-7)	40-80% of maximum capacity*	10-150 reps	56	16 (3-24)	2 (0.75 -18)
Aerobic	3 (2-5)	30-75% of maximum capacity*	10-55 minutes	42	21 (16-24)	2 (0.5-18)
Flexibility/ skills	3 (2-7)	–	16-32 reps	53	6 (4-24)	2 (0.5-6)
Mind-body	5 (2-6)	–	30-60 minutes	100	12 (8-16)	2 (2-3)
Mixed exercise	3 (2-7)	variable	Varies with exercise components	100	12 (4-24)	2 (0.5-12)

*Maximum capacity include measurements using maximum heart rate, heart rate reserve and rate of perceived exertion for aerobic exercise; for strengthening exercise, measurements were made based on peak or mean torque, body weight, maximum repetition and fatigue scale.

[#]Values are expressed as median (range)

4.3 Characteristics of studies analysed

4.3.1 Overall

A total of 9264 participants, of which 2/3 were female, were involved in the 106 trials included (refer Table 4-2). Although the recruitment setting was generally well described in most studies, this information was missing in 17 of the reports. Recruitment occurred most commonly in GP and community setting, followed by specialist/hospital setting. In 53 trials, no additional eligibility criteria for OA participants was described, beyond the 'standard' requirement for a confirmed diagnosis. The remainder of trials described additional criteria of specific OA subset, of which 19 trials focused on participants awaiting joint replacement, 11 trials on bilateral joint OA, 13 trials on OA with some degree of co-morbidity (e.g. obesity, difficulty with daily activity) and others (e.g. women, abnormal knee alignment).

More than 90% of the included trials recruited single joint OA, while the remainder recruited mixed group of hip and knee OA. These 106 studies contributed a total of 165 exercise groups for analysis. Mixed exercise was the most common exercise administered, being used in 50% of the studies. Usual care was the single most common non-interventional comparator, being used by nearly 50% of the studies.

Table 4-2 Characteristics of studies included for conventional meta-analysis or network meta-analysis

Total studies (translated)	**106 (7)**
Total participants (women[#])	**9264 (6312)**
Total study arms (number exercise arms)[§]	**260 (165)**
Median age, years	65 (41, 84)
Median number of exercise days/week	3 (1, 7)
Median duration of interventions, months	2 (0.5, 18)
Number of studies by:	
Recruitment	
Specialist/hospital	38
GP/ Community	43
Mixed	8
Unclear/ not specified	17
Joint	
Knee	89
Hip	10
Mixed	7
Type of exercise delivered[‡]	
Strengthening	43
Aerobic	14
Mind-body	8
Skills/Flexibility	23
Mixed	54
Outcomes Extracted	
Pain	96
Function	95
Performance	96
Quality of life	48
Geography	
UK, European continent	29
US, Canada, South America	29
Africa, Asia, Australia	48
Types of non-intervention comparator	
Usual care	46
Usual physical activity	18
Waiting-list	14
*Trial data points**	
<1 month -	6
1 month -	36
2 months -	46
3 months -	48
6 months -	21
12 months -	21

Other than count data, values are range (min, max)

[#] Number indicates minimum number of women as some studies do not provide breakdown of gender (cont.)

§ Count is based on study design. For example, a study may have three separate arms of the same exercise, but training intensity is different for each arm.
ǂ Total number exceeds the number of studies included (i.e. 106) because some studies delivered more than one type of exercise.
* Data is exclusive of studies that reported post-operative outcomes only.

Pain, function or performance outcomes were reported by almost all of the included trials (i.e. over 90 trials), only 48 trials provided QoL measures. There were 40 trials that performed measurement in all 4 outcomes of interest. Except for 7 trials, all other studies contributed data to at least two outcomes.

Almost all studies presented their results in a form that was extractable. European countries, North America and South America together contributed more than half of the eligible studies. There were 7 studies which required translation to English.

4.3.2 **Primary time point**

The two most common measurement time points used by the included studies were 8 weeks and 12 weeks. However, 8 weeks was chosen as the primary time point considering that more than half (58%) of the included trials did not deliver intensive exercise program for period longer than 8 weeks. This implied that at 12-week time point, a larger proportion of

study participants would probably have ceased to maintain the prescribed level/volume of exercise in comparison to 8-week time point. A 12 week time point would therefore result in an underestimated ES for exercise.

4.3.3 **Adherence**

Since there is no standard way to measure or report exercise adherence, it is difficult to summarise the exercise adherence characteristics across the studies or exercise groups. Few examples of different adherence indicators used include the average number of sessions attended by the group (Bennell et al., 2010), the number of participants who successfully attended a specified number of session (Abbott et al., 2013), the number of participants who completed the study (Baker et al., 2001), and the proportion of sessions completed/ attended (Bennell et al., 2005). Despite the numerous ways adherence had been reported, data was mainly obtained using either one, or both, of these approaches: attendance or exercise diary/ log book.

Of the total 106 studies included for analysis in this thesis, 62 (58%) reported the use of at least one of the two approaches of adherence monitor. The remainder 44 (42%) did not explicitly report administration of any measures to monitor adherence. Adherence method(s) used by each study is listed

in Appendix 8. Table 4-3 summarises the proportion of different exercise types for which the exercise adherence had been monitored either with attendance, exercise diary or both. Adherence monitoring for mixed exercise was the highest while skills/flexibility exercise was the lowest. Except for skills/flexibility and strengthening groups, monitoring of the aerobic, mind-body and mixed exercise groups were greater than 50%. Adherence rate – estimated by the proportion of participants remaining in the exercise group at primary time point – was higher than 90% in all exercise types. Adherence rate appeared to be similar between the different exercise types.

Table 4-3 Adherence of exercise groups, presented by exercise type.

Exercise types	Total number of exercise groups (N=165)			Adherence rate, % (min-max)
	Groups with adherence monitored (*a*)	Total number of groups (*b*)	% monitored (a/b)	
Strengthening	25	58	43	95 (53-100)
Aerobic	7	13	54	98 (88-100)
Mind-body	5	8	63	93 (78-100)
Skills/ Flexibility	8	23	35	100 (83-100)
Mixed exercise	43	63	68	95 (64-100)

Note: Adherence rate was estimated based on the retention rate of participants at primary time point (i.e. number remaining in exercise group divided by total number randomised to group)

4.4 **Risk of bias**

Homogeneity of participants was well established in most studies. The domains of included trials had high risk of bias in blinding of patients and physician because of the nature of exercise. Assessor blinding was only analysed for studies with objective performance outcomes because it was the only outcome that was not self-reported. Risk of bias for other domains are summarised in Fig. 4-2 while Appendix 8 provides the risk of bias assessment for each individual study.

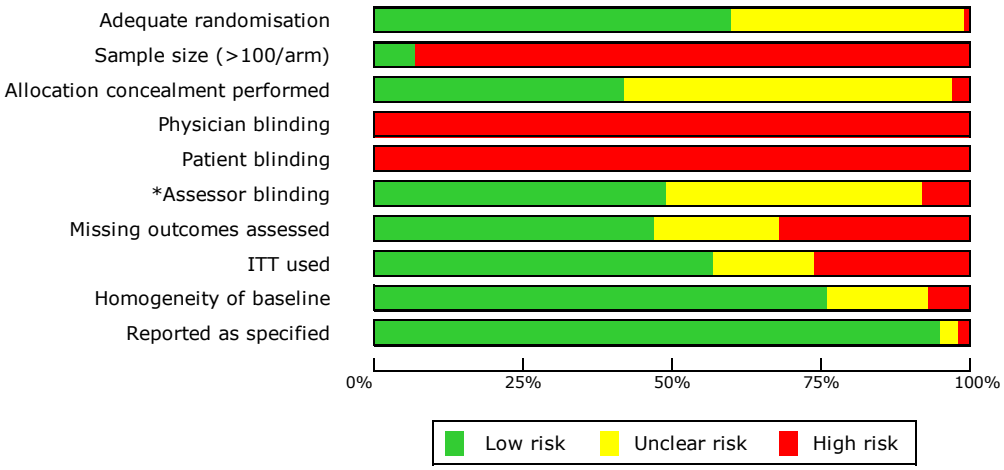


Fig. 4-2 Risk of bias assessment - Overall.
* Assessor blinding was for objectively measured performance outcomes because assessor blinding cannot be performed for other self-reported outcomes. (ITT= intention-to-treat)

5 Efficacy of exercise relative to usual care and potential predictors of exercise response

5.1 Introduction

This chapter examines the overall efficacy of exercise for four outcomes – pain, function, objective performance and QoL – using MA (frequentist approach), and to identify potential predictors of exercise response.

5.2 Method

Participants:

People with early and established OA as well as pre-joint replacement candidates were included in the analysis.

Primary time points:

Eight weeks (or nearest) post intervention

Comparison of interest:

Exercise-only versus usual care (e.g. aerobic alone versus usual care, mixed-exercise alone versus usual care).

Criteria of eligibility for interventions:

An exercise intervention qualified as an 'exercise-only' when no other types of therapy were administered concurrently.

Usual care refers to comparator groups that had no specific nor structured interventions imposed on them throughout the trial period (e.g. usual care, waiting-list, occasional home visits etc.) - they were 'observation only' groups receiving no interference to their usual treatment and care beyond those provided by their GPs or other healthcare professionals.

Handling of studies >2 arms

As per protocol, groups given exercise in combination with other interventions were excluded (refer Study 1 in Table 5-1). In some cases, where one study may have >1 exercise arm but had only one usual care group, such studies could only contribute one effect size according to the Cochrane handbook about using trials with multiple comparisons (Higgins JPT, 2011). Such studies were handled as follows: (i) if the types of exercise were distinctly different, the exercise that was less frequently investigated was chosen (refer Study 2 in Table 5-1); (ii) if the exercises were of similar type, the exercise intervention groups were aggregated for analysis (refer Study 3 in Table 5-1). SD for the composite group was calculated as described by the Cochrane Handbook (Higgins JPT, 2011) (refer Appendix 4).

Table 5-1 Hypothetical examples of how multi-arm trials were handled for analysis

Study	Study groups	Paired comparison
Study 1	• Mixed-exercise • Mixed-exercise + education • Usual care	Mixed-exercise *versus* Usual care
Study 2	• Aerobic (e.g. walking) • Strength training • Usual care	Aerobic *versus* Usual care
Study 3	• Home-based strength training • Group-based strength training • Usual care	Strength training (home+ group) *versus* Usual care

Study 1: Exercise-only arm was eligible**; Study 2**: Aerobic exercise that was relatively under-evaluated was chosen; **Study 3**: Exercises that were similar were aggregated for analysis

Subgroup analysis

Subgroup analysis was performed to determine the influence of the following study level characteristics (5 clinical characteristics; 10 methodological characteristics) on the overall estimates.

i. Clinical characteristics

   a. Mean age: <60 years old, ≥60 years old

   b. Percentage female: <60%, 60%-<80%, ≥80%

   c. Mean BMI: <30kg/m^2, ≥30kg/m^2

   d. Joint sites: knee OA, hip OA, mixed knee and hip OA

   e. Whether participants were on waiting-list for joint replacements

ii. Methodological characteristics

a. Whether additional pain criteria were used to determine eligibility
b. Whether ACR criteria was used for recruitment
c. Whether radiographic OA was a recruitment criteria
d. Whether adherence was monitored
e. Monitoring or control for analgesic reported
f. Centre of recruitment: specialist/hospital cohort, general practitioners (GP)/community, mixed cohort
g. Whether ITT analysis was used
h. Whether sample size was >100/ group
i. Whether the outcome was walking parameter or other performance test (for performance outcome)
j. Whether disease specific or generic QoL tool was used (for QoL outcome)

Meta-regression

Meta-regression was used to assess the relationship between covariates (study level characteristics) with the outcomes. The steps performed are summarised in Fig. 5-1. Firstly, univariate

meta-regression that included all covariates was performed without adjustment/correction for multiple testing. For covariates with p≤0.10, the covariates were then analysed using an adjusted univariate meta-regression and finally using adjusted multivariate meta-regression model if the p-values remained to be ≤0.10. Level of significance of multivariate meta-regression was set at p≤0.05. This would indicate if changes in the covariate could independently influence the changes in the outcome.

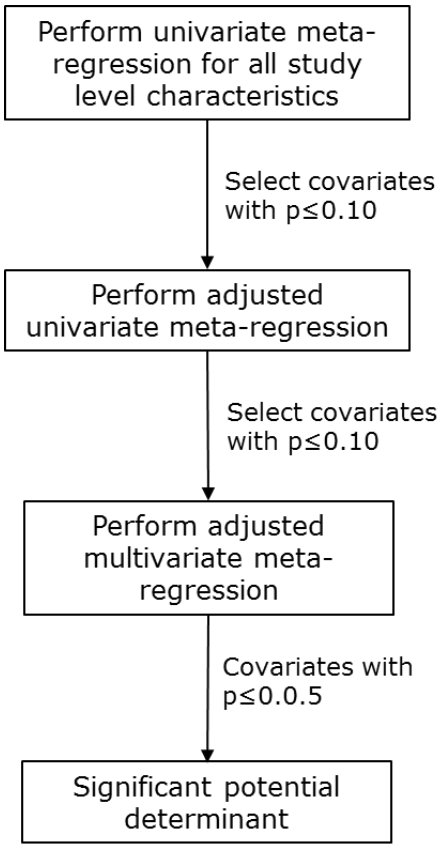


Fig. 5-1 Multi-regression steps

Adjustment for multiple testing was done through random permutation to maintain type 1 error (falsely detecting significant results) which would otherwise increase when the number of covariates being explored also increase (Harbord and Higgins, 2008). Considering that the data set may be too small and underpowered to examine more than 10 covariates, an unadjusted regression was used early in the analysis to 'short-list' potential covariates for the adjusted model.

Time dependent effect analysis

Outcome points during follow-up were grouped into intervals (i.e. <1 month, 1- months, 2- months, 3- months, 6- months, 9- months, 12- months and 18- months) for a secondary analysis for the time-dependent effect.

Sensitivity analysis

Analyses were repeated in the following ways to assess if the results were robust:

i. using scores at end points instead of change scores;

ii. including outliers;

iii. excluding studies that had imputed SD;

iv. excluding studies that assessed two, rather than one, index knee in each participant;

v. excluding translated publications;

vi. excluding studies with high heterogeneity as assessed by Baujat plots (Baujat et al., 2002). An example of its use is shown in Fig. 5-2. Studies were excluded sequentially until the I^2 statistics was less than 30% - a level of 25% is indicative that the influence of subgroup diversity is unremarkable (Higgins et al., 2003, Borenstein, 2009).

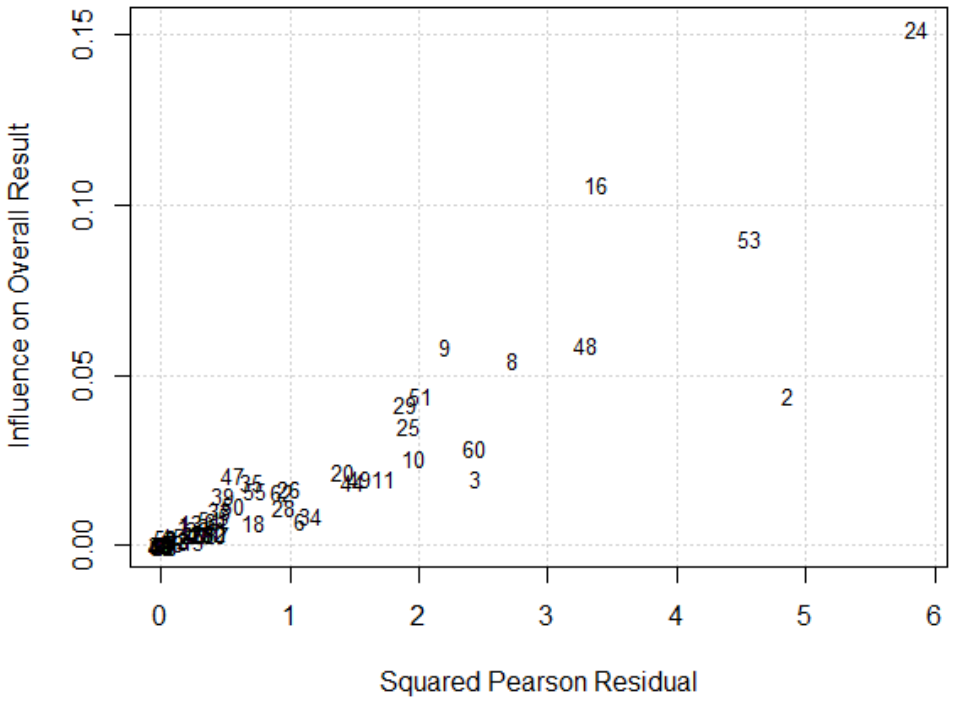


Fig. 5-2 Example of Baujat plot.
This plot is useful for visually assessing the sources of heterogeneity. As a study (as identified by a number) moves towards the right, its contribution in heterogeneity increases; upward shift indicates higher contribution towards the overall pooled summary of effect.

Post-hoc analysis

This analysis attempted to investigate if the effect of mixed exercise was influenced by the absence or presence of an aerobic exercise component.

5.3 **Results**

5.3.1 **Characteristics of included studies**

A total of 77 studies (n=6472) were found to be eligible to investigate the efficacy of exercise versus usual care. The two-arm design (i.e. exercise-only versus usual care) contributed the most studies (49) for this analysis (see Fig. 5-3). The remaining 28 studies had multiple arms, details of which can be seen in Fig. 5-3.

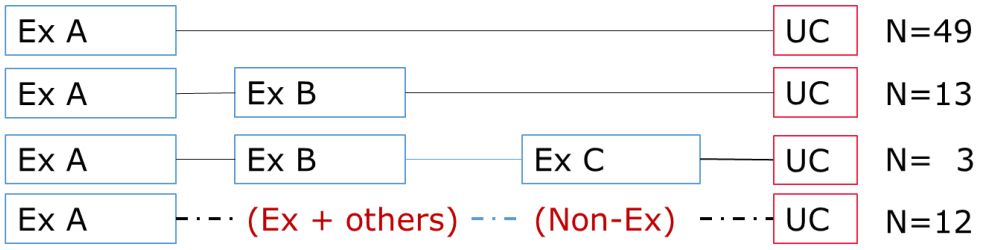


Fig. 5-3 Study design – Exercise (Ex) versus usual care (UC): Number of included studies.
Some studies included interventions that were not of interest (red in colour) but were included if they had at least a standalone exercise arm and an UC arm. A, B and C represented different types of standalone exercises.

As summarized in Table 5-2, almost all included studies measured pain. A total of 6072 participants were involved.

Functional and performance outcomes were reported by more than 80% but outcomes for QoL were reported in less than half of the included studies. The age and gender of participants were comparable across all outcomes. Knee OA was the most prevalent joint site for all outcomes.

Table 5-2 Study characteristics – Exercise versus usual care: Pain, function, performance and quality of life.

Total studies =77
Participants = 6472
Translated citations = 6

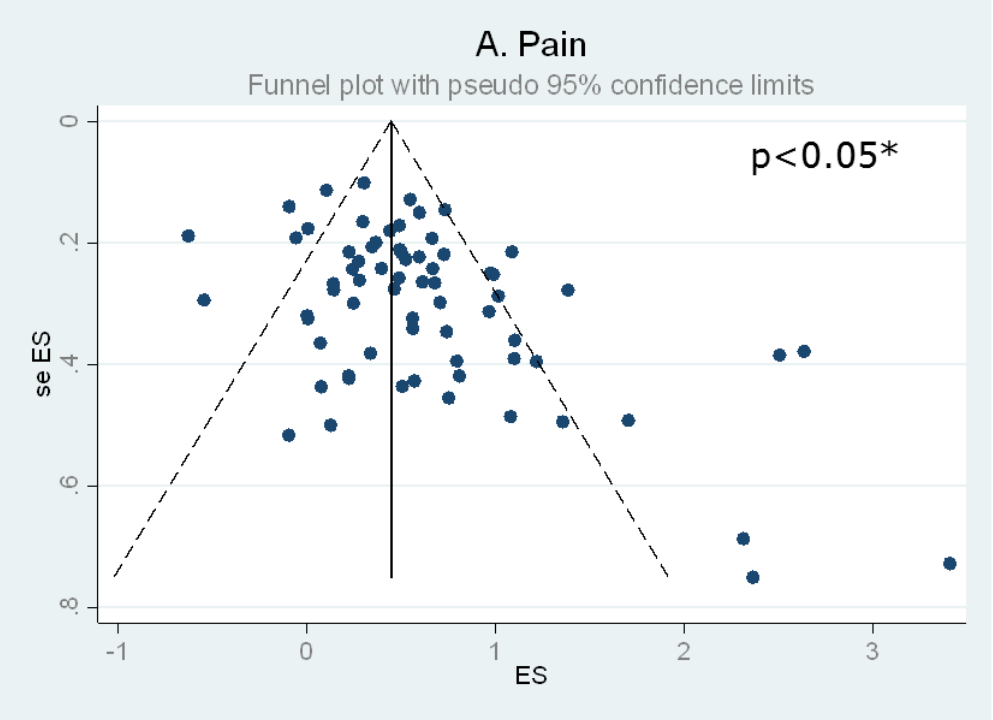
	Reported outcomes			
	Pain	**Function**	**Performance**	**QoL**
Number of comparisons (number of RCTs)	70 (69)	65 (64)	73 (72)	34 (34)
Number of participants	6072	5829	5913	3058
% Female per trial (min-max)	73.2 (40.4,100.0)	73.2 (40.4-100.0)	73.3 (40.4-100.0)	72.6 (40.4-100.0)
Median Age, years (min-max)	64.8 (41.3-84.4)	65 (41.3-84.4)	64.8 (41.3-77.0)	64.9 (49.4-84.4)
Median BMI, kg/m^2 (min-max)	29.8 (23.8-38.1)	29.8 (23.8-38.1)	29.6 (23.8-38.1)	29.9 (23.8-37.3)
Joint studied, no. RCTs (%)				
Knee	55 (80)	50 (78)	56 (78)	24 (71)
Hip	8 (12)	9 (14)	9 (13)	7 (21)
Both	6 (9)	5 (8)	7 (10)	3 (9)
OA definition				
ACR	32	31	35	13
Radiographic	38	37	39	19
Number of study data points, num used in analysis/ num reported				
<1 month -	-/1	-/2	-/1	-/2
1 month -	17/22	16/21	16/21	13/17
2 months -	26/32	26/31	30/35	9/13
3 months -	21/38	17/36	21/37	7/24
6 months -	3/16	3/16	1/15	3/9
12 months -	3/15	3/16	5/15	2/10

ACR=American College of Rheumatology; BMI= body mass index; H= hip; K= knee; num = number; QoL= quality of life; RCT= randomised controlled trial

5.3.2 **Handling of outliers and publication bias**

In the preliminary funnel plots (refer to Appendix 9), it was observed that pain and QoL had one outlier each (Swank et al., 2011, Evcik and Sonel, 2002). These studies were excluded from subsequent analyses. Fig. 5-4 shows the funnel plots for studies that were being used for analyses thereafter.

Funnel plots on the remaining studies indicated that the evidence was not symmetrically distributed for pain, function and performance. Unlike QoL outcomes, the plots in these three outcomes had obvious void in the lower left corner compared to the lower right corner. This means that smaller studies (or studies with larger standard errors) with negative or insignificant findings were unlikely to be published, suggesting that selective publication could be a significant problem for pain, function and performance but not for QoL.



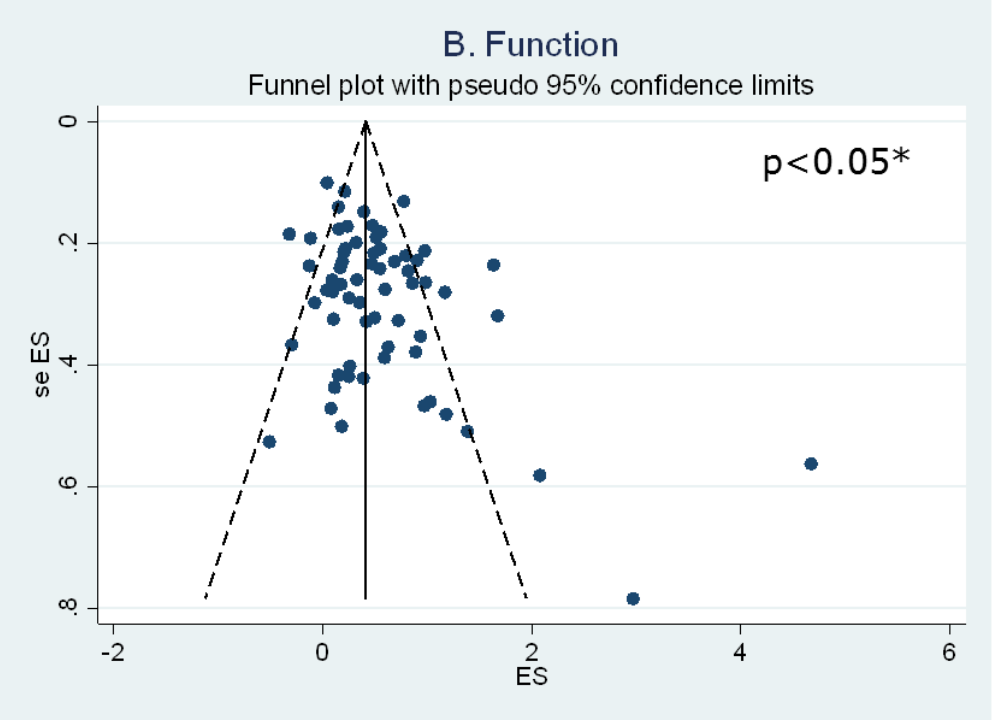
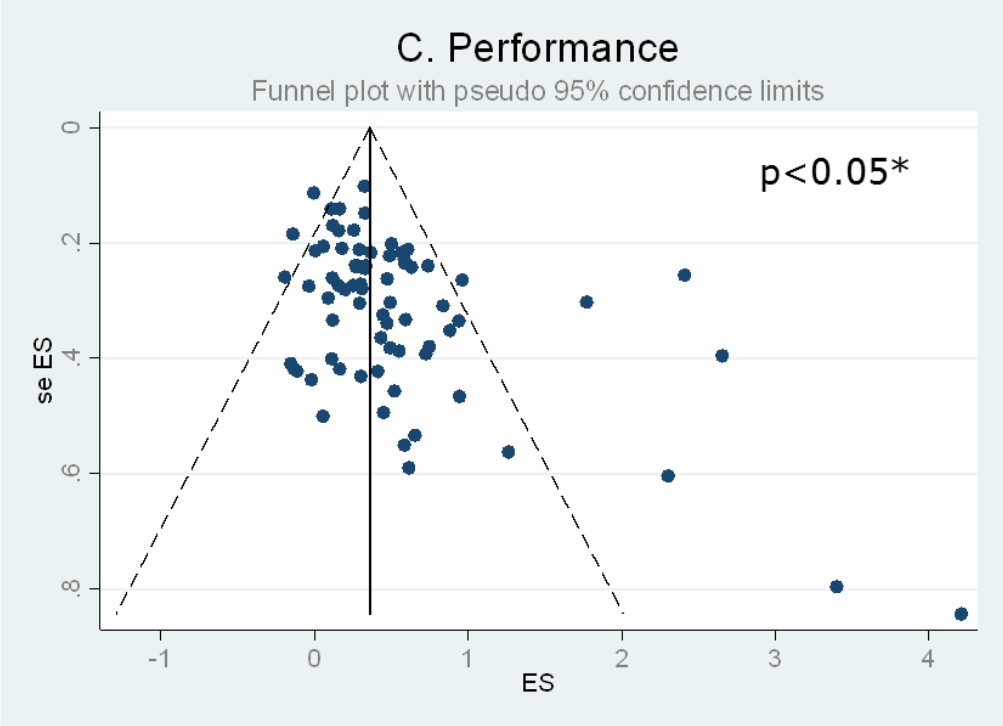


Fig. 5-4 Funnel plot – Exercise versus usual care: Pain, function, performance and quality of life.
* Egger's test suggestive of publication bias when p<0.05

(cont.)



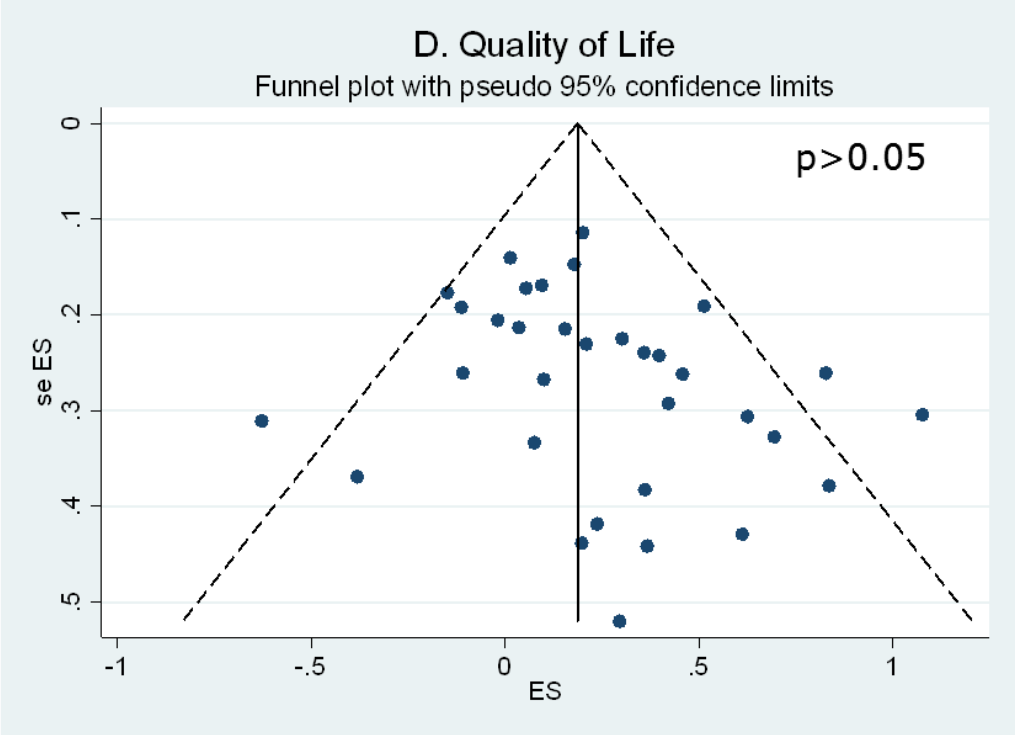


Fig. 5-4 Funnel plot – Exercise versus usual care

5.3.3 **Benefits of exercise**

5.3.3.1 Overall effects

Fig. 5-5 shows that, relative to usual care, exercise in general conferred moderate benefit for pain relief (ES 0.56; 95%CI 0.44, 0.68). From similar forest plots in Appendix 10, it can be seen that the benefits of exercise on function (ES 0.50; 95%CI 0.38-0.63) and performance (ES 0.46; 95%CI 0.35, 0.57) were also moderate at eight weeks, but improvement for QoL was only small (ES 0.21; 95%CI 0.11, 0.31).

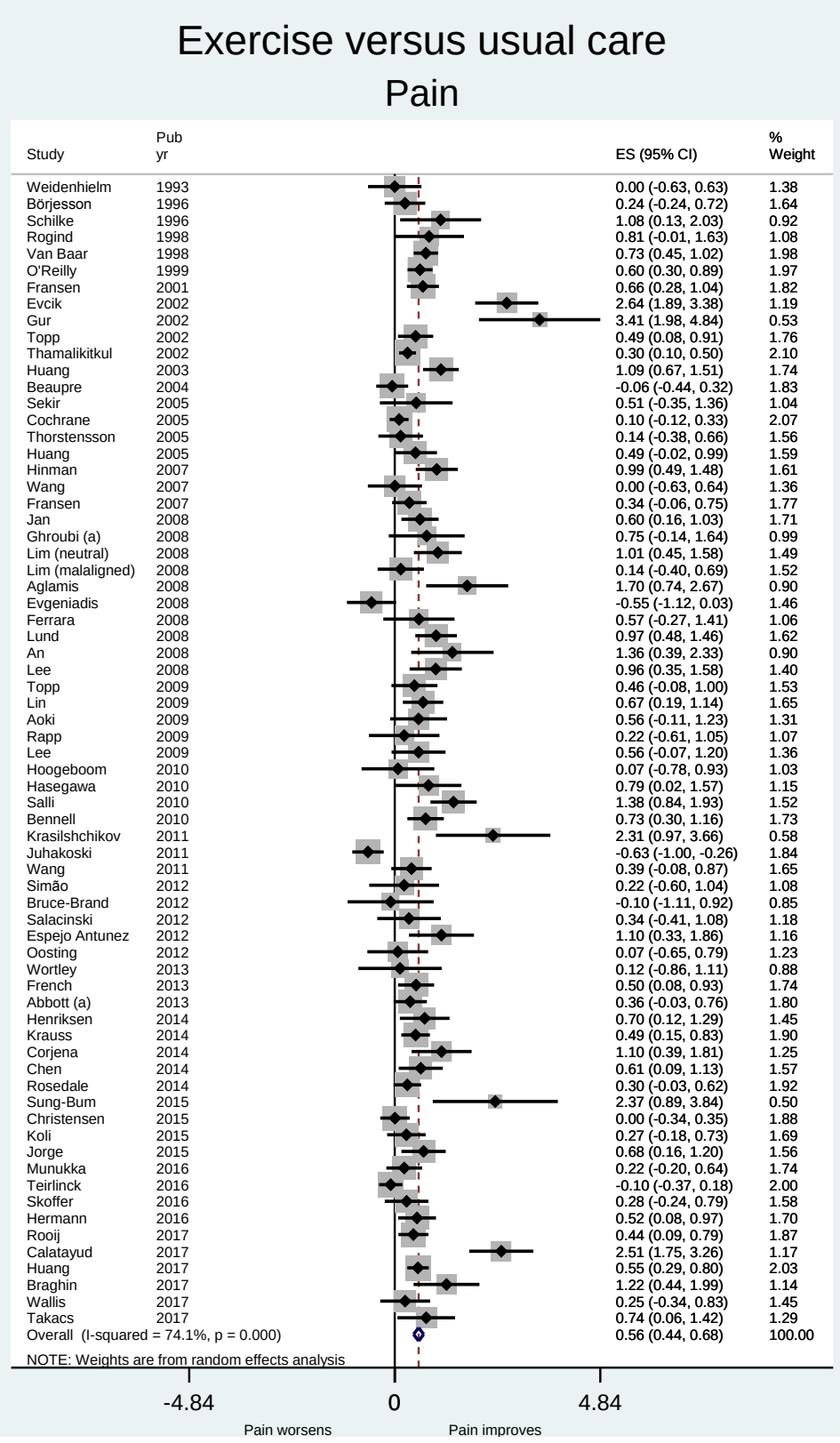


Fig. 5-5 Forest plot – Exercise versus usual care: Pain
Black diamond=point estimates for each study; grey shaded area= proportional contribution by each study to the pooled estimate

The cumulative meta-analysis demonstrates that the pooled estimates of exercise for pain have largely remained unchanged since 2005 (refer to Fig. 5-6). A similar trend was also demonstrated in estimates for function, performance and QoL (refer to Appendix 11).

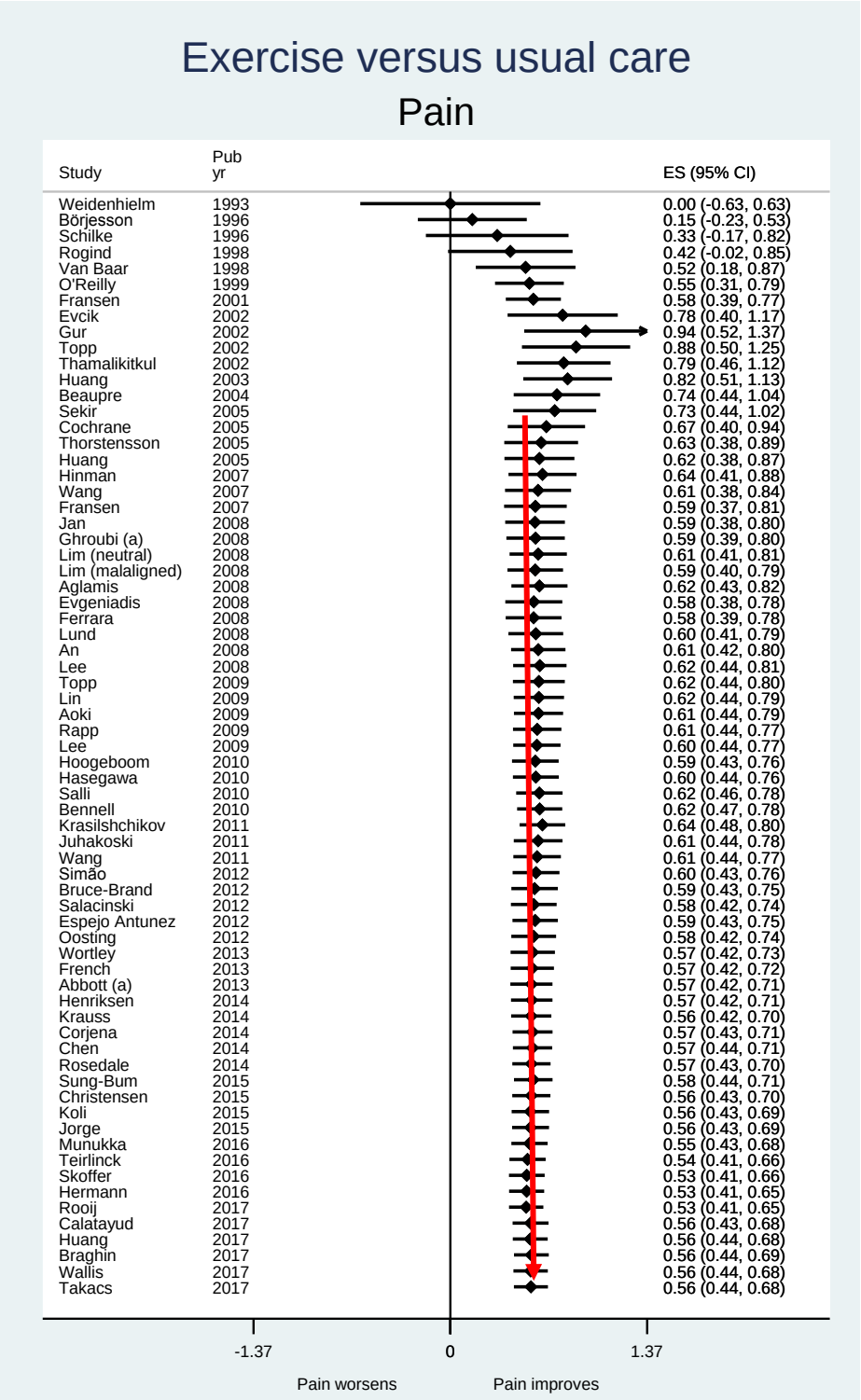


Fig. 5-6 Cumulative plot – Exercise versus usual care: Pain
Cumulative plot updates pooled effect size as new studies become available. It shows stabilizing of effect size since 2005 (red arrow).

5.3.3.2 Effects by type of exercise

Strengthening exercise (n=26) and mixed exercise (n=34) interventions were the most commonly evaluated. Relatively fewer trials investigated the efficacy of aerobic (n=6), mind-body (n=6) and flexibility (n=1) or skills (n=4) exercises. Potential for publication bias was detected (Egger's test $p<0.05$) for mixed exercise in pain and performance outcomes, and for strengthening exercise in functional outcome (refer to Fig. 5-7 for pain and Appendix 12 for other outcomes).

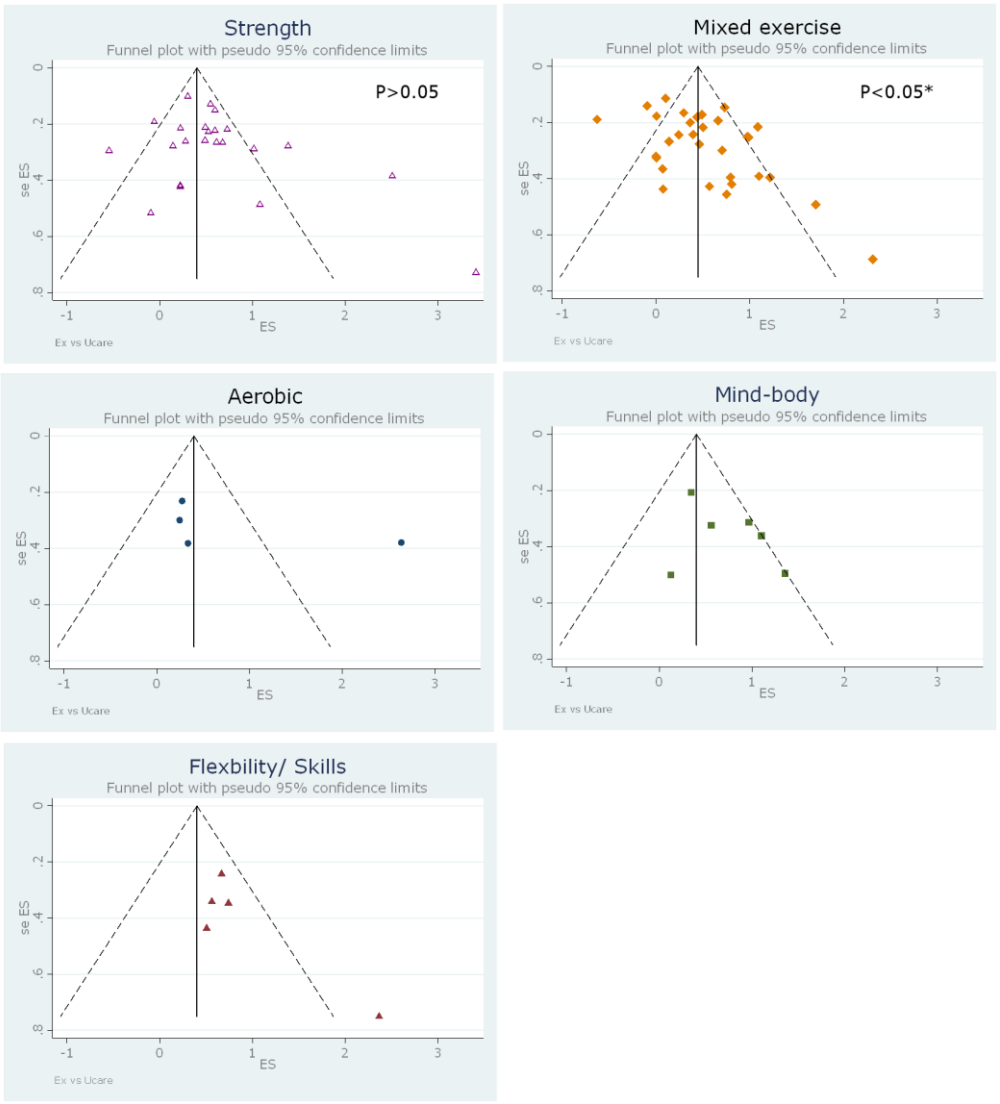


Fig. 5-7 Funnel plot – Exercise versus usual care (by exercise types): Pain.
* Egger's test suggestive of publication bias when p<0.05. This test was not performed if there were <10 studies.

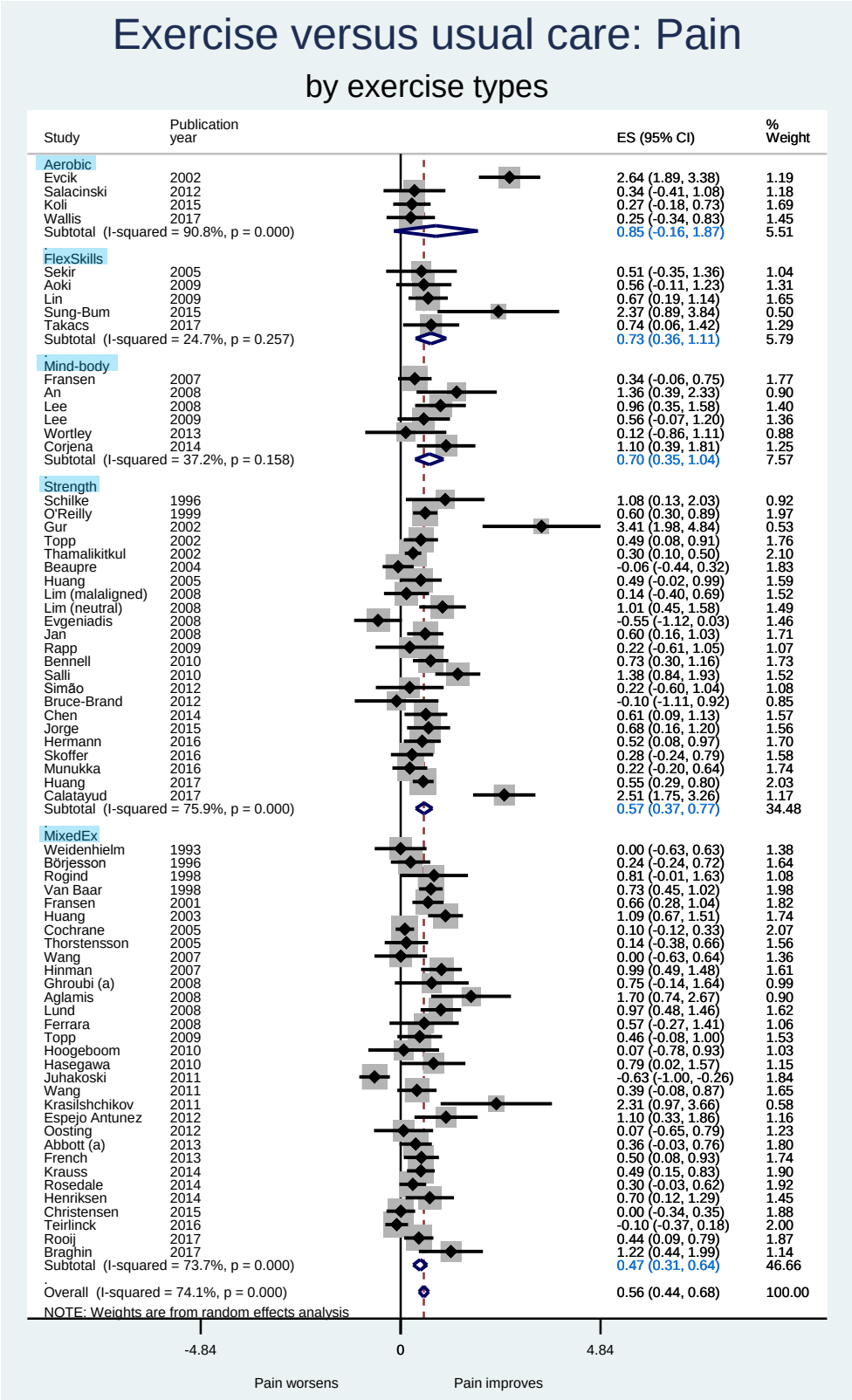


Fig. 5-8 Forest plot – Exercise versus usual care: Pain (by exercise types)

Analysis by type of exercise showed a graded pain response to different types of exercise (refer Fig. 5-8). Aerobic exercise provided the greatest benefit for pain relief (ES 0.85; 95%CI -0.16, 1.87) although the confidence around this estimate was wide and crossed zero. This was followed by flexibility/skills exercise, mind-body exercise, strength exercise and lastly mixed exercise. QoL and performance parameters also showed the largest magnitude of improvement with aerobic exercise, while the most effective exercise to improve function was flexibility/skills exercise (refer Table 5-3). Forest plot by exercise types for each function, performance and QoL outcomes are shown in Appendix 13.

The most commonly evaluated type of exercise was strengthening. Relative to aerobic and mind-body exercise, strength exercise did not appear to be remarkably effective for any of the outcomes of interest. The highest magnitude of response conferred by strength training was observed for function (ES 0.69; 95%CI 0.43, 0.94) followed by pain (ES 0.57; 95%CI 0.37, 0.77), performance (ES 0.51; 95%CI 0.33, 0.69) and then QoL (ES 0.23; 95%CI -0.03, 0.50).

Table 5-3 Effect size – Exercise versus usual care: Pain, function performance and quality of life (by exercise types)

Exercise types	No. Comp.	No. Patients	Effect Size (95%CI)	Egger's test*	I^2 (%)
Pain					
Mixed exercise	31	2606	0.47 (0.30, 0.64)	p<0.05	73.7
Strength	23	2021	0.57 (0.37, 0.77)	p>0.05	75.9
Mind-body	6	262	0.70 (0.35, 1.04)	-	37.2
Aerobic	4	203	0.85 (-0.16, 1.90)	-	90.8
Flex/ Skills	5	180	0.73 (0.36, 1.11)	-	24.7
Function					
Mixed exercise	28	2315	0.32 (0.19, 0.45)	p>0.05	50.9
Strength	23	2093	0.69 (0.43, 0.94)	p<0.05	85.7
Mind-body	6	262	0.58 (0.32, 0.83)	-	0.0
Aerobic	5	221	0.50 (-0.14, 1.13)	-	79.8
Flex/ Skills	3	134	0.82 (0.47, 1.17)	-	0.0
Performance					
Mixed exercise	32	2543	0.37 (0.20, 0.55)	P<0.05	75.0
Strength	26	1930	0.51 (0.33,0.69)	p>0.05	69.6
Mind-body	6	262	0.47 (0.09, 0.84)	-	49.7
Aerobic	4	167	0.93 (0.20, 1.67)	-	75.7
Flex/ Skills	5	180	0.60 (0.30, 0.90)	-	0.0
Quality of life					
Mixed exercise	16	1515	0.17 (0.05, 0.28)	p>0.05	14.6
Strength	10	767	0.23 (-0.03, 0.50)	p>0.05	66.1
Mind-body	4	198	0.21 (-0.12, 0.54)	-	18.6
Aerobic	3	149	0.36 (0.04, 0.69)	-	0.0
Flex/ Skills	-	-	-	-	-

No. comp.= Number of comparators; CI= confidence interval; Flex = flexibility

* Egger's test suggestive of publication bias when p<0.05. Test not performed if there are <10 studies

Substantial heterogeneity (I^2 statistics >50 %) – particularly in studies that assessed strength and mixed exercises (shown in Table 5-3) – implied that the true underlying effects in these studies may be significantly different across studies. As I^2 quantifies the percentage of unexplained heterogeneity/ variance in the measured ES, a high value indicates that the

observed effects seen following strength and mixed exercises could be moderated by factors such as variations in OA subgroup, study methodology or exercise program.

