

THE EFFECT OF A COMBINED PROGRAMME OF DIETARY RESTRICTION AND
PHYSICAL ACTIVITY ON THE PHYSICAL FUNCTION AND BODY
COMPOSITION OF OBESE MIDDLE-AGED AND OLDER ADULTS WITH KNEE
OSTEOARTHRITIS

BY
ASMA ALRUSHUD

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ABSTRACT

The work reported in this thesis was driven by the limited existing evidence investigating the effect of a combined intervention programme of dietary restriction and physical activity on overweight/obese older adults with knee osteoarthritis (OA).

This thesis comprises three phases: 1) a systematic literature review to synthesise the effectiveness of a combined programme on the musculoskeletal function of this population; 2) the development of a protocol to evaluate the feasibility and acceptability of a combined programme; and 3) a feasibility study conducted using a mixed methods approach to collect data to inform a definitive trial.

One pilot and two definitive trials (n=794) and two articles reporting additional data and outcome measures for one of the randomised controlled trials (RCTs) were included in the systematic review. Only mobility (a 6-minute walk test) at 6 months was possible to evaluate by meta-analysis and a pooled random effect of 15.05 (95% CI: -11.77 to 41.87) across two trials (with n=155 participants) did not support a combined intervention programme. Clear differences in relation to a reduced body weight and increased 6-minute walk test result in the intervention compared with the control groups were shown by narrative synthesis. However, the quality of the evidence was not clear. In addition, no UK studies were identified.

A single-centre feasibility study, consisting of one arm (a combined programme) with an embedded qualitative component (a focus group for participants and a questionnaire for physiotherapy staff), was conducted at the Royal Orthopaedic Hospital and the University of Birmingham. The programme was found to be acceptable and feasible for the target population and physiotherapy staff involved in terms of integration and expansion.

The results of the feasibility study may inform the design of future work to optimise diet and exercise interventions utilising a multimodal approach.

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2. Alrushud, A.S., Rushton, A.B., Bhogal, G., Pressdee, F. and Greig, C.A., 2018. Effect of a combined programme of dietary restriction and physical activity on the physical function and body composition of obese middle-aged and older adults with knee OA (DRPA): protocol for a feasibility study. *BMJ open*, 8(12), p. e021051.
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ABBREVIATIONS

25-OHD	25-hydroxyvitamin D
ACR	American College of Rheumatology
Acrp30	Adiponectin
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADAPT	Arthritis, Diet and Activity Promotion Trial
ADLs	Activities of daily living
ALP	Alkaline phosphatase
AMI	Arthrogenic muscle inhibition
AMRC	Association of Medical Research Charities
AMSTAR2	A MeaSurement Tool to Assess systematic Reviews
ApM1	Adiponectin
BIA	Body impedance analysis
BMI	Body mass index
BML	Bone marrow lesions
BMR	Basal metabolic rate
C1M	Markers of MMP mediated degradation of type I collagen
CI	Confidence interval
CMO	Chief Medical Office
COMP	Collagen oligomeric matrix protein
CONSORT	Consolidated Standards of Reporting Trials
COREQ	COnsolidated criteria for REporting Qualitative research
COX-2	Cyclooxygenase
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CRPM	Marker of C-reactive protein (CRP) degradation
CTX-1	Cross-linked C-terminal telopeptide of type I collagen
DRPA	Dietary restriction physical activity
ECM	Extracellular matrix
ELISA	Enzyme-linked immunosorbent assay
ERN	Ethics Research Number
EULAR	European League Against Rheumatism

FAST	Fitness Arthritis and Seniors Trial
GBP28	Adiponectin
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HRA	Health Research Authority
HWFL	Healthy Weight for Life
IDEA	Intensive Diet and Exercise for Arthritis
IGF-1	Insulin-like growth factor-1
IL	Interleukin
IPA	Interpretative Phenomenological Analysis
IPFP	Infrapatellar fat pad
ISRCTN	International Standard Randomised Controlled Trials Number
KS	Keratan sulphate
LASA	Longitudinal Aging Study Amsterdam
LLI	Leg length inequality
MCID	Minimum Clinically Important Difference
MCRN	NIHR Medicines for Children Research Network
MMP	Matrix metalloproteinases
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NJR	National Joint Registry
NSAIDs	Non-steroidal anti-inflammatory drugs
NSW GHS	New South Wales Get Healthy Service
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
ob	Obese gene
Ob-Rb	leptin receptor
OC	Osteocalcin
OIS	Optimal information size
OP	Organising participants
OPT	Organising physiotherapists

PACT	Physical Activity, Inflammation and Body Composition
PASS	Patient Acceptable Symptom State
PG	Proteoglycan
PICP	Procollagen type I carboxyterminal propeptide
PIICP	Procollagen type II carboxyterminal propeptide
PIINP	N-terminal type IIA collagen N-propeptide
PPIE	Patient and public involvement and engagement
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PROSPERO	International Prospective Register of Systematic Reviews
PT	Physiotherapy
QoL	Quality of life
RCT	Randomised controlled trial
RG	Research governance
RNA	Ribonucleic acid
ROH	Royal Orthopaedic Hospital
ROM	Range of motion
SAA3	Serum amyloid 3
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36 Health Survey Questionnaire
SportExR	School of Sport, Exercise and Rehabilitation Sciences
SR	Systematic review
TENS	Transcutaneous electrical nerve stimulation
TGF- β	Transforming growth factor- β
TIDeR	Template for Intervention Description and Replication
TKR	Total knee replacement
TNF- α	Tumour necrosis factor alpha
UoB	University of Birmingham
WAT	White adipose tissue
WC	Waist circumference
WCPT	World Confederation for Physical Therapy
WHO	World Health Organisation
WML	Weight maintenance level

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CHAPTER 1

INTRODUCTION

The research presented in this thesis investigates the influence of a combined programme of physical activity and dietary restriction on the physical function of overweight and obese individuals, who are middle-aged and older, with knee osteoarthritis (OA). This introductory chapter outlines how databases, mainly Google Scholar, were searched to identify the most recent systematic reviews (SR), reviews, and randomised controlled trials (RCTs) relevant to this topic. Websites of OA and knee OA organisations were also accessed to identify up-to-date guidelines regarding the assessment and management of the condition. Four main key areas were covered: the background of knee OA, ageing, physical activity and dietary restrictions. A standardised definition, pathophysiological changes, diagnosis, prevalence and incidence, risk factors, and guidelines for management, especially the role of physiotherapy, were the most important points covered when searching the literature for information regarding knee OA. Ageing-related issues, including demographic data, the most common changes in ageing (at the muscle, bone and joint levels) and the relation between ageing and OA were reviewed to build the second section of this chapter. More information about the main intervention of this thesis (physical activity and dietary restriction) is highlighted in the last two sections of this chapter.

The intervention study reported in this thesis was conducted in the UK. Hence, most of the information presented in this initial chapter, such as prevalence data for the disease and recommended guidelines for physical activity, focuses on the UK.

1.1 Knee osteoarthritis

1.1.1 Definition

Osteoarthritis has been defined in a number of ways. For example, a working definition of OA was developed by Brooks (2003), who defined OA as “a condition of synovial joints characterised by cartilage loss and evidence of accompanying periarticular bone response” (p.689). OA is also defined as “the most common musculoskeletal condition, is a long-term chronic disease involving the thinning of cartilage in joints which results in bones rubbing together, creating stiffness, pain, and impaired movement. OA is related with age, but is associated with a variety of both modifiable and non-modifiable risk factors, including obesity, lack of exercise, genetic predisposition, bone density, occupational injury, trauma, and gender” (Woolf and Pfleger, 2003; Wittenauer, Smith and Aden, 2013, p.3). Historically, most OA definitions described the causes, characteristics and effect of the condition. However, definitions have been developed recently that are more specific. For example, Favero et al. (2015) defined OA as “the most common joint disease, causing disability and reduction of quality of life (QoL) and participation in social activity” (p.1).

In addition to the numerous definitions of OA within the literature, health organisations and research societies have published specific definitions of OA. For instance, the American College of Rheumatology (ACR) defines OA as a “heterogeneous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins” (Sarzi-Puttini et al., 2005, p.1). The World Health Organisation (WHO) defines OA as “a long-term chronic disease characterised by the deterioration of cartilage in joints which results in bones rubbing together and creating stiffness, pain, and impaired movement. The disease most commonly affects the joints in the knees, hands, feet, and spine and is relatively common in

shoulder and hip joints” (WHO, 2013, p.1). Arthritis Research UK and the Arthritis Foundation have defined OA as “the most common musculoskeletal condition in older people. Around a third of people aged 45 years and over in the UK, a total of 8.75 million people, have sought treatment for osteoarthritis. Osteoarthritis affects the joints, causing them to become painful and limiting their movement. The condition occurs in different sites, but often affects the knee, hip or finger joints” (Arthritis Research UK, 2013, p.5).

However, the Osteoarthritis Research Society International (OARSI) endorsed the most recent and standardised definition of OA in 2016, which has achieved global agreement and facilitated communication in the field: “Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness” (Mobasheri et al., 2017, p. 200).

1.1.2 Pathophysiology of OA

The aetiology of OA remains unknown but it is characterised as a non-inflammatory disease, despite the contribution of inflammation to its symptoms and progression (Spector et al., 1997; Conrozier et al., 1998; Conde, Scotece et al., 2011). It is also described as a heterogeneous disorder, due to the pathological changes that take place in all the connective tissues within and around the joint, including the articular cartilage, subchondral bone, synovium, the skeletal muscle, and the nervous system (Aigner, Schmitz, and Soder, 2010; Hunter, 2011; Loeser et al., 2012; Hunter, 2015). However, OA is known to be most common

in the knee joints, feet, hands and spine and is relatively common in hip and shoulder joints (Wittenauer, Smith and Aden, 2013). In knee OA specifically, the whole joint is affected by the disease, including cartilage loss, synovial inflammation, subchondral bone changes and meniscus degeneration (Figure 1.1) (Loeser et al., 2012). More details of cartilage and subchondral bone degeneration and the link between this degeneration and the release of cartilage, bone and joint remodelling biomarkers are presented in the following sections.

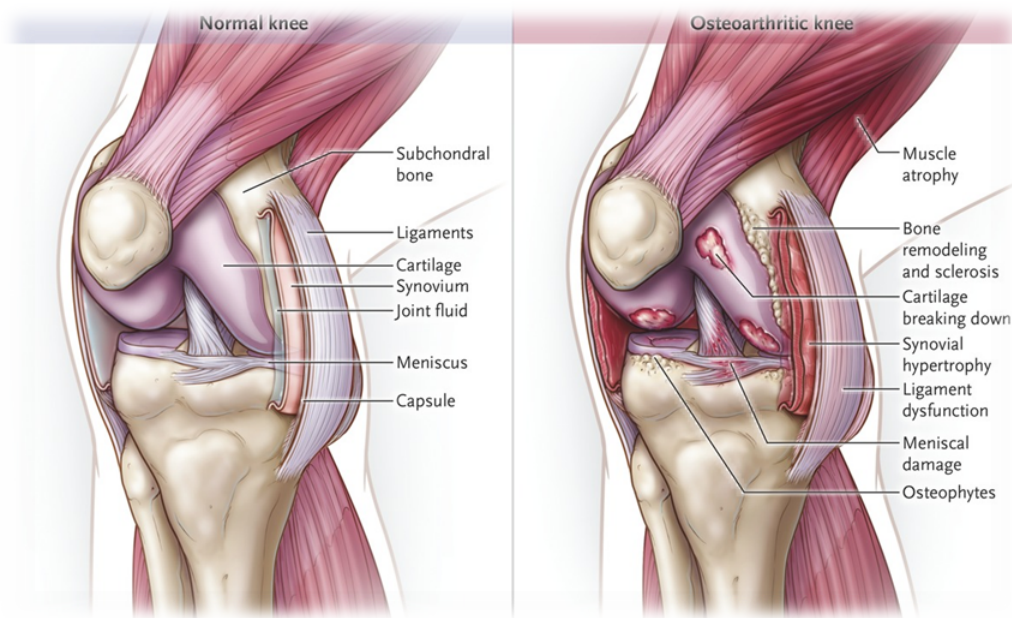


Figure 1.1 Schematic of the knee joint, showing the synovial joint tissues affected in OA (Hunter, 2015)

1.1.2.1 OA and cartilage degradation

The knee joint is a synovial joint that consists of different features, including articular cartilage, an articular capsule, synovial cavity, synovial fluid and fatty pads (Singh, 2015). Articular cartilage is designed to allow smooth movement of the knee joint across the range of motion (ROM) (Buckwalter, Mankin and Grodzinsky, 2005). (see Table 1.1).

Table 1.1 Summary of the articular cartilage and its role under normal and abnormal conditions

Structure of articular joint	Under normal conditions	Under abnormal conditions
The cartilage in the knee joint is very specialised tissue, which can be morphologically separated into distinguished zones: the superficial zone, the transitional zone and the deep zone, each with its own function and cellular organisation (Buckwalter, Mankin and Grodzinsky 2005). The superficial zone consists of parallel collagen fibres and chondrocyte cells, which are the only cells found in articular cartilage (Archer and Francis-West, 2003). These cells are surrounded by the extracellular matrix (ECM), which comprises high collagen proteins, such as collagen types II, IV, IX and XI, and a low proteoglycan (PG) concentration, including aggrecans (Buckwalter, Mankin and Grodzinsky 2005). The majority of the ECM is formed by the inter-territorial matrix, which contains wide-diameter collagen fibrils, consisting of collagen oligomeric matrix protein (COMP), plentiful PGs, and type II collagen (Buckwalter, Mankin and Grodzinsky 2005; Guilak et al. 2006).	Chondrocytes appear to be quiescent, and this maintains the integrity of the ECM (Hunziker, Quinn and Häuselmann 2002). The primary function of the inter-territorial matrix is to maintain the tensile stiffness and strength of the ECM (Buckwalter, Mankin and Grodzinsky 2005; Guilak et al. 2006). The procollagen form of type II collagen is synthesised by pre-propeptide with C- and N-terminal globular domains. These domains are removed later to give tropocollagen. This splinting process, through extracellular proteinases C- and N-proteinase, PIICP, and PIINP/PIIANP, is necessary to ensure the prevention of intracellular helix formation. Normally, the levels of PIICP and PIINP/PIIANP are very low in adult cartilage and reach their highest proportion in foetal cartilage (Nelson et al. 1998; Garvican et al. 2010).	Abnormal conditions, such as biochemical conditions or mechanical stress, can cause several alterations to the chondrocyte composition, including overt hypertrophy (marked by the up-regulation of collagen X), cellular proliferation, and the secretion of matrix remodelling proteins and matrix-degrading enzymes. Furthermore, chondrocyte clusters associated with the calcification of chondrocytes in the subchondral bone lead to an advanced tidemark and vascular intrusion (Goldring 2012a). Cartilage contains several matrix-degrading enzymes, such as matrix metalloproteinases (MMP) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) aggrecanases (Goldring 2012b). It has been shown that MMP-1, MMP-3, and MMP-13 enzymes are involved in the progression of OA due to their role in the degradation of type II collagen and the activation of aggrecanases, such as ADAMTS-4 and ADAMTS-5, which degrade aggrecan PG (Goldring 2012b). Normally, a PG coating protects collagen from degradation by MMP-1 and MMP-13. When the PG coating is removed and the collagen network subsequently degrades, the irreversible degradation of cartilage begins. Moreover, protein fragments are produced as a result of the degradation of cartilage matrix proteins. These fragments may lead to further matrix destruction by interacting with inflammatory cytokine receptors, matrix-degrading proteinases, and chemokines (Goldring 2012b).

Collagen oligomeric matrix protein (COMP) and N-terminal type IIA collagen N-propeptide (PIIANP) are two important markers of cartilage remodelling in knee OA. There is an association between high serum COMP level and knee OA severity (Clark et al., 1999; Vilim et al., 2002). The PIIANP isoform is produced by chondrocytes in human OA cartilage (Zhu, Sandell, and Matyas, 2001; Garvican et al., 2010), which indicates a hypertrophic change and a shift in cartilage type like that of a developing joint (Garvican et al., 2010). Measuring the PIIANP isoform, either in relation to concentrations of PIINP or in absolute concentrations, may indicate a shift in phenotype towards that of OA chondrocytes (Garvican et al., 2010).

1.1.2.2 OA and subchondral bone degeneration

The remodelling of subchondral bone that occurs in OA not only precedes cartilage degeneration, but may also guide it (Bailey and Mansell, 1997; Tat et al., 2010). Many pathological changes, such as the formation of bone marrow lesions (BML) and osteophytes, the thickening of cortical bone, the formation of sclerotic bone and increased subchondral bone volume, despite reduced bone mineral density, can be observed in OA subchondral bone (Radin and Rose, 1986; Gryn timer et al., 1991; Li and Aspden, 1997). These pathological changes would probably lead to weakness in the bones and minimise the bone capacity to absorb and reduce forces transmitted through the joint during mobility (Neogi, 2012). The major structural component of bone is fibrous type I collagen, which accounts for approximately 90% of the organic matrix (Mansell and Bailey, 1998). To measure the synthesis of type I collagen, the level of procollagen type I carboxy-terminal propeptide (PICP) is used (Mansell and Bailey, 1998). However, the metabolism of type I collagen is increased in OA subchondral bone, together with altered fibril cross-linking and subsequent hypomineralisation (Mansell and Bailey, 1998).

Furthermore, the osteoblast phenotype changes, referred to as the phenotypic shift, in the ratio of type I collagen homo/heterotrimer in OA subchondral bone (Bailey and Knott, 1999). In OA, the structural integrity of subchondral bone undergoes several changes, which lead to significant cartilage degradation (Radin et al., 1978; Radin and Rose, 1986). For example, thinning of the cartilage layer is a result of the thickening of the subchondral plate during OA (Radin et al., 1978; Shimizu et al., 1993). In addition, cartilage deformation is affected by bone cysts and BML (Kothari et al., 2010; Tanamas et al., 2010). Importantly, bone-specific type I collagen level in bone turnover can be determined by the release of the C-terminal of type I collagen (CTX-1) (Garnero et al., 2003). In summary, PICP and CTX-1 are important biomarkers of bone remodelling in knee OA.

1.1.2.3 OA and adipokines

In OA, inflammation can occur as a primary event or secondary to biochemical changes within the cartilage (Conde, Gomez et al., 2011). Obesity is classified as a chronic low-grade inflammatory status, which is mostly related to the release, by white adipose tissue (WAT), of a plethora of factors of a pro-inflammatory nature, including classical cytokines, such as interleukins (IL) (IL-1 and IL-6), tumour necrosis factor alpha (TNF- α), adipokines, such as leptin, adiponectin, resistin and visfatin, and other recently identified factors, such as chemerin, lipocalin, and serum Amyloid 3 (SAA3) (Hotamisligil, Shargill and Spiegelman, 1993; Fantuzzi, 2008; Conde, Gomez et al., 2011; Conde, Scotece et al., 2011). Adipokines are the main secretion product of WAT, which is a highly metabolic, active endocrine organ involved in activities such as the modulation of immune and inflammatory responses in addition to glucose and lipid metabolism (Gualillo, González-Juanatey, and Lago 2007; Conde, Scotece et al. 2011). However, certain adipokines, such as leptin and adiponectin,

can be considered as potential factors that could contribute to obesity, inflammation and arthritis (Conde, Scotece et al., 2011).

Leptin

Leptin is a 16 kDa non-glycosylated peptide hormone, which is encoded by the obese (ob) gene. Although this hormone is secreted by adipocytes, it requires inflammatory mediators for its synthesis. There is a genetic correlation between leptin and OA development, as the leptin gene is increasingly expressed in the OA cartilage chondrocyte (Iliopoulos, Malizos and Tsezou, 2007; Yan et al., 2018). In addition to this genetic correlation, there is an inflammatory relationship between leptin and OA (Yan et al., 2018). Furthermore, leptin serum levels are usually significantly high in obese adults (Vuolteenaho, Koskinen, and Moilanen 2014; Yan et al., 2018). Patients with OA also experience symptoms of joint relief upon losing weight (Miller et al., 2004; Yan et al., 2018). Overall, leptin has been shown to participate in the inflammatory response and may also play a role in OA development and progression (Scotece et al., 2014; Yan et al., 2018). Circulating levels of leptin are related to the amount of body fat and WAT mass (Gualillo et al., 2000; Conde, Scotece et al., 2011). The significant role of leptin in the pathophysiology of OA is now clear (Conde, Scotece et al., 2011) and is because of its anabolic activities in cartilage. It has been shown that leptin is more highly expressed in the osteoarthritic cartilage of humans compared with normal cartilage. Serum leptin is significantly higher in obese adults compared with non-obese (Vuolteenaho, Koskinen and Moilanen, 2014; Yan et al., 2018). It has been shown that leptin participates in the inflammatory response and it may play a role in OA development and progression (Scotece et al., 2014; Yan et al., 2018).

Mechanistically, leptin stimulates the synthesis of insulin-like growth factor-1 (IGF-1) and transforming growth factor-beta (TGF- β) at both the messenger RNA (mRNA) and protein levels, which can exert anabolic activities in the metabolism of joint cartilage (Dumond et al., 2003; Conde, Scotece et al., 2011). Interestingly, obese patients have higher levels of leptin, which is required to protect their cartilage from osteoarthritic degeneration (Conde, Scotece et al., 2011). Body mass index (BMI) was also found to be significantly correlated to a high concentration of leptin in synovial fluid ($r=0.572$, $P<0.01$) when measured in older subjects with severe knee OA ($n=20$) and aged 56-80 years (Dumond et al., 2003; Conde, Scotece et al., 2011).

However, leptin can act as a pro-inflammatory factor in cartilage metabolism, indicating a catabolic effect in OA joints, which makes leptin essential in the pathophysiology of OA. Obesity is associated with the development and progression of knee OA. In addition to the mechanical effect of obesity in developing knee OA, fat cells have a non-mechanical effect by producing adipokines (Conde, Scotece et al., 2011).

The pro-inflammatory and catabolic role of leptin in cartilage metabolism could be explained by its ability to stimulate the expression of MMPs, such as MMP-9 and MMP-13, which are involved in damage to OA cartilage (Toussiot, Streit, and Wendling, 2007; Conde, Scotece et al., 2011) and increase IL-8 production in human chondrocytes (Conde, Gomez et al., 2011; Gomez et al., 2011). It has been suggested that OA subchondral osteoblasts show abnormal function due to the production of leptin, which is associated with high levels of alkaline phosphatase (ALP), osteocalcin (OC), type I collagen, and TGF- β 1 (Mutabaruka et al., 2010; Conde, Gomez et al., 2011). The expression of leptin and its receptor (Ob-Rb) is significantly increased in synovial fluid and advanced OA cartilage. As a result of the association between the concentration of synovial fluid leptin and the radiographic severity

of OA, leptin is shown to be a potential marker of OA (in OA patients) (Ku et al., 2009; Conde, Scotece et al., 2011).

Adiponectin

Adiponectin is a 244-residue protein that is mainly secreted by WAT and is also known as GBP28, apM1, Acrp30 and AdipoQ. In the blood, it can present in different molecular forms in large amounts, as its structure shows homology with collagens VIII and X and complement factor C1q (Kadowaki and Yamauchi, 2005; Oh, Ciaraldi and Henry, 2007; Conde, Scotece et al., 2011). Many studies have shown that adiponectin has an important role in increased oxidation of fatty acid and a reduction in glucose synthesis in the liver, and that its circulating level increases with weight loss and seems to be less in obese patients (Kadowaki and Yamauchi, 2005; Oh, Ciaraldi and Henry, 2007; Conde, Scotece et al., 2011).

At the joint level, the role of adiponectin in OA is controversial. On the one hand, adiponectin might function as a pro-inflammatory factor, which is necessary for matrix degradation, as it is able to induce the expression of IL-6 in human synovial fibroblasts (Tang et al., 2007; Conde, Scotece et al., 2011). There is an increase in IL-6 and adiponectin production in the infrapatellar fat pad in knee OA (Distel et al., 2009; Conde, Scotece et al., 2011). Clinically, there is an inverse correlation between adiponectin and disease severity (Honsawek & Chayanupatkul, 2010; Conde, Scotece et al., 2011). Evidence has shown that patients with high adiponectin levels had a decreased risk of hand OA progression, suggesting that adipokine may be considered as a protective hormone against cartilage damage (Conde, Scotece et al., 2011; Yusuf et al., 2011).

1.1.3 Diagnosis

Taking the history of a patient and performing a physical examination are important considerations in forming a diagnosis of knee OA (Kellgren and Lawrence, 1957; Risberg, 1999; Luyten et al., 2012; Wittenauer, Smith and Aden, 2013). A typical physical examination of knee OA in individuals aged above 50 years old usually includes the following signs/symptoms: knee pain with stiffness, functional limitation and joint crepitus (Kellgren and Lawrence, 1957; Risberg et al., 1999; Luyten et al., 2012). The early diagnosis of knee OA is a very complicated process because the patient may still not have noticed any signs/symptoms of the disease. Symptoms may only be stimulated by specific situations of long-term loading activities, such as jogging or other sports activities. Frequently in these cases, patient history and clinical examination are not helpful in identifying early knee OA but may reflect a local mechanical problem (Risberg et al., 1999; Oiestad et al., 2010; Luyten et al., 2012).

Therefore, physical examination may not be enough to verify a diagnosis of knee OA and the clinician may need radiographic evidence to confirm the condition. Usually, narrowing of the joint space, the appearance of osteophytes and subchondral bone sclerosis and cysts are the most obvious radiographic changes (Kellgren and Lawrence, 1957; Risberg et al., 1999; Luyten et al., 2012). Criteria for classifying a diagnosis of knee OA based on combining clinical and radiographic findings have been published by the ACR (Altman et al., 1986). The classification criteria have been used worldwide as a standard definition of knee OA cases for research purposes (Zhang, Doherty et al., 2010). Participants in OA intervention studies were included if they were older than 50 years, they had stiffness for less than 30 minutes after a period of inactivity, crepitus, as well as structural changes, i.e., osteophytes and narrowing of the knee joint space (Kellgren stage II on standardised

radiographs). The Kellgren and Lawrence radiographic scoring system was the most widely used assessment tool to diagnose OA in the past (Ahlback, 1968; Spector et al., 1993). The grading system had an emphasis on the presence of osteophytes and was used widely in most studies until 1990 (Croft et al., 1990; Spector et al., 1993). However, there was a debate about measurable joint space loss, and there were no agreed criteria for knee OA in population studies. It was also not clear whether the presence of osteophytes without joint space narrowing was really indicative of pathological changes (Croft et al., 1990; Spector et al., 1993). The criteria for the radiographic diagnosis of knee OA have subsequently been modified, to include either the presence of osteophytes or a moderate to severe narrowing of the joint space (Felson et al., 1997).

In 2011, Kerkhof et al. suggested that joint space narrowing is required, in addition to at least one definite osteophyte, to establish the radiological evidence of knee OA, and this is considered the current recommendation on the standardisation of OA phenotypes. Moreover, the criteria for the Kellgren and Lawrence radiographic OA classification (Table 1.2) are still used with consideration of the presence of osteophyte and joint narrowing.

Table 1.2 Kellgren and Lawrence radiographic OA classification (Luyten et al., 2012)

Grade 0	No changes
Grade 1	Doubtful narrowing of the joint space and possible osteophytic lipping.
Grade 2	Definite osteophytes and possible narrowing of the joint space.
Grade 3	Moderate multiple osteophytes, definite narrowing of the joint space, some sclerosis, and possible deformity of the bone ends.
Grade 4	Large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends.

Radiography, mainly conventional X-ray, is considered the gold standard method of assessing knee OA and is widely applied in clinical and scientific settings (Wick, Kastlunger and Weiss, 2014). In practice, using the classical, and strict, radiographic criteria defined by Kellgren is not helpful in capturing early knee OA (Risberg et al., 1999; Oiestad et al., 2010; Luyten et al., 2012). Conventional X-ray has some technical limitations that may affect the analysis of knee OA, although these could be overcome by using high-quality structural assessment tools to allow a more comprehensive classification, such as magnetic resonance imaging (MRI), ultrasonography (Wick, Kastlunger and Weiss, 2014) and arthroscopy (Luyten et al., 2012). Pre-radiographic structural changes, such as meniscus lesions, cartilage defects, synovitis, and BML, can be detected using MRI and ultrasound (Favero et, 2015). The significance of MRI findings such as BML, cartilage defects, meniscal tears and synovial inflammation/effusions in patients without radiographic signs of OA is not fully understood. For symptomatic knee OA, therefore, identifying the source of pain via radiographic findings must be combined with a detailed clinical examination, including a patient history review and a physical examination (Kornaat et al. 2006; Bedson and Croft 2008).

The structural changes that develop with knee OA, such as progressive destruction of the articular cartilage, joint capsule, and ligaments, synovial membrane inflammation and subchondral bone calcification (Bijlsma, Berenbaum and Lefeber, 2011), usually lead to clinical signs and symptoms, which include knee pain and muscle impairment, mainly crepitus, reduced joint ROM, impaired proprioception, joint line and periarticular tenderness on palpation, and mild synovitis (Bennell et al., 2008; Bijlsma, Berenbaum and Lefeber, 2011; Knoop et al., 2011; Walker, 2011; Bączkiewicz and Majorczyk, 2014). Early changes in joint tissue are mainly associated with symptoms, but sometimes these relate to disease

progression (Favero et al, 2015). These symptoms may lead to a limitation of daily activities, restriction of participation and impairment of body functions (Bijlsma, Berenbaum and Lafeber, 2011). In addition to patient history and physical examination, a special test (see below) may assist in the clinical diagnosis of knee OA (Cook and Hegedus, 2008). A test, such as the Ober test or modified Ober test for the iliotibial band, is the most commonly recommended physical examination tool to examine muscle length and flexibility (Willett et al., 2016). Knee joint integrity/stability can also be assessed using ligamentous tests as a proxy for changes in knee biomechanics secondary to muscular tightness or changes in lower limb alignment (Cook and Hegedus, 2008). In diagnosis, one important indicator of OA is type II collagen breakdown. Synthesis and degeneration of collagen are measured by numerous biomarker assays, which provide information of cartilage turnover (more details are presented in section 1.1.2.1). The products of cartilage collagen metabolism can be found in synovial fluid, blood and urine (Garvican et al., 2010). However, there is a lack of information regarding effective biomarkers that can be used in OA diagnosis in clinical settings (Wittenauer, Smith and Aden, 2013).

In 2003, OARSI provided a set of recommended performance-based measures to assess physical function in adults with knee OA. These measures include the assessment of aerobic conditioning, walking speed, lower extremity strength and functional mobility (Dobson et al., 2013). A recent cross-sectional study assessed the relationships between the results of the findings of physical examination (muscle assessment, function and special tests), functional performance tests and self-reported function in 87 participants aged 40 and older with symptomatic and radiographic knee OA (Iversen et al., 2016). The results of functional performance tests suggested impairment in balance and walking ability, which was associated with physical examination findings of hip muscle weakness, muscle length

imbalance, and patella dysfunction. There was also a stronger association between the results of physical examination and functional performance tests ($P < 0.05$) than self-reported pain and function (Iversen et al., 2016).

Clinically, practitioners depend on a patient history review that includes patient age; gender; swollen knee occurrences; and a current description of knee pain, morning stiffness, or both in the knees or hips when getting up from a seated position or while climbing stairs (Claessens et al. 1990). A working diagnosis of OA was suggested by the National Institute for Health and Care Excellence (NICE) in their 2014 guidelines. This clinical diagnosis depends on the exhibited symptoms and can be made without an X-ray. It states the following: “the patient is > 45 years old, exhibits chronic joint pain (3 months or more) that worsens with use, experiences morning joint stiffness lasting less than 30 minutes, and, overall, an alternative diagnosis is unlikely” (Finney, Lambourne, and Cottrell 2019, p.114).

The Outcome Measures for the Rheumatology Clinical Trials group recommended four domains for evaluating OA patients, including pain, physical function, joint imaging, and patient global assessment (Bellamy et al., 1997; Dreinhofer et al., 2004). In physical therapy and rehabilitation medicine, the International Classification of Functioning, Disability, and Health (ICF) model is used as a clinical Problem-Solving tool (Steiner et al., 2002). The ICF Core Set for OA includes five domains: body functions/structures, activities, participation, personal and environmental factors (Peter et al., 2011). The health status of a patient primarily in terms of activity limitations and participation restrictions should be assessed by a physiotherapist. Activity limitations include transferring, sitting down and getting up from a bed or chair, kneeling, standing, walking, and climbing stairs. Participation includes the patient ability to participate in community life, recreation, leisure, and sport. In addition, any

impairment of body function and structure as well as personal and environmental factors must be assessed by the physiotherapist. Body function and structure include the assessment of proprioception, the sensation of pain, joint mobility and stability, muscle movement, power, structure, and alignment. Personal factors include patient history regarding age, gender, other articular disorders (i.e., heart and lung disorders, diabetes mellitus), and disease perception. Lastly, environmental factors include products and technology used in daily living, at the workplace, and in public (i.e., home adaptations and aids, special chairs at work, and elevators) (Peter et al., 2011).

In summary, processes including taking patient history and physical examinations, are essential considerations in the assessment of knee OA. However, radiographic evidence is the gold standard and is required to confirm diagnosis, especially in early cases. Biomarkers of the disease still need further investigation to explore their role in knee OA diagnosis and progression. The results of performance-based tests are also very important in the assessment of patients with knee OA and help in selecting appropriate rehabilitation interventions.

1.1.4 Prevalence and incidence

In 2003, OA was considered the sixth-leading cause of global disability (Woolf and Pfleger, 2003) and the most common form of musculoskeletal disease worldwide (Brooks, 2003). Factors such as population ageing and rising rates of obesity will further increase the prevalence of OA (WHO, 2014) and OA is estimated to become the fourth-leading cause of disability by 2020 (Woolf and Pfleger, 2003). According to the United Nations, people older than 60 will, by 2050, account for more than 20% of the world's population. It is estimated that 15% of them will have symptomatic OA, and severe disability will affect one-third of these people. Statistically, about 130 million people will suffer from OA worldwide and 40

million will be affected by the disease and suffer severe disability by 2050 (WHO, 2014). Knee OA is a highly prevalent disorder (Wallace et al., 2017), with one-quarter of adults aged 55 years or older reporting at least one episode of knee pain annually (Fernandes et al., 2013). In England, the recent percentage of obese adults/older adults who are affected by knee OA has been reported by Arthritis Research UK (the results are illustrated in Figure 1.2).

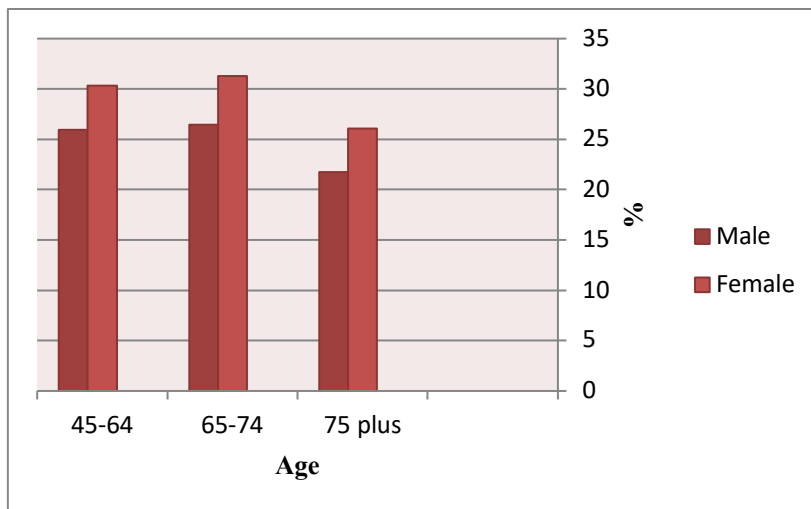


Figure 1.2 Total percentages of obese adults and older adults affected by knee OA in England (Arthritis Research UK, 2017)

1.1.5 Risk factors

The incidence of OA is increasing as a consequence of high rates of obesity and an ageing population (Johnson and Hunter, 2014). In addition to ageing and obesity, gender and previous injury are known to be significant risk factors for developing OA (Spector et al., 1996; Conrozier et al., 1998; Conde, Scotece et al., 2011). Risk factors for OA can be classified into person-level factors, including age, gender, obesity, diet, genetics and race/ethnicity, and diet, and joint-level factors, such as abnormal loading of the joints, injury and malalignment (Johnson and Hunter, 2014).

Another classification has been developed by Johnson and Hunter (2014), who divided OA risk factors into modifiable local risk factors, modifiable systemic risk factors, and non-modifiable systemic risk factors (see Figure 1.3). The identification of modifiable OA risk factors is no less important than understanding the impact of the disease, as they could be controlled and appropriate understanding of them will help to improve public health strategies towards the prevention and management of OA (Johnson and Hunter, 2014). However, the interaction between OA risk factors is complicated and makes the management of OA a challenge (Johnson and Hunter, 2014).

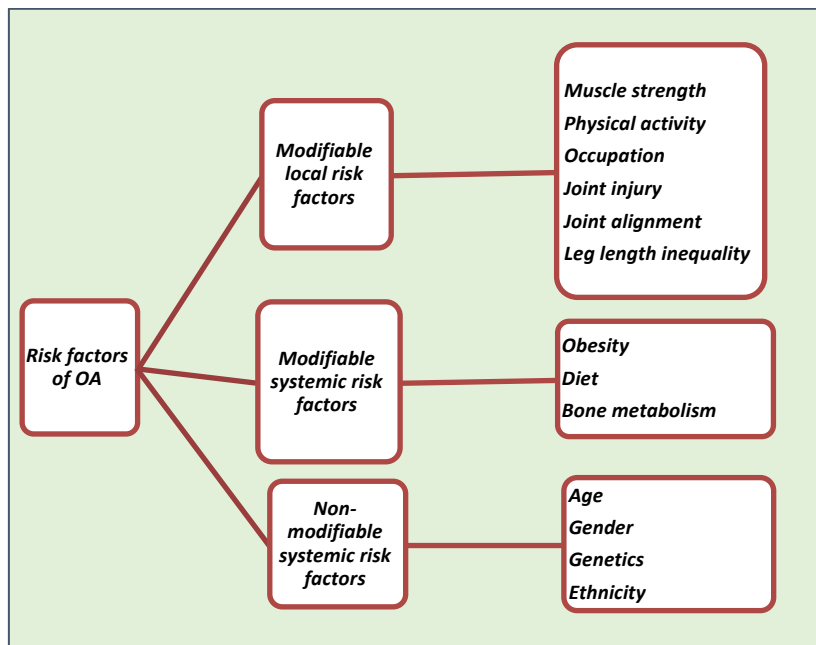


Figure 1.3 Risk factors for OA, based on the classification of Johnson and Hunter (2014)

1.1.5.1 Modifiable local risk factors

Muscle strength

Muscle strength is defined as the ability of muscle to produce a physical force (Kumar, 2004; Zwart et al., 2018). The force exerted by muscle is determined mainly by the properties of basic muscle, such as quantity, quality and activation (Lynch et al., 1999; Bruce, Phillips

and Woledge, 1997; Erdemiret al., 2007; Zwart et al., 2018). The amount of available muscle tissue is referred to as muscle quantity, while quality refers to the amount of force exerted per muscle unit. Muscle activation is the amount of muscle tissue that is activated during a contraction in relation to the available muscle tissue for that contraction in total (Bruce, Phillips and Woledge, 1997; Lynch et al., 1999; Erdemiret al., 2007; Zwart et al., 2018). There are other co-determinants of the force generated, which include the speed and type of muscle contraction and the muscle length during contraction (Kumar, 2004; Zwart et al., 2018).

The relationship between muscle strength and OA is complicated and may vary based on the specific muscles and joint sites examined (Zhang and Jordan, 2010; Neogi and Zhang, 2013; Allen and Golightly, 2015). Steultjens et al. (2001) measured the isometric muscle strength of 16 muscle actions around the knees (knee flexion and extension) and hips (flexion, extension, adduction, abduction, internal and external rotation), both right and left, in 52 patients with hip OA with a mean age of 67.8 years and 70 patients with knee OA with a mean age of 68.2 years. The results showed significant reduction of muscle strength around the affected joints compared with muscle strength around unaffected joints (Steultjens et al., 2001). Not only the strength of muscles surrounding a joint, but also the laxity of ligaments and proprioception are important local considerations that affect both the initiation and progression of OA (Vincent et al., 2012).

In knee OA particularly, weakness of the quadriceps femoris muscle is a risk factor for disease initiation and progression (Slemenda et al., 1998; Brandt et al., 1999; Bennell et al., 2013; Oiestad et al., 2015). However, weakness of the quadriceps may occur due to muscle disuse atrophy secondary to pain in the affected joint or by physiological mechanisms that

may inhibit muscle contraction (Slemenda et al., 1997). This phenomenon is called arthrogenic muscle inhibition (AMI), in which individuals with knee OA experience a gradual decline in quadriceps strength due to impairment in the central nervous system's ability to produce a maximal voluntary contraction of the quadriceps (Slemenda et al., 1997; Lewek et al., 2004). It is theorised that a failure of voluntary activation can result from progressive structural changes or inflammation that results in abnormal articular afferent information being sent to the α -motor neurons, thereby reducing their activation (O'Reilly et al., 1998; Lewek et al., 2004). Quadriceps weakness is involved in knee OA development due to its role during gait, as the quadriceps are responsible for providing shock absorption to the knee during an eccentric contraction (Mikesky, Meyer, and Thompson, 2000; Lewek et al., 2004). Quadriceps weakness will affect the ability of the knee to distribute the compressive forces adequately that lead to spontaneous loading, which accelerates damage to the articular cartilage of the knee (Slemenda et al., 1997; Lewek et al., 2004). Figure 1.4 presents the contribution of quadriceps muscle weakness to the development of knee OA.

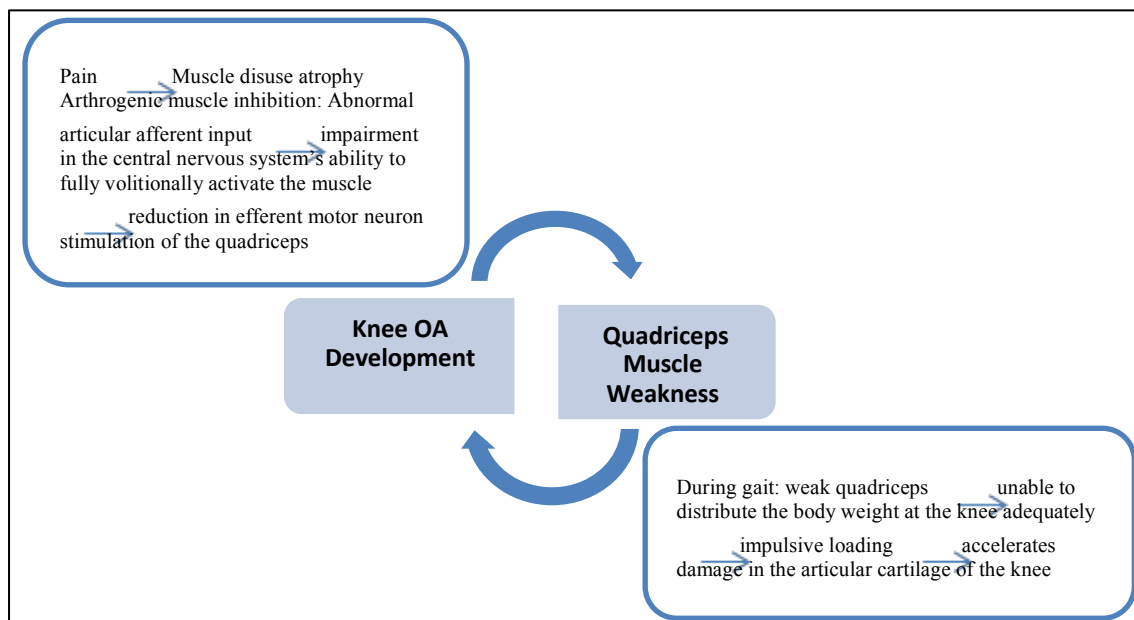


Figure 1.4 Mechanisms of the contribution of quadriceps muscle weakness to knee OA

Conversely, patients with knee OA attempt to avoid pain by developing antalgic patterns, and, as a consequence, a deficit in muscle strength may occur due to OA-related disuse (Fisher et al., 1997; Neogi and Zhang, 2013; Johnson and Hunter, 2014). In knee OA, weakness of the upper leg muscles is associated with four factors: lower muscle quality, physical inactivity, severe joint degeneration, and pain. Other factors determining upper leg muscle strength in knee OA, such as lower muscle quantity, muscle activation, nutrition and vitamins, and markers of inflammation are worth investigating in future research (Zwart et al., 2018).

Physical activity

The repetitive use of a joint is correlated with an increased risk of OA development (Johnson and Hunter, 2014). Despite the beneficial effect of physical activity on joint stabilisation through strengthening the surrounding muscles, physical activity may put an excessive load on a joint, especially a susceptible joint, which is liable to be weight-bearing (Neogi and Zhang, 2013; Johnson and Hunter, 2014). The general level of physical activity may also increase the risk of developing OA (Zhang and Jordan, 2010). A moderate level of physical activity is not associated with increased incidence of OA (Neogi and Zhng, 2013; Johnson and Hunter, 2014; Allen and Golightly, 2015). The findings of a recent study testing the association between meeting physical activity guidelines based on the Johnston County OA Project (Jordan et al., 2007) and risk of knee OA incidence reported no significant association in middle-aged and older adults who met the National Health Services (NHS) physical activity guidelines (>150 minutes/week) (Barbour et al., 2014). Whereas vigorous physical activity may increase the risk of developing knee OA, as shown in the Framingham Study on physical activity. Among the participants (n=598) without knee OA with a mean age of 70.5 years, 63.7% of whom were women, those who engaged in vigorous

physical activity were at greater risk of developing knee OA after 8 years of follow-up than sedentary ones (Hannan et al., 1993; Felson et al., 1997; McAlindon et al., 1999; Wang et al., 2011; Neogi and Zhang, 2013).

The association between sports activities and subsequent knee OA has been investigated in several studies. For example, elite soccer players are at higher risk of developing knee OA when compared with other types of sports people, i.e., long-distance runners, weight lifters and shooters (Kujala et al., 1995). In Finland, a large cohort study of Finnish male former athletes investigated the effects of long-term participation in vigorous sports on health compared with controls. After an average of approximately two decades of follow-up, the findings showed that endurance, mixed sports and power sports athletes had a higher incidence of hospitalisation for lower limb OA than the referents (Sarna et al., 1997). The general findings of high-quality studies suggest an increased risk of knee OA in individuals who have exercised more intensely or regularly (Blagojevic et al., 2010). In other studies, discrepant findings were noted, i.e., that recreational (moderate) long-distance running and jogging were associated with an increased risk of OA (Lane et al., 1993; Newton et al., 1997). However, there are conflicting results with regard to the relationship between sports activities and subsequent OA (Zhang and Jordan, 2010).

Occupation

Previous studies show that specific occupations are associated with a risk of hip and knee OA, especially those that require abnormal or excessive lower extremity joint loading (Blagojevic et al., 2010; Zhang and Jordan, 2010; Neogi and Zhang, 2013; Johnson and Hunter, 2014; Allen and Golightly, 2015). Loading activities, such as squatting or kneeling, and heavy physical work, such as carrying or lifting weights, double the risk of developing

knee OA, especially if individuals have a BMI ≥ 25 (Messier et al., 2009; Zhang and Jordan, 2010; Johnson and Hunter, 2014). A SR by Blagojevic et al. (2010) investigated the relationship between general occupational physical workload/stress and knee OA development. The results of five of the studies of adults aged ≥ 50 included in the review showed a correlation between specific occupation and knee pain development, such as construction work, farming and physical education teaching (Blagojevic et al., 2010).

Joint injury

In addition to vigorous physical activities, joint injuries can also lead to OA development (Roos, 2005). The knee is considered one of the most commonly injured joints (Johnson and Hunter, 2014), with typical causes of injury including anterior cruciate ligament rupture, or direct articular cartilage injury and meniscal damage (Blagojevic et al., 2010; Zhang and Jordan, 2010; Allen and Golightly, 2015). Early intervention after joint trauma are very important because, once damage occurs to a joint, continuing use may accelerate the degenerative changes (Hopman-Rock and Westhoff, 2000; Sharma, 2002). Two meta-analyses reported that knee injury increased the risk of knee OA in older adults (Blagojevic et al., 2010; Muthuri et al., 2011).

Some joint injuries lead to post-traumatic OA clinical syndrome, such as intra-articular fractures. Restoration of joint congruity, stability and alignment are the main treatment targets. Despite optimal treatment, many patients experience crippling joint pain and dysfunction of the affected joint (Buckwalter and Brown, 2004). However, not only sport, but also some occupation-related activities increase the risk of meniscal tears and lead to OA development (Englund et al., 2009). For instance, those who work at laying floors are at

greater risk of having degenerative meniscal tears than graphic designers, because their jobs demand a lot of time spent kneeling and excessive bending (Rytter et al., 2009).

Joint alignment

The alignment of the knee, for example, the hip-knee-ankle angle, is a key element of load distribution and any shift of the neutral or collinear alignment of the hip, knee and ankle will lead to abnormal load distribution at the knee (Blagojevic et al., 2010). Malalignment of the knee joint is one of the strongest predictors of knee OA progression (Neogi and Zhang, 2013; Johnson and Hunter, 2014; Allen and Golightly, 2015). A prospective cohort study has been conducted with 237 subjects with a mean age of 64.0 years with primary knee OA, which is defined as the presence of tibiofemoral osteophytes and activity limitation due to discomfort at the knee joint. The participants reported a significant association between abnormal knee alignment of more than 5° and increased structural degradation in the stressed compartment at least over 18 months of observation (Sharma et al., 2001; Johnson and Hunter, 2014). Varus alignment abnormality contributes to a four-fold increased risk of medial progression of knee OA, while valgus alignment abnormality contributes to a five-fold increase in the risk of lateral progression (Sharma et al., 2001; Zhang and Jordan, 2010).

Despite the strong association between joint alignment and the progression of knee OA, the relation between the incidence of knee OA and malalignment is not clear (Johnson and Hunter, 2014). Results from the Framingham Study showed no significant association between the alignment of the knee joint and the risk of radiographic knee OA incidence (Hunter et al., 2007). However, no study has yet shown a reduction in disease progression if alignment is corrected (Neogi and Zhang, 2013; Johnson and Hunter, 2014).

Leg length inequality (LLI)

In addition to joint alignment, LLI is another factor which may change the biomechanics of the knee and hip joint by altering or increasing the joint forces (Zhang and Jordan, 2010). LLI is a potentially modifiable risk factor for knee OA development (Allen and Golightly, 2015). Results from the Multicentre Osteoarthritis Study found that $LLI \geq 1$ cm is associated with higher prevalence of radiographic knee OA and increases the risk of incident symptomatic and progressive knee OA (Harvey et al., 2010). Radiographic knee OA is significantly associated with LLI according to results from the Johnston County Osteoarthritis Project, with subjects with $LLI \geq 2$ cm being almost twice as likely to have radiographic evidence of knee OA and 40% more likely to experience symptoms of knee OA because LLI accelerates the degeneration of joint structures (Golightly et al., 2007). Further examination of the relationship between LLI and OA to include a consideration of more time to evaluate disease development and progression has been proposed (Allen and Golightly, 2015). Thus, it can be summarised that muscle weakness, inappropriate levels of physical activity, specific types of occupation, joint injury, joint malalignment and LLI are known to be modifiable risk factors for developing knee OA. Understanding the role of these factors in initiating knee OA may help to control its incidence and probably its progression.

1.1.5.2 Modifiable systemic risk factors

Obesity

Individuals' body weight, such as being overweight or obese, increases the risk of OA incidence and progression. Obesity and overweight have long been identified as risk factors for developing OA, particularly in the knee joint (Blagojevic et al., 2010; Zhang and Jordan, 2010; Neogi and Zhang, 2013; Johnson and Hunter, 2014; Allen and Golightly, 2015). They

are also considered to be accelerator factors of disease progression (Sharma, 2002) and this can be attributed to an alternation of body weight distribution which leads to putting mechanical stress on the weight-bearing joints and results in cartilage destruction (Blagojevic et al., 2010). In a SR and meta-analysis conducted by Blagojevic et al. (2010), being overweight or obese was shown to increase the risk of developing knee OA by almost three times compared with people of normal weight (95% confidence interval [CI]: 2.56-3.43) (Blagojevic et al., 2010). Increased adipose tissue contributes to the risk of knee and hip replacement (Wang et al., 2009; Berry et al., 2011). Obesity is also considered a risk factor for OA development in non-weight-bearing joints, such as the hands (Cicuttini Baker and Spector, 1996; Oliveria et al., 1999; Berry et al., 2011). Furthermore, weight loss is likely to be an effective intervention to prevent structural deterioration (Felson and Hodgson, 2014). For example, results from the Framingham Study reported that losing approximately 5 kg decreases the risk of the development of symptomatic knee OA in women by 50% (Felson and Chaisson, 1997). In general, the relationship between obesity and knee OA is bidirectional, as obesity may initiate knee OA and limited activity caused by pain in patients with knee OA may increase the patient's body weight (Felson and Chaisson, 1997).