5.3.3.3 Effects by medium of exercise

As shown in Table 5-4, a great proportion of studies was land-based exercise programs. Water-based exercise was being performed in less than 6 studies and exercise in combined medium was even fewer. Pain and QoL outcomes did not differ significantly between groups of exercise medium. Function and performance outcomes, on the other hand, appeared to be 2 times better with land-based exercise than water-based exercise. There are too few trials for exercise performed on both land and water to make reliable comparison with other subgroups.

Table 5-4 Effect size – Exercise versus usual care: Pain, function performance and quality of life (by exercise medium)

Exercise types	No. Comp.	No. Patients	Effect Size (95%CI)	I^2 (%)
		Pain		
Land	63	4609	0.58 (0.45, 0.71)	74.3
Water	4	506	0.32 (-0.08, 0.72)	72.2
Combination	2	157	0.68 (0.11, 1.25)	63.8
		Function		
Land	57	4300	0.56 (0.42, 0.70)	76.2
Water	5	550	0.23 (0.07, 0.40)	0.0
Combination	3	175	0.50 (-0.29, 0.34)	0.0
		Performance		
Land	66	4427	0.47 (0.35, 0.59)	70.1
Water	5	559	0.20 (-0.01, 0.41)	24.0
Combination	1	78	0.27 (-0.20, 0.74)	-
		Quality of Life		
Land	29	2084	0.21 (0.08, 0.33)	42.8
Water	3	467	0.22 (0.03, 0.40)	0.0
Combination	1	78	0.40 (-0.08, 0.87)	-

No. comp.= Number of comparisons; CI= confidence interval

5.3.3.4 Subgroup analysis

The analysis carried out for subgroups of OA, recruitment criteria, interventional and statistical analysis characteristics demonstrated differences in some subsets of studies. The detailed results for pain subgroup analysis together with the unadjusted univariate meta-regression p-values are shown in Table 5-5. Results for other outcomes can be found in Appendix 14.

The most obvious difference for pain outcome was observed between studies with mean age <60 years old (ES 1.32; 95%CI 0.79, 1.86) versus those with mean age ≥60 years old (ES 0.44; 95%CI 0.34, 0.55), and in studies of knee OA (ES

0.64; 95%CI 0.51, 0.78) versus hip OA (ES 0.17; 95%CI -0.17, 0.51). Subgroups not on the surgical waiting-list (ES 0.62; 95%CI 0.49, 0.75) also showed greater pain improvement compared to those who were awaiting surgery (ES 0.33; 95%CI 0.04, 0.63). The p-values for these three covariates (age, joint site and surgical waiting-list) along with the p-values for percentage female and ITT were significant at ≤0.10 (Table 5-5).

Table 5-5 Subgroup analysis – Exercise versus usual care: Pain

	No. comp. (No. trials)	No. patients	Effect Size (95%CI)	I^2 (%)	p-value (univariate)
Overall	**69 (68)**	**5272**	**0.56 (0.44, 0.68)**	**74.1**	
Age					
<60 years old	12	591	1.32 (0.79,1.86)	86.9	<0.01*****
≥60 years old	57	4681	0.44 (0.34,0.55)	62.6	
Percentage female[a]					
<60%	14	1156	0.27 (0.10,0.44)	46.2	0.09*
60% -<80%	30	2731	0.60 (0.41,0.78)	79.0	
≥80%	22	1291	0.56 (0.39,0.74)	50.2	
Mean body mass index[a]					
<30	26	2052	0.46 (0.38,0.60)	53.3	0.78
≥30	18	1187	0.56 (0.28,0.84)	79.8	
Joint					
Knee	55	3750	0.64 (0.51, 0.78)	71.2	0.02*
Hip	8	703	0.17 (-0.17, 0.51)	76.8	
Mixed	6	819	0.43 (0.13, 0.72)	73.6	
On JR waiting-list					
No	55	4481	0.62 (0.49, 0.75)	74.0	0.10*
Yes	14	791	0.33 (0.04, 0.63)	73.5	
'Explicit' pain criteria					
None	56	3965	0.59 (0.44, 0.73)	76.2	0.64
Yes	13	1307	0.49 (0.30, 0.68)	62.0	
ACR criteria					
Yes	33	2585	0.64 (0.45, 0.82)	78.8	0.39
No/Unclear	36	2687	0.46 (0.32, 0.60)	66.7	
Radiographic requirement					
Yes	39	2649	0.66 (0.46, 0.85)	80.9	0.27
No/Unclear	30	2623	0.46 (0.33, 0.59)	53.4	
Adherence monitored					
Yes	45	3961	0.49 (0.36, 0.63)	73.2	0.17
No/Unclear	24	1311	0.73 (0.48, 1.00)	74.7	
Analgesic controlled/monitored					
Yes	33	2821	0.55 (0.38, 0.73)	77.8	0.86
No/ Unclear	36	2451	0.58 (0.41, 0.74)	70.1	
Recruitment centre[a]					
Specialist/hospital	27	1867	0.50 (0.31, 0.69)	72.4	0.91
GP/Community	26	2405	0.50 (0.32, 0.67)	72.7	
Mixed	7	680	0.46 (0.30, 0.60)	7.1	
Intention-to-treat use					
Yes	44	3574	0.47 (0.33, 0.60)	73.7	0.06*
No/Unclear	25	1698	0.76 (0.55, 1.00)	72.7	
Sample >100/ group					
Yes	5	1356	0.31 (0.05, 0.58)	82.9	0.25
No	64	3916	0.60 (0.46, 0.73)	72.5	

No. comp.= Number of comparators; ACR= American College of Rheumatology; GP= general practitioner; OA= osteoarthritis; JR= joint replacement

[a]Data was missing in some studies; * significant covariates from unadjusted univariate meta-regression (p≤0.10)

The subgroup differences in function were relative similar in trend to those observed for pain and are presented in Appendix 14. For performance outcomes on the other hand, greater subgroup differences were found in covariates related to study methodology (e.g. recruitment centre, sample size, ITT use) while for QoL greater differences were noted in covariates related to patient and OA characteristics. Specifically for performance, ES of exercise was not influenced by whether walking parameters or other physical tests were used; for QoL, ES remained the same irrespective of whether a disease-specific or generic instrument was used.

Overall, patients recruited from hospitals and specialist clinics were more responsive to exercise therapy than those from general practitioner (GP)/community settings.

5.3.4 **Potential determinants of response to exercise therapy**

Table 5-6 lists the various study-level clinical and methodological covariates with $p \leq 0.10$ that had been identified from univariate meta-regression in the preceding subgroup analysis (5.3.3.4). The relevant p-values for these covariates after adjusting for multiple testing are indicated in black (for univariate regression) and in blue (for final multivariate regression) in Table 5-6.

Except for study mean age (more or less than 60 years of age) which had a multivariate p-value of ≤0.05, none of the other covariates had a significant and independent moderating effect on pain. Age was also a significant potential determinant for function and QoL but not for performance outcomes. For performance, only recruitment centre appeared to be an independent determinant. Another potential determinant for functional outcome was joint site.

Table 5-6 Univariate and multivariate meta-regression: Pain, function, performance and quality of life (QoL) outcomes

Study level characteristics	p-values			
	Pain	Function	Performance	QoL
Clinical				
Age	0.03/**<0.01**	<0.01/**<0.01**	0.31/ -	0.05/ -
Female	0.35/ -			
Joint	0.07/0.08	0.03/**0.04**	0.27/ -	0.53/ -
Waiting-list	0.05/0.64			
Methodological				
Intention-to-treat	0.04/1.00		0.32/ -	
Adherence		0.19/ -	0.10/0.42	0.78/ -
Pain criteria			1.00/ -	
Recruitment			0.02/**0.04**	

Study characteristics with p≤0.10 identified from Table 5-5 and Appendix 14 subgroup analysis were modelled in adjusted univariate meta-regression. The new p-values are in black. If the new p-values remained ≤0.10, the covariates were then included in the final adjusted multivariate regression (blue). Significant covariate (p≤0.05) after multivariate regression are shown in bold. For QoL, only one covariate was significant in univariate analysis, hence no multivariate analysis was performed.

5.3.5 **Time dependant effect of exercise**

Although the evidence to support exercise benefits within the first month of intervention is lacking, there is strong evidence

to support significant exercise benefits after the first month for pain, function and performance (refer to Fig. 5-9). Significant QoL improvement, on the other hand, was only evident in the second month. All benefits appear to peak in the second month. From three months onwards, irrespective of the implementation of booster session or contact with the investigation team, the overall exercise response gradually diminished. By nine months, almost all measurements had become non-significantly different from usual care.

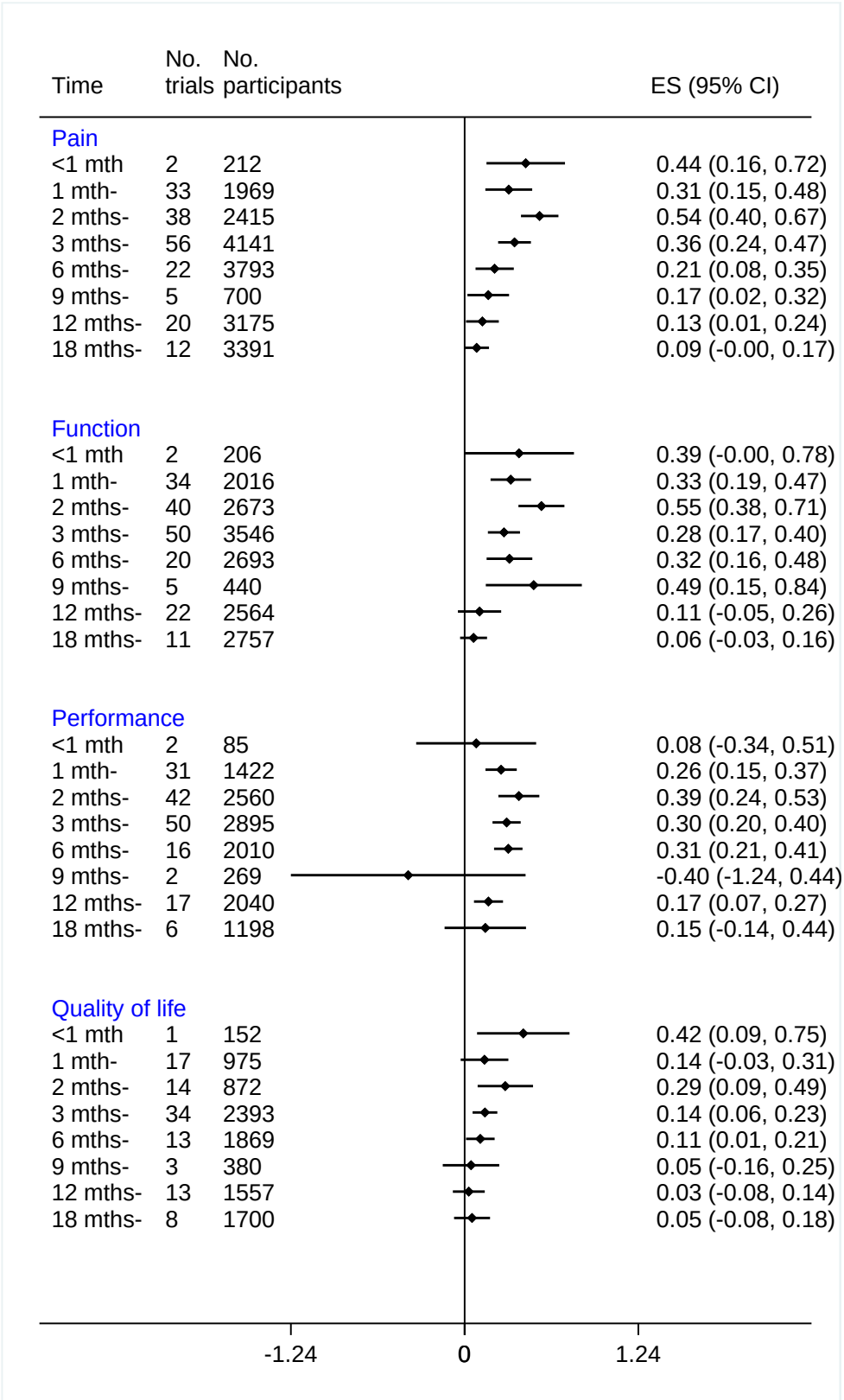


Fig. 5-9 Time dependent effect – Exercise versus usual care: Pain, function, performance and quality of life.
Positive values favour exercise, negative values favour usual care.

5.3.6 **Risk of bias**

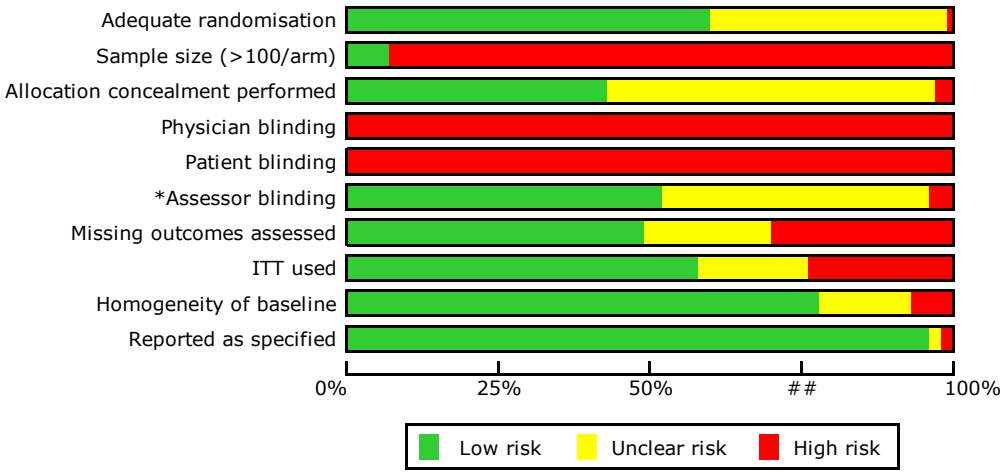


Fig 5-10 Risk of bias assessment – Exercise versus usual care
* Data is for studies with objective performance test since assessor blinding is not possible for self-reported outcomes.
ITT= intention to treat analysis

Apart from domains related to physician and patient blinding, the domain with highest risk of bias (i.e. the greatest proportion of red shading) was the sample size (shown in Fig 5-10). Less than 10% of the studies had sample size of 100 or more participants per group. The domain with the least risk of bias was related to study reporting – nearly all of the studies provided report on the outcome(s) that had been pre-specified.

5.3.7 **Sensitivity analysis**

Overall, the estimates of exercise effects for all outcomes were relatively robust. Changes in estimated ES was ≤ 0.1, irrespective of whether final scores were used instead of

change scores or whether the included studies had imputed SD, analysed two knees in one patient instead of one knee per patient, or whether the source of data were from translated publications (refer Table 5.7).

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Table 5-7 Sensitivity analysis – Exercise versus usual care: Pain, function, performance and quality of life

A. Pain

		No. comp. (No. trials)	No. Patients	ES (95%CI)	I^2 (%)
Overall, *Ch Sc*		**69 (68)**	**5272**	**0.56 (0.44, 0.68)**	**74.1**
Endpoint score				0.59 (0.47, 0.71)	76.3
Outlier (ES>40)	(+1)	70	5343	0.60 (0.45, 0.74)	82.5
Imputed SD	(-2)	67	4821	0.56 (0.44, 0.69)	74.4
Unit (knee)	(-3)	66	5026	0.55 (0.43, 0.68)	74.3
Translated	(-5)	64	5150	0.55 (0.43, 0.67)	75.0

B. Function

		No. comp. (No. trials)	No. Patients	ES (95%CI)	I^2 (%)
Overall, *Ch Sc*		**65 (64)**	**5025**	**0.51 (0.38, 0.63)**	**74.5**
Endpoint score				0.51 (0.38, 0.64)	78.2
Outliers		**-**	**-**	-	**-**
Imputed SD	(-1)	64	4775	0.50 (0.38, 0.62)	74.0
Unit (knee)	(-2)	62	4779	0.48 (0.35, 0.60)	73.8
Translated	(-4)	61	4852	0.50 (0.38, 0.63)	75.9

C. Performance

		No. comp. (No. trials)	No. Patients	ES (95%CI)	I^2 (%)
Overall, *Ch Sc*		**73(72)**	**5082**	**0.46 (0.35, 0.58)**	**70.5**
Endpoint score				0.49 (0.37, 0.62)	75.6
Outliers		-	-		-
Imputed SD		-	-		-
Unit (knee)	(-3)	70	4836	0.39 (0.29, 0.48)	55.8
Translated	(-5)	68	4898	0.42 (0.32, 0.53)	66.9

D. Quality of life

		No. comp. (No. trials)	No. Patients	ES (95%CI)	I2 (%)
Overall, *Ch Sc*		**33**	**2629**	**0.21 (0.10, 0.31)**	**36.4**
Endpoint score				0.34 (0.17, 0.52)	77.7
Outlier (ES>5)	(+1)	34	2683	0.30 (0.14, 0.46)	73.3
Imputed SD	-	**-**	**-**	**-**	**-**
Unit (knee)	-	-	-	-	-
Translated	(-2)	32	2598	0.19 (0.10, 0.30)	34.6

The signs '+' and '-' in brackets indicate the number of studies added or removed from primary analysis for sensitivity analysis, respectively. Ch Sc: change score was used to calculate effect size; No. comp: number of pairs; Endpoint score= if raw endpoint score were used in lieu of changed scores; Unit (knee)= knee was used as unit of analysis instead of individuals; SD imputed= studies where missing SD were imputed; Translated= translated publication

The variability across study/ heterogeneity for pain, function and performance were high (I^2>70%). However, when I^2 statistics were reduced to <30% by excluding deviant studies (i.e. studies contributing to the heterogeneity identified from Baujat plot), the corresponding 95%CIs remained relatively unchanged (refer Table 5-8). This suggests that the pooled results obtained were robust to deviant studies and the wide variability across studies did not have a significant impact on the results.

Table 5-8 Effect size (ES) obtained after excluding heterogeneous studies and reducing heterogeneity (I^2) to less than 30% – Exercise versus usual care: Pain, function, performance and quality of life

	ES (95%CI)	**I^2 (%)**	**N**
Pain	0.50 (0.43, 0.58)	27.4	56
	0.56 (0.44, 0.68)	*74.1*	*69*
Function	0.43 (0.35, 0.51)	23.5	51
	0.51 (0.38, 0.63)	*74.5*	*65*
Performance	0.32 (0.25, 0.39)	20.9	68
	0.46 (0.35, 0.58)	*70.5*	*73*
Quality of life	0.18 (0.09, 0.27)	20.4	32
	0.21 (0.10, 0.31)	*36.4*	*33*

Results of analyses obtained before excluding heterogeneous studies are given in blue for comparison. 95%CI: 95% confidence interval, I^2=I^2 statistic, n=number of studies

5.3.8 **Post-hoc analysis**

Although aerobic exercise appeared to be the most promising single exercise type for many of the outcomes, when included as part of mixed exercise it did not demonstrate any additional benefits for any outcomes. The efficacy of mixed exercise was not affected by the inclusion or omission of a specified aerobic exercise component in the program (Table 5-9).

Table 5-9 Differences in efficacy between mixed exercise with and without aerobic exercise component – Exercise versus usual care: Pain, function, performance and quality of life

	Effect size (95% CI)	
	With	Without
Pain	0.42 (0.22, 0.62)	0.53 (0.25, 0.80)
Function	0.32 (0.15, 0.49)	0.32 (0.12, 0.53)
Performance	0.36 (0.13, 0.59)	0.36 (0.10, 0.62)
Quality of life	0.16 (0.01, 0.30)	0.20 (-0.01, 0.41)

5.4 **Summary**

This chapter formulated an updated summary on efficacy of exercise compared to usual care at eight weeks (or nearest to eight weeks), using nearly 80 studies (participants=6472). Neuro-motor training or skills training were combined with flexibility exercise for analysis as these exercises were scarce.

Age was a significant determinant for many of the outcomes. As outcomes were better in studies with younger patients, there is an inverse relationship between exercise benefits and

age. This is consistent with evidence that beneficial cellular response to exercise may be attenuated by aging (Done et al., 2016)

On the other hand, if age is an indicator of OA severity, it would not explain why performance outcome were better among specialist/ hospital recruits, who would generally have more severe OA than patients from GP or community settings. Instead, the greater response shown by studies with tertiary centres recruits could be attributed to the more advanced facilities and exercise delivery settings. It could also be related to the perception of better care by patient, leading to a positive contextual effect in these patients.

The results of RCTs that used less rigorous methods or with higher risks of bias (small sample size, unclear/no exercise adherence monitoring, no explicit use of ITT) and deviant studies appeared to inflate the estimation of exercise effect. Although a quality assessment tool specially designed for exercise trials has recently been made available (Smart et al., 2015) no composite scoring system has been developed to grade if a particular exercise trial is of good or bad quality. Therefore, a single point estimate for exercise effect based only on good quality studies could not be performed. Instead, a subset of selected indicators of study quality which were

likely to be most relevant for exercise trials were used to assess the robustness of the results through subgroup and sensitivity analyses (Viswanathan et al., 2012).

6 Which exercise is better: Network meta-analysis

6.1 Introduction

This chapter specifically examines the relative efficacy of five exercise types (i.e. aerobic, strengthening, mind-body, flexibility/skills and mixed) for four outcomes – pain, function, QoL and objective performance – using network meta-analysis (NMA) (Bayesian approach).

6.2 Method

This NMA is an extension of the conventional meta-analysis in the preceding chapter. The types of participants and primary time points remained the same. The eligibility criteria however, had been extended to include studies that performed direct comparison between different types of exercises (e.g. aerobic versus strengthening). A study administering complex exercise program would still be eligible if the only difference between group was the type of exercise use, with all other aspects of treatment and testing condition remain comparable between groups.

Subgroup analysis

Subgroup analyses could only be performed for selected subgroups that had an adequate number of studies to maintain reasonable network connectivity. From the subgroup analyses performed in the preceding chapter, only three variables were identified to be suitable.

i. Site of OA (knee OA versus hip OA)

   Subgroup of mixed OA (studies which included both knee and hip OA) were excluded because participants in these studies were non-homogenous.

ii. Sample size (<30 participants/arm versus ≥30 participants/arm) following the convention of the minimum sample size for a trial (Corder and Foreman, 2009)

iii. Recruitment cohort (on waiting-list for joint replacement surgery or not)

All other variables were unsuitable as they had subgroups with too sparse data to support network formation.

Data analysis

A Bayesian random effect model was used for the primary analysis. The codes are provided in Appendix 15. Posterior mean of ES was reported with its 95% credible intervals (CrI).

Ranking of different exercises was evaluated based on the median ranking together with the respective 95%CrI. That is to say, the exercise with the highest median ranking was regarded as the best exercise, whereas, the exercise with the lowest median ranking was regarded as the least effective.

Non-informative prior distributions were used for Bayesian analysis so that the posterior inferences or results (e.g. ES, ranking probability) were predominated by the data, and not affected by any prior information. This assumption is represented by (a) in Fig. 6-1.

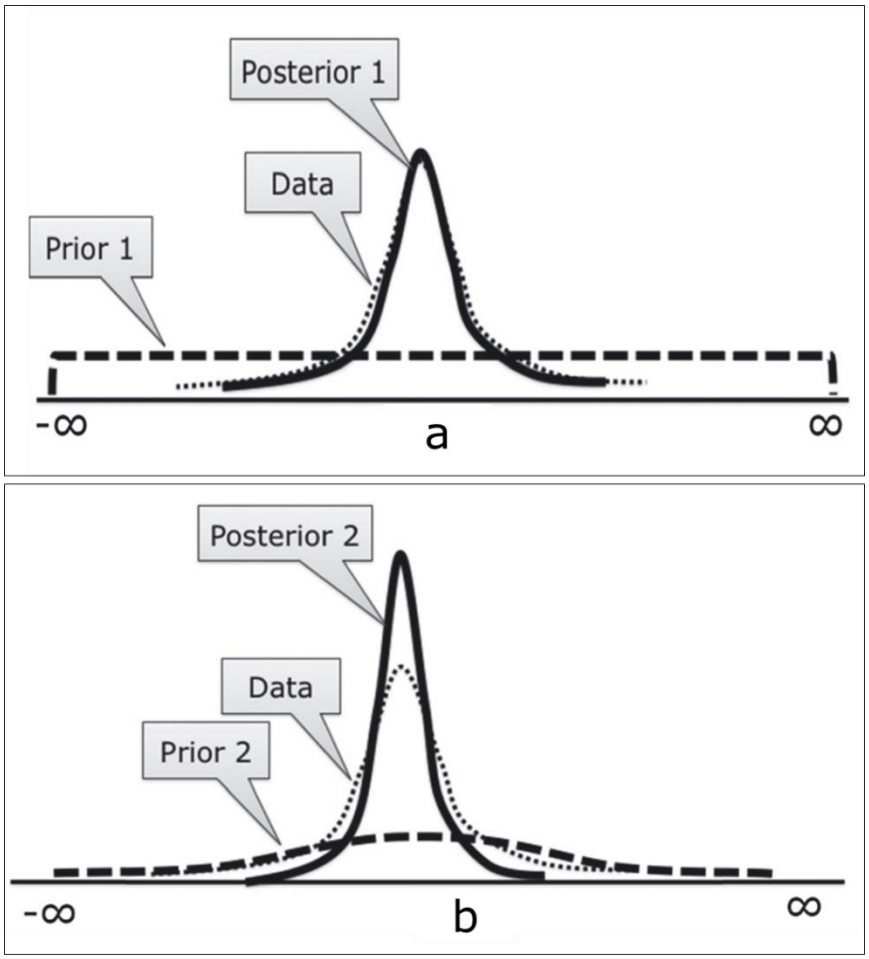


Fig. 6-1 Effects of different priors on the posterior distribution/result.
(a) A flat/non-informative prior (prior 1) is assumed so that the results (posterior 1) that was calculated is identical to the data acquired; (b) when some prior information (prior 2) is assumed, the result (posterior 2) does not precisely overlap with the data – the amount of overlap is determined by the type of prior information used. Schoot et al. (2014)

Three Markov chains were run. The initial burn-in simulations of 40,000 were discarded and this was then followed by an additional 120,000 simulations from which the results were estimated. These specifications were made in order for sufficient number of simulations to take place across three

series/chains of analysis to generate stable results. As the initial segment of the chain is relatively unstable, omission of the initial 40,000 simulations was done to improve the precision of results. Convergence or stabilisation of the simulations was confirmed by inspection of Gelman-Rubin tracing.Model fit was performed to assess how well predictions from the model were supported by the observed data. A model was considered a good fit when the difference between the posterior mean residual deviance value ($\overline{D}_{res}$ – a measure of heterogeneity between studies) with the number of data points (i.e. a number corresponding to the total number of arms used in the analysis) was <3.

The node-splitting method and design-by-treatment forest plot based on frequentist analysis were used to assess consistency in the network (Dias et al., 2010, Higgins et al., 2012). The node-splitting method examines the agreement between direct and indirect comparisons. The design by treatment forest plot, on the other hand, visually demonstrates agreement between studies of different designs (e.g. whether estimation between A and C, obtained from 2-arm design is consistent with those obtained from multi-arm ABC or ACD designs).

6.3 **Results**

6.3.1 **Characteristics of included studies**

There were 103 trials (knee OA – 86, hip OA – 10, mixed knee and hip OA – 7) with a total recruitment of 9,134 participants that fulfilled the inclusion criteria. The characteristics of each trial are listed in Appendices 7a (i) and 7b (i) while Table 6-1 summarizes the study characteristics for each of the outcomes. The active monitoring/formal intervention phase of the studies ranged from 2 weeks to 18 months. Only 37% of the studies performed follow-up of the patients post intervention. The follow-up period varied from one week to 21 months. Duration for the entire exercise trials ranged from 2 weeks to 2 years.

Table 6-1 Study characteristics – Relative exercise efficacy: Pain, function, performance and quality of life (QoL)

		Pain	Function	Performance	QoL
No. of comparisons		**97**	**97**	**105**	**42**
Ex-Usual care		70	67	74	34
Ex-Ex		27	30	31	8
No. of trials (%)		**89**	**87**	**95**	**40**
a. Joint:	Knee	75 (84)	73 (84)	78 (82)	30 (75)
	Hip	9 (10)	9 (10)	10 (11)	7 (18)
	Both	6 (7)	5 (6)	7 (7)	3 (8)
b. Surgical waiting-list:					
	No	75 (84)	76 (87)	81 (85)	30 (75)
	Yes	14 (16)	11 (13)	14 (15)	10 (25)
Total participants eligible (%)		**8137**	**8147**	**7783**	**3539**
Number analysed*		7184	7153	6760	3190
a. Joint:	Knee	6333 (79)	6461 (79)	6000 (74)	2298 (65)
	Hip	824 (10)	907 (11)	1059 (11)	706 (20)
	Both	980 (12)	779 (10)	1004 (10)	535 (15)
b. Surgical waiting-list:					
	No	7309 (90)	7486 (92)	7322 (92)	2908 (82)
	Yes	828(10)	661 (8)	741 (8)	631 (18)
Age, years (median, IQR)		64.9 (62.0, 68.7)	64.9 (62.0, 69.1)	65.1 (62.4, 69.8)	65.3 (62.0, 69.7)
BMI, kg/m² (median IQR)		29.0 (27.1, 31.5)	29.4 (27.2, 31.5)	29.0 (27.1, 31.5)	29.5 (27.1, 31.5)
% female per study (median, IQR)		73.0 (61.0, 80.7)	73.4 (62.8, 81.0)	73.0 (64.1, 81.0)	73.7 (61.0, 93.2)
Study design					
	2-arms	86	83	91	39
	3-arms	3	4	4	1
Data time points					
	<1 month -	2/97	2/97	2/105	0/42
	1 month -	23/97	26/97	22/105	16/42
	2 months -	36/97	38/97	47/105	12/42
	3 months -	28/97	24/97	27/105	10/42
	6 months -	5/97	4/97	2/105	2/42
	12 months -	3/97	3/97	5/105	2/42

Data presented for each outcome excludes outliers and un-extractable data.
BMI= Body mass index; Ex= Exercise; IQR=Interquartile range
*number of participants used for analysis

It can be seen that the pain and function network were each formed by 97 pairs of comparison, but the data for the pain

network were derived from 89 trials and the data for the function network were derived from 87 trials. The QoL network only contained 42 comparisons (40 trials) while the performance network had the highest number of comparisons – 105 (95 trials). The sample size for each of the network was approximately 7000 participants, except for QoL which had only half the number of participants. More than half of the outcomes were obtained within three months of study commencement.

6.3.2 **Funnel plot**

Fig. 6-2 is the funnel plot to visually assess small study effects for two types of comparisons (exercise versus usual care and head-to-head exercise comparison). Results from large studies are typically located at the top while smaller studies with less precise estimate (i.e. larger variance) are located at the bottom. Each study is represented by a dot. The greater the effect size, the further it is located from 0.

Small studies comparing exercise and usual care tended to produce a larger effect size than head–to–head comparison trials. This is more obvious for pain than for other outcomes. The distribution of head-to-head comparisons of exercise trials, on the other hand, appeared to be more symmetrical.

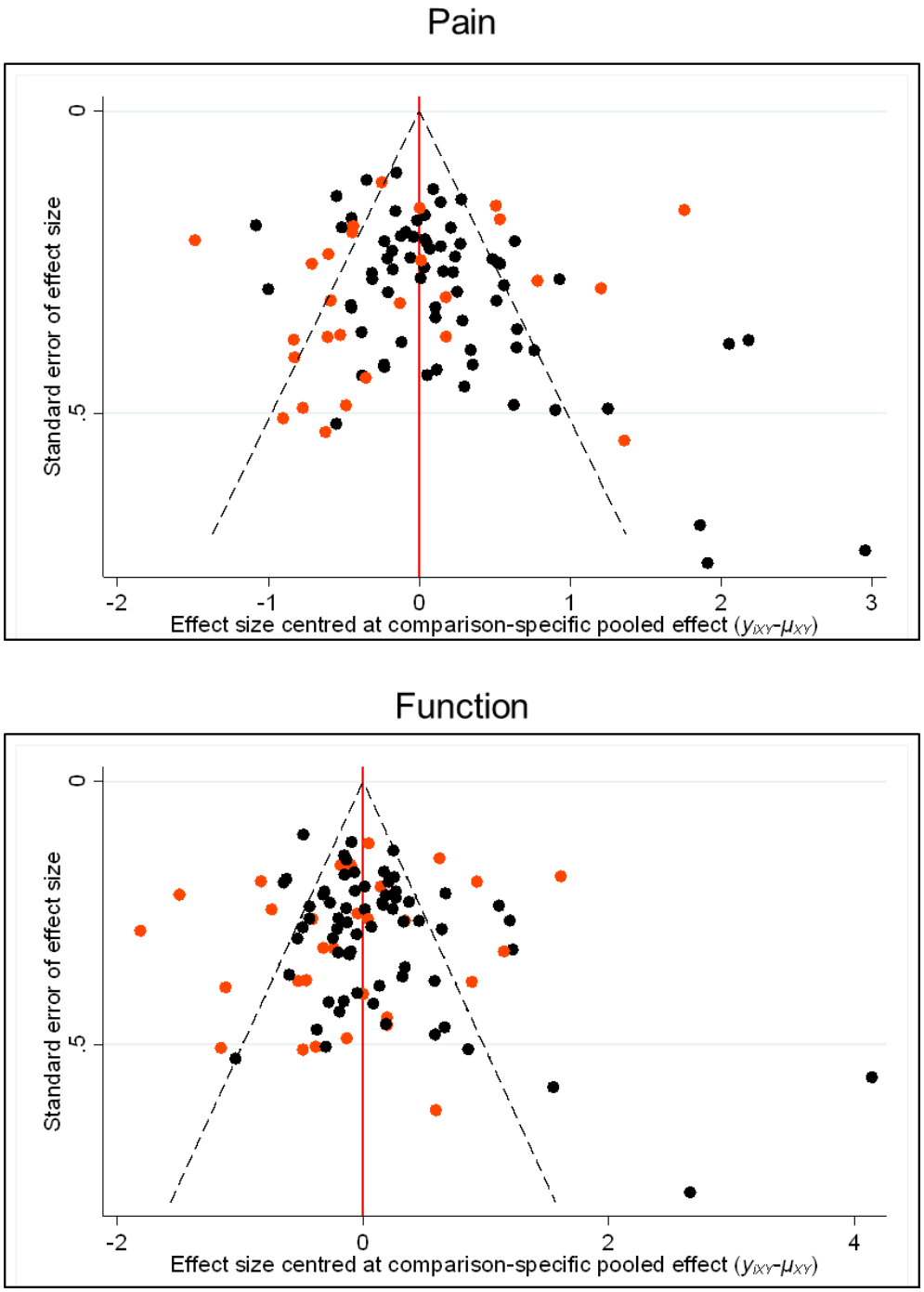


Fig. 6-2 Funnel plots – Relative exercise efficacy: Pain, function, performance and quality of life

Black dots represents exercise versus usual care comparison, yellow dots exercise versus another exercise comparison. The distance between each study (each dot) and the red line corresponds to the difference in estimates from each of the study to the comparison-specific pooled effect (Chaimani et al., 2013)

(cont.)

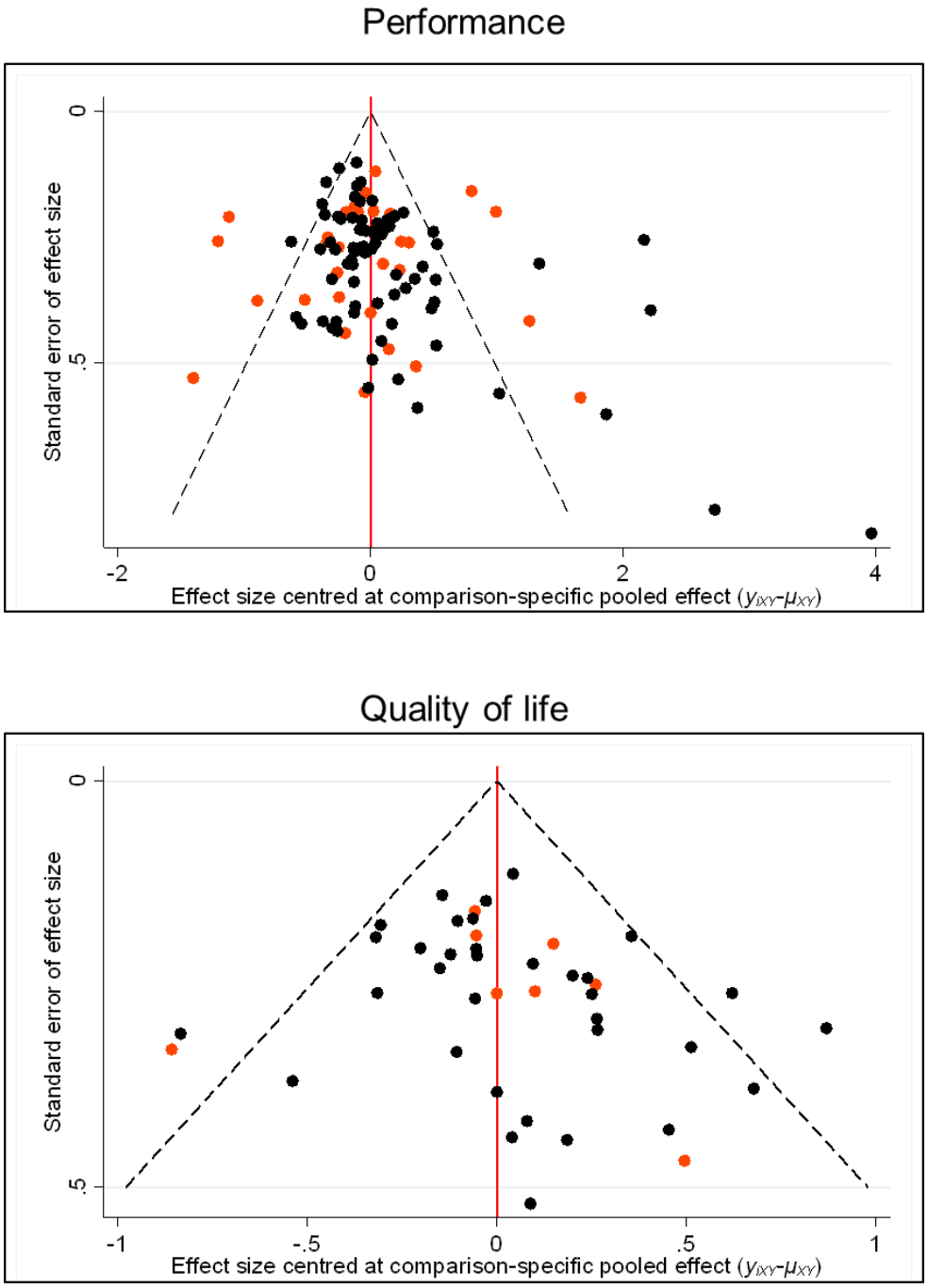


Fig. 6-2 Funnel plots – Relative exercise efficacy: Pain, function, performance and quality of life

6.3.3 **Network diagram**

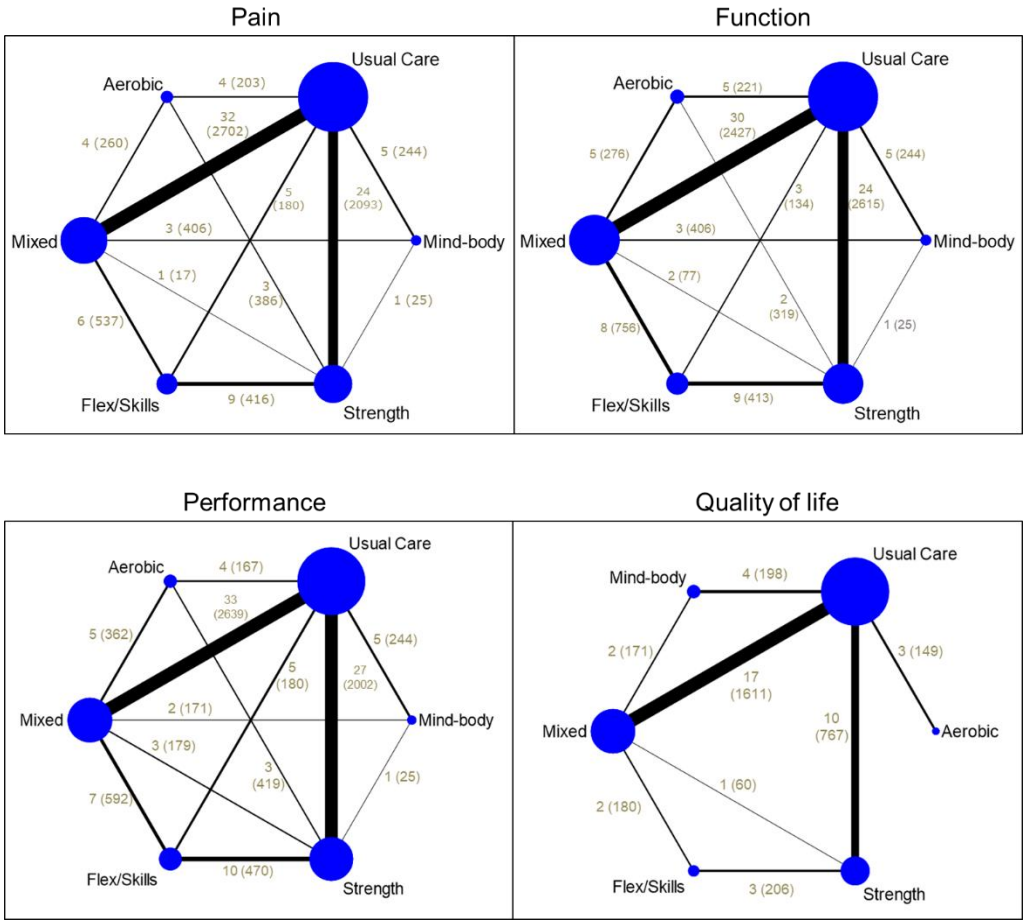


Fig. 6-3 Network map – Relative exercise efficacy: Pain, function, performance and quality of life.
Figure illustrating the connectivity of the comparisons and the strength of evidence for each pair of comparison. Data in grey represents number of trials (number of participants).

The network formed for each outcome is shown in Fig. 6-3. The nodes (each representing a treatment) were well connected especially for pain, function and performance outcomes. However, trials performing comparisons between usual care and mixed exercise, and between usual care and strengthening exercise considerably outnumbered the other

pairs of comparisons. For three of the networks (pain, function and QoL) there were at least 20–30 trials for each of mixed-usual care and strengthening-usual care comparisons, involving over 2,000 participants. In contrast, the comparison of strengthening versus mind-body exercise had only one study with less than 30 participants. The QoL network on the other hand was relatively sparse with a smaller number of available trials. However, it also reflected a similar trend where networks for strengthening and mixed exercises trials were more common.

6.3.4 **Comparison between different types of exercise**

The efficacy of different exercises compared to usual care and to each other is illustrated in Fig. 6-4. For pain, function and performance, all types of exercise were significantly better than usual care. All exercises conferred benefits ranging from 0.4 to 1.1 (moderate to large effect). By contrast, only strengthening and mixed exercises were significantly better than usual care for QoL. Overall, the benefits of exercise on QoL was not as marked as for the other outcomes, the magnitude of response ranging 0.2 to 0.4. Mixed exercise was the least efficacious across all outcomes. However, it still demonstrated statistically significant benefits over usual care.

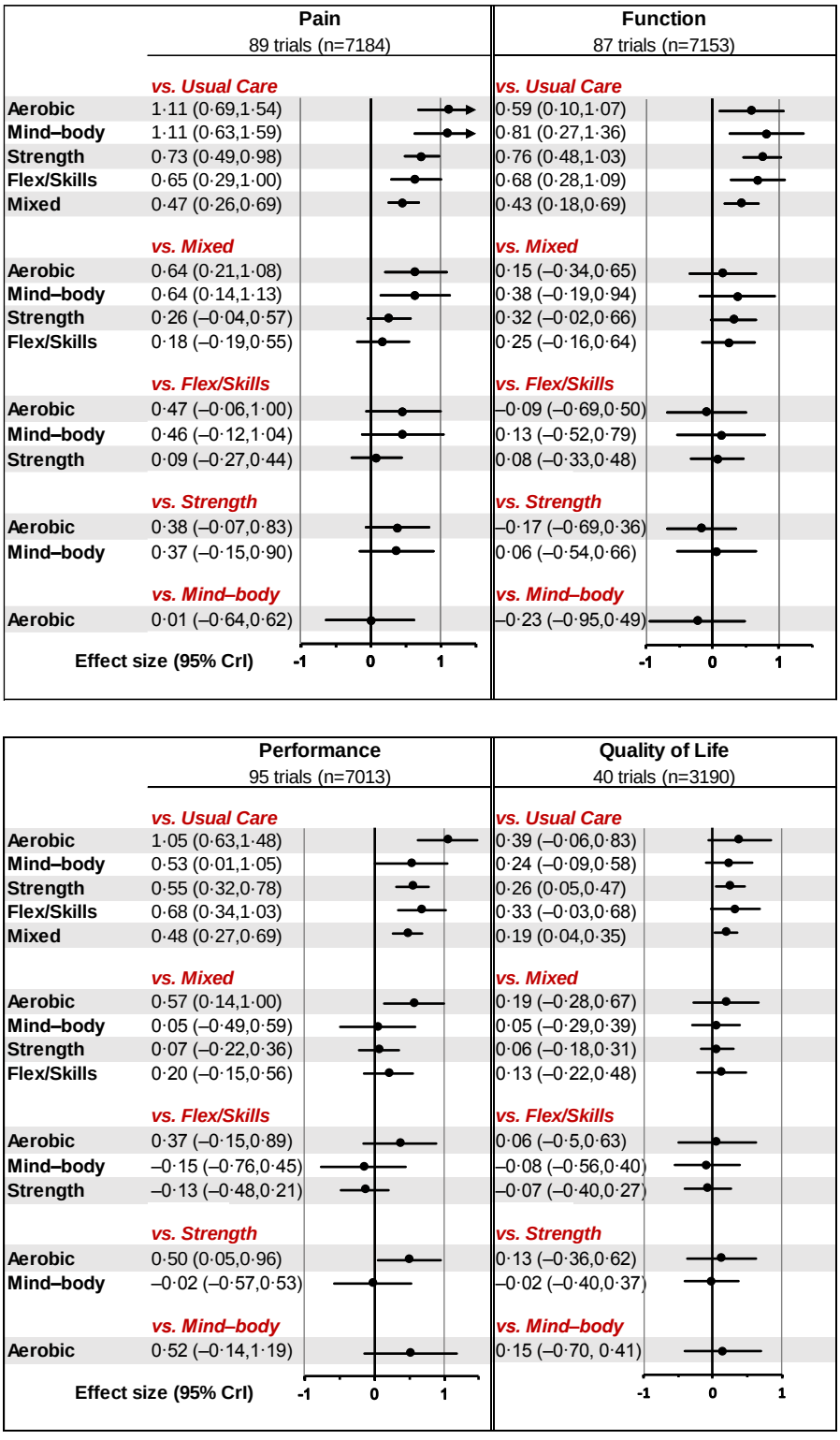


Fig. 6-4 Forest plot – Relative exercise efficacy: Pain, function, performance and quality of life.
Relative exercise efficacy presented in standardized means difference (95% credible interval, CrI). Positive values favour intervention in black
Flex/Skills= Flexibility and skills exercises; n=number analysed

Relative to each other, aerobic was superior to mixed exercise for pain and performance, whereas mind-body was superior to mixed exercise for pain outcome (see Fig. 6-4). There appeared to be no marked differences between other types of exercise.

6.3.5 **Ranking probability**

Ranking probability was obtained from over 100,000 simulations to rank of each exercise types. The results suggested that aerobic and mind-body exercise were likely to be two of the best ranked for pain outcomes (see Table 6-2) with the median ranking for aerobic being first (95%CrI 1,3) and mind-body being second (95%CrI 1,4). Aerobic exercise was also observed to be the best for performance (95%CrI 1, 3).

For function and QoL, none of the exercises appeared to have number "1" as the median. Instead, there were two exercises sharing the median of number "2" for each of these outcome. Although the 95%CrI for mind-body exercise was wider than strengthening exercise, the results suggested that both mind-body and strengthening exercises were likely to be the best for improving function. For QoL outcome, two of the best ranked exercises (aerobic and flex/skills exercises) had equally wide CrI from 1 to 6, indicating considerable uncertainty. Mixed

exercise was consistently among the worst ranked exercise for all outcomes which concurred with the hierarchy observed based on ES.

Table 6-2 Median ranking (95% credible interval) of each exercise for pain, function, performance and quality of life outcomes

	Pain	Function	Performance	Quality of Life
Aerobic	1 (1, 3)	4 (1, 5)	1 (1, 3)	2 (1, 6)
Mind–body	2 (1, 4)	2 (1, 5)	4 (1, 5)	3 (1, 6)
Strength	3 (2, 5)	2 (1, 4)	4 (2, 5)	3 (1, 5)
Flex/Skills	4 (2, 5)	3 (1, 5)	2 (1, 5)	2 (1, 6)
Mixed	5 (3, 5)	4 (3, 5)	4 (2, 5)	4 (2, 5)
Usual care	6 (6, 6)	6 (6, 6)	6 (6, 6)	6 (5, 6)

1= First; 2= Second; 3= Third; 4= Fourth, 5= Fifth, 6= Sixth. The highest ranking is the best (i.e. if there is no median ranking of 1st, the 2nd ranking will be the best)

6.3.6 **Model check (model fit, node splitting, forest plot)**

Evidence of lack of model fit (differences between $\overline{D}_{res}$ and data points exceeded 3) were found for pain (deviant studies are mainly small studies), performance (the deviant study recruited younger than average patients – mean age 40 years old) and QoL (possibly due to non-homogeneous groups). The fit of model for function, on the other hand, was good ($\overline{D}_{res}$: 183.2, 182 data points). There was significant heterogeneity in the evidence for all outcomes – the mean between studies standard deviation ranged from 0.25 – 0.74.

No disagreements were found between direct and indirect evidence (see Appendix 16) nor between estimates from different study designs (see Appendix 17).

6.3.7 **Subgroup analysis**

As summarized in Table 6.3, most evidence in hip OA and in pre-operative patients were for strengthening and mixed exercise, other exercises were under-evaluated in these patients. Both strengthening and mixed exercises showed greater ES in knee OA compared to hip OA for pain and performance, however the differences were not significant with overlapping CrIs. Although strengthening and mixed exercises conferred equivalent benefits for knee and hip OA in function and QoL outcomes, there were greater uncertainties in the estimates for hip OA.

The direction of effects was generally in favour of exercise for all outcomes with no obvious subgroup differences. Although the magnitude of pain relief and QoL improvement appeared to be greater in patients not awaiting joint replacement compared to those awaiting joint replacement, the differences were not significant as evidenced by overlapping CrIs. Yet, exercise appeared to confer no additional advantage over usual care only for the latter cohorts which were awaiting joint replacements because the CrI crossed zero. Due to the wide

CrIs for subgroups of OA awaiting joint replacements, further studies are still needed to confirm the results.

Table 6-3 Subgroup analysis – Relative exercise efficacy: Pain, function, performance and quality of life

		Effect size (95% Credible interval)			
		Joint		Recruitment cohort	
		Knee OA	Hip OA	Not Awaiting JR	Awaiting JR
PAIN		**75 trials (n=5607)**	**8 trials (n=703)**	***75 trials (n=6393)***	**14 trials (n=791)**
89 trials	**Aerobic**	1.16 (0.70,1.61)	-	*1.15 (0.73,1.59)*	-
(n=7184)	**Mind-body**	1.30 (0.73,1.86)	-	*1.13 (0.65,1.61)*	-
	Strength	0.76 (0.50,1.02)	0.53 (-0.74,1.80)	*0.81 (0.54,1.08)*	0.46 (-0.28,1.18)
	Flex/Skills	0.69 (0.31,1.07)	-	*0.70 (0.33,1.07)*	0.58 (-1.20,2.35)
	Mixed	0.57 (0.29,0.85)	0.12 (-0.36,0.62)	*0.52 (0.29,0.76)*	0.25 (-0.42,0.93)
	Heterogeneity	*0.67 (0.54,0.82)*	*0.54 (0.22,1.20)*	0.62 (0.51, 0.77)	*0.81 (0.47, 1.37)*
FUNCTION		**73 trials (n=5733)**	**9 trials (n=754)**	***76 trials (n=6564)***	**11 trials (n=589)**
87 trials	**Aerobic**	0.64 (0.11,1.17)	-	*0.63 (0.19,1.07)*	0.12 (-3.11,3.38)
(n=7153)	**Mind-body**	0.93 (0.27,1.59)	-	*0.83 (0.35,1.30)*	-
	Strength	0.78 (0.47,1.09)	0.69 (-0.17,1.54)	*0.72 (0.46,0.99)*	0.90 (-0.58,2.36)
	Flex/Skills	0.74 (0.29,1.19)	-	*0.68 (0.33,1.03)*	-
	Mixed	0.55 (0.21,0.89)	0.15 (-0.17,0.46)	*0.46 (0.23,0.69)*	0.09 (-1.53,1.71)
	Heterogeneity	*0.81 (0.67,0.98)*	*0.32 (0.05,0.75)*	0.61 (0.50, 0.74)	*1.69 (1.00, 2.97)*
PERFORMANCE		**78 trials (n=5208)**	**10 trials (n=905)**	***81 trials (n=6331)***	**14 trials (n=682)**
95 trials	**Aerobic**	1.12 (0.61,1.62)	0.81 (0.23,1.42)	*1.05 (0.62,1.49)*	-
n=7013	**Mind-body**	0.68 (0.03,1.31)	-	*0.53 (0.01,1.07)*	-
	Strength	0.60 (0.33,0.87)	0.29 (-0.13,0.75)	*0.51 (0.25,0.77)*	0.78 (0.13,1.43)
	Flex/Skills	0.76 (0.38,1.14)	-	*0.66 (0.30,1.03)*	0.90 (-0.72,2.53)
	Mixed	0.60 (0.31,0.90)	0.17 (-0.04,0.41)	*0.50 (0.27,0.74)*	0.35 (-0.26,0.97)
	Heterogeneity	*0.72 (0.58,0.87)*	*0.18 (0.01,0.51)*	0.65 (0.53, 0.79)	*0.71 (0.41,1.21)*
QUALITY OF LIFE		**30 trials (n=2073)**	**7 trials (n=585)**	***30 trials (n=2620)***	**10 trials (n=570)**
40 trials	**Aerobic**	0.39 (-0.13,0.93)	-	*0.38 (-0.02,0.79)*	-
n=3190	**Mind-body**	0.37 (-0.11,0.86)	-	*0.25 (-0.05,0.55)*	-
	Strength	0.27 (0.00, 0.54)	0.30 (-0.37,0.97)	*0.36 (0.12,0.62)*	0.13 (-0.40,0.66)
	Flex/Skills	0.35 (-0.10,0.80)	-	*0.41 (0.07,0.74)*	-
	Mixed	0.25 (-0.02,0.52)	0.06 (-0.21,0.36)	*0.22 (0.07,0.38)*	0.10 (-0.56,0.79)
	Heterogeneity	*0.35 (0.19,0.54)*	*0.19 (0.00,0.70)*	0.19 (0.03, 0.36)	*0.53 (0.19, 1.09)*

JR= joint replacement surgery

6.3.8 **Risk of bias**

According to the Cochrane risk of bias tool 60% of trials had low risk of bias on adequate randomisation, 52% on assessor blinding, 58% on ITT use, 78% on baseline homogeneity, 96% reporting as specified. Due to the nature of the interventions, physician and patient blinding were not possible. As such, these domains had the highest risk of bias where 100% had high risk of bias (Fig. 6-5).

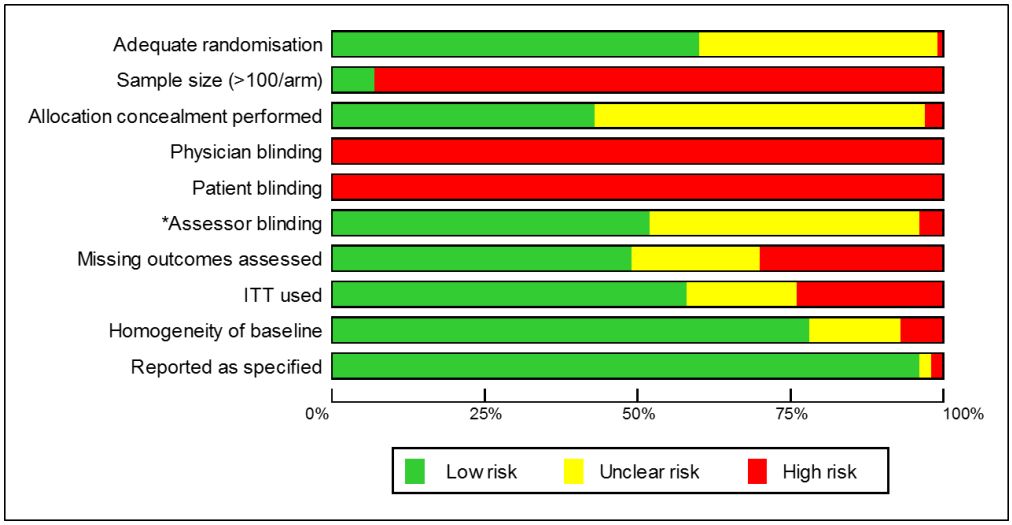


Fig. 6-5 Risk of bias assessment – Relative exercise efficacy
* Data is for studies with objective performance test since assessor blinding is not possible for self-reported outcomes.
ITT= intention to treat analysis

6.3.9 **Sensitivity analysis**

Sensitivity analysis was performed to show if some underlying assumptions (i.e. high risk of allocation concealment, imputed SD, sample size <30/group) would significantly alter the conclusion of the primary analysis. The results (shown in

Appendix 18) were not much affected by the use of imputed SD as the number of studies with missing SD was small. By contrast, when more than half of the studies had to be excluded to examine the impact of allocation concealment and study sample size, the change in ES was more variable and could occur in any direction. However, the highest and lowest ranking exercises generally retained their rank, implying that their rankings were robust to these underlying assumptions.

6.4 **Summary**

Due to the limited number of studies on hip OA, the network for hip OA subgroup analysis was sparse, and in most studies only strengthening and mixed exercise results were available. Overall, the hierarchical order of exercise efficacy was consistent with those shown in the conventional MA (Chapter 4). However, NMA is the more powerful method for evidence synthesis as it is able to incorporate both direct and indirect evidence while conventional pairwise meta-analysis can only compare different exercises via usual care group. With more trials being included in the NMA compared to conventional MA (103 versus 77), estimations from NMA would be more precise. Furthermore in NMA results from direct and indirect evidence can be separately estimated using various methods

(e.g. node-splitting and design-by-treatment forest plots) to evaluate the consistency of evidence.

7 Efficacy of pre-operative exercises on postoperative outcomes

7.1 Introduction

This chapter examines the effects of pre-operative exercise programs on four postoperative outcomes – pain, function, performance and QoL– using conventional meta-analysis (MA) (frequentist approach).

7.2 Method

Participants:

Participants with knee OA and hip OA undergoing joint replacement surgery were eligible. Participants who had already undergone surgery were excluded.

Primary time points:

The primary time point was three months post operation, or the nearest to this. This time point was chosen because firstly, it is reasonably distant from the operation for outcomes to be uninfluenced by postoperative pain and functional deficits and secondly, it was expected to be the commonest reported time point.

Effect size measure:

Raw end-point score was used as the primary effect size measure. Change score (i.e. endpoint score minus score recorded just before operation) was used if the raw score was not available.

Comparison of interest:

Exercise versus usual care or non-intervention group.

Examples are:

- aerobic exercise alone versus usual care,
- mixed-exercise alone versus waiting list

Criteria of eligibility for interventions:

An exercise intervention qualified as an 'exercise-only' when no other types of therapy (beyond what is normally given in their usual course of treatment) were administered concurrently. Usual care refers to comparator groups that had no specific interventions imposed on them throughout the trial period (e.g. usual care, waiting-list, occasional home visits, etc.).

Sensitivity analysis

Analyses were repeated in the following ways to assess if the results were robust:

i. restricting analysis to replacement surgery for knee OA only;

ii. using change scores (postoperative score minus the score recorded just before operation) instead of endpoint score as primary type of data for calculation of ES.

7.3 Results

7.3.1 Characteristics of included studies

Out of the 217 trials, only 9 studies (n= 467 participants) met the inclusion criteria to investigate whether pre-operative interventions improve postoperative outcomes. Fig. 7-1 is reproduced from Fig. 4-1 reiterating the study selection flow of included studies in this chapter.

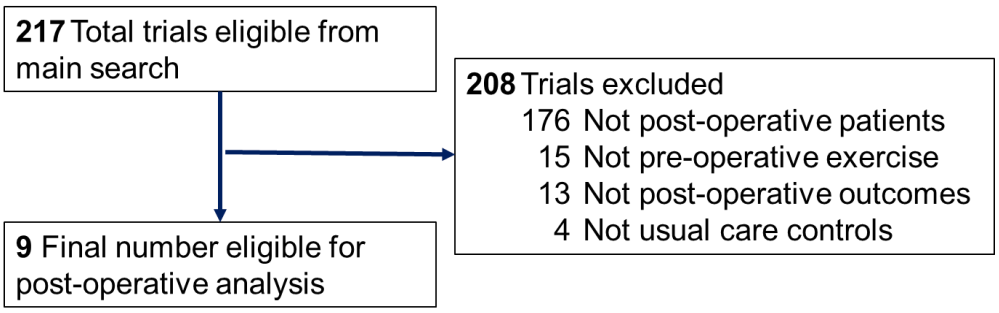


Fig. 7-1 Flow chart of study selection – Exercise versus usual care (postoperative)

A summary of study characteristics by outcome is shown in Table 7-1, and the characteristics of each study is shown in Appendix 7a and Appendix 7b.

Table 7-1 Study characteristics – Exercise versus usual care (postoperative): Pain, function, performance and quality of life

	Total studies 9 (n=467)			
	Outcomes			
	Pain	**Function**	**Performance**	**QoL**
No. trials	7	6	7	3
Number of participants	384	321	405	193
Median % women per trial (min,max)	69.5 (51.3,83.3)	68.8 (46.7,83.3)	70.9 (51.3,83.3)	67.5 (55.0,80.0)
Median age, years (min,max)	64.5 (63.5,69.7)	68.4 (64.5,76.0)	67.0 (63.5,76.0)	67.0 (67.0,76.0)
Median BMI, kg/m^2 (min,max)	28.2 (24.8,36.8)	28.0 (24.8,36.8)	28.2 (24.8,34.0)	31.5 (28.2,36.8)
Joint studied (K/H/Both)	6/1/0	5/1/0	6/1/0	2/1/0

BMI= body mass index; H= hip; K= knee; QoL= quality of life

There were seven studies that reported pain, six reported function, seven reported performance and only three reported QoL outcomes. All included studies investigated people with knee OA except one which recruited hip OA. Age of participants ranged from 63 to 76 years-old. The proportion of female participants was approximately 70%.

The duration of pre-operative interventions was typically short (range: 3 to 6 weeks). The follow-up duration for the patients

in seven studies spanned across three months at least, while the follow-up period in the remaining two studies lasted only six weeks. The longest follow-up period observed was one year post joint replacement surgery.

With the exception of Beaupre et al. (2004), all studies had 30 or less participants in the exercise intervention group (Table 7-2). Although a few studies had specified the use of ITT analysis, methods to impute missing data from patients who cancelled operation, or who did not complete the trial were not provided.

Table 7-2 Characteristics of participants in exercise arms

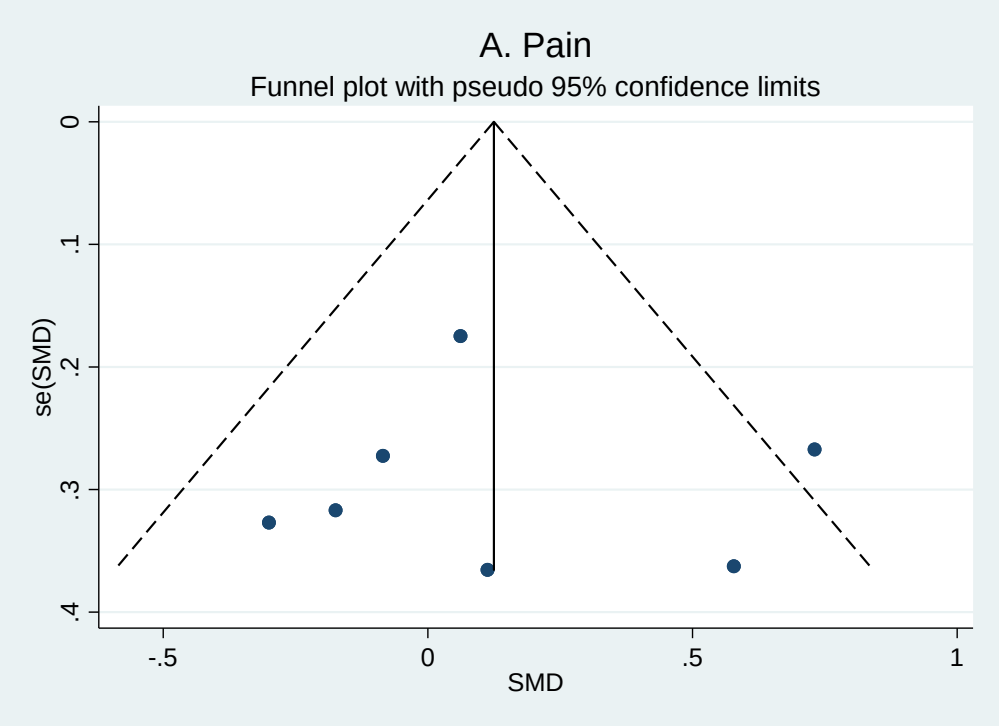
Study	N randomised to pre-operative exercise (N total)	N available for analysis at primary time point (by outcomes)				Reason for missing data in exercise arm	ITT pre-specified by authors	Notes
		Pain	Function	Performance	QoL			
Beaupre et al. 2004	65 (131)	51	51	42	51	10 - cancelled surgery; 2 - withdrew from study before op; 2 - deceased after op	Yes	Unclear how missing data was handled even though ITT was specified.
Brown 2012	17 (32)	11	11		11	Surgical/ medical complications, refuse to continue study, lost to follow up, incomplete surveys returned	No	Unclear if ITT or only available data was used for analysis
D'Lima 1996	20 (30)		Unclear			Unclear if there is missing data or if all participants underwent surgery	No	Two exercise arms (mixed and aerobic exercise) each with 10 participants randomised, were aggregated for analysis. Of the total recruited participants, 5 were RA patients.
Evgeniadis 2008	24 (72)			18		3 - did not receive exercise intervention; 3 - excluded for analysis with unclear reason.	Yes	Unclear how missing data was handled even though ITT was specified.
Gstoettner 2011	18 (38)	15	15	15		1 - refused op; 1 - uncontactable; 1 - post-op complication	No	Only those with data were analysed
Oosting 2012	15 (30)	14	14	14	14	1 - cancelled op	Yes	Number analysed = 15
Topp 2009	26 (54)	26		26		All completed trial	No	

Tungtrongjit 2012	30 (60)	30	30	30	No description of missing data provided.	No	Presumably no missing data with number analysed =15
Weidenhielm 1993	20 (40)	19		-	1 – heart attack	No	Not explicitly mentioned by author but number analysed is presumed to be 19

N= number; ITT= intention to treat, op= operation; QoL= quality of life

7.3.2 **Publication bias and outlying studies**

The number of included studies were insufficient to justify statistical evaluation of small study effect. Therefore, assessment of funnel plot symmetry was performed visually. Funnel plots for all outcomes shown in Fig. 7-2 suggested that the evidence was symmetrically distributed for all outcomes. No outlying reports were found.



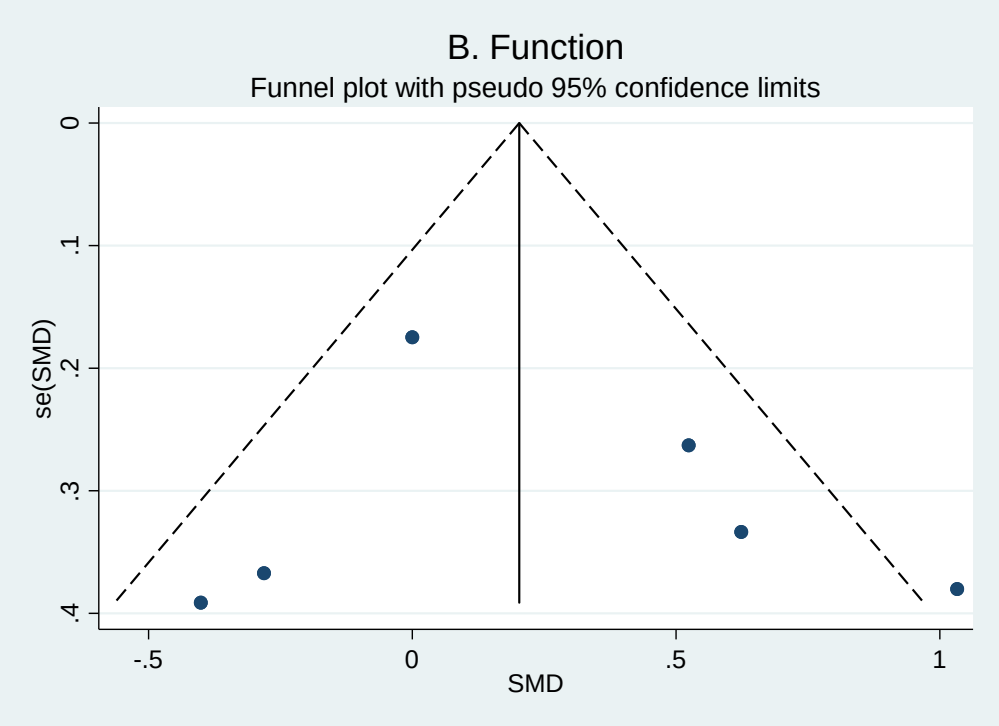


Fig. 7-2 Funnel plot – Exercise versus usual care (postoperative): Pain, function, performance and quality of life.

(cont.)

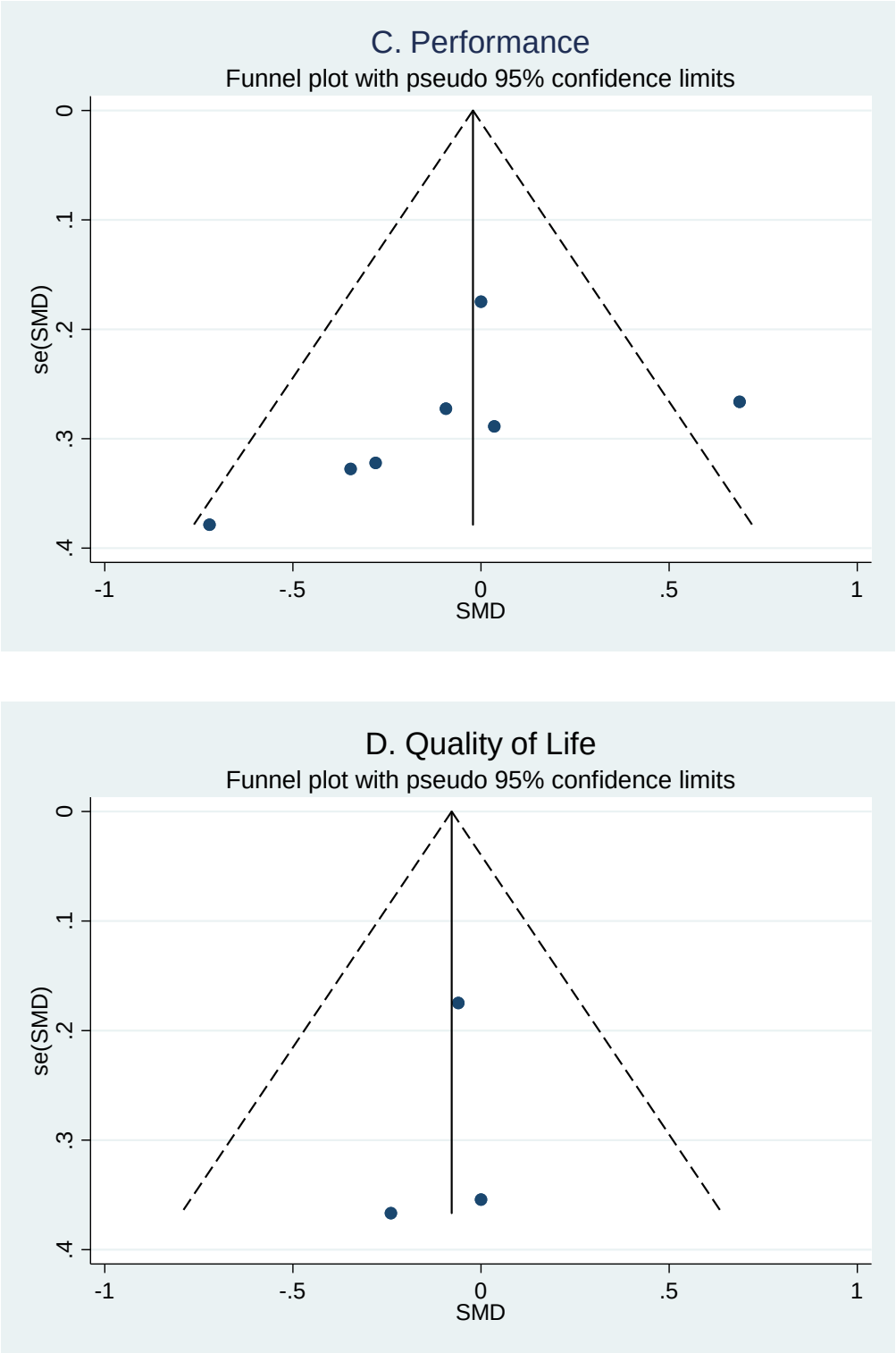


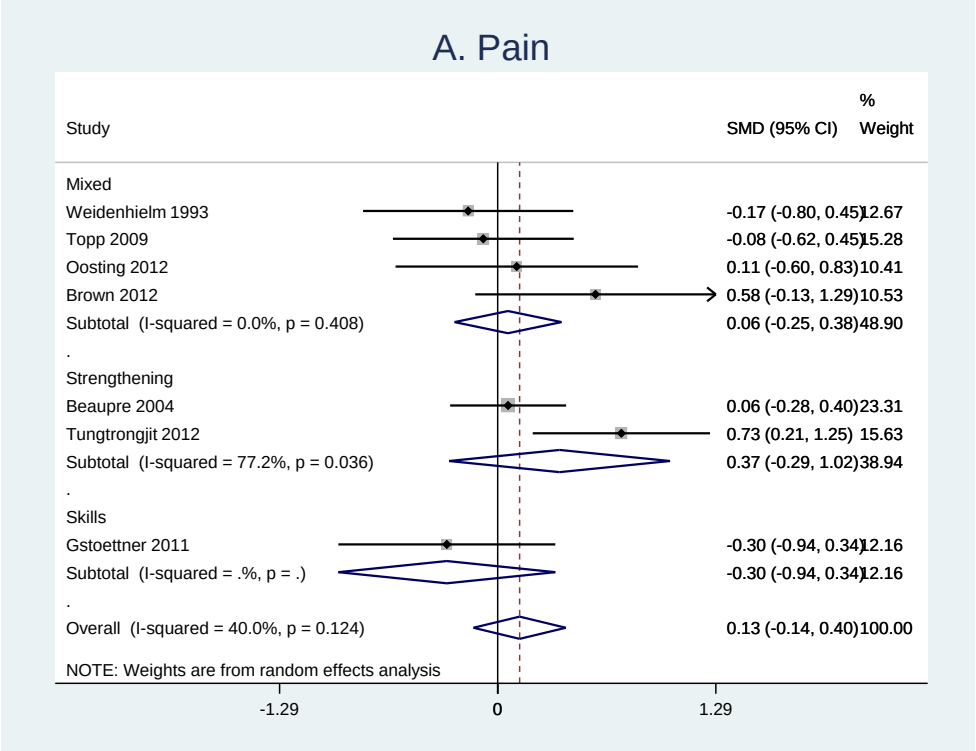
Fig. 7-2 Funnel plot – Exercise versus usual care (postoperative): Pain, function, performance and quality of life.

7.3.3 **Benefits of exercise versus usual care**

No apparent advantage of pre-operative exercise programs could be seen in any of the postoperative outcomes (see Fig. 7-3). The point estimates for pain and function were in favour of exercise while point estimates for performance and QoL were in favour of usual care. The largest effect was observed for function (ES 0.25; 95%CI -0.15, 0.64) and the smallest effect was for QoL measure (ES -0.08; 95%CI -0.36, 0.20). However, none of the point estimates were statistically significant.

The most common exercise types were mixed and strengthening exercises. No obvious difference between exercise types were observed but strengthening exercise appeared to be marginally better than mixed exercise for pain, function and performance.

Apart from QoL, other outcomes were subjected to moderate heterogeneity (I^2 statistic), specifically: 40% for pain; 62.5% for function; and 51% for performance. Only the heterogeneity for function was statistically significant.



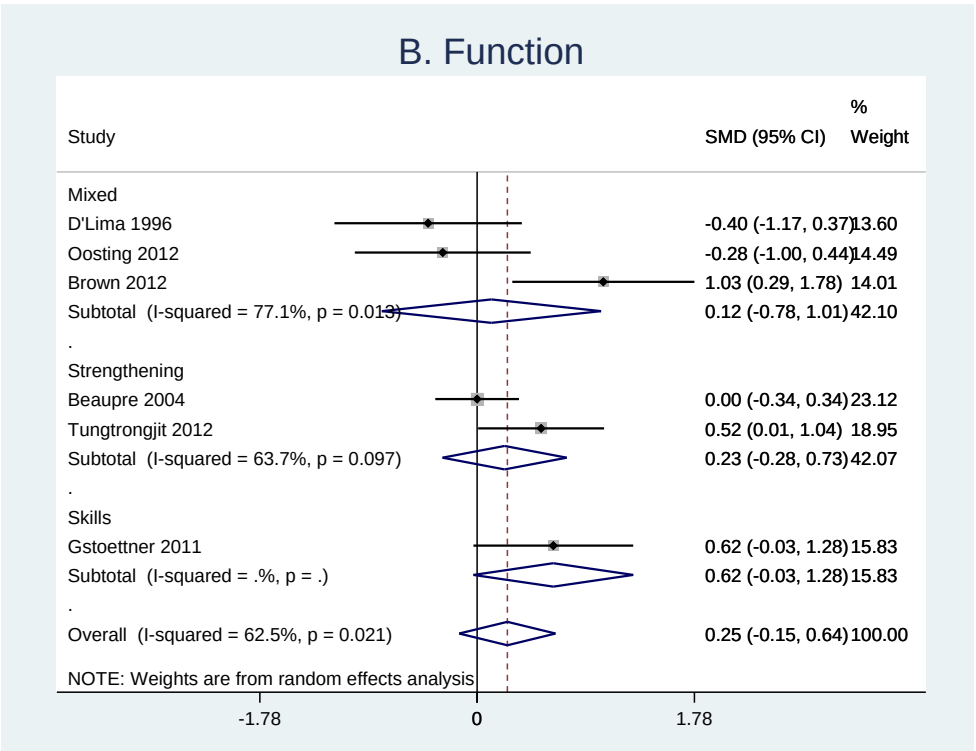


Fig. 7-3 Forest plots – Exercise versus usual care (postoperative): Pain, function, performance and quality of life (by exercise types).
Positive values favour exercise, negative values favour usual care.
(cont.)

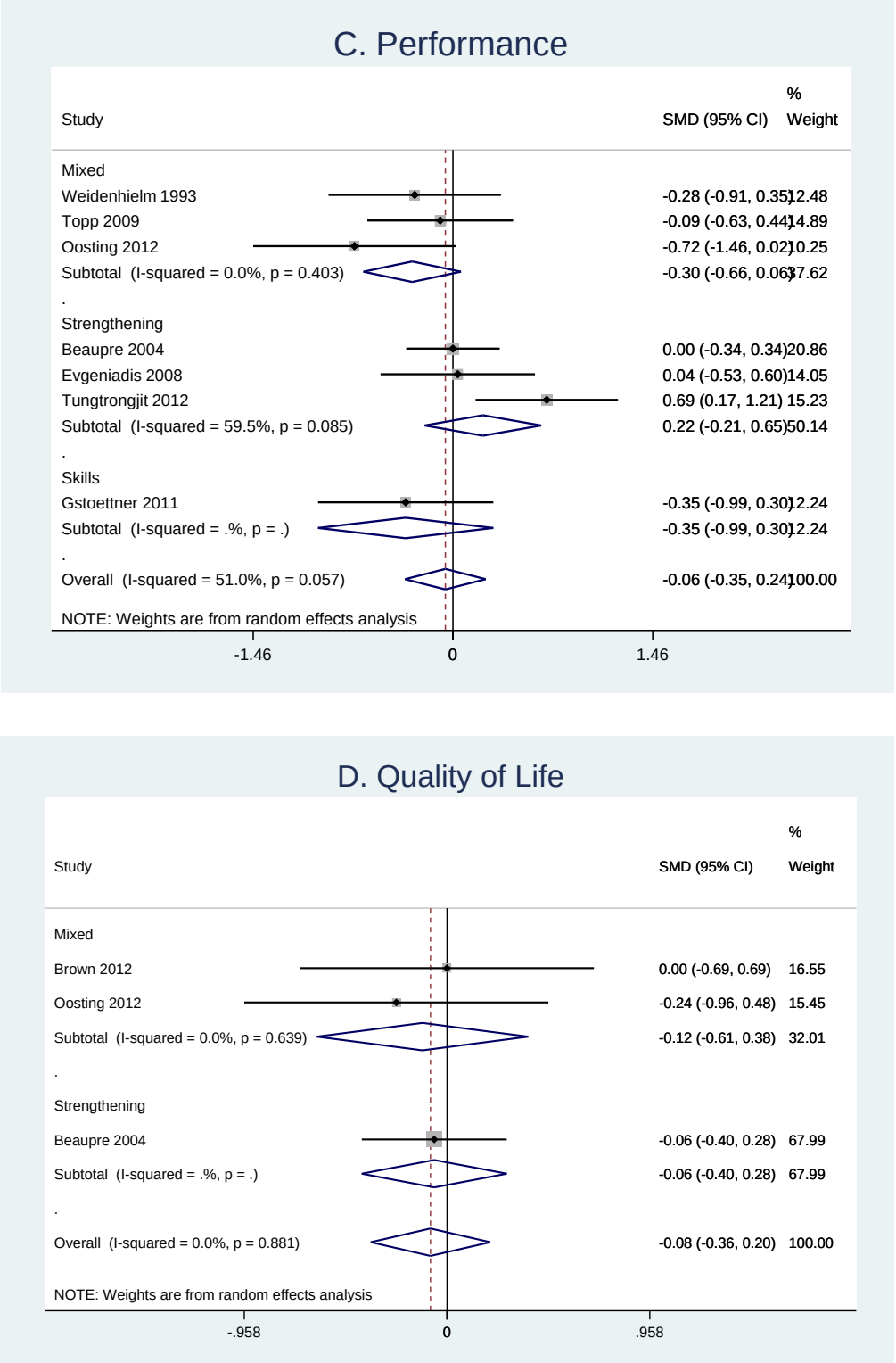


Fig. 7-3 Forest plots – Exercise versus usual care (postoperative): Pain, function, performance and quality of life (by exercise types).

7.3.4 **Meta-regression**

This analysis was not performed as the number of studies were too small to ensure sufficient power to detect any differences.

7.3.5 **Risk of bias**

As is typical of exercise trials, blinding of the physician and patient is not possible and this therefore had high risk of bias (see Fig. 7-4). Additionally, none of the included studies had a big study sample (i.e. >100 persons per arm). Only 2 items were identified to have low risk of bias in most of the included studies (i.e. baseline homogeneity 67%, and pre-specified reporting 100%).

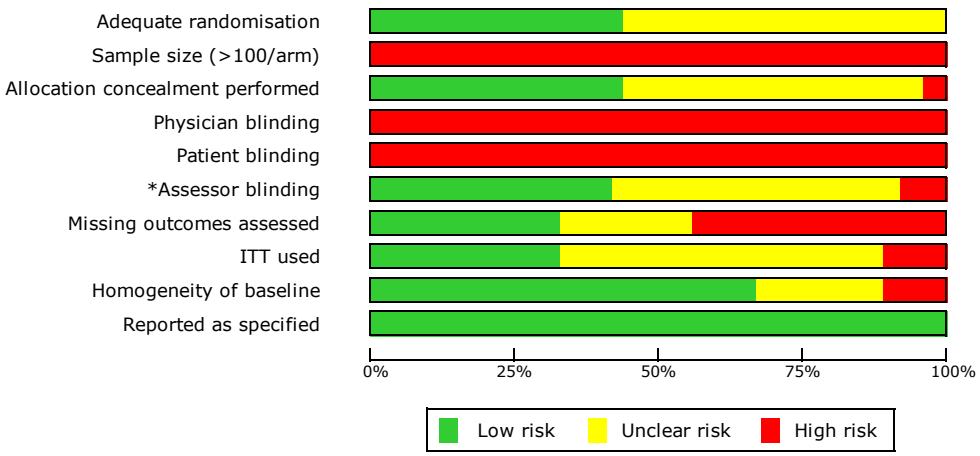


Fig. 7-4 Risk of bias assessment – Exercise versus usual care (postoperative)
* Assessor blinding was for objectively measured performance outcomes because assessor blinding cannot be performed for self-reported outcomes. ITT= intention to treat

7.3.6 **Sensitivity analysis**

The analysis was repeated by removing the only study on hip OA. Removal of hip OA generally improved the point estimates for many of the outcomes (see Table 7-3) with the exception of pain which remained unchanged.

When the analysis was performed using change score instead of raw endpoint score, the point estimate reduced by 0.1 for pain and performance outcomes but for function the point estimate remained unchanged. Unlike the other outcomes, the use of change score improved the estimation of exercise effect on QoL. However, across all outcomes, overall exercise effect still was not statistically significant.

Table 7-3 Sensitivity analysis – Exercise versus usual care (postoperative): Pain, function, performance and quality of life

Sensitivity analysis	**No. Studies**	**ES (95%CI)**	**I^2 (%)**
		Pain	
Primary analysis:	*7*	*0.13 (-0.14, 0.40)*	*40.0*
Knees only	6	0.13 (-0.18, 0.45)	50.0
Change score	7	0.03 (-0.40, 0.46)	74.9
		Function	
Primary analysis:	*6*	*0.25 (-0.15, 0.64)*	*62.5*
Knees only	5	0.34 (-0.10, 0.77)	64.9
Change score	6	0.26 (-0.14, 0.67)	64.1
		Performance	
Primary analysis:	*7*	*-0.06 (-0.35, 0.24)*	*51.0*
Knees only	6	0.02 (-0.26, 0.30)	41.7
Change score	7	-0.07 (-0.39, 0.24)	57.2
		Quality of life	
Primary analysis:	*3*	*-0.08 (-0.36, 0.20)*	*0*
Knees only	2	-0.05 (-0.36, 0.26)	0
Change score	3	0.01 (-0.41,0.42)	39.6

7.4 **Summary**

By prescribing pre-operative exercise to only one group, the measurements between groups may no longer be comparable immediately before surgery. An equivalent change in postoperative measurements, therefore does not necessarily imply that these two groups of patients were experiencing the same level of pain severity or functional capabilities. For this reason, the primary data used for the analysis in this chapter was raw endpoint score and not the difference in change score (between two groups), as was the case for preceding chapters.

The overall estimate for each outcome appeared to indicate no benefits from performing pre-operative exercise. However, there are a few methodological limitations such as small number of participants and insufficient study duration (brief pre-operative intervention and short follow-up period) that could reduce the power to detect any difference or to elicit the true effect of exercise intervention.

Additionally, considering that sedentary individuals are at higher risk of undergoing joint replacements (Manninen et al., 2001), factors facilitating physical activity such as motivation and social support might be lacking among candidates of joint replacements (Petursdottir et al., 2010). As a result, the gains observed might be smaller than what would be expected if the

motivation for exercise was greater. Barriers to physical activity, in addition to age-related decline in physiological functions including sarcopenia (loss of muscle mass)(Fielding et al., 2011), might be collectively responsible for the lack of efficacy in exercise in candidates awaiting joint replacements.

8 General discussion

8.1 Novelty

There are indeed many systematic reviews and meta-analyses to elucidate the efficacy of exercise in knee and hip OA. However, many of these systematic reviews have restricted scope. Some authors determined eligibility for inclusion based on medium of exercise such as land-based only (Fransen and McConnell, 2015) or water-based only (Lu et al., 2015). Some were selective of the types of exercise such as strengthening exercise only ((Bartholdy et al., 2017) or mind-body exercise only (Lauche et al., 2013). There are even reviews which focused on specific strengthening subtypes such as isokinetic exercise (Coudeyre et al., 2016). This present work is different as it did not observe any limitations with regards to the medium or setting of exercise delivery, or the types of exercise prescribed. The various distinctions made by authors mentioned above, for example, were instead incorporated in the subgroup analyses in Chapter 5 to determine if these variables are potential effect modifiers of exercise response.

To date, there is only one NMA that examined the efficacy of exercise in knee and hip OA (Uthman et al., 2014). However, the aim of Uthman et al. was primarily to demonstrate

whether further trials for exercise are needed using sequential analysis, and the secondary analysis of different exercise types by Uthman et al. did not differentiate mind-body exercise from conventional exercise types. Furthermore, only two self-reported outcomes (i.e. pain and function) were included by the authors.

In MA and NMA of exercise in OA, there is a common methodological flaw, which is, the loose inclusion of exercise control groups. In the absence of a standardised exercise control that could be held in similar regard to 'placebo' in pharmacological trials, many published work chose to combine all types of non-exercise control ranging from active interventions (e.g. education, behavioural therapy, electrotherapy) to non-intervention (e.g. usual care, wait-list, usual physical activity) (Tanaka et al., 2013a, Fransen and McConnell, 2015, Uthman et al., 2014). Combination of active treatments and non-intervention comparators in the same analysis would naturally dilute the exercise effects and produce misleadingly smaller ESs compared to when only non-intervention controls were used in the analysis.

In short, the novelty of this work is that it is the most updated review on all types of exercise, irrespective of mode or medium of exercise delivery, in knee and hip OA. Although no

distinction with regards to the differences in exercise types/ setting or delivery method were made in eligibility, the differences were explored in subgroup analyses. This approach has the advantage of producing more coherent comparisons across different subgroups as there is no methodological heterogeneity in regards to study eligibility, data extraction or assumptions made as the evidence is synthesise using a single study protocol. Secondly, this is the first NMA that compared mind-body exercise to other non-conventional types of exercise for four different outcomes (pain, function, performance and QoL). The results obtained from this NMA are likely to be more precise compared to previous NMA as the comparator groups used for this analysis were standardised to non-intervention groups. Unlike most reviews, non-exercise comparator groups involving active therapy were excluded from this analysis. To isolate the effects of exercise more accurately, exercise groups that had been combined with other active therapies were also excluded from analysis. Lastly, this work also attempted to examine the efficacy of different exercises for use as pre-joint replacements rehabilitation in order to improve post-operative outcomes in knee and hip OA.

8.2 **Main findings**

With the latest update performed in December 2017, a total of 217 trials (239 citations, 20419 participants) had been identified for inclusion based on the initial eligibility criteria. However, the number of trials eligible for conventional MA or NMA throughout this thesis was only 106 (9264 participants). Data from 77 RCTs (6472 participants) were used in conventional MA to confirm the effect of exercise therapy in knee and hip OA and to explore study level determinants of response to exercise therapy. A total of 103 RCTs (9134 participants) were used for NMA to work out the relative efficacy of different exercises. Another nine studies were used to investigate if exercise before joint replacement surgery is useful to improve postoperative pain, function, performance and QoL outcomes. Of these, only 3 studies contributed exclusively to post-operative outcomes and were not included for assessment of non-operative outcomes (Chapter 5 and 6).

Overall, exercise was better than usual care, providing greater benefits for pain (ES 0.56), function (ES 0.51) and performance (ES 0.46) than for QoL (ES 0.21). The results were largely driven by short-term studies (≤3 months) which mainly focused on knee OA, and by studies on strengthening and mixed exercise more than by studies on other exercise types. Younger mean age of study participants (<60 years-

old) appeared to be more responsive to exercise therapy in pain, function and QoL outcomes. Participants recruited from specialist centres or hospitals tended to respond better than those recruited from GP or community on performance parameters.

The maximum exercise response for all outcomes were likely to occur between two to three months after commencement of exercise. Thereafter, the magnitude of effect declined gradually to become no better than usual care by 9 months for QoL, and by 12 months for function. However, efficacy for pain and performance may be more sustainable, lasting longer than 12 months.

With respect to different exercise types, exercise programs that focused on a single exercise type were evidently more superior to programs that combined different types of exercise. The greatest improvements were generally seen following aerobic and mind-body exercises. However, the number of trials included in these two types of exercise was less than those in strengthening and mixed exercises. Other single component exercises such as strengthening and flexibility or skills exercises produced moderate benefits throughout all four outcomes although they were not the best. This trend was observed in both conventional MA (direct

evidence) and NMA, with the trend being more precise in the latter analysis because of the combined use of direct and indirect evidence. Despite this, the confidence intervals for aerobic and mind-body exercise remained wide, indicating considerable uncertainty.

8.3 Findings in context to existing literature

8.3.1 Magnitude of effect size in comparison to previous meta-analyses and other non-pharmacological interventions

As previously mentioned, the estimates of exercise efficacy throughout this work had been standardised to usual care, consisting of groups of comparator that were not assigned to any intervention. The ES obtained this way should be expected to greater than that observed in instances where the comparator groups had been 'treated' in some ways (Henriksen et al., 2016).

This may explain why the ES 0.64 (95%CI 0.51, 0.78) for pain in knee OA, estimated from this present work, is greater than the corresponding ES 0.49 (95%CI 0.39, 0.59) reported by a previous meta-analyses on land-based exercise (Fransen and McConnell, 2015). By contrast, in a separate meta-analytic report involving hip OA (Fransen et al., 2014), the ES obtained for pain (ES 0.38; 95%CI 0.20, 0.55) was greater than that

observed in the present work (ES 0.17; 95%CI -0.17, 0.51). The larger estimates in hip OA may be attributed to several methodological differences, one of which is the inclusion of complex exercise interventions by Fransen et al. (2014). When exercise therapy is delivered in combination with other therapy, the exercise effects may theoretically be enhanced. Nevertheless the findings from knee and hip OA from both meta-analyses are in agreement that exercise efficacy is greater for knee OA compared to hip OA.

Efficacy of exercise for relief of knee OA pain at 8 weeks may be significantly better than the pain relief shown by Celebrex (ES 0.33; 95%CI 0.25, 0.42) and naproxen (0.38; 95%CI 0.27, 0.49) over placebo at 3 months follow up (Bannuru et al., 2015). Although a more recent indirect comparison performed between exercise and oral analgesics did not produce any findings of significance, it was unclear how studies with different time points were pooled for comparison (Henriksen et al., 2016).

Compared to non-pharmacological interventions such as acupuncture and ultrasound, there seemed to be no clear differences at about 8 weeks. The point estimates for pain achieved by exercise may be greater than those achieved by weight loss (Christensen et al., 2007) or self-management

(McAlindon et al., 2014), but may be no different than those obtained by ultrasound (Loyola-Sanchez et al., 2010) or acupuncture (Manheimer et al., 2007). However, more studies are still needed as the evidence surrounding these non-pharmacological interventions are scarce and low quality.

8.3.2 **Different time points**

Only a small number of meta-analyses presented time-dependent analysis of exercise effects. Even then, the time interval used are relatively wide (Zacharias et al., 2014, Pelland et al., 2004). Even though there is evidence that significant exercise gains can occur as early as three weeks (Duman et al., 2012), many primary reports and meta-analyses commonly report results from six weeks onwards, providing little information on acute responses before six weeks.

It is important to consider the influence of time point in establishing exercise efficacy because the effect is not constant across time. Without continuous training (McKnight et al., 2010), exercise benefits may be lost by six months after cessation of therapy in people with OA (Pisters et al., 2010), and by four months after surgery in those with joint replacements (Minns Lowe et al., 2007). The trend of exercise response beyond six months is poorly described in meta-

analysis and the pooled estimate is likely to be diluted by data points which were obtained at a time that is very distant from six months, especially when analysis was pre-specified as 'beyond six months'. Overall, the time dependent effects of exercise demonstrated in Chapter 5 appeared to be consistent with previous report except that the change over time had been analysed with much smaller time bracket to produce a 'tighter' trend.

8.4 **Strengths**

This is the second NMA for the relative efficacy between different types of exercise therapies for knee and hip OA. Unlike the previous NMA (Uthman et al., 2014) that primarily focused on sequential analysis to determine whether further exercise trials are needed, this NMA focused on the relative efficacy between exercises instead. With an updated search, this analysis yielded more trials (103 trials and 9134 participants) to examine the efficacy of exercise for four different outcomes (pain, function, performance and QoL) whereas the previous NMA examined only two outcomes (pain and function) and included only 60 trials and 8218 participants.

The classification used in this present analysis were not only based on those used by ACSM (aerobic, strengthening, flexibility and skills exercises) (Deschenes and Garber, 2013), but also incorporated the additional category of mind-body and mixed exercises. Mind-body exercise is an increasingly popular exercise for OA (Brosseau et al., 2017) which should be separately examined because it is distinctively different from the other exercise types. It is unclear how this exercise was analysed by Uthman et al.