Diet

The effect of modifiable dietary factors in individuals with OA is ambiguous (Zhang, Nuki et al., 2010; Neogi and Zhang, 2013; Allen and Golightly, 2015). Knee joint cartilage is influenced by insufficient levels of serum 25-hydroxyvitamin D (25-OHD), which leads to knee OA development and progression (Heidari, 2011). There was a significant association ($P=0.01$) between serum 25-OHD deficiency and knee OA in patients aged < 60 years in a study by Heidari et al. (2011). Serum was measured by the enzyme-linked immunosorbent assay (ELISA) method and considered deficient when 25-OHD levels were less than 20

ng/ml (Heidari, Heidari and Hajian-Tilaki, 2011). Low intake of antioxidant vitamins, such as C and E, may accelerate the progression of knee OA (McAlindon et al., 1996; Johnson and Hunter, 2014). Vitamin K is also associated with hand and knee OA (Neogi and Zhang, 2013). However, there is a need for additional studies to clarify the effect of dietary factors and vitamins on OA risk and outcomes (Allen and Golightly, 2015).

Bone metabolism

High bone density is strongly associated with the initiation of OA, although a causal relationship or mechanism is unclear (Blagojevic et al., 2010; Neogi and Zhang, 2013; Allen and Golightly, 2015; Hardcastle et al., 2015). One mechanism suggested for OA onset is stiffness of the subchondral bone, as mentioned earlier (section 1.1.2.2) OA may begin at the bone level before affecting the cartilage, which makes this a bone disease rather than a cartilage disease, as high forces are shifted by the stiff bone to the overlying cartilage (Dequeker, Mokassa and Aerssens, 1995). Interestingly, women with OA have quantitative and qualitative differences in bone, such as bone stiffness, higher OC, greater compressive strength, and a mineralisation profile shifting to higher densities (Dequeker, Mokassa and Aerssens, 1995).

In summary, reducing body weight, by following a healthy diet, and avoiding high bone density may reduce the risk of developing knee OA.

1.1.5.3 Non-modifiable systemic risk factors

Age

Ageing is one of the strongest risk factors for OA (Zhang and Jordan, 2010; Neogi and Zhang, 2013; Johnson and Hunter, 2014). Despite research into OA, the exact mechanism

underlying its increased incidence and prevalence with age is not completely understood (Gossan, Boot-Handford and Meng, 2015). The common concept of the contribution of ageing to OA development is that the normal process of ageing increases OA progression. Changes related to ageing affect the tissues of the articular cartilage, which promotes the development of arthritis (Loeser, Collins and Diekman, 2016). More details about the relationship between ageing and OA are presented in section 1.2.3.

Gender

Previous studies have shown a higher prevalence and severity of OA, especially of the hand, foot and knee, in women compared with men (Blagojevic et al., 2010; Zhang and Jordan, 2010; Neogi and Zhang, 2013; Johnson and Hunter, 2014). Following menopause, women are also more likely to have severe radiographic knee OA (Srikanth et al., 2005; Johnson and Hunter, 2014).

Genetics

Osteoarthritis is a disease that is affected by hereditary factors (genes) and may vary by joint site (Zhang and Jordan, 2010; Neogi and Zhang, 2013; Johnson and Hunter, 2014). Genotype not only plays an important role in the initiation, but also affects the progression of cartilage degeneration mechanisms and their subsequent influence on biomechanical and biochemical changes (Abramson and Attur, 2009).

Ethnicity

Among racial and ethnic groups, both the prevalence of OA and the pattern of joints affected by OA vary. The Framingham Study concluded that OA is more common in Europeans compared with the Asian population (Zhang et al., 2001; Zhang and Jordan, 2010). Factors

such as smoking, oral contraceptives, hysterectomy, hypertension, depression, and meniscectomy have been investigated using meta-analysis, the results showing either no significant effect or no association between them and the onset of knee OA (Blagojevic et al., 2010).

From this section, it could be said that knee OA may be initiated as a result of non-modifiable risk factors, such as ageing, gender, genetics and ethnicity.

1.1.6 Management of OA

The early intervention and initiation of therapeutic procedures for OA may help to delay or prevent the progression of severe structural changes in the joint that are usually associated with advanced stages of the disease and confirms the importance of the identification of patients who have early knee OA (Crossley et al., 2015; Favero et al., 2015). Despite the high interest of experts in several study groups in the OA field and national and international scientific societies in defining early OA, there is still no agreed definition (Favero et al., 2015). There is currently no cure for OA degeneration, with treatment ranging from using painkillers to eventual joint replacement (Gossan, Boot-Handford and Meng, 2015). Surgical management is a high-cost intervention: it is estimated that the cost of each total knee replacement (TKR) surgery plus five years follow-up care is about £7,458 (Dakin et al., 2012). In 2012, 90,842 TKRs were carried out in the UK, according to the National Joint Registry (NJR), representing a 7.3% increase compared with 2011. More joint replacements than ever before were carried out in the financial year 2016/17, with just under 243,000 cases submitted to the NJR. This seems a significant increase of more than 20,000 joint replacement operations recorded in the NJR for the previous period) (NJR, 2014). Joint replacement was recommended only for appropriate patients with hip or knee OA. For

patients with symptomatic knee OA, debridement arthroscopy was not recommended (Nelson et al., 2014).

Despite a great deal of high-quality evidence of the beneficial effect of non-pharmacological treatment modalities, there is a problem with their implementation in clinical practice for the management of knee and hip OA (McHugh et al., 2006; Nelson et al., 2014; Selten et al., 2016). This may be due to lack of knowledge of the beneficial effect of non-pharmacological, non-surgical treatment modalities among health care providers (Hofstede et al., 2014; Selten et al., 2016).

An earlier systematic literature review focused on non-pharmacological and non-surgical treatments for hip and/or knee OA to improve the available evidence for best practice treatment (Roos and Juhl, 2012). The review recommended education, exercise and weight loss on the basis of both research evidence and expert opinion as cost-effective first-line treatments of OA and an effective option for long-term intervention (Roos and Juhl, 2012). The researchers proposed an OA treatment pyramid and considered patient education, exercise and weight control for all patients as the first line of OA treatment, pharmacological pain relief and passive treatment as the second line, and surgical intervention as the last option of treatment. The OA treatment pyramid is presented in Figure 1.5 (Roos and Juhl, 2012). This was in line with the guidelines for the non-surgical management of knee OA published by OARSI, which stated that the core treatment of knee OA should focus on patients' education and self-management, water and land exercise, strength training and weight management (McAlindon et al., 2014). Moreover, the NICE recommended that non-surgical treatment should be offered for patients with OA before referral for surgery (NICE, 2014). The non-surgical management of OA includes three important strategies: education

and self-management, pharmacological management and non-pharmacological management (NICE, 2014).

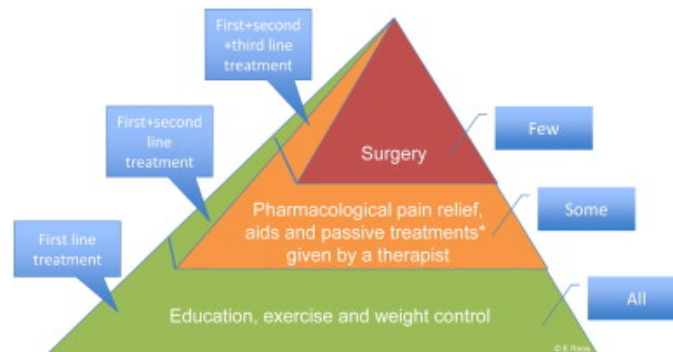


Figure 1.5 OA treatment pyramid. OA of the hip and knee is best managed using education, exercise and weight control, with the addition of pharmacological and surgical interventions when needed. All patients should be offered first-line treatment, while some will need second-line treatment, and a few will need third-line treatment. * Passive treatments include manual therapy, acupuncture, and other treatments given by a therapist and not requiring an active lifestyle change by the patient (Roos and Juhl, 2012).

1.1.6.1 Education and self-management

Patient education and self-management focus on providing information for patients to help them understand the condition and its management and extends to offering verbal or written information to all patients with OA. Patient self-management interventions are recommended to enhance positive behavioural changes. Self-management programmes, either individually or in groups, for people with OA include exercise, weight loss, use of suitable footwear, and thermotherapy, the last considered part of patient education by teaching how to use local heat or cold to relieve pain (NICE, 2014). In a SR by Nelson et al. (2014), 16 existing recommendations and management guidelines for OA were reviewed and critically evaluated. Five of them originated from the USA, eight from Europe, one from Canada, one from Asia, and one with international input from the USA, Europe and Canada

(Nelson et al., 2014). Most of the recommendations were directed towards physicians and professionals of allied health services, and most had multidisciplinary input from general practitioners (GPs), orthopaedists, rheumatologists and physiotherapists. Among the 15 articles, 12 had moderate to strong recommendations for education and self-management programmes as part of the management of OA. The self-management programmes included providing patient education, joint protection strategies, and regular contact to promote individualised plans of treatment and self-care to patients with OA (Nelson et al., 2014).

1.1.6.2 Pharmacological treatment

Pharmacological treatments are more likely to be undertaken by patients with OA compared with non-pharmacological approaches (Healey et al., 2018). Pharmacological management may include oral analgesics, topical non-steroidal anti-inflammatory drugs (NSAIDs), highly selective cyclooxygenase (COX-2) inhibitors, and intra-articular injections (NICE, 2014). The pharmacological modalities most recommended as first-line treatments include acetaminophen/paracetamol, with NSAIDs (topical or oral) as the second line of OA treatment. Intra-articular corticosteroids are generally recommended for hip and knee OA (Nelson et al., 2014).

1.1.6.3 Non-pharmacological modalities

Despite the positive effect of non-surgical interventions, such as regular physical activity, moderate exercise and patient education programmes, on improving the symptoms of OA (Hopman-Rock and Westhoff, 2000), these may have limited benefit, especially in the advanced changes of the disease and when structural degeneration is in the late stages. However, the prevention of disease progression is considered the key target of knee OA

management (Mahmoudian et al., 2017). Nevertheless, some studies have shown that there is no therapy which consistently delays the progression of OA (Felson and Hodgson, 2014).

Physiotherapy

Disability is the main consequence of knee OA (Mahmoudian et al., 2017). It affects patients' ability to perform activities of daily living (ADLs), such as getting up from a chair, standing, walking and climbing stairs (Felson, 1990; Felson et al., 2000). Physiotherapy is considered an important non-pharmacological intervention that provides effective care for patients with knee OA (Deyle et al., 2005) and is recommended by the ACR and the European League Against Rheumatism (EULAR) (ACR, 2000; Jordan et al., 2003; Bennell et al., 2005). Physiotherapists are qualified professionally to work with patients who have disability (World Confederation for Physical Therapy [WCPT], 2011). They are capable of setting management goals and prescribing treatment procedures (Bunning and Materson, 1991). In the management of knee OA, the main goals are to reduce knee pain and improve function, ROM and joint mobility, regain normal alignment of the lower limbs and restore normal neuromuscular function (Page, Hinman and Bennell, 2011).

Exercise is recommended by Cochrane reviews of physiotherapy interventions and guidelines relevant to practice in the UK to improve physical function and reduce pain in patients with lower limb OA (Walsh, Pearson and Healey, 2017). There are different types of therapeutic activities that can be used, such as strengthening (isotonic, isokinetic, and isometric), stretching, and aerobic exercise (Bunning and Materson, 1991). The combined intervention of home exercise and exercise classes has shown significant improvement in people with knee OA compared with home exercise alone. In one RCT, the combined programme was run by a physiotherapist with patients with radiographic knee OA (mean

age 64.5 ± 9.9). Patients were randomised into a home-based exercise group and a home-based exercise plus an 8-week class-based exercise group. The results showed significant improvement in locomotor function, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, physical function, strength, balance and pain items on the Short Form 36 Health Survey Questionnaire (SF-36) in the combined group (McCarthy et al., 2004).

There are some considerations that should be taken into account when prescribing exercise for patients, including age, pain severity or disability, and comorbidity (NICE, 2014). However, some factors, such as self-motivation, the availability of local facilities and the individual needs of the patient, are also essential to bear in mind to ensure the effective participation of participants in exercise (NICE, 2014). Low-intensity exercise for knee and hip OA has a beneficial effect and is included in 12 of the 15 recommendations for OA management (Nelson et al., 2014). Exercise focusing on general aerobic fitness and local muscle strengthening and body weight loss are recommended as a core treatment in non-pharmacological management. Manipulation, stretching, electrotherapy, and assistive devices (for example, walking sticks and tap turners) are considered as adjuncts to core treatments. However, some evidence recommends moderate physical activity (Vignon et al., 2006). To promote the optimal benefits of a moderate physical activity programme, it should be combined with weight reduction and focus on the strength of the muscles around the joint (Hochberg et al., 1995; Brooks, 2003). Some health care professionals face difficulty in discussing weight loss strategies with patients (Jinks and Ong, 2010; Flodgren et al., 2011) and may need further support and advice (NICE, 2006; Abbate and Jordan, 2012; Silverwood et al., 2015).

The findings of a recent SR and meta-analysis support NICE osteoarthritis guidelines (2014) about the importance of weight loss in OA management (Silverwood et al., 2015). It is not surprising that weight loss should be considered a core treatment of knee OA, given that being either overweight or obese attributed to 24.6% of cases of knee pain onset according to findings of a SR and meta-analysis of cohort studies (Silverwood et al., 2015). In OA prevention and management, obesity is still an important consideration due to its high prevalence worldwide (Brooks, 2003).

Most guidelines and recommendations agree that patients with OA should be encouraged to engage in exercise, specifically low-impact aerobics (land- or water-based), and to lose weight if overweight, with special considerations to other exercise, such as flexibility and ROM activities, exercise in combination with manual therapy, strengthening and endurance exercises, and physical or occupational therapy referral (Nelson et al., 2014).

In 2014, OARSI updated its evidence-based guidelines to inform patients and health care providers, including physicians and allied health care professionals worldwide. These evidence-based recommendations are applicable to all subjects with knee OA, with special consideration for patient preferences and needs (McAlindon et al., 2014). OARSI has also published its guidelines for the non-surgical treatment of knee OA. All patients with knee OA, with or without comorbidities, are recommended to do land-based exercise, manage their weight and engage in strength training (McAlindon et al., 2014).

The benefits of other physiotherapy modalities are supported by fewer high-quality studies. Manual therapy techniques and Transcutaneous electrical nerve stimulation (TENS), an electrotherapeutic pain-relieving device in addition to exercise interventions are suggested by NICE, but they are not recommended by OARSI due to the lack of sufficient evidence to

determine the effectiveness of manual techniques, and absence of conclusive evidence to support or rebut the use of TENS. Therapeutic ultrasound is not included in the NICE guidelines and OARSI because the low-quality level of the reported trial which made the evidence uncertain. Acupuncture is not recommended by NICE, whilst OARSI suggest that the evidence is uncertain (Walsh, Pearson and Healey, 2017).

In summary, there is an abundance of quality guidelines and recommendations for non-pharmacological modalities. Education and self-management, exercise, walking aids as required, and thermal modalities are recommended, with weight loss if overweight (Nelson et al., 2014). As much of OA care is delivered in primary care settings, there is a recommendation to improve future efforts to optimise the implementation of these modalities (Nelson et al., 2014).

1.2 Ageing

Ageing is a complex process influenced by many factors, such as genetics, chronic diseases and lifestyle (Cavanagh et al., 1998). The process of biological ageing is characterised by changes in body composition, such as an increase in body fat percentage and a decline in lean body mass; unfortunately, this process is unavoidable (Novak, 1972; Parizkova, 1973; Rogers and Evans, 1993). Fat mass increases may differ from one person to another, depending on the characteristics of the individual (Baumgartner et al., 1995; Lee and Gallagher, 2008). This alteration in body composition may cause a decline in physiological capacity (Rogers and Evans, 1993). The full scope of the causes of biological ageing at the cell and molecular levels is still unclear but there is agreement between most biogerontologists that ageing is an accumulative damage process; for example, failure to remove damaged constituents, stop their production and inability to replace damaged cells as a result (López-Otín et al., 2013).

1.2.1 Demographic data

Population ageing is a global phenomenon, the number of older adults aged 60 years or older and the “oldest-old”, i.e., people aged 80 or over, has increased globally in recent years (United Nations, 2017). In 2017, the proportion of people aged 60 or over worldwide was one in eight (United Nations, 2017). By 2050, the number of people in the world aged 60 or older is expected to increase by double compared with the 2017 population, i.e., from 962 million in 2017 to reach approximately 2.1 billion. The number of “oldest-old” people aged 80 or older is also expected to more than triple by 2050 compared with 2017, i.e., to grow to 425 million compared with 137 million in 2017 (United Nations, 2017).

During 2010-2015, there was an imbalance between the lifespan of men and women: women outlived men by an average of 4.5 years. In 2015, the proportion of women aged 60 or older and 80 or older was 54% and 61%, respectively. By 2050, the percentage of women aged 60 or older in the world’s population is expected to be 53% (United Nations, 2017). There is an expectation that the proportion of women aged 80 or older will decrease to 58% in 2050 globally due to the gradual improvement in male average survival (United Nations, 2017). The ageing process is most advanced in high-income countries. For example, Japan is home to the world’s most-aged population: 33% were aged 60 or older in 2015. Recently, the growth of population ageing in many developing countries has increased more rapidly than occurred in developed countries in the past (United Nations, 2017).

The UK, like most developed countries, is encountering significant demographic changes with increasing life expectancy and declining birth rates, resulting in an increase in the proportion of older people in the population. Figure 1.6 shows the population pyramid in the UK for those aged 60-104 years in 2000 and 2016 and the population that will feed into the

oldest-old in the future. The peak is people aged around 70 in 2016, which is indicative of the higher birth rates since World War II (National Statistics Online, November 2017). A higher proportion of older people will increase the number of patients who may have knee OA (Arthritis Research UK, 2013).

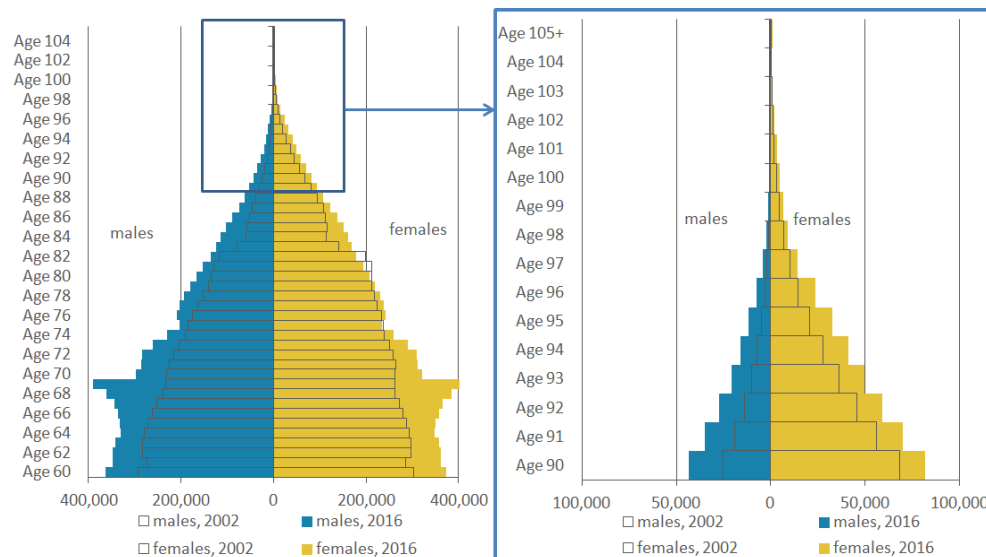


Figure 1.6 UK National Statistics 2000-2016. Source: Office for National Statistics, National Records of Scotland, Northern Ireland Statistics and Research Agency.
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/bulletins/estimatesoftheveryoldincludingcentenarians/2002to2016#statisticians-comment>

1.3 Physical activity

Physical activity is defined as “any physical bodily movement created by contractions of the skeletal muscle that raises the metabolic rate of energy expenditure above that of resting” (Kaminsky, 2006). Physical activity includes any activities in daily life, including unplanned activities such as physical work for a job or walking to a location (Bouchard, Blair and Haskell, 2012). There is confusion and interchangeable use, however, with regard to the terms ‘physical activity’, ‘exercise’, ‘physical fitness’ and ‘physical training’, which have different concepts and definitions. Exercise should be planned, structured, have repetition

and an intermediate or final objective to maintain or improve physical fitness, so exercise is a part of physical activity (Osthoff et al., 2018). Physical fitness is described as a physiological state of health that diminishes the risk of hypokinetic disease; a basis for participation in sports; and good well-being which assists one to complete the tasks of daily living. Components include cardio-respiratory endurance, muscle strength endurance, flexibility, and body composition (Donnelly et al., 2016, p.1199), while physical training means exercising in a systematic manner to improve exercise capacity and strength (Fagard, 2001). The next subsections focus on the importance of physical activity and its relationship with knee OA, recommended physical activity for older adults, and the most widely known barriers to and facilitators of physical activity in older adults with knee OA.

1.3.1 Importance of physical activity

Despite the critical importance of physical activity for older adults, they are the least physically active age group (Eurobarometer, 2010). The health benefits of physical activity are well-known, not only in terms of physical health, but also mental health and social aspects (Eurobarometer, 2010). It is important for the prevention of chronic diseases such as stroke, diabetes, some cancers and cardiovascular problems (Davis et al., 2011; Department of Health, 2004; US Department of Health and Human Services, 2008). Physical activity also has preventive and therapeutic effects on dementia (Hamer and Chida, 2009; Davis et al., 2011) and depression (Teychenne, Ball and Salmon, 2008; Davis et al., 2011). In addition to the effect of physical activity on disease prevention, it is also important for the maintenance of physical independence and QoL (Sun, Norman and While, 2013). Regular physical activity can improve the QoL of older people by extending years of active independent living and reducing disability (Sun, Norman and While, 2013). Conversely, the accumulation of more sedentary time with advancing age increases the risk of all-cause

mortality, such as overweight/obesity, mental health, and falls in adults aged 60 and older (de Rezende et al., 2014).

1.3.2 Recommended physical activity for older adults

The definitions of ‘recommended’ physical activity in older adults vary throughout the literature. Recommendations for older adults are different from those for other adults in some ways, such as the proscription of intense aerobic activity due to the limited aerobic fitness of older adults. Activities that maintain or improve flexibility are usually recommended, along with balance exercises to reduce the risk of falls (Nelson et al., 2007).

In the UK, physical activity guidelines were set by the Chief Medical Officer (CMO) in 2011 for adults aged 19 and over. The main aim of these guidelines is to encourage adults to be active daily and to minimise the amount of sedentariness, especially sitting for a long time. The guidelines recommend the following:

- Moderate intensity activity, such as brisk walking and cycling at least 150 minutes a week in bouts of ≥ 10 minutes to achieve 30 minutes on at least 5 days a week.
- Vigorous intensity activity, such as running, swimming and football, as an alternative to achieving benefits should be done 75 minutes a week.
- Alternatively, a combination of moderate intensity with vigorous activity is also recommended.
- Additionally, muscle strengthening should be done by adults at least 2 days per week in the form of physical activity.
- Older adults aged ≥ 65 who are at risk of falls should combine physical activity to improve both balance and coordination at minimum 2 days per week (Bull et al., 2010; Department of Health and Social Care, 2011).

1.3.3 Physical activity and knee OA

The ACR has identified physical activity among the main goals in management programmes for patients with OA (Shih et al., 2006; Hochberg et al., 2012). Patients with knee OA usually experience a lack of physical activity. A cross-sectional study was conducted across six European countries to compare the patterns of physical activity in older adults with knee OA with those without knee OA, using the Longitudinal Aging Study Amsterdam (LASA) Physical Activity Questionnaire. Participants with knee OA were less likely to be physically active compared with individuals without knee OA, with an average difference of 10.2 minutes/day ($P=0.011$). Country-specific analysis showed older adults with knee OA in the UK were most significantly less active ($P=0.010$) compared with older adults without knee OA (Herbolsheimer et al., 2016).

The national variation referred to above implies that low levels of physical activity among persons with knee OA cannot be explained exclusively by individual or disease-specific factors, but that social, environmental and other contextual characteristics should also be taken into account (Herbolsheimer et al., 2016). However, encouraging patients with knee OA to be more physically active is a very important factor in delaying disability and the progression of disease and enhancing functional activities. Walking > 6,000 steps/day provides a preliminary estimate of the level of walking activity that could protect against developing functional limitation in older adults with or at risk of knee OA (White et al., 2014). However, integrated physical activity in knee OA standard care is the first recommendation of the 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and OA (Osthoff et al., 2018).

1.3.4 Barriers to and facilitators of physical activity for knee OA

The literature shows that subjects with lower limb OA have some barriers and facilitators to physical activity. A recent SR synthesised the existing qualitative research evidence of physical activity barriers and facilitators in adults aged ≥ 45 years with a physician-made diagnosis or radiographic evidence of knee and hip OA (Kanavaki et al., 2017). Seven studies focusing on exercise regimen and three on overall physical activity were included in the review. The most important barriers to activity were pain and physical limitations, a resigned attitude and distress due to OA, absence of positive physical activity experiences and beliefs, lack of behavioural regulation, no support from health professionals, and negative social comparisons when exercising in a group (Kanavaki et al., 2017). Positive exercise experiences and beliefs, knowledge, enjoying exercise, a ‘keep going’ attitude, symptom relief and mobility, adjusting and prioritising physical activity, and having professional and social support were important physical activity facilitators (Kanavaki et al., 2017).

1.4 Dietary restriction

In the management guidelines for obesity, caloric restriction is considered the standard lifestyle therapy/approach used to improve the metabolic process and promote weight reduction in obese people (Barquissau et al., 2018). Weight reduction methods are recommended by level 1A evidence for the management of OA in obese patients (Bliddal and Christensen, 2006). The optimal method of weight loss in overweight/obese patients with knee OA is, however, unclear (Alrushud et al., 2017). Despite the positive effect of weight loss on knee OA outcomes, weight loss is more effective when combined with exercise (Cooper et al., 2018).

Chapter summary

This chapter introduced the most relevant information regarding the key subjects of this thesis. Risk factors for developing OA were presented, highlighting the bidirectional relationship between obesity and knee OA: obesity may cause knee OA initiation and the restricted movement caused by pain in patients with knee OA may cause weight gain. The most common diagnostic methods and guidelines for the management of OA were presented. The role of physiotherapy in knee OA and several physiotherapy approaches were also presented. Physical function is altered with ageing and ageing processes contribute to knee OA. International guidelines for knee OA management recommend weight loss and exercise for obese patients. The currently available evidence on the effectiveness of combined programmes of physical activity and dietary restriction in this population is presented in Chapter 2 as part of a comprehensive SR.

CHAPTER 2

EFFECT OF PHYSICAL ACTIVITY AND DIETARY RESTRICTION INTERVENTIONS ON WEIGHT LOSS AND THE MUSCULOSKELETAL FUNCTION OF OVERWEIGHT AND OBESE OLDER ADULTS WITH KNEE OSTEOARTHRITIS: A SYSTEMATIC REVIEW AND MIXED METHODS DATA SYNTHESIS

Chapter 1 introduced knee OA and highlighted the most widely recommended guidelines for its management. Exercise and body weight reduction if a patient is overweight or obese are mostly recommended. In clinical practice, most practitioners advise their patients (if overweight or obese with knee OA) to reduce their weight and exercise regularly. A scoping search of the literature was used to identify the evidence base for the effectiveness of a combined programme of diet and exercise in this special population of older overweight and obese adults with knee OA. A number of studies utilising different protocols were identified. This preliminary search of the literature emphasised the need to conduct a SR for two reasons. First, to construct evidence-based practice for an effective combined programme of diet and physical activity for weight loss and musculoskeletal function in the targeted population. Second, to inform the design of a protocol for an intervention trial. This chapter describes the development of the SR, the process and a synthesis of the findings.

2.1 Introduction

2.1.1 Preliminary scoping review

A preliminary search for intervention studies investigating the effect of a combined intervention programme of diet and physical activity for patients with knee OA was conducted in November 2014. Keywords, which included knee OA, overweight, obesity, diet and exercise, pain, function and QoL, were applied to search a number of databases, such as Web of Science and Google Scholar. Only seven studies matching the search criteria were identified: one pilot study (Messier et al., 2000), three trials (Messier et al., 2004; Miller et al., 2006; Messier et al., 2013), and three additional papers (Nicklas et al., 2004; VanGool et al., 2005; Focht et al., 2005) that reported secondary and additional data from Messier et al. (2004). However, there were differences in the protocols of these intervention trials, whether in the goal of body weight reduction, randomisation arms, outcome measures, period of intervention, or the diet and exercise programme concerned. Each trial presented its own limitations, with the most obvious reported by Miller et al. (2006), in that there is no radiographic evidence for knee OA. The investigators based their assessment on current symptoms and the participants reporting that they had been diagnosed with knee OA by their physician (Miller et al., 2006). It was hard to seek a conclusion about the effectiveness of a combined programme from this search, to identify the most effective way of delivering exercise, or the most suitable dietary intervention. In addition, the preliminary search showed that there were no SRs synthesising the effectiveness of combining physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese older adults with knee OA. Thus, a protocol for a SR was developed and registered (details of the protocol development and registration are provided in section 2.2.1).

2.1.2 Rationale

Current evidence shows that the burden of chronic musculoskeletal conditions, especially OA, increases with advancing age (Imamura et al., 2008). OA is the most common type of arthritis affecting older adults. It is a degenerative joint disease that may affect any joint within the body, causing chronic pain, functional limitation and emotional disturbance and may lead to disability and negatively affect QoL (Heidari, 2011; Messier et al., 2013; Pouli et al., 2014). Knee OA is a common condition in older adults, affecting about 3.64% of the global population in 2010 (Vos et al., 2012; Hammerich and Anemaet, 2016). In the UK, there are approximately 4.7 million older adults aged 45 or over who experience knee OA symptoms (Imamura et al., 2008; Arthritis Research UK, 2013). Given the increasing number of older adults in the population, combined with the greater prevalence of obesity and being overweight throughout the population, it is anticipated that the incidence of knee OA will rise rapidly over the next decade (Arthritis Research UK, 2013).

Unfortunately, there is no specific treatment for knee OA. Most recommendations describe three treatment modalities: non-pharmacological, pharmacological and surgical (Abbott et al., 2013; DeJaco et al., 2015). Most knee OA evidence-based guidelines recommend non-surgical treatment (Fernandes et al., 2013; McAlindon et al., 2014) and most GPs prefer non-pharmacological and non-surgical interventions as the first line of treatment (recognised as ‘usual care’) (Abbott et al., 2013). These interventions are focused on patient education, self-management, pain reduction, function and QoL improvement, body weight reduction and exercise (either land- or water-based) (Imamura et al., 2008; Ryan and Sawin, 2009; McAlindon et al., 2014; Kao et al., 2016; Yusuf, 2016). It is well known that obesity is an important risk factor for knee OA progression and several studies recommend obesity control for decreasing disease burden, since a decrease in body weight will lead to a

reduction of joint load and inflammation (Coggon et al., 2001; Messier et al., 2013; McAlindon et al., 2014; Yusuf, 2016). Weight reduction could be considered a functional treatment in knee OA rehabilitation, since a 12%-15% reduction compared with initial body weight has been shown to improve function and reduce pain (Huang et al., 2000). Moreover, the appropriate percentage of body weight reduction has been investigated in a SR and meta-analysis of five RCTs (Christensen et al., 2007). The review concluded that professional treatment of knee OA should include a weight reduction plan and patients should be encouraged to lose at least 5% of body weight over a 20-week period to achieve symptomatic relief (Christensen et al., 2007).

In addition to weight reduction, clinical guidelines for knee OA management and level 1 evidence recommend exercise therapy as the main intervention (Minor et al., 1989; Patrick et al., 2001; Roddy, Zhang and Doherty, 2005; Christensen et al., 2007; Messier et al., 2010). Moderate intensity aerobic exercise (e.g., walking) is recommended to maintain musculoskeletal function and reduce pain (Roddy, Zhang and Doherty, 2005; Christensen et al., 2007; Messier et al., 2010). However, the optimal exercise prescription for older adults is still unclear and further research is required (Hammerich and Anemaet, 2016). The demand for optimal exercise is increased in patients with obesity, who may face more challenges and believe in the greater importance of physical activity compared with dietary intervention (Ekram et al., 2016; Marks, 2016).

Clinically combining a weight loss programme with exercise therapy may help overweight and obese older adults with knee OA to achieve a 10% loss of total body weight, as well as safely relieve knee OA symptoms (Messier et al., 2013). A recent RCT which included older adults has also shown that a non-surgical treatment programme had longer-lasting beneficial effects, which was evidenced by a delayed requirement for elective TKR surgery in a

secondary health care setting (Skou, Rasmussen et al., 2015). Moreover, for those who are eligible for unilateral TKR, non-surgical intervention may delay their surgical intervention for several months (Skou, Roos et al., 2015). There are no systematic literature reviews synthesising the evidence for the effectiveness of combining physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese older adults with knee OA.

Therefore, the aim of this review was to evaluate the effectiveness of combined physical activity and dietary restriction programmes on the musculoskeletal function of overweight and obese older adults with BMI ≥ 25 kg/m², aged ≥ 55 years, with radiographic evidence of knee OA.

2.1.3 Objective

To evaluate the effectiveness of combined physical activity and dietary restriction programmes on body weight, BMI and the musculoskeletal function of overweight and obese older adults with knee OA.

2.2 Methods

2.2.1 Protocol and registration

A SR was conducted in accordance with a predefined protocol, following the Preferred Reporting Items for SRs and Meta-Analysis Protocols (PRISMA)-P guidelines (Moher et al., 2009) and the Cochrane Handbook (Higgins, Green et al., 2011). The review was registered on the International Prospective Register of SRs (PROSPERO) on 1 April 2015 (CRD42015019088) and reported in accordance with the PRISMA statement (Moher et al., 2009) (Appendix 2.1).

2.2.2 Eligibility criteria

2.2.2.1 Types of participants

Older adults aged ≥ 55 years, men and women, diagnosed with knee OA using radiographic evidence of tibiofemoral OA (unilateral or bilateral), grade I–III (mild to moderate) according to the Kellgren and Lawrence system for knee OA classification (Brandt et al., 1991) and classified as overweight or obese with BMI ≥ 25 kg/m² (Messier et al., 2013). Participant ages and BMIs were selected based on the findings of the preliminary scoping review (section 2.1.1).

2.2.2.2 Types of studies

RCTs reporting a combined physical activity and dietary restriction programme as an intervention and a comparison with usual care (including advice or physical activity alone or dietary restriction alone) or exercise (participants received an exercise programme similar to that of the intervention group). Full articles not written in English were excluded.

2.2.2.3 Types of outcomes measured

Primary outcome measures: body weight, BMI, musculoskeletal function, either self-reported function or objective functional performance measures, including mobility, joint ROM and muscle strength.

Secondary outcome measures: pain and QoL.

2.2.3 Information sources

The search employed sensitive, topic-based strategies designed for each database:

- The Cochrane Library: Controlled Trials Register, NHS Economic Evaluation Database.
- Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, MEDLINE, Web of Science.
- Hand searches in key journals and lists of references.
- Unpublished research and grey literature, such as OpenGrey.
- Government, official, organisational sources, such as the UK Department of Health, the WHO and the NHS (UK).
- Clinical trials registration, theses abstracts and Google Scholar.

2.2.4 Search

Search strategies of predefined search terms were developed and tested for applicability (ASA, and a specialist librarian from the University of Birmingham (UoB) on 13 February 2015). The definitive search strategy was run by two independent researchers (ASA/AMK, 10 December 2015). Endnote X7 software was used for data management. Search results were imported and duplicates removed. An example of the Ovid MEDLINE search strategy is presented in Table 2.1. The search was updated twice: first by ASA/AMK on 15 January 2017 to include studies published in 2016; the second update of the search was done by ASA on 23 January 2018 to include recent studies published in 2017. The search covered the Ovid, EMBASE, CINAHL and Web of Science databases, the Clinical Trials Register, NHS, NICE, WHO and Google Scholar, as well as grey literature, including OpenGrey.

Table 2.1 Example of an Ovid MEDLINE search strategy 1948-10 December 2015

#	Searches
1	Physical activity/
2	Physical* adj2 (activity or training or therapy*)
3	(Exercis* or rehabilitation* or treatment*)
4	(Closed kinetic chain* or open kinetic chain* or isokinetic* or isometric* or anaerobic* or muscle* or stretching* or aerobic* or isotonic* or treadmill* or endurance* or walking*) adj1 (exercise*)
5	(Resist* adj2 (exercise* or therapy or training))
6	1 or 2 or 3 or 4 or 5
7	Dietary restriction .mp.
8	Meal replacement.mp.
9	Weight loss/ or weight loss.mp. or intentional weight loss.mp.
10	Caloric Restriction/ or Obesity/ or Body Weight/ or hypo or hypochloric diet/
11	Energy intake/ or adipos*/ or Body Mass Index/ or Overweight/
12	Diet/ or Diet, Carbohydrate-Restricted/ or Diet, Reducing/ or Diet Therapy/ or Diet, Vegetarian/
13	Obesity/ or obesity.mp.
14	((Low carbohydrate* or low calor* or low fat* or vegetarian*) adj1 (diet*))
15	(Diet adj2 (therapy* or treatment*))
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	Aging/
18	Exp aged/
19	(55 adj2 (year* or age* or old*))
20	(old* adj (adult* or people or person* or population* or men or women))
21	(aging* adj (adult* or people or person* or population* or men or women))
22	(elder* or senior* or geriatric* or geriatric* or ageing)
23	(age* or aging or old* or elder*) adj1 (muscle*)
24	17 or 18 or 19 or 20 or 21 or 22 or 23
25	Pain/ or Knee Joint/ or Knee pain.mp. or Osteoarthritis, knee/
26	Knee osteoarthritis.mp. or Osteoarthritis, knee/
27	(Knee* adj (arthritis or osteoarthritis* or inflammation* or degeneration* or disease or pain*))
28	(radiographic* or symptomatic* or clinical* adj1 (knee osteoarthritis*))
29	25 or 26 or 27 or 28
30	Musculoskeletal function .mp.
31	Muscle function .mp.
32	Body composition/
33	Mobility.mp.
34	(Gait or walking) adj1 (speed)
35	Functional ability.mp.
36	“Activity of daily” living/ or .mp.
37	“Quality of life”/
38	Balance.mp.
39	(musculoskeletal adj2 (pain or disorder*))
40	(Musc* adj (power or strength or performance or function or weakness))
41	41. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42	6 and 16 and 24 and 29 and 41

2.2.5 Study selection

The eligibility of the studies to be included was independently assessed by two reviewers (ASA/AMK) in accordance with the eligibility criteria, except for the final update on 23 January 2018, which was done by ASA. The reviewers screened the results of the search by titles and abstracts, and then the full text. A study was considered to be eligible when both reviewers assessed the full text independently and found it to fulfil the eligibility criteria. A third reviewer (CAG) mediated in the case of disagreement. The inter-rater agreement was evaluated using Cohen's Kappa measure (Hsu and Field, 2003). The included and excluded studies generated by the first search up to 10 December 2015 are reported in Appendix 2.2.

2.2.6 Data collection

Using a standardised form (developed by ASA) based on the Cochrane Consumers and Communication Review Group's data extraction template ("Consumers and Communication Group" resources), two reviewers (ASA/AMK) extracted data independently. A third reviewer (CAG) checked for consistency and clarity.

2.2.6.1 Data items

Items reported on the data extraction form for each trial included demographic information, methodology, intervention details and all specified reported outcomes.

2.2.7 Risk of bias in individual trials

The internal validity of each included trial was assessed using the Cochrane risk-of-bias assessment tool (Higgins, Altman et al., 2011) recommended by PRISMA (Moher et al., 2009). All domains of the risk-of-bias tool were assessed independently by two reviewers (ASA/CAG). A third reviewer (ABR) mediated in the case of disagreement.

2.2.8 Risk of bias across trials

Risk of bias was considered high if the proportion of information from trials with a high risk of bias was sufficient to affect the interpretation of the results. Risk of bias was considered unclear if most information was from studies with a low or unclear risk of bias, and low if most information was from studies with a low risk of bias (Higgins, Altman et al., 2011).

2.2.9 Summary of measures

Following data extraction, meta-analysis was possible for one key outcome measure across trials that applied similar interventions and compared with exercise at one assessment time point (6 months). Meta-analysis was conducted using RevMan to assess the effectiveness of a combined intervention programme of diet and exercise on mobility (6-minute walk test at 6 months) using the random effects model (DerSimonian and Laird, 1986; Higgins, Green et al., 2011). Ninety-five per cent CIs were reported for the summary statistics and the SD was calculated from the standard errors (SEs) and CIs (Centre for Reviews and Dissemination, 2009; Deeks et al., 2016). Data for the other outcomes were available, but meta-analyses were not possible due to different assessment points or comparators. A modified narrative synthesis was used to present these data (Popay et al., 2006; Rodgers et al., 2006).

2.2.10 Synthesis of results

A mixed methods analysis was required to synthesise the available data (DerSimonian et al., 1986; Popay et al., 2006; Rodgers et al., 2006; Centre for Reviews and Dissemination, 2009; Higgins, Green et al., 2011; Deeks et al., 2016). No raw data were available for meta-analysis and, therefore, data analyses were conducted on the final summary statistics reports. SDs were estimated from reported SEs and CIs for all available data (DerSimonian et al.,

1986; Centre for Reviews and Dissemination, 2009). Heterogeneity in treatment effects was considered by computation of I^2 . An analysis of the quality of the interventions was undertaken as the basis for the interpretation of heterogeneity (DerSimonian et al., 1986; Centre for Reviews and Dissemination, 2009). For the modified narrative synthesis, change scores were used for trials when no other data were available (DerSimonian et al., 1986; Centre for Reviews and Dissemination, 2009; Deeks et al., 2016). It was possible to apply two stages of a narrative synthesis: the development of a preliminary synthesis of findings of included trials, and an exploration of the relationships within and between trials (Popay et al., 2006; Rodgers et al., 2006).

2.2.10.1 Developing a preliminary synthesis

A preliminary synthesis was developed using tabulation, textual description, grouping and clusters, and data transformation. Tables were designed presenting the main characteristics of the eligible studies and included the eligibility criteria, intervention (number of participants, goal of weight loss, intervention period, setting and brief information about the exercise and diet intervention), comparators, outcome measures and the main findings. Additional tables were used to organise studies with respect to specific outcome measures (primary or secondary) and the comparator group. Results were presented as the mean (SD) by converting the continuous data from SEs or CIs to SD (Popay et al., 2006; Rodgers et al., 2006).

2.2.10.2 Exploring the relationships within and between trials

A visual representation of the association between a study's characteristics and results was used to explore the relationships within and between trials (Popay et al., 2006; Rodgers et al., 2006).

2.2.11 Additional analyses

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to evaluate the quality of the evidence included in the meta-analysis (Schünemann, 2009; Guyatt et al., 2011). Specific software (GRADEpro) was used (Gradepro.org). This approach provided a system for rating the quality of the evidence and determining the strength of the recommendations for clinical practice guidelines (Schünemann, 2009; Guyatt et al., 2011). The approach has five components: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Quality of evidence was categorised as ‘high’, ‘moderate’, ‘low’ or ‘very low’ (Schünemann, 2009; Guyatt et al., 2011). Each RCT evaluated as having ‘high’ quality evidence was modified according to five negative and two positive factors (Schünemann, 2009; Guyatt et al., 2011).

The Cochrane risk-of-bias assessment tool was used for this component (Higgins, Altman et al., 2011). According to the software, risk of bias was classified as ‘not serious’, ‘serious’ or ‘very serious’. The quality of evidence was downgraded by one level if there was a serious limitation or by two levels if the limitation was very serious (Schünemann, 2009; Guyatt et al., 2011). Inconsistency was evaluated according to I^2 statistics. Inconsistency may be considered low if $I^2 < 40\%$, moderate if $I^2 = 30\%-60\%$, substantial if $I^2 = 50\%-90\%$ and considerable if $I^2 = 75\%-100\%$ (Schünemann, 2009). Inconsistency was not considered as serious if the reviewers were able to identify a plausible explanation for the heterogeneity and the quality of evidence was not downgraded (Schünemann, 2009). Otherwise, the quality of evidence was downgraded by one or two levels if inconsistency of the results was classified as serious or very serious (Schünemann, 2009). The quality of evidence was downgraded by one or two levels if there was indirectness between the study question and the applicability of the evidence (Guyatt et al., 2011).

Precision of evidence was downgraded in the presence of the following conditions: first, when the boundaries of the CI crossed the 'no effect' line (threshold is completely within the recommended effect); and second, when the criteria for optimal information size (OIS) were not met (Schünemann, 2009). The criterion for OIS was that the total number of participants included in a SR (calculated from a meta-analysis) was less than the number of participants generated by a conventional sample size calculation for a single adequately powered trial. Imprecision was downgraded by one level if one of these conditions was not met or by two levels if neither condition was met (Schünemann, 2009; Guyatt et al., 2011).

Publication bias was undetectable or strongly suspected in accordance with the GRADE software (Gradepro.org). The selective outcome reporting domain of the Cochrane risk-of-bias assessment tool was used to evaluate publication bias (Schünemann, 2009; Higgins, Altman et al., 2011). The quality of evidence was downgraded by one level if the selective outcome reporting domain was evaluated as unclear without justification, or downgraded by two levels if it was evaluated as high (Schünemann, 2009).

2.3 Results

2.3.1 Study selection

Three RCTs (n=794) were included. One was a pilot trial (Messier et al., 2000) and two were definitive trials: the Arthritis, Diet and Activity Promotion Trial (ADAPT) (Messier et al., 2004) and the Intensive Diet and Exercise for Arthritis (IDEA) trial (Messier et al., 2013). For ADAPT, there was a main trial report, and two additional articles with further analyses of additional outcome measures (Rejeski et al., 2002; Focht et al., 2005). The trials used two comparators: an exercise programme in the pilot study and the IDEA trial (Messier et al., 2000; Messier et al., 2013), while usual care (healthy lifestyle) was the comparator in

ADAPT (Messier et al., 2004). All the trials included were conducted by the same group from the USA and published in English. No relevant unpublished studies were identified. The inter-rater agreement of the study selection process was excellent, with $k = 0.82$ (Hsu and Field, 2003). There was one disagreement requiring consultation with a third reviewer (CAG), who was asked to clarify the eligibility of articles reporting the same trials. Specifically, one pilot study by Messier et al. (2000) did not clarify whether it was an external or internal pilot study. The senior author was contacted twice but no response was received. The third reviewer recommended it be treated as an external pilot study, as there was nothing to indicate it was an internal pilot study in the article reporting the main trial (Messier et al., 2004). The study flow diagram is presented in Figure 2.1 (Stovold et al., 2014).

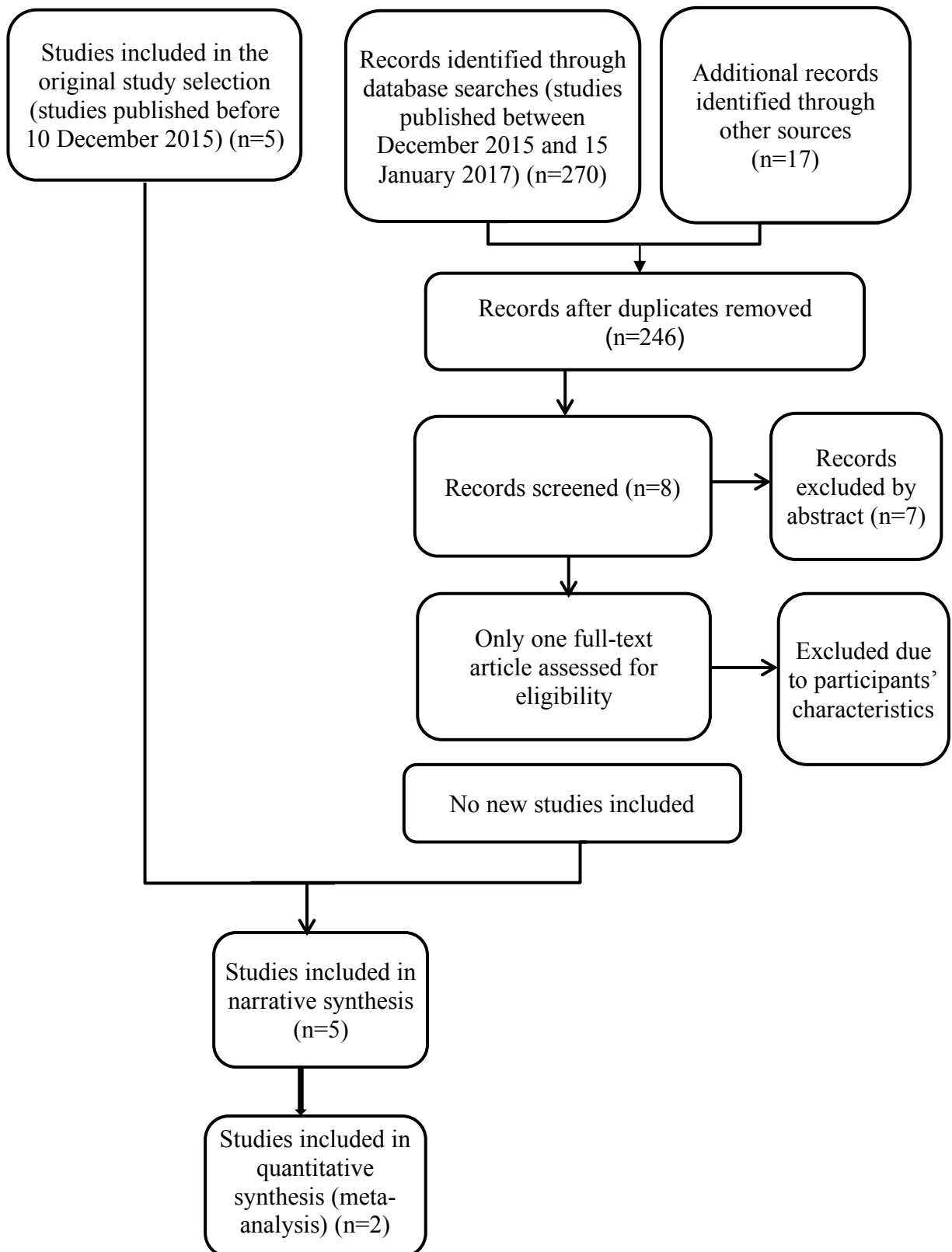


Figure 2.1 Study selection flow diagram

In the updated search on 23 January 2018, seven potentially eligible articles were screened by full text. None were eligible for inclusion. Four articles (Kumar et al., 2017; Loeser et al., 2017; Miller et al., 2017; Murillo et al., 2017) were excluded as they reported secondary and follow-up analysis of the IDEA trial. A further article was a follow-up of a previously reported quasi-experimental study (Saraboon, Aree-Ue and Maruo, 2015) to measure adherence (Aree-Ue, Saraboon and Belza, 2017). The final two studies were excluded due to the participants' age and the type of intervention (Allen et al., 2017; O'Brien et al., 2018) (Table 2.2).

2.3.2 Study characteristics

The main characteristics of the included trials are presented in Table 2.3.

Table 2.2 Summary of the second update of search findings (23 January 2018)

#	Article title	Author, year	Aim	Reason for exclusion
1.	Effects of dietary weight loss with and without exercise on interstitial matrix turnover and tissue inflammation biomarkers in adults with knee osteoarthritis: Intensive Diet and Exercise for Arthritis (IDEA) trial	Loeser et al., 2017	To examine the effects of dietary weight loss, with and without exercise, on selected soluble biomarkers (C1M, C2M, C3M and CRPM) and IL-6 in overweight and obese older adults with symptomatic knee OA.	The article is a secondary analysis of the IDEA trial. Outcome measures: interstitial matrix turnover and tissue inflammation biomarkers (C1M, C2M, C3M, and CRPM) and IL-6 are not eligible for these SR criteria. Outcome measures: SF-36, WOMAC pain and function had been reported and analysed previously.
2.	Impact of diet and/or exercise intervention on infrapatellar fat pad morphology: secondary analysis from the Intensive Diet and Exercise for Arthritis (IDEA) trial	Murillo et al., 2017	To examine the impact of weight loss by diet and/or exercise interventions on infrapatellar fat pad (IPFP) volume.	The article is a secondary analysis of the IDEA trial. Outcome measures: IPFP (surface area, and thickness using MRI), total body fat mass and subcutaneous thigh fat area are not eligible for these SR criteria. Outcome measures: body weight had been reported and analysed previously.
3.	Nutrient intake during diet-induced weight loss and exercise interventions in a randomised trial in older overweight and obese adults	Miller et al., 2017	To examine the effect of an 18-month weight loss programme based on social cognitive theory incorporating partial meal replacements on nutrient intake in older overweight and obese adults.	The article is a follow-up analysis of the IDEA trial. Outcome measures: nutrient intake during diet-induced weight loss and exercise (3-day food records were collected and analysed for total energy and macro- and micronutrient intake) is not eligible for these SR criteria.
4.	Effects of weight loss on patellofemoral loading in overweight and obese adults with patellofemoral osteoarthritis: secondary analysis from the IDEA randomised trial	Kumar et al., 2017	To determine whether weight loss induced by diet, with or without exercise, would reduce patellofemoral joint loading during walking more than exercise alone in overweight and obese adults with patellofemoral OA.	The article is a secondary analysis of the IDEA trial. Outcome measures: patellofemoral joint loading (the biomechanical outcomes of interest during walking included peak compressive force (N/kg), and peak joint compressive force impulse (N*s/kg) during the stance phase of walking are not eligible for these SR criteria. Other outcome measures: body weight and walking speed had been reported and analysed previously.

5.	Patient, provider, and combined interventions for managing osteoarthritis in primary care: a cluster randomised trial	Allen et al., 2017	To examine whether patient-based, provider-based, and patient-provider interventions improve osteoarthritis outcomes.	The participants were aged 18 years and older. Study design: intervention (involving exercise, weight management, and cognitive behavioural pain management), a provider-based intervention (involving provision of patient-specific recommendations for care, based on evidence-based guidelines), and a combination of the two interventions.
6.	Long-term adherence and effectiveness of a multicomponent intervention for community-dwelling overweight Thai older adults with knee osteoarthritis: 1-year follow-up	Aree-Ue et al., 2017	To determine participant adherence to a quadriceps exercise and weight management programme after completion of the intervention; and to examine whether a quadriceps exercise and weight management programme can reduce knee pain and improve knee function and weight loss in community-dwelling overweight Thai older adults with knee OA at 6- and 12-month follow-up.	This article is a follow-up to the authors' previously reported quasi-experimental study (Saraboon, Aree-Ue and Maruo, 2015).
7.	Telephone-based weight loss support for patients with knee osteoarthritis: a pragmatic randomised controlled trial	O'Brien et al., 2018	To determine the effectiveness of telephone-based weight loss support in reducing the intensity of knee pain in patients with knee osteoarthritis, who are overweight or obese, compared with usual care.	The participants were aged 18 years or older. The intervention design included two components. Trained telephone interviewers provided brief advice and education about the benefits of weight loss and physical activity for knee osteoarthritis immediately after randomisation. Intervention participants were then informed of the New South Wales (NSW) Get Healthy Information and Coaching Service (GHS) (www.gethealthynsw.com.au) and referred to the service for weight loss support. The GHS is an evidence-based public health non-disease-specific telephone-based coaching service funded by the NSW Government to support adults to make sustained lifestyle improvements, including diet, physical activity and achieving a healthy weight, and, where appropriate, access smoking cessation services.

Table 2.3 Descriptive data for the included trials

Title, author, year	Aim	Eligibility criteria	Methods	Outcome measures	Assessment points	Result
Exercise and weight loss in obese older adults with knee OA: a preliminary study. Messier et al., 2000	1] To determine if a combined dietary and exercise intervention results in significant weight loss in older obese adults with knee OA. 2] To compare the effects of exercise plus dietary therapy with exercise alone on gait, strength, knee pain, biomarkers of cartilage degradation, and physical function.	Inclusion Aged ≥ 60 years; BMI ≥ 28 kg/m ² ; knee pain, radiographic evidence of knee OA. Self-reported physical disability. Exclusion Serious medical condition affecting safety. Planned change of abode or admission to a nursing home within next 6 months. Unable to walk at least 420 ft in 6 minutes without assistive device. Unable to walk on treadmill without assistive device. Current participation in an exercise programme or other study. Unable to participate or complete the study protocol.	Participants N=24 community-dwelling obese older adults Goal of weight loss 15 lb (6.8 kg) Period of intervention 6 months Setting University Health and Exercise Science Centre, USA Exercise Combined weight training and walking programme for 1 hour three times per week. Dietary intervention Nutrition class 1 hour/week to instruct participants how to modify caloric intake, utilising cognitive behaviour modification to change dietary habits to reach a group goal of an average weight loss, then three group and one individual session held per month. Exercise group (control).	Body weight, self-report questionnaire, physical performance and gait analysis Synovial fluid biomarkers (total PG), keratan sulphate (KS) and IL-1 β Frequency and intensity of knee pain (Likert scale) Disability by self-reported physical function using the Fitness Arthritis and Seniors Trial (FAST) 6-minute walk test and timed stair climbing to measure physical performance Kinetics and kinematics analysis of gait using motion analysis and force plate recorded at 3 and 6 months	Data recorded at base line, 3 and 6 months	Body weight reduced significantly in diet plus exercise group compared with exercise group (P=0.007). Within-group differences: The combined intervention group lost a mean of 18.8 lb (8.5 kg) at 6 months compared with 4.0 lb (1.8 kg) in the exercise group (P=0.01). No statistical differences were found between groups in self-reported performance measures of physical function and knee strength. Statistically significant improvement in both groups in self-reported disability and knee pain intensity and frequency and physical performance. At 6 months, the combined intervention group had a significantly greater loading rate (P=0.03) and maximum braking force (P=0.01) during gait. No statistical differences were found between groups in knee pain scores. Concentration level of KS decreased similarly in both groups. The decrease in IL-1 correlated with joint pain ($r = -0.77$, P=0.043).

Title, author, year	Aim	Eligibility criteria	Methods	Outcome measures	Assessment points	Result
Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis Messier et al., 2004	To determine whether long-term exercise and dietary weight loss are more effective, either separately or in combination, than usual care in improving physical function, pain, and mobility in older overweight and obese adults with knee OA.	Inclusion Aged ≥ 60 years; BMI ≥ 28 kg/m ² . Knee pain, radiographic evidence of knee OA. Self-reported physical disability Exclusion Serious medical problem. Mini-Mental State Examination score of < 24.3 . Inability to finish the 18-month study. Inability to walk without assistive device. Participation in another study. Reported alcohol consumption > 14 unit per week. ST segment depression of at least 2 mm at an exercise level of 4 metabolic equivalents (METs) or less, hypotension, or complex arrhythmia during exercise. Inability to complete the study protocol due to frailty, illness or other reason.	Participants N=316 community-dwelling obese older adults Goal of weight loss 5% of total body weight over 18 months Period of intervention 18 months Setting The Claude D. Pepper Older Americans Independence Centre, Wake Forest University, USA Exercise 1 hour 3 days/week consisting of an aerobic phase, a resistance-training phase, a second aerobic phase, and a cool-down phase. Dietary intervention Based on principles from the group dynamics literature and social cognitive theory; divided into 3 phases: Intensive (months 1-4), Transition (months 5-6), and Maintenance (months 7-18). Dietary weight loss plus exercise Combined the exercise and dietary weight loss programmes. Usual care healthy life style (control)	Primary outcome Self-reported physical function using WOMAC Secondary outcomes Weight loss, 6-minute walk distance, stair-climb time, WOMAC pain and stiffness scores, and joint space width	Data recorded at baseline, 6 and 18 months	Significant body weight loss in diet groups ($P<0.05$). Diet plus exercise and diet group lost an average of 5.7% and 4.9% of their body weight, respectively, with 1.2% for the healthy lifestyle group. Significant improvements in self-reported physical function ($P<0.05$), 6-minute walk distance ($P<0.05$), stair-climb time ($P<0.05$), and knee pain ($P<0.05$) in the diet plus exercise group compared with the healthy lifestyle group. Significant improvement in the 6-minute walk distance in the exercise group ($P<0.05$). The diet-only group was not significantly different from the healthy lifestyle group with respect to any of the functional or mobility measures. Changes in joint space width were not significantly different between groups.

Title, author, year	Aim	Eligibility criteria	Methods	Outcome measures	Assessment points	Result
Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee OA in the IDEA randomised clinical trial Messier et al., 2013	To determine whether a 10% reduction in body weight induced by diet, with or without exercise, would improve mechanistic and clinical outcomes more than exercise alone.	Inclusion Aged ≥ 55 years. Kellgren-Lawrence 14 grade 2 or 3 (mild or moderate) radiographic tibiofemoral OA or tibiofemoral plus patellofemoral OA of one or both knees, pain on most days due to knee OA. BMI from 27 to 41. Sedentary lifestyle (<30 minutes per week of formal exercise for the past 6 months). Participants' usual medications could be maintained or adjusted Exclusion Significant comorbid disease that would pose a safety threat or impair ability to participate, previous acute knee injury, patellofemoral OA in the absence of tibiofemoral OA. Inability and unwillingness to modify dietary or exercise behaviours. Excess alcohol use. Inability to finish 18-month study or unlikely to be compliant. Conditions that prohibit MRI. Significant cognitive impairment or depression.	Participants N=454 Goal of weight loss 10%-15% of total body weight Period of intervention 18 months. Setting Wake Forest University and Wake Forest School of Medicine, USA Intensive weight loss intervention The diet included up to two meal-replacement shakes per day. For the third meal, participants followed a weekly menu plan and recipes that were 500 to 750 kcal, low in fat, and high in vegetables. Daily caloric intake was adjusted according to the rate of weight change between intervention visits. The initial diet plan provided an energy-intake deficit of 800 to 1,000 kcal/day⁻¹ as predicted by energy expenditure (estimated resting metabolism $\times 1.2$ activity factor). Exercise intervention This was conducted for 1 hour on 3 days/week for 18 months. Participation was centre-based for the first 6 months. After 6-month follow-up testing and a 2-week transition phase, participants could remain on the facility programme, opt for a home-based programme, or combine the two. The programme consisted of aerobic walking (15 minutes), strength training (20 minutes), a second aerobic phase (15 minutes), and cool-down (10 minutes). Exercise group (control group)	Primary outcomes Knee joint compressive force and plasma IL-6 concentration Secondary clinical outcomes Self-reported pain (range 0-20), function (range 0-68), mobility, and health-related QoL	Participants were assessed at baseline, 6 and 18 months	Body weight was reduced significantly in both diet groups (diet and diet plus exercise) more than the exercise group ($P<0.001$). Within-group differences: The diet plus exercise group lost about 10.6 kg (11.4%), the diet group lost 8.9 kg (9.5%) and 1.8 kg (2.0%) of baseline body weight. No significant difference in walking speed and 6-minute walk test between groups. Significant pain reduction was observed in the diet plus exercise group at 18 months compared with the exercise group (mean score 1.02; 95% CI: 0.33-1.71; $P=0.004$). The difference in the SF-36 physical subscale was 2.81 units in the diet plus exercise group relative to the exercise group (95% CI: -4.76 to -0.86; $P=0.005$). No significant difference in the mental subscale between groups.

2.3.2.1 Methods

In the pilot trial by Messier et al. (2000), participants were randomised into two groups: a combined intervention and a control group (Messier et al., 2000). The control group received an exercise programme similar to the intervention group. Messier et al. (2004) randomised the participants into four groups: combined intervention, exercise, diet, and a control group. The control group received health education plus telephone contact to obtain information on pain, medication use, illness and hospitalisation (Messier et al., 2004). Messier et al. (2013) randomised participants into three groups: combined intervention, a diet group and an exercise group. The exercise-alone group was the control. The duration of the trial was 6 months for the pilot trial (Messier et al., 2000) and 18 months for ADAPT (Messier et al., 2004) and IDEA (Messier et al., 2013).

2.3.2.2 Participants

All participants were community-dwelling, obese older adults with radiographic evidence of knee OA. A total of 794 participants aged 55 years or older were randomised into the studies included. One hundred and fifty-five participants were included in the meta-analysis.

2.3.2.3 Interventions

The pilot trial (Messier et al., 2000) and two definitive trials (Messier et al., 2004; Messier et al., 2013) were conducted by the same group from Wake Forest University, Winston-Salem, North Carolina, USA. The goal of weight loss varied from 6.8 kg over 6 months to 10%-15% of total body weight over 18 months of intervention. Outcomes were recorded at three time points for the pilot trial (baseline, 3 months and 6 months) and for the two definitive trials (baseline, 6 months and 18 months). Exercise duration and frequency were similar in all the trials included (1 hour, 3 times per week). Exercise types were aerobic

exercise and resistance training. Principles from group dynamics and social-cognitive theory were used for behavioural treatment in the diet group in IDEA trial (Messier et al., 2013). The diet sessions were graded from intensive (facilitating behavioural changes by using self-regulatory skills), a transition stage (assisting participants who had not reached their weight loss goals in establishing new goals) and a maintenance stage (assisting patients who had reached their weight loss goals to maintain their weight loss). For the intensive weight loss trial, the daily caloric intake was adjusted according to the rate of weight change between intervention visits (a low fat and high vegetable diet). The initial diet plan provided an energy-intake deficit of 800-1,000 kcal/day, as predicted by an energy expenditure (estimated resting metabolism $\times$ 1.2 activity factor) of at least 1,200 kcal for men and 1,100 kcal for women (Messier et al., 2013).

2.3.2.4 Outcome measures

As a result of the low number of eligible studies, analysis was based on all the outcomes of interest (body weight and BMI as well as musculoskeletal function), irrespective of whether they were specified as the primary or secondary outcome in the included trials (see below):

Messier et al. (2000): no primary or secondary outcomes were specified.

Messier et al. (2004): the ADAPT primary outcome was self-reported physical function measured using WOMAC. Secondary outcomes included weight loss, 6-minute walk distance, stair-climb time, WOMAC pain and stiffness scores, and joint space width.

Messier et al. (2013): in the IDEA trial, the primary outcomes were knee joint compressive force and plasma IL-6 concentration. Secondary outcome measures were WOMAC pain, WOMAC function, gait speed, 6-minute walk test, QoL, body weight, height, BMI and body composition.

2.3.3 Risk of bias within trials

Substantial inter-reviewer agreement was achieved on the risk-of-bias assessment ($k=0.73$) (Hsu and Field, 2003). All the trials included were evaluated as having an unclear risk of bias (Higgins, Altman et al., 2011). Most of the key domains were assessed as an unclear risk of bias within each trial (Table 2.4).

Table 2.4 Summary assessment of the overall risk of bias for each trial

Study (author, year)	Component of risk of bias						Summary of risk of bias
	1	2	3	4	5	6	
Messier et al., 2000	U	U	U	U	L	U	Unclear (5) Low (1)
Rejeski et al., 2002	U	U	U	L	L	U	Unclear (4) Low (2)
Messier et al., 2004	L	U	U	L	L	U	Unclear (3) Low (3)
Focht et al., 2005	U	U	U	L	L	U	Unclear (4) Low (2)
Messier et al., 2013	L	U	U	L	L	U	Unclear (3) Low (3)

2.3.4 Risk of bias across trials

Risk of bias across trials was evaluated as unclear (Higgins, Altman et al., 2011). Only component 5 (selective outcome reporting) was evaluated as a low risk of bias for all studies. For the ‘blinding of participants, personnel and outcome assessor’ component, all trials were evaluated as having an unclear risk of bias, as no strategies were reported to address the issue of outcome assessor unblinding. For the ‘other sources of bias’ component, all trials were evaluated with an unclear risk of bias due to unclear reporting.

2.3.5 Results of individual trials and synthesis of results

2.3.5.1 Quantitative synthesis

Meta-analysis was possible for only one outcome measure at one assessment time point. Meta-analysis was used to assess the effect of the combined intervention programme compared with exercise on the 6-minute walk test (metres) after 6 months of intervention. Only two trials (Messier et al., 2000; Messier et al., 2013), with an unclear risk of bias, with $n = 155$ participants were available for meta-analysis. The pooled random effects (15.05; 95% CI: -11.77 to 41.87) did not support a combined intervention effect (Figure 2.2).

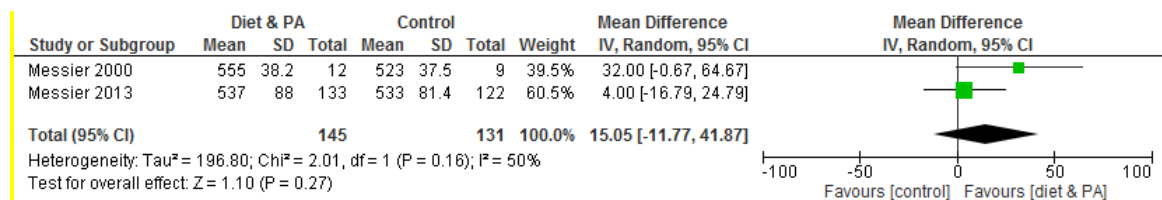


Figure 2.2 6-minute walk test (metres) at 6 months

2.3.5.2 Modified narrative synthesis

With respect to the guidelines for a narrative synthesis, only two elements could be applied: developing a preliminary synthesis and exploring the relationships within and between studies (Popay et al., 2006; Rodgers et al., 2006).

Developing a preliminary synthesis

Tabulation was used to present primary and secondary outcome measures that were not included in the meta-analysis: body weight, knee ROM, physical function, mobility, pain and QoL. Studies including a comparison of the combined intervention programme with an exercise intervention are presented in Tables 2.5 and 2.6.

Table 2.5 Preliminary synthesis of the primary outcome measures at baseline and after intervention; body weight, knee ROM, physical function and mobility comparing the combined intervention programme with an exercise intervention

Category	Outcome measure	Assessment point	Study	Intervention group				Control group			
				M0 (SD0)	N0	M1 (SD1)	N1	M0 (SD0)	N0	M1 (SD1)	N1
Body weight	Body weight (kg)	6 months	Messier et al., 2000	91 (13)	13	82.5 (4)	12	109 (17)	11	107.2 (15)	9
		6 months	Messier et al., 2013	93 (14.7)	152	84.3 (14.7)	133	92.3 (14.6)	150	92.4 (15.4)	122
		18 months	Messier et al., 2013	93 (14.7)	152	82.4 (15.2)	121	92.3 (14.6)	150	90.5 (15)	115
Knee ROM	ROM	6 months	Messier et al., 2000	55.27* (N/A)	13	56.47 (0.91)	12	55.27* (N/A)	11	56.73 (1.02)	9
	Estimated concentric extension (degree)	6 months	Messier et al., 2000	30.7 (N/A)	13	31 (N/A)	12	30.7 (N/A)	11	33.4 (N/A)	9
	Estimated concentric flexion	6 months	Messier et al., 2000	18.2 (N/A)	13	18.5 (N/A)	12	18.2 (N/A)	11	20.8 (N/A)	9
Physical function	Physical function (WOMAC)	18 months	Messier et al., 2013	24.6 (11.7)	152	14.2 (10.4)	121	23.1 (10.3)	150	17.6 (9.8)	115
Mobility	6-minute walk test (metres)	18 months	Messier et al., 2013	467 (87.9)	152	537 (92.6)	121	480 (90.3)	150	525 (79.2)	115
	Stair climb (seconds)	6 months	Messier et al., 2000	9.81* (0.32)	13	7.4 (0.32)	12	9.81* (0.32)	11	8.7 (0.36)	9

Abbreviations: M0 (SD0) = Mean and standard deviation at baseline; N0 = Number of participants at baseline; M1 (SD1) = Mean and standard deviation after intervention; N1 = Number of participants after intervention; N/A = Data not available; * = Adjusted baseline score.

Table 2.6 Preliminary synthesis of the secondary outcome measures at baseline and after intervention; pain and QoL comparing the combined intervention programme with an exercise intervention

Category	Outcome measure	Assessment point	Study	Intervention group				Control group			
				M0 (SD0)	N0	M1 (SD1)	N1	M0 (SD0)	N0	M1 (SD1)	N1
Pain	WOMAC Pain	6 months	Messier et al., 2013	6.7 (3.4)	152	4.6 (2.9)	133	6.1 (2.9)	150	4.5 (3)	122
	WOMAC Pain	18 months	Messier et al., 2013	6.7 (3.4)	152	3.7 (3.1)	121	6.1 (2.9)	150	4.4 (2.7)	115
QoL	SF-36 Physical component	6 months	Messier et al., 2013	36.6 (9.41)	152	43.5 (9)	133	36.8 (9)	150	41.5 (9)	122
	SF-36 Mental component	6 months	Messier et al., 2013	57.2 (6.6)	152	56.9 (7.3)	133	56.5 (8.4)	150	56.1 (7.6)	122
	SF-36 Physical component	18 months	Messier et al., 2013	36.6 (9.41)	152	44.7 (8.7)	121	36.8 (9)	150	42.0 (9)	115
	SF-36 Mental component	18 months	Messier et al., 2013	57.2 (6.6)	152	56.1 (6.5)	121	56.5 (8.4)	150	55.4 (7.6)	115

Abbreviations: M0 (SD0) = Mean and standard deviation at baseline; N0 = Number of participants at baseline; M1 (SD1) = Mean and standard deviation after intervention; N1 = Number of participants after intervention; N/A = Data not available.

Tabulation was used to compare the effect of the combined intervention programme with usual care (healthy lifestyle) on primary and secondary outcome measures: body weight, physical function, mobility, pain and QoL (Tables 2.7 and 2.8).

Table 2.7 Preliminary synthesis of the primary outcome measures at baseline and after intervention; body weight, physical function and mobility comparing the combined intervention programme with usual care

Category	Outcome measure	Assessment point	Study	Intervention group				Control group			
				M0 (SD0)	N0	M1 (SD1)	N1	M0 (SD0)	N0	M1 (SD1)	N1
Body weight	Body weight (kg)	18 months	Messier et al., 2004	92 (1.7)	76	86.8 (N/A)	58	96 (1.8)	78	94.9 (N/A)	67
Physical function	Physical function (WOMAC)	6 months	Messier et al., 2004	23.6 (12.2)	76	17.9* (N/A)	63	26 (11.4)	78	22.4* (N/A)	70
	Physical function (WOMAC)	18 months	Messier et al., 2004	23.6 (12.2)	76	29.3* (N/A)	58	26 (11.4)	78	29.4 (N/A)	67
Mobility	6-minute walk test (metres)	6 months	Messier et al., 2004	416.2 (98.7)	76	482.3 (100)	63	434.6 (96.4)	78	429 (108)	70
	6-minute walk test (metres)	18 months	Messier et al., 2004	416.2 (98.7)	76	477.8 (99.7)	58	434.6 (96.4)	78	429.9 (104.7)	67
	6-minute walk test (metres)	18 months	Focht et al., 2005	414.5 (85.3)	N/A	465 (96.3)	N/A	433.4 (81.9)	N/A	430 (79.5)	N/A
	Stair climb (seconds)	6 months	Messier et al., 2004	10.9 (5.8)	76	8.8 (6.2)	63	9.5 (5.6)	78	9.9 (6.3)	70
	Stair climb (seconds)	18 months	Focht et al., 2005	10.4 (7.3)	N/A	8.9 (5.4)	NA	9.4 (4.9)	N/A	9.9 (5.6)	N/A

* Estimated value from Figure 2 in Messier et al., 2004.

Abbreviations: M0 (SD0) = Mean and standard deviation at baseline; N0 = Number of participants at baseline; M1 (SD1) = Mean and standard deviation after intervention; N1 = Number of participants after intervention; N/A = Data not available.

Table 2.8 Preliminary synthesis of the secondary outcome measures at baseline and after intervention; pain and QoL comparing the combined intervention programme with usual care

Category	Outcome measure	Assessment point	Study	Intervention group				Control group			
				M0 (SD0)	N0	M1 (SD1)	N1	M0 (SD0)	N0	M1 (SD1)	N1
Pain	Pain scale (WOMAC)	6 months	Messier et al., 2004	7.3 (3.6)	76	5.5 (3.7)	63	7.3 (3.4)	78	6.2 (3.9)	70
	Pain scale (WOMAC)	18 months	Messier et al., 2004	7.3 (3.6)	76	5.1 (3.6)	58	7.3 (3.4)	78	6 (3.7)	67
QoL	SF-36 Physical component	Average of 6 and 18 months	Rejeski et al. 2002	35.39 (10.5)	68	40.57 (N/A)*	N/A	33.60 (8.4)	68	34.41 (N/A)*	N/A
	SF-36 Mental component	Average of 6 and 18 months	Rejeski et al. 2002	52.85 (10.7)	68	53.31 (N/A)*	N/A	52.70 (10.9)	68	53.51 (N/A)*	N/A

Abbreviations: M0 (SD0) = Mean and standard deviation at baseline; N0 = Number of participants at baseline; M1 (SD1) = Mean and standard deviation after intervention; N1 = Number of participants after intervention; N/A = Data not available; * = only SEM data available; SD1 data could not be calculated due to missing N1 value.

Exploring the relationships within and between studies

Characteristics of the trials are presented in Table 2.3. All the trials included were conducted by the same research group; the eligibility criteria were very similar across the studies; the exercise intervention included strengthening and aerobic exercise; and the intervention frequency (1 hour, three times per week) was the same across the trials included. Further details about the design of the trials are presented above.

Tables 2.5 and 2.7 show differences between the intervention group and the control group (despite the comparator) with respect to body weight and the 6-minute walk distance. These differences were consistent with the results from the trials included. The diet plus exercise group in the pilot study (Messier et al., 2000) lost weight compared with the control group ($P=0.01$) after 6 months of intervention (Messier et al., 2000). This was also the case with respect to the longer duration intervention trial (18 months) in which the intervention group lost significantly ($P<0.001$) more weight than the exercise group (Messier et al., 2013). However, in ADAPT (Messier et al., 2004), both groups (intervention and healthy lifestyle) lost weight ($P<0.05$) after 18 months of intervention (Messier et al., 2004), although there was a significant difference in the 6-minute walk test result in favour of the diet plus exercise group ($P<0.05$) (Messier et al., 2004). There was also a significant difference ($P=0.005$) in the 6-minute walk test result between the intervention and exercise groups in the IDEA trial (Messier et al., 2013).

2.3.6 Additional analysis

No further analyses were possible owing to the lack of reported information and the low number of trials included.

2.3.7 Grading the quality of evidence

A summary assessment was undertaken to draw conclusions about the overall quality of evidence for the combined intervention on mobility using GRADE software (grading the quality of evidence). Both trials included in the meta-analysis (Messier et al., 2000; Messier et al., 2013) were evaluated as having ‘high’ quality evidence before being downgraded, as they were RCTs, and then modified according to five negative and two positive factors (Schünemann, 2009; Guyatt et al., 2011). The quality of evidence for a combined intervention programme of physical activity and diet on walking distance (metres) for 6 minutes after a period of 6 months of intervention was evaluated as moderate (Table 2.9).

Table 2.9 Factors determining the quality of evidence according to GRADE

Factor	Judgement	Explanation
1. Risk of bias	Not serious	➤ Only two studies were included in the meta-analysis and both were evaluated as having an unclear risk of bias. ➤ No serious limitations to downgrade the quality of evidence. ➤ Sequence generation was not reported in one study; allocation concealment not specified in either study; no strategy reported to address issue of outcome assessor unblinding. ➤ Incomplete outcome data evaluated as ‘unclear’ in the pilot study; no mention of missing data or methods used to address missing data; no primary outcome stated for the pilot study.
2. Inconsistency	Not serious	➤ $I^2=50\%$, which may be evaluated as either low or substantial heterogeneity; this overlap affects the decision making. ➤ Magnitude of heterogeneity could be the result of high variability in the sample size and effect size, which justifies the decision.
3. Indirectness	Not serious	➤ Direct applicability of the included studies’ aims and objectives to their target populations, interventions and outcomes of interest.
4. Imprecision	Serious	➤ Boundaries of CI crossing the no effect line, which downgrades the quality of evidence by one level. ➤ Number of participants needed for a single powered trial is higher than the number of participants estimated from the meta-analysis; quality of evidence not downgraded on this basis.
5. Publication bias	Undetected	➤ Selective outcome reporting domain evaluated as low in both studies; publication bias considered as not serious by two reviewers.

2.4 Discussion

2.4.1 Summary of the evidence

This is the first SR and mixed methods analysis to investigate the effectiveness of combining dietary restriction and physical activity interventions for musculoskeletal function in overweight/obese older adults with knee OA. One pilot trial (Messier et al., 2000) and two definitive trials (Messier et al., 2004; Messier et al., 2013) (794 participants) conducted by the same research group (Wake Forest University) were included. The intervention programme was compared with exercise training in one definitive trial (IDEA) (Messier et al., 2013) and a pilot trial (Messier et al., 2000), while usual care was the comparator in the ADAPT (Messier et al., 2004). Two additional articles (Rejeski et al., 2002; Focht et al., 2005) which reported further outcomes of the ADAPT were identified (Messier et al., 2004).

Data syntheses for this review were conducted using both meta-analysis and modified narrative synthesis. Although visual inspection of the tables of results indicated that the combined programme enhanced body weight reduction and improved mobility, there was moderate evidence for no effect. Changes in BMI scores were not reported in the studies included. Meta-analysis was possible for only the 6-minute walk test at 6 months and was not possible for the other outcome measures due to the inconsistency of assessment points or the comparator. The pooled random effect of two trials (Messier et al., 2000; Messier et al., 2013) with 155 participants did not support the combined intervention programme (15.05; 95% CI: -11.77 to 41.87) (although with a total effect of 15 m deemed not clinically significant according to previous literature) (Perera et al., 2006; Gremeaux et al., 2011). Although the meta-analyses showed substantial heterogeneity ($I^2=50\%$), this was classified as not serious using the GRADE evaluation tool (Schünemann, 2009; Guyatt et al., 2011), as it was assessed as likely to be due to high variability in both the sample size and effect size.

Clinical heterogeneity across trials was limited to the comparator and duration. Overall, the quality of evidence was downgraded to moderate due to imprecision in the results according to GRADE (Gradepro.org). All the trials included were reported as having an unclear risk of bias, which was mainly due to unclear reporting of some information (Higgins, Altman et al., 2011). For instance, both the ‘blinding of participants, personnel and outcome assessor’ and the ‘other sources of bias’ components were evaluated as unclear for all trials.

Results from the trial by Messier et al. (2000) indicated no statistically significant differences across groups with regard to self-reported performance measures of physical function, knee pain scores, knee strength and biomechanical measures (synovial fluid, KS and IL-1 level) after 6 months of intervention. Findings from Messier et al. (2004) indicated a statistically significant benefit of the combined intervention in terms of self-reported physical function, 6-minute walk test, stair climb and knee pain. The findings from Messier et al. (2000) indicated a significant improvement in the 6-minute walk test and walking speed in the intervention group. Moreover, there was a significant reduction ($P<0.05$) in body weight among the intervention groups in all trials. In the current review, the finding of no effect of a combined intervention programme may be due to the very low number of trials (and participants) included but is probably not due to low compliance. Compliance of the diet and exercise group to the exercise programme at 6 months was higher in the pilot study (Messier et al., 2000) compared with the IDEA trial (Messier et al., 2013). In the pilot study (Messier et al., 2000), compliance (the ratio of the number of exercise sessions attended to the total number of exercise sessions prescribed with the exercise programme) was 82.6% for the exercise group and 94.7% for the diet plus exercise group. For the IDEA trial (Messier et al., 2013), 399/454 participants (88%) completed the

study; the compliance of the diet and exercise group was 70% at 6 months and 58% at 18 months, with no adverse events and no significant differences between groups.

In addition to diet and exercise, two current RCTs, MEDIC1 (Skou, Roos et al., 2015) and MEDIC2 (Skou, Rasmussen et al., 2015), have reported that a multimodal approach including education, neuromuscular exercise, insoles and, if indicated, a dietary weight loss programme and pain medication are effective for adults and older adults with moderate-to-severe knee OA. These studies were not included in this review due to the wide age range across participants. MEDIC1 (Skou, Roos et al., 2015) included nine participants and MEDIC2 (Skou, Rasmussen et al., 2015) included 12 participants below the age of 55 and there was no subgroup analysis of older participants. In MEDIC1 (Skou, Roos et al., 2015), the participants were eligible for TKR and were randomised to non-surgical and surgical treatment followed by the intervention programme. Both interventions showed substantial improvement, but the surgical treatment resulted in greater pain relief and functional improvement after 12 months compared with non-surgical treatment alone. However, only 26% of the patients who were assigned to receive non-surgical treatment alone underwent TKR in the following year (Skou, Roos et al., 2015). In MEDIC2 (Skou, Rasmussen et al., 2015), participants had radiographic confirmation of OA (Kellgren-Lawrence grade ≥ 1) but were not eligible for a TKR. The 12-week non-surgical treatment programme consisted of individualised progressed neuromuscular exercise, patient education, insoles, dietary advice and prescription of pain medication if indicated, while usual care comprised two leaflets with information and advice on knee OA and recommended treatments. This non-surgical treatment programme was found to be more effective with respect to pain, ADLs and QoL at 12 months compared with usual care, although it was not possible to determine which of the components within this multi-intervention programme were the most effective and

whether the intervention as a whole would be equally effective in older patients with OA (Skou, Rasmussen et al., 2015).

2.4.2 Discussion of the second update of search findings

The updated search for this SR did not identify any additional eligible studies but two separate study protocols were identified. The first was developed as a systematic, practical, cost-effective diet-induced weight loss and exercise intervention to be implemented in community settings to determine the effectiveness of reducing pain and improving other clinical outcomes in overweight and obese people aged ≥ 50 years with knee OA in three North Carolina counties (Messier et al., 2017). The second protocol compares a stepped care strategy with standard care (education pamphlets about knee OA and its management) over 32 weeks in Australia (Robbins et al., 2017). Overweight and obese adults with medial tibiofemoral OA are randomised into a diet and exercise group as a first step or a control group for 18 weeks. The exercise regimen is based on the Healthy Weight for Life (HWFL) programme, while diet is based on a low-caloric diet meal replacement. At week 20, the Patient Acceptable Symptom State (PASS) will be used to assess disease remission. PASS score is defined as the value beyond which patients can consider themselves well with respect to factors such as pain intensity, degree of functional impairment and the patient's global assessment of disease activity (Tubach et al., 2005; Robbins et al., 2017). Participants who achieve disease remission continue with their combined programme of diet and exercise in the second step. Participants who fail to have disease remission step up to subgroups of intervention, which include depression management, knee realignment or muscle strengthening for the last 12 weeks of the study.

A recent SR (Hall et al., 2018) was identified after completing the second update of the search. The review quality was evaluated using a measurement tool to assess SRs (AMSTAR2) which subsequently classified it as being of moderate quality (Shea et al., 2017). The review was conducted to investigate the effect of dietary interventions and combined diet and exercise interventions on pain and physical function and to determine the effect of these interventions on inflammatory biomarkers in overweight and obese adults with knee OA (Hall et al., 2018). Only RCTs examining the effect of non-surgical non-pharmacological weight loss interventions with or without exercise were included. In the RCTs included, participants had knee OA assessed by self-reported symptoms or clinically, with or without radiographic evidence, were aged > 45 years and with a BMI > 25 kg/m². In studies that included samples of a mixed population of OA, at least 80% of the sample had to have knee OA. The comparator (control) groups were active (any non-dietary treatment) or no treatment (including placebo and waiting list groups). Clinical outcomes included pain and/or physical dysfunction and/or inflammatory biomarkers (including any inflammatory biomarkers collected from plasma, serum or synovial fluid). Nineteen articles were included in the qualitative synthesis and 16 in the quantitative synthesis; nine of these were reports of RCTs that were included in a meta-analysis and seven were additional reports of these studies. Of the 16 articles included in the quantitative synthesis, three were also included in our SR (Messier et al., 2000, Messier et al., 2004; Messier et al., 2013). Seven studies were screened by our reviewers but excluded: three were additional reports of the ADAPT (Messier et al., 2004) and presented data for inflammatory biomarkers and serum lipid (Miller et al., 2004; Nicklas et al., 2004; Chua et al., 2008); one article (Beaverse et al., 2015) was an additional report of the IDEA trial reporting data of plasma CRP and IL-6 (Messier et al., 2013); and three further studies were excluded from our SR because of the

absence of radiographic evidence for knee OA (Miller et al., 2006; Miller et al., 2008; Miller et al., 2012). More details about the 19 studies reviewed by Hall et al. (2018) are presented in Table 2.10. The remaining six studies were not selected by our reviewers because of the absence of a combined programme (Christensen, Astrup and Bliddal, 2005; Gudbergson et al., 2011; Somers et al., 2012; Budiman-Mak, 2014; Christensen et al., 2015; Huebner et al., 2016). In this review, no trials were evaluated as having a low risk of bias when using the Cochrane risk-of-bias tool (Hall et al., 2018). Of the nine clinical trials, seven studies were dietary and four were diet and exercise interventions with treatment duration ranging from 2 to 24 months and the average body weight loss approximated 10.5% following diet and 4.7% for combined diet and exercise (Hall et al., 2018). However, in Hall et al. (2018), meta-analysis was possible for pain and physical function in both < 12 months and ≥ 12 months and the findings support a combined programme of diet and exercise in reducing pain (standardised mean differences [SMD] -0.37; 95% CI: -0.69 to -0.04; $I^2=54\%$) and improving physical function (SMD -0.32; 95% CI: -0.56 to -0.08; $I^2=24\%$); this also supports diet intervention in improving function only. Whereas, meta-analysis was only possible for the 6-minute walk test at 6 months in Alrushud et al. (2017) and the findings did not support the combined programme. Narrative syntheses also support a combined programme in reducing weight and improving mobility (Alrushud et al., 2017). In terms of the serum concentration of inflammatory biomarkers, the effect of both a combined diet and exercise and diet only intervention was not clear, as only IL-6 was reduced by diet intervention (Hall et al., 2018). However, the results of this SR were consistent with Alrushud et al. (2017) on some points. First, only a few studies were available to investigate the effect of a combined programme on subjects with knee OA. Second, the quality of the available evidence is at best moderate when evaluated by GRADE. However, both reviews recommended

conducting high-quality studies to investigate the benefits of a combined programme (Alrushud et al., 2017; Hall et al., 2018).

Table 2.10 Reviewing of the 19 studies included in Hall et al. (2018)

Author, year	Screened by Alrushud et al., 2017 reviewers	Included/excluded in Alrushud et al., 2017	Comment
Huang, 2000	Yes	Excluded, participants' age ≥ 40 years old	Hall et al. (2018) included this in the qualitative analysis but did not include in the bibliography. In Alrushud et al. (2017), the following was screened: Huang, M.H., Chen, C.H., Chen, T.W., Weng, M.C., Wang, W.T. and Wang, Y.L., 2000. The effects of weight reduction on the rehabilitation of patients with knee osteoarthritis and obesity. <i>Arthritis Care & Research</i> , 13(6), pp.398-405.
Rejeski, 2002	Yes	Included in narrative synthesis	Hall et al. (2018) included this in the qualitative analysis but did not mention it in the references list. In Alrushud et al. (2017), the following was included: Rejeski, W.J., Focht, B.C., Messier, S.P., Morgan, T., Pahor, M. and Penninx, B., 2002. Obese, older adults with knee osteoarthritis: weight loss, exercise, and QoL. <i>Health Psychology</i> , 21(5), p.419.
Bliddal, 2011	No		Hall et al. (2018) included it in the qualitative analysis but did not mention it in the references list.
Messier, 2000	Yes	Yes, included in meta-analysis and narrative synthesis	Hall et al. (2018) included it as a diet treatment only as the intervention group received exercise and diet and the comparator group received exercise only.
Messier, 2004	Yes	Included in narrative synthesis	Hall et al. (2018) included it as two independent interventions; they compared the combined programme group with a healthy lifestyle intervention and diet group with a healthy lifestyle.
Miller, 2004	Yes	Excluded, an additional report of the ADAPT (Messier et al., 2004) presented data for inflammatory biomarkers and serum lipid	Hall et al. (2018) included it as an additional report of the ADAPT.
Nicklas, 2004	Yes	Excluded, an additional report of the ADAPT (Messier et al., 2004) presented data for inflammatory biomarkers and serum lipid	Hall et al. (2018) included it as an additional report of the ADAPT.
Christensen, 2005	Yes	Excluded by abstract, no exercise intervention	Hall et al. (2018) included it as diet treatment only.
Miller, 2006	Yes	Excluded, absence of radiographic evidence for knee OA	Hall et al. (2018) included it as a diet and exercise treatment, physical activity, inflammation and body composition (PACT).
Chua, 2008	Yes	Excluded, an additional report of the ADAPT (Messier et al., 2004) presented data for inflammatory biomarkers and serum lipid	Hall et al. (2018) included it as an additional report of the ADAPT.

Author, year	Screened by Alrushud et al., 2017 reviewers	Included/excluded in Alrushud et al., 2017	Comment
Miller, 2008	Yes	Excluded, absence of radiographic evidence for knee OA	Hall et al. (2018) included it as an additional report of the PACT study.
Gudbersen, 2011	No		Hall et al. (2018) included it as a diet treatment only.
Miller, 2012	Yes	Excluded, absence of radiographic evidence for knee OA	Hall et al. (2018) included it as an additional report of the ADAPT but in fact it is an additional report of the PACT study.
Somers, 2012	No		Hall et al. (2018) included it as a diet and exercise treatment; this study (called OA life) was designed to investigate the effect of pain-coping skills training and lifestyle behavioural weight management in subjects with knee OA. Participants in this study received supervised group exercise training. However, this study is not eligible to be included in Alrushud et al. (2017), as there is no radiographic evidence of knee OA and the participants were aged ≥ 18 years old.
Messier, 2013	Yes	Included in the meta-analysis and narrative synthesis	Hall et al. (2018) included it as a diet treatment only. In this RCT, participants were randomised into three groups: combined diet and exercise, diet, and exercise. They compared the combined programme group with the exercise only group.
Budiman-Mak, 2014	No		Hall et al. (2018) included it as a diet treatment and diet plus exercise treatment. The full text of this study could not be accessed to provide more details.
Beavers, 2015	Yes	Excluded, an additional report of the IDEA trial reporting data of plasma CRP and IL-6	Hall et al. (2018) included it as an additional report of the IDEA trial (Messier et al., 2013).
Christensen, 2015	No		Hall et al. (2018) included it as a diet treatment only. This study (called the CAROT study) is the Influence of Weight Loss or Exercise on Cartilage in Obese Knee Osteoarthritis Patients Trial. There was no combination of diet and exercise, the participants received an intensive weight loss programme for 16 weeks and were then randomised into three groups: a weight maintenance group, an exercise group and a control group, with no attention provided to this group.
Huebner, 2016	No		Hall et al. (2018) included it as an additional report of the OA life study (Somers et al., 2012).

2.4.3 Strengths and limitations of the SR

- This is the first SR of combined physical activity and dietary restriction interventions in overweight and obese older adults with knee OA.

- The protocol of this review was registered on PROSPERO and followed the PRISMA-P guidelines and the Cochrane Handbook; GRADE was used to evaluate the quality of the trials included.
- The review included a mixed methods analytical approach.
- Only a few eligible studies were identified; however, important information is highlighted which could inform clinical practice.

Chapter summary

This chapter has described the process of conducting the SR and presented the findings of evaluating the effectiveness of combined physical activity and dietary restriction programmes on body weight, BMI and the musculoskeletal function of overweight and obese older adults with knee OA. The SR was published in 2017 as: Alrushud, A. S., Rushton, A. B., Kanavaki, A. M., & Greig, C. A. (2017). Effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese older adults with knee osteoarthritis: a SR and mixed methods data synthesis. *BMJ open*, 7(6), e014537 (Appendix 2.3).

One pilot and two definitive trials (with n=794 participants) were included. Two articles reporting additional data and outcome measures for one of the RCTs were identified. All the RCTs included had an unclear risk of bias. Meta-analysis was only possible to evaluate mobility (6-minute walk test) at 6 months and a pooled random effect of 15.05 (95% CI: -11.77 to 41.87) across two trials (with n=155 participants) did not support the use of a combined intervention programme. Narrative synthesis showed clear differences in favour of reduced body weight and an increased 6-minute walk test result in the intervention group compared with the control groups. Based on current evidence synthesised in this review, it

is hard to judge the effectiveness of a combined programme of diet and physical activity due to the low number of trials and participants included and the quality of the available evidence. Only moderate-quality evidence was available to investigate the intervention programmes. However, the narrative synthesis suggests that interventions with a focus on a reduction of body weight and/or improved mobility are worthy of further evaluation. Further adequately powered RCTs testing the effects of a combined intervention against each component individually are required to optimise diet and exercise interventions using a multimodal approach. A protocol for a feasibility study was developed based on the findings of this SR and presented in Chapter 3.

CHAPTER 3

EFFECT OF A COMBINED PROGRAMME OF DIETARY RESTRICTION AND PHYSICAL ACTIVITY ON THE PHYSICAL FUNCTION AND BODY COMPOSITION OF OBESE MIDDLE-AGED AND OLDER ADULTS WITH KNEE OA (DRPA): PROTOCOL FOR A FEASIBILITY STUDY

The results from Chapter 2 showed that the optimal components of dietary and exercise interventions in terms of type, duration and quantity suitable for overweight/obese patients with knee OA are still unclear, as only a few eligible studies were identified. There were also no published UK trials applying a combined programme of diet and exercise in overweight/obese older adults with knee OA. A protocol for a feasibility study titled “Effect of a combined programme of dietary restriction and physical activity on the physical function and body composition of obese middle-aged and older adults with knee OA (DRPA)” was developed to address the gap in the literature. This chapter presents the protocol for the feasibility study, in which qualitative and quantitative methods are incorporated to provide comprehensive data about the combined intervention programme. This chapter was written with reference to two checklists to ensure study quality: one for reporting feasibility and pilot studies and the other for reporting qualitative studies.

Abstract

Introduction Knee OA is the most common chronic illness among older adults. Up to the date of developing this protocol, there are no published UK studies reporting the efficacy of a combined intervention programme of physical activity and dietary restriction on the musculoskeletal function of obese older adults with knee OA, in spite of the clinical recommendation for exercise and diet for people with this condition. The aim of this study is to assess the feasibility and acceptability of a combined dietary restriction and physical activity intervention programme and collect preliminary data.

Method and analysis This single-arm intervention study was scheduled to begin in September 2017 and conclude in November 2018. It took place at the Royal Orthopaedic Hospital (ROH) in Birmingham and the School of Sport, Exercise and Rehabilitation Sciences (SportExR) at the UoB. Participants received a physiotherapy usual care programme for knee OA for 1 month, after which they continued to exercise in their local gym/leisure facility for 3 months. Participants also followed dietary restrictions throughout the 4-month intervention. Mixed analysis techniques were used to analyse the quantitative and qualitative outcome measures.

Ethics and dissemination The study was approved by the ROH Research and Development Foundation Trust and the Health Research Authority (HRA).

Trial registration number ISRCTN (International Standard Randomised Controlled Trials Number) 12906938.

3.1 Introduction

3.1.1 Background

Knee OA is a major public health problem worldwide and a common condition in older adults due to high incidence and prevalence rates (Hootman and Helmick, 2006; Saraboon, Aree-Ue and Maruo, 2015). Approximately 3.64% of the global population is affected by knee OA (Vos et al., 2012). In 2010, 4.71 million people aged ≥ 45 years sought treatment for knee OA in England (Arthritis Research UK, 2013). The impact of knee OA includes pain, decline in physical function, reduced QoL and increased disability (Mahmoudi et al., 2016).

In addition to advancing age, obesity is also a known risk factor for developing OA and causing disability (Janssen and Mark, 2006; Lementowski and Zelicof, 2008; Silverwood et al., 2015; Loeser, Collins and Diekman, 2016). Obesity increases the negative impact of the disease and patients with arthritis may need surgical intervention to reduce body weight and thereby relieve pain (Lementowski and Zelicof, 2008).

In overweight and obese adults, knee OA management should focus mainly on weight reduction (WHO, 2000). The evidence supports a calorie-restricted diet in adults but the optimal method(s) for weight reduction still varies in terms of intervention length. Introducing a low-calorie diet is challenging in older adults with knee OA because of the need to maintain an appropriate intake of important nutrients. For example, maintenance of the recommended daily calcium intake is essential for women who may be at risk of osteoporosis (Riddle and Stratford, 2013). For overweight and obese patients with knee OA, previous studies have indicated that the ultimate goal of weight loss should be at least 10% of body weight, in order to provide significant pain reduction (Christensen, Astrup and

Bliddal, 2005; Christensen et al., 2007). Recently, an SR recommended that total body weight should be reduced by at least 5% over a period of 20 weeks in this population to experience symptom improvement (Christensen et al., 2007).

EULAR and OARSI guidelines recommend exercise as a core intervention for knee OA management (Fernandes et al., 2013; McAlindon et al., 2014). Patients with mild-to-moderate knee OA have been shown to benefit from muscle strengthening and aerobic exercises, with respect to decreasing pain and improving mobility (Castrogiovanni and Musumeci, 2016). In the UK, usual care is considered the first line of knee OA treatment in clinical practice (Abbott et al., 2013) and its main foci are exercise and advice (Foster et al., 2014; Foster et al., 2015). Exercise intervention may include different types of exercise, for example, strengthening exercise (weight-bearing and non-weight-bearing) and ROM and stretching exercises. Advice may concentrate on the importance of exercise and provide patients with information about pain relief strategies, such as the use of analgesics and home heat therapy (Foster et al., 2014; Foster et al., 2015). However, the most effective way of delivering exercise to optimise patient outcome is still unclear, particularly in older people with knee OA (Foster et al., 2015). A SR of the published literature reports that both aerobic walking and quadriceps strengthening exercises have a positive effect on participants with knee OA and there is no overall superiority of one approach over another (Roddy, Zhang and Doherty, 2005).

Combining weight loss and exercise regimens is recommended for older adult patients with knee OA (Messier et al., 2000; Messier et al., 2004; Messier et al., 2013; Skou, Rasmussen et al., 2015). The results from Chapter 2 showed that the optimal components of dietary and exercise interventions in terms of type, duration and quantity suitable for overweight/obese patients with knee OA are still unclear, as only a few eligible studies were identified. Thus,

a feasibility study was required to optimise outcome measures and methods of delivering a programme prior to a future adequately powered definitive trial. This necessitated a study incorporating a mixed methods approach to investigate the acceptability, feasibility and efficacy of a combined intervention programme in older adults with knee OA in the UK, as there are no published UK studies reporting efficacy of a combined intervention programme for older adults with knee OA.

3.1.2 Research questions and objectives

The central research question:

Will the combined intervention programme be feasible and acceptable for the participants and the ROH physiotherapy staff?

Two additional research questions were formulated:

1. What is the potential for efficacy of the proposed combined intervention programme, as indicated by preliminary data evaluating improvement in outcome measures, including weight loss (i.e., body weight, BMI and Waist Circumference [WC]), body composition, patient reported measures (i.e., WOMAC and SF-36), performance-based measures (i.e., RoM, muscle power, stair climb, and timed up and go), and biomarker measurements?
2. Are there any associations between changes in body weight, knee pain, BMI and markers of joint remodelling?

Primary objective:

Will the combined intervention programme be feasible and acceptable for the targeted population and the physiotherapy staff who deliver the intervention?

Secondary objectives:

1. To collect data about the efficacy of the combined programme and assess the appropriateness of the main study measures.
2. To investigate associations between changes in body weight, knee pain, BMI and markers of joint remodelling.

3.2 Methods

3.2.1 Mixed methods

Combining qualitative and quantitative methods in the same study design is termed mixed methods research. Mixed methods research is usually used to provide comprehensive data, as participants can provide their perspective in this type of research, which increases confidence in the findings (O'cathain, Murphy and Nicholl, 2008; O'Cathain, 2009). Based on the rationale that the feasibility of a combined programme was the primary objective of this study, a mixed method was chosen as the most appropriate design. A qualitative component was used to provide comprehensive data regarding the feasibility of the combined programme after completing the intervention phase of the quantitative design. This provided more details of the acceptability and practicality of the combined programme through procedural and methodological issues, as well as the clinical experience of the participants and physiotherapy department staff (Creswell and Clark, 2017). In addition to ensuring data comprehension, the main advantage of this method is that it can provide depth to the interpretation of the findings (Denzin and Lincoln, 2002; Johnson, Onwuegbuzie and Turner, 2007; Wisdom et al., 2012). Thus, this method provided subjective and objective data to inform feasibility issues, as the underlying goal of this study is to explore implications for a larger study.

3.2.2 Study design

This was a single-centre feasibility study, consisting of one arm (a combined programme of dietary restriction and physical activity) with an embedded qualitative component (a focus group for the participants and a questionnaire for the physiotherapy staff).