Another important strength of this study is the use of standard control groups by limiting the comparison groups to 'untreated' controls (usual care, waiting-list or usual physical activity). Many other meta-analyses often included more heterogeneous controls which were both 'treated' and 'untreated' (e.g. usual care, waiting-list, education, electrotherapy, behavioural or self-management therapy). Such approach had been shown to compromise the precision of the results (Bannuru et al., 2015). Furthermore, inclusion of different comparator groups under the "non-exercise control" umbrella would also violate the principal of transitivity and similarity of NMA.

8.5 Limitations

8.5.1 Classification of exercise and control groups

The classification of exercises and control groups was heavily reliant on the description provided by the authors. Exercise programs and 'usual care' are not standardised and vary considerably between studies. Even when the focus of exercise is strength improvement, it is typical to also find some element of flexibility and/or aerobic exercise incorporated into the program. Since it is also difficult to different types of exercise combinations (e.g. aerobic plus flexibility, aerobic plus strengthening etc.), all different combinations were grouped together and analysed as mixed exercise. Although there would have been some merit in separating the analysis of different exercise combinations, often the primary report was not informative enough to allow clear classifications to be made. For example, if no detailed exercise regime or intention of treatment target is provided by the authors, cycling in combination with walking can be regarded as predominantly an aerobic exercise or it can also be a combination of strengthening and aerobic exercises. As far as possible, classification presented by the authors was used. Studies that examined flexibility and neuro-motor skills individually, were grouped together for analysis because the number of trials were very small.

The decision to combine different types of controls such as waiting-list, usual physical activity and usual care together for the analysis may be questioned. Unlike psychotherapy trials, where significantly inferior treatment effects have been suggested in waiting-list group compared to non-intervention group (Furukawa et al., 2014), no such distinction has been reported in exercise interventions for OA. Instead, many published reports in this field extended the controls to include other types of non-exercise interventions (e.g. patient education and behavioural therapy) rather than limiting only to 'usual care' controls (Tanaka et al., 2013a, Fransen and McConnell, 2015).

Although 'usual care' has no unifying definition and some might argue that the control group is still being 'treated as usual' by their GPs or other healthcare professionals, it is still an acceptable non-intervention control for exercise groups for practical reason. Irrespective of group assignment, all participants (i.e. exercise and non-exercise groups) in the trials would most likely be allowed to continue their 'usual care' from GPs or other healthcare professionals. Withholding or withdrawing existing treatments from participants, irrespective of group assignment would be deemed unethical in most cases. In this regard, where all participants would in

fact be receiving their usual treatment and follow-up outside of the trial, it is acceptable to consider 'usual care' as an appropriate 'non-intervention' controls for exercise trials.

In short, there may be differences in what constitutes "usual care" across studies, but these differences do not affect the in-between group comparison within each study. Therefore, the effect size obtained from each study could still provide a reasonably robust estimation of efficacy for exercise intervention alone – irrespective of the heterogeneity of "usual care" controls across studies.

8.5.2 **Heterogeneity**

The reason for the heterogeneity was not fully explored because efforts to identify covariates for exercise effect in OA have generally been unsuccessful in many meta-analyses (Smith et al., 2012, Bartholdy et al., 2017). A wide range of patient recruitment and study methodological differences, and variation in the exercise regime itself (intensity, duration, settings, number of monitored sessions) are potential sources of heterogeneity which cannot be adequately controlled for across all analyses. This aspect of the evidence would probably require more sophisticated analytical approaches and warrant separate study. A more feasible alternative of exploring the heterogeneity through subgroup analyses has been attempted

instead in most instances to identify potential effect modifiers such as OA joint sites, patient characteristics and study qualities. An additional analysis was also performed by excluding studies which had been identified to be significant sources of heterogeneity (deviant studies) in order to assess the impact of these studies on the overall results.

8.5.3 **Choice of outcomes**

There were 4 core outcome measures recommended by harmonise OMERACT (Outcome Measures in Arthritis Clinical Trials) to reporting of clinical trials on pharmacological benefits (Bellamy et al., 1997), 3 of these were subsequently adopted by OMERACT-OARSI to establish treatment response criteria (Pham et al., 2004). In this thesis however, only 2 of the core outcomes (i.e. pain and function) were included in addition to QoL and performance outcomes. QoL and performance outcomes were also outcomes accepted by OMERACT, but were not considered to be the core outcomes.

The main reason QoL and performance outcomes were included for this thesis is that the recommendations by OMERACT were predominantly concerned with pharmacological trials. Unlike the mechanism of action of pharmacological agents, the mechanism of action of exercise is relatively more complex and multi-dimensional. It is prescribed with specific

purpose of improving physical impairments, hence the need to include performance parameter. Furthermore, by including performance outcomes, the results can complement our understanding of exercise impact on patient function (both perceived and actual physical abilities) (Dobson et al., 2013).

It should also be acknowledged that exercise benefits are not limited to the outcomes that were investigated in this present work. There are many other equally meaningful outcomes such as fall rate, weight control, and improvement of structural and biological markers of OA (Song et al., 2010), which had not been evaluated in this present study.

8.5.4 **Quality of studies**

The other limitation is related to the poor quality of clinical trials in exercise. In addition to inadequate blinding of participants and investigators due to the nature of the intervention, a great proportion of exercise RCTs demonstrated high risks of bias in other domains such as reporting bias, allocation concealment and small sample size. Many of these biases could potentially lead to misleadingly high estimates in favour of exercise. The presence of small study effects in some of the outcomes further downgrade the quality of the evidence. Although a quality assessment tool specially designed for exercise trials has recently been made

available (Smart et al., 2015), no composite scoring system has been developed to grade if a particular exercise trial is of good or bad quality. Therefore, a single point estimate for exercise effect based only on good quality studies could not be performed. Instead, a subset of indicators of study quality (e.g. ITT, sample size) which were deemed most relevant for the present collection of exercise trials were used to assess the robustness of the results through subgroup and sensitivity analyses (Viswanathan et al., 2012).

8.5.5 **Other caveats**

In order to establish the actual treatment effect of any therapy, inert placebo agents and sham procedures (Harden et al., 2016) are often used in trials to control for the contextual elements of treatment. In exercise, it is difficult to conceive or conjure a control for exercise that is truly 'inert'. Most of our understanding on exercise effects is benchmarked against usual or standard care, which in reality, embodies everything but 'inert' therapies and without any agreed definition of what 'standard care' of people with OA might comprise. Elucidating the true treatment effect of exercise is difficult because the result could vary with different 'usual care' controls, especially when no appropriate measures were instituted to control for this difference. When the intervention such as exercise cannot

be blinded, additional difficulties may be introduced by performance bias where participants in the control group may choose to perform exercise on their own. This could lead to estimate of exercise efficacy that is smaller than it should be.

It is also important to bear in mind that results from explanatory and controlled trials in exercise, where patients have been carefully selected and protocols stringently applied, do not always mirror real-world evidence accurately (Zuidgeest et al., 2017). Another factor that hampers a pragmatic understanding of exercise effect is the short duration of exercise trials, with period of intervention averaging 8 weeks and rarely lasting beyond 6 months. Based on this premise, a considerably short-term primary time point (i.e. 8 weeks) was deemed to be the most appropriate to pool the analysis. Despite being recommended for long term management of OA, the evidence of exercise efficacy is still largely inferred from short term results. Therefore the generalisability of the information obtained should always be questioned and may be of limited use to inform long term decision making for OA which can cause symptoms over many years.

Ideally, screening and data extraction should be performed independently by at least two reviewers. Due to the large

number of studies and amount of data involved, the process was undertaken mainly by one reviewer. However, throughout the various stages (especially at the early phase) of screening, data extraction and analysis, opinion and validation were actively sought from other reviewers to determine agreement and consensus.

8.6 Clinical implications

Some useful consideration for exercise prescription can be inferred from this NMA, allowing stakeholders to make better informed decisions when customising exercise.

8.6.1 Minimum clinically important improvement

In 2005, a group of French researchers (Tubach et al., 2005) introduced the minimum clinically important improvement (MCII) concept to allow results from clinical trials to be interpreted in a more meaningful way. This concept helps readers to understand if the improvement (endpoint minus baseline score) observed in clinical trial has met the minimal threshold considered to be important. From a 4-week prospective study involving more than 1000 participants of knee and hip OA, Tubach and colleagues proposed that MCII for pain and self-reported function - on scales normalised from 0 to 100mm - to be 19.9mm and 18.3mm, respectively. These

values had been subsequently validated by a larger multinational study involving different rheumatic conditions (Tubach et al., 2012).

To determine if the exercise effects meet the MCII values, ESs obtained from conventional MA was back transformed to absolute values by multiplying them with the pooled SDs (i.e. absolute change= ES*SD_{pooled}) (Borenstein, 2009). Since the ES in this thesis has been calculated based on between group difference and not based on pre-post score difference as was done by Tubach et al, a meaningful comparison with values proposed by Tubach et al requires the assumption that the baseline measure of exercise controls having remained unchanged throughout the trials.

Pooled SDs of commonly used instruments, obtained from trials with relatively large samples: Van Baar et al. (1998) for pain (0-100mm) – SD_{pooled} 23.27; Krauss et al. (2014) for WOMAC function (0-100) – SD_{pooled} 13.15; Kuptniratsaikul et al. (2002) for 6 minute walk test – SD_{pooled} 86; French et al. (2013) for SF-36 (0-100) – SD_{pooled} 12.3), were used to calculate the absolute difference between groups. Calculations based on these pooled SDs indicated that exercise group, in comparison to usual care, can expect improvement of 13mm when evaluated with 0-100mm visual analogue scale

(0.56*23.27), 7 points with WOMAC function 0-100 subscale (0.51*13.15), 40 meters with 6-minute walk test (0.46*86), and 3 points with SF-36 QoL 0-100 subscale (0.21*12.3). Assuming that the baseline status of usual care group was unchanged, the improvements in pain and function shown by the exercise group did not seem to meet the MCII proposed by Tubach and colleagues (2005).

Should the most efficacious exercise for each outcome be prescribed, the largest improvement we may potentially observe for pain would be the equivalent of 25.87mm on a 100mm VAS scale (using aerobic or mind-body exercise), 11 points on the WOMAC 1-100 function score (using mind-body exercise), 90.3 meters on a 6 minute walk test and 5 points on the SF-36 0-100 scale (using aerobic exercise). Even then, the exercise benefits for function would still be below the proposed MCII of 18.3mm. Pain relief with aerobic exercise would be able to exceed the MCII of 19.9mm though. As there is evidence to indicate that the values for MCII vary with age, gender and ethnicity and subscale used (Singh et al., 2014, Bellamy et al., 2015), further validation is still needed to determine if pain and function benefits from exercise are able to meet the proposed MCII. By contrast, there are no adequate MCII recommendations for performance and QoL in

OA for clear comparisons (Wright et al., 2011, Keurentjes et al., 2012).

8.6.2 **Pain phenotype**

The results suggest that patients with knee and hip OA would benefit the most from exercises that focus on central aspects of pain more than just peripheral biomechanical improvements. Although the exact mechanism is unknown, the observed effect may be attributable to the potentials of aerobic and mind–body exercises to mediate pain through central pathways by enhancing descending inhibitory signals, improving sleep quality and reducing anxiety-depression disorder (Reid et al., 2010, Chan et al., 2014). Various central risk factors, along with other peripheral risk factors, have established modifying effects on pain, function and quality of life outcomes (Parmelee Patricia et al., 2014). This may indirectly imply that people with chronic OA and clinical features suggestive of central pain sensitization may benefit most from exercises that are characteristically centrally-acting, whereas those with uncomplicated or localised pain may achieve equivalent improvements predominantly with locally-acting exercises. However, this study can only draw conclusions from results relating to group effects in RCTs. Individual patient data is required to determine whether

selection of exercise according to such patient characteristics enhances treatment benefits.

8.6.3 **Single or multi-component exercises**

People with lower limb OA have multiple physical impairments involving muscle strength, joint flexibility, proprioception/balance and general fitness. A combination of exercises that target these deficits simultaneously is seemingly ideal. Human performance studies have demonstrated that gains from one type of exercise do not necessarily attenuate the effect of another exercise and may even be additive when different exercises are performed concurrently (Dudley and Djamil, 1985, Paavolainen et al., 1999). By contrast, this meta-analysis showed that mixed exercise was consistently inferior compared to single component exercises.

Considering that there is no satisfactory biological explanation, it is highly probable that the answer may lie in the logistic difficulty of delivering and practicing mixed exercises. From the therapist perspective, a more complex program would require extra attention for customisation and supervision. From the patient perspective, considerable familiarity and commitment would be needed in order to reap the benefits of more complex combination exercises. A prudent management plan might be to first introduce a single component exercise

and subsequently, through addition of other types, progress to multi-component exercise. Studies may be needed to investigate whether the performance of multi-component exercise could be improved by better implementation methods. Extra considerations may be required in people with concomitant cognitive impairment which could hamper implementation of complex exercise programs.

The results showing mixed exercise being the least effective compared to single exercise types is also not in line with the conclusion shown in the previous NMA undertaken by Uthman et al. (2014). This discrepancy may have arisen for a number of reasons. One is that this analysis confined the comparator to 'usual care' or any 'non-intervention' comparator (e.g. waiting-list or usual physical activity) while the comparators used by Uthman et al included a range of different non-exercise controls (e.g. education, electrotherapy) in addition to the usual care or non-intervention controls. Another important reason for the discordance may be the difference in how mixed exercise was classified. While this meta-analysis considered any program that used >1 exercise to be mixed, Uthman et al defined mixed exercise as programs that used >2 types of exercise. Other differences between this meta-analysis and the previous meta-analysis include the use of different primary

time point and different inclusion criteria with regards to peri-operative clinical studies.

Lastly, it should be acknowledged that not all types of mixed exercise may be similar in efficacy (Uthman et al., 2014) – one combination of exercise may be better than another exercise combination. However, in the current NMA, no differentiation was made between different exercise combinations and all multi-component exercises were analysed together. Another aspect worth exploring is that mixed component exercise may have greater potential in meeting the psychosocial needs rather than addressing symptoms and impairments of OA (Tarazona-Santabalbina et al., 2016). Therefore, there are still many questions surrounding the lack of efficacy for mixed exercises that need further investigation.

8.6.4 **Other modifiers of exercise effects**

The efficacy of exercise programs is not solely dependent on the types of exercise used. The setting (group/ individual) and medium of exercise (land/ water) are potential modifiers of exercise effects but current evidence, which is primarily informed by RCTs, does not support one setting or one medium over another (Batterham et al., 2011, Bennell and Hinman, 2011). Considerations for the type of exercise setting and medium, in practice, are applicable to specific OA

subgroups (e.g. patients with poor social support, those who require assistance in mobility, those who have low pain threshold) who might typically had be excluded from trials. In practice, decisions are made based on clinical indications (e.g. water-based exercise would normally be given to those who cannot tolerate certain land-based exercises). To be clinically relevant, therefore, differentiating exercise effects by setting and medium would probably be best achieved through individual patient data and not RCTs in which the programs are normally delivered with "one-size-fits all" approach.

Other variables of the exercise program such as frequency, duration and intensity may also determine the size of exercise benefits (Garber et al., 2011). However, this premise was not supported by the work of Bartholdy et al. (2017). In their systematic review, the authors demonstrated that exercise programs with frequency, duration and intensity that fulfilled the recommended guidelines, did not result in significantly better pain and function outcomes when compared to programs that did not follow the guidelines. Although the objective of this present work was not to determine the influence of these exercise variables (apart from exercise type) on the magnitude of exercise response, it confirms that exercises performed on average 3 times a week is effective in

improving a number of clinical outcomes. Inferences with regards to exercise intensity level and duration, on the other hand, is more uncertain. This is because the measurement tool for intensity is not standardised across studies. Furthermore, the intensity and duration of exercise might vary within the same study. Occasionally, investigators used less strenuous exercise protocols in the early phase when participants were poorly conditioned. As patient gets familiarised and accustomed, the investigator would then increase the exercise intensity and duration.

Since exercise volume is collectively determined by the frequency, intensity and duration of exercise program, these variables are linked and are not independent. For example, to achieve the same volume of exercise of 150min/week, the exercise may be prescribed as 50 minute session performed 3 times a week or as 30 minutes session performed 5 times a week. Therefore, identifying the appropriate and effective exercise frequency, intensity and duration is not straightforward and would require future study. However, based on the summary of exercise characteristics in Table 4-2, it appeared that all exercise types practiced across a spectrum intensity and duration are generally helpful in OA.

As a complex intervention, the efficacy of exercise programs would depend on the delivery mechanism. In most part this entails the therapists' experience, practices and beliefs. Although exercise guidelines are in place, outcomes of surveys found that these guidelines generally had little influence on the practices, beliefs and attitudes of therapists - many of whom doubted the safety of some exercise types (Holden et al., 2009, Liddle et al., 2009). Despite their uncertainties, therapists are still required to play major role in rehabilitative care including delivering exercise therapy in NHS. In order to encourage adherence to the guidelines, it is pertinent to address the concerns of therapists, dispel misconceptions and provide opportunity for therapists who lack confidence/ experience to initiate exercise programs jointly with the attending physicians.

Among the many patient-related factors proposed to influence the outcomes of exercise, sustaining adherence is one of the most challenging (Nicolson et al., 2018). Despite their adherence being most frequently monitored (refer section 4.3.3), participants in the mixed exercise group experienced the least improvements. This beg the question of whether exercise adherence can be improved with monitoring alone. Especially when many measures of self-reported adherence

had not been tested for reliability and validity (Bollen et al., 2014), it also raises the question of whether current measure of exercise adherence is a good predictor of response. Adherence as measured with attendance may suffer from similar limitation as there is no means to determine if the participants had correctly performed the exercise as intended despite attending a session or reported that they had.

In short, the benefits of exercise are determined by multiple factors and involved multiple dimensions of health care. Identifying the best exercise type is just one (but an important) piece of information to be considered in designing the most appropriate exercise program for OA.

8.6.5 Effects of exercise across different performance-based parameters

The ES of exercise across different physical parameters is expected to be 0.46 (95% 0.35, 0.57). Although measurements from a wide range of physical tasks had been pooled throughout this thesis, special attention was made to ensure that the outcome measures used for analysis came primarily from tasks that had been tested in the most consistent manner (i.e. walking performance). The pooling of different tasks did not appear to increase the statistical heterogeneity of performance outcome beyond those seen for

pain and functional outcomes (I^2 pain: 74.1%; function: 74.5%; performance: 70.5%) probably because the calculation of the ES had already been standardised and adjusted for within-study variance.

There may, however, be concerns of clinical heterogeneity as a range of physical test measuring different abilities had been pooled – masking the true exercise efficacy for individual construct of physical abilities. For physical performance in general, this concern may not hold ground because all physical movement and action are the result of complex interaction between different constructs of physical ability (Kaminsky, 2014). None of the physical construct can act independently. For example, walking is not only dependent on strength, but also endurance, joint motion and balance. Similarly, balancing tasks would not only require skills/balance but also conditioned upon sufficient muscle strength to perform the tasks.

Across many conditions, investigators would attempt to resolve this by performing battery of physical tests in their assessments (Narazaki et al., 2014, Tieland et al., 2012). Furthermore, systematic examination of 24 reports on objective measures of physical abilities in knee and hip OA by Dobson et al. (2012) concluded that most of the physical tests

(either individually or in combination) have indeterminate internal consistency, reliability, measurement error, validity and responsiveness.

Due to poor specificity of the physical tests and overlapping constructs, the effects of all types of exercise on different physical parameters were pooled in this thesis to provide an indication of the global efficacy of exercise (i.e. irrespective of exercise type or outcome measure used). Result from the subgroup analysis of walking and non-walking tests (presented in Chapter 5) is suggestive of no significant difference between the types of test used.

From the clinical perspective, the results from this study do not imply that other exercises should be ignored. Although exercises that corrects biomechanical deficits such as muscle weakness, limited joint mobility or impaired proprioception were not demonstrated to be the most superior exercises, such exercises should still be considered when specific indications to improve gross muscle strength or to regain joint range of movement exist. This is because many of these biomechanical impairments have been widely implicated in OA progression and self-reported outcomes. In instances where there is no clear advantage of one exercise over another (i.e. when no one physical component appear to be significantly

impaired compared to another), the findings from this NMA may then be useful to guide decision making between patients and their health care providers.

8.6.6 **Time dependent effect**

Intensive intervention and patient follow-up in exercise studies for OA were characteristically short-term. Thus there is a good evidence base to support the short term effects of exercise, typically from the second to third month after the commencement of exercise. Although the presence of a gradual but obvious decline in effect size from this point onwards strongly suggests that exercise benefits will diminish after achieving a peak effect at two to three months, the effect is still likely to remain significantly better than usual care until six months post intervention. A similar trend was also shown by Fransen and McConnell (2015) and Pisters et al. (2007) where after six months, exercise effects eventually declined and became no better than controls.

The actual reason for the decline in exercise effect is complex. Poor adherence is widely regarded as a prevailing factor (Marks, 2012, Van Gool et al., 2005) although in practice, the quality of exercise session may be a more precise determinant of exercise benefits than adherence measure. Given that reduction or avoidance of physical activity is detrimental to

structural and physiological health of joints and tissues, promotion of adherence to exercise is still necessary regardless.

Strategy to addressed exercise adherence is often advocated through implementation of patient education that encompasses a wide scope of knowledge area and skills sets – which should lead to behavioural changes and improvements in self-management or self-efficacy (NICE.org.uk., 2014). Booster sessions for program are also feasible approaches. However, these strategies are not necessarily effective. Even when exercise is delivered in conjunction with education, the adherence rate can still be poor (53%) as observed by Svege et al. (2016). Bennell et al. (2014b) implemented two booster sessions over a period of 24 weeks in addition to a 12 week exercise program. At the end of the study, no difference in patient-centred outcomes or adherence rate was seen between groups of participants with and without booster sessions.

Additional factors from providers such as their level of knowledge, beliefs and expertise are also important considerations in the implementation of effective exercise programs (Bennell et al., 2014a). Exercise programs that are designed according to the abilities of individuals and take into

account the unique barriers faced by each individual are more likely to be adhered to than a 'one-size-fits-all' program.

8.6.7 **Joint site of OA**

Results from this study, which is in line with existing evidence (Bennell and Hinman, 2011), demonstrated that there is stronger pain and functional benefits for people with knee OA than those with hip OA. This may imply that exercise has a greater role in knee OA than hip OA.

The overall lack of response in hip OA may be because hip OA tends to have more severe symptoms and more advanced structural joint changes upon presentation than knee OA (Le Marshall et al., 2013). Since the number of studies on people with hip OA was comparatively small, the result has to be interpreted with caution. More studies are required especially since there is some evidence to show that people with hip OA can derive a better response than people with knee OA if the exercise interventions given are more complex (i.e. exercise programs being customised and combined with other interventions) (Pisters et al., 2010). What this implies is that exercise can be as useful for people with hip OA as for those with knee OA, but for any given improvement a more complex exercise program as part of a package of care is likely to be needed for those with hip OA compared to knee OA.

8.6.8 **Pre-joint replacements exercise programs**

8.6.8.1 Before surgery

Advantages of exercise in combination with other therapy for hip OA is again demonstrated in those awaiting joint replacement surgery. When combined with education, exercise therapy has been previously reported to be effective in prolonging the median time to hip replacement from 3.5 years to 5.4 years compared to controls who received only education (Svege et al., 2013). Even though the authors did not investigate knee OA, the result from Svege et al, which implied considerable influence of exercise on the clinical course of end-stage OA, does not fully accord with the conclusion from this meta-analysis. Back transformation of pooled estimates to the absolute scale (as illustrated in section 7.2.1) suggest that the mean improvement to be expected is small-moderate and is unlikely to impart substantial influence on the clinical course of patients awaiting surgery.

One possible reason is that the present study focused on the efficacy of 'exercise-only' interventions and did not examine combination therapy (i.e. exercise combined with other treatment such as education). It is possible for exercise programs to interact with additional interventions to exert greater treatment effect and to potentiate exercise response.

Furthermore, education alone without concurrent exercise interventions had been shown to be effective in improving the coping abilities of patients (Grønning et al., 2016), which may then delay the need for surgical interventions.

8.6.8.2 After surgery

Although patients on waiting-list for surgery did experience significant but modest positive changes in all outcomes of interest before surgery, the positive effects of exercise gained before surgery were not sustained postoperatively. The first review of this scenario was performed in 2004, based on five reports, and concluded that pre-surgical exercise was not useful in improving postoperative outcomes (Ackerman and Bennell, 2004). To date, there seems to be little change to the overall conclusion and poor design of the exercise programs had been suggested as a possible reason (Hoogeboom et al., 2012).

Nevertheless, some work does support the positive impact of pre-surgical exercise by showing that there may be small and transient pain and functional benefits at four weeks after surgery (Wang et al., 2016). In addition, it may also be useful for reducing healthcare cost through reduction of hospital stay or utility of health services after operation (Fernandes et al., 2017, Rooks et al., 2006).

8.7 **Future work**

Although the evidence supporting the use of exercise in general has been well established, evidence to elucidate the optimal exercise content is conflicting. So far, apart from strengthening exercises, single component exercises such as mind-body or aerobic exercises have not been rigorously investigated. More studies on these single component exercises are warranted in order to guide individualisation of these exercises and to demonstrate whether aerobic or mind-body exercise would be more beneficial for patients with marked abnormalities in central pain pathways, and whether local strengthening exercise would produce greater response in patient whose pain are mainly of peripheral in origin. Appropriate full characterisation of participants and use of individual patient data analyses are required to adequately address these questions.

Other than the need for more clinical trials to establish the efficacy of selected exercises, there is also a need to conduct studies with longer follow-ups to reaffirm or refute the waning of the exercise benefit, to expand the focus of research to include more people with hip OA and OA awaiting surgery, to determine the appropriate exercise volume with regards to frequency, intensity and duration, to name but a few.

Equally important is the need to address significant biases in exercise studies. Although blinding of participants and investigators may not be possible, a great proportion of exercise RCT demonstrated high risk of biases in other domains that are amendable to improvement such as reporting bias, allocation concealment and small sample size. These have to be addressed alongside efforts to expand the scope of exercise trials in OA.

8.8 General conclusion

In general, the results suggest that exercise is more effective than usual care in improving a wide range of OA-related outcomes in the short term (8 weeks). The overall trend indicated that exercise is better for knee OA than hip OA, and better in people who were not on the waiting-list for surgery compared to those who were. The differences between these subgroups are not statistically significant however.

Aerobic and mind-body exercise specifically, are potentially the most promising exercises for knee OA and hip OA. However, the estimation of treatment response for aerobic and mind-body exercises is considerably uncertain due to paucity of clinical trials. The estimate of efficacy for the lower ranking

strengthening and mixed exercises, on the other hand, are more precise and could be interpreted with greater confidence.

All evidence considered together, single component exercise should probably be the first line exercise program for knee and hip OA while mixed exercise would still be useful for those who do not prefer to perform single exercise type or who wish to expand the exercise regimen in additive fashion. Aerobic and mind-body exercise could be the most appropriate exercises in patients whose pain show a large component of central sensitisation. However, due to insufficient evidence, it is difficult to establish which of the two exercises (aerobic or mind-body) is more superior.

This work was mainly undertaken to provide a comprehensive summary of the best exercise for different OA-related outcomes. Additionally, it has revealed gaps in this area, especially the lack of evidence for selected exercise types and selected patient subgroup (e.g., hip OA), and has highlighted the consistently poor performance of mixed exercise, all of which warrant further study.

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Appendices

Appendix 1 Summary of systematic reviews of different exercise elements

Study subgroup	Number of studies, (number of subjects)	Comparator	ES by outcome*		
			Pain (95%CI)	Function (95%CI)	QOL (95%CI)
Knee only					
Lu et al. (2015)- immediate effects	*6 studies*				
Aquatic-based	Pain, 5 studies; Function, 3 studies; QoL, 3 studies	Land-based	0.25 (-0.24, 0.74)	-0.31 (-0.63, 0.01)	-0.26 (-0.58, 0.05)
	Pain and function 2 each; QoL 2	Non-exercise	1.16 (-0.71, 3.03)	0.55 (0.16, 0.94)	0.21 (-0.18, 0.59)
Fransen and McConnell (2015)	*54 Studies*				
All land-based	Pain, 44 studies, (3537); Function, 44 Studies, (3913)	Non exercise or no treatment/ waiting list	0.49 (0.39, 0.59)	0.52 (0.39, 0.64)	0.28 (0.15-0.40)
Juhl et al. (2014)	*48 studies* (>4028)				
Strength	Pain, 29 studies; Function, 20 studies	Non-exercise	0.62 (0.45, 0.79)	0.6 (0.37, 0.83)	
Aerobic	Pain, 8 studies; Function, 7 studies		0.67 (0.39,0.94)	0.56 (0.24, 0.87)	
Mixed	Pain, 9 studies; Function, 7 studies		0.16 (-0.04,0.37)	0.22 (0.07, 0.37)	
Performance	Pain, 3 studies; Function 3 studies		0.48 (0.11,0.85)	0.56 (0.14,0.98)	
Tanaka et al. (2013a)	*8 studies*				
Strength (WB)	6 studies	Non-intervention or psycho-educational	1.42 (0.75, 2.09)		
Strength (Non-WB)	2 studies		0.7 (0.35, 1.05)		

Aerobic	3 studies		0.45 (0.13, 0.77)		
(Tanaka et al., 2013b)	*33 studies*				
Any form of exercise	Pain (1095) Strength (1692)	Non-intervention or psycho-educational intervention	0.77 (0.29,1.24)	0.37 (0.24, 0.50)	
Lauche et al. (2013)	*5 studies*, (252)				
Tai Chi	Pain & Function - 5; QoL- 2	No exercise/ minimal exercise emphasis	0.72 (0.44, 1.0)	0.72 (0.44, 1.78)	Mental QoL 0.35 (-0.31, 1.01) Physical QoL 0.88 (0.42, 1.34)
Roddy et al. (2005)	*13 studies*				
Aerobic	Pain, 4; Function 2	No exercise	0.52 (0.34, 0.70)	0.46 (0.25, 0.67)	
Strength	Pain 11; Function 11		0.32 (0.23,0.42)	0.32 (0.23, 0.41)	
Hip only					
Fransen et al. (2014)	*10 studies*				
All land-based: immediate effects	Pain, 9 studies, (549); Function 9 studies (521)	Non-exercise/ no treatment/ waiting list	0.38 (0.20, 0.55)	0.3 (0.05, 0.54)	
All land-based: long term effects (3-6 months)	Pain, 5 studies, (391); Function, 5 studies,(365)	Non-exercise/ no treatment/ waiting list	0.38 (0.18, 0.58)	0.37 (0.16,0.57)	
Hernández-Molina et al. (2008)	*9 studies*, (1234)				
Mixed elements		No exercise	0.46 (0.28,0.64)		
Mixed					
Uthman et al. (2014)	*60 studies* (8218)				
Strength		No exercise	0.81 (0.5, 1.13)	0.37 (-0.09, 0.84)	
Aerobic			0.41 (-0.3, 1.13)	0.30 (-0.92, 1.53)	
Flexibility			0.66 (0, 1.33)	0.17 (-0.93, 1.26)	

Mixed			0.69 (0.35-1.04)	0.63 (0.1-1.16)	
Kang et al. (2011)	*9 studies*				
Tai Chi	Pain, 3 studies; Function, 3 studies	Attention control	1.18 (0.54,1.82)	1.2 (0.67, 1.74)	
	Pain, 3 studies; Function, 3 studies	Routine care	0.47 0.14, 0.79	0.6 (0.28, 0.93)	
	Pain, 6 studies; Function, 6 studies		Overall 0.79 (0.39,1.19)	Overall 0.86 (0.52,1.2)	
Bartels et al. (2016)	*13 studies*				
Aquatic	Pain, 12 studies, (1135); Function, 12 studies, (1116); QoL, 10 studies, (1027)	Usual care, information	0.31 (0.15, 0. 47)	0.32 (0.17, 0. 47)	0.25 (0.01, 0.49)
Waller et al. (2014)	*11 studies*				
Aquatic	Pain, 10 studies; Function, 11 studies; QoL, 8 studies		0.26 (0.11, 0.41)	0.30 (0.18, 0.43)	0.24 (0.04, 0.45).

*Positive value favours intervention, negative favours comparator

Abbreviation: CI: confidence interval; ES: Effect size ; OA: osteoarthritis; QoL: quality of life; WB : weight bearing

Appendix 2 Medline search strategy

1. exercise/ or physical conditioning, human/
2. Circuit-Based Exercise/
3. exercise therapy/ or motion therapy, continuous passive/ or muscle stretching exercises/ or plyometric exercise/ or resistance training/ or hydrotherapy/ or rehabilitation/ or 'activities of daily living'/ or dance therapy/
4. muscle strength/ or physical endurance/ or anaerobic threshold/ or exercise tolerance/ or physical fitness/ or postural balance/ or posture/ or psychomotor performance/ or 'range of motion, articular'/
5. Pliability/
6. movement/ or motor activity/ or exercise/
7. Physical Exertion/
8. Mind-Body Therapies/
9. running/ or jogging/ or swimming/ or walking/
10. Isometric Contraction/
11. exercise movement techniques/ or breathing exercises/ or qigong/ or tai ji/ or yoga/ or pilates
12. propriocepti$.ab,ti.
13. balanc$.ab,ti.
14. aqua$.ab,ti.
15. cycl$.ab,ti.
16. aerobic.ab,ti.
17. strength$.ab,ti.
18. (tai-ji or taiji or taijiquan or tai ji quan or tai chi or taichi or t ai chi or t'ai chi or tai chi chuan).ab,ti.
19. (qigong or qi gong or chi kung or chikung or ch i kung or ch'i kung).ab,ti.
20. therap$.ab,ti.
21. physiotherap$.ab,ti.
22. train$.ab,ti.
23. neuromuscular training.ab,ti.
24. treadmill.ab,ti.
25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. Osteoarthritis, Hip/ or Osteoarthritis, Knee/
27. coxarthritis.mp.
28. coxarthr$.ab,ti.
29. gonarthr$.ab,ti.
30. (knee$ adj3 pain).ab,ti.
31. (hip adj3 pain).ab,ti.

32. osteoarthr$.ab,ti.
33. degenerative joint disease?.ab,ti.
34. osteoarthritis/
35. (Osteoarthriti$ or OA or osteo arthriti$ or osteoarthros$ or osteo arthros$ or arthropath$ or arthrosis or arthroses).ti,ab.
36. Hip Joint/
37. Hip/
38. hip$.ab,ti.
39. Knee/
40. knee$.ab,ti.
41. knee joint/ or patellofemoral joint/
42. 26 or 27 or 28 or 29 or 30 or 31
43. 32 or 33 or 34 or 35
44. 36 or 37 or 38 or 39 or 40 or 41
45. 43 and 44
46. 42 or 45
47. randomized controlled trial.pt.
48. controlled clinical trial.pt.
49. (placebo or (standard adj3 care)).ab.
50. clinical trials as topic.sh.
51. random$.ab,ti.
52. trial$.ab,ti.
53. RCT.ab,ti.
54. 47 or 48 or 49 or 50 or 51 or 52 or 53
55. limit 54 to humans
56. 25 and 46 and 55

Appendix 3 Data extraction form

DATA EXTRACTION FORM

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

Title of article : enter article title.

Author(s) : first 3 authors.

A. <u>Study characteristics</u>

<table>
<tr><td colspan="3">Country: Country where study was done. Year: State study date</td></tr>
<tr><td colspan="3">Setting: Group ☐ Individual ☐ Home based ☐ Unclear ☐ Others:</td></tr>
<tr><td colspan="3">Definition of OA used: Self-reported ☐ Radiographic ☐ Symptomatic ☐ ACR ☐ Unclear ☐ Others: Click here to enter text.</td></tr>
<tr><td colspan="3">Grouping:</td></tr>
<tr><td><u>Control</u></td><td><u>Intervention 1</u></td><td><u>Intervention 2</u></td></tr>
<tr><td>Detail description:
Enter description of exercise details</td><td>☐ Body
☐ Mind
☐ Mixed
☐ Unclear
Detail description:
Enter description of exercise details</td><td>☐ Body
☐ Mind
☐ Mixed
☐ Unclear
Detail description:
Enter description of exercise details</td></tr>
<tr><td colspan="3">Design: Parallel ☐ Crossover ☐ Others: Other types</td></tr>
<tr><td colspan="3">Follow-up duration:
Time point 1 - First ; Time point 2 - Second ;
Time point 3 – Third</td></tr>
<tr><td colspan="3">Intervention duration: wks</td></tr>
</table>

Outcome:

Primary 1 - text.

Primary 2 - text.

Secondary 1 - text

Secondary 2 - text.

Secondary 3 - text

B. <u>Participants Characteristics</u>

Data based on: **per protocol** ☐ **ITT analysis** ☐

Types of OA: **Knee** ☐ **Hip** ☐

Demographic	Control	Intervention 1	Intervention 2	Total
Number of participants				
Age (mean ± SD)				
Male/ Female				
Knee/Hip (if mixed cohort)				
Severity/grading of OA				
Duration of OA (mean ± SD)				
Attrition (number)				
Adherence of exercise (if relevant)				

C. Outcome

Outcome: **Adjusted:☐**

	Control			Intervention 1			Intervention 2		
	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI
Baseline									
T1									
T2									
T3									

Outcome: Primary 2 **Adjusted:☐**

	Control			Intervention 1			Intervention 2		
	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI
Baseline									
T1									
T2									
T3									

Outcome: Secondary 1 **Adjusted:☐**

	Control			Intervention 1			Intervention 2		
	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI
Baseline									
T1									
T2									
T3									

Outcome: Secondary 2. **Adjusted:☐**

	Control			**Intervention 1**			**Intervention 2**		
	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI
Baseline									
T1									
T2									
T3									

Outcome: Secondary 3. **Adjusted:☐**

	Control			**Intervention 1**			**Intervention 2**		
	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI	Mean/ proportion	SD	95% CI
Baseline									
T1									
T2									
T3									

Comments:

Appendix 4 Calculations of summary data

Equations for effect size calculations*

Calculations	Note

1. *Calculation for summary data*
   a. When combining groups
   - $M_{Gp} = \frac{M_E N_E + M_C N_C}{N_E + N_C}$
   - $SD_{Gp} = \sqrt{\frac{(N_E-1)SD_E{}^2 + (N_C-1)SD_C{}^2 + \frac{N_E N_C}{N_E+N_C}(M_E{}^2 + M_C{}^2 - 2M_E M_C)}{N_E+N_C-1}}$

   b. When calculating SD from other summary data for exercise or control group
   - $SD = SE \times \sqrt{N}$
   - $SD = \frac{(UpCI - LwCI)\times\sqrt{N}}{3.92}$

   c. When estimating SD from range
   - $SD \approx \frac{1}{\sqrt{12}}[(b-a)^2 + \frac{(a-2m+b)^2}{4}]^{\frac{1}{2}}$ N≤15
   - $SD \approx \frac{b-a}{4}$ 15 < N≤70
   - $SD \approx \frac{b-a}{6}$ N>70

   d. When estimating SD from interquartile range
   - $SD \approx \frac{q_3 - q_1}{\eta(N)}$ 5≤N< 200

2. *Calculation of effect sizes*
   a. Cohen's *d* from post treatment scores
   - $d = \frac{M_{post,E} - M_{post,C}}{SD_{post,pooled}}$
     Where,
     $$SD_{pooled} = \sqrt{\frac{(N_E-1)SD_E{}^2 + (N_C-1)SD_C{}^2}{N_E+N_C-2}}$$

   b. Cohen's *d* from change scores
   - $d = \frac{(M_{post,E} - M_{pre,E})}{SD_{change,E}} - \frac{(M_{post,C} - M_{pre,C})}{SD_{change,C}}$

   c. Hedge's *g*
   - J x d
     Where,
     $$J = 1 - \frac{3}{4(N_E+N_C)-9}$$

   d. Variance *g*
   - $V_g = J^2 \times V_d$
     Where,
     $$V_d = \frac{N_E+N_C}{N_E N_C} + \frac{d^2}{2(N_E+N_c)}$$

   e. Standard error of *g*
   - $SE_g = \sqrt{V_g}$

M = mean

SD = standard deviation

N = sample size

Gp = new group

E = exercise group;

C = comparator group

SE = Standard error of means

UpCI = upper confidence interval

LwCI = lower confidence interval

a = minimum value

b = maximum value

m = median

q_3 = third quartile

q_1 = first quartile

η (N) = function of N (value provided by Wan et al.)

Post = post-treatment score

Pre = pre-treatment score

V = variance

*for study designs with two independent groups (only equations relevant for means are listed since this is expected to be the main form of data encountered)

Appendix 5 Quality assessment form

QUALITY ASSESSMENT FORM

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

Title of article : enter article title. Comments: enter any comments

Author(s) : first 3 authors.

Please see Appendix 1 for criteria	Yes	No	Unclear
1. Was the randomisation procedure adequate? Comments:	☐	☐	☐
2. Were there more than 100 subjects in each treatment group? Comments:	☐	☐	☐
3. Was the treatment allocation adequately concealed? Comments:	☐	☐	☐
4. Were physicians blinded to the intervention? Comments:	☐	☐	☐
5. Were patients blinded to the intervention? Comments:	☐	☐	☐
6. Were outcome assessors blinded to the intervention? Comments:	☐	☐	☐
7. Was incomplete outcome data adequately assessed?	☐	☐	☐

Comments:			
8. Was intention-to-treat analysis used?	☐	☐	☐
Comments:			
9. Were the treatment and control group similar at baseline?	☐	☐	☐
Comments:			
10. Are all pre-specified outcomes of interest reported in the pre-specified way?	☐	☐	☐

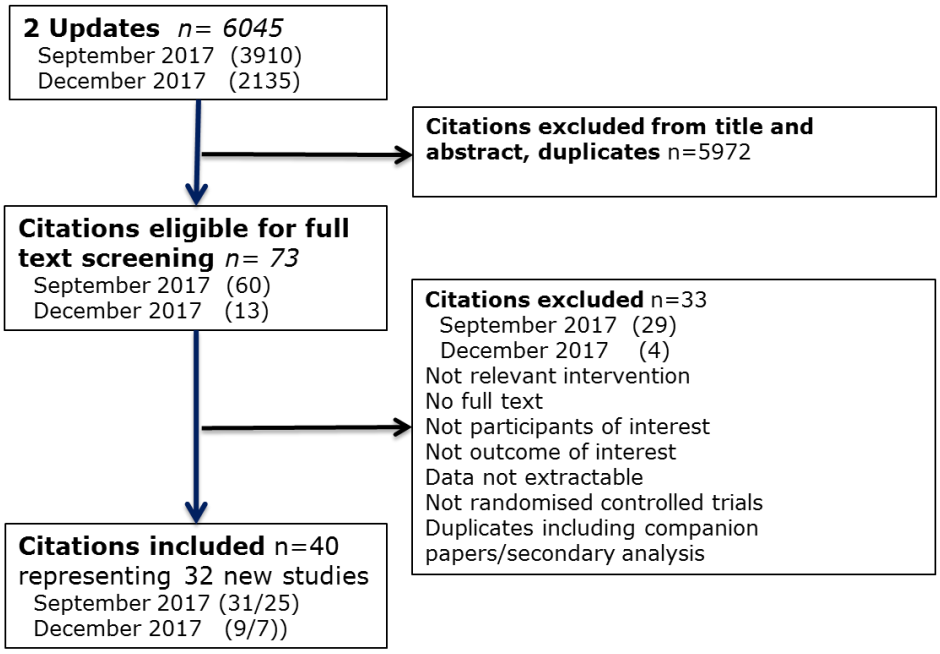
Criteria for risk of bias assessment

Criteria	Yes	No
Was the randomisation procedure adequate?	A random component in the sequence generation process is used, such as: • Using to a random number table • Using a computer random number generator • Tossing a coin • Shuffling cards or envelopes • Throwing dice • Drawing lots • Minimisation	A non-random component is used in the allocation process, such as: • Sequence generated using odd or even date of birth • Sequence based on a rule based on date of admission or hospital number • Allocation decision is made by clinician or patient • Allocation is based on clinical or laboratory test findings
Were there more than 100 patients in each treatment group?	More than 100 patients were randomized in each group	Less than 100 patients were randomized to each group
Was the treatment allocation adequately concealed?	Patients and physicians could not foresee allocation assignment, because an adequate method was used to conceal allocation. Adequate allocation concealment methods include: • Central allocation • Opaque, sealed, sequentially numbered assignment envelopes are used	Patients or physicians could potentially foresee allocation. Inadequate allocation concealment procedures include: • The use of an open random allocation schedule • Assignment envelopes are not appropriate, such that envelopes may be unsealed, not sequentially numbered, or see-through • Rotation or alternation • Methods based on date of birth, case record number, or

		other patient identifiers
Were physicians blinded to the intervention?	Physicians were adequately blinded and it is unlikely that the blinding could be broken	No blinding, incomplete blinding, or blinding attempted but likely to have been broken
Were patients blinded to the intervention?	Patients were adequately blinded and it is unlikely that the blinding could be broken	No blinding, incomplete blinding, or blinding attempted but likely to have been broken
Were outcome assessors blinded to the intervention?	Treatment choice is not evident when measuring outcome. • If outcome is patient-reported, then the answer for 'Were patients blinded to the intervention?' will be the same for this question. • For physician-assessed outcomes, this is dependent on whether the treatment allocation can be identified from examination of the patient or their tests	Treatment choice is likely to be evident when measuring outcome • If outcome is patient-reported, then the answer for 'Were patients blinded to the intervention?' will be the same for this question. • For physician-assessed outcomes, this is dependent on whether the treatment allocation can be identified from examination of the patients or their tests
Was incomplete outcome data adequately assessed?	YES – ≥2 of the following questions as 'yes' • Is there any missing outcome data? • Are the reasons for missing data unlikely to be related to the outcome? • Has missing data been imputed using	NO – < 2 of the following questions as 'yes' • Is there any missing outcome data? • Are the reasons for missing data unlikely to be related to the outcome? • Has missing data been imputed using

	appropriate methods, such as multiple imputations	appropriate methods, such as multiple imputations
Was intention-to-treat analysis used?	• All randomised patients are analysed according to the group they were allocated to, regardless of non-compliance • No patients were lost throughout the trial • The analysis has been characterised by the authors	• Per-protocol analysis is used to analyse only patients that adhered fully to their allocated treatment, • Patients who dropped-out or moved between treatment groups were excluded from analysis
Were the treatment and control group similar at baseline?	Treatment and control group were similar regarding patient demographics and pain parameters	Treatment and control groups were dissimilar with regards to patient demographics and pain parameters
Are all pre-specified outcomes of interest reported in the pre-specified way?	All the study's pre-specified outcomes of interest are reported in the pre-specified way	Outcome measures were not pre-specified, such as: • Not all the pre-specified outcomes have been reported • Outcomes are not reported using the measurements or methods pre-specified • Outcomes reported had not been pre-specified • Outcomes of interest have been incompletely reported • The report does not report outcomes that would be expected from such a study

Appendix 6 Prisma flow diagram of updates performed in 2017



Appendix 7a Summary of included studies and references

i) Characteristics of studies included for non-operative outcomes (Chapter 5 - Exercise versus usual care: meta-analysis, Chapter 6 – Relative efficacy of different exercises: network meta-analysis)

Study	Age (SD)	BMI (SD)	No. (fem %)	Jt	Diagnosis	Pre-surgical	Study arms			Tool and outcome time point (month)			
							1	2	3	Pain	Function	Performance	QoL
[1]Abbott 2013	67 (10)	29 (6)	206 (55)	K, H	A	N	MEx	UC	-	Pain intensity score (0-10), 12	WOMAC (0-240), 2.25	40m walk time (s), 12	-
[2]Aglamis 2008[†] *[3]Aglamis 2009*	56 (5)	33 (5)	31 (100)	K	A, I	N	MEx	UC	-	VAS (0-10), 1.5-	WOMAC (total), 1.5	6MWT (m), 1.5	SF-36 (0-100) General health (0-100), 1.5
[4]An 2008	65 (7)	26 (3)	28 (100)	K	A	N	MB	UC	-	WOMAC pain, 2	WOMAC (physical fx), 2	6MWT (m), 2	SF-36 Mental health (0-100), 2
[5]Aoki 2009	73 (6)	26 (3)	36 (100)	K	I	Y	Fl/Sk	UC	-	VAS (0-100), 3	-	Walking speed (m/min), 3	-
[6]Arnold 2010	74 (6)	30 (5)	83 (68)	H	A	N	MEx	UC	-	Arthritis Impact measurement scale -2,	Activity specific balance confidence	6MWT (m), 2.75	-

										results Not reported	(0-100), 2.75		
[7]Beaupre 2004	67 (7)	32 (6)	131 (55)	K	UClr	Y	Str	UC	-	WOMAC pain (0-100), 1.5	WOMAC fx (0-100), 1.5	Quadriceps strength, 1.5	SF-36 Mental health, 1.5
[8]Bennell 2010	65 (8)	28 (4)	89 (48)	K	A, I	N	Str	UC	-	NRS (0-10), 3.25	WOMAC fx (0-68), 3.25	Timed stair task (s), 3.25	-
[9]Bennell 2014	62 (7)	30 (4)	100 (52)	K	I	N	Fl/Sk	Str	-	VAS (0-100), 3	WOMAC fx (0-68), 3	Walking speed (m/s), 3	AQoL (-0.04-1), 3
[10]Bieler 2017	70 (-)	27 (-)	152 (68)	H	A	N	Ae	MEx	Str	WOMAC pain, not extractable	WOMAC fx, not extractable	6MWT (m), 2	SF-36, not extractable
[11]Börjesson 1996	64 (5)	- (-)	68 (50)	K	I	Y	MEx	UC	-	NRS (0-10), 3	-	Walking speed (m/s), 3	-
[12]Braghin 2017	60 (-)	31 (-)	42 (74)	K	I	N	MEx	UC	-	WOMAC pain, 2	WOMAC fx, 2	Timed movement (s), 2	-
[13]Bruce-Brand 2012	64 (5)	33 (4)	26 (42)	K	I	Y	Str	UC	-	WOMAC pain (0-20), 1.5	WOMAC fx, 1.5	Timed walk (s), 1.5	SF-36 MCS, 1.5
[14]Calatayud 2017	50 (-)	32 (-)	50 (-)	K	A, I	Y	Str	UC	-	VAS (0-10), 2	WOMAC fx, 2	Timed up and go (s), 2	SF-36 Physical fx, 2
[15]Chaipinyo 2009	66 (7)	25 (4)	48 (77)	K	A	N	Fl/Sk	Str	-	KOOS pain (0-100), 1	KOOS fx daily activity (0-100), 1	Timed walk (s), 1	KOOS QoL (0-100), 1
[16]Chen 2014	63 (7)	- (-)	120 (85)	K	A, I	N	Str	UC	-	VAS (0-10), 2	Lequesne's index (1-26), 2	Knee range of motion, 2	-
[17]Cheung 2016	72 (8)	29 (7)	83 (84)	K	A	N	MB	MEx	-	VAS (0-10), 2	WOMAC fx (0-68), 2	Walking 50ft (s), 2	SF-12 MCS, 2