3.3 Feasibility study

This study was written in line with the extension checklist of the Consolidated Standards of Reporting Trials (CONSORT), which is a checklist of information to include when reporting a pilot or feasibility study (Thabane et al., 2010; Eldridge, Chan et al., 2016) (Appendix 3.1). The checklist was adapted for this non-randomised feasibility trial (www.consort-statement.org).

3.3.1 Participant eligibility and recruitment

Inclusion criteria

1. Obese older adults (n=30) (men and women aged ≥ 45 to 90 years) with BMI ≥ 30 kg/m².
2. Diagnosis of knee OA (with or without radiographic evidence).
3. Not participating in regular exercise more than twice a week.
4. Able to understand verbal and written English.
5. Willing to participate and gave informed consent for the study.

Exclusion criteria

1. *Potential participants* were excluded if they had any significant comorbid diseases that would pose a safety threat or impair ability to participate, such as coronary artery disease, severe hypertension, peripheral vascular disease, stroke, congestive heart failure, chronic obstructive pulmonary disease, insulin-dependent diabetes, psychiatric disease, renal

disease, liver disease, active cancer other than skin cancer, advanced osteoporosis, and anaemia.

2. Previous acute knee injury (moderate-severe) in the last three months.
3. Resting systolic blood pressure greater than 200 mmHg and resting diastolic blood pressure greater than 100 mmHg.
4. Neuromuscular impairments that precluded participation in physical activity, visual, hearing, or moderate/severe cognitive impairments.
5. Unwillingness to modify diet or physical activity patterns or being unable to comply with the intervention because of an inability to access a gym/local leisure facility, food allergies or reactions to the calorie-restricted diet.

Participants were recruited via the ROH outpatient clinic and the physiotherapy department by either a GP referral or a self-referral. Potential participants were identified by an ROH clinician (i.e., a doctor in the orthopaedic clinic) or a senior physiotherapist in accordance with the eligibility criteria. Eligible participants were provided with a copy of the participant information sheet and a response slip, which included a telephone number and email address to contact the study team directly and a stamped addressed envelope for those who preferred to respond by post. In the case of participants who had given blood recently (i.e., within the last 3 months), after obtaining permission from the participants, their GPs were contacted by the study team to provide the results. Participants were invited to attend the SportExR, UoB, where the study procedures were explained in further detail. Participants were given the opportunity to ask questions and informed consent was obtained. Baseline data were collected by the study team. Participants were asked to complete a 3-day food diary (weekday and weekend) and to return it by post to a member of the study team (using the stamped addressed envelope

provided), and a date was scheduled to begin the exercise classes at the ROH. The rate of attrition was recorded, including the reason. The dietary restriction and physical activity (DRPA) trial flow diagram is presented in Figure 3.1.

3.3.2 Interventions

This section is written in line with the Template for Intervention Description and Replication (TIDeR) checklist to ensure quality (Hoffmann et al., 2014). This intervention was developed based on a number of meetings that were conducted with the health care providers at the ROH who were involved in the study as co-investigators (a medical expert and senior physiotherapist) in the study. The main discussion points were the process of recruitment and recruitment rate, study sample, study design, procedure and duration of the intervention, characteristics of the participants, selected outcome measures, clinical resources, including gym availability and usual care delivery, such as the number of participants in the usual care class, and who would introduce the exercise. The same programme of physiotherapy usual care that is applied in the ROH was used. The dietary restriction component was added to this programme to assess the feasibility of a combined programme. The involvement of the public was used to design this component and more details are given in section 3.7. The intervention consisted of a single educational session and physical activity and dietary restriction components (Martin et al., 2005; Persch and Page, 2013; Blekken et al., 2015; Gibbs et al., 2015).

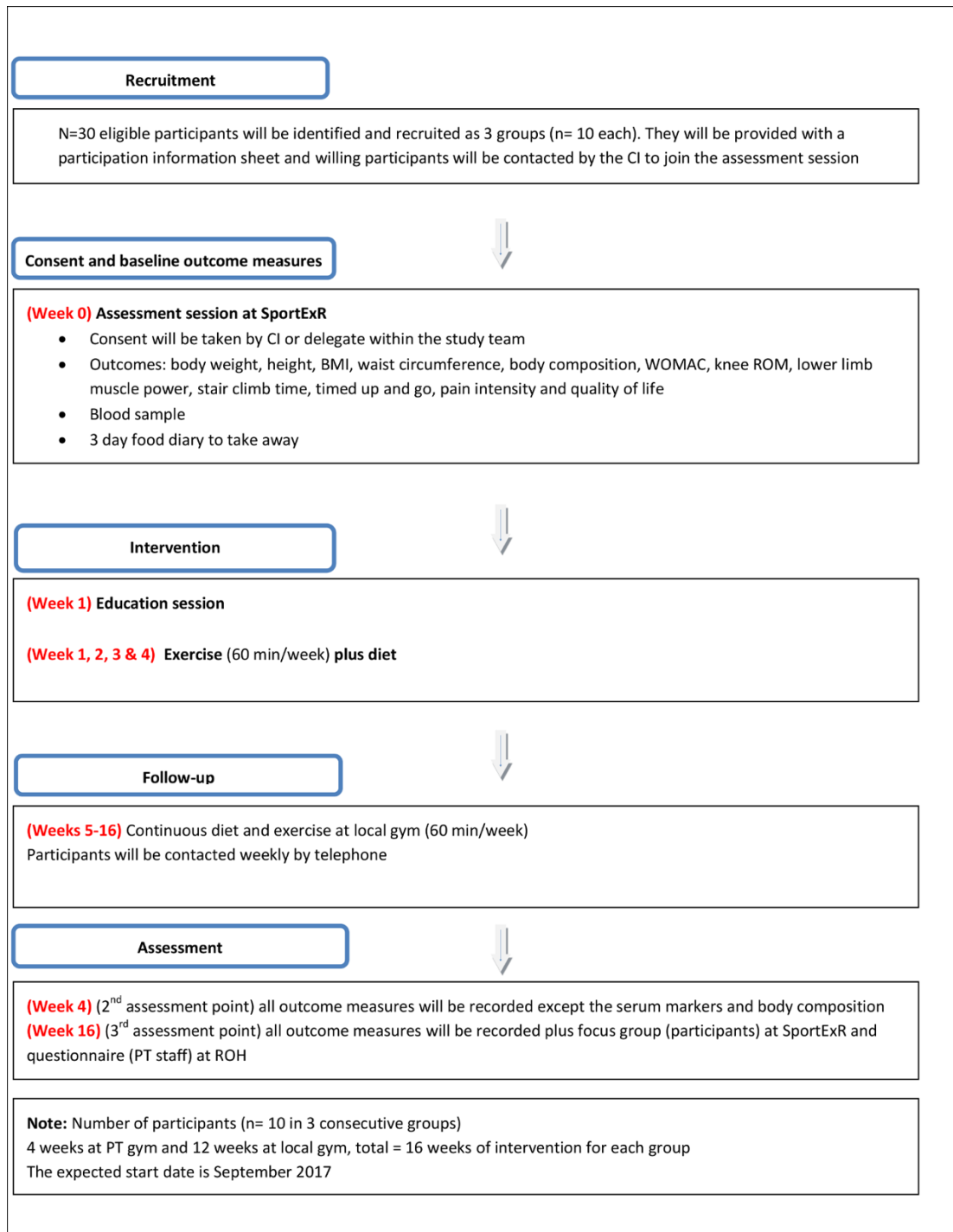


Figure 3.1 Flowchart showing the dietary restriction and physical activity (DRPA) trial flow diagram

Abbreviations: BMI = body mass index; CI = chief investigator; PT = physiotherapy; ROM = range of motion; ROH = Royal Orthopaedic Hospital; SportExR = School of Sport, Exercise and Rehabilitation Sciences; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

3.3.2.1 Educational session

This component is part of the usual physiotherapy care. The first physical activity class was preceded by an educational session lasting 60 minutes, which was introduced by a qualified physiotherapist. Information about the causes and management of knee OA, the importance of exercise and diet and safety considerations was given as part of the physiotherapy usual care for patients with knee OA. Additional information about dietary restrictions was added specifically for this study and introduced by a clinical dietician in the last 10-15 minutes of the session. Information was based on the principles of self-management theory (Devos-Comby, Cronan and Roesch, 2006; Ryan and Sawin, 2009; Nilsen, 2015), self-efficacy theory (Allegrante et al., 1993) and the framework of behaviour change (Michie, 2008), and addressed changing lifestyle and coping with pain, stiffness and limited ADLs. Participants were given the opportunity to ask any further questions. Slides of the education session are attached in Appendix 3.2.

3.3.2.2 Physical activity

Participants received an existing physiotherapy usual care programme for knee OA (moderate intensity stretching and strengthening exercise) in the ROH physiotherapy gym under the supervision of a physiotherapy technician for 1 month (60 minutes per week); the programme was developed by the physiotherapy department at the ROH based on social cognitive theory and group dynamics, in accordance with the NICE (2014) Guidelines for knee OA (Cartwright and Zander, 1960). The classes were group based as opposed to individualised. The participants were divided into two small groups working across several workstations and spent approximately 2 minutes at each station. Each participant exercised according to his/her ability and progression was tailored accordingly. Personalisation was based around the individual participants' hobbies/interests and ADLs, with advice being

offered accordingly. Participants monitored their own symptom levels and modified exercise intensity accordingly to work within their own defined tolerance levels.

Participants began with a warm-up exercise for 5 minutes around the gym that included quadriceps, hamstring and gastrocnemius stretches. The group was divided into two small groups working across several workstations on ROM, strength, cardio, gait stations for a further 40 minutes, for example, a cycle ergometer, treadmill, leg press, TheraBand, inner range quads with band gait work using light hand weights. The exercises also included sit to stand with a medicine ball, marching on a trampette, lunges and extension stretches on a step, stepovers, tandem walking (eyes open–eyes closed), straight leg raising with weights, hamstring curls with weights, bridging, posterior gluteus medius with band, slight hip abduction and through range quads over the edge of a plinth. Group balance work was carried out towards the end of the session. A cool-down was completed with stretches. All stations were run for approximately 2 minutes with additional weights and resistance being added for progression. All participants received a home exercise programme as part of their usual care. Home exercise was based on the NICE (2014) Guidelines for knee OA.

After 1 month, participants continued to exercise in their local gym/leisure facility for a further 3 months. The study team assisted participants with an application for a free (or discounted through funding by the study) gym pass available through the Birmingham City Council Be Active scheme. Participants were provided with a programme of recommended exercises to continue in this setting. The Chief Investigator (ASA) contacted the participants weekly by telephone to record/ encourage adherence. The first 4 weeks were the adoption stage, in which the participants were educated and supported to change their behaviours and the remaining 12 weeks of the study were for maintenance (Allegrante et al., 1993).

3.3.2.3 Dietary restriction

This component was developed specifically for this study based on the findings from a previous SR (Chapter 2). Participants were asked to complete a 3-day food diary and then follow dietary restrictions during the 4 months of the intervention, aiming for a decrease of 300-500 kcal/day or 500-1,000 Kcal.day⁻¹, as appropriate, based on initial BMI (Messier et al., 2000; Messier et al., 2004; Messier et al., 2013). The diet was planned and modified (if required) by a clinical dietician. Participants monitored themselves by completing a daily log.

3.3.3 Outcome measures

Selection of outcome measures was based on a previously published SR (Alrushud et al., 2017) and OARSI recommendations of performance-based tests to assess the physical function of people with knee OA (Dobson et al., 2013) taking into account the study aims and practical considerations. Preliminary data regarding the potential efficacy of the combined intervention programme on weight loss (i.e., body weight, BMI and WC), body composition, patient reported measures (i.e., WOMAC and SF-36), performance-based measures (i.e., RoM, muscle power, stair climb, and timed up and go), and biomarker measurements were chosen using the following outcome measures (Figure 3.2).

The physical functioning WOMAC subscale was the planned primary outcome measure for the definitive study (Bellamy, 1988; Bellamy and Buchanan, 1988; Bellamy, 1995; Thiese, 2014). It was selected for a number of reasons: in clinical trials of knee OA, WOMAC has a disease-specific purpose and is a high-performance instrument used in evaluative research (Bellamy and Buchanan, 1988); it is an important outcome measure that is usually used to determine sample size for OA trials (Bellamy, 1995); and OARSI has recommended

WOMAC when designing a clinical trial as a patient-reported outcome which directly evaluates patients' perceptions of disease and treatment (McAlindon et al., 2015).

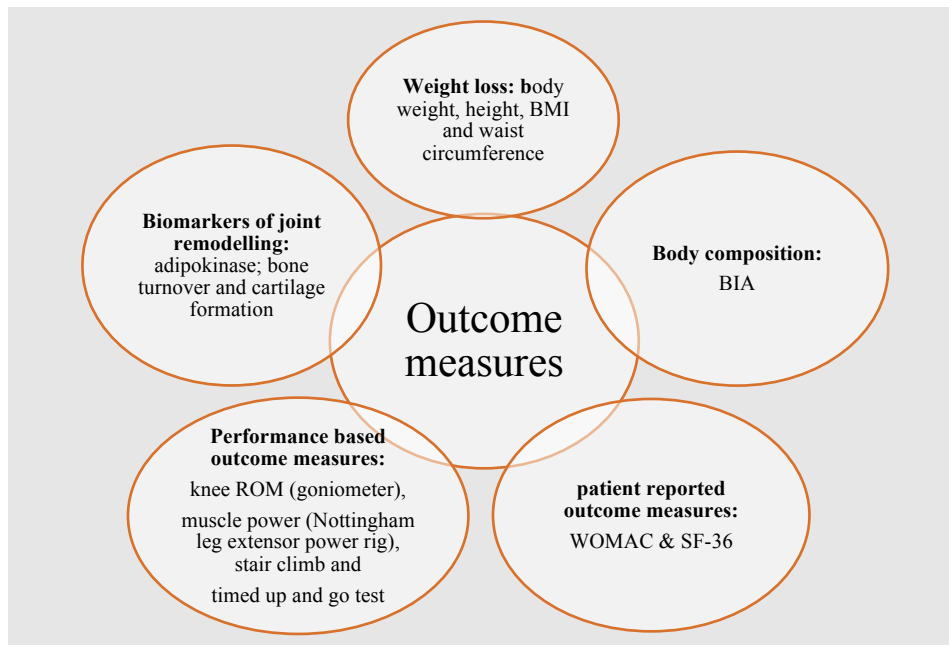


Figure 3.2 Selected outcome measures for assessing the potential efficacy of the combined programme

Weight loss

Losing body weight was one main aim of this study as it was hypothesised that participants' body weight, BMI and WC would be decreased after the intervention programme. Participant body weight and height were measured by the Chief Investigator (ASA) according to the protocol of the International Society for the Advancement of Kinanthropometry (Marfell-Jones, Olds and Carter, 2006). Body weight was measured to compare the participants' body weight before, during and after the intervention programme, to calculate the caloric restriction as well as to measure BMI.

The BMI is a popular and established measure that is defined as weight in kilograms divided by the square of height in meters (Garrouste-Orgeas et al., 2004; Hall and Cole, 2006). It is also classified by the WHO as a normal weight range of 18.5–24.99 kg.m⁻² and BMI ≥ 30

kg.m⁻² are obese (WHO, 2000). BMI is associated with the incidence and progression of knee OA (Reijman et al., 2007) (More details are presented in Chapter 1 section 1.1.5). The healthy weight calculator available on the NHS website was used to calculate the participants' BMI (NHS.UK).

To determine the effect of the combined programme on the abdominal fat, WC was selected (Fayh et al., 2013). Knee OA is strongly correlated with WC; in a cross-sectional study of older adults aged ≥ 60 years, those with highest WC were at high risk of knee OA (Janssen and Mark, 2006). While WC was stated as an outcome measure in the IDEA trial protocol (Messier et al., 2009) the WC data were not reported in the main trial (Messier et al., 2013). For WC measurement, the participant was asked to stand with feet apart (25 to 30 centimetres) and with back straight. The researcher located the top of the hip bone and aligned the bottom edge of the measuring tape with it. The tape measure was wrapped around the waist while ensuring that the tape measure tape was parallel to the floor and not twisted. The participant was asked to take two normal breaths and on the exhalation of the second breath the researcher tightened the tape measure and took the reading (Fayh et al., 2013).

A 3-day food record is an acceptable dietary assessment tool (Yang et al., 2010) hence it was selected to record food and drink over the course of 3 days (including weekdays and weekend). Nutritics software (Version 5.0; 2011-2018) was recommended by the study clinical dietician to analyse the participants' food diaries and set their diet plans.

Body composition

It was hypothesised that total body fat would be reduced after the intervention programme. The rationale for measuring body composition was to monitor whether participants lost body fat mass and not essential minerals or lean mass. Body composition varies between

individuals, even if they have the same height and weight; body composition cannot be estimated by the BMI (Duren et al., 2008). Body composition can be estimated using a number of laboratory and assessment techniques and in this study Body Impedance Analysis (BIA) was selected to measure the body composition pre and post-intervention (Dittmar, 2003). BIA measures total body water and subsequently estimates body density and thus amount / percentage of body fat. Knowing body weight allows calculation of lean body mass ((Dittmar, 2003). It was recommended due to several advantages such as relatively low cost, portability, safety and ease of application (Lee and Gallagher, 2008). This method is also valid and reliable for measuring body composition (Von Hurst et al., 2016). Measurement properties of the included outcome measures are presented in Table 3.1. The participant was asked to lie down on the bed, two electrodes (one proximal and one distal) were placed on the participant's ankle and two on the wrist and recordings were made over the following minute (Hlubik, Hlubik and Lhotska, 2010).

Patient reported outcome measures

It was hypothesised that the participants physical function would be increased after the intervention programme. The WOMAC was selected to measure physical function because it is a validated and reliable, self-administered health status instrument for patients with hip or knee OA (Bellamy et al., 1988) (Table 3.1). The WOMAC is a multidimensional instrument designed to evaluative research in clinical trials of OA; it measures three main subscales; pain, stiffness and physical function (Bellamy et al., 1988; WOMAC.org).

Table 3.1 Measurement properties of the included outcome measures

Outcome measure	Article	Population	Sample size	Reliability	Validity
WOMAC	Williams et al. (2012)	Participants with knee OA, mean age 63.9 ± 8.8 years	N = 168	Intra-class correlation coefficients (ICC) with model 2,1 being used range 0.75 to 0.93 (95% CI)	
SF-36	Jenkinson, Peto and Coulter (1994)	Community adult sample, age range of 18–64 years	N = 13042, response rate 72%	High internal reliability, Cronbach's alpha ≥ 0.70 for all scales except social scale (Cronbach's alpha > 0.5)	A strong association ($p < 0.0001$) between patient reports of overall general health and the seven dimensions of the SF-36 evaluating functioning and well-being
BIA	Von Hurst et al. 2016	Adults with age range of 19-71 years and BMI 19–38 kg.m-2	N = 166	Significant difference ($t = 6.33$, 165 df, $P < 0.001$ [two-tailed], small to medium effect size of $r = 0.44$)	High validity coefficients, ρ (95% CI) were reported for all BIA 0.974 (0.964, 0.983)
Goniometric measure	Gogia et al. (1987)	Healthy participants with age range of 20-60 years	N = 30	High inter-tester reliability ($r = 0.98$; ICC = 0.99)	($r = .97-.98$; ICC = .98-.99)
Nottingham Leg Extensor Power Rig	Hurst et al. (2018)	Adults aged 62.7 ± 8.6 years	N = 72	High short-term reliability (0.88–0.96) and long-term reliability (0.94–0.96)	
Climbing stairs	Humby and Alison (2018)	Postmenopausal women with bilateral knee OA, aged > 50 years	N = 21	Kappa = 0.79 which indicates substantial agreement	

Knee pain was hypothesised to be decreased after the intervention programme. To measure self-reported pain pre, during and post the intervention programme, the pain subscale of WOMAC was selected. The pain subscale has been used in previous combined intervention RCTs for measuring pain in patients with knee OA (Messier et al., 2004; Messier et al., 2013).

It was hypothesised that the combined intervention programme would provide a positive effect on the QoL of the participants. QoL was compared for each participant pre, during and posts the intervention using SF-36. It is a multipurpose short-form health survey with 36 questions. It is a generic measure yielding physical and mental health summary measures and eight-scale profile of scores (Ware, 2000). The SF-36 is a valid and reliable instrument for measuring health perception among the general population (Brazier et al., 1992) (Table 3.1). The SF-36 has also been used in previous RCTs for knee OA to measure the QoL (Messier et al., 2000; Messier et al., 2013). Participants were asked to complete SF-36 (McHorney et al., 1994).

Performance based outcome measures

It was hypothesised that knee ROM would be improved after the intervention. It is often limited in individuals with knee OA (Lijima et al., 2018). A goniometer is a reliable device that has been used frequently to measure lower, upper limb and spine ROM (Reese and Bandy, 2016). In the orthopaedic and rehabilitative communities, it is used to measure knee ROM (Naylor et al., 2011). It was selected to measure knee ROM before, during and after the intervention (Table 3.1). For the measurements of knee flexion and extension ROM, the participant was asked to lie in supine position with the lower extremities in the anatomical position. Bony landmarks for goniometer alignment are (greater trochanter, lateral femoral epicondyle, lateral malleolus) were palpated by the researcher to align goniometer

accordingly, the stationary arm was placed with the lateral midline of femur toward greater trochanter and axis on the lateral epicondyle of the femur. The moving arm was placed with the lateral midline of the fibula, in line with fibular head and lateral malleolus. Knee flexion was carried by sliding foot toward pelvis and knee extension was done by asking the participant to straighten the knee as far as possible and ROM was recorded (Naylor et al., 2011; Reese and Bandy, 2016).

Lower limb muscle power was measured using The Nottingham Leg Extensor Power Rig. The Nottingham Leg Extensor Power Rig is a reliable measure of the maximum lower limb muscle power during a single thrust of the lower limb (Table 3.1). The test was performed in an upright position with arms folded across chest and the test leg on a push pedal. Each participant was instructed to push the pedal forcefully. Data were digitised into watts, normalised to body weight (W.kg^{-1}) and stored on a PC with Nottingham Leg Extensor Power Rig Software. The test was repeated five times for each leg and the best attempt was recorded.

It was hypothesised that the stair climb test would be improved after the intervention programme. It is recommended by the OARSI as performance-based tests to assess physical function in people diagnosed with hip or knee OA (Dobson et al., 2013). It was selected for measuring lower body strength and balance (Table 3.1). It consists of ascending and descending stair activity and recording the time (Dobson et al., 2013). Participants were asked to ascend and descend a flight of stairs (12 steps) as quickly as possible but in a safe manner. They were permitted to use of a handrail and walking aid if needed and this was recorded. The time taken to climb a flight of stairs was recorded and the same stairs were used for reassessment (Dobson et al., 2013).

It was hypothesised that the Timed-up-and-go test of the participants would be improved after the intervention programme. It was recommended by the OARSI as performance-based tests to assess physical function in people diagnosed with hip or knee OA (Dobson et al., 2013). The Timed-up-and-go test was also selected to address physical performance pre, during and after the intervention programme. It is designed to test strength, agility and dynamic balance (Dobson et al., 2013). It includes three tests; sit-to-stand activity, walking short distances and changing direction during walking (Dobson et al., 2013). The 6-minute walk was to be included as an outcome measure, but this was not applicable due to practical considerations, (there was no appropriate place for indoor walking within SportExR). Participants were asked to rise from a chair and walk 3 metres to a cone, turn around and walk back to the chair and sit down again. This test was repeated 3 times and the lowest value (i.e., fastest speed) was used in subsequent analysis (Dobson et al., 2013).

Blood markers of joint remodelling

Losing body weight may help to decrease systemic inflammation and one could therefore, hypothesise that the concentration of selected serum inflammatory biomarkers would be reduced as a consequence of the intervention. ELISA was chosen to provide exploratory data for new biomarkers in knee OA including: Adipokines (serum adiponectin and leptin) and for bone turnover; Bone formation (PICP); Bone (type I collagen) degradation (CTX-1); Cartilage formation: serum N-terminal type IIA collagen N-propeptide (PIIANP), Cartilage (type II collagen) degradation: fragments of COMP (Berry et al., 2011). ELISA incorporates quantitative analytical methods that show antigen–antibody reactions through the colour change obtained by using an enzyme linked conjugate and enzyme substrate which help to identify the molecules present and their concentration in biological fluids (Zhang et al., 2002). It has been used previously in clinical trials for analysing biomarkers of knee OA

(Berry et al., 2011; Huang and Liu, 2017). (Details of these biomarkers are presented in section; 1.1.2). Venous blood samples were taken from each participant and incubated in an upright position at room temperature for 30-45 minutes but no longer than 60 minutes to allow clotting. Samples were centrifuged for 10 minutes at 2000G in a refrigerated centrifuge (4 degrees) then serum was aspirated at room temperature, aliquoted into cryovials and stored at -80° (Berry et al., 2011). Serum biomarkers were measured at baseline and 4 months after the intervention programme. Biomarker assays were sourced as follows: Human Adiponectin ELISA Kit/ DRP300; Human Leptin ELISA Kit/ DLP00; Human COMP ELISA Kit/ DCMP0 (Bio-Techne Ltd, Abingdon, OX14 3NB, UK); Human PICP ELISA Kit – 96T/ E-EL- H0196; Human CTXI ELISA Kit/ E-EL- H0835 (Caltag Medsystems Limited, Buckingham MK18 1T, UK) and PIIANP ELISA/ EZPIIANP-53K (Millipore (UK) Ltd, Watford Hertfordshire WD18 8YH, UK).

3.3.4 Sample size

A formal sample size calculation was not appropriate for a feasibility study and one of the study outcomes was to collect data to inform estimates of SDs for use in a sample size calculation for a future definitive trial. The sample size of 30 participants was based on previous reviews of the literature (Lancaster, Dodd and Williamson, 2004; Billingham, Whitehead and Julious, 2013). To ensure a suitably reliable estimate of SDs (to power a future trial), sample sizes between 24 and 50 have been recommended (Julious, 2005; Sim and Lewis, 2012).

3.3.5 Blinding

Blinded outcome assessment is important to prevent measurement bias but it was not possible in this study due to the limited resources. Blinding of outcome assessment will be applied in the definitive trial.

3.3.6 Statistical methods

Quantitative analysis was used to address the efficacy objective. All data were entered into a database and analysed using the Statistical Package for the Social Sciences (SPSS) (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, Version 21.0). The baseline characteristics were descriptively summarised using frequencies and percentage or means and SD depending on the frequency distribution of the data. The baseline characteristics were then compared with the post-intervention data via SPSS. Moreover, paired t-tests were used to compare the means of the outcome measures that were assessed at two points and a repeated measures Analysis of Variance (ANOVA) test was used to compare the means of the outcome measures that were assessed at three points. This was conducted following guidance from statistical textbooks (Pallant, 2011; Field, 2012). All statistical tests were two-sided with an alpha level of 0.05. Details of the selected statistical tests are presented in Table 3.2.

Table 3.2 Summary of statistical tests

Variable	Form of analysis	How it will be reported	Test
Age (years)	Continuous	M (SD)	Means and SD
Gender	Categorical	Frequency and percentage	Frequency
Height (m)	Continuous	M (SD)	Means and SD
Weight (kg)	Continuous	M (SD)	Repeated measures ANOVA
BMI (kg/m ²)	Continuous	M (SD)	Repeated measures ANOVA
WC (m)	Continuous	M (SD)	Repeated measures ANOVA
WOMAC	Continuous	M (SD)	Repeated measures ANOVA
Knee ROM (degree)	Continuous	M (SD)	Repeated measures ANOVA
Lower limb muscle power	Continuous	M (SD)	Repeated measures ANOVA
Physical function (stair climb and timed up and go)	Continuous	M (SD)	Repeated measures ANOVA
Pain intensity (WOMAC)	Continuous	M (SD)	Repeated measures ANOVA
QoL (SF-36)	Continuous	M (SD)	Repeated measures ANOVA
Body composition	Continuous	M (SD)	Paired t-tests
Markers of joint remodelling	Continuous	M (SD)	Paired t-tests
Associations between changes in body weight, knee pain, BMI and markers of joint remodelling	Continuous	R	Pearson's correlation

Abbreviations: ANOVA = ANalysis Of VAriance; BMI = body mass index; ROM = range of motion; SF-36 = short form-36; WC = waist circumference; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

3.4 Embedded qualitative component

A qualitative component was included in this study to obtain comprehensive data from participants and the physiotherapy staff to ensure their perspective and increased confidence in the findings (O'Cathain, 2009). A post-intervention focus group for the participants and a questionnaire for the physiotherapy staff involved were included to assess the feasibility of the combined intervention programme, which is the primary objective of this study. This qualitative component was reported with reference to the Consolidated Criteria for Reporting

Qualitative Research (COREQ) to ensure study quality (Tong, Sainsbury and Craig, 2007) (Appendix 3.3).

3.4.1 Theoretical framework for the embedded qualitative component

The qualitative component was underpinned by the interpretative phenomenological analysis (IPA) approach, as it aimed to explore the participants' and physiotherapy staff's knowledge, experience and views regarding the combined intervention programme, which would help in assessing the feasibility, acceptability and practicality of the combined programme in a comprehensive way (Kitzinger, 1995; Rabiee, 2004; Hale, Treharne and Kitao, 2008; Bowen et al., 2009; Tickle-Degnen, 2013; Alase, 2017; Rushton et al., 2017).

3.4.2 Participant selection

At week 16, all participants in each group were contacted by the Chief Investigator (ASA) and invited to participate in the focus group discussion. Each focus group was conducted immediately after each wave (4 months of intervention for each group) thus three focus groups would be conducted by the end of the study. All physiotherapy staff who participated in the DRPA study with a role in leading the usual care classes, delivering the education session and recruiting participants were contacted by ASA and a study co-investigator (a senior physiotherapist, FP) and provided with the participant information sheet, and given time to read it and ask questions if they had any before giving their consent and completing a questionnaire to provide feedback on the physiotherapy department staff experience.

3.4.3 Setting

The participant focus group sessions were conducted at the UoB, UK and completion of the physiotherapy staff questionnaire was carried out within the ROH, Birmingham.

3.4.4 Data collection

3.4.4.1 Focus group

The focus group discussion technique was selected to provide deep and rich data about the perspectives and feelings of the participants toward the programme. The group dynamics feature and social interaction of the focus group were used to encourage the participants to produce more information and express more feelings than they might when compared to one-to-one interviews (Rabiee, 2004). Focus groups were conducted at the end of each wave of the intervention to explore the participants' knowledge, experience and views of the combined intervention programme (Kitzinger, 1995; Rabiee, 2004; Bowen et al., 2009; Tickle-Degnen, 2013; Rushton et al., 2017). The focus group sessions were audio-taped then transcribed and analysed by ASA. A topic guide regarding the exploration of participant experiences with the combined intervention was designed by the chief investigator (ASA) and then reviewed by her supervisors (CAG/ ABR). This guide was informed and developed based on categories of feasibility presented by Bowden et al. (2009), including efficacy, adherence, adaptation, acceptability, implementation and practicality, and integration and expansion (Table 3.3). An example of the participant focus group discussion guide is presented in Appendix 3.4. The discussion was led by an experienced researcher (ABR: co-investigator, physiotherapist, PhD) outlining the purpose of the session and discussing consent and confidentiality. Participants' engagement was encouraged by asking introductory questions about their previous treatment options for knee OA. Audio-taping and observing the session, taking notes, and overseeing data analyses was the responsibility of ASA (chief investigator, MSc in physiotherapy).

3.4.4.2 Questionnaire

A mixed questionnaire consisting of open-ended and closed questions was designed to seek the perceptions and views of the physiotherapy department staff about the feasibility of the combined intervention programme (Bowen et al., 2009; Tickle-Degnen, 2013). The questionnaire consisted of 15 items and its design was developed by ASA based on the categories of feasibility (Table 3.3) and then reviewed by her lead supervisor (CAG).

Table 3.3 Feasibility measurement categories based on Bowden et al. (2009)

Categories	For participants	For physiotherapy staff
1. Efficacy	Do they report benefit?	Do they notice improvement?
2. Adherence	Using a sheet for recording their gym sessions.	Record participant attendance.
3. Adaptation	Does the intervention need adaptation, for example, time or procedure?	Does the intervention require adaptation?
4. Acceptability	• Satisfaction with programme and outcomes. • Perceived appropriateness. • Expressed interest.	• Satisfaction with participants' outcomes. • Intent to use again. • Fit within hospital culture. • Perceived positive or negative effects on their time, gym availability.
5. Implementation and Practicality	• Degree of execution, success or failure of execution. • Positive/negative effects on target participants. • Ability of participants to carry out intervention activities and cost.	• Amount, type of resources needed to implement. • Factors affecting implementation ease or difficulty, efficiency, speed, or quality of implementation.
6. Integration and expansion	Do they recommend expanding the intervention to other hospitals?	• Does it fit with the hospital goals and physiotherapy department goals? • Is cost suitable to an organisation wishing to include it? • Could it be applied in the future and how? • Any positive or negative effects on the ROH or the department?

ROH, Royal Orthopaedic Hospital.

3.4.5 Data analysis

Qualitative analysis techniques were used to address the feasibility objective. The results of this feasibility study were underpinned by a phenomenological theoretical orientation, as the participants and the physiotherapy staff expressed their experiences towards the combined

programme of intervention (Magana, 2002; Tong, Sainsbury and Craig, 2007; Onwuegbuzie et al., 2009). The guidelines provided by Kitzinger (1995) were followed to conduct the analysis of data obtained from the focus groups and the surveys. The framework analytic approach by Spencer and Ritchie (2002) was used to categorise data. The selected analytic methodology for categorising the qualitative data was thematic analysis with a framework analysis approach. Thematic analysis is used to analyse qualitative research and is described as a methodological approach that was developed to compare sets of research interviews (Braun and Clarke, 2006). In general, this method is applied within raw qualitative data for identifying, analysing and reporting patterns (themes) (Braun and Clarke, 2006). It is considered an aspect of framework analysis that allows the development of themes from research questions and participants' records (Rabiee, 2004). There are six phases of thematic analysis: familiarisation with data, generalisation of initial codes, search for themes, refining and naming of themes, use of triangulation to integrate findings, and producing a report with extracts embedded in an analytic narrative (Braun and Clark, 2006).

3.5 Integration of quantitative and qualitative data

Data were analysed separately by ASA as follows: quantitative data from the participants at 16 weeks; quantitative data from the physiotherapy questionnaires; qualitative data from the participants' focus groups; and qualitative data from the physiotherapy staff questionnaires. Data from the quantitative and qualitative resources (for both participants and physiotherapy staff) were integrated using a triangulation protocol (Farmer et al., 2006; O'Cathain, Murphy and Nicholl, 2010; Silverman, 2011). There are four types of integration (methodological, data, theoretical and investigator), two of which it was possible to apply in this feasibility study: methodological and data triangulation (Tonkin-Crine et al., 2015). Methodological triangulation was applied by using multiple techniques for collecting data (focus group and

questionnaires). Data triangulation was undertaken by comparing different sources of data (numbers and text). Investigator triangulation was not applicable due to the limited resources. Theoretical triangulation was not possible as the methodology of this study was developed based on previous theories (Farmer et al., 2006; Tonkin-Crine et al., 2015).

Key findings from the quantitative and qualitative data resources were interpreted and presented as a statement to facilitate comparison between them. For the qualitative data, a description of the themes was summarised into multiple key findings specified within each theme to aid comparison with the key findings of the quantitative data. Four datasets (quantitative data from the participants' outcome measures; quantitative data from the closed questions of the physiotherapy staff questionnaire; qualitative data from the participants focus groups; and qualitative data from the open-ended questions of the physiotherapy staff questionnaire) were developed and a key finding from each of them was compared with the key finding of the other four datasets to generate a convergence coding matrix (O'Cathain, Murphy and Nicholl, 2010). If the same key finding was repeated in another dataset, it was removed from the overall number of key findings.

The matrix created displayed the final list of key findings emerging from the four different datasets. A comparison was made of each statement in one set to other statements in the other datasets and the relation between them was categorised as not applicable, silence, dissonance, partial agreement or agreement (O'Cathain, Murphy and Nicholl, 2010; Tonkin-Crine et al., 2015). Agreement reflected convergence in the data, partial agreement represented complementarity between data, dissonance indicated conflicting findings in the data, and silence reflected an absence of a key finding in the other sets of data, and not applicable indicated that a statement was identified in one dataset but no statements were

identified in the others, which made comparisons between the datasets not applicable (O’Cathain, Murphy and Nicholl, 2010).

3.6 Success criteria of the feasibility study

Success criteria were used to determine the primary objective of the combined intervention programme based on the qualitative and quantitative outcomes (Thabane et al., 2010; Stow, Rushton et al., 2015; Stow, Ives et al., 2015). The success criteria are presented in Table 3.4.

3.7 Patient and public involvement and engagement (PPIE)

The design and process of this study were informed by PPIE and with reference to INVOLVE recommendations to optimise acceptability and compliance of the study protocol (www.invo.org.uk). The Chief Investigator (ASA) had met seven older adults aged 67-78 years, diagnosed with knee OA, during the Control of Movement and Active Ageing Open Day on 21 June 2016 at SportExR. The adults were asked about their views towards the study outcome measures and intervention programme, such as their acceptance regarding giving a blood sample before and after the programme, the duration of the programme and diet type.

3.8 Registration and ethical approval

The study was registered with the ISRCTN registry (ISRCTN 12906938). The study was approved by the West Midlands-Solihull Research Ethics Committee, REC ref: 17/WM/0122, protocol number ERN_16-1432; RG_17- 024, and V.6.0 approved on 10 January 2018 by the Health Research Authority and the ROH Research and Development Foundation Trust.

Table 3.4 Success criteria of the combined intervention programme in accordance with the feasibility categories, using the participants and physiotherapy department staff outcomes

Feasibility categories	Participants' quantitative outcomes <i>The combined intervention programme is considered feasible if:</i>	Participants qualitative outcomes <i>The combined intervention programme is considered feasible if:</i>	Physiotherapy questionnaire <i>The combined intervention programme is considered feasible if there is consensus across the PT dept. staff to support the following points:</i>
1. Efficacy	Significant changes (P<0.05) on the planned primary outcome for the definitive study (WOMAC subscale) from baseline to 4 months intervention (Blekken et al., 2015).		When they notice any improvement in the participants' outcomes and think that the combined intervention programme is better than usual care.
2. Adherence	≥ 80% in exercise compliance; ≥ 80% in dietary compliance (Martin et al., 2005; Persch & Page, 2013).		Adherence to the classes is similar compared with usual care.
3. Adaptation		None or just minor changes suggested.	The combined programme does not require adaptation.
4. Acceptability		Participants report (during the focus group discussion) that they are satisfied and the intervention programme fits with their activities of daily living.	They are satisfied with participants' outcomes. They would support the use of the combined programme. The combined intervention programme fits within the hospital culture. Delivering the combined intervention programme has not increased their workload.
5. Implementation and practicality	< 10% missing data in each completed questionnaire (WOMAC and SF-36) (Blekken et al., 2015; Gibbs et al., 2015).		They would not need any additional resources to implement the programme. There are no factors that may affect the implementation, efficiency, speed or quality of delivery.
6. Integration and expansion		Participants recommend the combined intervention programme to other patients.	The programme could be applied in future. The expansion of the programme would have a positive effect on the physiotherapy department and/or the ROH. The cost of the programme will be feasible for the ROH and/or other hospital trusts.

Abbreviations: PT = physiotherapy; ROH = Royal Orthopaedic Hospital; SF-36 = Short Form-36; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Chapter summary

The protocol of this feasibility study was developed to address an identified gap in the literature relating to the most effective combined programme for physical activity and dietary restriction in older adults with knee OA. This study was designed primarily to answer the central question of whether a combined intervention programme is feasible and acceptable to adults with obesity and knee OA. In addition, it was hypothesised that a combined

intervention programme of physical activity and dietary restriction for older adults with obesity and knee OA would be feasible and acceptable for the ROH physiotherapy staff. Overall, the intervention was determined to be feasible if the success criteria in Table 3.4 were met. The mixed methods approach was chosen to maximise the study design, with the qualitative component of the study allowing the participants to express their views regarding the combined intervention programme, which informed the optimal body weight reduction methods and exercise initiatives in order to help achieve better outcomes. Furthermore, the views of the physiotherapy staff were considered invaluable in confirming whether a combined intervention programme of dietary restriction and usual physiotherapy care is feasible in a hospital setting and could be incorporated into usual care. This study design incorporated several factors to improve compliance with the exercise in the remaining 12 weeks of the intervention, such as knowledge, providing local gym facilities, and weekly phone calls. Overall, the results of this study were intended to provide clinical evidence regarding knee OA management in older, obese adults to subsequently inform the type of usual care given to knee OA patients. The protocol was published in the BMJ Open Journal as: Alrushud, AS, Rushton, AB, Bhogal, G, Pressdee, F, and Greig, CA 2018, The effect of a combined programme of dietary restriction and physical activity on the physical function and body composition of obese middle-aged and older adults with knee OA (DRPA): Protocol for a feasibility study, BMJ Open, vol. 8, no. 12, p. e021051 (Appendix 3.5).

CHAPTER 4

RESULTS OF THE FEASIBILITY STUDY

The previous chapter presented the protocol for the DRPA study. This chapter focuses on the results of the feasibility study and the embedded qualitative element. Data presented in this chapter include a summary of the recruitment procedure; quantitative data, including baseline characteristics of the participants; changes in the participants' outcomes over 4 and 16 weeks of intervention; qualitative data presenting the feedback from both the participants and physiotherapy staff regarding the study; and finally, the integration of the quantitative and qualitative data.

4.1 Recruitment and attrition

4.1.1 Recruitment

Recruitment of participants began in October 2017 and was completed in July 2018. Initially, participants were recruited through the ROH outpatient clinic but recruitment was very slow, mainly due to patients within the originally specified age range (55-90 years) having more comorbidities limiting their participation. In order to address this, it was proposed to reduce the minimum age for recruitment from 55 years to 45 years and extend recruitment to cover the ROH physiotherapy department as well as the outpatient clinic. An amendment was submitted to UoB Research Governance on 10 January 2018 and approved by the HRA on 1 March 2018 and the ROH Research and Development Directorate on 19 March 2018. Participants were recruited into three groups; further details are presented in Figure 4.1.

4.1.2 Attrition

In the first group, one participant withdrew from the study at week 4 due to disc prolapse. In the second group, one participant failed to attend the educational session and usual care classes at ROH due to her work demands and she then decided to withdraw during week 2 of the intervention. In the third group, one participant decided to withdraw during week 4 of the intervention due to her work, although she was able to attend the first two usual care classes. Figure 4.1 presents the flow of participants in each group and includes the number of potential participants who returned the reply slip, potential participants excluded following phone screening, participants who consented, participants excluded after consenting, follow-up of participants, and analysis at weeks 4 and 16 of the intervention in each group. In total, n=5 participants completed 4 weeks of the intervention and n=3 participants completed 16 weeks (i.e., the whole) of the intervention.

4.2 Quantitative data

4.2.1 Baseline characteristics of the participants

Eight participants consented to take part and completed the baseline assessment at SportExR. Their age range was 48-63 years with a mean age of 54.3 ± 5.3 years. Group one (n=3) had a mean age of 57 ± 1.0 years; group two (n=3) a mean age of 53.7 ± 8.08 years; and group three (n=2) a mean age of 51 ± 4.24 years. All the participants were women. A summary of the participants' baseline characteristics is presented in Table 4.1.

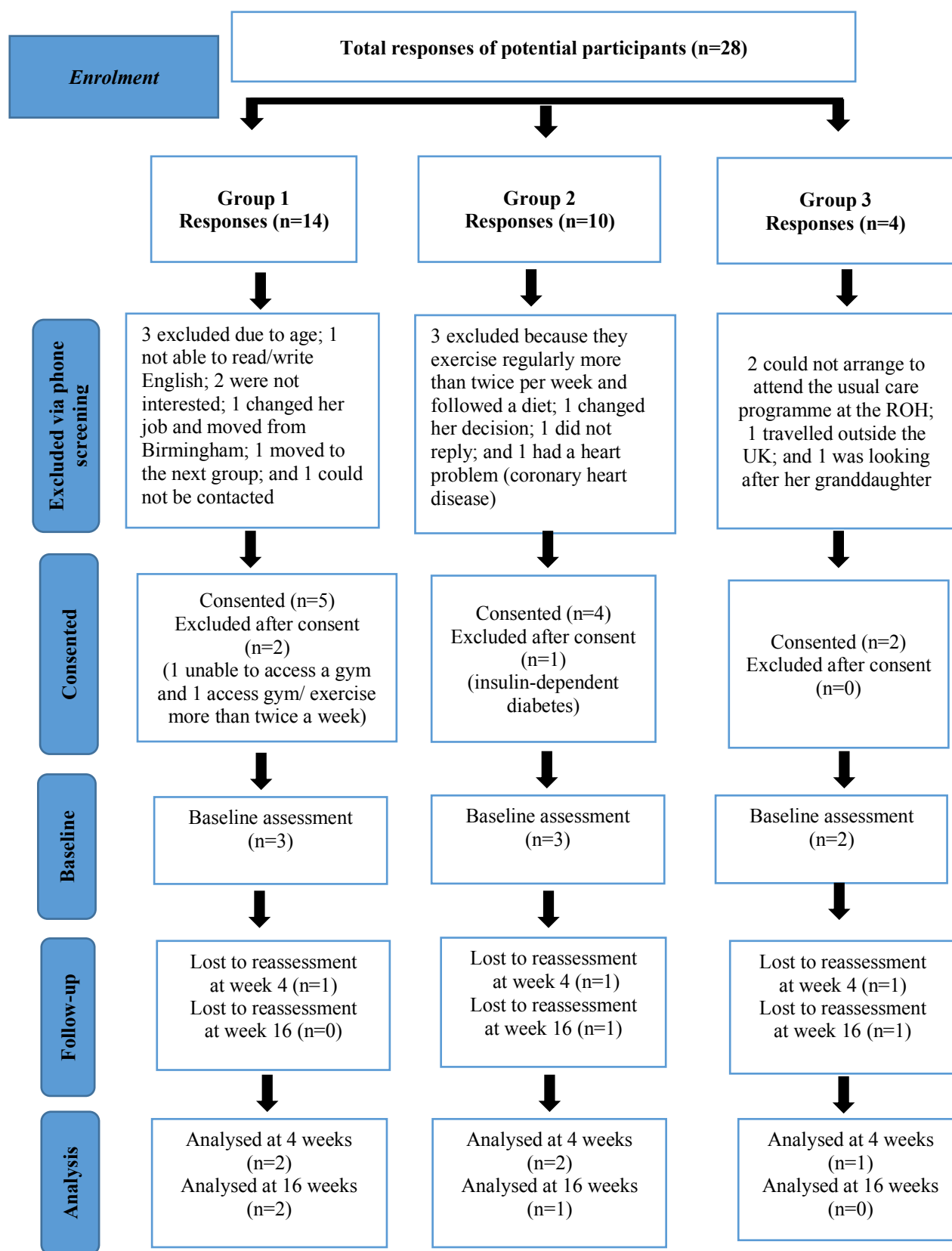


Figure 4.1 Modified flow diagram of the DRPA study participants based on a CONSORT 2010 flow diagram

Table 4.1 Physical characteristics and baseline data for all participants (n=8)

Characteristics		Group one (n=3)			Group two (n=3)			Group three (n=2)		Total (n=8)
		P01	P02	P03	P04	P05	P06	P07	P08	Mean (SD)
Gender		100% female			100% female			100% female		
Age (years)		57	58	56	49	63	49	48	54	54.3(5.29)
Affected knee		1*	1*	1*	1*	2*	4*	3*	4*	
Height (cm)		153	157.5	157.6	166	159	153	154	168.2	158.5 (5.77)
Weight (kg)		88.20	89.50	92.40	146.70	116.80	101.20	98.40	99.90	104.1 (19.41)
BMI (kg/m ²)		37.60	36	37.20	53.20	46.20	43.20	41.40	35.4	41.3 (6.13)
Waist circumference (cm)		112	110	114	124	111	117	113	97	112.3 (7.59)
WOMAC function		77	40	60	96	62	87	75	37	66.8 (21.07)
WOMAC pain		18	7	12	20	13	17	14	8	13.6 (4.63)
SF-36 (physical component)		26	35	36	15	17	26	10	36	25 (10.24)
SF-36 (mental component)		26	58	38	17	30	23	18	35	30.5 (13.23)
Physical performance	Stair climb (seconds)	28.4	14.1	38.4	29.9	35.5	22.5	22.1	16.1	25.6 (8.4)
	Timed up and go (seconds)	12.1	8.6	11.4	9.5	7.7	7.2	10.1	7.8	9.3 (1.81)
Range of motion (degree)	Right knee flexion	115	120	115	105	98	109	115	130	114 (9.19)
	Left knee flexion	85	65	90	110	104	102	105	120	97.6 (17.11)
	Right knee extension	10	16	12	9	9	10	30	0	12 (8.54)
	Left knee extension	5	10	9	8	7	10	40	30	6.5 (6.14)
Muscle power (w.kg-1)	Right limb	65	74	101	108	67	59	80	123	84.6 (23.22)
	Left limb	14	74	51	55	95	57	117	67	66.3 (30.79)
Body composition	Fat percentage	49.1	50.2	50.2	38.7	58.6	56.4	51.3	43.8	49.8 (6.36)
	Fat mass (kg)	43.20	44.90	46.4	56.70	68.40	57.1	50.50	43.80	51.4 (8.79)
	Lean percentage	50.9	49.8	49.8	61.3	41.1	43.6	48.7	56.2	50.1 (6.38)
	Lean mass (kg)	44.90	44.60	46.0	90	48.40	44.1	47.90	50.10	52 (15.49)
Biomarkers of joint remodelling	Adiponectin (ng/ML)	44.7	28.44	64	48.03	54.69	44.42	14.97	81.78	47.6 (20.49)
	Leptin (Pg/ML)	81.27	507.18	374.45	722.64	599	405.36	1258.55	1.73	492.1 (400.64)
	PICP (Pg/ML)	3886.17	3134.71	3215.38	3279.59	2971.79	3117.73	2136.48	1736.87	2934.8 (681.37)
	CTX-1 (ng/ML)	0.08	0.03	0.08	0.01	0	0.08	0.03	0.06	0.05 (0.03)
	PIIANP (ng/ML)	631.61	756.3	718	711.7	572.6	708.18	360.44	497.08	619.5 (135.87)
	COMP (ng/ML)	1.75	0.02	1.27	0.09	2.13	0.24	2.26	3.95	1.5 (1.35)

Abbreviations: 1* = both knees, left worse; 2* = both knees, right worse; 3* = only right knee affected; 4* = only left knee affected; COMP = cartilage oligomeric matrix protein; CTX-1 = cross-linked C-telopeptide of type I collagen; PIIANP = type IIA collagen N-propeptide; PICP = procollagen I C-terminal propeptide.

4.2.1.1 Analysis of 3-day food diary

Completed 3-day food diaries were returned (n=7) after the baseline assessment; one participant in group two (P06) did not complete the diary. Data were entered into Nutritics software (Version 5.0; 2011-2018) as whole days and mean reported daily intakes of energy, macronutrients and micronutrients were calculated. The basal metabolic rate (BMR) was calculated to develop a diet plan using the Harris-Benedict equation (Henry, 2005; Amirkalali et al., 2008). Then the weight maintenance level was calculated by multiplying the BMR by the activity level. Participants reported very low levels of activity during the baseline assessment, so 1.2 was selected as the activity level. For participants with a minimum level of weight maintenance < 1,500 kcal, the clinical dietitian determined 1,500 kcal as the minimum level of weight maintenance to avoid nutritional deficiency, as food supplements were not provided in the study (Raynor and Champagne, 2016). For example, the calculated weight maintenance level for participant 01 was 1,811 kcal per day; reducing by 500 kcal resulted in a weight maintenance level of 1,311 kcal per day. Thus, the diet plan for this participant was developed based on a minimum level of weight maintenance of 1,500 kcal. Further details of the reported data and the calculated weight maintenance level of each participant are presented in Table 4.2.

Table 4.2 Summary of 3-day food diary analysis and calculated weight maintenance level

Data		Participants' ID							
		P01	P02	P03	P04	P05	P06	P07	P08
BMI (kg/m ²)		37.6	36	37.2	53.2	46.2	43.20	41.4	35.4
Reported average intake of energy (kcal)		1,333	2,202	1,226	2,090	1,549		2,368	1,498
Macronutrient analysis	Carbohydrate (kcal %)	42	41.8	41.8	53.7	51.6		37.4	55.2
	Protein (kcal %)	15.3	22.7	22.7	23.3	16.7		18.8	17.7
	Fat (kcal %)	42.7	35.6	35.6	23	31.7		40.9	26.1
	Alcohol (kcal %)	0	0	0	0	0		3	1
BMR (kcal) using the Harris-Benedict equation		1,509	1,525	1,563	2,149	1,779		1,651	1,663
WML (kcal); BMR (Harris-Benedict equation) X activity level		1,811	1,830	1,876	2,570	2,135		1,981	1,996
Diet plan (WML 500 kcal)		1,311*	1,330*	1,576	2,070	1,635		1,481*	1,469*

Abbreviations: BMI = body mass index; kcal = kilocalories; BMR = basal metabolic rate; WML = weight maintenance level. * = Plan of diet developed for 1,500 kcal/day if the participant at risk of malnutrition if we stayed with a 500 kcal reduction.