[18]Chopp-Hurley 2017	54 (-)	29 (-)	24 (79)	K, H	A	N	Str	UC	-	ICOAP, not extractable	HOOS/KOOS, not extractable	6MWT (m), 3	HOOS/KOOS, not extractable
[19]Christensen 2015† *[20]Henriksen 2014*	63 (6)	37 (-)	192 (81)	K	I	N	MEx	UC	-	VAS (0-100), 12	KOOS (daily fx) (0-100), 12	6MWT (m), 12	SF-36 Mental health (0-100), 12
[21]Cochrane 2005	70 (7)	30 (-)	312 (63)	K, H	UClr	N	MEx	UC	-	WOMAC pain (0-96), 6	WOMAC fx (0-96), 6	Timed walk (s), 12	SF-36 Mental health (0-100), 6
[22]Cheung 2014	72 (6)	29 (-)	36 (100)	K	A	N	MB	UC	-	WOMAC pain (0-20), 2	WOMAC fx (0-68), 2	8 min walk (m), 2	SF12 MCS (0-100), 2
[23]D'Lima 1996	70 (6)	- (-)	30 (47)	K	UClr	Y	Ae	Mex	UC	-	Hospital for Special Surgery Knee rating (0-100), 1.5	-	-
[24]Duracoglu 2005	- (-)	- (-)	66 (100)	K	A, I	N	MEx	Str	-	-	WOMAC fx, 2	Timed walk (s), 2	SF-36 vitality, 2
[25]Ebnezar 2012† *[26]Ebnezar 2012 (a)* *[27]Ebnezar 2012 (b)* *[28]Ebnezar 2011*	60 (10)	- (-)	250 (70)	K	A, I	N	MB	MEx	-	NRS (0-10), 3-mth	WOMAC (0-96), 3	-	-

[29]Espejo Antunez 2012	84 (8)	- (-)	31 (77)	K	A	N	MEx	UC	-	VAS, 1-mth	WOMAC fx (0-96), 1	-	SF-36 Mental health, 1
[30]Ettinger 1997	69 (6)	- (-)	439 (70)	K	I	N	Ae	Str	-	Likert scale (1-6), 3	Self reported physical disability (1-5), 3	6MWT (m), 3	-
[31]Evcik 2002	56 (6)	- (-)	90 (62)	K	I	N	Ae	UC	-	VAS (0-100), 6	WOMAC fx (0-68), 6	-	NHP - emotional reaction, 6, Outlier
[32]Evgenia dis 2008	68 (4)	34 (-)	53 (79)	K	A, I	Y	Str	UC	-	SF-36 body pain, 1	SF-36 physical fx, 1	Active range of motion (flexion), 1	SF-36 Mental health, 1
[33]Ferrara 2008	63 (8)	- (-)	23 (61)	H	UClr	Y	MEx	UC	-	VAS (0-10), 1	WOMAC fx (0-68), 1	Quads strength, 1	SF-36 Mental health, 1
[34]Fitzgerald 2011	64 (9)	30 (-)	183 (67)	K	A, I	N	Fl/Sk	MEx	-	NRS (0-10), 2	WOMAC fx (0-68), 2	Up n Go (s), 2	Global rating of change, 2
[35]Fransen 2001	67 (9)	29 (5)	126 (73)	K	I	N	MEx	UC	-	WOMAC pain (0-100), 2	WOMAC fx (0-100), 2	Gait speed (cm/s), 2	SF-36 Mental health, 2
[36]Fransen 2007	70 (6)	30 (-)	152 (74)	K, H	A	N	MB	MEx	UC	WOMAC pain (0-100), 3	WOMAC fx (0-100), 3	Timed walked (s), 3	SF-12 MCS (Mean+/- SD 50+/- 10), 3
[37]French 2013	62 (10)	- (-)	131 (64)	H	A, I	N	MEx	UC	-	NRS, 2	WOMAC fx (0-68), 2	50 ft walk test (s), 2	SF-36 Mental health (0-100), 2
[38]Ghroubi 2008 (a)	41 (10)	38 (-)	56 (-)	K	I	N	MEx	UC	-	VAS pain(0-10), 2	WOMAC, 2	6MWT (m), 2	-

[39]Gomiero 2017	62 (-)	24 (-)	64 (95)	K	A	N	Fl/Sk	Str	-	VAS (0-100), 4	WOMAC (total), 4	Timed up and go (s), 4	SF-36 Mental health, 4
[40]Gondhalekar 2013	63 (6)	- (-)	30 (50)	K	A, I	N	Fl/Sk	Str	-	VAS (0-10), 0.75	WOMAC, 0.75	Hip extensor strength, 0.75	-
[41]Gur 2002	56 (12)	- (-)	23 (-)	K	I	N	Str	UC	-	NRS (0-10), 2	NRS of functional capacity (0-10), 2	15m walk (s), 2	-
[42]Hasegawa 2010	77 (4)	24 (4)	28 (64)	K	UClr	N	MEx	UC	-	NRS (0-10), 3	-	Time up and go (s), 3	-
[43]Henriksen 2014a[†] [44]*Henriksen 2017*	64 (8)	29 (-)	60 (80)	K	I	N	MEx	UC	-	KOOS pain (0-100), 3	KOOS fx (0-100), 3	Walking speed (m/s), 3	KOOS QOL (0-100), 3
[45]Herman 2016	70 (8)	28 (5)	80 (65)	H	UClr	Y	Str	UC	-	HOOS pain, 2.5	HOOS ADL, 2.5	Quadriceps power, 2.5	HOOS QoL, 2.5
[46]Hinman 2007	62 (9)	33 (7)	71 (68)	K, H	A, I	N	MEx	UC	-	VAS (0-10) on movement, 1.5	WOMAC fx (0-1700), 1.5	6MWT (m), 1.5	Assessment of QoL (-0.04 to1), 1.5
[47]Hiyama 2012	73 (5)	24 (-)	40 (100)	K	UClr	N	Ae	MEx	-	Japanese Knee Osteoarthritis Measure pain (0-125), 1	Japanese Knee Osteoarthritis Measure (total) (0-125), 1	Timed up and go (s), 1	-
[48]Hoogeboom 2010	76 (4)	27 (-)	21 (67)	H	UClr	Y	MEx	UC	-	VAS, 1	HOOS ADL fx (0-100), 1	6MWT (m), 1	HOOS QoL (0-100), 1

[49]Huang 2003	62 (5)	- (-)	132 (71)	K	A, I	N	MEx	UC	-	VAS (0-10), 2	Lequesne index, 2	Walking speed (m/s), 2	-
[50]Huang 2005	65 (6)	- (-)	140 (81)	K	A	N	Str	UC	-	VAS (standing/walking) (0-10), 2	Lequesne index (1-26), 2	Walking speed (m/min), 2	-
[51]Huang 2017	68 (6)	25 (2)	250 (80)	K	A	N	Str	UC	-	VAS (0-100), 3	WOMAC (0-68), 3	-	-
[52]Hunt 2013	66 (11)	27 (-)	17 (53)	K	A, I	N	Str	UC	-	-	-	Walking speed (m/s), 2.5	-
[53]Ikuta 2015	72 (6)	- (-)	27 (100)	K	UClr	N	Fl/Sk	MEx	-	KOOS pain, 1	KOOS ADL, 1	Walking speed (km/h), 1	SF-36 Mental health, 1
[54]Jan 2008	63 (7)	- (-)	98 (81)	K	A, I	N	Str	UC	-	WOMAC pain (0-20), 2	WOMAC fx (0-68), 2	Timed walk (s), 2	-
[55]Jan 2009	63 (7)	- (-)	106 (69)	K	A, I	N	Str	UC	-	-	WOMAC fx (0-68), 2	Timed walk (s), 2	-
[56]Jorge 2015	61 (7)	31 (4)	60 (100)	K	A	N	Str	UC	-	VAS (0-10), 1.5	WOMAC (0-68), 1.5	6MWT (m), 1.5	SF-36 Mental health (0-100), 1.5
[57]Juhakoski 2011	67 (6)	- (-)	118 (70)	H	A, I	N	MEx	UC	-	WOMAC pain (0-100), 3	WOMAC fx (0-100), 3	6MWT (m), 3	SF-36, not reported
[58]Koli 2015	59 (4)	27 (4)	78 (100)	K	I	N	Ae	UC	-	KOOS pain (0-100), 12	KOOS fx (0-100), 12	Strength, 12	KOOS QOL (0-100), 12
[59]Krasilshchikov 2011	58 (5)	28 (5)	16 (100)	K	I	N	MEx	UC	-	WOMAC pain, 2	WOMAC fx, 2	6MWT (m), 2	-
[60]Krauss 2014† [61]*Steinhilber 2017*	59 (10)	27 (4)	218 (40)	H	A	N	MEx	UC	-	WOMAC pain (0-100), 3	WOMAC fx (0-100), 3	Hip abd peak torque, 3	SF-36 Mental health (0-100), 3

[62]Kreindler 1989	- (-)	- (-)	32 (75)	K	UClr	N	Str	UC	-	-	-	Quadriceps strength (180), 1.5	-
[63]Kumar 2013	53 (6)	25 (3)	44 (57)	K	UClr	N	Fl/Sk	Str	-	NRS, 1	WOMAC fx, 1	Joint position sense error, 1	-
[64]Lee 2008	76 (6)	- (-)	46 (78)	K	UClr	N	MB	UC	-	WOMAC pain (0-96), 3	WOMAC fx (0-96), 3	Timed up and go test (s), 3	-
[65]Lee 2009	69 (5)	- (-)	44 (93)	K	I	N	MB	UC	-	WOMAC pain (26-130), 2	WOMAC fx (0-100), 2	6MWT (m), 2	SF-36 Mental health (0-100), 2
[66]Lim 2008* (neutral, malaligned)	66 (8)	29 (-)	107 (55)	K	A, I	N	Str	UC	-	WOMAC pain (0-100), 3	WOMAC fx (0-100), 3	Stair climb (s), 3	-
[67]Lin 2007	62 (7)	- (-)	89 (70)	K	I	N	Fl/Sk	Str	-	-	WOMAC fx (0-69), data not extractable	Knee extensor torque (180°), 2	-
[68]Lin 2009	63 (7)	- (-)	108 (69)	K	I	N	Fl/Sk	Str	UC	WOMAC pain (0-20), 2	WOMAC fx (0-68), 2	Timed walk (s), 2	-
[69]Lund 2008	68 (14)	- (-)	79 (79)	K	A	N	MEx	UC	-	Vas at rest (0-100), 2	KOOS ADL (0-100), 2	Strength, 2	-
[70]Messier 1997	69 (6)	31 (6)	103 (74)	K	I	N	Ae	Str	-	Pain intensity (1-6), 3	-	-	-
[71]Moghadam 2017	67 (-)	25 (-)	20 (-)	K	A	N	Ae	UC	-	-	-	6MWT (m), 2	-
[72]Munukka 2016† [73]*Waller 2017*	64 (-)	27 (-)	87 (100)	K	I	N	Str	UC	-	KOOS pain (0-100), 4	KOOS ADL (0-100), 4	Walking speed (m/s), 4	KOOS QoL (0-100), 4

[74]Oida 2008	74 (5)	25 (4)	88 (86)	K	I	N	MEx	UC	-	-	WOMAC (0-300), 3	Timed walk (s), 3	-
[75]Oosting 2012	76 (6)	28 (-)	30 (80)	H	UClr	Y	MEx	UC	-	NRS (0-10), 1.25	HOOS ADL fx (0-100), 1.25	6 MWT (m), 1.25	HOOS QoL (0-100), 1.25
[76]O'Reilly 1999	62 (10)	- (-)	180 (66)	K	UClr	N	Str	UC	-	WOMAC pain (0-20), 6	WOMAC fx (0-68), 6	Quadriceps strength, 6	SF-36 Mental health, 6
[77]Petrella 2000	74 (5)	- (-)	179 (58)	K	I	N	Fl/Sk	MEx	-	WOMAC pain, 8	WOMAC fx, 8	Timed walk (s), 8	-
[78]Rapp 2009	60 (8)	- (-)	39 (56)	K	A	N	Str	UC	-	VAS (0-10), 2	-	Strength, 2	-
[79]Rathi 2014	54 (7)	- (-)	20 (-)	K	I	N	Ae	MEx	-	NRS, 0.5	WOMAC fx (0-28), 1.5	Strength, 0.5	-
[80]Rogers 2011	71 (11)	33 (7)	20 (80)	K	UClr	N	Fl/Sk	Str	-	WOMAC pain (0-20), 2	WOMAC fx (0-68), 1.5	Timed up and go test (s), 2	-
[81]Rogers 2012	70 (9)	29 (-)	33 (61)	K	A	N	Fl/Sk	MEx	Str	WOMAC pain (0-20), 2	WOMAC fx (0-68), 2	Timed up and go (s), 2	-
[82]Rogind 1998	71 (7)	27 (4)	25 (84)	K	A, I	N	MEx	UC	-	VAS at rest (0-10), 3	Algofunctional index, 3	20m walk speed (m/s), 3	-
[83] Rooij 2016	64 (-)	36 (-)	126 (75)	K	A	N	MEx	UC	-	NRS (0-10), 2.5	WOMAC fx (0-68), 2.5	6MWT (m), 2.5	-
[84]Rosedale 2014	65 (10)	31 (7)	158 (56)	K	I	Y	MEx	UC	-	KOOS pain (0-100), 3	KOOS fx (0-100), 3	-	KOOS QoL (0-100), 3
[85]Salacinski 2012	58 (10)	24 (-)	37 (73)	K	I	N	Ae	UC	-	VAS rest (0-100), 3	WOMAC fx (0-100), 3	Walking speed (m/s), 3	KOOS-QoL (0-100), 3
[86]Salli 2010 [87]*Salli 2006*	57 (7)	32 (-)	75 (77)	K	A, I	N	Str	UC	-	VAS (rest), 2	WOMAC fx, 2	Strength (180°/s peak torque), 2	SF-36 Mental health, 2
[88]Samut 2015	60 (7)	32 (-)	42 (100)	K	A	N	Ae	Str	-	VAS (0-10), 1.5	WOMAC (total) (0-96), 1.5	6MWT (m), 1.5	-

[89]Sayers 2012	67 (7)	31 (7)	45 (56)	K	A	N	Fl/Sk	Str	-	WOMAC pain (0-20), 3	WOMAC fx (0-68), 3	Walking speed (s), 3	-
[90]Schilke 1996	66 (-)	- (-)	23 (74)	K	UClr	N	Str	UC	-	Osteoarthritis screening index pain, 2	Arthritis Impact Measurement Scales activity, 2	Strength, 2	-
[91]Sekir 2005	60 (9)	- (-)	22 (73)	K	A	N	Fl/Sk	UC	-	VAS (0-100) after inactivity, 1.5	NRS subjective functional rating (0-10), 1.5	Timed walk (s), 1.5	-
[92]Simão 2012	72 (6)	28 (-)	35 (80)	K	A, I	N	Str	UC	-	WOMAC pain (0-500), 3	WOMAC fx (0-1700), 3	6MWT (m), 3	-
[93]Singh 2011* (female, male)	57 (6)	28 (3)	200 (69)	K	UClr	N	Ae	MEx	-	VAS, 2	WOMAC fx, 2	Strength (isotonic), 2	-
[94]Skoffer 2016	70 (-)	31 (-)	59 (61)	K	I	Y	Str	UC	-	KOOS pain (0-100), 1	KOOS ADL (0-100), 1	6MWT (m), 1	KOOS QoL (0-100), 1
[95]Sung-Bum 2015	65 (3)	- (-)	14 (100)	K	A, I	N	Fl/Sk	UC	-	VAS, 2-mth	-	Strength (isokinetic), 2	-
[96]Swank 2011	63 (7)	34 (-)	71 (65)	K	UClr	Y	MEx	UC	-	VAS (after walk test) (1-10), 1.5, outlier	-	6MWT (m), 1.5	-
[97]Takacs 2017	67 (-)	29 (-)	40 (80)	K	I	N	Fl/Sk	UC	-	NRS (0-10), 2.5	WOMAC fx (0-68), 2.5	Composite peak lower limb strength, 2.5	-
[98]Teirlinck 2016	66 (-)	28 (-)	203 (59)	H	A	N	MEx	UC	-	NRS (0-10), 1.5	HOOS fx (0-100), 1.5	Timed up and go (s), 12	EQ-5D, 1.5

[99]Teixeira 2011	65 (9)	30 (6)	159 (65)	K	A, I	N	Fl/Sk	MEx	-	-	WOMAC fx - single item, 1.5	-	-
[100]Kuptniratsaikul 2002	68 (6)	- (-)	392 (78)	K	I	N	Str	UC	-	Pain score, 2	Functional incapacity score (0-20), 2	6MWT (m), 2	-
[101]Thorstensson 2005	56 (6)	30 (-)	61 (51)	K	I	N	MEx	UC	-	KOOS pain (0-100), 1.5	KOOS (ADL) (0-100), 1.5	One leg semi squatting, 1.5	SF-36 Mental health, 1.5
[102]Topp 2002	63 (11)	- (-)	102 (73)	K	A	N	Str	UC	-	WOMAC pain (0-20), 4	WOMAC fx (0-68), 4	Upstairs (s), 4	-
[103]Topp 2009	64 (7)	32 (6)	54 (69)	K	UClr	Y	MEx	UC	-	VAS (0-10) at 6 MWT, 1	-	6MWT (m), 1	-
[104]Tsauo 2008	62 (9)	27 (5)	54 (87)	K	A, I	N	Fl/Sk	MEx	-	WOMAC pain (0-500), 2	WOMAC fx (0-1700), 2	60m walking (s), 2	-
[105]Vaittianadane 2014	- (-)	- (-)	60 (-)	K	UClr	N	Fl/Sk	MEx	-	-	WOMAC (total), 1.5	Timed up and go (s), 1.5	-
[106]Van Baar 1998[†] [107]*Van Baar 2001*	68 (9)	- (-)	201 (78)	K, H	A	N	MEx	UC	-	VAS past week 0-100), 3	Influence of Rheumatic disease on general health and lifestyle disability (-28--7), insufficient data	Muscle strength (knee), 3	-
[108]Wallis 2017	68 (-)	34 (-)	46 (44)	K	I	N	Ae	UC	-	NRS (0-10), 3	WOMAC ADL(0-68), 3	40m walk test (m/s), 3	EQ5D (0-1), 3
[109]Wang 2007	66 (12)	- (-)	38 (84)	K, H	UClr	N	MEx	UC	-	VAS (0-100), 1.5	Multidimensional health	Strength knee extension, 1.5	-

										assessment questionnaire, 1.5			
[110]Wang 2011	68 (6)	26 (2)	78 (86)	K	UClr	N	MEx	UC	-	KOOS pain (0-100), 1.5	KOOS ADL (0-100), 1.5	6MWT (m), 1.5	KOOS QOL (0-100), 1.5
[111]Weidenhielm 1993	64 (5)	- (-)	39 (51)	K	UClr	Y	MEx	UC	-	Pain 10-grade scale (walking), 3	-	Max Walking speed (m/min), 3	-
[112]Weng 2009	64 (8)	- (-)	132 (80)	K	A	N	Fl/Sk	MEx	-	VAS after walking (0-10), 2	Lequesne index (1-26), 2	Peak torque, 2	-
[113]Wortley 2013	69 (6)	32 (6)	31 (71)	K	A, I	N	MB	Str	-	WOMAC pain, 2.5	WOMAC fx, 2.5	6 MWT (m), 2.5	-

ii) Characteristics of studies included for post-operative outcomes (Chapter 7 – *Exercise versus usual care: meta-analysis*)

Study	N (% female)	Age (SD)	BMI (SD)	Joint	Exercise	Follow-up duration	Outcomes			
							Pain	Function	Performance	QoL
Beaupre et al. 2004	131 (55.0)	67 (6.5)	31.5 (5.5)	Knee	Strength	12 months	WOMAC pain (0-100)	WOMAC fx (0-100)	Quads strength	SF-36 (mental health)
Brown 2012	32 (-)	-	36.8 (8.4)	Knee	Mixed	12 weeks	SF-36 pain	SF 36 physical fx		SF-36 (mental health)
D'Lima 1996	30 (46.7)	69.9 (5.9)	-	Knee	Mixed	48 weeks		HSS Knee rating (0-100)		
Evgeniadis 2008	53 (79.2)	68.4 (4.2)	34 (4.8)	Knee	Strength	14 weeks			Active range of motion	
Gstoettner 2011	38 (78.9)	69.7 (4.9)	27.8 (-)	Knee	Flex/ Skills	6 weeks	WOMAC pain	WOMAC fx	Walking speed (s)	
Oosting 2012	30 (80.0)	76.0 (6.3)	28.2 (4.9)	Hip	Mixed	6 weeks	NRS (0-10)	HOOS fx (0-100)	6MWT(m)	HOOS QoL (0-100)
Topp 2009	54 (68.5)	63.8 (6.8)	32.1 (5.9)	Knee	Mixed	4 months	VAS (0-10)		6MWT (m)	
Tungtrongjit 2012	60 (83.3)	64.5 (7.5)	24.8 (3.2)	Knee	Strength	6 months	VAS (0-10)	WOMAC fx (0-240)	Quads strength	
Weidenhielm 1993	39 (51.3)	63.5 (4.5)	-	Knee	Mixed	12 weeks	10-grade scale		Max walking speed (m/min)	

* Two sets of comparison were obtained

† Trials with multiple reporting available

6MWT= 6 minute walk test; ACR=American College of Rheumatology criteria; ADL= activity of daily living; Ae=Aerobic; BMI= Body mass index; fem= female; Fl/Sk= Flexibility and Skills; fx=function; H= Hip; HOOS= Hip disability and Osteoarthritis Outcome Score; I=Imaging criteria; Jt= joint; K= Knee; KOOS= Knee injury and Osteoarthritis Outcome Score; m=meter; MB= Mind-body; MEx= Mixed exercise; N=No; No.= sample size; NRS= Numeric rating score; QoL= Quality of life; s= seconds; Str= Strengthening; UC= usual care; Ucl= Unclear; VAS= visual analogue scale; WOMAC= Western Ontario & McMaster Universities Osteoarthritic Index; Y=Yes

Appendix 7b Summary of exercise groups and comparators

i) Characteristics of exercise groups and comparators in studies with non-operative outcomes (Chapter 5 - *Exercise versus usual care: meta-analysis*, Chapter 6 – *Relative efficacy of different exercises: network meta-analysis*)

[1]Abbott 2013

Group	G1	G2	G3	G4
Ex content	Mixed ex	Mixed ex	-	-
Non-Ex content	Usual care	Usual care, Manual therapy	Usual care	Usual care, Manual therapy
Land/water	Land	Land		
Home-/ Centre-based	Mixed	Mixed		
Individual/Group	Unclear	Unclear		
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)		
Min Ex days/wk	3	3		
Strengthening	Type: Hip OA: abd, ext, Lat rotation, knee ext Knee OA: ext, flexion, hip ext; Freq:3x/wk; Intensity:-; Rep:3sets x10 reps	Type: Hip OA: abd, ext, Lat rotation, knee ext Knee OA: ext, flexion, hip ext; Freq:3x/wk for 1 year; Intensity:-; Rep:3sets x10 reps		
Aerobic	Type: Cycle or walk; Freq: 3x/wk; Intensity:-; Duration: 10 min	Type: Cycle or walk; Freq: 3x/wk for 1 year; Intensity:- ; Duration: 10 min		
Skills	Type: standing weight-shifting exercises; standing balance on uneven surfaces; side-stepping, forward-backward and shuttle-walking drills; or stair walking; Freq: 3x/wk; Intensity:	Type: standing weight-shifting exercises; standing balance on uneven surfaces; side-stepping, forward-backward and shuttle-walking drills; or stair walking; Freq: 3x/wk; Intensity: 3sets x 2 mins; Duration:		

	3sets x 2 mins; Duration:	
Flexibility	Type: Hip: hip flexors; knee extensors; hip extensors; knee flexors; hip abductors and lateral rotators; ankle plantarflexors. Knee: knee flexors; knee extensors; ankle plantarflexors;; Freq: 60 sec; 3x/wk; Rep:	Type: Hip: hip flexors; knee extensors; hip extensors; knee flexors; hip abductors and lateral rotators; ankle plantarflexors. Knee: knee flexors; knee extensors; ankle plantarflexors;; Freq: 60 sec; 3x/wk; Rep:
Mind-body	-	-
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 9wk; Follow-ups: 9wk 26wk 52wk		

[2]Aglamis 2008

Group	**G1**	**G2**
Ex content	Mixed ex	-
Non-Ex content	-	Wait-list
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Individual	
Supervision (total no.)	Yes(36)	
Min Ex days/wk	3	
Strengthening	Type:- ; Freq: 3x/wk; Intensity:; Rep: start: 12 rep x 1 set; 12 rep x 3 sets by 3rd wk	
Aerobic	Type:- ; Freq: 3x/wk; Intensity: start: 50% heart rate reserve; 5% increment every 2 wks until 6th wk; Duration: 20 min	
Skills		
Flexibility	Type: static stretch of multiple lower limb muscles; Freq: 3x/wk; Rep: 20 seconds x 3 rep per muscle	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 12wk; Follow-ups: 6wk 12wk		

[4]An 2008

Group	G1	G2
Ex content	Mind-body	-
Non-Ex content	-	Usual care
Land/water	Land	
Home-/ Centre-based	Unclear	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	5	
Strengthening		
Aerobic		
Skills		
Flexibility		
Mind-body	Type: Baduanjin; Freq: 5 times/wk; Duration:30 mins each session	
MA design	Mind-body	
NMA design	Mind body-Usual care	
Intervention period: 8wk; Follow-ups: 8wk		

[5]Aoki 2009

Group	G1	G2
Ex content	Flexibility	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Home-based	
Individual/Group	Individual	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	7	
Strengthening		
Aerobic		
Skills		
Flexibility	Type: knee ROM; Freq:daily; Rep: > 10 rep x 30 seconds each day ; Duration: 5 mins	
Mind-body		
MA design	Flexibility	
NMA design	Flex/Skills-Usual care	
Intervention period: 80D; Follow-ups: 3mth		

[6]Arnold 2010

Group	G1	G2	G3
Ex content	Mixed ex	Mixed ex	
Non-Ex content		Education	Usual physical activity, Wait-list
Land/water	Water	Water	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(22)	Yes(22)	
Min Ex days/wk	2	2	
Strengthening	+	+	
Aerobic			
Skills	+	+	
Flexibility			
Mind-body			
MA design	Mixed ex		
NMA design	Mixed ex-Usual care		
Intervention period: 11wk; Follow-ups: 11wk			

Note: Mixed exercise for 45 min each session. Education (in group) was delivered once a wk (30min).

[7]Beaupre 2004

Group	**G1**	**G2**
Ex content	Strength	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: hamstring and quads strengthening; Freq:3x/wk for 4 wks; Intensity:3 sets x10 reps x 5 ex; Rep: unclear	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
Intervention period: 4wk; Follow-ups: pre-op (i.e. 6 wks after commencement of intervention) then 12wk 6mth 12mth post-op		

[8]Bennell 2010		
Group	**G1**	**G2**
Ex content	Strength	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Individual	
Supervision (total no.)	Yes(7)	
Min Ex days/wk	5	
Strengthening	Type: weight/elastic band hip abductors & add strengthening; Freq:5x/wk; Intensity:10RM; Rep:10 rep x3sets x 6 exercises	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 12wk; Follow-ups: 13wk		

[9]Bennell 2014

Group	G1	G2
Ex content	Strength	Skills
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Mixed	Mixed
Individual/Group	Individual	Individual
Supervision (total no.)	Yes(14)	Yes(14)
Min Ex days/wk	5	5
Strengthening	Type: 5 types of non Wt bearing quads strengthening; Freq:5x/wk; Intensity:5 out of 10 on modified Borg scale; Rep:2-3 sets x 10 reps x 5 exercises	
Aerobic		
Skills		Type: forward/ backward sliding, sideways ex, fx hip strengthening, fx knee strengthenin, steps up and down; balance; Freq: 5x/wk for 12 wks; Intensity: 3sets x 10 reps x 5 exercises; 2 sets x 5 reps x 1 exercise; Duration: -
Flexibility		
Mind-body		
MA design	-	
NMA design	FlexSkills-Strength	
Intervention period: 12wk; Follow-ups: 12wk		

[10]Bieler 2017

Group	G1	G2	G3
Ex content	Strength	Aerobic	Mixed ex
Non-Ex content			
Land/water	Land	Land	Unclear
Home-/ Centre-based	Mixed	Mixed	Home-based
Individual/Group	Both	Both	Unclear
Supervision (total no.)	Yes(32)	Yes(32)	Yes(Unclear)
Min Ex days/wk	3	3	
Strengthening	Type:- leg press, seated knee extension, and hip extension in the standing position leaned forward 45 degrees with trunk and pelvis resting against an abdominal platform support; Freq:3x/wk for 4 months; Intensity: Varies; Rep: vaires	Type:- Nordic walking; Freq:3x/wk for 4 months; Intensity:12-14 on Borg scale; Rep:vaires	Type: Chair stand, pelvic lift, isometric hip flexion in standing position, gluteus medius in side lying position, elastic bands; Freq: -; Intensity:-; Rep:-
Aerobic			
Skills			
Flexibility			Type: Hip ROM
Mind-body			
MA design	-		
NMA design	Aerobic-Mixed ex-Strength		
Intervention period: 4mth; Follow-ups: 2mth 4mth 12mth			

Note: Both strength and Nordic walking group given education on exercise adherence, counselling via phone

[11]Börjesson 1996

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Group	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: hamstring and quads; Freq:3x/52 for 5 wks and 2x/52 at home; Intensity: without wt initially then increase to 10 RM; Rep:2sets x10 reps x 4 ex	
Aerobic	Warming up on bicycle without resistance 10 mins	
Skills		
Flexibility	Type: knee ROM; Freq: 3x/52 for 5 wks and 2x/52; Rep: 2sets x10 reps x3 ex	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 5wk; Follow-ups: 12wk		

[12]Braghin 2017

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Unclear	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	2	
Strengthening	Type: SLR, isometric quads,; Freq:2x/wk for 8 wks; Intensity:30% 1 RM to 70% 1RM; Rep:Varies	
Aerobic	Type: cycle; Freq: 2x/wk for 8 wks; Intensity: 65-70% HR max 85-90% Hrmax; Duration: 20min	
Skills	Type: sit to stand, changing direction, walking on thin mattress, one leg support etc; Freq: 2x/wk for 8 wks; Intensity: varies; Duration:-	
Flexibility		
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 8wk; Follow-ups: 8wk		

[13]Bruce-Brand 2012

Group	G1	G2	G3
Ex content	Strength		
Non-Ex content		Usual care	Electrotherapeutic
Land/water	Land		
Home-/ Centre-based	Home-based		
Individual/Group	Individual		
Supervision (total no.)	Yes(12)		
Min Ex days/wk	3		
Strengthening	Type: Knee presses, leg raise, leg extension, squat, hamstring curls; Freq:3x/wk for 6 wks; Intensity:RPE > 14 (15-point Borg scale); Rep:3sets X 10rep x 6 exercises		
Aerobic			
Skills			
Flexibility			
Mind-body			
MA design	Strength		
NMA design	Strength-Usual care		
Intervention period: 6wk; Follow-ups: 6wk 12wk			

[14]Calatayud 2017

Group	G1	G2
Ex content	Strength	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(24)	
Min Ex days/wk	3	
Strengthening	Type: seated leg press, knee ext, leg curl, hip abd; step up; calf raise); Freq:3x/wk for 8 wks; Intensity:10RM; Rep:5 sets x 10 reps x 5 ex ; 2 sets x 20reps x 2 ex	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 8wk; Follow-ups: 1mth 3mth		

[15]Chaipinyo 2009

Group	G1	G2
Ex content	Strength	Skills
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Home-based	Home-based
Individual/Group	Individual	Individual
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	5	5
Strengthening	Type: knee extension in sitting; Freq:5x/wk; Intensity:; Rep:30 reps (each leg)	
Aerobic		
Skills		Type:- ; Freq: 5x/wk; Intensity: 30 rep stepping front/back, 30 rep stepping sideways (for both legs), 30 mini squats; Duration:
Flexibility		
Mind-body		
MA design		
NMA design	FlexSkills-Strength	
Intervention period: 4wk; Follow-ups: 4wk		

[16]Chen 2014

Group	G1	G2	G3	G4
Ex content	Strength	Strength	Strength	
Non-Ex content		Electrotherapeutic (ultrasound)	Electrotherapeutic (ESWT)	Usual care
Land/water	Land	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	3	
Strengthening	Type: Isokinetic; Freq:3x /wk for 8 wks; Intensity:60 % of peak torque; Rep:from 2nd wk onwards: 5 repsx 6 sets x 2 speeds	Type: Isokinetic; Freq:3x /wk for 8 wks; Intensity:60% of peak torque; Rep:from 2nd wk onwards: 5 repsx 6 sets x 2 speeds	Type: Isokinetic; Freq:3x /wk for 8 wks; Intensity:60% of peak torque; Rep:from 2nd wk onwards: 5 repsx 6 sets x 2 speeds	
Aerobic				
Skills				
Flexibility	Type: cycle; Freq: 3x/wk for 8 wks; Rep: 5 min of cycle	Type: cycle; Freq: 3x/wk for 8 wks; Rep: 5 min of cycle	Type: cycle; Freq: 3x/wk for 8 wks; Rep: 5 min of cycle	
Mind-body				
MA design	Strength			
NMA design	Strength-Usual care			
Intervention period: 8wk; Follow-ups: 8wk 6mth				

[17]Cheung 2016

Group	G1	G2	G3
Ex content	Mixed ex	Mind-body	
Non-Ex content			Education, Phone contact
Land/water	Land	Land	
Home-/ Centre-based	Mixed	Mixed	
Individual/Group	Both	Both	
Supervision (total no.)	Yes(8)	Yes(8)	
Min Ex days/wk	3	5	
Strengthening	Type: isotonic, isometric; Freq:30 min, 3x/wk; Intensity: Unclear; Rep: unclear		
Aerobic	"Type: unlcear; Freq: 5d/wk; Intensity: unclear; Duration: 15 min x1d, 15-30min x4d		
Skills			
Flexibility			
Mind-body		Type: Yoga; Freq: 5d/wk; Duration: 45min x 1d; 30min x 4d	
MA design	-		
NMA design	Mind-body –Mixed ex		
Intervention period: 8wk; Follow-ups: 4wk 8wk			

[18]Chopp-Hurley 2017

Group	G1	G2
Ex content	Strength	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(36)	
Min Ex days/wk	3	
Strengthening	Type: static strengthening: squats, lunges; Freq:3x/wk for 12 wks; Intensity: RPE 5-7/10; Rep: unclear	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 12wk; Follow-ups: 12wk		

[19]Christensen 2015

Group	G1	G2	G3
Ex content	Mixed ex		
Non-Ex content		Usual care	Diet
Land/water	Land		
Home-/ Centre-based	Mixed		
Individual/Group	Unclear		
Supervision (total no.)	Yes(52)		
Min Ex days/wk	3		
Strengthening	Type: ; Freq:3x/wk for 52 wks; Intensity:; Rep:1-2 types of ex; each exercise 2-3 setsx10-15 reps; both knees		
Aerobic			
Skills	Type: ; Freq: 3x/wk for 52 wks; Intensity: 1-2types x 3 categories; each ex 2-3 sets x 10-15 reps; Duration: -		
Flexibility			
Mind-body			
MA design	Mixed ex		
NMA design	Mixed ex–Usual care		
Intervention period: 52wk; Follow-ups: 52wk			

[21]Cochrane 2005

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Water	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(84)	
Min Ex days/wk	2	
Strengthening	Type: ; Freq:2x/ wk for 12 months; Intensity:46-60% maximum voluntary contraction; Rep:1-10 rep	
Aerobic	Type: ; Freq: 2x/ wk for 12 months; Intensity: 46-60% HR max; Duration: 20-30 min	
Skills	Type: ; Freq: 2x/ wk for 12 months; Intensity: ; Duration:	
Flexibility	Type: Key muscles; Freq: 2-3x/ wk for 12 months; Rep: 3-5 stretches per muscle group	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 12mth; Follow-ups: 6mth 12mth 18mth		

[22]Corjena 2014

Group	G1	G2
Ex content	Mind-body	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Both	
Supervision (total no.)	Yes(8)	
Min Ex days/wk	5	
Strengthening		
Aerobic		
Skills		
Flexibility		
Mind-body	Type: Yoga; Freq: 5x/wk; Duration: 60 min x1 session/wk; 30 min x 4 sessions/wk	
MA design	Mind-body	
NMA design	Mind-body-Usual care	
Intervention period: 8wk; Follow-ups: 4wk 8wk 20wk		

[23]D'Lima 1996

Group	G1	G2	G3
Ex content	Mixed ex	Aerobic	
Non-Ex content			Usual care
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Individual	Unclear	
Supervision (total no.)	Yes(18)	Yes(18)	
Min Ex days/wk	3	3	
Strengthening	Type: quads, gastroc, hamstring, hip flexor/ ext, hip abd, shoulder flex/ abd, triceps brachii; Freq:3x/wk for 6 wks; Intensity:unclear ; Rep:unclear. Total exercise session duration 45 mins		
Aerobic		Type: Cycle and arm ergometry, aquatic exercises (presumed to be aerobic as well); Freq: 3x/wk for 6 wks; Intensity: 40% HRR; Duration: 45 mins	
Skills			
Flexibility	Type: gastroc, hamstring, quads stretch; Freq: 3x/wk for 6 wks; Rep: unclear		
Mind-body			
MA design	Aerobic		
NMA design	Mixed £x-Aerobic-Usual care		
Intervention period: 6wk; Follow-ups: 1wk pre-op then 3wk 12wk 24wk 48wk postop			

[24]Duracoglu 2005		
Group	**G1**	**G2**
Ex content	Skills, Strength	Strength
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Centre-based	Centre-based
Individual/Group	Group	Group
Supervision (total no.)	Yes(24)	Yes(24)
Min Ex days/wk	3	3
Strengthening	Type: Isometric and isotonic of quads, hamstring hip abd and add; Freq:3x/wk for 8 wks; Intensity: started with isometric quads and hamstrings: 8 reps; progress to isotonic targetting for 10 reps of 10 RM;	Type: Isometric and isotonic of quads; Freq:3x/wk for 8 wks; Intensity: started with isometric quads and hamstrings: 8 reps; progress to isotonic targetting for 10 reps of 10 RM;
Aerobic		
Skills	Type: complex program; Freq: 3x/wk for 8 wks; Intensity: unclear; Duration: unclear	
Flexibility		
Mind-body		
MA design	-	
NMA design	Mixed ex-Strength	
Intervention period: 8wk; Follow-ups: 8wk		

[25]Ebnezar 2012

Group	G1	G2
Ex content	Mind-body	Mixed ex
Non-Ex content	Electrotherapeutic, Phone contact	Electrotherapeutic, Phone contact
Land/water	Land	Land
Home-/ Centre-based	Mixed	Mixed
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes(12)	Yes(12)
Min Ex days/wk	6	6
Strengthening		Type: Non specific- upper limb, back, thigh and calf; Freq:6x/wk for 3 months; Intensity:unlcear; Rep: at least 5 reps for different exercise; Duration: 15 min/session
Aerobic		
Skills		
Flexibility		Type: foot and ankle, knee, hip and waist, upper limb, neck; Freq: 6x/wk for 3 months; Rep: 10 reps each exercise
Mind-body	Type: Yoga; Freq: 6x/wk for 3 months; Duration: 40 min	
MA design	-	
NMA design	Mind body- Mixed ex	
Intervention period: 3mth; Follow-ups: 2wk 3mth		

[29]Espejo Antunez 2012

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water		
Home-/ Centre-based	Unclear	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	2	
Strengthening	Type: isotonic strengthening of lower limb, bridge; Freq:2x/wk for 4 wks; Intensity:; Rep:10 rep	
Aerobic		
Skills		
Flexibility	Type: stretches of lower limb in supine, seated and lateral decubitus position; Freq: -; Intensity:- ; Duration: 20s hold	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 4wk; Follow-ups: 4wk		

[30]Ettinger 1997

Group	G1	G2	G3
Ex content	Aerobic	Strength	
Non-Ex content	Home visits, Phone contact	Home visits	Education
Land/water	Land	Land	
Home-/ Centre-based	Mixed	Mixed	
Individual/Group	Both	Both	
Supervision (total no.)	Yes(40)	Yes(40)	
Min Ex days/wk	3	3	
Strengthening		Type: leg ext, leg curl, step up, heel raise, chest fly, upright row, military press, biceps curl, pelvic tilt; Freq:3x/wk; Intensity:; Rep:2x10 rep (minimum)x 9 exercises	
Aerobic	Type: walking; Freq: 3x/ wk; Intensity: 50-70% of Heart rate reserve; Duration: 40min		
Skills			
Flexibility			
Mind-body			
MA design	-		
NMA design	Aerobic-Strength		
Intervention period: 3mth; Follow-ups: 3mth 9mth 18mth			

[31]Evcik 2002

Group	G1	G2	G3
Ex content	Aerobic	Strength	
Non-Ex content		Phone contact	Usual physical activity
Land/water	Land	Land	
Home-/ Centre-based	Unclear	Home-based	
Individual/Group	Unclear	Individual	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	7	
Strengthening		Type: Isometric isotonic lower limb (quads); Freq: Twice ?daily; Intensity: Unclear; Rep:10 reps bd x 3 ex	
Aerobic	Type: Walking; Freq: 3x/wk; Intensity: unclear; Duration: 10-30 mins		
Skills			
Flexibility			
Mind-body			
MA design	Aerobic		
NMA design	Aerobic-Usual care		
Intervention period: 3mth; Follow-ups: 6mth			

[32]Evgeniadis 2008

Group	G1	G2	G3
Ex content	Strength (pre-op)	Strength (post-op)	
Non-Ex content			Usual care
Land/water	Land	Land	
Home-/ Centre-based	Home-based	Home-based	
Individual/Group	Individual	Individual	
Supervision (total no.)	Yes(9)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening	Type: upper back, shouler, bicpes and triceps, deltoid, rectus abdominis, femoral flexor; Freq:3x/52 for 3 wks pre-op; Intensity:modest fatigue after 8th rep; Rep:(1-3)set x (10-14) reps	Type: ant&post tibialis, ant&post femoral muscles, hip abductors; Freq:3x/52 for 8 wks; Intensity:mod fatigue after 8th rep; Rep:(1-3) set x (10-14) rep	
Aerobic			
Skills			
Flexibility			
Mind-body			
MA design	Strength		
NMA design	Strength-Usual care		
Intervention period: 3wk; Follow-ups: 2wk 6wk 10wk 14wk			

[33]Ferrara 2008

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Both	
Supervision (total no.)	Yes(20)	
Min Ex days/wk	5	
Strengthening	Type: hip abductor, femoral quadriceps; Freq:5x/wk; Intensity:Unclear; Rep:3-4 sets x 8-12 rep	
Aerobic	Type: Recumbent stationary bike; Freq: ; Intensity: low-moderate; Duration: 10-15 min	
Skills		
Flexibility	Type: hamstrings, hip adductor , hip flexor; Freq: 5x/wk; Rep: 3-4 sets X 8-12 rep	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 4wk; Follow-ups: 0wk 2wk 4wk 3mth		

[34]Fitzgerald 2011

Group	G1	G2
Ex content	Skills	Mixed ex
Non-Ex content	Phone contact	Phone contact
Land/water	Land	Unclear
Home-/ Centre-based	Mixed	Unclear
Individual/Group	Individual	Unclear
Supervision (total no.)	Yes(12)	Yes(Unclear)
Min Ex days/wk	2	
Strengthening	Type: quads set, SLR, hip extensions, seated knee ext, single leg press, hamstring curls, heel raises; Freq:2x/wk; Intensity:; Rep:	Type: quads set, SLR, hip extensions, seated knee ext, single leg press, hamstring curls, heel raises; Freq:2x/wk; Intensity:; Rep:
Aerobic	Type: walking; Freq: 3x/wk; Intensity: ; Duration: 30 min/day	Type: walking; Freq: 3x/ wk; Intensity: ; Duration: 30 mins/ day
Skills	Type: side stepping, braiding, front crossover steps, shuttle walking, single leg stand on different surfaces; Freq: 2x/wk; Intensity: ; Duration:	
Flexibility	Type: quads, hamstrng, calf stretches; knee ROM (Flexion and ext); Freq: 2x/wk; Rep:-	Type: quads, hamstrng, calf stretches; knee ROM (Flexion and ext); Freq: 2x/wk; Rep:-
Mind-body		
MA design	-	
NMA design	FlexSkills-Mixed ex	
Intervention period: 6mth; Follow-ups: 2mth 6mth 12mth		

[35]Fransen 2001

Group	G1	G2	G3
Ex content	Mixed ex (Individual)	Mixed ex (Group)	
Non-Ex content			Wait-list
Land/water	Land	Land	
Home-/ Centre-based	Mixed	Mixed	
Individual/Group	Individual	Group	
Supervision (total no.)	Yes(16)	Yes(16)	
Min Ex days/wk	2	2(gym)+3(home)	
Strengthening	Individualised	Type: Weight and non-weight bearing quadriceps strengthening; Intensity: 10-30Ib weight; Rep: 20-40 reps	
Aerobic	Individualised	Type: Bicycle; Intensity: 50-60% HR max; Duration 20 min	
Skills	Individualised		
Flexibility	Individualised	Type: Quads, hamstring, gastroc stretches; Freq:5x/wk; Intensity: 3x30s hold each muscle	
Mind-body			
§MA design	Mixed ex		
§NMA design	Mixed ex-Usual care		
Intervention period: 8wk; Follow-ups: 8wk			

Note: Study was actually 16 wks long but control group crossed over to intervention at end of 8 wks. Hence, for the purpose of this thesis, data beyond 8 wks was omitted. G1 and G2 were aggregated for comparison with Wait-list controls

[36]Fransen 2007

Group	G1	G2	G3
Ex content	Mixed ex	Mind-body	
Non-Ex content			Wait-list
Land/water	Water	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Group	Group	
Supervision (total no.)	Yes(24)	Yes(24)	
Min Ex days/wk	2	2	
Strengthening	Type: enter/exit pool x3-10, deep water cycling, scissors; Freq: 2x/wk for 12 wks; Intensity:-; Rep:-		
Aerobic	Type: walking/ running/ cycling		
Skills	Type: stand on 1 leg; Freq: 2x/wk for 12 wks; Intensity: -; Duration: -		
Flexibility	Type: touch knee with opposite hand, leg flex/abd/add; Freq: 2x/wk for 12 wks; Rep:-		
Mind-body		Type: Tai-chi; Freq: 2x/wk for 12 wks; Duration:-	
MA design	Mind-body		
NMA design	Mind-body-Mixed ex-Usual care		
Intervention period: 12wk; Follow-ups: 12wk 24wk			

Note: Detail program for Mixed exercise is as shown on next page

APPENDIX A: HYDROTHERAPY PROTOCOL (Water temperature 34°C).
Patients exercise with the water at approximately waist height. Patients are required to bring a bottle of water and the classes pause between blocks for a drink.