4.2.2 Second assessment point (4 weeks)

All outcome measures, except body composition and biomarkers of joint remodelling, were measured at the second assessment point immediately after completing the usual care programme for each group. Six participants completed 4 weeks of intervention at the ROH but one participant in group one withdrew during the 4th week and did not attend the assessment session. Table 4.3 presents a comparison between the baseline data and data measured after 4 weeks of intervention for each participant (n=5). Despite the negative changes for one participant at week 4 (P02), there was a positive difference in WOMAC

mean scores. The difference in both components of the SF-36, ROM of left knee flexion and leg muscle power showed some improvement.

However, the difference in the mean values of body weight, WOMAC pain or physical performance over the first 4 weeks of the intervention were of a smaller magnitude.

4.2.3 Final assessment point (16 weeks)

All outcome measures were assessed at 12 weeks after completion of the usual care programme for each group. Five participants completed the 16 weeks of intervention and were in weekly phone contact with the study team but two participants did not attend their final assessment sessions at week 16. Table 4.4 presents a comparison between the baseline data, data measured after 4 weeks of intervention and data measured after 16 weeks of intervention. Only n=3 participants were able to complete the study requirements. Repeated measures ANOVA was not possible due to the low number of participants. Therefore, descriptive analysis was used to outline the changes within the means over 16 weeks of intervention. The data showed positive changes in the mean values of WOMAC, both components of the SF-36, the range of knee flexion and leg muscle power. However, the difference in the mean values of body weight, WOMAC pain, physical performance and body composition were of a smaller magnitude over the whole 16 weeks of intervention.

Table 4.3 Comparison between the baseline data and data collected after 4 weeks of intervention (n=5)

Characteristics		Group one (n=2)				Group two (n=2)				Group three (n=1)		Total (n=5)	
		P01 W0	P01 W4	P02 W0	P02 W4	P04 W0	P04 W4	P05 W0	P05 W4	P5 W07	P5 W07	Mean (SD) W0	Mean (SD) W4
Weight (kg)		88.20	86.30	89.50	90.50	146.70	146.50	116.80	113.00	98.40	100.20	107.9 (24.50)	107.3 (24.24)
BMI (kg/m ²)		37.60	36.80	36	36.40	53.20	53.10	46.20	44.60	41.40	42.20	42.90 (6.98)	42.60 (6.83)
Waist circumference (cm)		112	116	110	110	124	124	111	110	113	114	114 (5.70)	114.8 (5.76)
WOMAC function		77	62	40	68	96	93	62	44	75	59	70.0 (20.70)	65.2 (17.88)
WOMAC pain		18	10	7	14	20	18	13	9	14	11	14.4 (5.03)	12.4 (3.65)
SF-36 (physical component)		26	21	35	22	15	35	17	34	10	19	20.5 (9.87)	26.2 (7.66)
SF-36 (mental component)		26	45	58	48	17	32	30	50	18	21	29.6 (16.49)	39.2 (12.35)
Physical performance	Stair climb (seconds)	28.4	31.1	14.1	27.3	29.9	18.8	35.5	21.9	22.1	14.2	25.6 (7.64)	22.7 (6.70)
	Timed up and go (seconds)	12.1	8.5	8.6	16.3	9.5	7.6	7.7	5.9	10.1	6.6	9.6 (1.67)	8.9 (4.21)
Range of motion (degree)	Right knee flexion	115	104	120	105	110	105	98	110	115	114	111.6 (8.39)	107.6 (4.28)
	Left knee flexion	85	75	65	107	110	115	104	115	105	108	93.8 (18.70)	104 (16.64)
	Right knee extension	10	10	16	17	9	10	9	8	30	8	14.8 (8.99)	10.6 (3.72)
	Left knee extension	5	8	10	7	8	16	7	13	40	8	14 (14.65)	10.4 (3.91)
Muscle power (w.kg ⁻¹)	Right limb	65	65	74	60	108	100	67	87	80	114	78.8 (17.37)	85.2 (22.88)
	Left limb	14	10	74	63	55	109	95	101	117	116	71 (39.39)	79.8 (44.07)

Abbreviations: W0 = Week 0; W4 = Week 4; BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 = Short Form-36. Shaded boxes indicate a notable difference between baseline data and data collected after 4 weeks of intervention.

Table 4.4 Comparison between the baseline data and data collected at 4 and 16 weeks of intervention (n=3)

Characteristics		Group one (n=2)						Group two (n=1)			Total (n=3)		
		P01 W0	P01 W4	P01 W16	P02 W0	P02 W4	P02 W16	P05 W0	P05 W4	P05 W16	Mean (SD) W0	Mean (SD) W4	Mean (SD) W16
Weight (kg)		88.20	86.30	84.10	89.50	90.50	91.10	116.80	113.00	107.40	98.17 (16.15)	96.53 (14.40)	94.20 (11.96)
BMI (kg/m ²)		37.60	36.80	35.90	36	36.40	36.70	46.20	44.60	42.40	39.9 (5.49)	39.3 (4.62)	38.3 (3.54)
Waist circumference (cm)		112	116	113	110	110	113	111	110	105	111 (1.00)	112 (3.46)	110 (4.62)
WOMAC function		77	62	47	40	68	22	62	44	39	59.7 (18.61)	58 (12.49)	36 (12.77)
WOMAC pain		18	10	11	7	14	5	13	9	10	12.7 (5.51)	11 (2.65)	8.7 (3.22)
SF-36 (physical component)		26	21	18	35	22	47	17	34	49	25.8 (9)	25.5 (7.39)	37.7 (17.55)
SF-36 (mental component)		26	45	44	58	48	51	30	50	74	37.7 (17.30)	47.7 (2.52)	56.1 (15.84)
Physical performance	Stair climb (second)	28.4	31.1	48.6	14.1	27.3	12.6	35.5	21.9	11.5	25.3 (10.06)	26.8 (4.62)	24.2 (21.11)
	Timed up and go (seconds)	12.1	8.5	11.7	8.6	16.3	7.4	7.7	5.9	5.7	9.5 (2.32)	10.2 (5.41)	8.3 (3.09)
Range of motion (degree)	Right knee flexion	115	104	116	120	105	125	98	110	113	111 (11.53)	106.3 (3.22)	118 (6.25)
	Left knee flexion	85	75	60	65	107	123	104	115	117	84.7 (19.50)	99 (21.17)	100 (34.77)
	Right knee extension	10	10	12	16	17	20	9	8	8	11.7 (3.79)	11.7 (4.73)	13.3 (6.11)
	Left knee extension	5	8	10	10	7	13	7	13	10	7.3 (2.52)	9.3 (3.22)	11 (1.73)

Table 4.4 Comparison between the baseline data and data collected at 4 and 16 weeks of intervention (n=3) (continued)

Characteristic		Group one (n=2)						Group two (n=1)			Total (n=3)		
		P01 W0	P01 W4	P01 W16	P02 W0	P02 W4	P02 W16	P05 W0	P05 W4	P05 W16	Mean (SD) W0	Mean (SD) W4	Mean (SD) W16
Muscle power (w.kg-1)	Right limb	65	65	53	74	60	123	67	87	95	68.7 (4.73)	70.7 (14.36)	90.3 (35.23)
	Left limb	14	10	5	74	63	112	95	101	119	61 (42.04)	58 (45.71)	78.7 (63.89)
Body Composition	Fat (%)	49.1	NA	51.4	50.2	NA	51.8	58.6	NA	58.1	52.6 (5.19)	NA	53.7 (3.76)
	Fat mass (kg)	43.30		43.20	44.90		47.20	68.40		62.3	52.2 (14.05)		50.9 (10.07)
	Lean mass (%)	50.9		48.6	49.8		48.2	41.4		41.9	47.4 (5.19)		46.2 (3.76)
	Lean mass (kg)	44.90		40.90	44.60		43.90	48.40		45.1	45.9 (2.11)		43.3 (2.16)
Biomarkers of joint remodelling	Adiponectin (ng/mL)	44.7		24.9	28.4		51.1	54.7		23.2	42.6 (13.25)		33 (15.66)
	Leptin (pg/mL)	81.27		482.2	507.2		651.7	559		974.5	382.5 (262.14)		702.8 (250.08)
	PICP (pg/mL)	3886.17		3534.3	3134.7		3185.7	2971.8		3541.8	3330.9 (487.74)		3420.6 (203.48)
	CTX-1 (ng/mL)	0.08		0.08	0.03		0.04	0		0	0.04 (0.04)		0.07 (0.09)
	PIIANP (ng/mL)	631.6		681.1	756.3		781.6	572.6		346.4	653.5 (93.79)		603.1 (227.87)
	COMP (ng/mL)	1.75		2.33	0.02		3	2.1		1.47	1.3 (1.12)		2.3 (0.77)

Abbreviations: W0 = Week 0; W4 = Week 4; W16 = Week 16. BMI = body mass index; COMP = cartilage oligomeric matrix protein; CTX-1 = cross-linked C-telopeptide of type I collagen; NA = Not applicable, as outcomes were not measured at this assessment point; PICP = procollagen I C-terminal propeptide; PIIANP = type IIA collagen N-propeptide; SF-36 = Short Form-36; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index. Shaded boxes indicate a notable difference between baseline data and data collected after 16 weeks of intervention.

4.2.4 Correlation between body weight, BMI, knee pain and biomarkers of joint remodelling

Assessing the correlation between body weight, BMI, knee pain and biomarkers of joint remodelling was not possible due to insufficient sample size.

4.2.5 Participant adherence

Compliance with exercise was recorded by the study Chief Investigator (ASA). Each participant was asked to attend a total of four usual classes at the physiotherapy gym and subsequently visit a local gym once a week for 12 weeks. Weekly phone calls were used to record attendance and sometimes, if the participants did not have time to answer, they replied by sending text messages. During the phone calls, the participants reported if they had visited the gym, the type of exercises undertaken, any changes, such as pain, aches or discomfort, and updated the study team member about their adherence to the diet plan and whether it needed any modification. All participants contacted the clinical dietician at least once to discuss their diet plans. Moreover, three out of five asked to speak to him a second time in order to modify their plans. At the end of the call, they were encouraged to continue. Using a bike, treadmill and straight leg, lifting a weight from a sitting position were the most common exercises reported. Participants reported pain and aches in the first couple of weeks and they did the exercise by themselves with no assistance from a gym instructor. Figure 4.2 presents the percentage of exercise compliance over 16 weeks. Participant compliance ranges from 3 to 14 weeks. One participant (P02) did not access her local gym due to muscle pain and spasm.

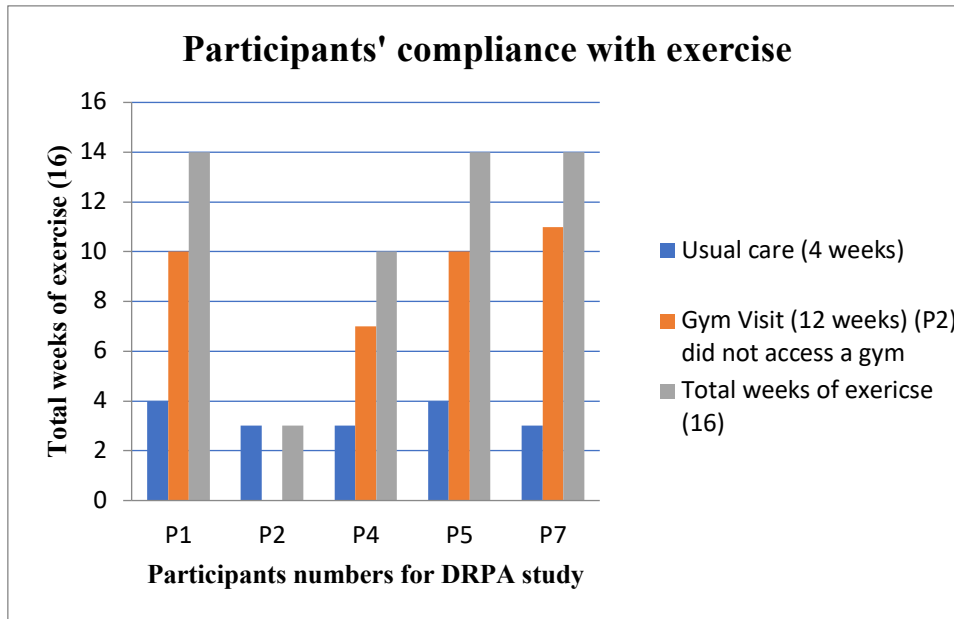


Figure 4.2 Participants' compliance with exercise showing the number of usual care classes and gym exercise sessions attended by each participant (n=5)

Five participants followed the diet intervention but only n=3 returned the diet adherence sheet when they attended for their final assessment session at SportExR. Their data are presented in Figure 4.3. Percentage adherence ranges from 29.5% to 98% over 16 weeks.

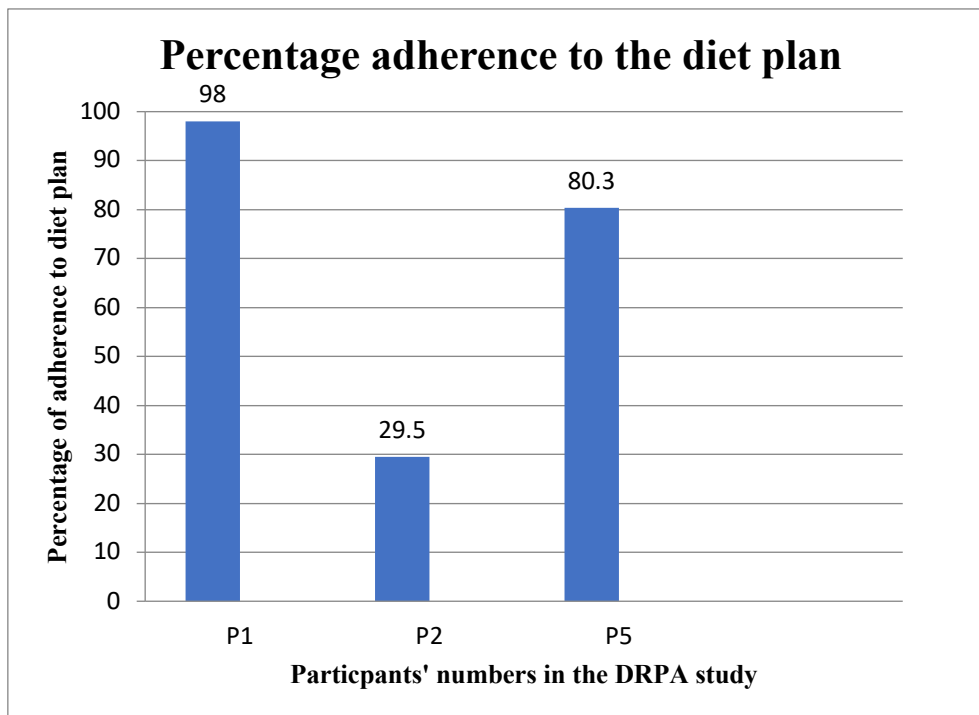


Figure 4.3 Percentage adherence to the diet plan over 16 weeks (n=3)

4.2.6 Physiotherapy staff questionnaire

A mixed questionnaire consisting of open and closed questions was introduced to the physiotherapy staff to seek their feedback about the study. The questionnaire was completed by n=4 staff members. The staff participated in the study either by recruiting participants or delivering the education sessions or usual care classes. The closed questions were analysed using frequencies and percentages (see Table 4.5). All the staff who participated (100%) supported the combined intervention programme and stated that it was a good fit with the hospital culture and did not increase their respective workloads.

Table 4.5 Analysis of closed question answers from the physiotherapy staff questionnaire

Question	Yes (frequency/ percentages)	No (frequency/ percentages)	Unsure (frequency/ percentages)	N/A
1. Did you notice any improvement in the participants?	1 (25%)	1 (25%)	2 (50%)	0 (0%)
2. If 'yes' to the previous question, do you think improvement was greater compared with usual care?	1 (100%)	0 (0%)	0 (0%)	0 (0%)
3. Do you think that participants' adherence to the classes was similar compared with usual care or was there a difference?	2 (50%)	1 (25%)	1 (25%)	0 (0%)
4. Are you satisfied with the participants' outcomes?	1 (25%)	0 (0%)	2 (50%)	1 (25%)
5. Would you support the use of the combined programme?	4 (100%)	0 (0%)	0 (0%)	
6. Do you think that the combined programme requires adaptation?	3 (75%)	1 (25%)	0 (0%)	0 (0%)
7. Do you think the combined programme fits within the hospital culture?	4 (100%)	0 (0%)	0 (0%)	0 (0%)
8. Did delivering the combined programme increase your workload?	0 (0%)	4 (100%)	0 (0%)	0 (0%)
9. Do you think that you would need additional resources to implement the combined programme effectively?	1 (25%)	2 (50%)	0 (0%)	1 (25%)
10. Did you notice factors that may affect implementation, efficiency, speed, or quality of delivery?	3 (75%)	1 (25%)	0 (0%)	0 (0%)
11. Do you think that the combined programme could be applied in the future?	2 (50%)	0 (0%)	0 (0%)	0 (0%)
12. Do you think expansion of the combined programme would have positive effects on the physiotherapy department and/or the ROH?	3 (75%)	0 (0%)	1 (25%)	0 (0%)
13. Do you think that it would be possible to run more than one knee OA usual care class/week besides other classes and individual sessions to serve more patients?	3 (75%)	0 (0%)	1 (25%)	0 (0%)
14. Do you think the combined intervention programme would/would not conflict with the hospital and physiotherapy departmental structure or strategy?	0 (0%)	3 (75%)	1 (25%)	0 (0%)
15. Do you think the combined programme cost would be feasible within the ROH and/or other hospital trusts?	2 (50%)	1 (25%)	1 (25%)	0 (0%)

4.3 Qualitative data

4.3.1 Overview of findings

Qualitative data were collected from the participants and the physiotherapy staff involved to assess the feasibility of the combined intervention programme. Conducting three focus groups was not possible due to the low number of participants. A focus group discussion was conducted for only group one (n=2). This was not possible for group two as only one participant attended and completed the final assessment session. The DRPA study team decided to invite this participant to the discussion in focus group three. One participant from the third group completed the 16 weeks of intervention but missed the final assessment session and focus group discussion. The study team decided to interview the remaining participant from group two. A topic guide for the focus group discussion for the participants was used to guide the participant's interview.

4.3.2 Participants' feedback (focus group)

One focus group discussion was conducted at the SportExR to seek the participants' feedback about the combined intervention programme (Appendix 4.1). It was conducted immediately after completing the 16 weeks of intervention (n=2) on 14 May 2018. Consents were obtained before starting the intervention. A topic-guided group discussion was used to answer specific questions about the feasibility of the DRPA study. Specific topics covered the following: benefits of the combined interventions, the most important facilitators and barriers to adherence, satisfaction with the programme and any required adaptations. The findings of the thematic analysis are presented in Figure 4.4. The figure shows underlying issues and descriptives that were colour-coded into subthemes before being categorised into themes and a superordinate theme.

Superordinate participant theme: Feasibility (SP)

This superordinate theme comprised six organising themes: **Organising participant themes: (OP.1) = Efficacy of the combined programme; (OP.2) = Adherence; (OP.3) = Adaptation; (OP.4) = Acceptability; (OP.5) = Implementation and practicality; and (OP.6) = Integration and expansion.** Each subtheme was provided with evidenced references from the discussion (quotations from the transcripts) to synthesise the relevant theme. A “Thematic network map” (Figure 4.5) was developed to synthesise the findings from relevant and interesting themes. Further interpretation of the findings is presented below and supported with evidence theme by theme.

Organising participant theme: (OP.1) = Efficacy of the combined programme

Participants reported a number of benefits from involvement in the combined intervention programme. Based on the discussion, two further subthemes were categorised: first, reported benefits from the exercise intervention; and second, reported benefits from the diet intervention.

Subtheme: Benefits from the exercise intervention

Participants reported some benefits from exercise. Both participants attended the usual care programme at ROH. One of them was able to access a local gym and the other could not, but continued to exercise at home. They reported two main changes after exercise. First, physical benefits in terms of functional ability: one participant reported that her ability to stand up and perform ADLs, such as housework, was improved after the programme; the other participant also reported some benefits of the programme on her functional activities, such as an improvement in her ability to walk properly:

‘A lot.... it’s getting better ... I can stand up quickly whereas before ... I do the housework perfect.’ (P01)

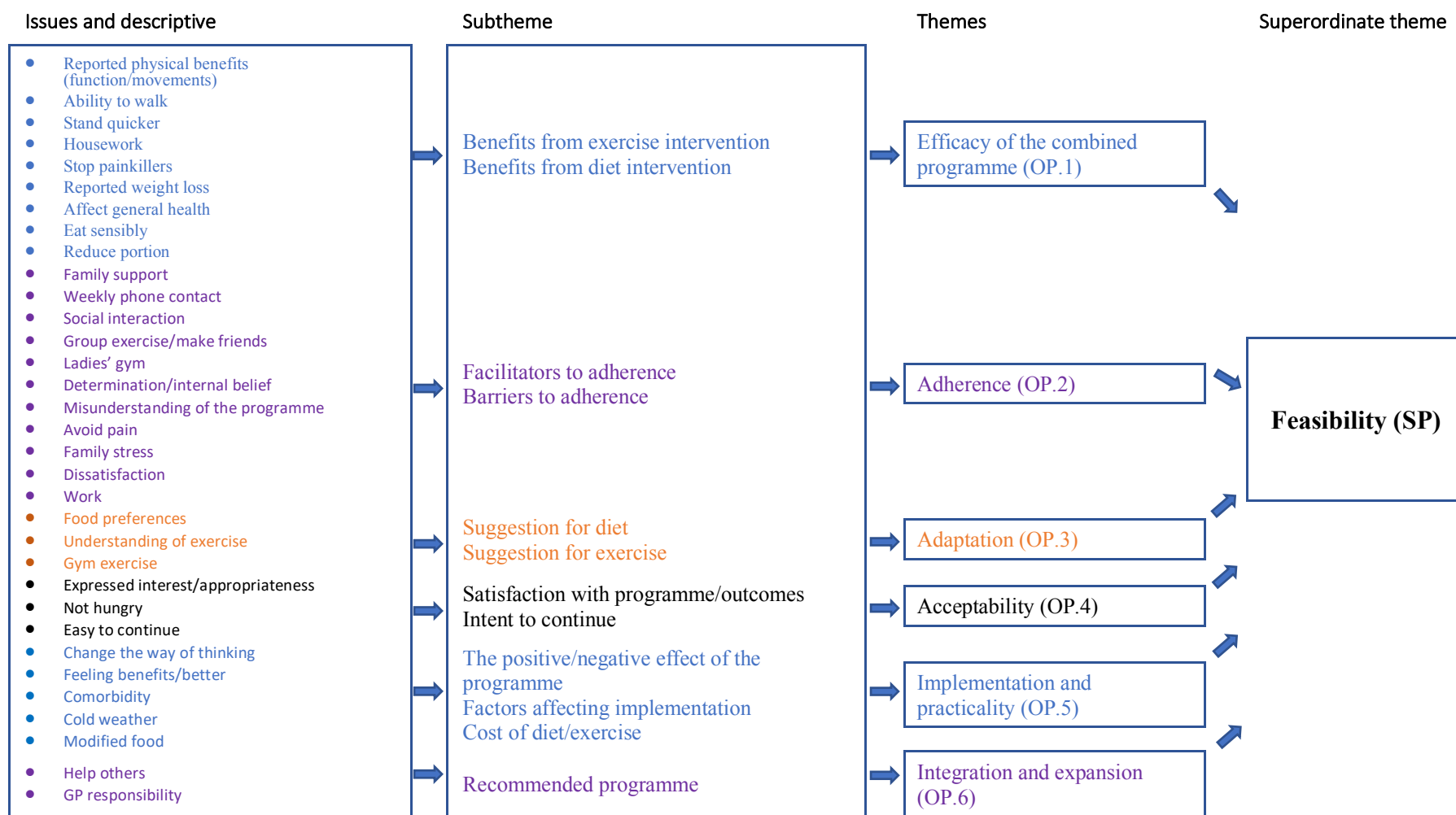


Figure 4.4 Thematic analyses of the findings of the participants' focus group discussion

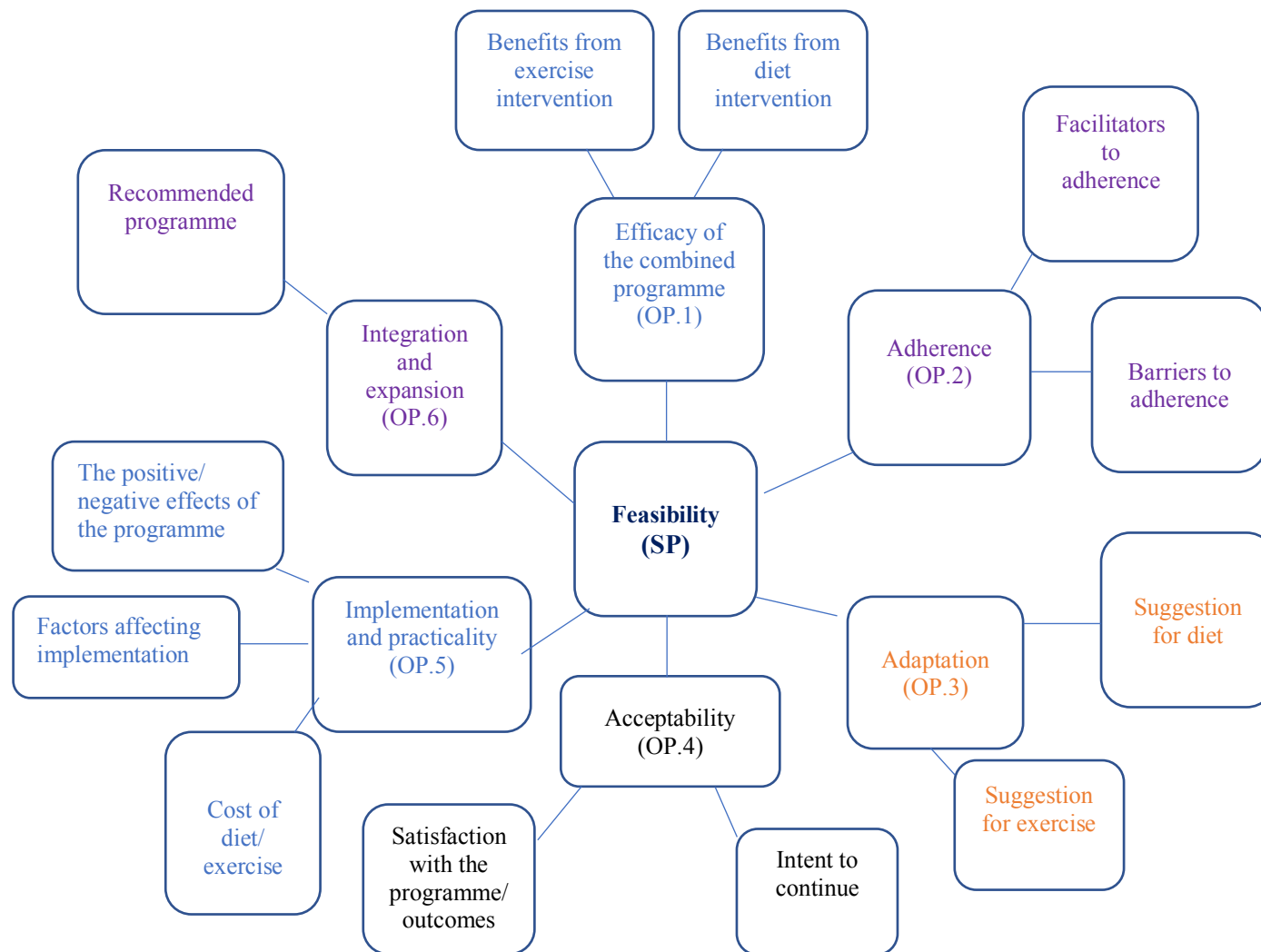


Figure 4.5 Thematic map of the superordinate theme of the participants' focus group discussion (SP): feasibility of the combined programme

'It's a big difference I feel I'm better in myself and my knees I mean I'm walking I'm not limping like I was ... to be honest, what is the additional exercise of walking or something it made the joints movable I don't know I'm not medical!' (P02)

Second, they reported some changes in pain. One participant suffered from pain, particularly after visiting the gym. In contrast, the other experienced a lot of improvement in pain. She compared her situation before and after the programme and was pleased with the outcomes, as she had reduced or almost stopped taking painkillers for knee pain.

'The movement better but the pain getting worse... I went to the gym I explained to the gym person there I told that my problem is with my knee she showed me what exercises to do on my leg but she said not overdo it just do it slowly! I worked on that after I finish the exercise on the knee I got a lot of pain ... I tried a new thing in the gym and feeling better.' (P01)

'I can see the benefits from the exercises simply because I don't have the pain that I'm experiencing before and the fact that I am not reaching out of the tablet, the fact I can't remember the last time I had a tablet probably Jan/Feb was so it obviously has an effect ...I'm not using anything on my knees the only thing is having a box of Proxin when they are very bad, I took one of those. I am not taking anything for them at all.' (P02)

Subtheme: Benefits of diet intervention

Despite their difference in losing weight (one participant lost weight and the other did not) both of them gained benefits from the diet intervention and noticed an improvement in their general health:

'It is four months does not matter but I got here, I tried very hard to lose that weight... my hair is growing and my nails are growing.' (P01)

'I did not lose weight.... I notice that my hair grow back I feel its fuller than it was.'
(P02)

The diet intervention had a general impact on the participants and their families, subsequent to changing their way of eating. They started to eat sensibly and reduced the quantity of their intake.

'My sons are helping, they are on the diet as well whatever I eat they're eating the same thing because they trying to improve their selves as well.... Yah, they said Mom always buy broccoli buy always buy vegetables get chicken, get fish then once I cooked they watching me how I cook food they do it for their selves when they want to eat. My elder son day his portion is small as well my portion is once.'
(P01)

'Yes reducing portion size I started of using the three suggested new portions then I started to use the way which recipes book just for variety and reducing how much I'm eating and also maintaining recipes as well to suit the family because I have to cook for the family... I recently notice my nails, I'm eating sensibly.' (P02)

Organising participant theme: (OP.2) = Adherence

Subtheme: Facilitators to adherence

The participants raised a number of factors which they think helped them to adhere to the programme. They considered family support as an important factor that helped them to adhere to the programme:

'Yes, my sons are supporting me, very supporting. Encouraging me to carry on, carry on Mom! Because they said "Mum, you only young you're not old yet" ... My son was really pleased he said "Mum you did very well".' (P01)

'Yes, family support is important and it's for your self-esteem as well.' (P02)

They were asked about the weekly phone contact by a study member and if that motivated them and both of them agreed that it did:

'Yes.' (P01)

'Yes, sometimes I was bit short with you because it depends on what is happening at home! I must apologise. Sometimes, I don't have time to speak to you.' (P02)

They also mentioned two factors related to the exercise intervention: group exercise to make friends and gym preferences, as both of them preferred ladies only gyms and think this will help them to focus on their exercise and make them feel more comfortable:

'Well I go to a gym I go to work but if I preferred is taking somebody with me... Yeah, make friends, even in my gym.' (P01)

'... but trouble it's I don't have anyone to go with but ...What I think, going to the gym together.... but to be with someone. I think being with someone helps you because when you on your own... I don't know.' (P02)

'I think the distraction, men distract women.' (P01)

'I prefer ladies only as well... whatever it would be I don't know and hopefully, it will be ladies only.' (P02)

In addition to social interaction, they believed that internal desire and determination were important factors to improve adherence:

'Determination.' (P01)

'I'm determined to go and start this programme in May... Thinking that this will help to ease the pain because when the pain was bad you seeking anything to make the pain less and something like this will possibly work keeping it to go.' (P02)

Subtheme: Barriers to adherence

Two barriers were raised by one participant who could not access a gym after the usual care programme. First, she misunderstood the exercises and overdid them in the third class of usual care. In that session, she exercised too intensely, which caused pain and stiffness that prevented her from attending the fourth session or accessing a gym later, but she continued to exercise at home. Second, two members of her family were not well, which she reported was stressful for her:

'I think...too much so I have not tried the proper squat and I am not lunging properly, like baby lunges ... It was one time in the gym when week 3 or 4 I can't remember now, I overworked it and I have not attended it since... I worked from the body have not moved too much and sat myself back but for diet point I mean it always in terms of understandable, for me not understanding the exercises.' (P02)

'I did some exercise but it's just so low because you know how much spend time in hospital driving home, grabbing sandwiches or something at the hospital set other factors that take these factors away, I think my answer would be different so when I describe good and bad days, those possibly days when I faced these, it was not depression but it was...' (P02)

One participant was not satisfied with her diet plan but she adapted it with some help from the study clinical dietician over the phone. However, the other participant could not remain on the diet plan throughout 4 months of intervention and she referred to family stress as the reason:

'It was easy to follow but it was making me hungrier then I have done it for a month and then I said let change so what I did was go back to what I was eating but reduce everything, the oils, the salt, the spices and then reduce the portions as well, so that's worked fine for me. I'm not hungry, I'm satisfied, and I'm not snacking here and there and everywhere.' (P01)

'I haven't lost weight but I think stress, family stress in my life... I think stress makes you hungry... When you get an ill person at home and sometimes these days made me think I can't do that... I do have two family members who are not very well at the moment. So it's very, very stressful, so diet all the time is being very difficult especially if you just grabbing the hospital sandwiches.' (P02)

They mentioned an interesting barrier in terms of the challenge of attending the usual care classes when in employment:

'I think one of the barriers from going to physio is the time of work person does whether they got the time off to go. I mean the four sessions but depending on the employer whether they allow the person time off.... I got time from work to attend the classes so it's fine.' (P02)

'To me because I coming to the classes on my days off but some people who can't get time go so it depends on them, you know!' (P01)

Organising participant theme: (OP.3) = Adaptation

The participants suggested a few factors to be considered when applying the intervention, although these were not major adaptations.

Subtheme: Suggestion for diet

The participants suggested that food preferences are very important to consider when developing the diet plan:

'The one thing I did not like and I did say very early I don't like smoothies, I need the crunches, so it's the whole fruits that I'm eating that supposed to eating, I need the crunches.' (P02)

Subtheme: Suggestion for exercise

An understanding of exercise and the knowledge that exercise needs to be built up is very important before starting the exercise intervention:

'I think from my point personal of view, someone hadn't exercised for 50 years, to tell them the exercise need to build up as opposed to just going in... Just do gentle exercise rather than taking yourself down.' (P02)

Organising participant theme: (OP.4) = Acceptability

The participants expressed interest and accepted the intervention programme, as they were satisfied with the programme and its outcomes and they wished to continue independently after the intervention.

Subtheme: Satisfaction with the programme and its outcomes

The participants were satisfied with the programme in general and the diet intervention specifically, even if they were not following the exact diet plan. However, they mentioned that they understood the general concept of diet:

'I'm not hungry, I'm satisfied, and I'm not snacking here and there and everywhere even my hair is growing back...' (P01)

I found the advice that has been given and gentle exercise it supposed to go for it, I feel better! I feel better!... In myself, I feel healthier and not hungry, my feeling always before to go to bed and eat a piece of food but I don't do that at all.' (P02)

Subtheme: Intent to continue

Both participants expressed their intent to continue the programme and they found following both a diet plan and an exercise programme equal in terms of effort and adherence and one was no easier than the other:

'To me they are equal...It will be easy for me to continue... yes, it would be fine.'
(P01)

'To me, both of them the sensible eating and doing exercise ... See I'm going to continue.' **(P02)**

However, the participants' acceptance of the exercise types was different: one participant found cycling difficult but the other found it easy:

'For me, I found the bicycle was the most difficult because you know turning the pedals it's hurting my knees because I can't bend so I found that difficult but any others exercise is fine.' **(P01)**

'I found that easy, which I found difficult is the squat or aerobic exercise ... I find it very difficult.' **(P02)**

Organising participant theme: (OP.5) = Implementation and practicality

Three subthemes were developed to inform the implementation and practicality of the combined intervention programme: the positive effect of the programme, the factors that may affect implementation and the cost of the programme

Subtheme: Positive effect of the programme

The participants reported a positive effect of the study in terms of thinking about their conditions:

'When you get in your mind set this is for your own good, which over that pressure this is a feeling benefit.' (P01)

'I feel better in myself and "touch wood" my knees aren't too bad... So I haven't lost any weight but I, it's just doing gentle, gentle exercise and going for walk ... But certainly, I feel better.' (P02)

Subtheme: Factors affecting implementation

The participants reported that they experienced some comorbidity diseases that may interfere with the outcomes of the programme. One experienced lymphoedema and a thyroid problem and the other had a thyroid problem. Both participants thought that a thyroid problem may interfere with their ability to lose weight:

'I got underactive thyroid problem which slow metabolism, I mean 4 months I should lose a little bit more than 4 kilos. It is good to lose 4 kilos over 4 months but should be more because of the thyroid slow. I am not gonna complain you know but it's gonna take time and I accept that.' (P01)

'...but it's the fact I know that I'm not losing any weight and now been suggested to me not rely on medical where I got thyroid problem. Because I recently notice my nails are, I'm eating sensibly but the time not losing any weight but I'm going to continue and I'm going to proceed that thyroid problem.' (P02)

The weather was also raised during the discussion as a factor that might cause knee stiffness and affect the participants' levels of functional activity:

'Yah because I feel that in the other leg. When it's cold I can feel my knee big tense than that, but when it warm, I feel fine, no problems either the whole month work ...' (P01)

'When it is a warm day, I go downstairs and gosh I didn't feel that but you know in those wet cold days it's still a little slower to walk down than to go up.' (P02)

Subtheme: Cost of diet and exercise

Both participants found the cost of dieting was acceptable and did not require additional expenses:

'No, everything was bought already in house just to use what was there and just carried on normal food.' (P01)

'It was not an expensive thing to do, I already buy food but I need to modify it so it was not expensive to doing anything at all.' (P02)

Only one participant had accessed a gym, paid for each session and received a refund from the study team. The other participant did not access a gym, so she could not provide feedback about the cost of exercise:

'Well, I paid to the gym because I have not paid to monthly membership, I paid for every session that I go to and paid for new trainers.' (P01)

'I haven't joined the gym and I don't know what is going to be like [she looked to P01] I have to speak to you where to go, linked up with you but no, not at all because I mean if anything cheaper.' (P02)

Organising participant theme: (OP.6) = Integration and expansion

From the discussion transcript, one subtheme was synthesised to inform the expansion of the intervention programme.

Subtheme: Recommended programme

The participants were asked if they thought the intervention worth offering to other people with knee OA and both of them agreed and supported the suggestion:

'Yes, because I know that I'm suffering a lot and obviously the other person suffering you know if this helping me, it should help them as well.' (P01)

'Definitely yes... depends on the time of their work, it depends on their job, for me, I would recommend it for anyone.' (P02)

One participant focused on the importance of the programme and the role of physiotherapy and suggested that GPs are responsible for educating patients with knee OA and referring them to intervention programmes:

'I think work with people to get more physio doctors referred other people to go whether they do it or not, but they need to be educated about that physiotherapy is good you know....doing this programme a lot of people, my sister, as well she is waiting for her GP to refer her, what I'm telling she suffered the same thing like me I told her I am going to the classes and I am doing physio then going to the gym, I told her that. She said, "I just wait to my GP to tell me" But if somebody with authority telling ... I told her to go to the gym, come with me because I'm in a ladies' gym getting her education so is difficult talk.' (P01)

4.3.3 Participants' feedback (interviews)

From group two, only one participant completed the intervention programme and a second focus group was not possible. Therefore, the study team decided to interview this participant. Consent was obtained before starting the study and the interview was recorded.

Superordinate participant theme: Feasibility (SP)

This superordinate theme comprised six organising themes: **Organising participant's interview themes: (OPI.1) = Efficacy of the programme; (OPI.2) = Adherence; (OPI.3) = Adaptations; (OPI.4) = Acceptability; (OPI.5) = Implementation and practicality; and (OPI.6) = Integration and expansion.** Thematic analysis of the findings was used (see Figure 4.6), in which each subtheme was provided with evidenced references from the interview (i.e., quotations from the transcription). A "Thematic network map" (see Figure

4.7) was developed to synthesise the findings from relevant and interesting themes. Further interpretation of the findings is also presented and supported with evidence theme by theme.

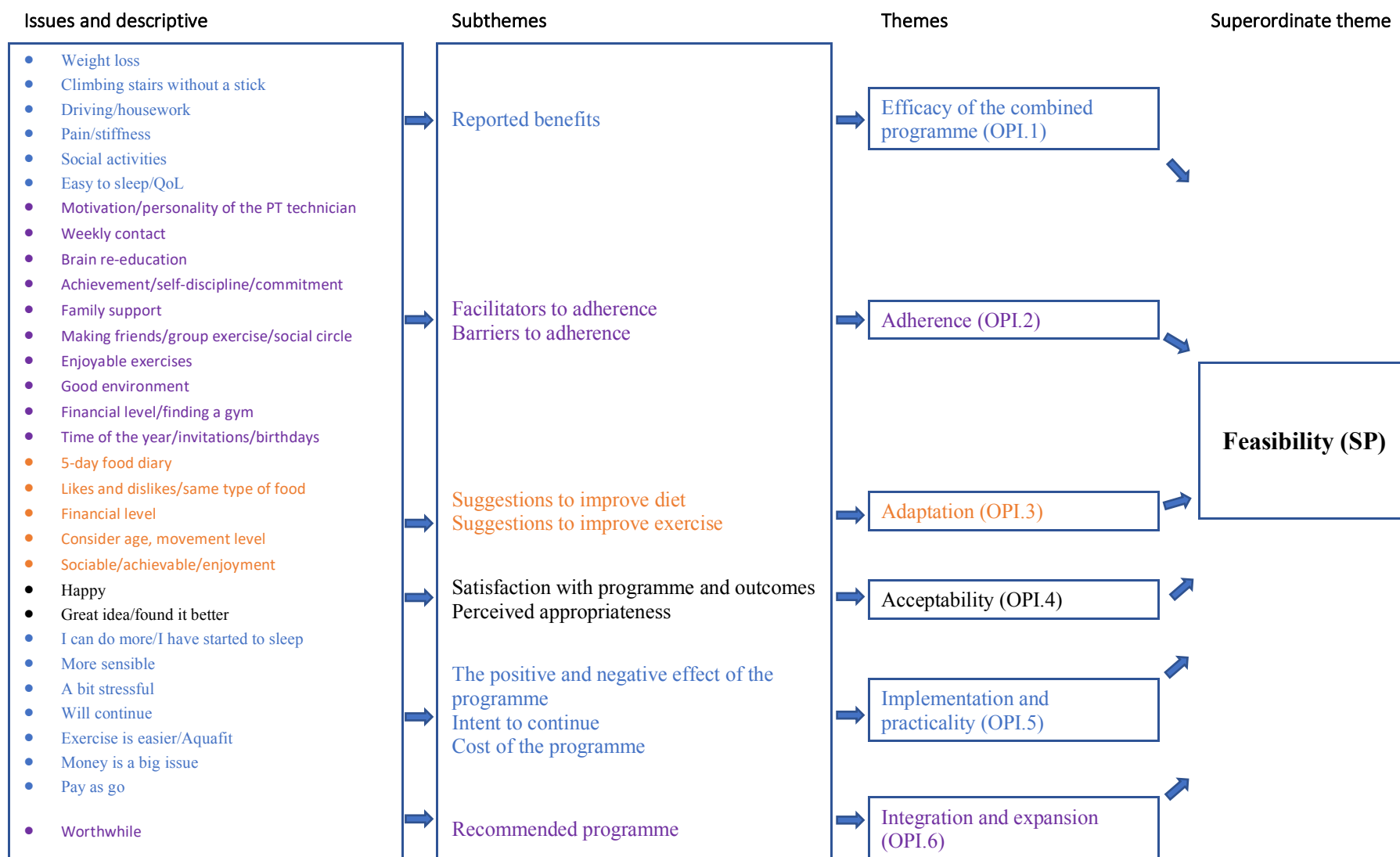


Figure 4.6 Thematic analysis of the findings from the participant's interview

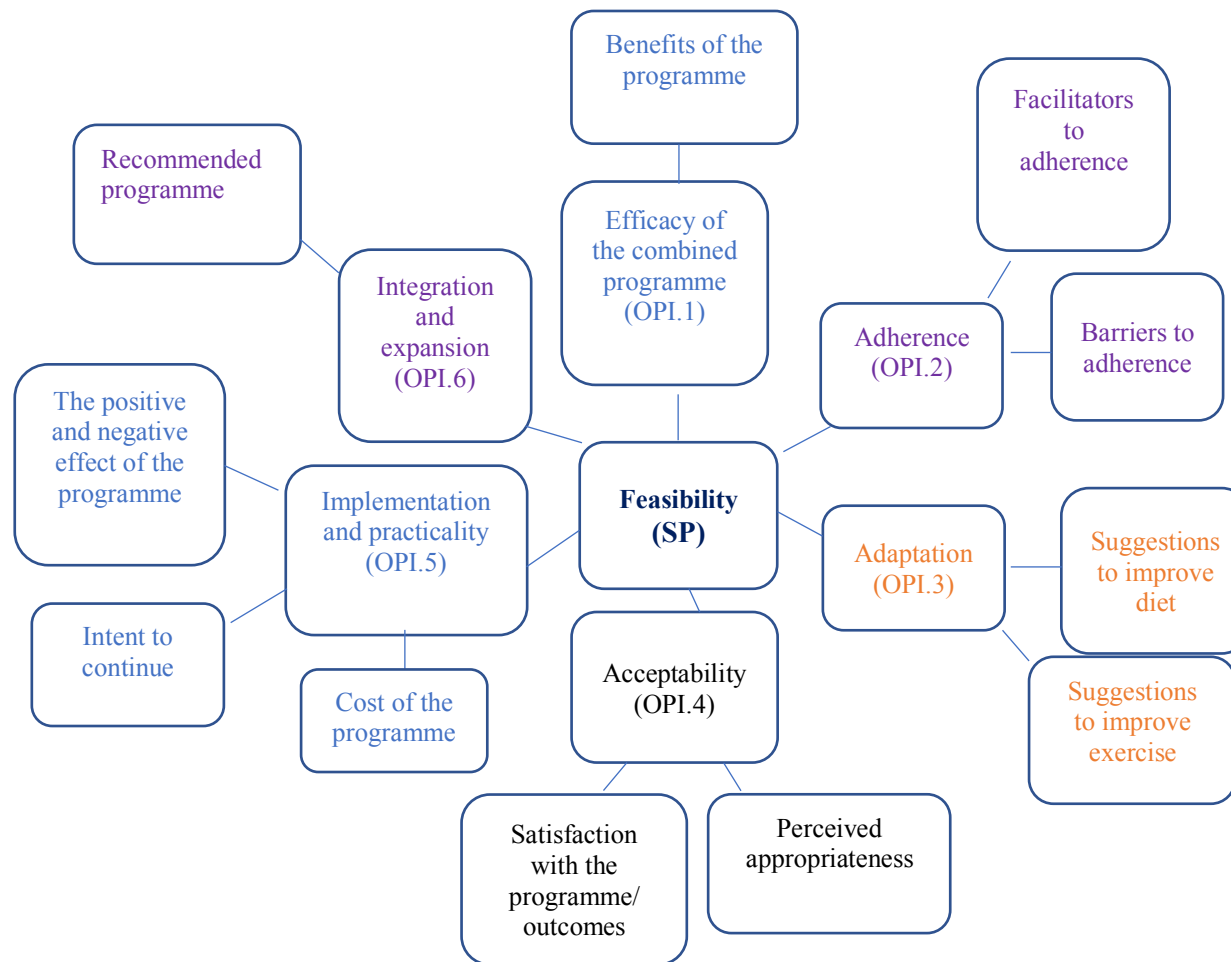


Figure 4.7 Thematic network map of the superordinate theme of the participant's interview (SP): feasibility of the combined programme

Organising participant theme: (OPI.1) = Efficacy of the combined programme

Subtheme: Benefits of the programme

The participant mentioned a number of benefits from the combined programme. She had lost about 11 kg in weight since participating in this study up to the time of the interview:

'I've plateaued off of lost 11 kilos.' (P05)

She reported a difference in her physical function level, mainly in the ability to climb stairs. The participant also noticed a difference in her ADLs, mainly in being able to drive for longer without feeling pain and the ability to achieve housework faster:

'Yeah, lots absolutely lots. I could I go up and down stairs without a stick and I can drive an hour, over an hour without having to stop... Because that was the two key things, I couldn't go upstairs and I couldn't drive for any longer than 40-45 minutes, so yeah no been great.' (P05)

She reported changes in knee pain and stiffness and how this had affected her social life and had a positive impact on her QoL:

'Probably I can drive now without pain for an hour-and-a-half, after about an hour-and-a-half it begins to twitch a bit but I can do so I can do 2 hours, before it was 40 minutes at maximum housework so fine now it's quicker... the stiffness actually like you know such sort of thing...I just feel better and it's not actually stopping me now from doing anything where before I was thinking I can't go to their house because the toilets upstairs and things like that so socially it's improved that as well'. (P05)

Organising participant theme: (OPI.2) = Adherence

Several factors had helped her to stick to the programme. Other factors might be considered a barrier for other people, but she overcame them.

Subtheme: Facilitators to adherence

The participant mentioned a number of factors that had helped her to adhere to the programme. She thought the motivation that she gained from the PT technician helped her to adhere to the usual care programme, which was difficult in the beginning:

'I don't ever take the sessions without Tina at the Royal Orthopaedic because she really spurs you on maybe... and Tina, well, I just challenge anybody to do that with Tina was really good...a personality comes across.' (P05)

After completing the four sessions at the ROH, the participant found the weekly phone contact by a study member also helped her to adhere to the programme:

'It was the support really from yourself and that's kind of things ... You phoned me every week when it was really, really hard the first couple.' (P05)

Brain re-education, achievement, commitment and self-discipline were other factors raised by the participant that she thought had helped her to adhere to the diet intervention in particular:

'You have to re-educate your brain and that too like the facts it's very easy to get into, specially in this old or living on your own but I did it now.' (P05)

'I need little a bit of self-discipline, like you know it has got harder since you're not phoning every week.' (P05)

Support from family and friends was another factor that motivated her to adhere to the programme:

'People have said you look so different and you know you doing really well and you've lost the weight. ' (P05)

Finding suitable and enjoyable exercise, a good environment, group exercise and having friends were other important motivators to continue exercising in a gym:

'I could do but, to be honest, I never really enjoyed it, I felt really lonely on my own ... the ladies' gym there is people that were really slim and really young and fit so I thought that they can do more than me ... where in the Aquafit, I keep up the song that is better the song there a worse so I'm quite happy Where I enjoy the Aquafit, you know it hard work on a Monday morning to get out of bed and go but that's my purpose that's very good... You need to be with a group of people who understand the difficulties regarding your age, regarding your mobility. ' (P05)

'I took her and paid for both of us and she loved it, absolutely loved it. ' (P05)

'I met a group of friends to go to the Aquafit and we'll have a chat in the water and laugh and that, so it's opened a new social circle... I've got my little group of friends on a Monday morning ... when you see somebody else is struggling with the same thing and that that was important for me to see somebody else. ' (P05)

Subtheme: Barriers to adherence

Barriers to adherence included cost, finding a gym and social commitments in terms of invitations, birthdays and the time of year:

'The cost is a big issue ... Finding a gym was a bit stressful. ' (P05)

'It's a really difficult time of the year to tweak things when you been invited out with friends and that so as long as I can keep it off... I can say in the new year, which is always a struggle isn't? ... I'll have to find the right time...January is always horrible month. ' (P05)

Organising participant's theme: (OPI.3) = Adaptations

Subtheme: Suggestions to improve diet

The participant made a few suggestions about modifying the diet intervention. She found it suitable but she thought a 5-day food diary would be better to record participants' likes and dislikes and the clinical dietician needs to discuss the participants' preferences before developing their plans. The participants' financial level should also be considered when developing the plan of diet:

'I think the diet it needs to be looked at a bit more.... what they're actually eating over a longer period, 5 days, what they could cut out and what they could compensate, rather than change the whole thing.... what people like, what they can afford and how they actually cook.' (P05)

She emphasised the importance of considering the same type of food when developing the diet plans, as changing the type of food is hard, particularly for older adults:

'I couldn't change the whole ... there was a lot of, a lot of new foods ... I think it's at my age you're not going to change me into eating superfoods and the other younger type food... I'd never heard of, I've tried them I don't like them... I'm not gonna eat them.' (P05)

Subtheme: Suggestions to improve exercise

The participant thought that finding a gym was stressful and she suggested that the study team needed to advise their participants to find a 'pay-as-you-go' gym:

'Just tell them to go on pay-as-you-go the gym ... most of them do a free day trial so you can go and find out if you like, you just booking ... is very easy, just go onto this pay-as-you-go gym and put your postcode in and it comes up with the gyms that most local to you.' (P05)

Gym exercise might be hard for older people with knee OA and the participant thought that finding an appropriate, sociable and enjoyable type of exercise is important to this population:

'I think you should be saying to people maybe that they've got to find something that they enjoyed you doing in those 12 weeks, it doesn't have to be the gym, it could be, you know, something else, a yoga class or something where they feel they fit in... people of our age, if they have not done any exercise, then need to find something they enjoy do it, especially if you on your own and that may be something there is more sociable, like the Aquafit, walking group or something like that, not saying don't do the gym ... but I think that is really important.' (P05)

She thought that accessing a gym may affect the participants negatively if they started to compare their abilities with those of young people, so finding a suitable type of exercise with people of their age and who have similar abilities is important:

'People in my age, once they go to the gym and see all these young fit people ... just think well, I should have done it years ago, I can't do it ... all I can see is other people to do more than me, you know and I can rationalise it ...they younger or they fitter.' (P05)

Organising participant's theme: (OPL4) = Acceptability

Issues and descriptions were used to synthesise the subthemes of satisfaction with programme outcomes and perceived appropriateness. Further synthesis was used to categorise them into the theme of acceptance.