WALKING	Each direction 6 laps minimum
Forward, backward, sideways	Large steps, arms draw through the water, bent knees
Forward	With board (after 4 weeks)
Forward running	2 minutes
BAR WORK: One hand hold	Upright posture maintained throughout
Swinging outside leg forward/backward	Straight knees, picking up speed
Hip abduction 20 reps bilateral	Straight knees, picking up speed, big toe shows down
BAR WORK: Both hands on bar	
Hip abduction 20 reps; bilateral	Abducted leg flexed
Hip rotations 10 reps; bilateral	Flexed knee, small circle, forward, side, back, down
Tipping	Big toe touches to side, straight leg
Push ups	Knee/hip extensors activated, lift elbows out of water
Push ups	As before right leg, left knee forward
Walking up the wall on toes	Knees fully flexed
Knees open and close	Knees fully flexed
Both knees together to right and left	Knees fully flexed
Bend and straight knees	Rhythmic swinging forward and backward
Heel raise to squat	Emphasize quadriceps and gluteus activation
Side to side lunges	On the floor or feet under the bar
Squats 10 reps	Back to wall, touching wall with buttocks
Running backward	2 minutes
SEATED	
Lift legs × 20, right then left	Keep thighs on seat, increase speed with improvement
Lift legs alternatively × 40	Really pumping
DEEP WATER NOODLE	
Scissors	Legs swing forward and backward
Cycling	
Knees to chest	Leg flexion
Open/cross	Leg abduction/adduction
STEP	Activate correct posture
Step up then over, turn and repeat	Picking up speed with improved skill
Step up and down sideways	Holding on only if necessary
BAR WORK WITH RINGS/NOODLES	
Push noodle/large ring underwater with foot	10 times each, assist patients from outside of pool
Hook small ring over foot, extend knee	
FREE STANDING	Advanced: closed eyes, closed arms
Swinging one leg forward and backward	Standing on 1 leg, both knees straight
Circle ankle, knee, and hip and reverse	Standing on 1 leg, other knee is bent to 90°
Trunk rotations	The Hula
Twist	Knees bent
Alternate cross leg lifts slow change into	Touch knee with opposite hand
RUNNING	
On the spot	Advance through waist high water, gaiters
Sideways	1–2 minutes
Forward/backward/quick successions	After week 4
STAIRS	
Entry/exit pool ×3–10	Practice, increase repetition and speed as able

[37]French 2013			
Group	**G1**	**G2**	**G3**
Ex content	Mixed ex	Mixed ex	
Non-Ex content		Manual therapy	Wait-list
Land/water	Land	Land	
Home-/ Centre-based	Mixed	Mixed	
Individual/Group	Individual	Individual	
Supervision (total no.)	Yes(6)	Yes(6)	
Min Ex days/wk	5	5	
Strengthening	Type: lower limb muscles but primarily gluteals, core; Freq:Daily; Intensity:Unclear; Rep:Unclear	Type: lower limb muscles but primarily gluteals, core; Freq:Daily; Intensity:Unclear; Rep:Unclear	
Aerobic	Type: Swimming/cycling/walking; Freq: 5x/wk; Intensity: Unclear; Duration: 30 mins	Type: Cycling/walking/swimming; Freq: 5x/wk; Intensity: Unclear; Duration: 30 mins	
Skills			
Flexibility	Type: Hip ROM- all directions, but only2 types for each pt; Freq: Daily; Rep: 15 reps/day	Type: Hip ROM- all directions, but only2 types for each pt; Freq: Daily; Rep: 15 reps/day	
Mind-body			
MA design	Mixed ex		
NMA design	Mixed ex-Usual care		
Intervention period: 8wk; Follow-ups: 8wk			

[38]Ghroubi 2008

Group	G1	G2	G3	G4
Ex content	Mixed ex	Mixed ex		
Non-Ex content		Weight loss/ diet	Usual care	Weight loss/ diet
Land/water	Land	Land		
Home-/ Centre-based	Unclear	Unclear		
Individual/Group	Unclear	Unclear		
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)		
Min Ex days/wk	3	3		
Strengthening	Type: hamstring and quads; Freq:3x/wk for 8 wks; Intensity:60% of 1 RM; Rep:30 mins	Type: Hamstring and quads; Freq:3x/wk for 8 wks; Intensity:60% of 1 RM; Rep:30 min		
Aerobic	Type: treadmill; Freq: 3x/wk for 8 wks; Intensity: 50-60% HR max; Duration: 30 mins	Type: Treadmill; Freq: 3x/wk for 8 wks; Intensity: 50-60% HR max; Duration: 30 min		
Skills				
Flexibility				
Mind-body				
MA design	Mixed ex			
NMA design	Mixed ex-Usual care			
Intervention period: 8wk; Follow-ups: 8wk				

	[39]Gomiero 2017	
Group	**G1**	**G2**
Ex content	Strength	Skills
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Centre-based	Centre-based
Individual/Group	Group	Group
Supervision (total no.)	Yes(32)	Yes(16)
Min Ex days/wk	2	2
Strengthening	Type: quads and hamstring; Freq:2x/wk; Intensity: Unclear; Rep:3 sets x 10RM	
Aerobic		
Skills		Type: walking different direction, crossing steps, trampoline; Freq: 2x/wk; Intensity: Unclear; Duration: Unclear
Flexibility		
Mind-body		
MA design	-	
NMA design	FlexSkills-Strength	
Intervention period: 16wk; Follow-ups: 16wk		

[40]Gondhalekar 2013		
Group	**G1**	**G2**
Ex content	Skills	Strength
Non-Ex content	Electrotherapeutic	Electrotherapeutic
Land/water	Land	Land
Home-/ Centre-based	Unclear	Unclear
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes (Unclear)	Yes(Unclear)
Min Ex days/wk	7	
Strengthening	Type: quads, hip: flexion, abd, ext, knee bending; Freq: Twice daily for 3 wks; Intensity: Unclear; Rep:1-3 setsx10 reps bd progressively fr wk 1 - wk 3, for each exercise;	Type: quads, hip: flexion, abd, ext; Freq: Twice for 3 wks; Intensity:; Rep:1-3 setsx10 reps bd progressively fr wk 1 - wk 3 for each exercise
Aerobic		
Skills	Type: Retrowalking; Freq: 3 times daily for 3 wks; Intensity: ; Duration: 10 mins/session	
Flexibility		
Mind-body		
MA design		
NMA design	FlexSkills-Strength	
Intervention period: 3wk; Follow-ups: 2wk 3wk		

	[41]Gur 2002		
Group	**G1**	**G2**	**G3**
Ex content	Strength (Concentric)	Strength (Concentric+ eccentric)	
Non-Ex content			Usual physical activity
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening	Type: concentric; Freq:3x/wk for 8 wks; Intensity:-; Rep:12 rep for ext; 12 rep for flexion	Type: concentric and eccentric ; Freq:3x/wk for 8 wks; Intensity:-; Rep:6 con+6 ecc for ext; 6 con+6 ecc for flexion; at 6 different speeds	
Aerobic			
Skills			
Flexibility			
Mind-body			
§MA design	Strength		
§NMA design	Strength-Usual care		
Intervention period: 8wk; Follow-ups: 8wk			

[42]Hasegawa 2010		
Group	**G1**	**G2**
Ex content	Mixed ex	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Both	
Supervision (total no.)	Yes(12)	
Min Ex days/wk	3	
Strengthening	Type: hip flexion, hip ext, squats, heel rise, toe rise; Freq:3x/wk for 12 wks; Intensity:12 RPE borg scale; Rep:12 reps x 5 exercises	
Aerobic		
Skills	Type: different surfaces; Freq: 3x/wk for12 wks; Intensity: Unclear; Duration: 40mins	
Flexibility		
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 12wk; Follow-ups: 12wk		

[43]Henriksen 2014

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(36)	
Min Ex days/wk	3	
Strengthening	Type: hip abd, squats, step up,; Freq:3x/wk for 12 wks; Intensity:-; Rep:-	
Aerobic		
Skills	Type: core and hip stability; Freq: 3x/wk for 12 wks; Intensity:-; Duration:-	
Flexibility		
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 12wk; Follow-ups: 12wk		

[45]Hermann 2016

Group	G1	G2
Ex content	Strength	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(20)	
Min Ex days/wk	2	
Strengthening	Type: Hip ext, knee ext, knee flex, leg press; Freq:2x/wk for 10wks; Intensity:-; Rep:3 sets 8-10reps	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 10wk; Follow-ups: 10wk		

[46]Hinman 2007		
Group	**G1**	**G2**
Ex content	Mixed ex	
Non-Ex content		Usual physical activity
Land/water	Water	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(12)	
Min Ex days/wk	2	
Strengthening	Type: lower limb; Freq:2x/wk for 6 wks; Intensity: variable; Rep: variable 2 x 10	
Aerobic		
Skills	Type: ; Freq: 2x/wk for 6 wks; Intensity: ; Duration: Unclear, combination exercise	
Flexibility		
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 6wk; Follow-ups: 6wk 12wk		

[47]Hiyama 2012

Group	G1	G2
Ex content	Aerobic	Mixed ex
Non-Ex content		
Land/water	Land	Unclear
Home-/ Centre-based	Home-based	Home-based
Individual/Group	Unclear	Individual
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	7	7
Strengthening	Type: Unclear; Freq: daily; Intensity:Unclear; Rep:Unclear	Type: Unclear; Freq: daily for 4 wks; Intensity: Unclear; Rep: Unclear
Aerobic	Type: walking; Freq: additional 3000 steps daily; Intensity: Unclear; Duration: Unclear	
Skills		
Flexibility	Type: Unclear; Freq: daily; Rep: Unclear	Type: Unclear; Freq: daily; Rep: Unclear
Mind-body		
MA design	-	
NMA design	Aerobic-Mixed ex	
Intervention period: 6wk; Follow-ups: 6wk 12wk		

[48]Hoogeboom 2010

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Unclear	
Supervision (total no.)	Yes(6)	
Min Ex days/wk	2	
Strengthening	Type: leg press; Freq:2x/wk for 3-6 wks; Intensity:13-14 Borg scale; Rep:10-20 rep	
Aerobic	Type: Bicycle; Freq: 2x/wk for 3-6 wks; Intensity: 13-14 Borg scale; Duration: 20-30 min	
Skills	Type:-; Freq: 2x/wk for 3-6 wks; Intensity: unclear; Duration: Unclear	
Flexibility		
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 4wk; Follow-ups: 4wk		

[49]Huang 2003

Group	G1	G2	G3	G4
Ex content	Mixed ex (isokinetic)	Mixed ex (Isotonic)	Mixed ex (Isometric)	
Non-Ex content				Usual care
Land/water	Land	Land	Land	
Home-/ Centre-based	Unclear	Unclear	Unclear	
Individual/Group	Unclear	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	3	
Strengthening	Type: Isokinetic machine; Freq:3x /wk for 8/52; Intensity:Initial: 60% of peak torque; Rep:5 reps x 6 sets x 2 speeds in each session from 2nd wk onwards	Type: isokentic machine; Freq:3x/wk for 8/52; Intensity:max velocity; Rep:5 reps x 6 sets	Type: Isokinetic machine; Freq:3x/wk for 8/52; Intensity:; Rep:5 reps x 6 sets	
Aerobic				
Skills				
Flexibility	Type: Passive ROM on cycle; Freq: 3x/wk for 8/52, 5 min; Rep: 5 min (100 rotations)	Type: Passive ROM on cycle; Freq: 3x/wk for 8/52, 5 min; Rep: 5 min (100 rotations)	Type: Passive ROM on cycle; Freq: 3x/wk for 8/52, 5 min; Rep: 5 min (100 rotations)	
Mind-body				
§MA design	Mixed ex			
§NMA design	Mixed ex-Usual care			
Intervention period: 8wk; Follow-ups: 8wk 52wk				

[50]Huang 2005

Group	G1	G2	G3	G4
Ex content	Strength	Strength	Strength	
Non-Ex content		Electrotherapeutic	Electrotherapeutic, Pharmacotherapy	Usual care
Land/water	Land	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	3	
Strengthening	Type: Isokinetic; Freq:3x/wk for 8 wks; Intensity:60-80% mean peak torque; Rep:1-5 sets x5 reps for 5 sessions, then 6 sets x5 rep; each flexor & extensor; 30deg/sec & 120deg/sec	Type: Isokinetic; Freq:3x/wk for 8 wks; Intensity:60-80% mean peak torque; Rep:1-5 sets x5 reps for 5 sessions, then 6 sets x5 rep; each flexor & extensor;	Type: Isokinetic; Freq:3x/wk for 8 wks; Intensity:60-80% mean peak torque; Rep:1-5 sets x5 reps for 5 sessions, then 6 sets x5 rep; each flexor & extensor;	
Aerobic	Type: cycling at home; Freq: unclear; Intensity: unclear; Duration: 15 min	Type: cycling at home; Freq: Unclear; Intensity: Unclear; Duration: 15 min	Type: cycling at home; Freq: Unclear; Intensity: Unclear; Duration: 15 min	
Skills				
Flexibility				
Mind-body				
MA design	Strength			
NMA design	Strength-Usual care			
Intervention period: 8wk; Follow-ups: 8wk 52wk				

[51]Huang 2017		
Group	**G1**	**G2**
Ex content	Strength	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Home-based	
Individual/Group	Individual	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk		
Strengthening	Type: SLR, Hip abd, hip add; Freq:unclear; Intensity:; Rep:2 exercises x2 setsx10repxbd 1 exercise x2sets x20repxbd	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 3mth; Follow-ups: 1mth 3mth		

[52]Hunt 2013		
Group	**G1**	**G2**
Ex content	Strength	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Unclear	
Supervision (total no.)	Yes(5)	
Min Ex days/wk	4	
Strengthening	Type:-; Freq:4 x/wk, for 10 wks; Intensity: Unclear; Rep:3 sets x10 rep	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 10wk; Follow-ups: 10wk		

[53]Ikuta 2015

Group	G1	G2
Ex content	Mixed ex	Skills
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Unclear	Unclear
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	7	7
Strengthening	Type: hip abductors, quads and hamstring; Freq:daily for 4 wks; Intensity:Unclear; Rep:Unclear	
Aerobic		
Skills		Type: knee rotation exercise; Freq: daily for 4 wks; Intensity: ; Duration: 10 min
Flexibility	Type: hip abductors; Freq: daily for 4 wks; Rep: Unclear	
Mind-body		
MA design		
NMA design	FlexSkills-Mixed ex	
Intervention period: 4wk; Follow-ups: 4wk		

[54]Jan 2008

Group	G1	G2	G3
Ex content	Strength (High intensity)	Strength (Low intensity)	
Non-Ex content			Usual care
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Individual	Individual	
Supervision (total no.)	Yes(24)	Yes(24)	
Min Ex days/wk	3	3	
Strengthening	Type: Leg press; Freq:3x/wk for 8 wks; Intensity: started at 60% 1RM; Rep:3 sets x 8 reps	Type: Leg press; Freq:3x/wk for 8 wks; Intensity: started at 10% of 1RM; Rep:10sets x 15 reps	
Aerobic			
Skills			
Flexibility			
Mind-body			
§MA design	Strength		
§NMA design	Strength-Usual care		
Intervention period: 8wk; Follow-ups: 8wk			

	[55]Jan 2009		
Group	**G1**	**G2**	**G3**
Ex content	Strength (Weight bearing)	Strength (Non-weight bearing)	
Non-Ex content			Wait-list
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening	Type: leg press; Freq:3x/wk for 8 wk; Intensity: started with 50% 1 RM; Rep:4 sets x 6 reps	Type: active knee ext; Freq:3x/wk for 8 wks; Intensity: started with 50% 1RM; Rep:4sets x 6 reps	
Aerobic			
Skills			
Flexibility			
Mind-body			
§MA design	Strength		
§NMA design	Strength-Usual care		
Intervention period: 8wk; Follow-ups: 8wk			

	[56]Jorge 2015	
Group	**G1**	**G2**
Ex content	Strength	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(24)	
Min Ex days/wk	2	
Strengthening	Type: Knee flex/ext, Hip abd/add; Freq:2x/wk for 12 wks; Intensity:50-70% of 1RM; Rep:2sets x 8 reps x 4 exercises	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 12wk; Follow-ups: 6wk 12wk		

[57]Juhakoski 2011		
Group	**G1**	**G2**
Ex content	Mixed ex	
Non-Ex content	Usual care	Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Group	
Supervision (total no.)	Yes(16)	
Min Ex days/wk	3	
Strengthening	Type: Unclear.; Freq: once a wk for 3 months then 3x/wk for 21 months; Intensity: unclear; Rep: Unclear	
Aerobic		
Skills		
Flexibility	Type: Unclear; Freq: once a wk for 3 months then 3x/wk for 21 months?; Rep: Unclear	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 3mth; Follow-ups: 3mth 6mth 12mth 18mth 24mth		

[58]Koli 2015

Group	G1	G2
Ex content	Aerobic	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(144)	
Min Ex days/wk	3	
Strengthening		
Aerobic	Type: step aerobic; Freq:3x/wk for 1 year; Intensity: 5-20cm of fence height, height of benches 10-20cm ; Duration: 55 mins	
Skills		
Flexibility		
Mind-body		
MA design	Aerobic	
NMA design	Aerobic-Usual care	
Intervention period: 12mth; Follow-ups: 12mth		

[59]Krasilshchikov 2011

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: quads and hamstring strengthening; Freq:3x/wk for 8 wks; Intensity: Unclear; Rep:2sets x 2-3reps x 5 ex	
Aerobic	Type: Walking; Freq: 3x/wk for 8 wks; Intensity: 50-75% HR max; Duration: 15 min	
Skills		
Flexibility		
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 8wk; Follow-ups: 8wk		

[60]Krauss 2014

Group	G1	G2	G3	G4
Ex content	Mixed ex			
Non-Ex content		Usual care	Sham (Sham ultrasound)	Electrotherapeutic (Ultrasound)
Land/water	Land			
Home-/ Centre-based	Mixed			
Individual/Group	Both			
Supervision (total no.)	Yes(10)			
Min Ex days/wk	3			
Strengthening	Type: knee and hip flex/ ext/ add/abd; Freq:3x/wk for 12 wks; Intensity:30-40% max strength; Rep:1-3 sets x 10-30 rep			
Aerobic				
Skills	Type: Postural control; Freq: 3x/wk for 12 wks; Intensity: Unclear; Duration: Unclear			
Flexibility	Type: flexibility of spine, pelvis and hip, knee; Freq: 3x/wk for 12 wks; Rep: Unclear			
Mind-body				
MA design	Mixed ex			
NMA design	Mixed ex-Usual care			
Intervention period: 12wk; Follow-ups: 12wk				

[62]Kreindler 1989

Group	G1	G2	G3	G4
Ex content	Strength (Protocol1)	Strength (Protocol2)	Strength (Protocol3)	
Non-Ex content				Usual physical activity
Land/water	Land	Land	Land	Unclear
Home-/ Centre-based	Mixed	Mixed	Mixed	
Individual/Group	Unclear	Unclear	Unclear	
Supervision (total no.)	Yes(18)	Yes(18)	Yes(18)	Yes(Unclear)
Min Ex days/wk	3	3	3	
Strengthening	Type: Quads and hamstring strengthening ; Freq:3x/wk for 6 wks; Intensity: Unclear; Rep: Unclear	Type: Kinetron strengthening; Freq:3x/wk for 6 wks; Intensity:100 -150 psi , 25-150 steps; Rep:25-150 steps	Type: Cybex; Freq:3x/wk for 6 wks; Intensity:60 , 120, 150, 180, 210, 240, 270, 300 deg/sec; Rep:10-35 reps x 4-8 speeds	
Aerobic				
Skills				
Flexibility				
Mind-body				
§MA design	Strength			
§NMA design	Strength-Usual care			
Intervention period: 6wk; Follow-ups: 6wk 12wk				

[63]Kumar 2013

Group	G1	G2
Ex content	Skills	Strength
Non-Ex content	Electrotherapeutic	Electrotherapeutic
Land/water	Land	Land
Home-/ Centre-based	Centre-based	Centre-based
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	3	3
Strengthening	Type: Knee and hip strengthening; Freq:3x/wk for 4 wks; Intensity: Unclear; Rep:3 sets x 10 rep each ex	Type: Knee and hip strengthening; Freq:3x/wk for 4 wks; Intensity:-; Rep:3 sets x 10 reps each exercise
Aerobic		
Skills	Type: 11 exercises; Freq: 3x/wk for 4 wks; Intensity:- ; Duration:-	
Flexibility		
Mind-body		
MA design	-	
NMA design	FlexSkills-Strength	
Intervention period: 4wk; Follow-ups: 4wk		

[64]Lee 2008

Group	G1	G2
Ex content	Mind-body	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Unclear	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	2	
Strengthening		
Aerobic		
Skills		
Flexibility		
Mind-body	Type: Tai-chi Sun style; Freq: 2x/wk; Duration: 60 mins	
MA design	Mind-body	
NMA design	Mind-body-Usual care	
Intervention period: 12wk; Follow-ups: 12wk		

	[65]Lee 2009	
Group	**G1**	**G2**
Ex content	Mind-body	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Unclear	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	2	
Strengthening		
Aerobic		
Skills		
Flexibility		
Mind-body	Type: Tai-chi; Freq: 2x/wk for 8 wks; Duration: 1 hour	
MA design	Mind-body	
NMA design	Mind-body-Usual care	
Intervention period: 8wk; Follow-ups: 8wk		

[66]Lim 2008

Group	G1	G2	G3	G4
Ex content	Strength (neutral knee alignment)	Strength (malaligned knee)		
Non-Ex content			Usual care (neutral knee alignment)	Usual care (malaligned knee)
Land/water	Land	Land		
Home-/ Centre-based	Mixed	Mixed		
Individual/Group	Unclear	Unclear		
Supervision (total no.)	Yes(7)	Yes(7)		
Min Ex days/wk	5	5		
Strengthening	Type: Variations of SLR; Freq:5x/wk for 12 wks; Intensity: unclear; Rep:10 reps x 2-3 sets x 5 exercises	Type: variations of SLR; Freq:5x/wk for 12 wks; Intensity: unclear; Rep:10 reps x 2-3 sets x 5 exercises		
Aerobic				
Skills				
Flexibility				
Mind-body				
§ **MA design**	Strength			
§ **NMA design**	Strength-Usual care			
Intervention period: 12wk; Follow-ups: 12wk				

[67]Lin 2007

Group	G1	G2	G3
Ex content	Strength	Skills	
Non-Ex content			Education
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening	Type: supine knee extension; Freq:3x/wk for 8 wks; Intensity:10-25% of body weight; Rep:10 sets x 10 reps x bilateral		
Aerobic			
Skills		Type: seated facilitated knee proprioceptive ex with apparatus/game; Freq: 3x/wk for 8 wks; Intensity:- ; Duration: 20 mins x bilateral	
Flexibility			
Mind-body			
MA design	-		
NMA design	FlexSkills-Strength		
Intervention period: 8wk; Follow-ups: 8wk			

[68]Lin 2009

Group	G1	G2	G3
Ex content	Skills	Strength	
Non-Ex content			Usual care
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening		Type: Knee extension, non weight bearning; Freq:3x/wk for 8 wks; Intensity:50-7-% 1 RM; Rep:4sets x 6 reps x 2 sides	
Aerobic			
Skills	Type: computer game; Freq: 3x/wk for 8 wks; Intensity: ; Duration: 20 mins x 2 sides		
Flexibility			
Mind-body			
MA design	FlexSkills		
NMA design	FlexSkills-Strength-Usual care		
Intervention period: 8wk; Follow-ups: 8wk			

[69]Lund 2008			
Group	**G1**	**G2**	**G3**
Ex content	Mixed ex	Mixed ex	
Non-Ex content			Usual care
Land/water	Land	Water	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(16)	Yes(16)	
Min Ex days/wk	2	2	
Strengthening	Type: leg press, steps, hip extension/ abduction, chair sit/stand; Freq:2x/wk for 8 wks; Intensity:Not definitive; Rep:10min	Type: leg press, steps, hip ext/ abd, ±body/water resistance; Freq:2x/wk for 8 wks; Intensity:Not definitive; Rep:10min	
Aerobic	Type: ?circuit training; Freq: 2x/wk for 8 wks; Intensity: Unclear; Duration: 10min	Type: aquatic running with belt; Freq: 2x/wk for 8 wks; Intensity: Unclear; Duration: 10min	
Skills	Type: Trampoline, balance board, balance cushion; Freq: 2x/wk for 8 wks; Intensity: ; Duration: 10min	Type: Staying erect in deep part of pool with aqua belt, balance cushion; Freq: 2x/wk for 8 wks; Intensity: ; Duration: 10 min	
Flexibility	Type: Lower limb (triceps surae, quads, hamstring, iliopsoas; Freq: 2x/wk for 8 wks; Rep: 5 min	Type: Lower limb (triceps surae, quads, hamstring, iliopsoas; Freq: 2x/wk for 8 wks; Rep: 5 min	
Mind-body			
§ **MA design**	Mixed Ex		
§ **NMA design**	Mixed Ex-Usual care		
Intervention period: 8wk; Follow-ups: 8wk 20wk			

[70]Messier 1997

Group	G1	G2	G3
Ex content	Aerobic	Strength	
Non-Ex content			Attention control
Land/water	Land	Land	Unclear
Home-/ Centre-based	Mixed	Mixed	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening		Type: Upper and lower body ex; Freq:3x/wk for 18 months; Intensity: Unclear; Rep:2 setsx10-12 repx 9 exercises	
Aerobic	Type: walking; Freq: 3x/wk for 18 wks; Intensity: 50-85% HRR; Duration: 40min		
Skills			
Flexibility			
Mind-body			
MA design	-		
NMA design	Aerobic-Strength		
Intervention period: 18mth; Follow-ups: 3mth 9mth 18mth			

[71]Moghadam 2017

Group	G1	G2
Ex content	Aerobic	
Non-Ex content		Usual physical activity
Land/water	Unclear	
Home-/ Centre-based	Unclear	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening		
Aerobic	Type: ; Freq: 3/wk; Intensity: Unclear; Duration: Unclear	
Skills		
Flexibility		
Mind-body		
MA design	Aerobic	
NMA design	Aerobic-Usual care	
Intervention period: 8wk; Follow-ups: 8wk		

[72]Munukka 2016

Group	G1	G2
Ex content	Strength	
Non-Ex content		Usual physical activity
Land/water	Water	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(48)	
Min Ex days/wk	3	
Strengthening	Type: Knee ext/flex; hip flex/ ext; Hipabd/add; kickback; Freq:3x/wk for 16 wks; Intensity:RPE 12-17 (borg 6-20); Rep:3 sets	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 16wk; Follow-ups: 16wk 16mth		

[74]Oida 2008

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Both	
Supervision (total no.)	Yes(8)	
Min Ex days/wk	7	
Strengthening	Type: -; Freq:1x/wk visit for 1 mth then fortnightly visit for 2 mths. Daily home ex for 3 months; Intensity:-; Rep:-	
Aerobic		
Skills	Type:- ; Freq: 1x/wk visit for 1 mth then fortnightly visit for 2 mths. Daily home ex for 3 months; Intensity: ; Duration:	
Flexibility	Type:- ; Freq: 1x/wk visit for 1 mth then fortnightly visit for 2 mths. Daily home ex for 3 months; Rep:-	
Mind-body		
MA design	Mixed Ex	
NMA design	Mixed Ex-Usual care	
Intervention period: 3mth; Follow-ups: 3mth		

[75]Oosting 2012

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content	Usual care	Usual care
Land/water	Land	
Home-/ Centre-based	Home-based	
Individual/Group	Individual	
Supervision (total no.)	Yes(10)	
Min Ex days/wk	6	
Strengthening		
Aerobic	Type: Walking; Freq: Daily; Intensity: 55-75% HR max; Duration: 30mins	
Skills	Type: unclear; Freq: 2x/wk for 5 wks, supervised. Additional 4 days a wk on their own; Intensity: unclear; Duration: 30min	
Flexibility		
Mind-body		
MA design	Mixed Ex	
NMA design	Mixed ex-Usual care	
Intervention period: 5wk; Follow-ups:6wk		

[76]O'Reilly 1999

Group	G1	G2
Ex content	Strength	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Home-based	
Individual/Group	Individual	
Supervision (total no.)	Yes(4)	
Min Ex days/wk	7	
Strengthening	Type: Quads and hamstring strength, steps; Freq: daily for 6 months; Intensity: Unclear; Rep:20 reps x Bilateralx5 ex	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 6mth; Follow-ups: 6mth		

[77]Petrella 2000

Group	G1	G2
Ex content	Mixed ex	Flexibility
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Home-based	Home-based
Individual/Group	Individual	Individual
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	3	
Strengthening	Type: SLR, Wal slide, resistance band for quads; Freq:3 x/wk for 8 wks; Intensity:Not standard; Rep:2 reps of each ex per session	
Aerobic		
Skills		
Flexibility	Type: knee flexion and extension; Freq: 3 x/wk for 8 wks; Rep: 2 reps each session	Type: knee flexion and extension; Freq: Unclear; Rep: Unclear
Mind-body		
MA design	-	
NMA design	FlexSkills-Mixed ex	
Intervention period: 8wk; Follow-ups: 8mth		

[78]Rapp 2009			
Group	**G1**	**G2**	**G3**
Ex content	Strength		
Non-Ex content		Usual care	Electrotherapeutic
Land/water	Land		
Home-/ Centre-based	Unclear		
Individual/Group	Group		
Supervision (total no.)	Yes(16)		
Min Ex days/wk	2		
Strengthening	Type: Leg press, knee ext, knee flexion; Freq:2x/wk for 8 wks; Intensity:20 RM; Rep:3 sets x 20reps x 3 exercises		
Aerobic			
Skills			
Flexibility			
Mind-body			
MA design	Strength		
NMA design	Strength-Usual care		
Intervention period: 8wk; Follow-ups: 8wk			

	[79]Rathi 2014	
Group	**G1**	**G2**
Ex content	Aerobic	Mixed ex
Non-Ex content	Electrotherapeutic	Electrotherapeutic
Land/water	Land	Land
Home-/ Centre-based	Unclear	Unclear
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	3	3
Strengthening	Type: SLR,static quads; Freq:3x/wk for 2 wks; Intensity:Unclear; Rep:Unclear	Type: SLR,static quads; Freq:3x/wk for 2 wks; Intensity:Unclear; Rep:Unclear
Aerobic	Type: wallking- retro; Freq: 3x/wk for 2 wks; Intensity: Unclear; Duration: unclear	
Skills		
Flexibility	Type: Hamstring stretch; Freq: 3x/wk for 2 wks; Rep: Unclear	Type: Hamstring stretch; Freq: 3x/wk for 2 wks; Rep: Unclear
Mind-body		
MA design	-	
NMA design	Aerobic-Mixed ex	
Intervention period: 2wk; Follow-ups: 2wk		

[80]Rogers 2011		
Group	**G1**	**G2**
Ex content	Skills	Strength
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Centre-based	Centre-based
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	3	3
Strengthening		Type: ankle, knee hip strengthening; Freq:3x/wk for 8 wks; Intensity: unclear (theraband); Rep:10-15 reps for more than 10 lower limb muscles
Aerobic		
Skills	Type: different marches, walks, static and dynamic balance; Freq: 3x/wk for 8 wks; Intensity: variable; Duration: 30 min	
Flexibility		
Mind-body		
MA design	-	
NMA design	FlexSkills-Strength	
Intervention period: 8wk; Follow-ups: 2wk 4wk 6wk 8wk		

[81]Rogers 2012

Group	G1	G2	G3	G4
Ex content	Skills	Strength	Skills, Strength	
Non-Ex content	Usual care	Usual care	Usual care	Sham_Rx (inert lotion)
Land/water	Land	Land	Land	
Home-/ Centre-based	Unclear	Unclear	Unclear	
Individual/Group	Individual	Individual	Individual	
Supervision (total no.)	Yes(5)	Yes(5)	Yes(5)	
Min Ex days/wk	3	3	3	
Strengthening		Type: ankle, knee and hip muscles; Freq:3x/wk for 8 wks; Intensity:based on theraband; Rep:15 reps x 11 exercises	Type: ankle, knee and hip muscles; Freq:3x/wk for 8 wks; Intensity:According to theraband; Rep:15 reps x 5 exercises	
Aerobic				
Skills	Type: Walking, marching, balance; Freq: 3x/wk for 8 wks; Intensity: varialbe; Duration: 30-40 mins		Type: Walking, marching, balance; Freq: 3x/wk for 8 wks; Intensity: Variable; Duration: 30-40 mins combined ex duration	
Flexibility				
Mind-body				
MA design	-			
NMA design	FlexSkills-Mixed ex-Strength			
Intervention period: 8wk; Follow-ups: 4wk 8wk				

[82]Rogind 1998

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Group	
Supervision (total no.)	Yes(24)	
Min Ex days/wk	2	
Strengthening	Type: quads, hip add/abd, hamstring, back, abdominal; Freq:2x/wk for 3 months; 4x/wk at home; Intensity:70% of 1RM?; Rep:3 -10 reps depending on exercise	
Aerobic		
Skills	Type: balance and coordination; Freq: 2x/wk for 3 mths; 4x/wk at home; Intensity: unclear; Duration: unclear	
Flexibility	Type: mobility of lower back, hip, knee,ankle, shoulder, elbow; Freq: 2x/wk for 3 months; 4x/wk at home; Rep: unclear	
Mind-body		
MA design	Mixed Ex	
NMA design	Mixed ex-Usual care	
Intervention period: 3mth; Follow-ups: 3mth 12mth		

	[83]Rooij 2016	
Group	**G1**	**G2**
Ex content	Mixed ex	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Unclear	
Supervision (total no.)	Yes(40)	
Min Ex days/wk	7	
Strengthening	Type: SLR, squats, lunges and steps; Freq:2x/wk; Intensity:60-80 % of 1RM; Rep:the selected resistance should permit the completion of 2-4 sets of 8-12 repetitions, or the number needed to induce muscle fatigue but not exhaustion), rest intervals of 2-3 min between each set of reps	
Aerobic	Type: cycle, rowing, stepping; Freq: 2x/wk; Intensity: 50-80% of VO2max/HRR/HRmax/ maximal workload (moderate intensity) 30-<40% or VO2max/HRR/HRmax/maximal workload (light intensity) is appropriate for individuals with arthritis who are deconditioned; Duration: Start with short bouts of 10 min (or less if needed), according individual's pain levels	
Skills		
Flexibility	Type: Quads, hamstring, iliopsoas and calf muscles stretches; Freq: 2x/wk; Rep: 2-4 repetitions, 2 or three times per wk. Hold a static stretch 10-30 seconds	
Mind-body		
MA design	Mixed Ex	
NMA design	Mixed ex-Usual care	
Intervention period: 20wk; Follow-ups: 10wk 20wk 32wk		

[84]Rosedale 2014			
Group	**G1**	**G2**	**G3**
Ex content	Mixed ex	Flexibility	
Non-Ex content			Wait-list
Land/water	Land	Land	
Home-/ Centre-based	Mixed	Mixed	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(4)	Yes(4)	
Min Ex days/wk	3	3	
Strengthening	Type: quads strengthening: sit to stand, wall slide, step up/down; Freq:3-4x/wk for 12 wk; 1-2x/day; Intensity:unclear; Rep:3setsx 10 rep x 3 exercises		
Aerobic	Type: walking, swimming, bike, etc; Freq: 3-5x/wk for 12 wks; Intensity: unclear; Duration: variable		
Skills			
Flexibility	Type: knee ROM; Freq: 2-3x per day for 12 wks; Rep: 1 set x 10 rep	Type: knee ROM; Freq: unclear but had to attend 4-6 physio sessions; Rep: 10 rep every 2-3 hours	
Mind-body			
MA design	Mixed ex		
NMA design	Mixed ex-Usual care		
Intervention period: 2wk; Follow-ups: 2wk 12wk			

	[85]Salacinski 2012	
Group	**G1**	**G2**
Ex content	Aerobic	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(24)	
Min Ex days/wk	2	
Strengthening		
Aerobic	Type: cycling; Freq: 2x/wk for 12 wks; Intensity: 70-75% HR max; Duration: 40 mins	
Skills		
Flexibility		
Mind-body		
MA design	Aerobic	
NMA design	Aerobic-Usual care	
Intervention period: 12wk; Follow-ups: 12wk		

	[86]Salli 2010		
Group	**G1**	**G2**	**G3**
Ex content	Strength (Isokinetic)	Strength (Isometric)	
Non-Ex content			Usual care
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(24)	Yes(24)	
Min Ex days/wk	3	3	
Strengthening	Type: isokinetic dynamometer (concentric-ecc); Freq:3x/wk for 8 wks; Intensity:70% of max voluntary contraction; Rep:10 rep x 5 speeds x 2 muscles (ext flexion)	Type: isometric (knee flex and ext); Freq:3x/wk for 8 wks; Intensity:70% Mx voluntary contraction; Rep:10 rep x 5 speed x 2 muscles (knee ext, flexion)	
Aerobic			
Skills			
Flexibility			
Mind-body			
§**MA design**	Strength		
§**NMA design**	Strength-Usual care		
Intervention period: 8wk; Follow-ups: 8wk 20wk			

[88]Samut 2015

Group	G1	G2	G3
Ex content	Strength	Aerobic	
Non-Ex content			Education
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Unclear	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening	Type:-; Freq:3x/wk for 6 wks; Intensity:60, 90, 120,180/sec; Rep:5 reps x 1-6setx 4 speeds x bilateral		
Aerobic		Type: treadmill; Freq: 3x/wk for 6 wks; Intensity: 65-75% HR max?; Duration: unclear	
Skills			
Flexibility			
Mind-body			
MA design	-		
NMA design	Aerobic-Strength		
Intervention period: 6wk; Follow-ups: 6wk			

[89]Sayers 2012			
Group	**G1**	**G2**	**G3**
Ex content	Strength (Low intensity)	Strength (High intensity)	Flexibility
Non-Ex content			
Land/water	Land	Land	Unclear
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	3	3	
Strengthening	Type: leg press and knee extensions; Freq:3x/wk for 12 wk; Intensity:40% 1RM; Rep:3 setsx12-14 reps	Type: leg press, knee extension; Freq:3x/wk for 12 wk; Intensity:80% 1RM; Rep:3 sets 8-10 reps	
Aerobic			
Skills			
Flexibility	Type: 12 stretches of back, trunk, lower extremity; Freq: 3x/wk for 12 wk; Rep: Unclear	Type: Unclear; Freq: 3x/wk for 12 wk; Rep: Unclear	Type: 12 back, trunk and lower extremity stretch; Freq: 3x/wk for 12 wk; Rep: Unclear
Mind-body			
MA design			
§ **NMA design**	FlexSkills-Strength		
Intervention period: 6wk; Follow-ups: 6wk			

[90]Schilke 1996

Group	G1	G2
Ex content	Strength	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: Isokinetic; Freq:3x/wk for 8 wks; Intensity:90 deg/sec; Rep:1-6 sets x 5 reps	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 8wk; Follow-ups: 8wk		

[91]Sekir 2005

Group	G1	G2
Ex content	Skills	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	1	
Strengthening		
Aerobic		
Skills	Type: 11 exercises; Freq: 1-3x/wk for 6 wks; Intensity: Unclear; Duration: Unclear	
Flexibility		
Mind-body		
MA design	FlexSkills	
NMA design	FlexSkills-Usual care	
Intervention period: 6wk; Follow-ups: 6wk		

[92]Simão 2012

Group	G1	G2	G3
Ex content	Strength	Strength	
Non-Ex content		Electrotherapeutic	Usual physical activity
Land/water	Land	Land	
Home-/ Centre-based	Unclear	Unclear	
Individual/Group	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening	Type: squat; Freq:3x/wk for 12 wks; Intensity:10 degree to 60 degree of knee flexion; Rep:20-40 sec x 6-8 sets	Type: squats; Freq:3x/wk for 12 wks; Intensity:10-60 degree of knee flexion; Rep:20-40 sec x6-8 reps	
Aerobic			
Skills			
Flexibility			
Mind-body			
MA design	Strength		
NMA design	Strength-Usual Care		
Intervention period: 12wk; Follow-ups: 12wk			

[93]Singh 2011

Group	G1	G2
Ex content	Aerobic	Mixed ex
Non-Ex content		
Land/water	Land	Unclear
Home-/ Centre-based	Unclear	Unclear
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	5	
Strengthening	Type: isometric quads/hamstring; Freq:Unclear; Intensity:Unclear; Rep:Unclear	Type: isometric quads/hamstring; Freq:Unclear; Intensity:Unclear; Rep:Unclear
Aerobic	Type: walking, cycling; Freq: 5x/wk for 8 wks; Intensity: 60% HR max; Duration: 20-30 min	
Skills		
Flexibility	Type: Unclear; Freq: Unclear; Rep: Unclear	Type: Unclear; Freq: Unclear; Rep: Unclear
Mind-body		
MA design	-	
NMA design	Aerobic-Mixed ex	
Intervention period: 2mth; Follow-ups: 1mth 2mth		

[94]Skoffer 2016

Group	G1	G2
Ex content	Strength	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(12)	
Min Ex days/wk	3	
Strengthening	Type: leg press, knee ext, knee flex, hip ext, hip abd, hip add; Freq:3x/wk for 4 wks; Intensity:12 RM progress to 8 RM; Rep:3 sets	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 8wk; Follow-ups: 4wk		

[95]Sung-Bum 2015

Group	G1	G2
Ex content	Skills	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening		
Aerobic		
Skills	Type: walking in place, half squat, straight lunge, side lunge, one-legged balance,; Freq: 3x/wk for 8 wks; Intensity: 3 sets x 10 reps; Duration: (20 mins/session)	
Flexibility		
Mind-body		
MA design	FlexSkills	
NMA design	FlexSkills-Usual care	
Intervention period: 8wk; Follow-ups: 8wk		

[96]Swank 2011

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Unclear	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: knee ext/flex, hip abd/add/flex/ext, foot ext/flex, Squat; Freq:3x/wk for 6 wks; Intensity: low resistance-moderate; Rep:1- 2 sets x 10 reps x 9 exercises	
Aerobic		
Skills	Type: steps up and sideways (increasing height); Freq: 3x/wk for 6 wks; Intensity: 8-20 steps each direction; Duration:-	
Flexibility		
Mind-body		
MA design	Mixed ex	
NMA design	Mixed Ex-Usual care	
Intervention period: 6wk; Follow-ups: 6wk		

[97]Takacs 2017

Group	G1	G2
Ex content	Skills	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Unclear	
Supervision (total no.)	Yes(6)	
Min Ex days/wk	4	
Strengthening		
Aerobic		
Skills	Type: Dynamic balance; Freq: 4x/wk for 10 wks; Intensity: 2-3 sets, 8-12 reps. NRS of difficulty>3; Duration: unclear	
Flexibility		
Mind-body		
MA design	Skills	
NMA design	FlexSkills-Usual care	
Intervention period: 10wk; Follow-ups: 10wk		

[98]Teirlinck 2016

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content	Usual care	Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Individual	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk		
Strengthening	Type: Hip muscles especially extensors and abductors; Individualised program	
Aerobic	Type:cycling, walking, swimming; Individualised program	
Skills		
Flexibility	Type: hip joint muscles ; Freq: Unclear; Rep: -	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex Usual care	
Intervention period: 3mth; Follow-ups: 6wk 3mth 6mth 9mth 12mth		

[99]Teixeira 2011

Group	G1	G2
Ex content	Mixed ex	Skills
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Centre-based	Centre-based
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes(12)	Yes(12)
Min Ex days/wk	2	2
Strengthening	Type: lower limb; Freq:-; Intensity:-; Rep: Unclear	
Aerobic	Type: Unclear ; Freq:- ; Intensity:- ; Duration: Unclear	
Skills		Type: side stepping, braiding, front cross-over steps, shuttle walking change in direction drills, foam surfaces, tilt boards; Freq: 2x/wk for 6 wks; Intensity: ; Duration:
Flexibility	Type: lower limb; Freq:- ; Rep:-	
Mind-body		
MA design	-	
NMA design	Mixed ex-FlexSkills	
Intervention period: 6wk; Follow-ups: 6wk		

[100]Thamalikitkul 2002

Group	G1	G2
Ex content	Strength	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(16)	
Min Ex days/wk	2	
Strengthening	Type: quads strengthening; Freq:2x/wk for 8 wks; Intensity:1 hour; Rep: Unclear	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
NMA design	Strength-Usual care	
Intervention period: 8wk; Follow-ups: 2mth 6mth 12mth		

[101]Thorstensson 2005

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Group	
Supervision (total no.)	Yes(12)	
Min Ex days/wk	7	
Strengthening	Type: core stability, hip strengthening all directions, quads; Freq: 2x/wk for 6 wks, supervised. Home daily; Intensity:60% of HR max; Rep:15 reps x 9 movements x bilateral	
Aerobic	Type: cycling; Freq: 2x/wk for 6 wks, supervised. Home daily; Intensity: 60% of HR max; Duration: 10 mins	
Skills	Type: Trampoline, step board; Freq: 2x/wk for 6 wks, supervised. Home daily; Intensity: unclear for trampoline, 15 reps for step board; Duration: 10 mins	
Flexibility	Type: triceps surae, quads, hamstrings iliopsoas; Freq: 2x/wk for 6 wks, supervised. Home daily; Rep: Unclear	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 6wk; Follow-ups: 6wk 6mth		

[102]Topp 2002

Group	G1	G2	G3
Ex content	Strength (Dynamic)	Strength (Isometric)	
Non-Ex content			Usual physical activity
Land/water	Land	Land	
Home-/ Centre-based	Mixed	Mixed	
Individual/Group	Both	Both	
Supervision (total no.)	Yes(16)	Yes(16)	
Min Ex days/wk	3	3	
Strengthening	Type: ankle, knee, hip; Freq:3x/wk for 16 wks; Intensity: RPE - mild to moderate fatigue; Rep:1-3 sets x8-12 reps x 6 exercises x bilateral	Type: ankle, knee, hip; Freq:3x/wk for 16 wks; Intensity: RPE mild to moderate fatigue; Rep:1-3 sets x 8-12 reps x bilateral	
Aerobic			
Skills			
Flexibility			
Mind-body			
§**MA design**	Strength		
§**NMA design**	Strength-Usual care		
Intervention period: 16wk; Follow-ups: 16wk			

[103]Topp 2009

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Unclear	
Supervision (total no.)	Yes(4)	
Min Ex days/wk	3	
Strengthening	Type: 9 exercises: hips, ankle and knee muscles; Freq:3x/wk for at least 4 wks; Intensity:Unclear; Rep:Unclear	
Aerobic		
Skills	Type: forward and lateral step; Freq: 3x/wk for at least 4 wks; Intensity: Unclear; Duration: Unclear	
Flexibility	Type: whole body; Freq: 3x/wk for at least 4 wks; Rep: Unclear	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 4wk; Follow-ups: 4wk 12wk		

	[104]Tsauo 2008	
Group	**G1**	**G2**
Ex content	Skills	Mixed ex
Non-Ex content	Electrotherapeutic	Electrotherapeutic
Land/water	Land	Land
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(24)	Yes(Unclear)
Min Ex days/wk	3	
Strengthening	Type: SLR, short arc extension; Freq: Unclear; Intensity: Unclear; Rep: Unclear	Type: SLR, Short arc extension; Freq: Unclear; Intensity: Unclear; Rep: Unclear
Aerobic	Type: Walking; Freq: Unclear; Intensity: Unclear; Duration: 30min	Type: Walking; Freq: Unclear; Intensity: Unclear; Duration: 30min
Skills	Type: rhythmic active motion, angle reposition, standing on air cushion; Freq: 3x/wk for 8 wks; Intensity: complex; Duration: Unclear	
Flexibility		
Mind-body		
MA design	-	
NMA design	FlexSkills-Mixed ex	
Intervention period: 8wk; Follow-ups: 8wk		

[105]Vaittianadane 2014

Group	G1	G2
Ex content	Skills	Mixed ex
Non-Ex content		
Land/water	Land	Land
Home-/ Centre-based	Unclear	Unclear
Individual/Group	Unclear	Unclear
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	5	5
Strengthening	Type: SLR, hip ext, knee ext,; Freq:5x/wk for 6 wks; Intensity: without weight and progress with 1 pound wt after completion of 30 reps; Rep:10-30 reps	Type: SLR, hip ext, knee ext,; Freq:5x/wk for 6 wks; Intensity: without weight and progress with 1 pound weight after completion of 30 reps; Rep:10-30 reps
Aerobic	Type: walking; Freq: 5x/wk for 6 wks; Intensity: self-paced; Duration: 1-15 mins	Type: walking; Freq: 5x/wk for 6 wks; Intensity: self-paced; Duration: 1-15 mins
Skills	Type: side stepping, braiding activities, crossover steps shuttle walk etc; Freq: 5x/wk for 6 wks; Intensity:- ; Duration:-	
Flexibility	Type: calf, hamstring and quads stretch; Freq: 5x/wk for 6 wks; Rep: 2 reps	Type: calf, hamstring and quads stretch; Freq: 5x/wk for 6 wks; Rep: 2 reps
Mind-body		
MA design	-	
NMA design	FlexSkills-Mixed ex	
Intervention period: 6wk; Follow-ups: 6wk		

[106]Van Baar 1998

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Individual	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk		
Strengthening	Freq:1-3x/wk depending on pain level; content and intensity were individualised	
Aerobic		
Skills	Freq:1-3x/wk depending on pain level; content and intensity were individualised	
Flexibility	Freq:1-3x/wk depending on pain level; content and intensity were individualised	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 12wk; Follow-ups: 12wk 24wk 36wk		

[108]Wallis 2017

Group	G1	G2
Ex content	Aerobic	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Both	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk		
Strengthening		
Aerobic	Type: Walking; Freq: 70 mins/wk in divided session; Intensity: RPE 3/10; Duration: Unclear	
Skills		
Flexibility		
Mind-body		
MA design	Aerobic	
NMA design	Aerobic-Usual care	
Intervention period: 12wk; Follow-ups: 12wk		

[109]Wang 2007		
Group	**G1**	**G2**
Ex content	Mixed ex	
Non-Ex content		Usual physical activity
Land/water	Water	
Home-/ Centre-based	Centre-based	
Individual/Group	Group	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: upper and lower body; Freq:3x/wk for 12 wk; Intensity: RPE (borg scale) 2-4; Rep:29 ex x 10-15 reps each	
Aerobic		
Skills		
Flexibility	Type: neck, trunk, shoulder, pelvic; Freq: 3x/wk for 12 wks; Rep: 24 ex x 10-15 reps each	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 12wk; Follow-ups: 6wk 12wk		

[110]Wang 2011

Group	G1	G2	G3
Ex content	Mixed ex	Mixed ex	
Non-Ex content			Usual care
Land/water	Water	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Group	Group	
Supervision (total no.)	Yes(36)	Yes(36)	
Min Ex days/wk	3	3	
Strengthening	Type: trunk, shoulders, arms, and legs; Freq:3x/wk for 12 wks; Intensity:; Rep:17 sests of lower limb, 12 sets of upper limb, each set 10-15 reps	Type:-; Freq:3x/wk for 12 wks; Intensity:-; Rep:20 sets of upper limb, 15 sets of lower limb; each set 10-15 reps	
Aerobic	Type: walking; Freq: 3x/wk for 12 wks; Intensity:- ; Duration: 10 mins	Type: walking; Freq: 3x/wk for 12 wks; Intensity:-; Duration: 10 mins	
Skills			
Flexibility	Type: trunk, shoulders, arms, and legs; Freq: 3x/wk for 12 wks; Rep: 24 sets x 10-15 reps	Type:- ; Freq: 3x/wk for 12 wks; Rep: 10 sets x10-15 reps	
Mind-body			
§**MA design**	Mixed ex		
§**NMA design**	Mixed ex-Usual care		
Intervention period: 12wk; Follow-ups: 6wk 12wk			

[111]Weidenhielm 1993

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Both	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: Unclear; Freq:3x/52 for 5 wks then daily at home; Intensity: Initially unloaded; Rep:20 reps each exercise	
Aerobic		
Skills		
Flexibility	Type: Unclear; Freq: 3x/52 for 5 wks then daily at home; Rep: Unclear	
Mind-body		
MA design	Mixed ex	
NMA design	Mixed ex-Usual care	
Intervention period: 5wk; Follow-ups: 12wk		

[112]Weng 2009

Group	G1	G2	G3	G4
Ex content	Strength, Flexibility (passive ROM)	Strength, Flexibility (static stretch + passiveROM)	Strength, Flexibility (PNF+ passive ROM)	Flexibility (passive ROM)
Non-Ex content	Electrotherapeutic (hotpack)	Electrotherapeutic (hotpack)	Electrotherapeutic (hotpack)	Electrotherapeutic (hotpack)
Land/water	Land	Land	Land	Land
Home-/ Centre-based	Centre-based	Centre-based	Centre-based	
Individual/Group	Unclear	Unclear	Unclear	
Supervision (total no.)	Yes(Unclear)	Yes(Unclear)	Yes(Unclear)	Yes(Unclear)
Min Ex days/wk	3	3	3	3
Strengthening	Type: Isokinetic; Freq:3x/wk for 8 wks; Intensity:60% of average torque; Rep:6 sets x 5 reps x 2 speeds	Type: Isokinetic; Freq:3x/wk for 8 wks; Intensity:60 % of average torque; Rep:6 sets x 5 reps x 2 speeds	Type: Isokinetic; Freq: 3x/wk for 8 wks; Intensity:60% of average torque; Rep:6 sets x 5 reps x 2 speeds	
Aerobic				
Skills				
Flexibility	Type: cycling; Freq: 3x/wk for 8 wks; Rep: 10 min cycling;	Type: cycling, Static stretch; Freq: 3x/wk for 8 wks; Rep: 10 mins cycling; Static stretch: 10 reps	Type: cycling, PNF stretches; Freq: 3x/wk; Rep: 10 min cycling, 10 reps of PNF	Type: cycling; Freq: 3x/wk for 8 wks; Rep: 10 min cycling;
Mind-body				
MA design	-			
§**NMA design**	FlexSkills-Mixed ex			
Intervention period: 8wk; Follow-ups: 8wk 12mth				

[113]Wortley 2013

Group	G1	G2	G3
Ex content	Strength	Mind-body	
Non-Ex content			Usual physical activity
Land/water	Land	Land	
Home-/ Centre-based	Unclear	Centre-based	
Individual/Group	Group	Group	
Supervision (total no.)	Yes(Unclear)	Yes(20)	
Min Ex days/wk	2	2	
Strengthening	Type: Lower limb: leg ext, hamstring curl, SLR, hip abd/add/flex, calf raise; Freq:2x/wk for 10 wk; Intensity:5-10 lb ankle weights; Rep:2-3 sets x 8-12 reps		
Aerobic			
Skills			
Flexibility			
Mind-body		Type: Tai-chi; Freq: 2x/wk for 10 wks; Duration: 1 hour	
§**MA design**	Mind-body		
§**NMA design**	Mind-body-Strength-Usual Care		
Intervention period: 10wk; Follow-ups: 10wk			

ii) Characteristics of exercise arms and comparators in studies with post-operative outcomes (Chapter 7 – *Exercise versus usual care: meta-analysis*)

	[7]Beaupre 2004	
Group	**G1**	**G2**
Ex content	Strength	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Centre-based	
Individual/Group	Unclear	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: hamstring and quads strengthening; Freq:3x/wk for 4 wks; Intensity:3 sets x10 reps x 5 ex; Rep: Unclear	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
Intervention period: 4wk before op; Follow-ups: 12wk 6mth 12mth after op		

[114]Brown 2012		
Group	**G1**	**G2**
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Unclear	
Supervision (total no.)	Yes(8)	
Min Ex days/wk	3	
Strengthening	Type: squats, ankle dorsi, ankle plantar, hamstring, biceps, tricep, chest press, seated row; Freq:3x/wk for 8 wks; Intensity: moderate fatigue at final rep of theraband ex; Rep:1 set x10 rep (initial) ; 2 sets x10 rep towards the end of program	
Aerobic		
Skills	Type: step training, (forward, Lt and Rt sideway); Freq: 3x/wk for 8 wks; Intensity: 8 reps progressed to 20 reps x 3 step exercise; Duration: -	
Flexibility	Type: knee extension and flexion, hip flexion and extension, trunk extension and flexion, and shoulder flexion, extension, and rotation; Freq: 3x/wk for 8 wks; Rep: 2 reps each, 20 sec hold	
Mind-body		
MA design	Mixed ex	
Intervention period: 8wk before op; Follow-ups: 12wk after op		

[23]D'Lima 1996

Group	G1	G2	G3
Ex content	Mixed ex	Aerobic	
Non-Ex content			Usual care
Land/water	Land	Land	
Home-/ Centre-based	Centre-based	Centre-based	
Individual/Group	Individual	Unclear	
Supervision (total no.)	Yes(18)	Yes(18)	
Min Ex days/wk	3	3	
Strengthening	Type: quads, gastroc, hamstring, hip flexor/ ext, hip abd, shoulder flex/ abd, triceps brachii; Freq:3x/wk for 6 wks; Intensity:unclear ; Rep:unclear. Total exercise session duration 45 mins		
Aerobic		Type: Cycle and arm ergometry, aquatic exercises (presumed to be aerobic as well); Freq: 3x/wk for 6 wks; Intensity: 40% HRR; Duration: 45 mins	
Skills			
Flexibility	Type: gastroc, hamstring, quads stretch; Freq: 3x/wk for 6 wks; Rep: Unclear		
Mind-body			
MA design	Aerobic		
Intervention period: 6wk before op; Follow-ups: 1wk before op then 3wk 12wk 24wk 48wk after op			

[32]Evgeniadis 2008

Group	G1	G2	G3
Ex content	Strength (pre-op)	Strength (post-op)	
Non-Ex content			Usual care
Land/water	Land	Land	
Home-/ Centre-based	Home-based	Home-based	
Individual/Group	Individual	Individual	
Supervision (total no.)	Yes(9)	Yes(Unclear)	
Min Ex days/wk	3	3	
Strengthening	Type: upper back, shoulder, biceps and triceps, deltoid, rectus abdominis, femoral flexor; Freq: 3x/52 for 3 wks pre-op; Intensity: moderate fatigue after 8th rep; Rep: 1-3 set x 10-14 reps	Type: anterior & posterior tibialis, anterior & posterior femoral muscles, hip abd; Freq: 3x/52 for 8 wks; Intensity: moderate fatigue after 8th rep; Rep: 1-3 set x 10-14 rep	
Aerobic			
Skills			
Flexibility			
Mind-body			
MA design	Strength		

Intervention period: 3wk before op;
Follow-ups: before op (i.e. 4 weeks after commencement of intervention) then 2wk 6wk 10wk 14wk after op

[115]Gstoettner 2011

Group	G1	G2
Ex content	Skills	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Unclear	
Supervision (total no.)	Yes(6)	
Min Ex days/wk	7	
Strengthening		
Aerobic		
Skills	Type: slide step forward/backward; step forward/backward; singe leg stance; squats; Freq: daily for 6 wks; Intensity: Unclear; Duration: 45 mins	
Flexibility		
Mind-body		
MA design	FlexSkills	
NMA design	FlexSkills-Usual care	

Intervention period: 6wk before op;
Follow-ups: before op then 6wk after op

[75]Oosting 2012

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content	Usual care	Usual care
Land/water	Land	
Home-/ Centre-based	Home-based	
Individual/Group	Individual	
Supervision (total no.)	Yes(10)	
Min Ex days/wk	6	
Strengthening		
Aerobic	Type: Walking; Freq: Daily; Intensity: 55-75% HR max; Duration: 30mins	
Skills	Type: unclear; Freq: 2x/wk for 5 wks, supervised. Additional 4 days a wk on their own; Intensity: unclear; Duration: 30min	
Flexibility		
Mind-body		
MA design	Mixed Ex	

Intervention period: 5wk before op;
Follow-ups: before op (i.e. 6 wks after commencement of intervention) then 6wk after op

[103]Topp 2009

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Wait-list
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Unclear	
Supervision (total no.)	Yes(4)	
Min Ex days/wk	3	
Strengthening	Type: 9 exercises: hips, ankle and knee muscles; Freq: 3x/wk for at least 4 wks; Intensity:Unclear; Rep:Unclear	
Aerobic		
Skills	Type: forward and lateral step; Freq: 3x/wk for at least 4 wks; Intensity: Unclear; Duration: Unclear	
Flexibility	Type: whole body; Freq: 3x/wk for at least 4 wks; Rep: Unclear	
Mind-body		
MA design	Mixed ex	
Intervention period: 4wk before op; Follow-ups: before op then 4wk 12wk after op		

[116]Tungtrongjit 2012

Group	G1	G2
Ex content	Strength	
Non-Ex content		Usual physical activity
Land/water	Land	
Home-/ Centre-based	Home-based	
Individual/Group	Individual	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	7	
Strengthening	Type: knee extension; Freq: daily for 3 wks; Intensity: Unclear; Rep:10 times 3x/day	
Aerobic		
Skills		
Flexibility		
Mind-body		
MA design	Strength	
Intervention period: 3wk before op; Follow-ups: 1mth 3mth 6mth after op		

[111]Weidenhielm 1993

Group	G1	G2
Ex content	Mixed ex	
Non-Ex content		Usual care
Land/water	Land	
Home-/ Centre-based	Mixed	
Individual/Group	Both	
Supervision (total no.)	Yes(Unclear)	
Min Ex days/wk	3	
Strengthening	Type: Unclear; Freq: 3x/52 for 5 wks then daily at home; Intensity: Initially unloaded; Rep:20 reps each exercise	
Aerobic		
Skills		
Flexibility	Type: Unclear; Freq: 3x/52 for 5 wks then daily at home; Rep: Unclear	
Mind-body		
MA design	Mixed ex	
Intervention period: 5wk before op; Follow-ups: before op (i.e. 12 wks after commencement of intervention) then 12wks post-op		

'Min ex day/week' indicates the minimum number of exercising days prescribed.
abd= abductors; add= adductors; con=concentric; ex= exercise; ext= extensors; ecc=eccentric; flex= flexors; freq= frequency; gastroc= gastrocnemius; HR max= heart rate maximum; HRR= hear rate reserve; NRS= numeric rating scale; op=operation; PNF= proprioceptive neuromuscular facilitation; Reps= repetition; RM= repetition maximum; ROM= range of motion; RPE= rate of perceived exertion; SLR: straight leg raise; wk= week(s); min= min; quads= quadriceps;
§ Trials in which exercise groups had been aggregated for analysis
Banded column represents groups with exercise

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2. Aglamis B, Toraman NF, Yaman H. The effect of a 12-week supervised multicomponent exercise program on knee OA in Turkish women. *Journal of Back & Musculoskeletal Rehabilitation* 2008; 21(2): 121-8.
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Appendix 8 Risk of bias, country and adherence monitoring of studies – Overall

Study	Adequate randomization	>100 per group	Concealed Allocation	Physician Blind	Patient Blind	Assessor Blind	Missing Outcome Assess	Intention-to-treat Use	Homogeneous Group	Reported as Pre-specified	Country	Exercise adherence monitored
Abbott 2013	Yes	No	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	New Zealand	A,SR
Aglamis 2008	Yes	No	Unclear	Unclear	No	Yes	No	No	Unclear	Yes	Turkey	A,
An 2008	Unclear	No	Unclear	Unclear	No	No	Yes	No	Yes	Yes	China	-
Aoki 2009	Unclear	No	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Yes	Japan	SR
Arnold 2010	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Canada	A
Beaupre 2004	Unclear	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Canada	A
Bennell 2010	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Australia	A,SR
Bennell 2014	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Australia	A,SR
Bieler 2017	Yes	No	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	Denmark	SR
Börjesson 1996	Yes	No	Unclear	No	No	Unclear	Yes	Yes	Yes	Unclear	Sweden	-
Braghin 2017	Yes	No	Yes	No	No	Unclear	Unclear	Unclear	Unclear	Yes	Brazil	-
Brown 2012	Unclear	No	Unclear	No	No	Unclear	No	No	Unclear	Yes	US	SR
Bruce-Brand 2012	Yes	No	Unclear	No	No	Yes	Unclear	Unclear	Yes	No	UK	SR
Calatayud 2017	Yes	No	Unclear	No	No	Unclear	Yes	Yes	Yes	Yes	Denmark	-
Chaipinyo 2009	Unclear	No	Yes	No	No	Yes	No	Unclear	Unclear	Yes	Thailand	SR
Chen 2014	Yes	No	Yes	No	No	Unclear	Unclear	Yes	Unclear	Yes	Taiwan	A
Cheung 2016	Yes	No	Yes	No	No	Unclear	Yes	Yes	No	Yes	US	A,SR
Chopp-Hurley 2017	Yes	No	Unclear	No	No	Yes	No	Unclear	Yes	Yes	Canada	A
Christensen 2015	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Denmark	A,SR

Study	Adequate randomization	>100 per group	Concealed Allocation	Physician Blind	Patient Blind	Assessor Blind	Missing Outcome Assess	Intention-to-treat Use	Homogeneous Group	Reported as Pre-specified	Country	Exercise adherence monitored
Cochrane 2005	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	UK	A
Corjena 2014	Yes	No	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	US	A,SR
D'Lima 1996	Yes	No	Unclear	Unclear	No	Unclear	Yes	Unclear	No	Yes	US	-
Duracoglu 2005	Unclear	No	Unclear	No	No	Yes	No	No	Yes	Yes	Turkey	A
Ebnezar 2012	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	India	S R
Espejo Antunez 2012	Yes	No	No	No	No	Yes	Yes	Yes	Unclear	Yes	Spain	-
Ettinger 1997	Yes	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	US	A,SR
Evcik 2002	Unclear	No	Unclear	No	No	No	No	No	Yes	Yes	Turkey	SR
Evgeniadis 2008	Yes	No	Yes	No	No	Unclear	No	Yes	Yes	Yes	Greece	-
Ferrara 2008	Yes	No	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	No	Italy	-
Fitzgerald 2011	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	US	SR
Fransen 2001	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Australia	A
Fransen 2007	Yes	No	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	Australia	A
French 2013	Yes	No	Yes	No	No	Yes	Yes	Yes	Unclear	Yes	Ireland	A,SR
Ghroubi 2008	Unclear	No	Unclear	No	No	Unclear	No	No	Yes	Yes	Tunisia	-
Gomiero 2017	Yes	No	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Brazil	-
Gondhalekar 2013	Unclear	No	Unclear	No	No	Unclear	No	No	Unclear	Yes	India	-
Gstoettner 2011	Yes	No	Yes	No	No	Unclear	No	No	Unclear	Yes	Austria	-
Gur 2002	Unclear	No	Unclear	No	No	Unclear	Yes	Yes	Unclear	Yes	Turkey	-
Hasegawa 2010	Unclear	No	Unclear	No	No	Unclear	Yes	Yes	Yes	Yes	Japan	A,SR
Henriksen 2014	Yes	No	Yes	No	No	Yes	No	No	No	Yes	Denmark	A

Study	Adequate randomization	>100 per group	Concealed Allocation	Physician Blind	Patient Blind	Assessor Blind	Missing Outcome Assess	Intention-to-treat Use	Homogeneous Group	Reported as Pre-specified	Country	Exercise adherence monitored
Hermann 2016	Yes	No	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Denmark	A
Hinman 2007	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Australia	A,SR
Hiyama 2012	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Japan	-
Hoogeboom 2010	Unclear	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Netherland	A
Huang 2003	Unclear	No	Yes	No	No	Unclear	No	No	Unclear	Yes	Taiwan	A
Huang 2005	Unclear	No	Yes	No	No	Unclear	No	No	Unclear	Yes	Taiwan	-
Huang 2017	Yes	Yes	No	Unclear	No	No	Unclear	Unclear	Yes	Yes	China	-
Hunt 2013	Yes	No	Yes	No	No	Yes	No	Unclear	Yes	Yes	Canada	A,SR
Ikuta 2015	Unclear	No	Unclear	No	No	Unclear	Unclear	No	Yes	Yes	Japan	SR
Jan 2008	Yes	No	Unclear	No	No	Yes	No	Yes	Yes	Yes	Taiwan	-
Jan 2009	Yes	No	Unclear	No	No	Yes	Unclear	Yes	Yes	Yes	Taiwan	-
Jorge 2015	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Brazil	A
Juhakoski 2011	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Finland	A,SR
Koli 2015	Yes	No	Unclear	No	No	Yes	No	No	Yes	Yes	Finland	A
Krasilshchikov 2011	Unclear	No	Unclear	No	No	Yes	Unclear	Unclear	Yes	Yes	Malaysia	A
Krauss 2014	Unclear	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Germany	A,SR
Kreindler 1989	No	No	No	No	No	Unclear	Yes	Yes	Yes	Yes	US	-
Kumar 2013	Yes	No	Unclear	No	No	No	Yes	Yes	Yes	Yes	India	-
Lee 2008	Unclear	No	Unclear	No	No	Unclear	No	No	No	Yes	Korea	-
Lee 2009	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Korea	-
Lim 2008	Yes	No	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	Australia	SR

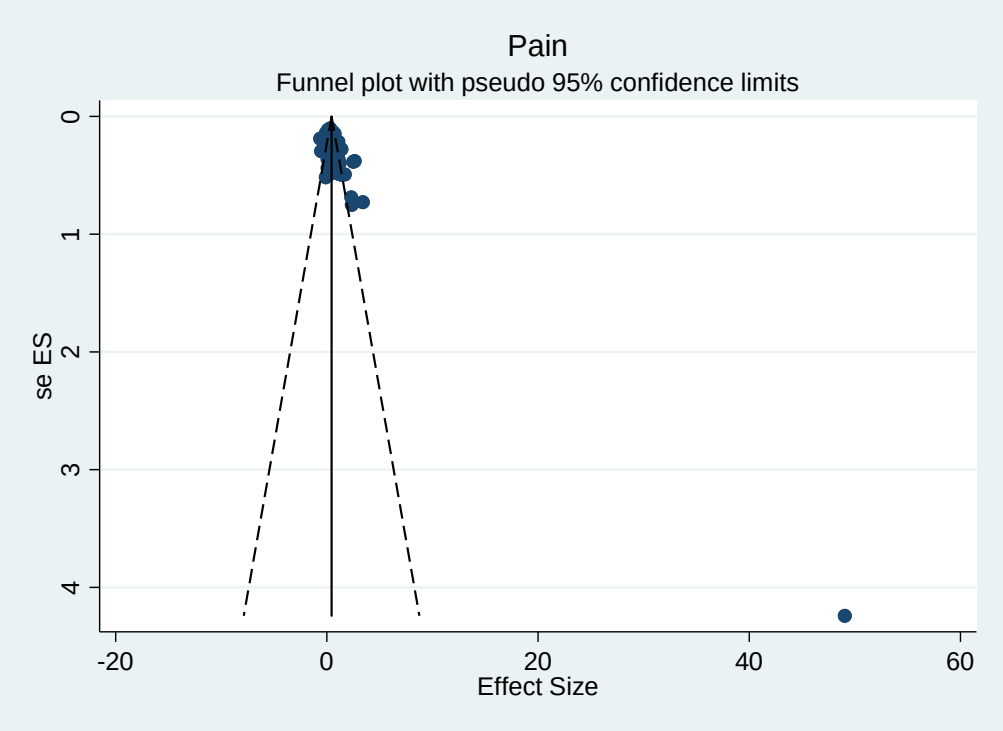
Study	Adequate randomization	>100 per group	Concealed Allocation	Physician Blind	Patient Blind	Assessor Blind	Missing Outcome Assess	Intention-to-treat Use	Homogeneous Group	Reported as Pre-specified	Country	Exercise adherence monitored
Lin 2007	Unclear	No	Unclear	No	No	Unclear	No	No	Yes	Yes	Taiwan	-
Lin 2009	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Taiwan	-
Lund 2008	Unclear	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Denmark	A
Messier 1997	Unclear	No	Unclear	No	No	Unclear	Unclear	Unclear	Yes	Yes	US	A,SR
Moghadam 2017	Unclear	No	Unclear	No	No	Unclear	No	Unclear	Yes	Unclear	Azerbaijan	-
Munukka 2016	Yes	No	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	Finland	A
Oida 2008	Yes	No	Unclear	No	No	Unclear	Unclear	No	No	Yes	Japan	SR
Oosting 2012	Unclear	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Netherlands	SR
O'Reilly 1999	Yes	No	Yes	No	No	Unclear	Unclear	Yes	Yes	Yes	UK	SR
Petrella 2000	Yes	No	Unclear	No	No	Yes	No	Yes	Yes	Yes	US	SR
Rapp 2009	Unclear	No	Unclear	No	No	Unclear	Yes	Yes	Unclear	Yes	Germany	-
Rathi 2014	Unclear	No	Unclear	No	No	Unclear	Yes	Yes	Yes	Yes	India	-
Rogers 2011	Yes	No	Unclear	No	No	Unclear	No	No	Yes	Yes	US	-
Rogers 2012	Yes	No	Unclear	No	No	Unclear	Unclear	No	Yes	Yes	US	SR
Rogind 1998	Yes	No	Unclear	No	No	Yes	Unclear	Yes	Yes	Unclear	Denmark	A
Rooij 2016	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Netherlands	A,SR
Rosedale 2014	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Canada	-
Salacinski 2012	Yes	No	Unclear	No	No	Unclear	No	No	No	Yes	US	A
Salli 2010	Unclear	No	Yes	No	No	Unclear	No	No	Yes	Yes	Turkey	-
Samut 2015	Unclear	No	Unclear	No	No	Unclear	No	Yes	Yes	Yes	Turkey	-

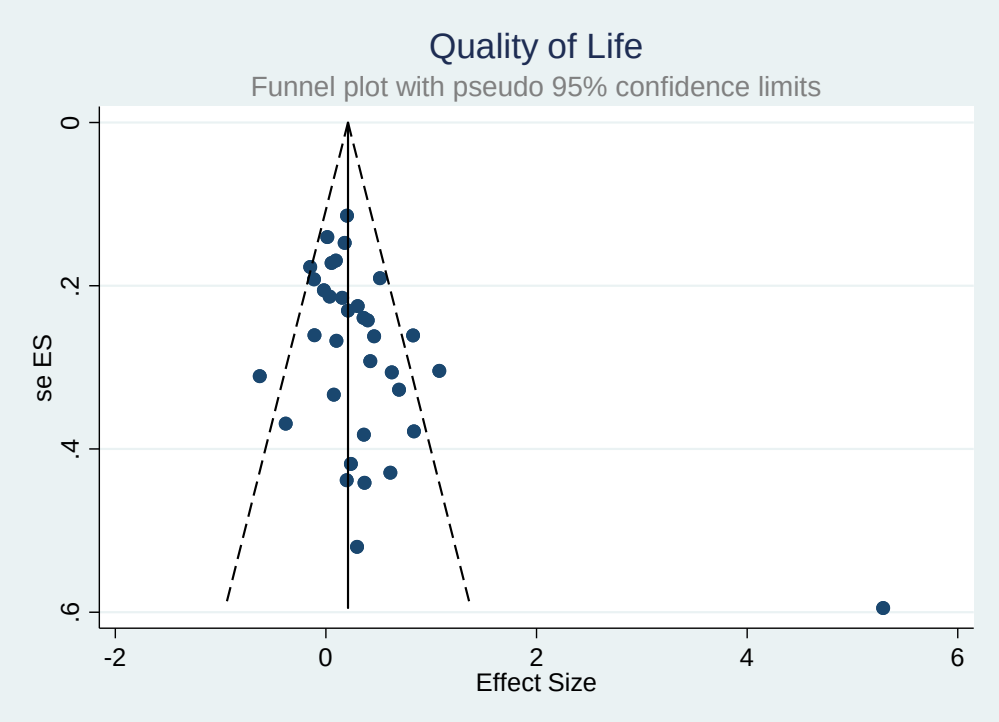
Study	Adequate randomization	>100 per group	Concealed Allocation	Physician Blind	Patient Blind	Assessor Blind	Missing Outcome Assess	Intention-to-treat Use	Homogeneous Group	Reported as Pre-specified	Country	Exercise adherence monitored
Sayers 2012	Yes	No	Unclear	No	No	Yes	Unclear	Yes	Yes	Yes	US	-
Schilke 1996	Unclear	No	Unclear	No	No	Unclear	No	No	Unclear	Yes	US	-
Sekir 2005	Unclear	No	Unclear	No	No	Unclear	Yes	Yes	Unclear	Yes	Turkey	-
Simão 2012	Unclear	No	Yes	No	No	Yes	No	Yes	No	Yes	Brazil	-
Singh 2011	Unclear	No	Unclear	No	No	Unclear	Unclear	Unclear	Unclear	Yes	Punjabi	-
Skoffer 2016	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Denmark	A
Sung-Bum 2015	Unclear	No	Unclear	No	No	Unclear	Unclear	Unclear	Yes	Yes	Korea	-
Swank 2011	Unclear	No	Unclear	No	No	Unclear	Yes	Yes	Yes	Yes	US	-
Takacs 2017	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	Canada	A,SR
Teirlinck 2016	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Netherlands	A,SR
Teixeira 2011	Unclear	No	Yes	No	No	No	No	No	Yes	Yes	US	-
Thamalikitkul 2002	Unclear	Yes	Unclear	No	No	Unclear	Unclear	Unclear	Yes	Yes	Thailand	A
Thorstensson 2005	Yes	No	Yes	No	No	Unclear	Unclear	Unclear	Yes	Yes	Sweden	A
Topp 2002	Unclear	No	Unclear	No	No	Unclear	Unclear	Unclear	Yes	Yes	US	SR
Topp 2009	Unclear	No	Unclear	No	No	Unclear	Unclear	Unclear	Yes	Yes	US	SR
Tsauo 2008	Yes	No	Unclear	No	No	Unclear	No	No	Yes	Yes	Taiwan	-
Tungtrongjit 2012	Unclear	No	Unclear	No	No	Yes	Unclear	Unclear	Yes	Yes	Thailand	-
Vaittianadane 2014	Unclear	No	Unclear	No	No	Unclear	Unclear	Unclear	Unclear	Yes	India	-
Van Baar 1998	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Netherland	SR
Wallis 2017	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Australia	SR

Study	Adequate randomization	>100 per group	Concealed Allocation	Physician Blind	Patient Blind	Assessor Blind	Missing Outcome Assess	Intention-to-treat Use	Homogeneous Group	Reported as Pre-specified	Country	Exercise adherence monitored
Wang 2007	Unclear	No	Unclear	No	No	Unclear	No	Yes	Yes	Yes	Taiwan	A
Wang 2011	Yes	No	Unclear	No	No	Yes	No	No	Yes	Yes	Taiwan	A
Weidenhielm 1993	Yes	No	Unclear	No	No	Unclear	Yes	Unclear	Yes	Yes	Sweden	-
Weng 2009	Yes	No	Yes	No	No	Yes	Unclear	Yes	Yes	Yes	Taiwan	-
Wortley 2013	Unclear	No	Unclear	No	No	Unclear	No	No	Unclear	Yes	US	A

A= Attendance; SR= Self-reported

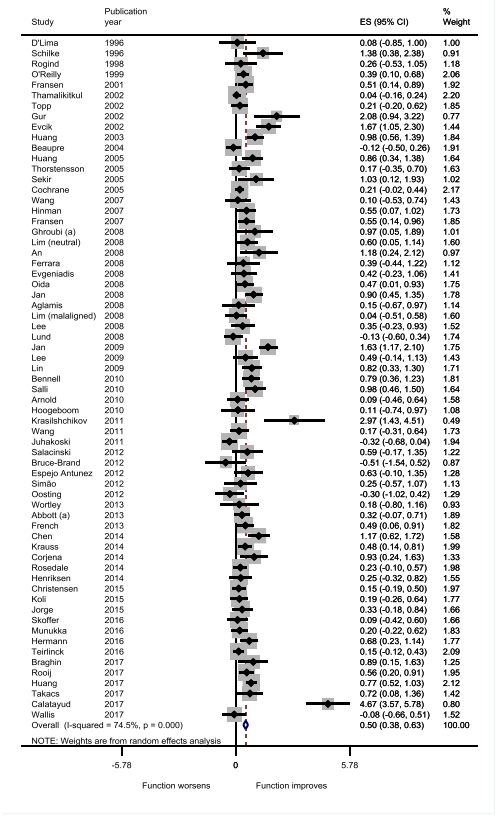
Appendix 9 Funnel plots – Exercise versus usual care (outliers): Pain and quality of life





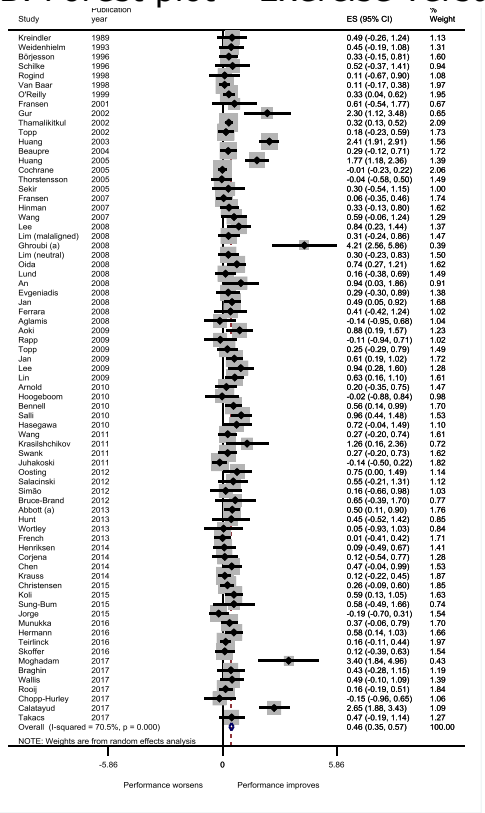
Appendix 10 Forest plot – Exercise versus usual care: Function, performance and quality of life

A. Forest plot - Exercise versus usual care: Function



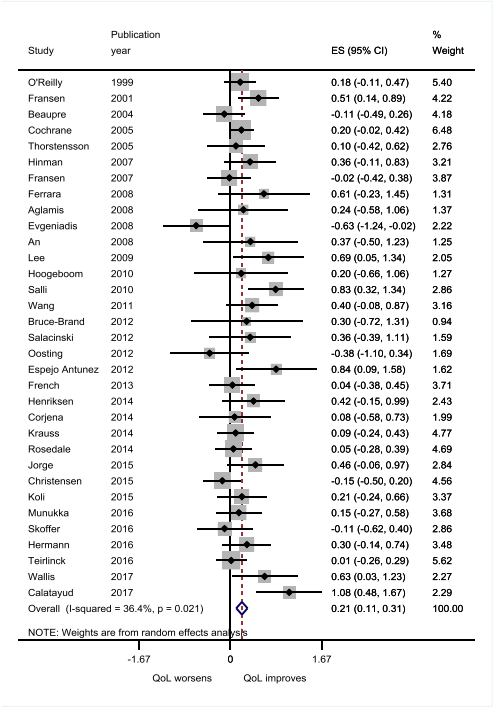
Overall ES 0.50; 95%CI 0.38, 0.63

B. Forest plot – Exercise versus usual care: Performance



Overall ES 0.46; 95%CI 0.35, 0.57

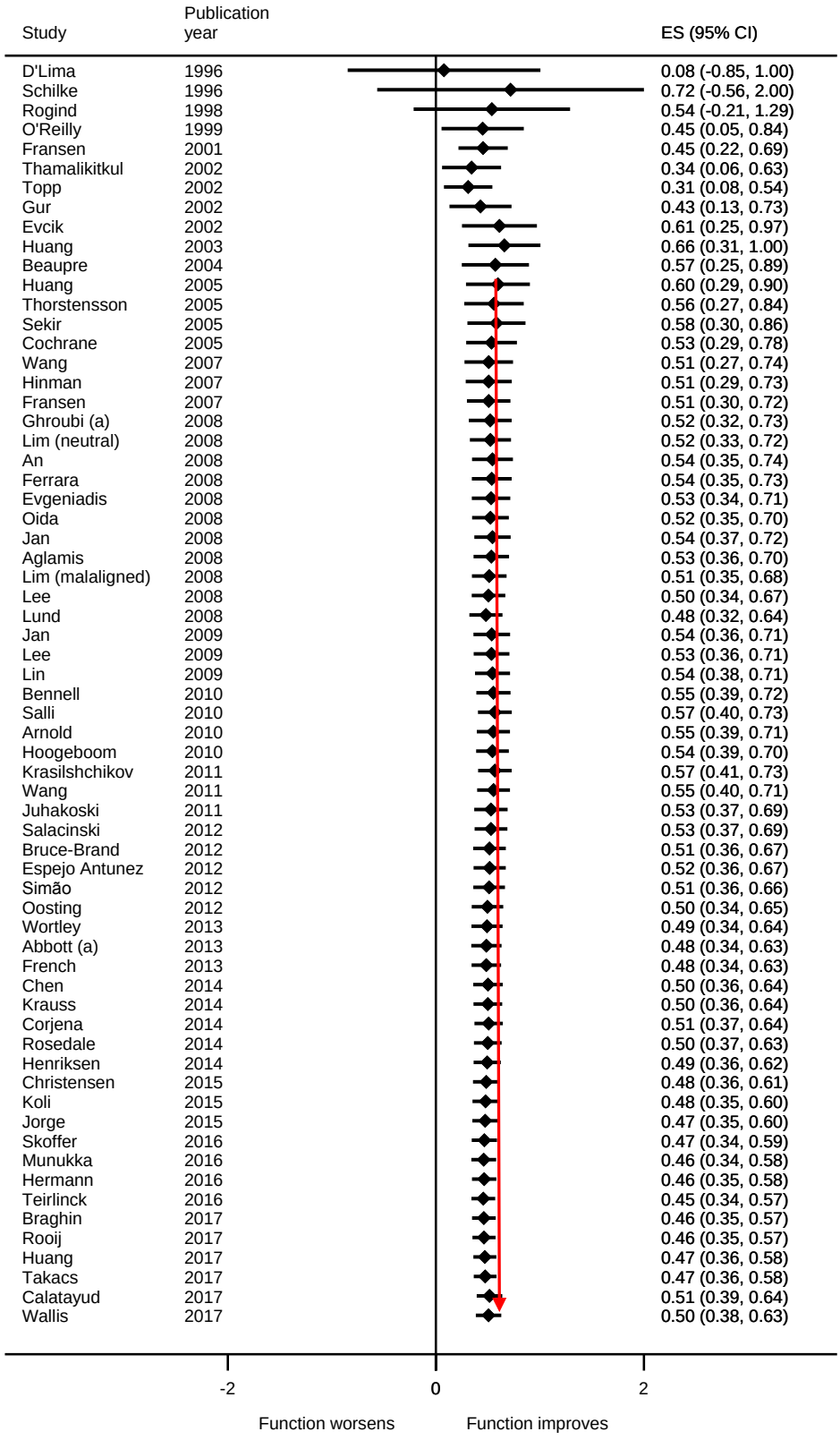
C. Forest plot – Exercise versus usual care: Quality of Life



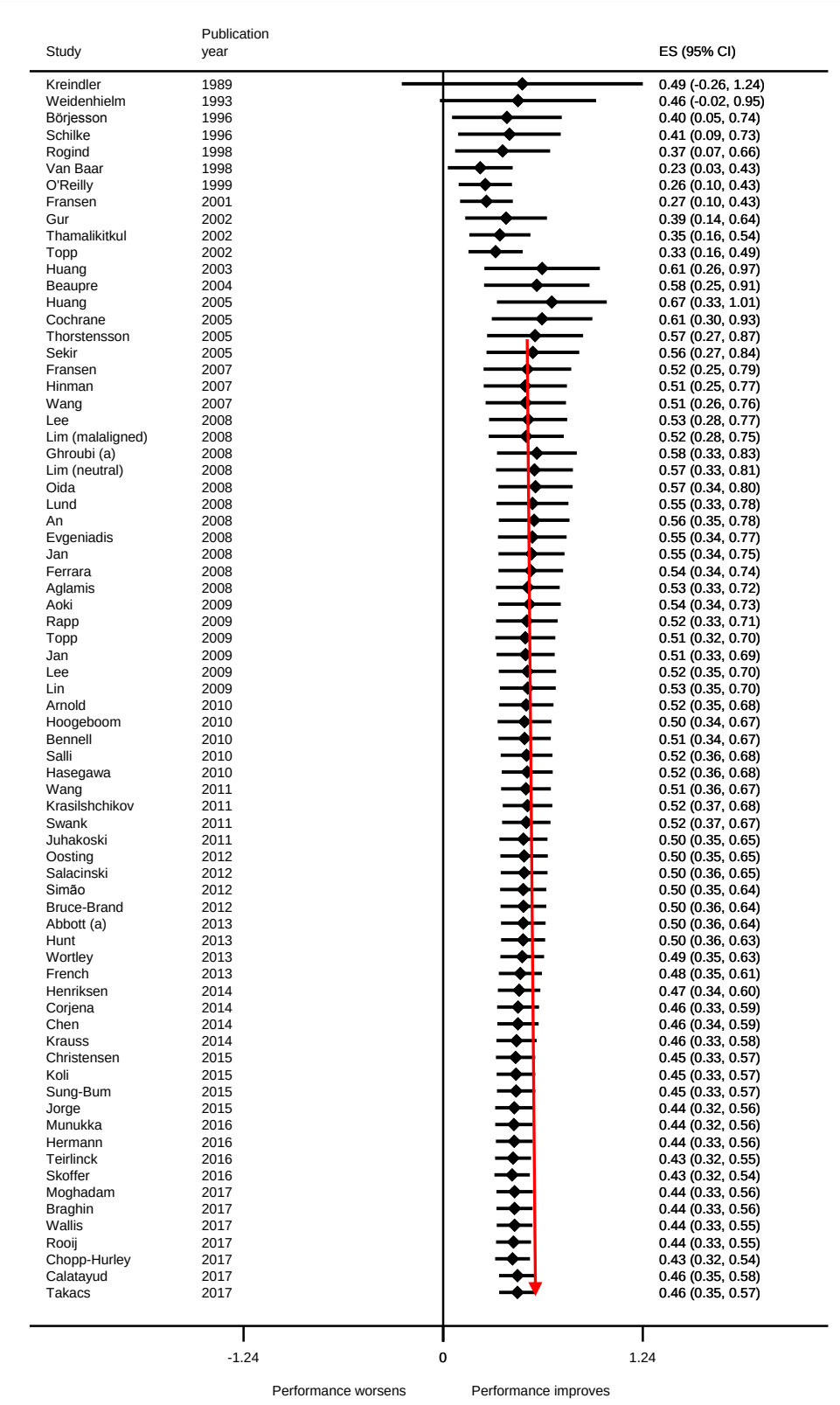
Overall ES 0.21; 95%CI 0.11, 0.31

Appendix 11 Cumulative plot – Exercise versus usual care: Function, performance and quality of life

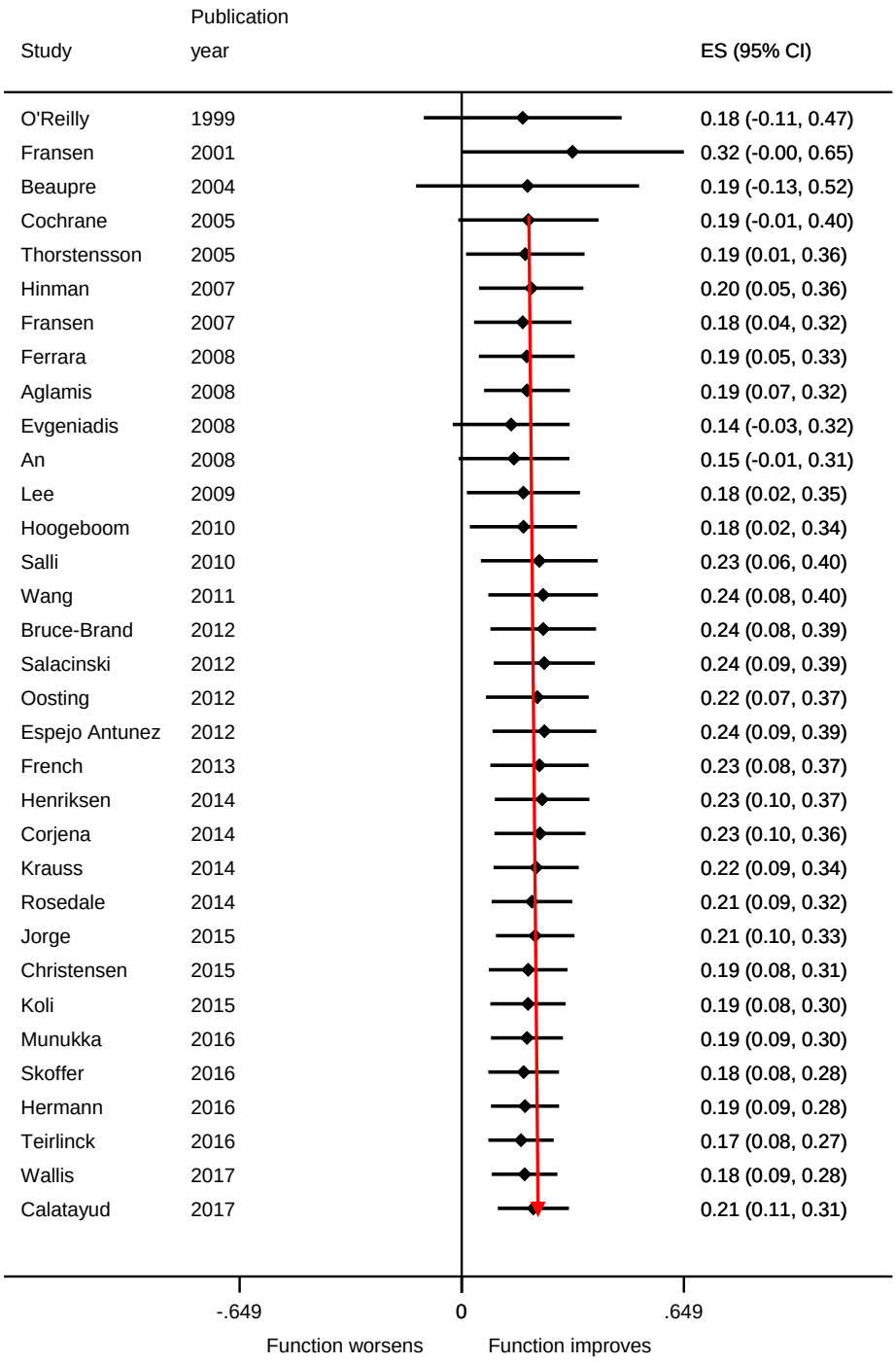
A. Cumulative plot - Exercise versus usual care: Function



B. Cumulative plot – Exercise versus usual care: Performance

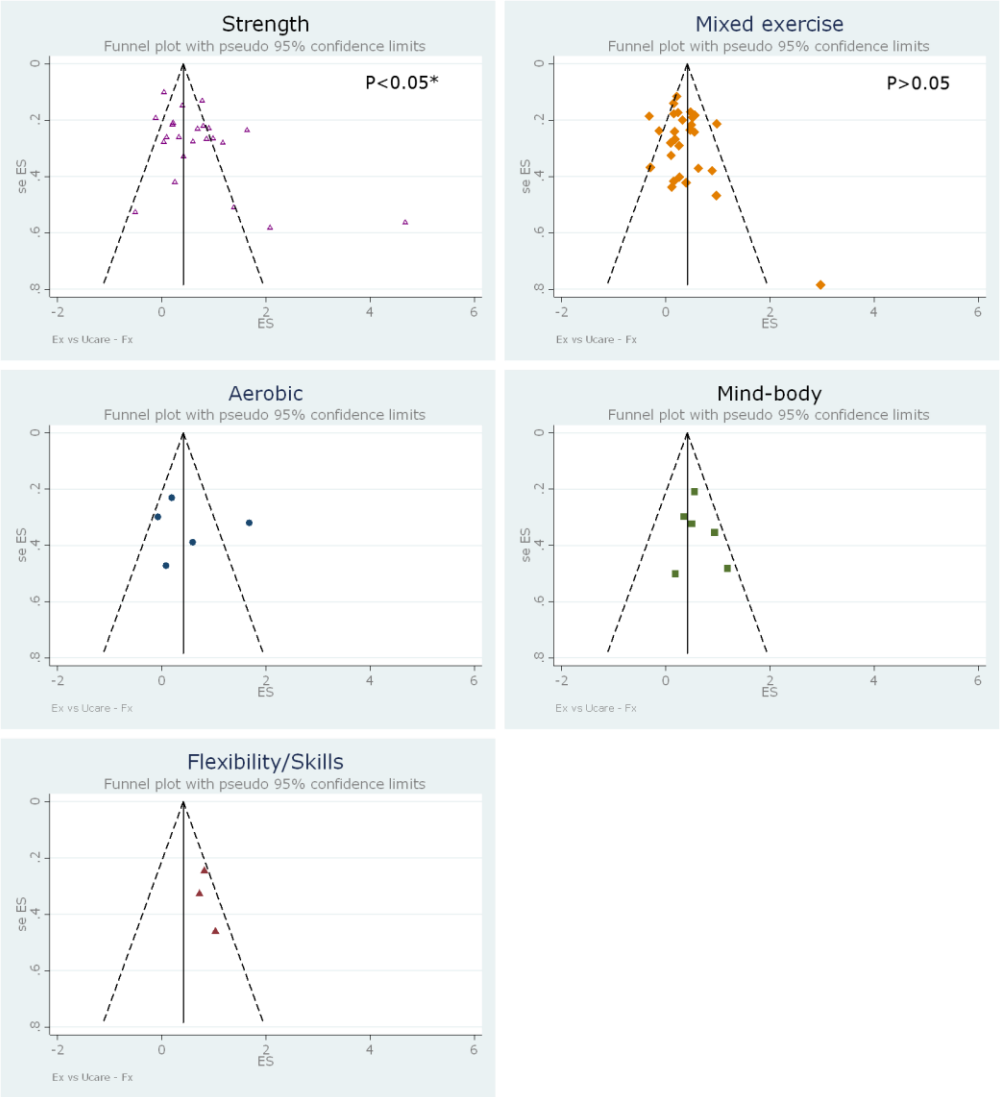


C. Cumulative plot – Exercise versus usual care: Quality of life



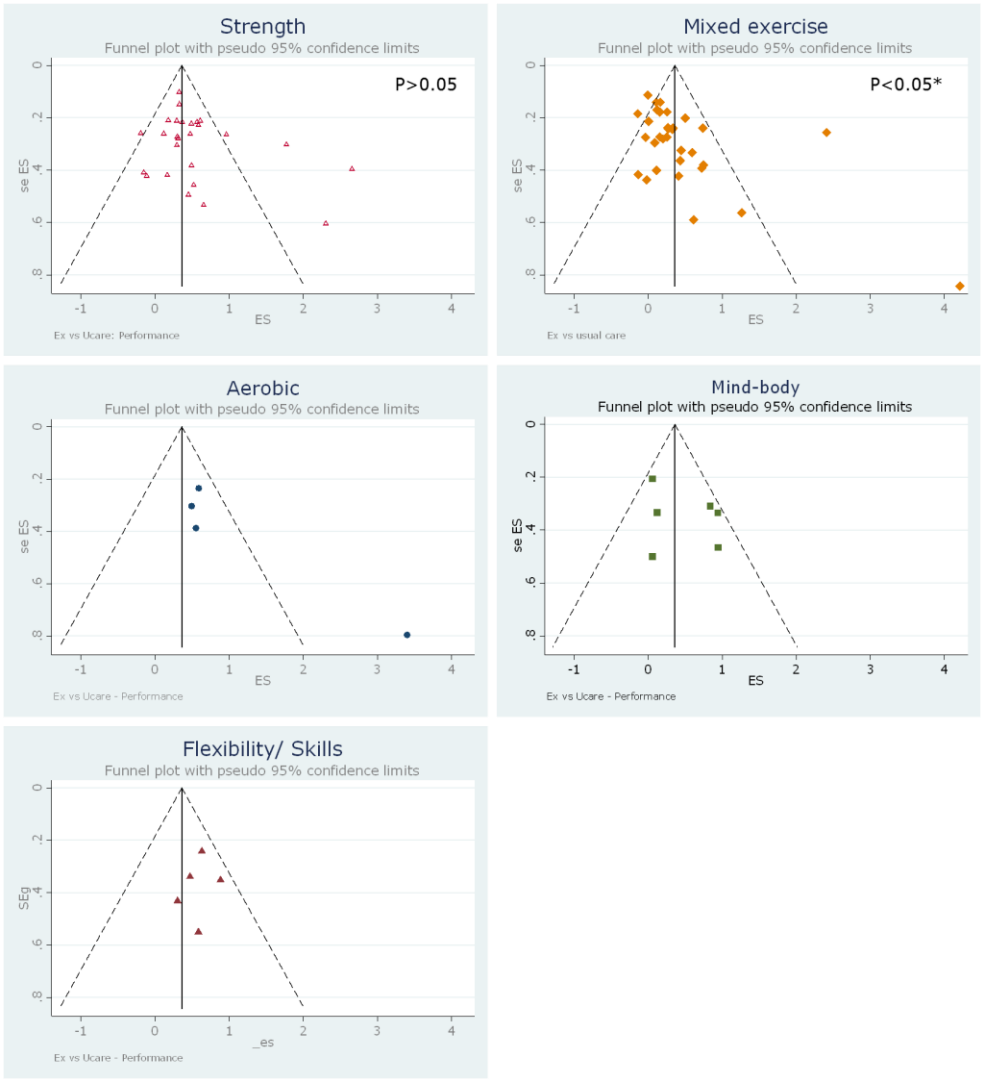
Appendix 12 Funnel plot – Exercise versus usual care: Pain, function, performance and quality of life (by exercise types)