Subtheme: Satisfaction with the programme and its outcomes

The participant was generally satisfied with the programme and the outcomes:

'I really enjoyed the sessions at the ROH, that really spurred me ...I dropped a dress size in trousers and top and I can't be any happier really. ' (P05)

Subtheme: Perceived appropriateness

In addition to satisfaction with the programme and its outcomes, the participant liked the idea of the programme and found each step to be appropriate, starting with the education session, the usual care classes at the ROH and the assessment sessions:

'I think the actual your support, your 4 weeks at the ROH with Tina there fine and the follow-up period in over 12 weeks after you've done your baseline in that I think there's a great idea. ' (P05)

The education session was important in changing the participant's way of thinking towards eating:

'It the way of put all, realising how many calories I was eating and that let you know to sort of thing ... I think that was important to have that in the study. ' (P05)

The advice and home exercises that were given were appropriate to her case and she followed them when she experienced pain, which helped her:

'I tend to do the stretching exercises if I'm in pain, even though it really hurts I try and do it, so that seems to help ... go for a little walk, that seems to be better than trying to rest it or anything, good 5-10 minutes before it will go off. ' (P05)

The diet plan was not appropriate at the beginning because it contained different kinds of food but this was modified by the clinical dietician and was then more suitable:

'I did find it difficult because it was a very different kind of food ... I have adapted it. The banana shakes smoothies I still have stuck with them, they're in there most days ... there's something like that I cut off bread and when I went back onto bread I had really bad stomach cramps, so there's no bread now ... Cheese is cut down ... I was eating a lot of cakes...now just something sweetie, yoghurt with fruit I found it better. ' (P05)

Finding an appropriate gym and exercise played an important role in accepting the exercise intervention. The participant had tried a City Council gym but she did not like it, so she tried another. Gym exercise was not appropriate at the beginning, as it aggravated her knee pain, so she was looking for a more appropriate exercise:

'I did go to Northfield, which is a Council one, and but I didn't find them as warm and have as welcoming as the Nuffield ... one has got a little gym for women, so that was quite nice and it's mainly women new in the water ... I don't mind men ... Yeah, that mean I know I tried the gym and that aggravated both knees dramatically. I don't know whether because there was nobody with me it's a sign you doing it wrong or right ... I was doing older ones that we did at the ROH ... I don't know whether it was because I was just concentrating too much on those joints!' (P05)

There was no restriction on doing exercise at the gym, so the participant tried Aquafit and found it the most appropriate activity:

'I could probably have 12 weeks at the gym but I'm not going to carry on after because I don't like the gym, it's not for me... you know pain but like! I do the Aquafit and I can bring my knees up and touch my feet in the water and it's all to music ... do lots of arm exercises ... the strength is more in my arms and my legs so I'm just taking with Aquafit... If I can fit in another one, I will do ... I like the Aquafit exercises fit me and it's just so easy in the water, I'm just like bobbing up and down in water, where the bike and a walking machine you need pounding in those machines and my knees do not like that kind.' (P05)

Organising participant's theme: (OPI.5) = Implementation and practicality

Three main subthemes were synthesised to inform the implementation and practicality of the programme: positive and negative effects of the programme, intent to continue, and the cost of the programme.

Subtheme: Positive and negative effects of the programme

Based on the participant's interview, it could be stated that the intervention programme has affected her in different ways. The participant's self-esteem had improved and she thought that she was able to do more. The participant's QoL had also improved in terms of her ability to sleep:

'I will sleep so easy,, piece of cake that's set do you know what I mean, and that's how...I've dropped a dress size and it's all fun and that so great, you know, so that spurs you on, I can do more, I can do anything... I can sleep now... I've noticed I've started to sleep.' (P05)

The participant's lifestyle had also partially changed, specifically, her way of eating and buying food:

'I'm only buying now what I eat and if I eat out it's a lot more sensible, even my friends are used to it now... I have had the idea I haven't had a takeaway, I haven't had a bag of chips or fish and chips from chip shop, which was probably a regular occurrence because I live on my own and quite lazy ... it has made me realise that I don't really need those ... the diet helped really.' (P05)

Only one negative impact of the study was raised by the participant, which was finding a gym after completing the 4 weeks of usual care. She had been advised to try a Council gym, but she did not like it:

'When we did the four sessions at the ROH, they were fine but when it came to finding a gym, that was a bit stressful... That was the most stressful thing, finding the gym after we'd stopped at the ROH.' (P05)

Subthemes: Intent to continue

The participant expressed her intent to continue the programme, which reflects the practicality of the approach:

'Yeah, I do if I can go on it again, that's fine, I'll be starting in a better place than I did...I wanna continue because I could see the difference... I will continue, I am not going to put those 11 kilos back... I think that's really important, that's why I wanted to carry on.' (P05)

Exercise and diet would be the same to follow but she thought the exercise was easier, as diet may be affected by social activities, such as invitations and parties:

'No about the same, they both been hard to do ... the exercise is easier than diet... too many birthdays ... I found personally doing the exercise was the easier one.' (P05)

The participant linked her intent to continue with her preferred exercise:

'If only had about this gym I don't think I don't think that I will carry on ... I could carry on doing the Aquafit, that's where I will continue with that (fingers crossed).' (P05)

Subtheme: Cost of the programme

The cost of the dietary intervention was a significant issue for the participant, as she receives a limited income. However, when she adapted her diet plan with some help from the study clinical dietician, she found it was easier to manage:

'No, the cost is a big issue, I only have £75 a week that set... Well, because I adapted it, that was fine, I think you'll find it what was on the diet sheet I couldn't have afforded it, I think there things like steak on there in a couple that I'd love, avocados I would love them, but there is quite an expensive fruit... some people are in a better financial position than I was.' (P05)

The cost of the exercise was acceptable. The participant had tried a City Council gym at the beginning but did not like it because of the environment at the gym and she did not find

support from the staff, so she accessed another gym. She raised a number of reasons that helped her to access the gym. First, she found a gym that provides special offers, such as a pay-as-you-go method:

'I could have had probably 3 months at Northfield for the same cost as it cost at Nuffield for one session a week, it is off-putting when you're on a low income ... I don't get my pension for 18 months' time I might find ... they're not cheaper there but pay-as-you-go gym ... I found this on the internet, pay-as-you-go gym and it's 8.50 for a day, if I wanted to stay there all day I could, I do most of them, the Aquafit, sauna and a jacuzzi.' (P05)

Second, having the gym expenses covered by the study motivated the participant to access a gym:

'I knew you were going to repay this year, so I borrow it ... you paid for the first 12 weeks, made a difference because I've kept that money now and that's what I'm using now for the gym because I am on a really tight budget ... and that made it financially affordable in a way which I would never ever have considered.' (P05)

Finally, the participant also mentioned that she avoided the coffee shop at the gym to keep the expense possible and she had changed some of her habits to be able to afford the gym:

'I avoided the coffee shop there because of it if I start doing that, I would not do it all... I've now rationalised with the fact that it is only the same as going out for a meal once a week, that meal wasn't doing me any good but the gym is... it has changed how I look at things.' (P05)

Organising participant's theme: (OPI.6) = Integration and expansion

Only one subtheme was synthesised to inform the integration and expansion theme.

Subtheme: Recommended programme

The participant found the programme of intervention worth offering to other people with knee OA:

'It would be worthwhile, I have told people about it, I presume you finished your study now but I have said to people, what a difference made, so thank you.' (P05)

4.3.4 Physiotherapy staff feedback

The responses to the open questions were analysed using a thematic analysis approach (see Figure 4.8) and a thematic map was constructed for the superordinate theme of the physiotherapy staff questionnaire (see Figure 4.9).

Superordinate theme of physiotherapy staff themes (SPT): Feasibility of combined intervention programme

The feasibility of a combined programme was the superordinate theme, which was composed of six organising physiotherapy staff themes: **(OPT.1) = Efficacy of the combined programme; (OPT.2) = Adherence; (OPT.3) = Adaptation; (OPT.4) = Acceptance; (OPT.5) = Implementation and practicality; and (OPT.6) = Integration and expansion.**

Further assessment was provided using subtheme analysis with evidenced references (quotations) from the responses to the open questions. Data were synthesised from relevant interesting themes using a thematic network map (see Figure 4.9). The findings from the physiotherapy staff questionnaires are analysed and presented with evidence below, theme by theme.

Organising physiotherapy staff theme: (OPT.1) = Efficacy of the combined programme

Subtheme: Observed improvement

The physiotherapy technician who delivered the greatest number of sessions of the usual care programme reported that she noticed an improvement in the participants and that there was no difference between them and the patients who received usual care only:

'Yes, same care received.' (PT2)

Subtheme: Barriers to reporting improvement

Three members of the physiotherapy staff did not observe any improvement in the participants, which they reported as being due to a number of reasons, including the low number of participants and they did not review the participants as the assessment was carried out by the study team. One therapist referred to her role in the study, as she delivered only one usual care class.

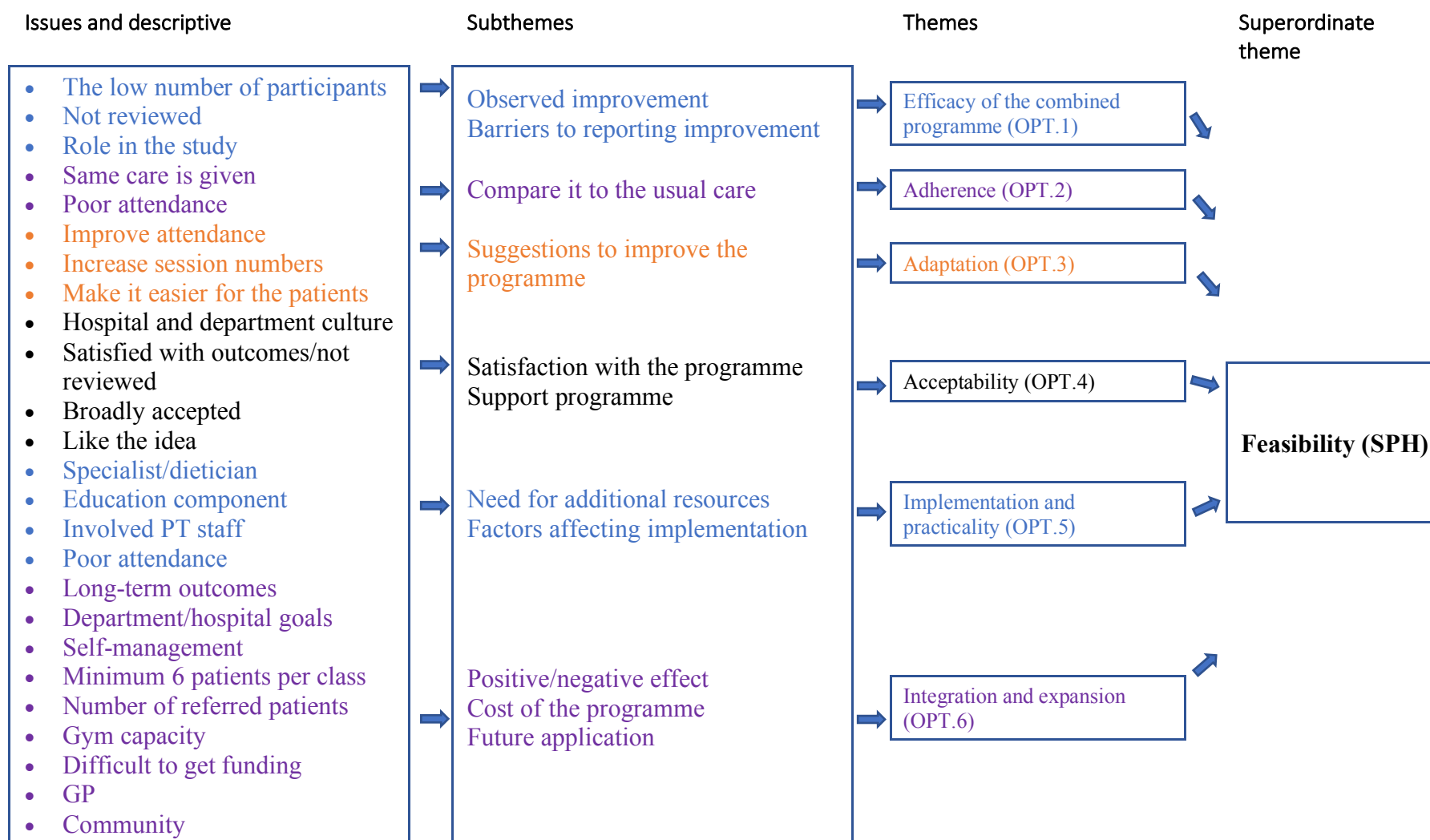


Figure 4.8 Thematic analysis of the findings of the physiotherapy staff questionnaire

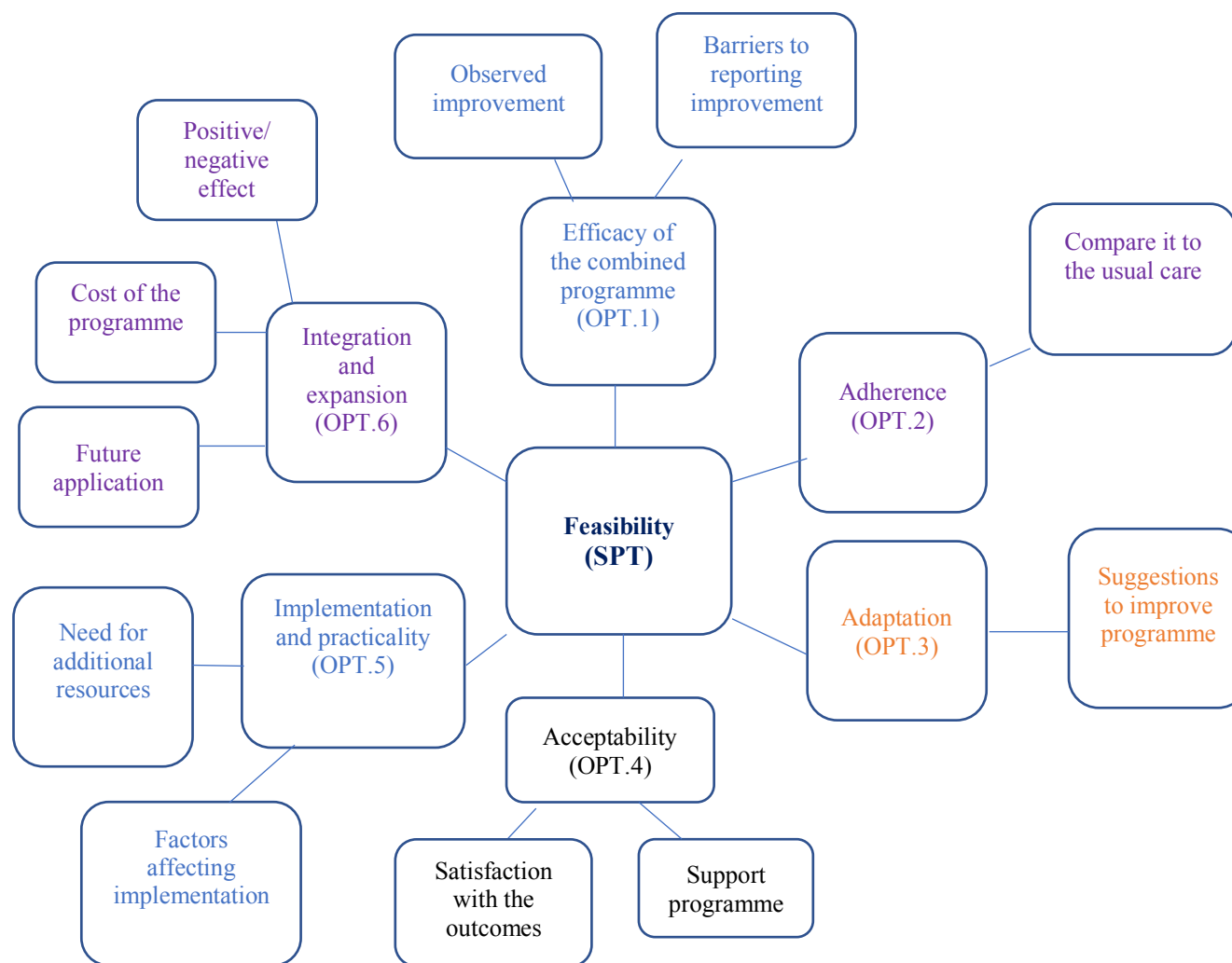


Figure 4.9 Thematic map of the superordinate theme of the physiotherapy staff questionnaire (SPT): feasibility of the combined programme

'Unsure, due to participant number.' (PT1)

'Not reviewed. Referred them only.' (PT3)

'I only delivered one session, so unable to see improvements.' (PT4)

Organising physiotherapy staff theme: (OPT.2) = Adherence

Subtheme: Compare it to the usual care

The physiotherapy technician who delivered the usual care classes thought the participant attendance was similar to that of patients who received usual care only. However, another member suggested that the attendance was different and participant attendance was poor:

'Yes, same care received.' (PT2)

'No. Only attended one session which was poorly attended, the second session I was due to lead did not go ahead due to DNAs [Did Not Attends].' (PT4)

Organising physiotherapy staff theme: (OPT.3) = Adaptations

Subtheme: Suggestions to improve the programme

Only one member thought the programme did not need any adaptation, whereas the others suggested some modifications, including finding a strategy to improve attendance, increase session numbers and make the programme easier for the patients.

'More sessions in a gym environment for patients to become more familiar with equipment.' (PT2)

'Yes, make it easier for patients.' (PT3)

'Yes, ways to improve attendance need to be considered.' (PT4)

Organising physiotherapy staff theme: (OPT.4) = Acceptability

Subtheme: Satisfaction with the programme

All the participating physiotherapy staff considered that the programme was a fit with hospital culture. However, only one member was satisfied with the participants' outcomes and two were not sure because no data were provided by the study group:

'Yes.' (PT1)

'Unsure, no feedback from Uni staff.' (PT2)

'N/A, followed up after class reviewed by group staff only.' (PT3)

Subtheme: Support the intervention programme

The intervention programme was supported by all the participating physiotherapy staff and they intended to apply it as it did not increase their workload.

'Yes, whilst participant numbers made analysis challenging. Broadly accepted that combined programme would improve care.' (PT1)

'Yes, I like the idea.' (PT3)

Organising physiotherapy staff theme: (OPT.5) = Implementation and practicality

Subtheme: Need for additional resources

One member of staff stated that delivering the intervention programme in the hospital would need additional resources, such as a specialist and a dietician:

'Specialist nutritional / dietician involvement.' (PT1)

Subtheme: Factors affecting implementation

Three main points were raised as important factors affecting the implementation of the programme: integrated physiotherapy, providing the physiotherapy staff with information about the combined programme, and poor attendance:

'Yes, integrated physiotherapy (exercise advice) nutritional involvement as opposed to being a separate area of education component.' (PT1)

'Yes, more explanation to the PT that study going on, etc.' (PT3)

'Yes, poor attendance.' (PT4)

Organising physiotherapy staff theme: (OPT.6) = Integration and expansion

Subtheme: Positive/negative effect

The staff considered that the expansion of the combined programme would have positive effects on the physiotherapy department and/or the ROH and only one member was not sure:

'Yes, the combined approach would improve long-term outcomes. At present, ROH has a cut off of BMI 35 for surgery, so would assist with those who end up with TKR.' (PT1)

'Yes.' (PT2)

'Yes.' (PT3)

Three of the staff members also agreed that the combined programme was a fit with ROH and PT department goals:

'Combined programme is in keeping with department + trust - encouraging self-management.' (PT1)

Subtheme: Cost of the programme

Two staff members thought the cost of the combined programme would be feasible within ROH and/or other hospital trusts:

'Yes. The cost would be feasible for providing a minimum of six participants/ patients wave recruited per group/class.' (PT1)

'Yes.' (PT4)

Subtheme: Future application

Running more than one knee OA usual care class/week in addition to other classes and individual sessions to serve more patients would not be possible in the future due to the low number of participants, poor attendance and gym capacity:

'No, at present, patient numbers would not make this financially viable.' (PT1)

'No, not enough number of patients at the moment to fill more than one class.' (PT2)

'Unsure.' (PT3)

'No, due to current gym capacity and poor attendance with current classes.' (PT4)

Two reasons were raised as barriers to applying the intervention in future: first, the low number of patients referred to usual care; and second, the lack of resources to support the combined programme. However, two members suggested the intervention could be applied in a primary care setting:

'Yes, if patient numbers allow. At present, referred numbers to normal care has reduced dramatically... currently difficult to get funding to support the combined programme.' (PT1)

'But would be better in the community.' (PT3)

'Yes.' (PT4)

'No, another setting, GP.' (PT2)

4.3.5 Summary of qualitative findings

The findings from the previous sections are presented in Table 4.6 to build a summary of the qualitative analyses. In Table 4.6, comparison can be made between the themes of the focus group, the participant interview and the physiotherapy staff questionnaire analysis, and each theme is supported by the main findings. The main goal of this table is to merge the participants' findings together to enable further analysis.

Table 4.6 Summary of qualitative data from the participant focus groups, participant interview and the physiotherapy staff questionnaire

Topic	Participant themes (Focus group)	Participant findings (Focus group)	Participant themes (Interview)	Participant findings (Interview)	PT staff themes	PT staff findings
Feasibility	(OP.1) Efficacy of combined programme	Functional improvement: Walk properly n=2 Standing time n=1 Weight loss: Lost weight n=1 Pain: Reduced/stopped painkillers n=1	(OPL1) Efficacy of combined programme	Functional improvement: Climb stairs ADLs: able to drive and achieve housework Weight loss Pain and stiffness: Reduction in pain and stiffness QoL: Social life improved and able to sleep	(OPT.1) Efficacy of combined programme	Observed improvement: Noticed a difference n=1 Barriers to seeing improvement: A low number of participant n=2 Participants assessed by the study team n=2
	(OP.2) Adherence	Facilitators: Family support n=2 Weekly contact n=2 Internal belief in the outcomes n=2 Social interaction/group exercise n=2 Gym preferences (ladies' gym) n=2 Barriers: Misunderstanding of exercise n=1 Family commitments and circumstances n=1	(OPL2) Adherence	Facilitators: Physio support, family support, weekly contact, social interaction/group exercise, type of exercise and environment, achievement and commitment and internal belief Barriers: Financial level, social commitments and timing of the programme	(OPT.2) Adherence	Compare it to usual care only: Similar attendance n=2 Poor attendance n=1 Unsure n=1
	(OP.3) Adaptation	Provide suggestions: Food preferences n=2 Understanding exercise n=1 Gym exercises need adaptation n=1	(OPL3) Adaptation	Suggestions to improve diet: Food preferences, the same type of food and financial level. Suggestions to improve exercise: <i>Exercise type considerations:</i> achievable, sociable and enjoyable <i>Personal considerations:</i> age and movement level	(OPT.3) Adaptation	Suggestions to improve exercise: More sessions in a gym environment for patients to become more familiar with equipment n=1 Make it easier for patients n=1 Find ways to improve attendance n=1

Topic	Participant themes (Focus group)	Participant findings (Focus group)	Participant themes (Interview)	Participant findings (Interview)	PT staff themes	PT staff findings
	(OP.4) Acceptability	Satisfaction with the programme: Find it appropriate n=2 Easy to continue n=2	(OPL4) Acceptability	Satisfaction with the programme: Happy and feel better Find it an appropriate and good idea	(OPT.4) Acceptability	Satisfied with the programme: All of them were satisfied with the programme n=4 Support programme: All of them supported the programme n=4 Broadly accepted n=1 Like the idea n=1
	(OP.5) Implementation and practicality	Positive effect: Only pain after the gym as a negative n=1 Factors affect: Comorbidity and weather n=2 Cost: No additional cost n=2	(OPL5) Implementation and practicality	Positive effect: Finding a gym was the only negative impact Intent to continue: Exercise is easier than diet, Aquafit. Cost: Pay-as-you-go	(OPT.5) Implementation and practicality	Need additional resources: Specialist and clinical dietician Factors affecting: Poor attendance Separate education component Involve PT staff
	(OP.6) Integration and expansion	Recommended programme: Found it worthwhile n=2 GP responsibility to enhance expansion n=1	(OPL6) Integration and expansion	Recommended programme: Found it worthwhile	(OPT.6) Integration and expansion	Positive/negative effect: A fit with hospital/department goals, self-management. Long-term outcomes. Cost of the programme: Minimum of six participants per class/group. Future application: Not applicable at the ROH due to the low number of referred patients. Gym capacity Funding support Might be better to apply it in other settings: GP and community

4.4 Integration

Data from both the quantitative (participants' outcomes measures and the closed questions in the physiotherapy staff questionnaire) and qualitative (participants' focus group, the participant interview and the open question responses from the physiotherapy staff questionnaire) resources were analysed separately. Participants' qualitative data from the focus group and interview were merged to reflect the participants' feedback. Forty-eight independent key findings were identified from the four datasets and were used to create a convergence coding matrix (Table 4.7). Using the matrix, 24 independent key findings were identified across the four sets of data. Two key findings appeared in all four sets of data. Four findings appeared in three sets of data, ten key findings appeared in two sets of data and eight related to a single dataset. Forty-eight were categorised as "silence", as no source of data was identified for one dataset (see Table 4.8).

Table 4.7 Convergence coding matrix

Key finding	Quantitative data		Qualitative data	
	Participants (5 statements)	Physiotherapy staff (11 statements)	Participant (17 statements)	Physiotherapy staff (15 statements)
1	*Recruitment was very slow; only 28 reply slips were received by the study team during 10 months.	Silence	Silence	*Number of the participants referred to physiotherapy usual care is low.
2	*The attrition level is high; only n=3 completed the 16 weeks of intervention, whereas n=8 completed the baseline assessment.	Silence	Silence	*The physiotherapy staff reported poor attendance of participants.
3	*Participant adherence to the diet ranged from 29.5/5 to 98%. Adherence to exercise was 3 hours for n=1 and 14/16 hours for n=2	*Two of the four PT staff thought that participants' adherence to the classes was similar compared with usual care.	*Some factors were identified as barriers to adherence, such as family commitment and financial level.	*The physiotherapy staff reported poor attendance of participants.
4	*A notable difference in the mean values of the functional tests (WOMAC, ROM of knee flexors and muscle power).	Only the clinician who delivered the programme noticed an improvement.	*Reported functional improvement (walk properly, stand quicker, climb stairs) and ADL improvement (housework and driving).	*The functional improvement was similar to those that received usual care only.
5	*A notable difference in the mean values of QoL.	Silence	*One participant reported that her social life was improved after the programme and her ability to sleep without pain.	Silence
6	Silence	*All of them supported the use of the combined programme (100%).	*All of them found it worthwhile and recommended it to other patients with knee OA.	*One PT said that she liked the idea and one said that the programme was accepted broadly.
7	Silence	*Most of them thought the combined programme required adaptation (75%).	*Exercise needs to be achievable, sociable and enjoyable. Participants' age and movement level should be considered.	*Exercise needs to be easier for patients.

Key finding	Quantitative data		Qualitative data	
	Participants (5 statements)	Physiotherapy staff (11 statements)	Participant (17 statements)	Physiotherapy staff (15 statements)
8	Silence	*All of them thought the combined programme fits within the hospital culture (100%).	Silence	*The combined programme fits within the hospital culture but it is difficult to get funding to support the combined programme.
9	Silence	*The combined programme did not increase their workload or impact them negatively (75%).	Silence	Silence
10	Silence	*There are some factors that affected implementation (75%).	*Comorbidity disease and weather affect implementation.	*Some factors affect the implementation of the programme; poor attendance required a specialist and clinical dietician.
11	Silence	*Most of them thought that expansion of the combined programme would have positive effects on the physiotherapy department and/or ROH (75%).	Silence	*A combined approach would improve long-term outcomes. It would assist with those who end up with TKR
12	Silence	*Most of them thought that it would be possible to run more than one knee OA usual care class/week in addition to other classes and individual sessions to serve more patients (75%).	Silence	*At present, patient numbers would not make running more than one knee OA usual care class financially viable, in addition to gym capacity and poor attendance.
13	Silence	*Most of them thought that the combined intervention programme would/would not conflict with the hospital and physiotherapy departmental structure or strategy (75%).	Silence	*It fits with hospital/department goals in encouraging self-management.
14	Silence	Silence	*Reported weight loss n=2	Silence
15	Silence	Silence	*Knee pain and stiffness were improved after the combined programme.	Silence

Key finding	Quantitative data		Qualitative data	
	Participants (5 statements)	Physiotherapy staff (11 statements)	Participant (17 statements)	Physiotherapy staff (15 statements)
16	Silence	Silence	*Food preferences, the same food and financial level should be considered when a diet plan is developed	Silence
17	Silence	Silence	*Pain after gym exercise and stress due to finding a gym were the only negative impacts of the programme.	Silence
18	Silence	Silence	*Participants need to understand the exercise and its progression.	*More sessions in a gym environment for patients to become more familiar with the equipment.
19	Silence	Silence	*There were some factors that helped adherence to the programme, such as family support, weekly phone contact, physio support, social interaction/group exercise, type of exercise and environment, achievement and commitment, and internal belief.	*It is important to find ways to improve attendance.
20	Silence	*Two of the four PTs thought the combined programme cost would be feasible within the ROH and/or other hospital trusts.	*Participants with a good income found the programme cost feasible, whereas one with a low income found it a big issue.	*The cost would be feasible for providing a minimum of six participants/patients wave recruited per group/class.
21	Silence	Silence	*The combined intervention programme is appropriate and easy to continue.	Silence
22	Silence	Silence	*Both exercise and diet are similar to continue after completing the intervention study but social commitments may affect participant adherence to diet.	Silence
23	Silence	Silence	*Participants need support to find a local gym; pay-as-you-go is a good option.	Silence
24	Silence	Silence	*GPs have an important role in enhancing the expansion of the programme.	*Might be better to apply it in other settings: GP and community.

Agreement between statements; Partial agreement between statements; dissonance between statements; statement not comparable.

Table 4.8 Number of statements within each convergence category that resulted from dataset comparison

Convergence category	Number of statements
Agreement	26
Partial agreement	12
Dissonance	2
Silence	48
Not comparable	8
Total	96

4.4.1 Interpretive analysis

Further analysis was made using the convergence coding matrix by comparing each statement in a dataset with the other statements in the other datasets and identifying relationships between the statements.

4.4.1.1 Instance of dissonance

Only one instance of dissonance was found between the statements: this was between the quantitative and qualitative data reporting the physiotherapy staff feedback. The physiotherapists thought running more than one knee OA usual care class/week alongside other classes would be possible, but it was also reported that it would not be possible due to gym capacity and patient numbers would not make it financially viable at present.

4.4.1.2 Instance of agreement

There was agreement in some statements across datasets, including the slow recruitment of participants, poor attrition and adherence level, improvement of participants' functional level, participants' QoL, acceptability, and suggestions for expansion of the programme. Two of the four physiotherapy staff thought participants' adherence to the classes was similar compared with usual care only, although it was reported within the qualitative data that the participants' attendance was poor. The staff members suggested finding a strategy to improve participant adherence, as the participants had also reported some important

factors which had helped them to adhere to the programme, including family support, weekly phone contact from the study team, physiotherapy technician support, social interaction/group exercise, environment and type of exercise, achievement, commitment and internal belief. The participants thought that understanding of the exercise and its progression was an important issue and the physiotherapy staff agreed and reported some adaptations to make the programme easier, such as adding more usual care classes to help participants become more familiar with the gym exercises/equipment. The physiotherapy staff also thought that the combined programme fitted within the hospital culture, but it was difficult to obtain funding to support the combined programme from the ROH/trust. They also thought the combined programme cost would be feasible within the ROH and/or other hospital trusts, providing a minimum of six participants/patients were recruited per group/class.

There was clear agreement that the combined programme was accepted but required some adaptations. The physiotherapy staff agreed that the expansion of the combined programme would have positive effects on the physiotherapy department and would not conflict with the hospital and physiotherapy departmental structure or strategy. Involvement of GPs was raised by a participant who thought GPs' position of authority could play an important role in enhancing expansion of the programme; the physiotherapy staff suggested conducting the intervention programme in other settings, such as primary care and the community.

4.4.1.3 Instance of silence

'Silence' was presented in the majority of pairwise comparisons between datasets. Silence appeared mainly between datasets reporting the feedback of participants and physiotherapy staff in which data mentioned by one population were not relevant to the other. For example, physiotherapy staff reported that the expansion of the combined programme would have

positive effects on the physiotherapy department and the ROH. A number of comparisons were categorised as ‘not applicable’; all of these pertained to participant feedback and opinions.

Chapter summary

This chapter presented the findings of the DRPA study. The qualitative and quantitative data were integrated using a triangulation protocol technique which provided a deeper insight than separate analyses would have achieved. Running more than one knee OA usual care class/week alongside other classes was the only area of dissonance. Further interpretation and discussion of these findings are presented in Chapter 5.

CHAPTER 5

DISCUSSION OF THE FINDINGS OF THE FEASIBILITY STUDY

This chapter was written according to the CONSORT checklist and interprets the main findings of the DRPA study, consistent with the study objectives, and compares these findings with other relevant evidence. The rates of participants recruitment, attrition and adherence plus the evaluation of success criteria of the feasibility study (presented in Chapter 3) are discussed in this chapter to answer the primary objective of this study. The secondary objectives regarding the efficacy of the combined programme of intervention in addition to the reflection on the DRPA study design and setting are also addressed and discussed within the main findings section. The main limitations of this feasibility study are highlighted by addressing potential sources of bias. An integrated analysis of the quantitative and qualitative data using a triangulation technique provides direction for future work. Implications for further clinical research and the conclusions of the DRPA study are presented in the final sections of this chapter.

5.1 Main findings

5.1.1 Feasibility of the DRPA study

Based on the findings from chapter 2, combining weight loss and exercise regimens is recommended for older adult patients with knee OA (Messier et al., 2000; Messier et al., 2004 and Messier et al., 2013). Despite the clinical recommendations for exercise and diet for people with knee OA, there are no published UK studies reporting the efficacy of a combined intervention programme of physical activity and dietary restriction on the musculoskeletal function of obese older adults with knee OA (Alrushud et al., 2017). There are UK studies that have combined education and exercise, for example, the Benefits of Effective Exercise for knee Pain (BEEP) trial which was conducted to investigate the effect of changing the characteristics of the exercise programme compared with usual physiotherapy care on pain and function outcomes in knee OA older adults aged >45 years (Foster et al., 2014). However, the DRPA study is the first UK study conducted using a multimodal design for assessing the feasibility of the combined intervention programme within clinical practice for both patients and physiotherapists. The primary objective of this study was to assess the feasibility and acceptability of a combined intervention programme for both the targeted population and the physiotherapy staff who delivered the intervention. The following sections discuss the feasibility assessment of the DRPA study based on the rate of participant recruitment, attrition and adherence, and the evaluation of the proposed success criteria.

5.1.1.1 Recruitment, attrition and adherence rates

Recruitment was a significant challenge in this feasibility study, the proposed sample size (n=30) was to be recruited over 3 months with n=10 participants each month that was

planned to start in March 2017 and end in June 2017. Due to the time taken to obtain all approvals, the recruitment process was delayed until October 2017. During this time the number of patients with knee OA who were referred to the clinic was reduced based on the clinician report; thus, the rate of recruitment was slow once recruitment was underway. Amendments to the study protocol were submitted to facilitate recruitment by reducing the lower age limit and involving the physiotherapy department (in addition to the clinics which had shown initial promise) as a recruiting site. Recruitment for this feasibility study took 10 months, with only 28 reply slips received.

Attrition rate in the DRPA study was high. The attrition rate was 37.5% at one month due to work demand and medical issues and 62.5% at 4 months due to a health issue and family demand. This attrition rate was high compared with that reported in the literature for similar studies, i.e., 7.7% in the intervention arm of a preliminary study at 6 months (Messier et al., 2000). In the DRPA study, loss to follow-up was not related to the study design or procedure. Family illness and medical reasons were also mentioned as causes for withdrawal in a previous study (Messier et al., 2000). In a review of nutritional RCTs and long-term studies, the loss to follow-up has been reported as between 5-20%, and it is suggested that a value of > 20% may affect the validity of the study. However, there are no agreed criteria for acceptable rates of follow-up (Fewtrell et al., 2008). A loss to follow-up of 20% was determined in a protocol for feasibility RCT conducted to improve physical activity and function in overweight and obese older adults with knee OA, mean age 63.2 ± 9.8 years. The results showed a 15% loss to follow-up in the intervention arm and 19% for both groups which included $n = 26$ participants at 6 months (Schlenk et al., 2011).

In the DRPA study, adherence to exercise for five participants who exercised for 4 months was 68.8%, which was lower than that recorded for 12 participants (94.7%) in the diet and exercise arm of a pilot study (Messier et al., 2000). A low rate of study completion was recorded in the DRPA study, as only three of the eight participants completed the study, compared with 12 out of 13 in the intervention arm of a previous pilot study (Messier et al., 2000).

5.1.1.2 Evaluation of the success criteria

A priori determined success criteria (Table 3.4) were used to evaluate the feasibility and acceptability of the combined programme. Findings from the detailed analysis of the mixed methods approach informed the decisions based on these criteria (see Table 5.1). With regard to adaptation, participants suggested minor changes to the combined programme based on their experiences. Furthermore, the programme was accepted by the participants, as they found it fitted with their ADLs. Participants thought the programme worthy of recommendation to other patients, which reflects the success of the combined programme based on integration and expansion. However, the average exercise compliance and diet adherence was < 80%, which did not meet the feasibility criterion for adherence. Overall therefore, the combined intervention programme was not considered feasible for participants, due to the low sample size and thus lack of appropriate representation of the target population (Patel, Doku and Tennakoon, 2003; Hoover et al., 2018).

The combined programme was found to be feasible for the physiotherapy staff in terms of efficacy, adherence, acceptability, and integration and expansion but was not feasible in terms of adaptation, implementation and practicality (Table 5). In terms of efficacy,

Table 5.1 Decisions regarding the feasibility study success criteria based on the study findings

Category	Participants' quantitative outcomes	Participants' qualitative outcomes	Physiotherapy questionnaire	Decisions
1. Efficacy	The analysis of efficacy was limited due to a small sample size. Descriptive analysis showed positive changes in the mean values of WOMAC, SF-36, the range of knee flexion and leg muscle power over the whole 16 weeks.	N/A	The PT clinician who delivered the usual care programme at the ROH reported improvement in the outcomes of participants.	This category met the success criteria for the physiotherapy staff (as the PT clinician noticed improvement in the participants' outcomes) but not the participants. However, the very low number of participants (n=3) is not representative of the target population which therefore made the combined programme unfeasible based on these data.
2. Adherence	Average exercise compliance (average numbers of attended weeks = 11/16) was less than 80% (68.6%). Average completed dietary sheets compliance was less than 80% (69.3%).	N/A	Two of the four physiotherapy staff involved (including the PT clinician who delivered the usual care programme) reported similar adherence of participants compared with patients who received usual care only.	This category met the success criteria for the physiotherapy staff (as they reported that adherence to the classes is similar compared with usual care) but not the participants. However, the very low number of participants (n=3) is not representative of the target population which therefore made the combined programme unfeasible based on these data.
3. Adaptation	N/A	Only minor changes were suggested.	The combined programme required adaptations, mainly to find ways to improve attendance.	This category met the success criteria for participants (as they suggested minor changes to the combined programme) but not the physiotherapy staff. However, the very low number of participants (n=3) is not representative of the target population which therefore made the combined programme unfeasible based on these data.
4. Acceptability	N/A	Participants were satisfied as the intervention programme fitted with their ADLs.	They were satisfied with the participants' outcomes and supported the use of the combined programme. The combined intervention programme fitted within the hospital culture and delivering the combined intervention programme did not increase their workload.	This category met the success criteria for both participants and physiotherapy staff as they were satisfied with the combined programme. However, the very low number of participants (n=3) is not representative of the target population which therefore made the combined programme unfeasible based on these data.
5. Implementation and practicality	Both questionnaires (WOMAC and SF-36) were fully completed.	N/A	Additional resources are needed to implement the programme, such as a clinical dietician. Some factors affected the implementation, efficiency, speed or quality of delivery, such as poor attendance and lack of physiotherapy staff awareness of the study.	This category met the success criteria for participants but not the physiotherapy staff. However, the very low number of participants (n=3) is not representative of the target population which therefore made the combined programme unfeasible based on these data.
6. Integration and expansion	N/A	Participants recommended the combined intervention programme to other patients.	The programme could be applied in future if the number of referred participants improved; expansion of the programme would have a positive effect on the physiotherapy department and the ROH. Despite the lack of current resources to support the combined programme, two of the four physiotherapy staff thought the cost of the combined programme was feasible for the ROH and/or other hospital trusts.	This category met the success criteria of the feasibility study for both participants and the physiotherapy staff. However, the very low number of participants (n=3) is not representative of the target population which therefore made the combined programme unfeasible based on these data.

improvement in the participant outcomes was reported by the PT clinician who led the physiotherapy usual care classes at the ROH. In addition, the PT clinician and a senior physiotherapist reported similar adherence of DRPA participants compared with patients who received only usual care. Based on acceptability, the PT staff expressed their satisfaction with and support for the combined programme, as it fitted within the hospital culture and did not increase their workload. They also thought the expansion of the combined programme would have a positive effect on the physiotherapy department and ROH if the number of referred participants increased, as it would then be more cost-effective for the ROH and/or other hospital trusts. The physiotherapy staff suggested some adaptations in the procedural implementation of the programme, mainly in terms of finding ways to improve attendance such as telephone and SMS reminders (Hasvold and Wootton, 2011). In terms of implementation, the PT staff reported that the programme needed additional resources for it to be implemented in the PT department, such as input from a clinical dietician. Some points were raised as factors affecting the implementation, efficiency, speed or quality of delivery, such as poor attendance and lack of physiotherapy staff awareness of the study. Generally, as two main categories of feasibility; adaption and implementation and integration did not meet the success criteria and with respect to the very low sample size, the combined intervention programme was evaluated as not feasible for the physiotherapy staff (Patel, Doku and Tennakoon, 2003; Hoover et al., 2018).

5.1.1.3 Reflection on the methods of the DRPA study and recruitment strategy

Robust feasibility assessment in sections (5.1.1.1 and 5.1.1.2), showed that the DRPA study was not feasible using the current methods and recruitment strategy. Inability to recruit the proposed sample size was the main issue. Despite the challenges regarding recruitment and the low number of participants, the DRPA study team tried to deliver the proposed protocol

as planned. The DRPA study was designed as a single arm study; conducting an RCT was not possible due to the limited resources. Moreover, several factors relating to the study setting may have impacted overall recruitment rates. Generally, researchers face challenges when recruiting participants to behavioural treatment programs. Recruiting inactive people to participate in feasibility studies of physical activity is a challenge as participants need to change their behaviour and dedicate effort and time to participate (El-Kotob and Giangregorio, 2018). Similarly, for recruiting participants to weight loss interventions (Wing and Jeffery, 1999). However, a strategy of recruiting participants with friends and social support was found helpful for weight loss and maintenance in both participants and friends (n=166) aged 25-55 years (Wing and Jeffery, 1999).

Another factor affecting the recruitment rate was recruiting participants as groups. Initially, the DRPA study team was not able to start the study without a cost-efficient number of participants in the first group as directed by the physio staff (at least 6 participants per group). Waiting for the efficient number delayed the starting date, and in the meantime 3 participants could not start the study, (one moved from Birmingham and two changed their interests). Even with the protocol amendment to include the physiotherapy department as a recruitment site the recruitment rate remained low, which indicated that recruitment was unsatisfactory, even with the physiotherapy department on board. However, increasing recruitment sites does not guarantee an improvement in recruitment rate, as even multicentre studies may fail to recruit the appropriate number of participants (Puffer and Torgerson, 2003). The study eligibility criteria could also be linked to the failure to recruit the proposed sample size, for example, the minimum age criterion was initially 55 years and was subsequently reduced to 45 years. Surprisingly, potentially eligible participants experienced a range of comorbidities, in spite of their relatively young age range.

The three components of the combined programme intervention were assessed in this study to ensure their feasibility. For the education component, only n=4 participants attended the education session. Interestingly, the participants who completed the programme (n=3) attended the education session at the ROH; the fourth participant who attended the session, unfortunately, withdrew from the study due to a medical reason (disc prolapse). In addition, participants considered the education session was an important component of the programme, which enforced the role of advice and education in promoting self-efficacy and improving adherence in knee OA patients (Rezende et al., 2018). The principles of introducing an education session are consistent with recommendations from a recent review promoting the benefits of physical activity and exercise, as patients with hip and knee OA need to be educated about the causes and processes of OA, the importance of physical activity, and provided with knowledge related to effective and ineffective treatments and strategies to self-manage symptoms (Skou et al., 2018). For the exercise component, the existing ROH physiotherapy intervention programme for patients with knee OA (usual care and gym exercise plus home exercise) was delivered to participants in this DRPA study. The Birmingham City Council Be Active scheme was found not to be applicable for the two participants who exercised at a local gym: one found the class times interfered with her work schedule and the other participant missed support from the gym team and instructor. Home exercise, specifically stretching exercises, were found to be helpful in improving pain and stiffness. Weekly phone contact was found helpful by participants to improve adherence but sometimes they did not answer and replied instead via text messages. Using the phone call contact to record exercise compliance in the last 3 months of intervention may not be practical in clinical practice for a large number of participants.

The dietary intervention was found to be acceptable, mainly due to advice that was given in addition to the flexibility to modify diet plans. Advice provided by a clinical dietician was found helpful based on the participants' reports. In a recent mixed methods SR conducted to determine appropriate weight loss interventions in overweight/obese individuals with chronic musculoskeletal pain, data were synthesised from a qualitative analysis of 17 study findings extracted from four studies (n = 58 participants) of older adults (aged ≥ 57 years), with two important findings. First, health care professionals need to understand that chronic pain makes healthy behaviour more challenging, as patients try to cope with pain by eating, which affects their self-efficacy for weight loss. The pain itself may also restrict their activity and create a barrier to weight loss (Cooper et al., 2018). Second, to achieve beneficial outcomes in terms of pain reduction and weight loss, the relationship between weight and chronic pain must be explained by health care professionals through patient education programmes (Cooper et al., 2018). The relation between body weight and knee pain was explained fully during the education session of the DRPA study.

5.1.2 Efficacy of the combined intervention programme

The collection of preliminary data regarding the potential efficacy of the combined intervention programme and assessment of the suitability of the selected outcome measures were secondary objectives of this feasibility study. The proposed statistical tests were not applied due to the low number of participants. Using significance tests for analysing findings from a very small sample size has been reported to be of limited utility (Bland, 2008; Skene and Kenward, 2010 a&b). Statistical analysis tests are not expected to show a significant difference or draw meaning from small samples of fewer than six observations (Bland and Altman, 2009). Therefore, descriptive analysis (visual interpretation) using tabulation was

used to compare the difference between the means and interpret the findings over 4 & 16 weeks of intervention (Liu, Parelius and Singh, 1999).

5.1.2.1 Efficacy of the combined programme on weight loss and body composition

It was hypothesised that the combined programme would help participants to lose approximately 5%-10% of their total body weight over 4 months. The mean body weight reduction was 4% in the DRPA study and this percentage was compared with changes in previous studies (Messier et al., 2000; Messier et al., 2013) at 6 months (details of these studies were presented in Chapter 2). Despite the number of participants, aims and parameters of the trials and the period of the intervention, a similar percentage of change (4%) was reported by Messier et al. (2000) (n=12) but it was found to be higher (9.4%) in the IDEA trial (n=133) (Messier et al., 2013). In the DRPA study, two of the three participants lost 4.6% and 8% of their body weight respectively, whereas the third participant did not lose weight due to low adherence to the diet (29.5%). Interestingly, the participant who lost 4.6% had thyroid dysfunction, which may demonstrate that the combined programme could be effective even with these patients. It is clinically known that hypothyroidism is correlated with a number of changes, including decreased thermogenesis and metabolic rate and weight gain leading to overweight and obesity (Sanyal and Raychaudhuri, 2016).

It was also hypothesised that reduction in body weight would be accompanied by losing more fat mass than lean mass. Body composition in the DRPA study changed slightly as the lean mass reduced from 45.97 ± 2.11 kg to 43.30 ± 2.16 kg and fat mass reduced from 52.20 ± 14.05 kg to 50.90 ± 10.07 kg respectively. These findings were compared with the IDEA trial at 18 months (n=121), which showed reduction in both lean mass and fat mass from

55.6 ± 12.6 kg to 50.8 ± 12 kg and from 36.8 ± 8.16 kg to 30.3 ± 10.10 kg, respectively. Importantly, in the DRPA study, fat mass decreased in participants who lost weight and increased in the participant who did not lose weight, while lean mass decreased (albeit to a lesser degree than fat loss) in all of them, which supports the study hypothesis. A review by Messier (2010) reported that calorie-restricted dietary intervention in overweight and obese adults with knee OA should have an appropriate calorie distribution (15%-20% from protein; 45%-60% from carbohydrate; and < 30% from fat).

Protein and carbohydrate intake were within the recommended amount, even before enrolling in this study; only fat percentage was higher and this was based on what was reported in the 3-day food diary (Chapter 4).

5.1.2.2 Efficacy of the combined programme on patient reported outcome measures

Improvement was detected in some outcome measures over the 4 months of the intervention, including WOMAC scores, knee flexor ROM and muscle power. Interestingly, the findings of the descriptive analysis are consistent with previously published trials with respect to the trial's aims, parameters and participant numbers. The post-intervention mean of WOMAC was reduced from 59.7 ± 18.6 to 36 ± 12.8, in agreement with the IDEA trial (from 24.6 ± 11.7 to 16.5 ± 9.88 (Messier et al., 2013)). The WOMAC pain scale did not show any notable improvement over 4 months of intervention. Improvement was detected in QoL over the 4 months of the intervention. The mean of the SF-36 physical component increased from 25.8 ± 9 to 37.73 ± 17.55 in the DRPA study compared with 36.6 ± 9.41 to 43.5 ± 9 in the IDEA trial (Messier et al., 2013). The mental component of SF-36 improved from 37.70 ± 17.30 to 56.13 ± 15.84 in the DRPA study and reduced from 57.2 ± 6.6 to 56.9 ± 7.3 in the IDEA trial (Messier et al., 2013). This lack of consistency between DRPA and IDEA could be due

to the low sample size and variable response in the DRPA trial; (the score of one participant (P5) clearly increased compared with another participant, who showed slight improvement, and a third participant did not show any improvement) taking into account the number of participants (n=133) in the IDEA trial.

5.1.2.3 Efficacy of the combined programme on performance-based outcome measures

The ROM improved from $111 \pm 11.5^\circ$ to $118 \pm 6.3^\circ$ for right knee flexors and from $84.7 \pm 19.5^\circ$ to $100 \pm 34.8^\circ$ for left knee extensors in the DRPA study, in which all the participants had bilateral knee OA, whereas the ROM improved from 56.2° to $56.74 \pm 0.91^\circ$ in a previous study (Messier et al., 2000). In the DRPA study, muscle power improved from $68.6 \pm 4.73 \text{ W.kg}^{-1}$ to $90.3 \pm 35.23 \text{ W.kg}^{-1}$ for the right leg and from $61 \pm 42.04 \text{ W.kg}^{-1}$ to $78.6 \pm 63.89 \text{ W.kg}^{-1}$ for the left leg, but it was not possible to compare this outcome with arthritic patients, so this was compared with the findings of an RCT that examined muscle power and strength in overweight or obese older adults after voluntary weight loss. For nine older women on a hypocaloric diet and a resistance training arm with a mean age 70.2 ± 3.7 years and BMI $32.5 \pm 4.8 \text{ kg.m}^{-2}$, the muscle power improved from $38 \pm 4.2 \text{ W.kg}^{-1}$ to $81.6 \pm 4.7 \text{ W.kg}^{-1}$ over 16 weeks (Marsh et al., 2013). There was slight improvement in the physical performance tests; stair time and time up and go test over 4 months of intervention.

5.1.2.4 Efficacy of the combined programme on the biomarkers of joint remodelling

The means of serum leptin, PICP, CTX-1 and COMP concentrations increased. Serum adiponectin and PIIANP concentrations decreased post-intervention, reduction in serum PIIANP may indicate a positive effect of the combined programme, as its proportion is high in affected cartilage (Nelson et al., 1998; Garvican et al., 2010). In the DRPA study, serum adiponectin decreased in participants who lost weight and increased in those who gained

weight; this may be interpreted as adiponectin and leptin being known as obesity-related inflammatory biomarkers (Attur et al., 2013). However, leptin increased in all the participants. Serum PICP concentration decreased only in one participant, who lost 4.6% of her body weight. Serum CTX-1 decreased in participants who lost weight and increased in a participant who gained weight. In the DRPA study, serum COMP and PIIANP concentrations decreased only in the participant who lost more weight. Serum COMP is known to increase with age and BMI and was found to be elevated in a patient with radiographic OA (Tseng, Reddi and Di Cesare, 2009). Serum COMP was elevated in patients with knee OA and is sensitive to OA disease severity (Attur et al., 2013). However, in the DRPA study there were insufficient data to make any inferences about utility as biomarkers in future trials but that the measurements themselves (i.e., blood sampling) was feasible.

Moreover, all outcome measures were found to be suitable for both the participants and the assessor. It was noted that not all participants could complete five attempts for lower limb extensor power output. Some participants in the DRPA study experienced knee pain when they made the first attempt and the assessor immediately stopped the test and thus only the first reading rather than a maximum was used in subsequent analysis. Assessing the correlation between body weight, BMI, knee pain and biomarkers of joint remodelling was not possible due to insufficient sample size.

Clinically, the Minimum Clinically Important Difference (MCID) is used to define the potential value of treatment outcomes. MCID may be determined by calculating the percentage of improvement from the baseline score (Copay, Eyberg et al., 2018). In rehabilitation interventions, an improvement greater than 12% of baseline score is considered as the MCID for both WOMAC and SF-36 (Angst et al., 2001). In the DRPA

study WOMAC improved by 39.7% and the physical and mental components of SF-36 were improved by 46.2% and 48.8% respectively over 16 weeks.

5.1.2.5 Discussion of the qualitative component findings

Some physical benefits were reported by the participants, such as improvement in ADLs, including standing, walking, climbing stairs, and the ability to drive for longer distances and to undertake housework. Additional benefits were mentioned, such as reduction in pain and stiffness, ability to sleep, and improvement in social life and QoL. These improvements were also reported in the IDEA trial, as a combined intervention of exercise and diet has been shown to help overweight/obese adults with knee OA to maximise self-efficacy, reduce pain and improve physical function (Mihalko et al., 2018).

5.2 Strengths and limitations

The strength of this study lies in having been designed as a robust feasibility study protocol based on a comprehensive review of evidence and informed by input from PPI (INVOLVE, Hanley et al., 2003) and health professionals. The DRPA study protocol was peer-reviewed and published in the BMJ open journal. The study used a mixed methods approach to optimise data collection and novel analysis techniques to integrate both the quantitative and qualitative data to provide a deeper insight into the study findings in this setting.

This feasibility study had, however, a number of limitations. The main limitation was the low number of participants due to a slow recruitment rate, despite the amendments to the study protocol to facilitate recruitment by reducing the lower age limit and involving the physiotherapy department as a recruiting site. The proposed sample size (n=30) was not recruited over 3 months and only 28 reply slips received over 10 months. Recruiting

participants from a single centre in Birmingham due to limited resources was another limitation. There was no overall score of the success criteria when developing this study protocol. The physiotherapy staff questionnaire was not piloted but was reviewed independently by a peer reviewer who provided useful and constructive feedback, mainly rewording some questions to ensure clarity, and it was also approved by the HRA. The staff involved did not report any problem when completing it adequately, there were no missing data and positive feedback was provided. Potential bias was not avoided due to the unblinding of assessors. Another limitation was the failure to conduct three focus groups as proposed; only one interview and one focus group were conducted. Despite the low number of participants (n=2) in the focus group, the discussion was successful. It is known that the optimal size for conducting focus groups is about six to eight participants but discussion can be carried out successfully with only a few or up to 14 participants. A risk of small groups is limited discussion, while large groups can make discussion difficult to manage, and frustrating for participants who feel they do not have enough opportunities to talk (Bloor et al., 2001; Gill et al., 2008). All participant who completed the 4 months of intervention (n=5) were women.

5.3 Implications for practice and future research

The UK National Institute for Health Research (NIHR) recommends researchers to conduct preliminary work before a large clinical trial to save resources (NIHR, 2015; Eldridge, Lancaster et al., 2016). The NIHR defined feasibility studies as “pieces of research done before the main study in order to answer the question “Can this study be done?” (NIHR, 2015). A robust feasibility assessment helps to identify any defects with study recruitment strategy and present any challenges that may happen at the involved sites. A feasibility assessment also identifies which research aspects need further planning (NIHR, 2015;

Eldridge, Lancaster et al., 2016). In the UK, feasibility assessment helps to support a high-quality grant application for a definitive trial, but sometimes clinical practice may change over the timescale and the feasibility assessment may need to be repeated (AMRC and MCRN, 2011). As the current feasibility study did not answer the research questions, conducting another feasibility study in multiple sites is required to test various parameters such as the willingness of clinician to recruit participants, the willingness of participants to be randomised and the number of eligible participants, where the critical parameter is measuring the recruitment rate (NIHR, 2015; Eldridge, Lancaster et al., 2016).

Despite the very low number of participants, the combined programme was accepted by the participants and involved physiotherapy staff who suggested some modifications in the procedural delivery of the protocol. These suggestions have been incorporated with the DRPA study findings and limitations to inform the design of the future feasibility study. The components included are the recruitment site, required sample size, eligibility criteria, components of the intervention and strategies to improve adherence.

In the DRPA study recruitment was a significant challenge which affects the study findings, with several aspects of the study methods needing reconsideration in order to optimise participant recruitment in future feasibility study. Involvement of GP clinics, community and several hospitals as recruitment sites should be attempted. Also, involvement of the NIHR primary care clinical research network may improve the recruitment rate in the preliminary study, given that knee OA is a common condition presenting to GP clinics (Jordan et al., 2010; Foster et al., 2014; Cottrell et al., 2016). Setting an appropriate sample size with justification is important when conducting a study (Billingham, Whitehead, and Julious, 2013). It has been suggested that a minimum of 30 patients for a preliminary study

is appropriate to estimate a study parameter (Browne, 1995). The eligibility criteria need to be reviewed and modified to include more participants and enhance generalisability.

Based on the DRPA participant feedback, conducting a similar education session to deliver the same information and explain safety considerations relating to exercise, such as how to avoid slips, trips and falls, is needed in the preliminary study. Participants also need to be educated about strategies of self-management and coping with mild aches and pains (Nicolson et al., 2017; Mihalko et al., 2018) and provided with the same detailed information about diet. A recent review included evidence from SRs and meta-analyses for the physiotherapy management of lower limb OA and identified the guidelines and recommendations relevant to practice in the UK. The review reported that there is general agreement about the beneficial effect of patient education and appropriate skills of self-management (Walsh, Pearson and Healey, 2017).

Based on the DRPA study results, some suggestions are proposed to review the exercise component. For example, four sessions of usual care classes at the physiotherapy gym were not enough for participants to become familiar with the equipment and understand the exercises and their progression adequately. With regard to exercise at a local gym, further support needs to be provided to participants in selecting and accessing local gyms. Particular attention should be given to personal preferences and movement level when selecting the type of exercise; for example, cycling might be easy for one participant but very hard for another. Importantly, exercise intensity needs to be built gradually to avoid adverse pain and muscle spasm. Participants could be recommended to use a pay-as-you-go gym as an option. Conducting a retrospective study to seek the experiences of patients (who received usual care classes only) regarding gym exercise might be essential to help other patients. As mentioned earlier, weekly phone contact may not be useful for larger samples but other methods

could be used to record the participants' exercise compliance such as training diaries (Lambert et al., 2017). Training diaries could be used to record Training diaries will be used to record exercise compliance, adverse events, muscle soreness, and any changes to exercise, diet or medications (Lambert et al., 2017).

Some further modifications in the dietary intervention need to be taken into account in the preliminary study, such as food preferences and avoiding introducing new types of food when developing diet plans, with respect to participants' income. These considerations would help to save the clinical dietician time and effort by minimising the need for consultations over the phone.

Some factors that may affect programme implementation were reported, such as cold weather, as participants noticed their movement was more restricted on cold days. Time of year was also mentioned as a factor that may interfere with a combined programme's delivery and outcomes; for example, participants may experience some difficulty in sticking to a diet during special occasions/holiday times. Other factors were raised as facilitators to combined programme adherence, such as weekly phone contact, family support, physiotherapy support, internal belief in the outcomes, social interaction and group exercise. This may be interpreted as knee OA patients needing support, as chronic pain and disability can cause mental disorders, such as stress perception and depression (Jung et al., 2018). A recent RCT conducted in Australia for knee OA patients found that communicating with patients using a phone to provide advice and care (Telerehabilitation) could improve their self-management of the disease (Lawford et al., 2018). Physiotherapists who introduced Telerehabilitation were trained in behaviour change support and communication skills to provide advice and prescribe, monitor, and progress a strengthening exercise programme which involves 5-10 calls over 6 months (Hinman et al., 2017; Lawford et al., 2018). Semi-

structured individual interviews with participants (n=20) who received exercise advice and support from physiotherapists showed acceptance of the service and positive perceptions of the intervention (Lawford et al., 2018). Generally, such services were not considered an alternative to face-to-face physiotherapy, but rather as a new option that could increase access to physiotherapy services, particularly for follow-up consultations (Lawford et al., 2018). The same concept of delivering advice and care by telephone was applied previously in the UK. Adults (aged ≥ 18 years) with musculoskeletal problems were randomised into a PhysioDirect group (in which physiotherapists assess patients initially by telephone and provide advice) and a usual care group (face-to-face sessions) (Salisbury et al., 2014). The results demonstrated no difference between groups in clinical outcomes. PhysioDirect allowed patients to access physiotherapy services faster. However, results regarding patient satisfaction were also limited, as only patients who contacted the physiotherapists completed the SF-36 (Salisbury et al., 2014).

Exercise environment, gym preferences, personal preferences and movement level were mentioned as facilitators to exercise compliance. For patients with knee and hip OA, patient preference is important to consider when setting treatment goals (e.g., pain relief or functional improvement) and selecting the most appropriate exercise (Goh et al., 2018). Exercise characteristics, such as being achievable, enjoyable and pain-free, were specified as facilitators to exercise adherence in this DRPA study. These aspects had already been recommended by a recent review, which emphasised that exercise needs to be tailored and targeted to individual patients and aquatic exercise needs to be considered when land-based exercise cannot be achieved due to pain (Skou et al., 2018). In addition, exercise intensity needs to be built gradually and this is consistent with the findings of a recent SR and meta-analysis which found the use of behavioural graded exercise in high-quality trials improved

adherence in people with lower limb OA among adults ≥ 45 years of age (Nicolson et al., 2017). However, most of these factors have been mentioned previously as components to be considered when prescribing exercise for patients, including age, pain severity or disability and comorbidity, self-motivation, and the availability of local facilities, as the individual needs of the patient are essential to ensure effective participation in exercise (NICE, 2014).

Other factors were reported by the participants as barriers to adherence, included a misunderstanding of exercise, financial level and timing of the programme. A scoping review was conducted to identify modifiable barriers and facilitators to participating in exercise among patients with knee and hip OA and highlighted similar findings to the DRPA study. It was found that lack of knowledge and inadequate instructions were identified as barriers to exercise, in addition to participants' ability to access facilities, such as transportation and cost and, in these situations, clinicians have an important role in helping their patients to overcome these barriers (Dobson et al., 2016). Social influence is another barrier that was raised in the DRPA study and could not be avoided, such as family illnesses/circumstances and social commitments. Interestingly, these were reported in the scoping review, as family commitments and lack of family support are barriers to exercise (Dobson et al., 2016). However, providing patients with education programmes aimed at promoting self-management and providing peer support can prepare and help these patients to deal with such challenges (Stenberg et al., 2016). The combined programme followed the guidelines for patients with OA which were systematically reviewed by Nelson et al. (2014), which stated that patients should be educated and engaged in a self-management programme, exercise and to lose weight if overweight.

Conclusions

This study was conducted to evaluate the feasibility and practicality of a combined intervention programme of diet and exercise for obese middle-aged and older adults with knee OA in the UK. A mixed methods approach was applied to collect preliminary data. Integration of qualitative and quantitative data provided a deeper insight into the study findings. The recruitment, attrition and adherence rate plus the evaluation of the success criteria showed that the combined programme was not feasible based on the recruitment strategy, sample characteristics, delivered study design and setting. However, despite the very low number of participants who completed the 16-week intervention, participants reported positive benefits of the combined programme and were satisfied with its outcomes. The involved physiotherapy staff recommended the programme but with additional amendments. Furthermore, some theoretical and clinical implications were drawn from the findings of this study for future research and clinical practice, despite the low number of participants. Considerations of the optimal components of exercise and dietary interventions in terms of type, duration and quantity suitable for overweight/obese patients with knee OA were addressed by gathering and analysing detailed information. Importantly, losing 5%-10% of total body weight within 4 months is achievable within this population and leads to functional, social and QoL improvement. A future feasibility study is required, taking into account the findings and limitations of the current study, as well as the suggestions of both the participants and the PT staff involved.

SUMMARY OF THE THESIS

As stated in the introduction of this thesis (Chapter 1), knee OA is the most frequent cause of chronic pain and disability among older adults. It is known that obesity is a risk factor for knee OA development. In addition, being overweight or obese is considered an accelerator factor of disease progression due to the alternation of body weight distribution, which adds mechanical stress to the weight-bearing joints and leads to cartilage destruction. Considering the adverse effects of drug therapy and surgical interventions, overweight/obese people with knee OA are recommended to exercise and diet as the safest way to improve symptoms. Weight loss plays a role in reducing joint loading and inflammation and thereby improves clinical outcomes.

A preliminary search was carried out to identify the effect of a combined intervention programme among clinical studies and results showed that there were no SRs synthesising the effectiveness of combining physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese older adults with knee OA. Hence, a protocol for a SR was developed that followed the Preferred Reporting Items for SRs and Meta-Analyses guidelines and the Cochrane Handbook. A mixed methods analytical approach was used to synthesise the findings and GRADE was used to assess the quality of the trials included (Chapter 2). Only a few studies, conducted by the same group in the USA, were identified as eligible. The quality of the evidence included was not clear, nor was optimal exercise and diet in terms of type, quantity and duration. Furthermore, in spite of clinical recommendations for exercise and diet for people with knee OA, there are no published UK studies reporting the efficacy of a combined intervention programme on the musculoskeletal function within this population.

The findings of the SR informed the development of a mixed methods study protocol that was designed to provide detailed information about a combined intervention programme (Chapter 3). This protocol was also informed by PPI and feedback from health care professionals. Participants received a usual care programme for knee OA for 4 months (four sessions at a PT gym for 1 month and 12 sessions at a local gym/leisure facility for 3 months). They also followed dietary restrictions throughout the 4-month intervention.

Mixed analysis techniques were used to analyse the quantitative and qualitative outcome measures. Outcomes across several domains were measured, including biomarkers for knee OA, to inform the selection of appropriate outcome measures for future study.

The findings of each method (qualitative and quantitative) were analysed and supported by the results of the other, using a triangulation technique (Chapter 4). During the 4 months of the intervention, losing 5%-10% of total body weight was found to be possible within this population and could lead to functional, social and QoL improvement. Positive feedback was reported by all participants who completed the intervention and the physiotherapy staff who participated in this intervention recruitment and delivery.

The combined intervention programme was found to be practical and recommended by both the physiotherapy staff involved and the participants (Chapter 5). Despite the low number of participants, a number of theoretical and clinical implications were drawn from the results of this study for a future trial, including optimal components of exercise and dietary interventions based on the reports of obese patients with knee OA. A number of facilitators and barriers to the combined programme were raised which would inform the implementation of a future trial. Conducting a future trial is required that considers the

findings and limitations of the current study, as well as suggestions from both the participants and the PT staff involved.

In summary, the work reported in this thesis has added to the body of knowledge of the influence of a combined programme of dietary restriction and exercise on the musculoskeletal function of obese older adults with knee OA and has laid the foundation for future trials within a UK health care setting to intervene to maintain or improve musculoskeletal health in this population.

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APPENDICES

APPENDIX 2.1 PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSIS (PRISMA) CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	44
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	81-82
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	46-48
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	48
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	48
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	49
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	49
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	50

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	52
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	52
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	52
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	52
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	53
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	53-54
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	53
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	55
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	56-59
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	59, 62-64
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	67
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	68
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	68-71

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	67
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	71-72
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	73-80
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	80
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	80
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

APPENDIX 2.2 INCLUDED AND EXCLUDED STUDIES GENERATED BY THE FIRST SEARCH UP TO 10 DECEMBER 2015

	Study	Reviewer judgment (Include, Exclude, Unsure)	Why	2 nd Reviewer judgment (Include, Exclude, Unsure)	Why
1-	Messier, 2000	Included		Unsure	Pilot study. Should be excluded if the sample has been included in the analysis of Messier (2004), Rejesky (2002), Focht (2005)
2-	Miller, 2003				<i>Didn't read full text, abstract states that only baseline data are reported. It is the ADAPT design and rational.</i>
3-	Rejeski, 2002	Included		Incl	Yes- outcomes different than other publications of same trial
4-	Messier, 2004	Included		Included in part	some outcomes same as Messier 2004 (i.e. mobility and pain)
5-	Nicklas, 2004	Unsure	ADAPT× (Biomarkers)		Didn't go through full text cause abstract states chronic inflammatory markers as the only outcomes
6-	Miller, 2004	Unsure	ADAPT× (Serum lipid)	excl	No- outcomes different than the ones you are interested in
7-	Messier, 2005	Unsure	ADAPT× (Joint moments)		
8-	Focht, 2005	Included		Included in part	some outcomes same as Messier 2004 (i.e. mobility and pain)
9-	Nicklas, 2005	Exclude	× (Physical disability+ DNA)		
10-	VanGool, 2005	Unsure	× (Exercise adherence)	Excl	No- different objective/ focus (effect of ex adherence on change in walking distance and disability)
11-	VanGol, 2006	Unsure	× (Determinates of adherence)		Didn't go through full text- determinants of adherence is different subject
12-	Chua, 2008	Unsure	× (Serum biomarkers)		ADAPT, but outcomes different than the ones you are interested in. didn't go through full text
13-	Shea, 2009	Unsure	× (Randomisation)		ADAPT, but outcomes different than the ones you are interested in. didn't go through full text
14-	Messier, 2011	Unsure	× (Muscle force)		<i>I didn't read the full text of this one cause in the abstract it is stated that it's a dietary (in contrast to dietary plus exercise) intervention. Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis</i>
15-	Sevick, 2009	Exclude	× (Cost of intervention)	Excl	No- diff. diagnostic criteria (knee pain)
16-	Miller, 2006	Unsure		Unsure	"symptomatic kOA" as inclusion criteria- need to contact authors for availability of radiographic evidence
17-	Miller, 2008	Exclude	× (Inflammatory biomarkers)	Unsure	"knee pain and self-reported physician diagnosed kOA"- need to contact authors for availability of radiographic evidence
18-	Miller, 2012	Exclude	× (Adipokine)	Excl	No- no radiographic evidence for participant selection

19-	Wang, 2007	Exclude	× (Knee strength)	Excl	No- diff diagnostic criteria (knee pain)
20-	Messier, 2009		!!!!!!! (Study protocol + some results!!)	Excl	IDEA Trial protocol
21-	Messier, 2011		√ (knee joint loads, inflammation and clinical outcomes)	Excl	No- subset of the ADAPT sample, outcome: gait analysis
22-	Beavers, 2014	Exclude	× Bone density	excl	Different outcomes (bone mineral density)
	Jenkinson, 2009	Exclude	(Age>45)	excl	different age group (45. plus no x-ray available)
24-	Jae-young, 2010	Exclude	(Age>50+ exercise only)		Exercise only, didn't go through full text
25-	Messier, 2010	Exclude	Review	excl	review
26-	Huang, 2000	Exclude	(Non-randomised)	excl	Age from 40 years
27-	Teda, 2001	Exclude	(Non-randomised+ age)		
28-	Cheon, 2005	Exclude	(FT in Korean)	Excl	No- not in English
29-	Martin, 2001	Exclude	(Pilot+ age 49-73)		
30-	Atukorala, 2014	Exclude	(FT Not available)		
31-	Messier, 2013	Included		Incl	

APPENDIX 2.3 EFFECT OF PHYSICAL ACTIVITY AND DIETARY RESTRICTION INTERVENTIONS ON WEIGHT LOSS AND THE MUSCULOSKELETAL FUNCTION OF OVERWEIGHT AND OBESE OLDER ADULTS WITH KNEE OSTEOARTHRITIS: A SYSTEMATIC REVIEW AND MIXED METHODS DATA SYNTHESIS

Open Access

Research

BMJ Open Effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese older adults with knee osteoarthritis: a systematic review and mixed method data synthesis

Asma S Alrushud,^{1,2} Alison B Rushton,^{1,3} Archontissa M Kanavaki,^{1,3} Carolyn A Greig^{1,3}

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¹School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK

²Department of Health Rehabilitation Sciences, King Saud University, Riyadh, Saudi Arabia

³MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Birmingham, Birmingham, UK

Correspondence to
Asma S Alrushud; asa314@student.bham.ac.uk

ABSTRACT

Background Despite the clinical recommendation of exercise and diet for people with knee osteoarthritis (OA), there are no systematic reviews synthesising the effectiveness of combining physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese older adults with knee OA.

Objective To evaluate the effectiveness of combined physical activity and dietary restriction programmes on body weight, body mass index (BMI) and the musculoskeletal function of overweight and obese older adults with knee OA.

Information sources A detailed search strategy was applied to key electronic databases (Ovid, Embase, Web of Science and Cumulative Index to Nursing and Allied Health Literature (CINAHL)) for randomised controlled trials (RCTs) published in English prior to 15 January 2017.

Participants Participants with BMI ≥ 25 kg/m², aged ≥ 55 years of age and with radiographic evidence of knee OA.

Interventions Physical activity plus dietary restriction programmes with usual care or exercise as the comparators.

Outcome measures Primary outcome measures were body weight, BMI or musculoskeletal function. Secondary outcome measures were pain and quality of life.

Results One pilot and two definitive trials with n=794 participants were included. Two articles reporting additional data and outcome measures for one of the RCTs were identified. All included RCTs had an unclear risk of bias. Meta-analysis was only possible to evaluate mobility (6 min walk test) at 6 months and the pooled random effect 15.05 (95% CI -11.77 to 41.87) across two trials with n=155 participants did not support the combined intervention programme. Narrative synthesis showed clear differences in favour of a reduced body weight and an increased 6 min walk in the intervention group compared with control groups.

Conclusion The quality of evidence of benefit of combining exercise and dietary interventions in older overweight/obese adults with knee OA is unclear.

Strengths and limitations of this study

- This is the first systematic review of combined physical activity and dietary restriction interventions in overweight and obese older adults with knee osteoarthritis.
- The protocol of this review was registered in PROSPERO and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Cochrane handbook; Grading of Recommendation, Assessment, Development and Evaluation was used to evaluate the quality of the included trials.
- The review included a mixed method analytical approach.
- Few eligible studies were identified; however, important information is highlighted which could inform clinical practice.

Trail registration number CRD42015019088 and ISRCTN, ISRCTN12906938.

INTRODUCTION

Rationale

Current evidence shows that the burden of chronic musculoskeletal conditions especially osteoarthritis (OA) increases with advancing age.¹ OA is the most common type of arthritis affecting older adults. It is a degenerative joint disease that may affect any joint within the body causing chronic pain, functional limitation and emotional disturbance and may lead to disability and negatively affect quality of life (QOL).²⁻⁵ Knee OA is a common condition in older adults affecting about 3.64% of the global population in 2010.^{6,7} In the UK, there is approximately 4.7 million older adults aged 45 years or over experiencing

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knee OA symptoms.^{1,8} In addition, more than 20 million people seek treatment for knee OA in the USA.^{9,10} Given the increasing numbers of older adults in the population, combined with the increasing prevalence of obesity and being overweight throughout the population, it is anticipated that the incidence of knee OA will increase rapidly over the next decade.⁸

Unfortunately, there is no specific treatment for knee OA. Most recommendations describe three treatment modalities: non-pharmacological, pharmacological and surgical.^{11,12} Most knee OA evidence-based guidelines recommend non-surgical treatment^{13,14} and most general practitioners prefer the non-pharmacological and non-surgical interventions as the first line of treatment (recognised as 'usual care').¹¹ These interventions are focused on patient education, self-management, pain reduction, function and QOL improvement, body weight reduction and exercise (either land-based or water-based).^{14–17} It is well known that obesity is an important risk factor for knee OA progression and several studies recommend obesity control for decreasing disease burden, since a decrease in body weight will lead to a reduction of joint load and inflammation.^{3,14,17,18} Weight reduction could be considered as a functional treatment in knee OA rehabilitation since a 12%–15% reduction compared with initial body weight has been shown to improve function and reduce pain.¹⁹ Moreover, the appropriate percentage of body weight reduction has been investigated in a systematic review and meta-analysis of five randomised controlled trials (RCTs).²⁰ The review concluded that professional treatment of knee OA should include a weight reduction plan and patients should be encouraged to lose at least 5% of body weight over a 20-week period to achieve symptomatic relief.²⁰

In addition to weight reduction, clinical guidelines for knee OA management and level 1 evidence recommend exercise therapy as the main intervention.^{20–24} Moderate intensity aerobic exercise (eg, walking) is recommended to maintain musculoskeletal function and reduce pain.^{20–22} However, the optimal exercise prescription for older adults is still unclear and further research is required.⁷ The demand for optimal exercise is increased in patients with obesity who may face more challenges and believe in the greater importance of physical activity compared with dietary intervention.^{25,26}

Clinically combining a weight loss programme with exercise therapy may help overweight and obese older adults with knee OA to achieve a 10% loss of total body weight as well as safely relieve knee OA symptoms.³ Also, a recent RCT which included older adults has shown that a non-surgical treatment programme had longer-lasting beneficial effects, evidenced by a delayed requirement for elective total knee replacement (TKR) surgery in a secondary healthcare setting.²⁷ Moreover, for those who are eligible for unilateral TKR, non-surgical intervention may delay their surgical intervention for several months.²⁸ There are no systematic literature reviews synthesising the evidence of the effectiveness of

combining physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese older adults with knee OA.

The aim of this review was to evaluate the effectiveness of combined physical activity and dietary restriction programmes on the musculoskeletal function of overweight and obese older adults with body mass index (BMI) ≥ 25 kg/m², aged ≥ 55 years of age and with radiographic evidence of knee OA.

Objective

To evaluate the effectiveness of combined physical activity and dietary restriction programmes on body weight, BMI and the musculoskeletal function of overweight and obese older adults with knee OA.

METHODS

Protocol and registration

A systematic review was conducted according to a predefined protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P guidelines²⁹ and the Cochrane handbook.³⁰ The review was registered on PROSPERO on 01 April 2015 (CRD42015019088), and is reported in accordance with the PRISMA statement (see online supplementary data).²⁹

Eligibility criteria

Inclusion criteria

- ▶ Older adults (aged ≥ 55 years, men and women).
- ▶ Overweight or obese with BMI ≥ 25 kg/m².³
- ▶ Radiographic evidence of tibiofemoral OA (unilateral or bilateral), grade I–III (mild to moderate) according to the Kellgren and Lawrence system for knee OA classification.³¹

Exclusion criteria

- ▶ Full article not written in English.

Studies

Randomised controlled trials.

Interventions

Combined physical activity and dietary restriction programmes.

Comparators

Usual care (including advice or physical activity alone or dietary restriction alone) or exercise (participants received an exercise programme similar to the intervention group).

Outcome measures

Primary outcome measures: body weight, BMI, musculoskeletal function either self-reported function or objective functional performance measures, also, including mobility, joint range of motion (ROM) and muscle strength.

Secondary outcome measures: pain and QOL.

Table 1 Example of Medline Ovid search strategy 1948 to 10 December 2015

#	Searches
1	Physical activity/
2	Physical* adj2 (activity or training or therapy*)
3	(Exercis* or rehabilitation* or treatment*)
4	(Closed kinetic chain* or open kinetic chain* or isokinetic* or isometric* or anaerobic* or muscle* or stretching* or aerobic* or isotonic* or treadmill* or endurance* or walking*) adj1 (exercise*)
5	(Resist* adj2 (exercise* or therapy or training))
6	1 or 2 or 3 or 4 or 5
7	Dietary restriction. mp.
8	Meal replacement.mp.
9	Weight loss/ or weight loss.mp. or intentional weight loss.mp.
10	Caloric Restriction/ or Obesity/ or Body Weight/ or hypo or hypochloric diet/
11	Energy intake/ or adipos*/ or Body Mass Index/ or Overweight/
12	Diet/ or Diet, Carbohydrate-Restricted/ or Diet, Reducing/ or Diet Therapy/ or Diet, Vegetarian/
13	Obesity/ or obesity.mp.
14	((Low carbohydrate* or low calor* or low fat* or vegetarian*) adj1 (diet*))
15	(Diet adj2 (therapy* or treatment*))
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	Aging/
18	Exp aged/
19	(55 adj2 (year* or age* or old*))
20	(old* adj (adult* or people or person* or population* or men or women))
21	(aging* adj (adult* or people or person* or population* or men or women))
22	(elder* or senior* or geriatric* ?enarian or ageing)
23	(age* or aging or old* or elder*) adj1 (musc*)
24	17 or 18 or 19 or 20 or 21 or 22 or 23
25	Pain/ or Knee Joint/ or Knee pain.mp. or Osteoarthritis, knee/
26	Knee osteoarthritis.mp. or Osteoarthritis, knee/
27	(Knee* adj (arthritis or osteoarthritis* or inflammation* or degeneration* or disease or pain*))
28	(radiographic* or symptomatic* or clinical* adj1 (knee osteoarthritis*))
29	25 or 26 or 27 or 28
30	Musculoskeletal function. mp.
31	Muscle function. mp.
32	Body composition/
33	Mobility.mp.
34	(Gait or walking) adj1 (speed)
35	Functional ability.mp.
36	'Activity of daily' living/ or. mp.
37	'Quality of life'/
38	Balance.mp.
39	(musculoskeletal adj2(pain or disorder*))
40	(Musc* adj (power or strength or performance or function or weakness))
41	41. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42	6 and 16 and 24 and 29 and 41

Information sources

The search employed sensitive, topic-based strategies designed for each database (to 10 December 2015):

- ▶ The Cochrane Library: Controlled Trials Register, NHS Economic Evaluation Database.
- ▶ Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Medline, Web of Science.
- ▶ Hand searches in key journals and lists of references.
- ▶ Unpublished research and grey literature such as Open Grey.
- ▶ Government, official, organisational such as UK Department of Health, WHO and National Health Service (UK).
- ▶ Clinical trials registration, theses abstracts and Google scholar.

Search

Search strategies of predefined search terms were developed and tested for applicability (ASA, and a specialist librarian from the University of Birmingham on 13 February 2015). The definitive search strategy was run by two independent researchers (ASA/AMK, 10 December 2015). Endnote X7 software was used for data management. Search results were imported and duplicates were removed. An example of the Medline Ovid search strategy is presented in table 1. The search was updated on 15 January 2017 to include studies published in 2016 by ASA/AMK and no eligible studies were identified.

Study selection

The eligibility of included studies was independently assessed by two reviewers (ASA/AMK) according to the eligibility criteria. The reviewers screened the results of the search by titles and abstracts, and then full text. A study was considered to be eligible when both reviewers assessed the full text independently and found it to fulfil the eligibility criteria. A third reviewer (CAG) mediated in the case of disagreement. The inter-rater agreement was evaluated using Cohen's Kappa measure.³²

Data collection

Using a standardised form (developed by ASA) based on the Cochrane Consumers and Communication Review Group's data extraction template,³³ two reviewers (ASA/AMK) extracted data independently. A third reviewer (CAG) checked for consistency and clarity.

Data items

Items reported on the data extraction form for each trial included demographic information, methodology, intervention details and all specified reported outcomes.

Risk of bias in individual trials

The internal validity of each included trial was assessed using the Cochrane risk of bias assessment tool³⁴ recommended by PRISMA.²⁹ All domains of the risk of bias

tool were assessed independently by two reviewers (ASA/CAG). A third reviewer (ABR) mediated in the case of disagreement.

Risk of bias across trials

Risk of bias was considered high if the proportion of information from trials with high risk of bias was sufficient to affect the interpretation of the results. Risk of bias was considered unclear if most information was from studies with a low or unclear risk of bias, and low if most information was from studies with a low risk of bias.³⁴

Summary measures

Following data extraction, meta-analysis was possible for one key outcome measure across trials that applied similar interventions and compared with exercise at one assessment time-point (6 months). Meta-analysis was conducted using RevMan to assess the effectiveness of a combined intervention programme of diet and exercise on mobility (6 min walk test at 6 months) using the random effects model.^{35 36} Ninety-five per cent CIs were reported for the summary statistics and the SD was calculated from the SEs and CIs.^{37 38} Data for the other outcomes were available, but meta-analyses were not possible due to different assessment points or comparators. A modified narrative synthesis was used to present these data.^{39 40}

Synthesis of results

A mixed method analysis was required to synthesise the available data.^{35–40} For the meta-analysis, no raw data were available, and therefore data analyses were conducted on the final summary statistics reports. SDs were estimated from reported SE and CI for all available data.³⁶ Heterogeneity in treatment effects was considered by computation of I^2 . An analysis of the quality of the interventions was undertaken as the basis for interpretation of heterogeneity.^{36 37} For the modified narrative synthesis, change scores were used for trials when no other data were available.^{36–38} Two stages of a narrative synthesis were possible to apply; these comprised the development of a preliminary synthesis of findings of included trials, and an exploration of the relationships within and between trials.^{39 40}

Developing a preliminary synthesis

A preliminary synthesis was developed using tabulation, textual description, grouping and clusters and data transformation. Tables were designed presenting the main characteristics of the eligible studies including eligibility criteria, intervention (number of participants, goal of weight loss, intervention period, setting and brief information about exercise and diet intervention), comparator, outcome measures and the main findings. Additional tables were used to organise studies with respect to specific outcome measures (primary or secondary) and the comparator group. Results were presented as mean (SD) by converting the continuous data from SEs or CIs to SD.^{39 40}

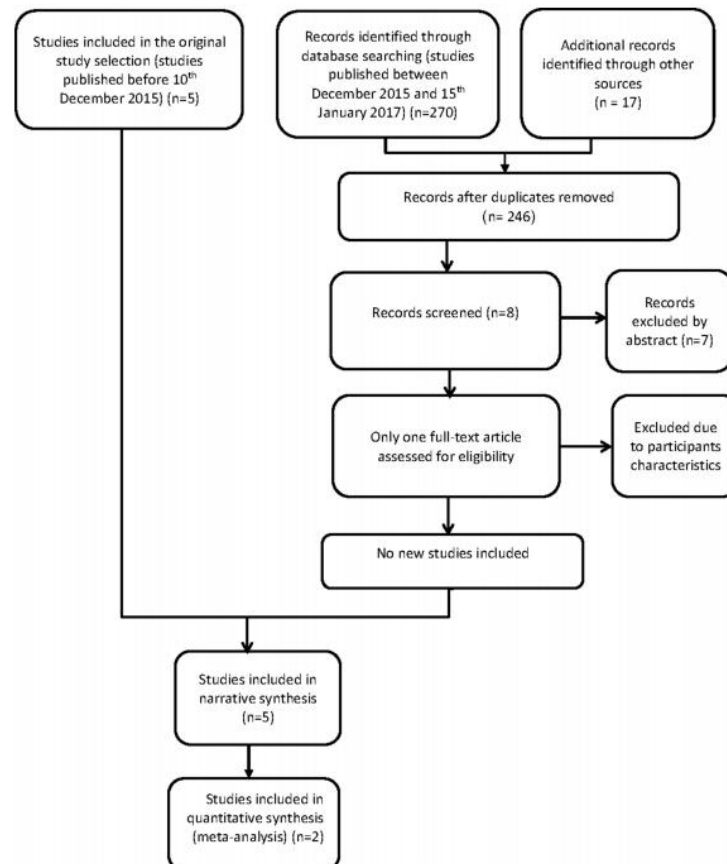


Figure 1 Study selection flow diagram.⁴⁸

Exploring the relationships within and between trials

A visual representation of the relationship between study characteristics and results was used to explore the relationships within and between trials.^{39 40}

Additional analyses

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence included in the meta-analysis.^{41 42} Specific software (GRADEpro) was used.⁴³ This approach provided a system for rating the quality of evidence and determining the strength of recommendations for clinical practice guidelines.^{41 42} It has five components: risk of bias, inconsistency, indirectness, imprecision and publication bias. Quality of evidence was categorised as 'high', 'moderate', 'low' and 'very low'.^{41 42} Each RCT evaluated as 'high' quality evidence was modified according to five negative and two positive factors.^{41 42}

The Cochrane risk of bias assessment tool was used for this component.³⁴ According to the software, risk of bias was classified as not serious, serious or very serious. The quality of evidence was downgraded by one level if there was a serious limitation or by two levels if the limitation was very serious.^{41 42} Inconsistency was evaluated according to I^2 statistics. It may be considered low if $I^2 < 40\%$, moderate if $I^2 = 30\% - 60\%$, substantial if $I^2 = 50\% - 90\%$ and considerable if $I^2 = 75\% - 100\%$.⁴² Inconsistency was considered as unserious if the reviewers were able to identify a plausible explanation for the heterogeneity and the quality of evidence was not downgraded.⁴² Otherwise, the quality of evidence was downgraded by one or two levels if inconsistency of the results was classified as serious or very serious.⁴² The quality of evidence was downgraded by one or two levels if there was indirectness between the study question and the applicability of the evidence.⁴¹

Imprecision of evidence was downgraded in the presence of the following conditions: first, when the boundaries of the CI crossed the no effect line (threshold is completely within the recommended effect) and second, when the criteria for optimal information size (OIS) were not met.⁴² The criterion for OIS was that the total number of participants included in a systematic review (calculated from a meta-analysis) was less than the number of participants generated by a conventional sample size calculation for a single adequately powered trial. Imprecision was downgraded by one level if one of these conditions was not met or by two levels if both conditions were not met.^{41 42}

Publication of bias was undetectable or strongly suspected according to GRADE software.⁴³ The selective outcome reporting domain of the Cochrane risk of bias assessment tool was used to evaluate the publication bias.^{34 42} The quality of evidence was downgraded by one level if the selective outcome reporting domain was evaluated as unclear without justification or downgraded by two levels if evaluated as high.⁴²

RESULTS

Study selection

Three RCTs (n=794) were included. One was a pilot trial⁴⁴ and two were definitive trials: the Arthritis, Diet and Activity Promotion Trial (ADAPT)⁴⁵ and the Intensive Diet and Exercise for Arthritis (IDEA).³ For the ADAPT, there was a main trial report, and two additional articles with further analyses of additional outcome measures.^{46 47} The trials used two comparators: an exercise programme in the pilot study and IDEA trial,^{3 44} while usual care (healthy lifestyle) was the comparator in ADAPT.⁴⁵ All of the included trials were conducted by the same group from the USA and published in English. No relevant unpublished studies were identified. The inter-rater agreement of the study selection process was excellent with $k=0.82$.³² There was one disagreement requiring consultation with the third reviewer (CAG), who was asked to clarify the eligibility of articles reporting the same trials. Specifically, one pilot study by Messier *et al*^{44 44} did not clarify whether it was an external or internal pilot study. The senior author was contacted twice but no response was received. The third reviewer recommended it be treated as an external pilot study as there was nothing to indicate it was an internal pilot study in the article reporting the main trial.⁴⁵ The study flow diagram is presented in figure 1.⁴⁸

Study characteristics

The main characteristics of the included trials are presented in table 2.

Methods

In the pilot trial by Messier *et al*,⁴⁴ participants were randomised into two groups, a combined intervention and control group.⁴⁴ The control group received an exercise programme similar to the intervention group. Messier *et*

*al*⁴⁵ randomised participants into four groups: combined intervention, exercise, diet and a control group. The control group received health education plus telephone contact to obtain information on pain, medication use, illness and hospitalisation.⁴⁵ Messier *et al*³ randomised participants into three groups: combined intervention, diet group and exercise group. The exercise-alone group was the control. Duration of the trial was 6 months for the pilot trial⁴⁴ and 18 months for ADAPT⁴⁵ and IDEA.³

Participants

All participants were community dwelling, obese older adults with radiographic evidence of knee OA. A total of 794 participants aged 55 years or older were randomised into the included studies. One hundred and fifty-five participants were included in the meta-analysis.

Interventions

The pilot trial⁴⁴ and two definitive trials^{3 45} were conducted by the same group from Wake Forest University, Winston-Salem, North Carolina, USA. The goal of weight loss varied from 6.8 kg over 6 months to 10%–15% of total body weight over 18 months of intervention. Outcomes were recorded at three time-points for the pilot trial (baseline, 3 months and 6 months) and for the two definitive trials (baseline, 6 months and 18 months). Exercise duration and frequency were similar in all included trials (1 hour/three times per week). Exercise types were aerobic exercise and resistance training. Principles from group dynamics and social-cognitive theory were used for behavioural treatment in the diet group in IDEA.³ The diet sessions were graded from intensive (facilitating behavioural changes by using self-regulatory skills) to transition stage (assisting participants who not reached their weight loss goals in establishing new goals) and maintenance stage (assisting patients who had reached their weight loss goals to maintenance of their weight loss). For the intensive weight loss trial, the daily caloric intake was adjusted according to the rate of weight change between intervention visits (low fat and high vegetable diet). The initial diet plan provided an energy-intake deficit of 800–1000 kcal/day, as predicted by an energy expenditure (estimated resting metabolism $\times$ 1.2 activity factor), of at least 1200 kcal for men and 1100 kcal for women.³

Outcome measures

Due to few eligible studies, analysis was based on all of the outcomes of interest (body weight and BMI as well as musculoskeletal function), irrespective of whether they were specified as the primary or secondary outcome in the included trials (see below):

Messier *et al*⁴⁴: no primary or secondary outcomes were specified.

Messier *et al*⁴⁵: the ADAPT primary outcome was self-reported physical function measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcomes included weight loss,

Table 2 Descriptive data for the included trials

Title/author/ year	Aim	Eligibility criteria	Methods	Comparator	Outcome measures	Assessment points	Result
Exercise and weight loss in obese older adults with knee OA: a preliminary study. Messier <i>et al</i> (2000) ⁴⁴	1) To determine if a combined dietary and exercise intervention results in significant weight loss in older obese adults with knee OA 2) To compare the effects of exercise plus dietary therapy with exercise alone on gait, strength, knee pain, biomarkers of cartilage degradation and physical function	Inclusion Aged ≥60 years BMI ≥28 kg/m ² Knee pain, radiographic evidence of knee OA Self-reported physical disability Exclusion Serious medical condition affecting safety Planned change of residence or admission to a nursing home within next 6 months Unable to walk at least 420 ft in 6 min Unable to walk on treadmill without assistive device Current participation in an exercise programme or other study Unable to participate or complete the study protocol	Participants n=24 community-dwelling obese older adults Goal of weight loss 15 lb (6.8 kg) Period of intervention 6 months Setting University Health and Exercise Science Centre, USA Exercise Combined weight training and walking programme for 1 hour three times per week Dietary intervention Nutrition class 1 hour/week to instruct participants how to modify caloric intake using cognitive behaviour modification to change dietary habits to reach a group goal of an average weight loss then three group and one individual session held per month	Exercise group (control)	Body weight, self-report questionnaire, physical performance and gait analysis Synovial fluid biomarkers (total proteoglycan (PG), keratan sulfate (KS) and interleukin-1β (IL-1β)) Frequency and intensity of knee pain (Likert scale) Disability by self-reported physical function using the Fitness Arthritis and Seniors Trial 6 min walk test and timed stair climbing to measure physical performance Kinetics and kinematics analysis of gait using motion analysis and force plate recorded at 3 and 6 months	Data recorded at baseline, 3 and 6 months	Body weight reduced significantly in diet plus exercise group compared with exercise group with (p=0.007) Within group differences: The combined intervention group lost a mean of 18.8 lb (8.5 kg) at 6 months compared with 4.0 lb (1.8 kg) in the exercise group (p=0.01) No statistical differences were found between groups in self-reported performance measures of physical function and knee strength Statistically significant improvement in both groups in self-reported disability and knee pain intensity and frequency and physical performance At 6 months, the combined intervention group had a significantly greater loading rate (p=0.03) and maximum braking force (p=0.01) during gait No statistical differences were found between groups in knee pain scores Concentration level of KS decreased similarly in both groups. The decrease in IL-1 correlated with joint pain (r=-0.77, p=0.043)

Continued

Table 2 Continued

Title/author/ year	Aim	Eligibility criteria	Methods	Comparator	Outcome measures	Assessment points	Result
Exercise and dietary weight loss in overweight and obese older adults with knee OA Messier <i>et al</i> (2004) ⁴⁵	1) To determine whether long-term exercise and dietary weight loss are more effective, either separately or in combination, than usual care in improving physical function, pain and mobility in older overweight and obese adults with knee OA	Inclusion Aged ≥60 years BMI ≥28 kg/m ² Knee pain, radiographic evidence of knee OA Self-reported physical disability Exclusion Serious medical problem Mini-Mental State Examination score of <24.3 Inability to finish 18 months study Inability to walk without assistive device Participation in another study 6-Reported alcohol consumption >14 drinks per week ST segment depression of at least 2 mm at an exercise level of 4 metabolic equivalent tasks (METs) or less, hypotension or complex arrhythmia during exercise Inability to complete the study protocol due to frailty, illness or other reason	Participants n=316 community-dwelling obese older adults Goal of weight loss 5% of the total body weight over 18 months Period of intervention 18 months Setting The Claude D Pepper Older Americans Independence Centre, Wake Forest University, USA Exercise 1 hour 3 days/week consisted of an aerobic phase, a resistance-training phase, a second aerobic phase and a cool-down phase Dietary intervention Based on principles from the group dynamics literature and social cognitive theory; divided into three phases: intensive (months 1–4), transition (months 5–6) and maintenance (months 7–18) Dietary weight loss plus exercise Combined the exercise and dietary weight loss programmes	Usual care healthy lifestyle (control) Exercise group Dietary weight loss group	Primary outcome Self-reported physical function using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Secondary outcomes Weight loss, 6 min walk distance, stair-climb time, WOMAC pain and stiffness scores and joint space width	Data recorded at baseline, 6 and 18 months	Significant body weight loss in diet groups ($p<0.05$). Diet plus exercise and diet group lost an average of 5.7% and 4.9% of their body weight, respectively with 1.2% for the healthy lifestyle group Significant improvements in self-reported physical function ($p<0.05$), 6 min walk distance ($p<0.05$), stair-climb time ($p<0.05$) and knee pain ($p<0.05$) in the diet plus exercise group compared with the healthy lifestyle group Significant improvement in the 6 min walk distance in the exercise group ($p<0.05$). The diet-only group was not significantly different from the healthy lifestyle group with respect to any of the functional or mobility measures Changes in joint space width were not significantly different between groups

Continued

Table 2 Continued

Title/author/ year	Aim	Eligibility criteria	Methods	Comparator	Outcome measures	Assessment points	Result
Effects of intensive diet and exercise on knee joint loads, inflammation and clinical outcomes among overweight and obese adults with knee OA is the intensive Diet and Exercise for Arthritis randomised clinical trial Messier <i>et al</i> (2013) ³	To determine whether a 10% reduction in body weight induced by diet, with or without exercise, would improve mechanistic and clinical outcomes more than exercise alone	Inclusion Aged ≥55 years Kellgren-Lawrence 1+ grade 2 or 3 (mild or moderate) radiographic tibiofemoral OA or tibiofemoral plus patellofemoral OA of one or both knees, pain on most days due to knee OA. BMI from 27 to 41 Sedentary lifestyle (<30min per week of formal exercise for the past 6 months) Participants usual medications could be maintained or adjusted depending on physician advice Exclusion Significant comorbid disease that would pose a safety threat or impair ability to participate, previous acute knee injury, patellofemoral OA in the absence of tibiofemoral OA Ability and willingness to modify dietary or exercise behaviours Excess alcohol use Inability to finish 18-month study or unlikely to be compliant Conditions that prohibit knee MRI Significant cognitive impairment or depression	Participants n=654 Goal of weight loss 10%–15% of the total body weight Period of intervention 18 months Setting Wake Forest University and Wake Forest School of Medicine, USA Intensive weight loss intervention The diet included up to two meal-replacement shakes per day For the third meal, participants followed a weekly menu plan and recipes that were 500–750 kcal, low in fat and high in vegetables. Daily caloric intake was adjusted according to the rate of weight change between intervention visits. The initial diet plan provided an energy-intake deficit of 800–1000 kcal/day as predicted by energy expenditure (estimated resting metabolism×1.2 activity factor) The exercise intervention was conducted for 1 hour on 3 days/week for 18 months Participation was centre-based for the first 9 months After 6-month follow-up testing and a 2-week transition phase, participants could remain in the facility programme, opt for a home-based programme or combine that two. The programme consisted of aerobic walking (15min), a second aerobic phase (15 min) and cool-down (10min)	Exercise group (control group) Dietary weight loss group	Primary outcomes knee joint compressive force and plasma IL-6 concentration Secondary clinical outcomes Self-reported pain (range 0–20), function (range 0–68), mobility and health-related quality of life	Participants were assessed at baseline, 6 and 18 months	Body weight was reduced significantly in both diet groups (diet and diet plus exercise) more than exercise group ($p<0.001$) Within group differences: the diet plus exercise group lost about 10.6kg (11.4%), the diet group lost 8.9kg (9.5%) and 1.8kg (2.0%) of base line body weight No significant difference in walking speed and 6 min walk test between groups Significant pain reduction was observed in the diet plus exercise group at 18 months compared with exercise group (mean score, 1.02; 95% CI 0.33 to 1.71; $p=0.004$) The difference in the SF-36 (36-Item short form survey) physical subscale score relative to diet plus exercise was 2.81 units in favour of diet plus exercise (95% CI 0.95 to 4.67; $p=0.005$) No significant difference in the mental subscale between groups

QA:osteoarthritis.

Table 3 Summary assessment of the overall risk of bias for each trial

Study (author, year)	Component of risk of bias						Summary risk of bias
	1	2	3	4	5	6	
Messier <i>et al</i> , 2000 ⁴⁴	U	U	U	U	L	U	Unclear (5) Low (1)
Rejeski <i>et al</i> , 2002 ⁴⁶	U	U	U	L	L	U	Unclear (4) Low (2)
Messier <i>et al</i> , 2004 ⁴⁵	L	U	U	L	L	U	Unclear (3) Low (3)
Focht <i>et al</i> , 2005 ⁴⁷	U	U	U	L	L	U	Unclear (4) Low (2)
Messier <i>et al</i> , 2013 ³	L	U	U	L	L	U	Unclear (3) Low (3)

6 min walk distance, stair-climb time, WOMAC pain and stiffness scores and joint space width.⁴⁵

Messier *et al*³ in the IDEA trial, the primary outcomes were knee joint compressive force and plasma interleukin (IL)-6 concentration. Secondary outcome measures included WOMAC pain, WOMAC function, gait speed, 6 min walk test, QOL, body weight, height, BMI and body composition.³

Risk of bias within trials

Substantial inter-reviewer agreement was achieved on the risk of bias assessment ($k=0.73$).³² All of the included trials were evaluated as unclear risk of bias.³⁴ Most of the key domains were assessed as unclear risk of bias within each trial (table 3).