A. Funnel plot - Exercise versus usual care (by exercise types): Function



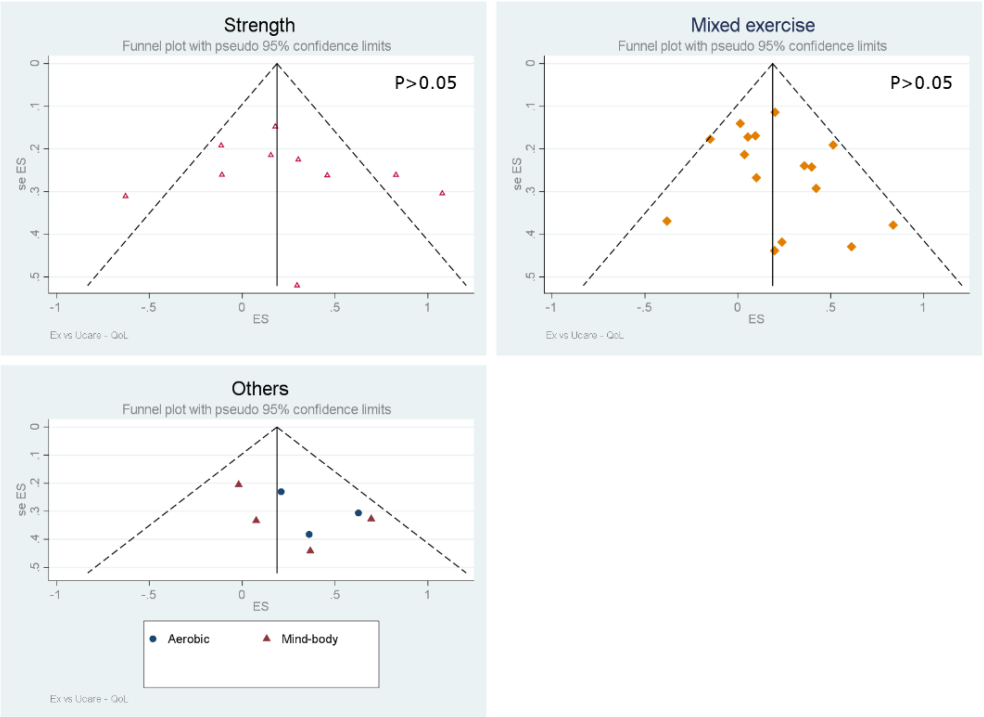
* Egger's test suggestive of publication bias when p<0.05. This test was not performed if there were <10 studies

B. Funnel plot – Exercise versus usual care (by exercise types): Performance



* Egger's test suggestive of publication bias when p<0.05. This test was not performed if there were <10 studies

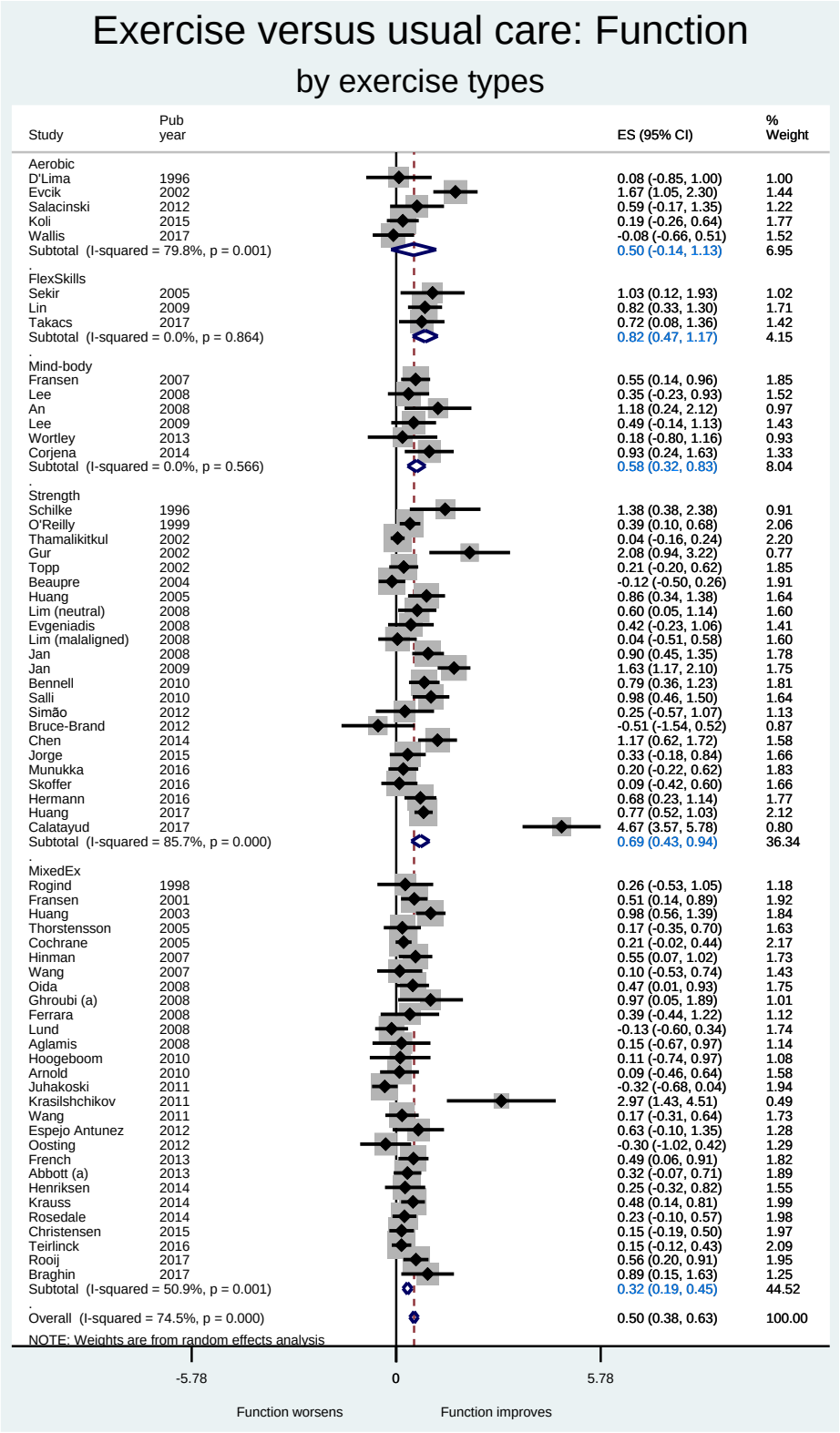
C. Funnel plot – Exercise versus usual care (by exercise types): Quality of life



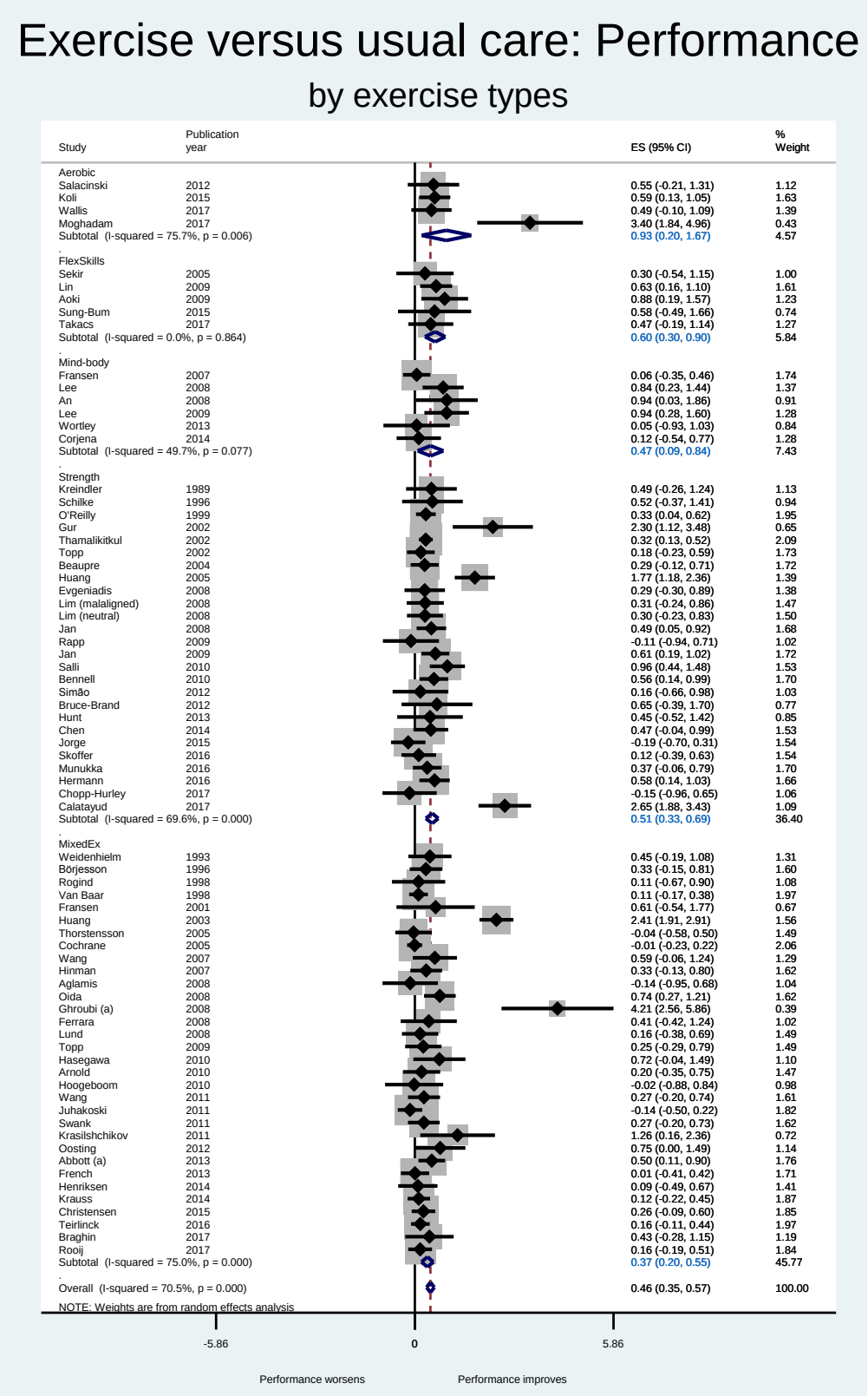
* Egger's test suggestive of publication bias when p<0.05. This test was not performed if there were <10 studies

Appendix 13 Forest plot – Exercise versus usual care: Function, performance and quality of life (by exercise types)

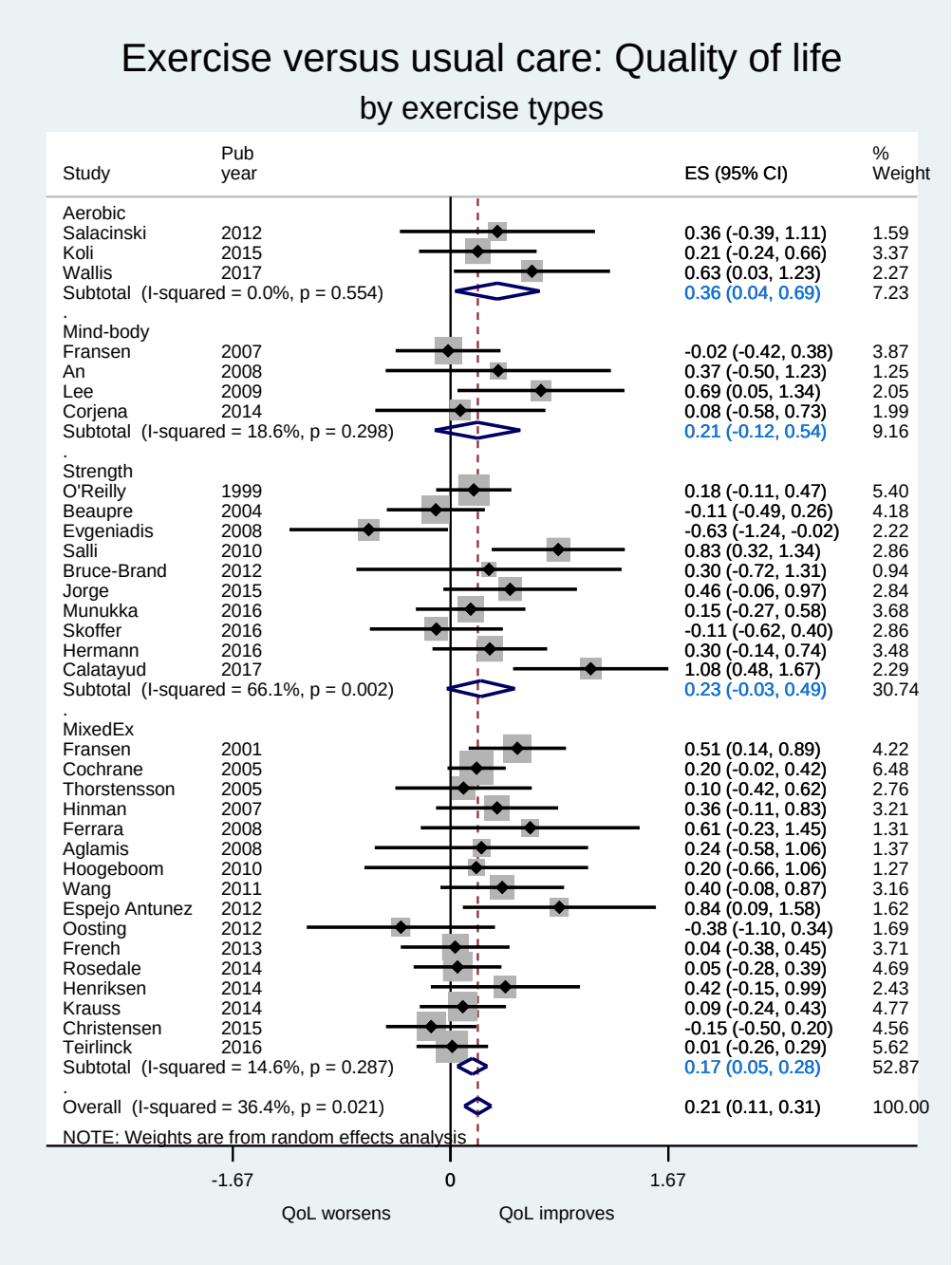
A. Forest plot – Exercise versus usual care: Function (by exercise types)



B. Forest plot – Exercise versus usual care: Performance (by exercise types)



C. Forest plot – Exercise versus usual care: Quality of life (by exercise types)



Appendix 14 Subgroup analysis – Exercise versus usual care: Function, performance and quality of life

A. Subgroup analysis – Exercise versus usual care: Function

	No. comp. (No. trials)	No. Patients	Effect Size (95%CI)	I^2 (%)	p-value (Univariate)
Overall	**65 (64)**	5025	0.51 (0.38, 0.63)	74.5	
Age					
<60 years old	12	591	1.18 (0.65, 1.72)	87.3	<0.01*
≥60 years old	53	4434	0.41 (0.30, 0.52)	64.6	
Percentage female[a]					
<60%	12	1023	0.24 (0.07, 0.41)	38.2	0.14
60%-<80%	29	2588	0.52 (0.35, 0.69)	74.4	
≥80%	21	1320	0.49 (0.31, 0.68)	57.6	
Mean body mass index[a]					
<30	26	2111	0.41 (0.27, 0.54)	47.5	0.77
≥30	17	1103	0.51 (0.21, 0.81)	81.1	
Joint					
Knee	52	4443	0.59 (0.44, 0.74)	76.9	0.07*
Hip	8	703	0.21 (-0.03, 0.46)	57.8	
Mixed	5	611	0.31 (0.15, 0.47)	0.0	
On JR waiting-list					
No	54	4443	0.52 (0.40, 0.64)	69.5	0.54
Yes	11	582	0.45 (-0.04, 0.95)	86.5	
'Explicit' pain criteria					
None	51	3758	0.50 (0.36, 0.65)	75.2	0.89
Yes	14	1267	0.53 (0.30, 0.75)	72.4	
ACR criteria					
Yes	32	2493	0.62 (0.43, 0.81)	79.4	0.19
No/unclear	33	2532	0.38 (0.24, 0.52)	61.0	
Radiographic requirement					
Yes	38	2686	0.61 (0.42, 0.81)	81.3	0.20
No/Unclear	27	2339	0.38 (0.25, 0.51)	49.1	
Adherence monitored					
Yes	43	3765	0.35 (0.24, 0.46)	62.0	<0.01*
No/Unclear	22	1260	0.88 (0.60, 1.15)	78.0	
Analgesic control/monitored					
Yes	31	2674	0.49 (0.33, 0.66)	74.5	0.92
No/ Unclear	34	2351	0.52 (0.34, 0.70)	74.8	
Recruitment centre[a]					
Specialist/hospital	24	1658	0.52 (0.28, 0.76)	79.7	0.33
GP/Community	25	3007	0.28 (0.16, 0.41)	41.9	
Mixed	7	680	0.46 (0.31, 0.61)	0.0	
Intention-to-treat use					
Yes	41	3337	0.47 (0.32, 0.62)	76.4	0.50
No/Unclear	24	1688	0.58 (0.37, 0.79)	71.0	
Sample >100/ group					
Yes	4	1148	0.29 (-0.02, 0.60)	85.6	0.41
No	61	3877	0.53 (0.40, 0.66)	72.8	

ACR= American College of Rheumatology; GP= general practitioner; JR= joint replacement; No. comp.= Number of comparators; OA=osteoarthritis

[a]Data was missing in some studies; *Unadjusted univariate regression p≤0.10

B. Subgroup analysis – Exercise versus usual care: Performance

	No. comp. (No. trials)	No. Patients	Effect Size (95%CI)	I^2 (%)	p-value (univariate)
Overall	**73(72)**	**5082**	**0.46 (0.35, 0.58)**	70.5	
Age					
<60 years old	14	613	0.81 (0.37, 1.26)	83.1	0.09*
≥60 years old	59	4469	0.41 (0.30, 0.52)	64.3	
Percentage female[a]					
<60%	14	993	0.29 (0.16, 0.41)	0.0	0.18
60%-<80%	33	2863	0.37 (0.22, 0.52)	70.2	
≥80%	22	1114	0.50 (0.31, 0.68)	50.3	
Mean body mass index[a]					
<30	30	1943	0.37 (0.24, 0.50)	41.1	0.91
≥30	18	1078	0.46 (0.19, 0.72)	76.2	
Joint					
Knee	57	3484	0.56 (0.41, 0.70)	71.9	0.04*
Hip	9	753	0.17 (0.00, 0.33)	16.9	
Mixed	7	845	0.17 (-0.00, 0.34)	25.9	
On JR waiting-list					
No	59	4400	0.45 (0.32, 0.57)	71.5	0.68
Yes	14	682	0.53 (0.25, 0.80)	66.4	
'Explicit' pain criteria					
None	58	3775	0.46 (0.33, 0.60)	73.3	0.89
Yes	15	1307	0.46 (0.25, 0.66)	63.3	
ACR criteria					
Yes	36	2488	0.45 (0.25, 0.64)	80.2	0.67
No/unclear	37	2594	0.45 (0.33, 0.57)	46.1	
Radiographic requirement					
Yes	40	2586	0.57 (0.39, 0.75)	75.7	0.14
No/Unclear	33	2496	0.33 (0.20, 0.46)	54.3	
Adherence monitored					
Yes	48	3985	0.32 (0.21, 0.43)	60.7	<0.01*
No/Unclear	25	1097	0.81 (0.54, 1.08)	74.4	
Analgesic control/monitored					
Yes	34	2924	0.32 (0.21, 0.43)	45.4	0.09*
No/ Unclear	39	2158	0.60 (0.39, 0.81)	78.3	
Recruitment centre[a]					
Specialist/hospital	26	1468	0.67 (0.41, 0.93)	79.4	<0.01*
GP/Community	29	2524	0.25 (0.16, 0.34)	11.4	
Mixed	7	676	0.17 (0.02, 0.32)	0.0	
Intention-to-treat use					
Yes	46	3559	0.34 (0.24, 0.44)	52.0	0.04*
No/Unclear	27	1523	0.70 (0.43, 0.96)	80.2	
Sample >100/ group					
Yes	4	1108	0.16 (0.00, 0.31)	38.5	0.19
No	69	3974	0.49 (0.37, 0.62)	69.8	
Performance measure					
Walking	37	2783	0.47 (0.29, 0.65)	78.6	0.91
Others	36	2299	0.45 (0.32, 0.59)	53.6	

C. Subgroup analysis – Exercise versus usual care: Quality of life

	No. comp. (No. trials)	No. Patients	Effect Size (95%CI)	I2 (%)	p-value (univariate)
Overall	33	2629	0.21 (0.11, 0.31)	36.4	
Age					
<60 years old	7	446	0.39 (0.10, 0.69)	52.6	0.06*
≥60 years old	26	2183	0.17 (0.06, 0.27)	27.8	
Percentage female[a]					
<60%	11	707	0.20 (0.03, 0.37)	10.5	0.91
60%-<80%	14	1239	0.24 (0.07, 0.40)	43.8	
≥80%	7	633	0.07 (-0.08, 0.22)	0.0	
Mean body mass index[a]					
<30	15	1339	0.19 (0.09, 0.30)	0.0	0.84
≥30	13	913	0.20 (-0.03, 0.43)	64.4	
Joint					
Knee	23	1567	0.27 (0.12, 0.41)	47.9	0.33
Hip	7	585	0.08 (-0.08, 0.25)	0.0	
Mixed	3	477	0.18 (-0.01, 0.36)	0.0	
On JR waiting-list					
No	23	2059	0.38 (0.18, 0.57)	76.7	0.31
Yes	10	570	0.10 (-0.18, 0.38)	58.7	
'Explicit' pain criiteria					
None	25	1823	0.20 (0.06, 0.33)	42.2	0.85
Yes	8	806	0.24 (0.08, 0.40)	17.3	
ACR criteria					
Yes	13	937	0.26 (0.04, 0.47)	59.5	0.74
No/unclear	20	1692	0.19 (0.08, 0.29)	8.3	
Radiographic requirement					
Yes	18	1200	0.26 (0.09, 0.44)	52.6	0.38
No/Unclear	15	1429	0.15 (0.05, 0.26)	0.0	
Adherence monitored					
Yes	25	2207	0.15 (0.07, 0.24)	0.0	0.57
No/Unclear	8	422	0.46 (0.06, 0.87)	72.0	
Analgesic control/monitored					
Yes	15	1358	0.16 (0.03, 0.29)	20.0	0.63
No/ Unclear	18	1371	0.25 (0.09, 0.41)	46.9	
Recruitment centre					
Specialist/hospital	16	1009	0.24 (0.02, 0.46)	62.9	0.57
GP/Community	12	1168	0.21 (0.10, 0.33)	0.0	
Mixed	5	452	0.10 (-0.08, 0.29)	0.0	
Intention-to-treat use					
Yes	24	2210	0.17 (0.05, 0.30)	45.0	0.10*
No/Unclear	9	419	0.37 (0.17, 0.57)	0.0	
Sample >100/ group					
Yes	2	512	0.13 (-0.06, 0.30)	6.3	0.65
No	31	2117	0.23 (0.11, 0.34)	38.4	
QoL tool					
Disease specific	10	645	0.17 (0.01, 0.32)	0.0	0.42
Generic	23	1984	0.24 (0.10, 0.38)	50.2	

Appendix 15 Bayesian program for Winbugs

A. Program for arm level data only i.e. within group differences

```
#Random effect
#multi-arm (include 3 and 4 arms)
# Random effects model for multi-arm trials, continuous outcome
# SMD, arm based data

model{
for(i in 1:ns){
  w[i,1] <- 0
  delta[i,1] <- 0
  mu[i] ~ dnorm(0,.0001)   # vague priors for 24 trial baselines
  for (k in 1:na[i])  {
    var[i,k] <- pow(se[i,k],2)
    prec[i,k] <- 1/var[i,k]        # set precisions
          y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood
          phi[i,k] <- theta[i,k] * Pooled.sd[i]
          theta[i,k] <- mu[i] + delta[i,k]
# deviance arm k, study i
    dev[i,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])/var[i,k]
  }
 for (k in 2:na[i]){
# distributions for trial-specific SMD
   delta[i,k] ~ dnorm(md[i,k], taud[i,k])
   md[i,k] <- (d[t[i,k]] - d[t[i,1]]) + sw[i,k]
#precision of diff in means distributions
  taud[i,k] <- tau *2*(k-1)/k
#adjustment, multi-arm RCTs
  w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]]
# cumulative adjustment for multi-arm trials
  sw[i,k] <-sum(w[i,1:k-1])/(k-1)
 }
 resdev[i] <- sum(dev[i, 1:na[i]])     # residual deviance for study i
}
d[1]<-0

# vague priors for basic parameters
for (k in 2:nt) {d[k] ~ dnorm(0,.0001) }
# vague prior for RE st dev
sd.d ~ dunif(0,10)
var.d <- pow(sd.d,2)
tau <- 1/var.d
```

```
# overall residual deviance
totresdev <- sum(resdev[])
# all pairwise differences
for (c in 1:(nt-1)) { for (k in (c+1):nt) {pwdiff[c,k] <- (d[k]-d[c])  } }


for (k in 1:nt) {
 # assumes events are 'good'
rk[k] <- nt+1-rank(d[],k)
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}
}
```

B. Program for arm level and trial level data i.e. within group and between group differences

```
#Random effect
#multi-arm (include 3 and 4 arms)
# Random effects model for multi-arm trials, continuous outcome
# SMD, arm based data and trial based data

model{
for(i in 1:ns.a){   #ARM-LEVEL DATA
  w[i,1] <- 0
  delta[i,1] <- 0
  mu[i] ~ dnorm(0,.0001)   # vague priors for trial baselines
  for (k in 1:na[i])  {
    var[i,k] <- pow(se[i,k],2)
    prec[i,k] <- 1/var[i,k]        # set precisions
          y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood
          phi[i,k] <- theta[i,k] * Pooled.sd[i]
          theta[i,k] <- mu[i] + delta[i,k]
# deviance arm k, study i
    dev[i,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])/var[i,k]
  }
 for (k in 2:na[i]){
# distributions for trial-specific SMD
   delta[i,k] ~ dnorm(md[i,k], taud[i,k])
   md[i,k] <- (d[t[i,k]] - d[t[i,1]]) + sw[i,k]
#precision of diff in means distributions
  taud[i,k] <- tau *2*(k-1)/k
#adjustment, multi-arm RCTs
  w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]]
# cumulative adjustment for multi-arm trials
  sw[i,k] <-sum(w[i,1:k-1])/(k-1)
 }
 resdev.a[i] <- sum(dev[i, 1:na[i]])     # residual deviance for study i
}
```

```
for(i in 1:ns.t2){   #TRIAL-LEVEL DATA, 2-arm trials
          y.t[i,2] ~ dnorm(phi.t[i,2], prec.t[i,2]) # normal likelihood
# deviance arm k, study i
    resdev.t[i] <- (y.t[i,2]-phi.t[i,2])*(y.t[i,2]-phi.t[i,2])*prec.t[i,2]
 }


for(i in (ns.t2+1):(ns.t2+ns.t3)) {    #TRIAL-LEVEL DATA: 3-ARM TRIALS

   for (k in 1:(na.t[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na.t[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var.t[i,(k+1)]*equals(j,k)
       }
     }
   Omega[i,1:(na.t[i]-1),1:(na.t[i]-1)] <- inverse(Sigma[i,,])  #Precision
# multivariate normal likelihood for 3-arm trials
   y.t[i,2:na.t[i]] ~ dmnorm(phi.t[i,2:na.t[i]],Omega[i,1:(na.t[i]-
1),1:(na.t[i]-1)])

#Deviance contribution for trial i
   for (k in 1:(na.t[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y.t[i,(k+1)] - phi.t[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na.t[i]-1)], ydiff[i,1:(na.t[i]-1)])
                }
   resdev.t[i]<- inprod2(ydiff[i,1:(na.t[i]-1)], z[i,1:(na.t[i]-1)])
 }

for(i in 1:(ns.t2+ns.t3)){   #TRIAL LEVEL DATA: RANDOM EFFECTS MODEL
  w.t[i,1] <- 0
  for (k in 2:na.t[i])  {
    var.t[i,k] <- pow(se.t[i,k],2)
    prec.t[i,k] <- 1/var.t[i,k]         # set precisions
          phi.t[i,k] <- delta.t[i,k] * Pooled.sd.t[i]
# distributions for trial-specific SMD
   delta.t[i,k] ~ dnorm(md.t[i,k], taud.t[i,k])
   md.t[i,k] <- (d[t.t[i,k]] - d[t.t[i,1]]) + sw.t[i,k]
#precision of diff in means distributions
  taud.t[i,k] <- tau *2*(k-1)/k
#adjustment, multi-arm RCTs
  w.t[i,k] <- delta.t[i,k] - d[t.t[i,k]] + d[t.t[i,1]]
# cumulative adjustment for multi-arm trials
  sw.t[i,k] <-sum(w.t[i,1:k-1])/(k-1)
 }
}

d[1]<-0
```

```
for (k in 2:nt){d[k] ~ dnorm(0,.0001) } # vague priors for basic
parameters
sd.d ~ dunif(0,10)                    # vague prior for RE st dev
var.d <- pow(sd.d,2)
tau <- 1/var.d
# overall residual deviance
totresdev.a <- sum(resdev.a[])
totresdev.t<-sum(resdev.t[])

# all pairwise differences
for (c in 1:(nt-1)) { for (k in (c+1):nt) {pwdiff[c,k] <- (d[k]-d[c])  } }
for (k in 1:nt) {
 # assumes events are 'good'
rk[k] <- nt+1-rank(d[],k)
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}

#all possible pair-wise comparison
for (c in 1:(nt-1)) {
 for (k in (c+1):nt) {
  SMD[c,k] <- (d[k]-d[c])
                }
        }
}
```

Appendix 16 Network side split – Relative exercise efficacy: Pain, function, performance and quality of life

A. Pain

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>|z|	
1 6	-.8152116	.3075985	-1.14888	.240504	.3336689	.3901575	0.392	.5236189
1 4	-1.035143	.3045988	-.3066422	.2461188	-.7285004	.3916186	0.063	.5132119
1 5	-.095269	.3351781	-.516621	.2470894	.421352	.4164352	0.312	.5226737
2 6	-.8128503	.2954439	-.4669747	.1858819	-.3458756	.3489486	0.322	.5232084
2 4	.0862144	.2475545	-.31004	.2169932	.3962544	.3292652	0.229	.5226443
2 5	.0829953	.208784	.0970792	.2448306	-.0140839	.321778	0.965	.5262166
3 6	-.8080597	.2744245	-1.469015	.33176	.6609557	.4311777	0.125	.512435
3 4	-1.063624	.3209872	-.3086946	.2921767	-.7549294	.4340654	0.082	.5133409
3 5	.4727619	.6580538	-.5493351	.2468025	1.022097	.702813	0.146	.5169744
4 6	-.4917782	.1045462	-.1469816	.2156953	-.3447965	.2393052	0.150	.5149916
4 5	.1207115	.7155758	.2306912	.1374173	-.1099797	.7286756	0.880	.5250352
5 6	-.6025586	.1224811	-.8351351	.2293748	.2325765	.2597609	0.371	.5233641

B. Function

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>|z|	
1 6	-.4954886	.3098013	-.5987786	.285097	.10329	.4210179	0.806	.6025632
1 4	-.2108495	.3120856	-.126588	.2927106	-.0842615	.4282305	0.844	.6025822
1 5	.175704	.465022	.1190215	.2592123	.0566825	.5323217	0.915	.6029969
2 6	-.8527704	.3994406	-.56817	.1949974	-.2846004	.444614	0.522	.6004119
2 4	-.0887613	.2369095	-.4139523	.2574827	.325191	.34997	0.353	.6007983
2 5	.0674359	.2333414	.0517797	.2686036	.0156562	.3559206	0.965	.602663
3 6	-.6657614	.3070963	-.9569768	.3752785	.2912154	.4853072	0.548	.6004666
3 4	-.5964789	.3656956	-.2398894	.3253298	-.3565895	.4894676	0.466	.6001951
3 5	.3371541	.7232646	-.1621658	.2751743	.4993199	.7738426	0.519	.6000416
4 6	-.3536727	.1226906	-.494487	.2277859	.1408143	.2585269	0.586	.6025349
4 5	-.3791741	.4953434	.3622059	.1522416	-.74138	.5182004	0.153	.5930116
5 6	-.7386111	.1368283	-.4978091	.2508195	-.2408019	.2856299	0.399	.6004529

C. Performance

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>|z|	
1 6	-.8613917	.3087427	-.9201929	.2142784	.0588012	.3758013	0.876	.4739605
1 4	-.6082192	.2472157	-.3855201	.2512261	-.2226991	.3524482	0.527	.4722372
1 5	-.308791	.3070921	-.4675803	.2306967	.1587893	.3843085	0.679	.4754823
2 6	-.585665	.2704661	-.6114036	.162876	.0257386	.3157903	0.935	.4746381
2 4	-.1220891	.2124999	-.2676955	.1922149	.1456065	.286633	0.611	.4729318
2 5	-.2292707	.1832721	.0395971	.210908	-.2688678	.2793404	0.336	.4723153
3 6	-.5379607	.2574559	-.3359258	.3798923	-.2020348	.4593549	0.660	.4736766
3 4	.1973271	.3691286	-.2184036	.2722317	.4157307	.4587543	0.365	.4707599
3 5	.0516997	.6205582	.0109859	.2436009	.0407138	.666659	0.951	.4741
4 6	-.3738369	.0976434	-.5047831	.1856052	.1309463	.2096181	0.532	.4725181
4 5	.0733801	.330833	.0905954	.1246508	-.0172153	.3536785	0.961	.4746961
5 6	-.515757	.1082578	-.4117013	.1919741	-.1040557	.2200976	0.636	.4729856

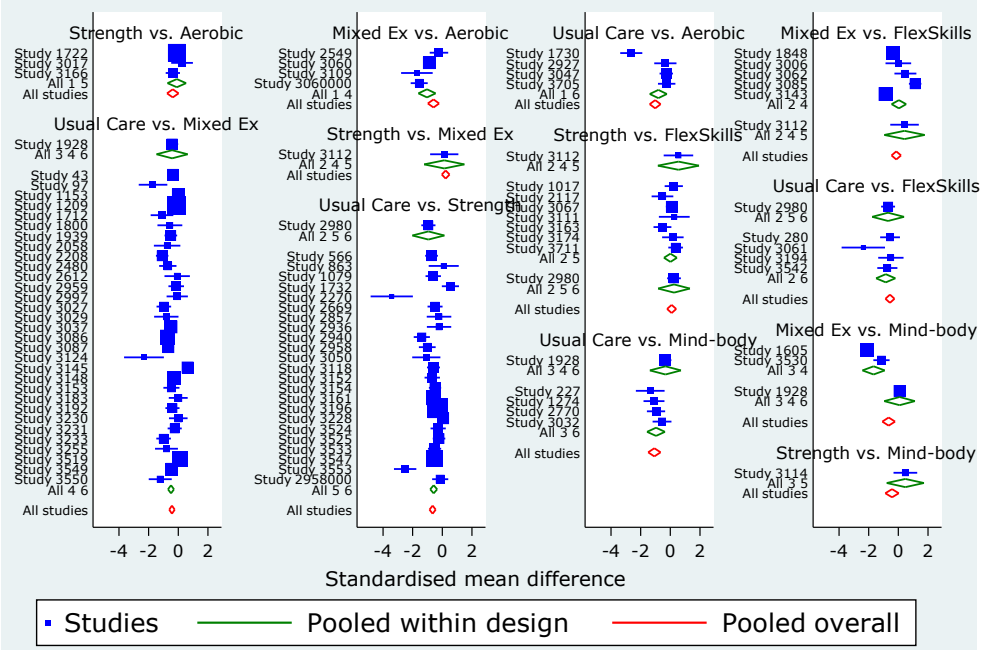
D. QoL

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>|z|	
1 6	.	.	.	.	.	.	.	.
2 4	-.437676	.2334468	.1462573	.2237425	-.5839333	.3258012	0.073	.2050863
2 5	.125791	.1891693	-.4580717	.2623667	.5838627	.3257937	0.073	.2050828
3 6	-.2224933	.1898343	-.1800116	.2998055	-.0424817	.3563815	0.905	.2190869
3 4	.0588979	.2184562	-.1318517	.2374747	.1907496	.3227516	0.555	.2152205
4 6	-.1805387	.079154	-.1873937	.2145692	.006855	.2287432	0.976	.2194878
4 5	-.4171229	.3277362	.1171926	.1147797	-.5343155	.3472541	0.124	.1979139
5 6	-.2259204	.105915	-.317447	.2428637	.0915266	.2644771	0.729	.2202541

No evidence of disagreement for each comparison pair if p>0.05 (in blue box).

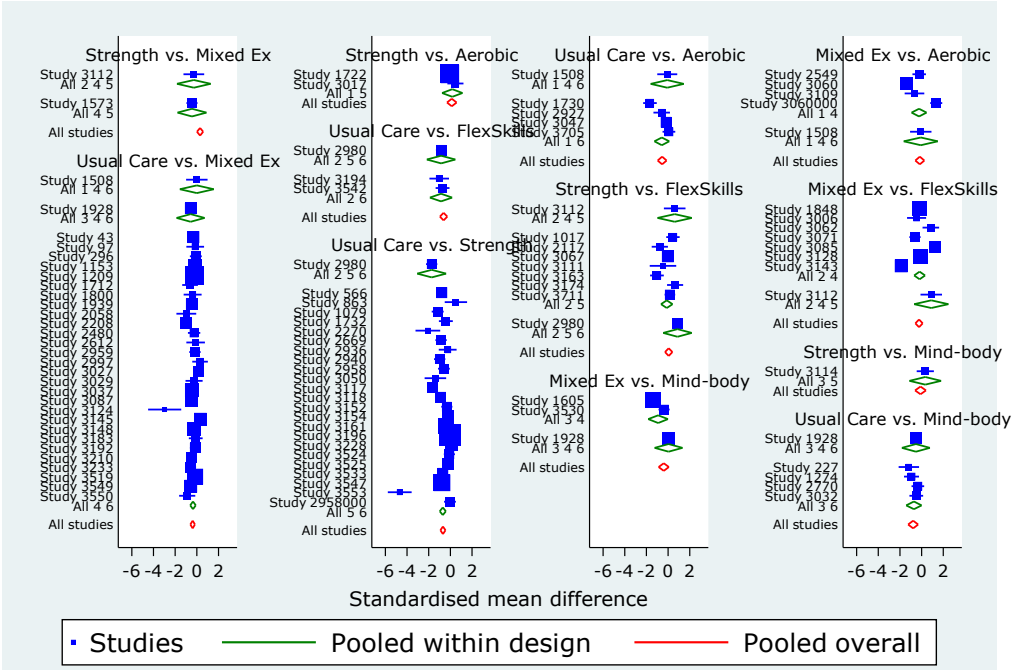
Appendix 17 Design-by-treatment forest plot – Relative exercise efficacy: Pain, function, performance and quality of life

A. Pain



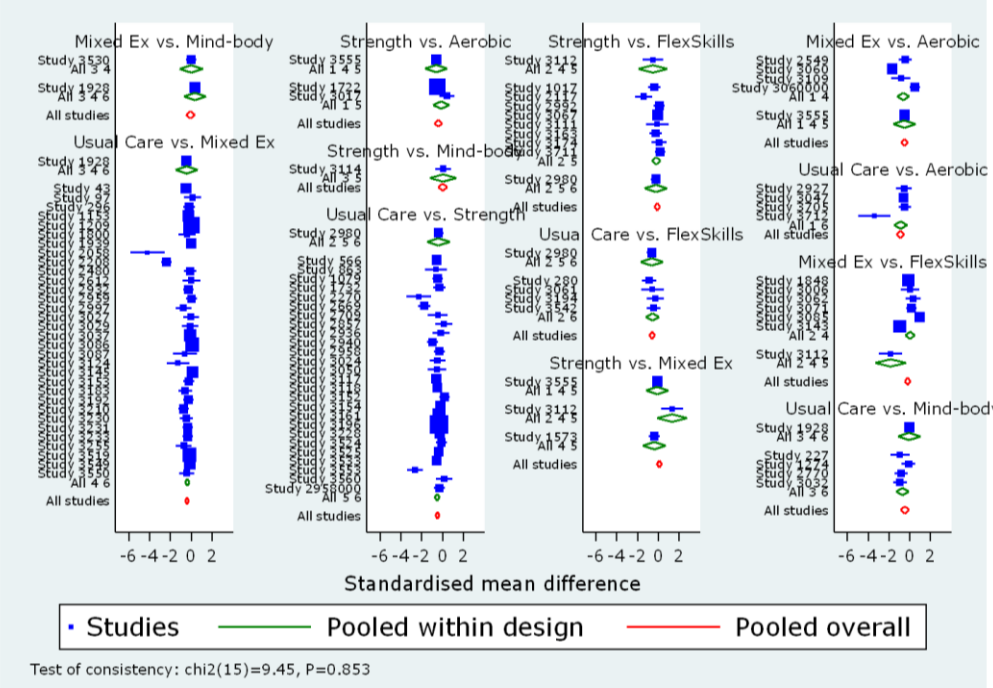
Test of consistency: chi2(12)=18.23, P=0.109

B. Function

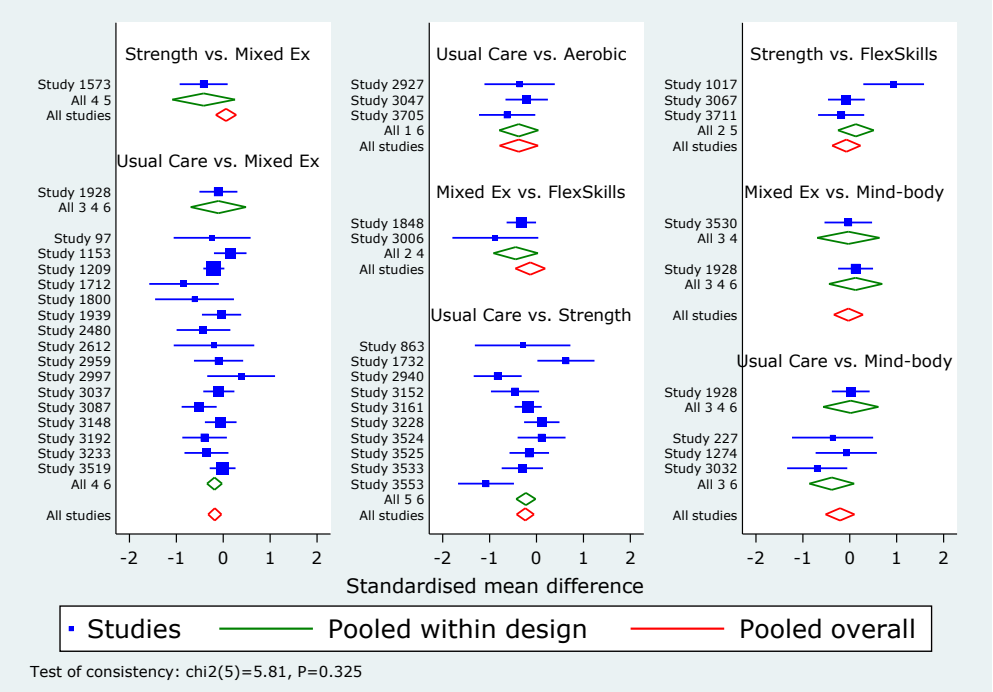


Test of consistency: chi2(15)=9.08, P=0.873

C. Performance



D. Quality of life



There is no inconsistency between study designs when there is overlap between green diamonds within the same treatment comparison. Each green diamond represents the pooled estimates for different study design.

Appendix 18 Sensitivity analysis – Relative exercise efficacy: Pain, function, performance and quality of life

	Effect size (95% credible interval) *versus usual care*			
	Primary analysis	Sensitivity analysis		
		Allocation concealment -low risk	SD not imputed	Sample size ≥30/arm
Pain	89 trials (n=7184)	41 trials (n=3975)	86 trials (n=6666)	37 trials (n=5245)
Aerobic	1.11 (0.69, 1.54)	0.43 (-0.39, 1.26)	1.12 (0.66, 1.57)	0.95 (0.43, 1.47)
Mind-body	1.11 (0.63, 1.59)	1.60 (0.95, 2.24)	1.10 (0.61, 1.60)	1.21 (0.48, 1.94)
Strength	0.73 (0.49, 0.98)	0.50 (0.19. 0.80)	0.74 (0.48, 1.00)	0.53 (0.24, 0.82)
Flex/Skills	0.65 (0.29, 1.00)	0.29 (-0.15, 0.73)	0.65 (0.29, 1.01)	0.35 (-0.12, 0.83)
Mixed	0.47 (0.26, 0.69)	0.40 (0.16, 0.64)	0.46 (0.24, 0.69)	0.27 (0.01, 0.53)
Function	87 trials (n=7153)	42 trials (n=3951)	85 trials (n=6843)	39 trials (n=5342)
Aerobic	0.59 (0.10, 1.07)	0.22 (-0.52, 0.95)	0.59 (0.10, 1.08)	0.45 (-0.26, 1.15)
Mind-body	0.81 (0.27, 1.36)	1.04 (0.46, 1.6)	0.81 (0.26, 1.37)	1.03 (0.13, 1.94)
Strength	0.76 (0.48, 1.03)	0.60 (0.34, 0.86)	0.75 (0.46, 1.04)	0.65 (0.31, 1.00)
Flex/Skills	0.68 (0.28, 1.09)	0.25 (-0.10, 0.61)	0.66 (0.24, 1.08)	0.60 (0.08, 1.13)
Mixed	0.43 (0.18, 0.69)	0.30 (0.09, 0.51)	0.44 (0.19, 0.70)	0.37 (0.05, 0.70)
Performance	95 trials (n=6760)	41 trials (n=3579)	93 trials (n=6955)	38 trials (n=4911)
Aerobic	1.05 (0.63, 1.48)	0.65 (-0.18,1.49)	1.06 (0.63, 1.48)	0.95 (0.42, 1.49)
Mind-body	0.53 (0.01, 1.05)	0.66 (-0.15, 1.47)	0.53 (0.02, 1.05)	0.05 (-0.98, 1.08)
Strength	0.55 (0.32, 0.78)	0.44 (0.14, 0.74)	0.53 (0.30,0.76)	0.47 (0.17, 0.77)
Flex/Skills	0.68 (0.34, 1.03)	0.37 (-0.07, 0.82)	0.64 (0.29, 0.99)	0.47 (-0.01, 0.95)
Mixed	0.48 (0.27, 0.69)	0.36 (0.11, 0.60)	0.50 (0.29, 0.71)	0.42 (0.15, 0.69)
Quality of life	40 trials (n=3190)	26 trials (n=2486)	NA	18 trials (n=2281)
Aerobic	0.39 (-0.06, 0.83)	0.62 (-0.16, 1.42)	-	0.20 (-0.32, 0.73)
Mind-body	0.24 (-0.09, 0.58)	0.42 (-0.11, 0.96)	-	0.00 (-0.40, 0.41)
Strength	0.26 (0.05, 0.47)	0.20 (-0.05, 0.45)	-	0.11 (-0.09, 0.30)
Flex/Skills	0.33 (-0.03, 0.68)	0.19 (-0.23, 0.56)	-	0.34 (0.04, 0.63)
Mixed	0.19 (0.04, 0.35)	0.12 (-0.06, 0.31)	-	0.14 (0.01, 0.27)

(cont.)

Sensitivity analysis performed to show if the underlying assumptions (i.e. high risk of allocation concealment, imputed standard deviation (SD), sample size <30/arm) would significantly alter the conclusion of primary analysis.