Risk of bias across trials

Risk of bias across trials was evaluated as unclear,³⁴ only component 5 (selective outcome reporting) was evaluated as low risk of bias for all studies. For the 'blinding of participants, personnel and outcome assessor' component, all trials were evaluated as having unclear risk of bias as no strategies were reported to address the issue of outcome assessor unblinding. Also, for the 'other sources of bias' components, all trials were evaluated with unclear risk of bias due to unclear reporting.

Results of individual trials and synthesis of results

Quantitative synthesis

Meta-analysis was possible for only one outcome measure at one assessment time-point. Meta-analysis was used to assess the effect of the combined intervention programme compared with exercise on the 6 min walk test (metres) after 6 months of intervention. Only two trials^{3,44} with unclear risk of bias with $n=155$ participants were available for meta-analysis. The pooled random effects (15.05, 95% CI -11.77 to 41.87) did not support a combined intervention effect (figure 2).

Synthesis of results

Modified narrative synthesis

With respect to the guidelines for a narrative synthesis, only two elements were possible to apply: developing a preliminary synthesis and exploring the relationships within and between studies.^{39 40}

Developing a preliminary synthesis

Tabulation was used to present primary and secondary outcome measures that were not included in the meta-analysis: body weight, knee ROM, physical function, mobility, pain and QOL. Studies including a comparison of the combined intervention programme with an exercise intervention are presented in tables 4-5.

Tabulation was used to compare the effect of the combined intervention programme compared with usual care (healthy lifestyle) on primary and secondary outcome measures: body weight, physical function, mobility, pain and QOL (tables 6-7).

Exploring the relationships within and between studies

Characteristics of the trials are presented in table 2. All included trials were conducted by the same research group. The eligibility criteria were very similar across studies. The exercise intervention included strengthening and aerobic exercise. The intervention frequency (1 hour/three times per week) was the same across the included trials. Further details about the design of the trials are presented above.

Tables 4 and 6 show differences between the intervention group and the control group (despite the comparator) with respect to body weight and the 6 min walk distance. These differences were consistent with the results from the included trials. The diet plus exercise group in the pilot study⁴⁴ lost weight compared with the control group ($p=0.01$) after 6 months of intervention⁴⁴ and this was also the case with respect to the

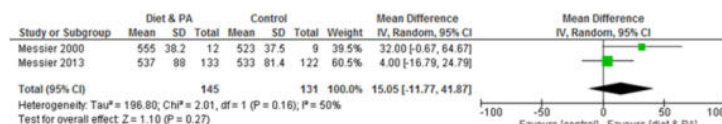
**Figure 2** 6 min walk test (metres) at 6 months.

Table 4 Preliminary synthesis for the primary outcome measures at baseline and after intervention: body weight, knee ROM, physical function and mobility comparing the combined intervention programme with an exercise intervention

Category	Outcome measure	Assessment point(months)	Study	Intervention group				Control group			
				M0 (SD0)	N0	M1 (SD1)	N1	M0 (SD0)	N0	M1 (SD1)	N1
Body weight	Body weight (kg)	6	Messier <i>et al.</i> , 2000 ⁴⁴	91 (13)	13	82.5 (4)	12	109 (17)	11	107.2 (15)	9
		6	Messier <i>et al.</i> , 2013 ³	93 (14.7)	152	84.3 (14.7)	133	92.3 (14.6)	150	92.4 (15.4)	122
		18	Messier <i>et al.</i> , 2013 ³	93 (14.7)	152	82.4 (15.2)	121	92.3 (14.6)	150	90.5 (15)	115
Knee ROM	ROM	6	Messier <i>et al.</i> , 2000 ⁴⁴	55.27* (N/A)	13	56.47 (0.91)	12	55.27* (N/A)	11	56.73 (1.02)	9
		6	Messier <i>et al.</i> , 2000 ⁴⁴	30.7 (N/A)	13	31 (N/A)	12	30.7 (N/A)	11	33.4 (N/A)	9
		6	Messier <i>et al.</i> , 2000 ⁴⁴	18.2 (N/A)	13	18.5 (N/A)	12	18.2 (N/A)	11	20.8 (N/A)	9
Physical function	Physical function (WOMAC)	18	Messier <i>et al.</i> , 2013 ³	24.6 (11.7)	152	14.2 (10.4)	121	23.1 (10.3)	150	17.6 (9.8)	115
		18	Messier <i>et al.</i> , 2013 ³	467 (87.9)	152	537 (92.6)	121	480 (90.3)	150	525 (79.2)	115
		6	Messier <i>et al.</i> , 2000 ⁴⁴	9.81*	13	7.4 (0.32)	12	9.81*	11	8.7 (0.36)	9

M0 (SD0), mean and SD at baseline; N0, participants number at baseline; M1 (SD1), mean and SD after intervention; N1; participants number after intervention; N/A, data not available.

Table 5 Preliminary synthesis for the secondary outcome measures at baseline and after intervention: body weight, pain and QOL comparing the combined intervention programme with an exercise intervention

Category	Assessment point(months)	Outcome measure	Study	Intervention group				Control group			
				M0 (SD0)	N0	M1 (SD1)	N1	M0 (SD0)	N0	M1 (SD1)	N1
Pain	WOMAC pain	6	Messier <i>et al</i> , 2013 ³	6.7 (3.4)	152	4.6 (2.9)	133	6.1 (2.9)	150	4.5 (3)	122
	WOMAC pain	18	Messier <i>et al</i> , 2013 ³	6.7 (3.4)	152	3.7 (3.1)	121	6.1 (2.9)	150	4.4 (2.7)	115
QOL	SF-36 physical component	6	Messier <i>et al</i> , 2013 ³	36.6 (9.41)	152	43.5 (9)	133	36.8 (9)	150	41.5 (9)	122
	SF-36 mental component	6	Messier <i>et al</i> , 2013 ³	57.2 (6.6)	152	56.9 (7.3)	133	56.5 (8.4)	150	56.1 (7.6)	122
	SF-36 physical component	18	Messier <i>et al</i> , 2013 ³	36.6 (9.41)	152	44.7 (8.7)	121	36.8 (9)	150	42.0 (9)	115
	SF-36 mental component	18	Messier <i>et al</i> , 2013 ³	56.1 (6.5)	152	57.2 (6.6)	121	56.5 (8.4)	150	55.4 (7.6)	115

M0 (SD0), mean and SD at baseline; N0, participants number at baseline; M1 (SD1), mean and SD after intervention; N1, participants number after intervention; N/A, data not available.

longer duration intervention trial (18 months) in which the intervention group lost significantly ($p<0.001$) more weight than the exercise group.³ However, in ADAPT⁴³ both groups (intervention and healthy lifestyle) lost weight ($p<0.05$) after 18 months of intervention,⁴⁵ although there was a significant difference in the 6 min walk result in favour of the diet plus exercise group ($p<0.05$).⁴⁵ Also, there was a significant difference ($p=0.005$) in the 6 min walk between the intervention and exercise groups in the IDEA trial.³

Additional analysis

No further analyses were possible owing to the lack of reported information and low number of included trials.

Grading the quality of evidence

A summary assessment was undertaken to draw conclusions about the overall quality of evidence for the combined intervention on mobility using GRADE software.⁴³ Both trials included in the meta-analysis^{3,44} were evaluated as 'high' quality evidence before being downgraded as they were RCTs, before being modified according to five negative and two positive factors.^{41,42} The quality of evidence for a combined intervention programme of physical activity and diet on walking distance (metres) within 6 min after a period of 6 months of intervention was evaluated as moderate (table 8).

DISCUSSION

Summary of evidence

This is the first systematic review and mixed method analysis investigating the effectiveness of combining dietary restriction and physical activity interventions for musculoskeletal function in overweight/obese older adults with knee OA. One pilot trial⁴⁴ and two definitive trials^{3,45} (794 participants) conducted by the same research group (Wake Forest University) were included. The intervention programme was compared with exercise training in one definitive trial (IDEA)³ and the pilot trial,⁴⁴ while usual care was the comparator in the ADAPT.⁴⁵ Two additional articles^{46,47} which reported further outcomes of the ADAPT were identified.⁴⁵

Data syntheses of this review were conducted using both meta-analysis and modified narrative synthesis. Although visual inspection of the tables of results indicated that the combined programme enhanced body weight reduction, and improved mobility, there was moderate evidence for no effect. Changes of BMI scores were not reported in the included studies. Meta-analysis was possible for only the 6 min walk test at 6 months and was not possible for the other outcome measures due to the inconsistency of assessment points or the comparator. The pooled random effect of two trials^{3,44} with 155 participants did not support the combined intervention programme (15.05, 95% CI -11.77 to 41.87) (although with a total effect of 15 m deemed not clinically significant according to previous literature).^{49,50} Although the meta-analyses showed substantial heterogeneity

Table 6 Preliminary synthesis for the primary outcome measures at baseline and after intervention: physical function and mobility comparing the combined intervention programme with usual care

Category	Outcome measure	Assessment point (months)	Study	Intervention group				Control group			
				M0 (SD0)	N0	M1 (SD1)	N1	M0 (SD0)	N0	M1 (SD1)	N1
Body weight	Body weight (kg)	18	Messier <i>et al.</i> , 2004 ⁴⁵	92 (1.7)	76	86.8 (N/A)	58	96 (1.8)	78	94.9 (N/A)	67
Physical function	Physical function (WOMAC)	6	Messier <i>et al.</i> , 2004 ⁴⁵	23.6 (12.2)	76	17.9* (N/A)	63	26 (11.4)	78	22.4* (N/A)	70
	Physical function (WOMAC)	18	Messier <i>et al.</i> , 2004 ⁴⁵	23.6 (12.2)	76	29.3* (N/A)	58	26 (11.4)	78	29.4 (N/A)	67
Mobility	6 min walk test (m)	6	Messier <i>et al.</i> , 2004 ⁴⁵	416.2 (98.7)	76	482.3 (100)	63	434.6 (96.4)	78	429 (108)	70
	6 min walk test (m)	18	Messier <i>et al.</i> , 2004 ⁴⁵	416.2 (98.7)	76	477.8 (99.7)	58	434.6 (96.4)	78	429.9 (104.7)	67
	6 min walk test (m)	18	Focht <i>et al.</i> , 2005 ⁴⁷	414.5 (85.3)	N/A	465 (96.3)	N/A	433.4 (81.9)	N/A	430 (79.5)	N/A
	Stair climb (s)	6	Messier <i>et al.</i> , 2004 ⁴⁵	10.9 (5.8)	76	8.8 (6.2)	63	9.5 (5.6)	78	9.9 (6.3)	70
	Stair climb (s)	18	Focht <i>et al.</i> , 2005 ⁴⁷	10.4 (7.3)	N/A	8.9 (5.4)	NA	9.4 (4.9)	N/A	9.9 (5.6)	N/A

*Estimated value from figure 2 in ref. 45.

M0 (SD0), mean and SD at baseline; N0, participants number at baseline; M1 (SD1), mean and SD after intervention; N1, participants number after intervention; N/A, data not available.

Category	Outcome measure	Assessment point (months)	Study	Intervention group				Control group			
				M0 (SD0)	N0	M1 (SD1)	N1	M0 (SD0)	N0	M1 (SD1)	N1
Pain	Pain scale (WOMAC)	6	Messier <i>et al.</i> , 2004 ⁴⁵	7.3 (3.6)	76	5.5 (3.7)	63	7.3 (3.4)	78	6.2 (3.9)	70
	Pain scale (WOMAC)	18	Messier <i>et al.</i> , 2004 ⁴⁵	7.3 (3.6)	76	5.1 (3.6)	58	7.3 (3.4)	78	6 (3.7)	67
QOL	SF-36 physical component	Average of 6 and 18	Rejeski <i>et al.</i> , 2002 ⁴⁶	35.39 (10.5)	68	40.57 (N/A)*	N/A	33.60 (8.4)	68	40.57 (N/A)*	N/A
	SF-36 mental component	Average of 6 and 18	Rejeski <i>et al.</i> , 2002 ⁴⁶	52.85 (10.7)	68	53.51 (N/A)*	N/A	52.70 (10.9)	68	53.31 (N/A)*	N/A

M0 (SD0), mean and SD at baseline; N0, participants number at baseline; M1 (SD1), mean and SD after intervention; N1, participants number after intervention; N/A, data not available, *, only SEM data available; SD1 data could not be calculated due to missing N1 value.

$I^2=50\%$, this was classified as not serious using the GRADE evaluation tool^{41 42} as it was assessed as likely to be due to high variability in both the sample size and effect size. Clinical heterogeneity across trials was limited to comparator and duration. Overall, the quality of evidence was downgraded to moderate due to imprecision of the results according to GRADE.⁴³ All included trials were reported as having an unclear risk of bias, which was mainly due to unclear reporting of some information.³⁴ For instance, both the 'blinding of participants, personnel and outcome assessor' and the 'other sources of bias' component were evaluated as unclear for all trials.

Results from the trial by Messier *et al*⁴⁴ indicated no statistically significant differences across groups with regard to self-reported performance measures of physical function, knee pain scores, knee strength and biomechanical measures (synovial fluid, keratan sulfate and level of IL-1) after 6 months of intervention. Findings from Messier *et al*⁴⁵ indicated a statistically significant benefit of the combined intervention in terms of self-reported physical function, 6 min walk test, stair climb and knee pain. The findings from Messier *et al*⁶ indicated a significant improvement in the 6 min walk test and walking speed in the intervention group. Moreover, there was a significant reduction ($p < 0.05$) of body weight among the intervention groups in all trials. In the current review, the finding of no effect of a combined intervention programme may be due to the very low number of included trials (and participants) but probably is not due to low compliance. Compliance of the diet and exercise group to the exercise programme at 6 months was higher in the pilot study⁴⁴ compared with the IDEA trial.³ In the pilot study,⁴⁴ compliance (ratio of the number of exercise sessions attended to the total number of the exercise sessions prescribed with the exercise programme) was 82.6% for the exercise group and 94.7% for diet plus exercise group. For the IDEA trial,³ 399/454 participants (88%) completed the study; compliance of the diet and exercise group was 70% at 6 months and 58% at 18 months with no adverse events and no significant differences between groups.

In addition to diet and exercise, two current trials MEDIC1²⁸ and MEDIC2²⁷ have reported that a multimodal approach of education, neuromuscular exercise, insoles and, if indicated, a dietary weight loss programme and pain medication are effective for adults and older adults with moderate-to-severe knee OA. These studies were not included in this review due to the wide age range across participants. MEDIC1²⁸ included 9 participants and MEDIC2²⁷ included 12 participants below the age of 55 years and there was no subgroup analysis of older participants. In MEDIC1,²⁸ the participants were eligible for TKR and were randomised to non-surgical and surgical treatment followed by the intervention programme. Both interventions showed substantial improvement, but the

Table 8 Factors determining the quality of evidence according to GRADE

Factor	Judgement	Explanation
1. Risk of bias	Not serious	▶ Only two studies included in meta-analysis and both of them evaluated as unclear risk of bias ▶ No serious limitations to downgrade the quality of evidence ▶ Sequence generation was not reported in one study; allocation concealment not specified in both studies; no strategy reported to address issue of outcome assessor unblinding ▶ Incomplete outcome data evaluated as 'unclear' in the pilot study; no mention of missing data or methods used to address missing data; no primary outcome stated for the pilot study
2. Inconsistency	Not serious	▶ $I^2=50\%$, which may be evaluated as either low or substantial heterogeneity; this overlap affects the decision making ▶ Magnitude of heterogeneity could be the result of high variability in the sample size and effect size which justifies the decision
3. Indirectness	Not serious	▶ Direct applicability of the included studies aims and objectives to their target populations, interventions and outcomes of interest
4. Imprecision	Serious	▶ Boundaries of CI crossing the no effect line which downgrades the quality of evidence by one level ▶ Number of participants needed for a single powered trial is higher than number of participants estimated from the meta-analysis; quality of evidence not downgraded on this basis
5. Publication bias	Undetected	▶ Selective outcome reporting domain evaluated low in both studies; publication bias considered as not serious by two reviewers

surgical treatment resulted in greater pain relief and functional improvement after 12 months compared with non-surgical treatment alone. However, only 26% of the patients who were assigned to receive non-surgical treatment alone underwent TKR in the following year.²⁸ In MEDIC2,²⁷ participants had radiographic confirmation of OA (Kellgren-Lawrence grade ≥ 1), but were not eligible for a TKR. The 12-week non-surgical treatment programme consisted of individualised progressed neuromuscular exercise, patient education, insoles, dietary advice and prescription of pain medication if indicated, while usual care comprised two leaflets with information and advice on knee OA and recommended treatments. This non-surgical treatment programme was found to be more effective with respect to pain, activities of daily living and QOL at 12 months compared with usual care, although it was not possible to determine which of the components within this multi-intervention programme were most effective and whether the intervention as a whole would be equally effective in older patients with OA.²⁷

The main limitation of this review is that only few eligible studies were identified. Thus, the optimal components of dietary and exercise interventions in terms of type, duration and quantity suitable for this population are still unclear. Future studies are required in this field to optimise outcome measures and methods of delivering a programme at an acceptable cost, prior to a future adequately powered definitive trial.

Conclusion

Based on current evidence synthesised in this review, it is hard to judge the effectiveness of a combined programme of diet and physical activity due to the low number of included trials and participants and the quality of available evidence. Only moderate quality evidence was available to investigate the intervention programmes. However, the narrative synthesis suggests that interventions with a focus on reduction of body weight and/or improved mobility are worthy of further evaluation. Further adequately powered RCTs testing the effects of a combined intervention against each component individually are required to optimise diet and exercise interventions using a multi-modal approach.

Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

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Contributors ASA led the review and contributed to all stages, including development of the search strategy, running the searches, assessing trials eligibility, data extraction and synthesis (including risk of bias and Grading of Recommendation, Assessment, Development and Evaluation analysis), and preparation of the manuscript. CAG and ABR provided expertise in systematic review methodology and risk of bias analysis. AMK assisted with assessment of eligibility of included studies and data extraction. All authors read and provided feedback on the preparation of this manuscript according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 checklist and approved the final manuscript.

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Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no additional unpublished data from the review.

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APPENDIX 3.1 CONSOLIDATED STANDARDS OF REPORTING TRIALS (CONSORT) CHECKLIST



CONSORT 2010 CHECKLIST OF INFORMATION TO INCLUDE WHEN REPORTING A RANDOMISED TRIAL*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	83
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	84
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	85-87
	2b	Specific objectives or hypotheses	87-88
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	88-89
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	89-90
	4b	Settings and locations where the data were collected	90, 106
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	91-95
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	95-103
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	103
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			N/A
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
Allocation concealment	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A

		mechanism	
	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Implementation			
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	104
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	104
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	117
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	115
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	118
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	117
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	119-126
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	187-188
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	175-187

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	175-187
Other information			
Registration	23	Registration number and name of trial registry	111
Protocol	24	Where the full trial protocol can be accessed, if available	111
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

EXERCISE SERVICE FOR KNEE OSTEOARTHRITIS



What is Osteoarthritis (OA)

- ☐ Osteoarthritis is a condition that causes joint pain and stiffness.
- ☐ It can cause problems with daily activities and affects quality of life
- ☐ Most common form of arthritis
- ☐ One of the leading causes of pain and disability worldwide.
- ☐ The knees, hips and hands are most commonly affected.



What is Osteoarthritis (OA)

- ☐ Localised loss of cartilage.
- ☐ Remodelling of adjacent bone
- ☐ Associated inflammation



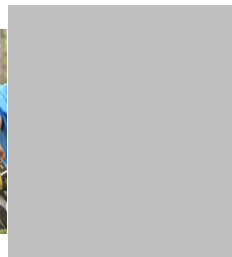
What causes OA?

- ☐ There are many factors that can increase your risk of getting osteoarthritis
- ☐ Age ☐ Gender ☐ Obesity ☐ Joint injury
- ☐ Osteoarthritis is the body's slow but efficient repair process to damage to the joint
- ☐ Often the structure of the joint changes but it can remain symptom free



What causes OA

- ☐ Sometimes this repair process is compromised and this is when we develop symptoms of osteoarthritis
- ☐ Muscle weakness ☐ Smoking ☐ Overweight ☐ Poor diet
- ☐ So some people can get pain with osteoarthritis, whilst others do not.



Pain and OA

- ☐ Pain can impact on us in many different ways, such as: ☐ Decreased confidence with activities
- ☐ Changes in our sleep patterns ☐ Changes in our mood
- ☐ Treatment of pain focuses as much on achieving targets to improve quality of life

How does pain affect these issues in your experience?

Common myths

- ☐ There is often a poor link between changes visible on an X-ray and symptoms of osteoarthritis
- ☐ Osteoarthritis is not caused by ageing but is more common as we get older
- ☐ It does not necessarily deteriorate
- ☐ Exercise will not cause your joints to wear out



How can it be treated?

- ☐ Unfortunately there is no cure for osteoarthritis as yet but there is a lot that you can do to improve your symptoms:
- ☐ Learn more about OA ☐ Weight management ☐ Exercise ☐ Medication

Exercise

- ☐ Exercise is a core treatment
- ☐ Exercise should include: ☐ muscle strengthening ☐ general aerobic fitness
- ☐ At least twice a week
- ☐ You should aim to be active daily
- ☐ e.g. get off bus one stop earlier



How much exercise?

- ☐ Exercise activity should add up to at least 150 minutes a week (2.5 hours)
- ☐ Moderate intensity
 - ☒ exercise should make you feel warmer, breathe harder, and your heart to beat faster (but you can still talk!)
- ☐ Such as brisk walking



How much moderate intensity exercise do you each week?

- ☐ Moderate intensity
- ☐ E.g. brisk walking, swimming, cycling ☐
- You can still talk but can't sing!
- ☐ Vigorous intensity ☐ E.g. running
- ☐ You have difficulty

Fitness and Exercise

Benefits include:

- Better range of movement and joint mobility
- Better pain management
- Increased muscle strength
- Stronger bones
- Weight control
- Improved balance and co-ordination
- Reduced stress
- Improved sleep patterns
- Increased energy levels
- Improved self esteem



Resources

- ☐ www.prescription4exercise.com
- ☐ www.walkingforhealth.org.uk
- ☐ <http://beactivebirmingham.co.uk/>
- ☐ <http://beactivebirmingham.co.uk/active-parks/>

Safety considerations

- ☐ Start gently and gradually increase
- ☐ See a doctor if you have chest pain, black outs or become breathless on mild exertion
- ☐ Stop exercising if you become dizzy, sick, unwell or very tired.
- ☐ See handout

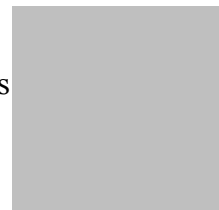
Prolonged rest

- ☐ You should minimise sedentary behaviour
- ☐ Reduce time spent watching TV
- ☐ Get off the bus one stop earlier
- ☐ Get up and take a walk outside
- ☐ PACE YOURSELF!



Staying Healthy

- Buy healthy ingredients
- Adapt cooking methods
- Portion sizes – smaller fatty foods and larger vegetables
- Eat slowly and do not do something else at the same time
- Pack up left overs before you sit down to avoid second helpings
- Avoid fad or starvation diets



Vitamins

Vitamin	Good Source
Calcium	Dairy products e.g. milk, yoghurt, cheese. Fish eaten with bones e.g. sardines
Vitamin D	Fish liver oil
Iron (best absorbed with Vit C therefore have fruit juice/ fruit/ veg with your meal)	Red meat oily fish (sardines) Pulses (haricot beans/lentils) Dark green veg (kale/spinach/watercress)
Selenium	Brazil nuts (meat and fish contain some)
Omega-3 Fatty Acids	Oily fish

Drugs

Those commonly used for treating OA:

- ☐ Non- steroidal anti-inflammatory drugs
 - Analgesics
 - Narcotics/central acting agents
 - Injections
 - Hyaluronic acid substitutes
 - Other



Consult your GP regarding medication

Supplements

- ☐ Try for three months – if it helps, continue – otherwise, don't bother



Alternative Therapies

- ☐ Hot and cold
- ☐ TENS
- ☐ Massage/self massage
- ☐ Complementary/alternative therapy

Conclusion

- ☐ No cure for osteoarthritis but there are things that you can do to improve your symptoms and slow down it's progression.
- ☐ Exercise regularly
- ☐ At least 150 mins (2.5 hours) each week
- ☐ Strengthening and aerobic exercise
- ☐ Eat healthily
- ☐ Weight management ☐ Pace yourself

APPENDIX 3.3 CONSOLIDATED CRITERIA FOR REPORTING QUALITATIVE RESEARCH (COREQ) CHECKLIST

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
<i>Personal characteristics</i>			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	107
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	107
Occupation	3	What was their occupation at the time of the study?	107
Gender	4	Was the researcher male or female?	107
Experience and training	5	What experience or training did the researcher have?	107
<i>Relationship with participants</i>			
Relationship established	6	Was a relationship established prior to study commencement?	107
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	107
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	107
Domain 2: Study design			
<i>Theoretical framework</i>			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	106
<i>Participant selection</i>			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	106
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	106
Sample size	12	How many participants were in the study?	103
Non-participation	13	How many people refused to participate or dropped out? Reasons?	N/A
<i>Setting</i>			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	106

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	N/A
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	107
<i>Data collection</i>			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	107, 108
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	N/A
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	107
Field notes	20	Were field notes made during and/or after the interview or focus group?	107
Duration	21	What was the duration of the inter views or focus group?	107
Data saturation	22	Was data saturation discussed?	107
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	N/A
Domain 3: analysis and findings			
<i>Data analysis</i>			
Number of data coders	24	How many data coders coded the data?	108-109
Description of the coding tree	25	Did authors provide a description of the coding tree?	131, 144, 158
Derivation of themes	26	Were themes identified in advance or derived from the data?	130, 142, 156
Software	27	What software, if applicable, was used to manage the data?	N/A
Participant checking	28	Did participants provide feedback on the findings?	N/A
<i>Reporting</i>			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	129-164
Data and findings consistent	30	Was there consistency between the data presented and the findings?	165-166
Clarity of major themes	31	Were major themes clearly presented in the findings?	129-164
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	129-164

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

APPENDIX 3.4 TOPIC GUIDE FOR THE FOCUS GROUP DISCUSSION



The effect of a combined programme of dietary restriction and physical activity on the physical function and body composition of obese middle aged and older adults with knee OA: Feasibility study

Focus group

Moderator: Asma Alrushud

Number of participants: /

Group:

Date:

*Note: the interview will be audio recorded for further analysis.

I will thank the participants for coming and completing the study. Then, I will outline the purpose of the session and discuss consent and confidentiality (the discussion will be audio recorded).

Agree ground rules for the group e.g. confidential to the group, allow everyone to contribute.

Then audio-recording will begin

Introductions and ice breaker

What treatment options have you had for your knee OA previously to this study?

Did you receive any physiotherapy programme before?

Have you done any type of exercise before (had a gym membership)?

What did you do before when you got pain or stiffness?

Q1: Do you feel you have gained any physical benefit from the combined intervention programme?

Discussion points:

- Specific benefits attributable to the exercise?

Has your pain decreased or your function increased? for example your walking distance has increased after participation in this programme?

Have you expressed any improvements in your activities of daily living?

- Specific benefits attributable to the diet?

Feeling Satisfied with diet?

Q2: Do you think the programme was easy to stick to?

Discussion points:

- Facilitators that affected your adherence (provide examples of facilitators).

Have you received support from your family members?

Modified your diet according to your preference?

Freedom to access gym any days of week?

Have you found the weekly contact from the study member motivating for you to adhere to the programme?

- Barriers that affected your adherence (provide examples of barriers).

Easy to stick to diet plan even in special occasions like parties?

Time of the usual care classes at ROH then access your local gym weekly?

Having to work?

Experiencing pain? Good days versus bad days?

- Discuss intervention as a whole but also try to explore specific challenges relating to exercise and diet.

Did you exercise at home and use the exercise notes/ guide that was handed to you by the physiotherapy technician?

What types of exercise did you do in your local gym over the 3 months? And was the trainer helpful to you in selecting these exercises or you did select them by yourself?

Did you progress your exercise or just repeat the same ones over the 3 months?

Q3: Do you think the programme could be adapted in any way in order for it to be more acceptable/ easier to follow?

- Provide examples such as timing of classes, help with diet plan.

Q4: Were you personally satisfied with the programme results?

Promote to all: yes/no/unsure

Discussion points:

- Why do you feel this?
- Did you feel that the programme was appropriate?

Do you think the type of exercise is suitable for you?

Did you find the exercise progression during the usual care (at ROH) was comfortable to you or beyond your abilities?

- Did you enjoy the programme?

Both diet or exercise or one of them?

Q5: In general do you think the study was successful?

Discussion points:

- Do you think the intervention affected you positively/negatively? Why?
- How easy or difficult would it be for you to continue to follow this programme?

Will you stop your diet and exercise? Or at least one of them?

Do you think the result of this programme will motivate you to continue? Or that a negative result will be letting you down!

- Do you think the cost of following this programme would/ would not be an issue?

Did following a special diet affect your budgets?

Did you pay for the local gym?

Q6: Do you think the intervention is worth offering to other people with knee OA? Why?

Do you think other people will have benefits from joining this programme even if you have not had benefits?

To close: Thank you for your contribution. Are there any questions that you would like to ask me or do you have any more comments?

APPENDIX 3.5 EFFECT OF A COMBINED PROGRAMME OF DIETARY RESTRICTION AND PHYSICAL ACTIVITY ON THE PHYSICAL FUNCTION AND BODY COMPOSITION OF OBESE MIDDLE-AGED AND OLDER ADULTS WITH KNEE OA (DRPA): PROTOCOL FOR A FEASIBILITY STUDY

Open access

Protocol

BMJ Open Effect of a combined programme of dietary restriction and physical activity on the physical function and body composition of obese middle-aged and older adults with knee OA (DRPA): protocol for a feasibility study

Asma S Alrushud,^{1,2} Alison B Rushton,^{1,3} Gurjit Bhogal,⁴ Fraser Pressdee,⁴ Carolyn A Greig^{1,3,5}

To cite: Alrushud AS, Rushton AB, Bhogal G, et al. Effect of a combined programme of dietary restriction and physical activity on the physical function and body composition of obese middle-aged and older adults with knee OA (DRPA): protocol for a feasibility study. *BMJ Open* 2018;8:e021051. doi:10.1136/bmjopen-2017-021051

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For numbered affiliations see end of article.

Correspondence to
Asma S Alrushud;
asa314@student.bham.ac.uk

ABSTRACT

Introduction Knee osteoarthritis (OA) is the most common chronic illness among older adults. Up to the submission date of this protocol, there are no published UK studies reporting the efficacy of a combined intervention programme of physical activity and dietary restriction on the musculoskeletal function of obese older adults with knee OA in spite of the clinical recommendation for exercise and diet for people with knee OA. The aim of this study is to assess the feasibility and acceptability of a combined dietary restriction and physical activity intervention programme and collect preliminary data.

Method and analysis This single-arm intervention study is scheduled to begin in September 2017 and conclude in November 2018. It will take place at the Royal Orthopaedic Hospital (ROH), Birmingham and the School of Sport, Exercise and Rehabilitation Sciences (SportExR), University of Birmingham. Participants will receive a physiotherapy usual care programme for knee OA for 1 month, after which they will continue to exercise in their local gym/leisure facility for 3 months. Participants will also follow dietary restriction throughout the 4-month intervention. Mixed analysis techniques will be used to analyse the quantitative and qualitative outcome measures.

Ethics and dissemination It is approved by ROH R&D Foundation Trust and the Health Research Authority. The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high-quality peer-reviewed journals.

Trial registration number ISRCTN12906938.

INTRODUCTION

Knee osteoarthritis (OA) is a major public health problem worldwide and a common condition in older adults due to high incidence and prevalence rates.^{1,2} Approximately 3.64% of the global population is affected by knee OA.³ In 2010, 4.71 million people

Strengths and limitations of this study

- Mixed-methods data collection to provide detailed information about the combined programme.
- Collaboration with secondary healthcare providers to conduct the study.
- Measurement of outcomes across several domains including biomarkers for knee osteoarthritis to inform the selection of the appropriate outcome measures for a future study.
- Due to limited resources, this will be a single-centre feasibility study.

aged ≥45 years sought treatment for knee OA in England.⁴ The impact of knee OA includes pain, decline in physical function, reduced quality of life (QOL) and increased disability.⁵

In addition to advancing age, obesity is also a known risk factor for developing OA and causing disability.^{6–10} Obesity increases the negative impact of the disease and patients with arthritis may need surgical intervention to reduce body weight and thereby relieve pain.⁷

In overweight and obese adults, knee OA management should focus mainly on weight reduction.^{11,12} The evidence supports a calorie-restricted diet in adults but the optimal method(s) for weight reduction are still varied in terms of intervention length. Introducing a low-calorie diet is challenging in older adults with knee OA because of the need to maintain the appropriate intake of the important nutrients. For example, maintenance of the recommended daily calcium intake is essential for women who may be at risk of osteoporosis.¹³ For overweight and obese patients with knee OA, previous studies

have indicated that the ultimate goal of weight loss should be at least 10% of body weight, in order to provide significant pain reduction.^{14,15} Recently, a systematic review (SR) recommended that total body weight should be reduced by at least 5% over a period of 20 weeks in this population to experience symptoms improvement.¹⁵

The European League Against Rheumatism and the Osteoarthritis Research Society International (OARSI) guidelines recommend exercise as a core intervention for knee OA management.^{16,17} Patients with mild to moderate knee OA have been shown to benefit from muscle strengthening and aerobic exercises with respect to decreasing pain and improving mobility.¹⁸ In the UK, usual care is considered as the first line of knee OA treatment in clinical practice¹⁹ and its main foci are exercise and advice.^{20,21} Exercise intervention may include different types of exercise, for example, strengthening exercise (weight bearing and non-weight bearing), range of motion (ROM) and stretching exercise. Advice may concentrate on the importance of exercise and provide patients with information about pain relief strategies, for instance, analgesics and home heat therapy.^{20,21} However, the most effective way of delivering exercise to optimise patient outcome is still unclear, particularly in older people with knee OA.²¹ The published literature reports that both aerobic walking and quadriceps strengthening exercises have a positive effect on participants with knee OA and, overall, there is no superiority of one approach over the other.²²

Combining weight loss and exercise regimens is recommended for older adult patients with knee OA.^{23–26} A recent SR investigated the effectiveness of combining physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese older adults with knee OA.²⁷ Only one pilot study²³ and two trials, the Arthritis, Diet, and Activity Promotion Trial²⁴ and the Intensive Diet and Exercise for Arthritis²⁵ were identified. The reviewers concluded that there was unclear quality of evidence for the benefit of combining interventions.²⁷ To date of developing this protocol, there are no published UK studies reporting efficacy of a combined intervention programme for older adults. As a consequence, there is a need to develop a study incorporating a mixed methods approach to investigate the acceptability, feasibility as well as the efficacy of a combined intervention programme in older adults with knee OA.

The aim of this feasibility study is to assess the feasibility, acceptability and collect preliminary data to inform the design of a definitive trial incorporating a combined intervention programme.

METHODS AND ANALYSIS

Research questions and objectives

This 4-month intervention study aims to answer the central question 'Will the combined intervention programme be

feasible and acceptable for the participants and the Royal Orthopaedic Hospital (ROH) physiotherapy staff?'

Additional research questions are formulated:

1. What is the potential for efficacy of the proposed combined intervention programme, as indicated by preliminary data evaluating improvement in outcome measures including: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), body weight, waist circumference (WC), body mass index (BMI), musculoskeletal function including: knee ROM and muscle power, musculoskeletal function including: stair climb and timed up-and-go, pain, QOL and markers of joint remodelling?

2. Are there any associations between changes in body weight, knee pain, BMI and markers of joint remodelling?

Primary objective: Will the combined intervention programme be feasible and acceptable, for the targeted population and the ROH physiotherapy department staff?

Secondary objectives:

1. Assess suitability of main trial measures.
2. Investigate associations between changes in body weight, knee pain, BMI and markers of joint remodelling.

It is hypothesised that the combined programme will be feasible and acceptable either for the targeted population or the ROH physiotherapy department or both. All outcome measures will be assessed for suitability. After 4 months of intervention, it is hypothesised that losing weight will be associated with improvement of knee pain and markers of joint remodelling.

Study design

This is a single-centre feasibility study, consisting of one arm (combined programme of dietary restriction and physical activity) with an embedded qualitative component (focus group for participants and questionnaire for physiotherapy staff).

Study setting

The combined programme intervention and the physiotherapy staff questionnaire will take place within the ROH, Birmingham. Participant assessments and focus group sessions will be conducted at the University of Birmingham (UoB), UK.

Participants

We will recruit 30 older adults (men and women aged ≥ 45 –90 years) with BMI ≥ 30 kg/m². They will have a diagnosis of knee OA (with or without radiographic evidence) and will not be participating in regular exercise more than twice a week. They will be able to understand verbal and written English and be willing to participate and give informed consent for the study. They will be excluded if they have any significant comorbid diseases that would pose a safety threat or impair ability to participate such as coronary artery disease, severe hypertension, peripheral vascular disease, stroke, congestive heart

failure, chronic obstructive pulmonary disease, insulin-dependent diabetes, psychiatric disease, renal disease, liver disease, active cancer other than skin cancer, advanced osteoporosis and anaemia or have had previous acute knee injury (moderate–severe). Additional exclusion criteria are resting systolic blood pressure greater than 200 mm Hg and resting diastolic blood pressure greater than 100 mm Hg, neuromuscular impairments that preclude participating in physical activity, visual, hearing or moderate/severe cognitive impairments as well as unwillingness to modify diet or physical activity patterns or inability to comply with the intervention because of inability to access a gym/local leisure facility, food allergies or reactions to the calorie-restricted diet.

Intervention

The intervention will consist of a single education session, physical activity and dietary restriction components.^{28–31}

Educational session

The first physical activity class will be preceded by an educational session lasting for 60 min introduced by a qualified physiotherapist. Information about causes and management of knee OA, importance of exercise and diet and safety considerations will be given as part of physiotherapy usual care for patients with knee OA. Additional information about dietary restriction will be introduced by a clinical dietician in the last 10–15 min of the session. Information in this session is based on the principles of self-management theory,^{32–34} self-efficacy theory³⁵ and the framework of behaviour change³⁶ and addresses changing lifestyle and coping with pain, stiffness and limited activities of daily living. Participants will have the opportunity to ask any further questions.

Physical activity

Participants will receive a physiotherapy usual care programme for knee OA (moderate intensity stretching and strengthening exercise) in the physiotherapy gym under the supervision of a physiotherapy technician for 1 month (60 min per week); it is based on social cognitive theory and group dynamics.³⁷ Participants will begin with a warm-up exercise for 5 min around the gym including quadriceps, hamstring and gastrocnemius stretches. The group will split into two small groups working across several work stations on ROM, strength, cardio, gait stations for a further 40 min, for example, cycle ergometer, treadmill, leg press, theraband, inner range quads with band gait work using light hand weights. Sit to stand with medicine ball, marching on a trampette, lunges and extension stretches on step, step overs, tandem walking (eyes open–eyes closed), straight leg raising with weights, hamstring curls with weights, bridging, posterior gluteus medius with band, slight hip abduction and through range quads over the edge of a plinth. Group balance work will be carried out towards the end of the session. Cool down will be completed with stretches. All stations will run for approximately 2 min with additional weights

and resistance to be added for progression. All participants will receive a home exercise programme as part of their usual care. Home exercise is based on the National Institute of Health and Care Excellence Guidelines for knee OA.³⁸ The classes are group based as opposed to individualised. The participants will split into two small groups working across several work stations and will spend approximately 2 min at each station. Each participant will exercise according to his/her ability and progression will be tailored accordingly. Personalisation is based around the individual participants hobbies/interests and Activities of Daily Livings (ADLs) with advice being offered accordingly. Participants will monitor their own symptom levels and modify intensity accordingly and work within their own defined tolerance levels. After 1 month, participants will continue to exercise in their local gyms/leisure facilities for a further 3 months. The study team will assist participants with application for a free (or discounted through funding by the study) gym pass via the Birmingham Be Active scheme. Participants will be provided with a programme of recommended exercises to continue in this setting. The participants will be contacted weekly by telephone to encourage adherence. The first 4 weeks will be the adoption stage where the participants will be educated and supported to change their behaviours and the remaining 12 weeks of the study will be for maintenance.³⁵

Dietary restriction

Participants will complete a 3-day food diary and then follow dietary restriction throughout the 4 months of the intervention, aiming for a decrease of 300–500 kcal/day or 500–1000 kcal/day as appropriate to initial BMI. The diet will be planned and modified (if required) by a clinical dietician. Participants will monitor themselves by completing a daily log.

Outcome measures

Qualitative component (feasibility objective)

Feasibility of the combined intervention programme will be measured using a post intervention focus group for participants and a questionnaire for the involved physiotherapy staff. The feasibility outcomes will be based on the categories reported in Bowden *et al.*³⁹ and listed in table 1.

Focus group

Three focus groups will be conducted at the end of the intervention to explore the participants' knowledge, experience and views about the combined intervention programme.^{39–43} The focus group will be audiotaped then analysed. A focus group will be conducted for each group (n=10) at the UoB. The chief investigator (CI) (ASA) will lead the discussion by outlining the purpose of the session and discussing consent and confidentiality. Participants' engagement will be encouraged by asking introductory questions about their previous treatment options for knee OA. An example of the participants' focus group

Table 1 Feasibility measurement categories

Categories	For participants	For physiotherapy staff
1. Efficacy	Do they report benefit?	Do they notice improvement?
2. Adherence	Using sheet for recording their gym sessions	Record participant attendance
3. Adaption	Does the intervention need adaption, for example, time or procedure?	Does the intervention require adaptation?
4. Acceptability	► Satisfaction with programme and outcomes ► Perceived appropriateness ► Expressed interest	► Satisfaction with participants' outcomes ► Intent to use again ► Fit within hospital culture ► Perceived positive or negative effects on their time, gym availability
5. Implementation and practicality	Degree of execution, success or failure of execution ► Positive/negative effects on target participants ► Ability of participants to carry out intervention activities and cost	Amount, type of resources needed to implement ► Factors affecting implementation ease or difficulty, efficiency, speed or quality of implementation
6. Integration and expansion	Do they recommend expanding the intervention to other hospitals?	► Does it fit with the hospital goals and physiotherapy department goals? ► Is cost suitable to organisation wishing to include it? ► Could it be applied in the future and how? ► Any positive or negative effects on the ROH or the department?

ROH, Royal Orthopaedic Hospital.

discussion guide is presented in online supplementary 1. This topic guide will inform exploration of the participants' experiences of the combined intervention. An experienced researcher (ABR, coinvestigator) will be responsible for audiotaping and observing the session, taking notes and overseeing data analyses.

Questionnaire

A mixed questionnaire consisting of open and closed questions has been designed to assess the feasibility of the combined intervention programme.^{39 42} The questionnaire consists of 15 items and its design is based on the categories of feasibility (table 1).

Quantitative measures (efficacy objective)

Preliminary data informing potential for efficacy of the combined intervention programme will be collected using:

1. Physical function (WOMAC) scale.
2. Body weight, WC and BMI.
3. Body composition (body impedance analysis).
4. Musculoskeletal function (knee ROM, lower limb muscle power).
5. Physical performance (stair climb, timed up-and-go).
6. Pain intensity (WOMAC pain subscale).
7. QOL (Short Form-36).
8. Blood markers of joint remodelling, including: Adipokines (serum adiponectin and leptin) and for bone turnover; Bone formation (Procollagen I C-Terminal Propeptide (PICP)); Bone (type I collagen) degradation (cross linked C-telopeptide of Type I collagen (CTX-1)); Cartilage formation: type IIA

collagen N-propeptide (PIIANP), Cartilage (type II collagen) degradation: fragments of cartilage oligomeric matrix protein (COMP).⁴⁴

These outcome measures were selected based on a previously published SR²⁷ and OARS recommendation of performance-based tests to assess physical function of people with knee OA⁴⁵ with consideration of the study aims and practical considerations. Physical function WOMAC scale is the planned primary outcome for the definitive study.⁴⁶

Sample size

A formal sample size calculation is not appropriate as one of the study outcomes is to collect data which will inform estimates of SDs for use in a sample size calculation for a future definitive trial. The sample size of 30 participants is based on previous reviews of the literature.^{47 48} To ensure a suitably reliable estimate of SDs (to power a future study), sample sizes between 24 and 50 have been recommended.^{49 50} This sample size is also recommended by The National Institute for Health Research.⁵¹

Procedure

Participants will be recruited via the ROH outpatient clinic and the physiotherapy department. Potential participants will be identified by a ROH clinician or senior physiotherapists according to the eligibility criteria. Eligible participants will be provided with a copy of the participant information sheet and a response slip, which will include a telephone number and email address to contact the study team directly and a stamped addressed envelope for those who prefer to respond by post. In

the case of participants who have given blood recently (within the last 3 months), their general practitioners will be conducted by the study team to provide the results. Participants will be invited to attend the School of Sport, Exercise and Rehabilitation Sciences (SportExR), UoB, where the study procedures will be explained in further detail. Participants will be given the opportunity to ask questions and informed consent will be obtained. An approved copy of the participants informed consent form is presented in online supplementary 2. Baseline data will be collected by the study team. Blinded outcome assessment will not be applicable in this study but will be applied in the definitive trial. Participants will be asked to complete a 3-day food diary (weekday and weekend) and

to return it by post to a member of the study team (using the stamped addressed envelope provided to them), and a date will be scheduled to begin the exercise classes at ROH. The first class will be preceded by an educational session about knee OA, during which participants will be given the opportunity to ask any further questions. See figure 1 for the DRPA trial flow diagram.⁵²

Patient and public involvement

The design of this study has been informed by data gained from several focus groups of older people ≥ 55 years with knee OA at the Control of Movement and Active Ageing Open Day on 22 June 2016 in the SportExR, UoB.

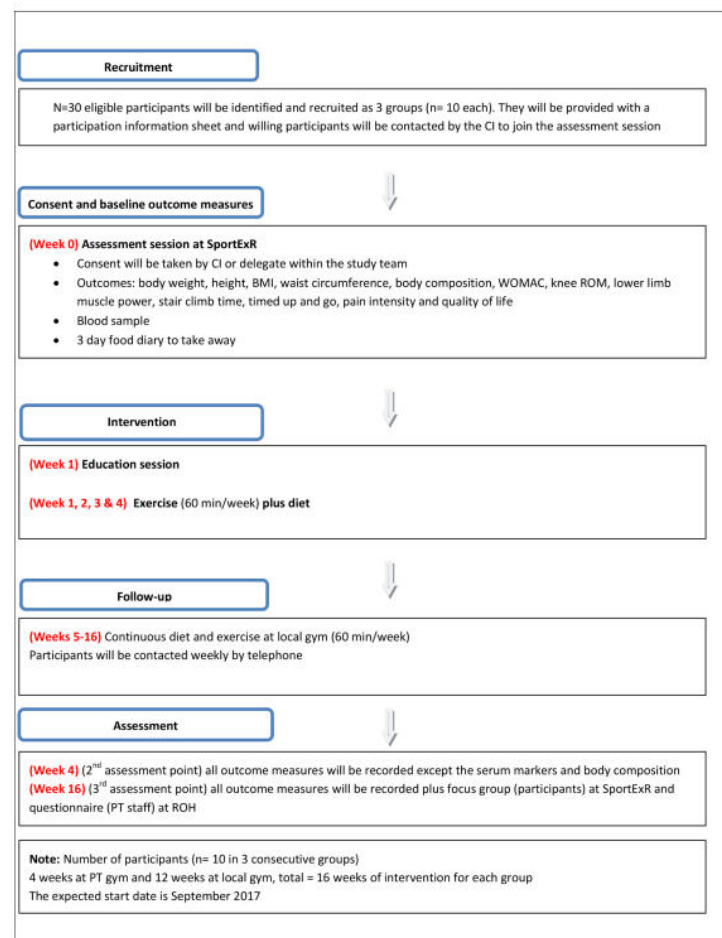


Figure 1 Flowchart of Dietary Restriction and Physical Activity (DRPA) trial flow diagram. BMI, body mass index; CI, chief investigator; PT, physiotherapy; ROM, range of motion; ROH, Royal Orthopaedic Hospital; SportExR, School of Sport, Exercise and Rehabilitation Sciences; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2 Summary of statistical tests

Variable	Form of analysis	How it will be reported	Test
Age (year)	Continuous	M (SD)	Means and SD
Gender	Categorical	Frequency and percentage	Frequency
Height (m)	Continuous	M (SD)	Means and SD
Weight (kg)	Continuous	M (SD)	Repeated measures ANOVA
BMI (kg/m ²)	Continuous	M (SD)	Repeated measures ANOVA
WC (m)	Continuous	M (SD)	Repeated measures ANOVA
WOMAC	Continuous	M (SD)	Repeated measures ANOVA
Knee ROM (degree)	Continuous	M (SD)	Repeated measures ANOVA
Lower limb muscle power	Continuous	M (SD)	Repeated measures ANOVA
Physical function (stair climb and timed up-and-go)	Continuous	M (SD)	Repeated measures ANOVA
Pain intensity (WOMAC)	Continuous	M (SD)	Repeated measures ANOVA
Quality of life (SF-36)	Continuous	M (SD)	Repeated measures ANOVA
Body composition	Continuous	M (SD)	Paired t-tests
Markers of joint remodelling	Continuous	M (SD)	Paired t-tests
Associations between changes in body weight, knee pain, BMI and markers of joint remodelling	Continuous	r	Pearson's correlation

ANOVA, analysis of variance; BMI, body mass index; WC, waist circumference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; ROM, range of motion; SF-36, short form-36.

Dissemination

Findings will be presented to members of the public through events held for the purpose of communicating research into ageing, such as the AgeWell event organised for members of the Birmingham 1000 Elders database.

Data analysis plan

Qualitative analysis techniques will be used to address the feasibility objective

The guidelines provided by Kitzinger⁴⁰ will be followed to conduct the analysis of data obtained from the focus groups. The phenomenology theoretical orientation^{53–55} will use the Krueger⁵⁶ and Ritchie and Spencer⁵⁷ framework analyses. Open questions from the questionnaire will be analysed similarly.

Quantitative analysis will be used to address the efficacy objective

All data will be entered into a database and analysed using SPSS statistics for Windows, V.21.0. Armonk, New York, USA: IBM Corp. Baseline characteristics will be descriptively summarised using frequencies, means and SD or median and IQRs, depending on the frequency distribution of the data. Baseline characteristics will be compared with postintervention data using SPSS, paired t-tests or repeated measures analysis of variance for interval or normal variables. All statistical tests will be conducted two-sided with an alpha level of 0.05. In addition, closed questions from the questionnaire will be analysed using frequencies and percentages. Details of the selected statistical tests are presented in [table 2](#).

Success criteria will be used to determine the feasibility of the combined intervention programme based on the

qualitative and quantitative outcomes.^{58–60} The success criteria are presented in [table 3](#).

Data collection, management and monitoring

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Personal addresses, email addresses and telephone numbers will be used to contact participants. Details will previously have been provided by individuals for this purpose, and all details will be kept securely. There will be no electronic storage of personal information, emails will be printed and then deleted. All paper data will be stored securely in a locked drawer. Personal data will be kept for 12 months after the end of the study to allow patient contact for dissemination of results.

Participants will always be identified using only their unique trial identification number on the case report form and correspondence between the participating sites. The investigator will maintain documents in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

Procedure(s) to account for missing or spurious data

Individual data sets will be checked by the CI at regular intervals and any discrepancies highlighted and listed. All missing and ambiguous data will be queried. These will be viewed and discussed by the supervisory team.

Table 3 Success criteria of the combined intervention programme according to the feasibility categories, using the participants and physiotherapy department staff outcomes

Feasibility categories	Participants quantitative outcomes	Participants qualitative outcomes	Physiotherapy questionnaire
	The combined intervention programme will be considered feasible if:	The combined intervention programme will be considered feasible if:	The combined intervention programme will be considered feasible if there is consensus across the PT department staff to support the following points:
1. Efficacy	Significant changes $p < 0.05$ on the planned primary outcome for the definitive study (WOMAC scale) from baseline to 4 months intervention ³⁰		When they notice any improvement in the participants outcomes and think that the combined intervention programme is better than usual care
2. Adherence	>80% in exercise compliance >80% in dietary compliance ^{29 30}		Adherence to the classes is similar compared with usual care
3. Adaption		None or just minor changes suggested	The combined programme does not require adaption
4. Acceptability		Participants report (during focus group discussion) that they are satisfied and the intervention programme is fitted with their activities of daily living	They are satisfied with participants outcomes They would support the use of the combined programme The combined intervention programme fits within the hospital culture Delivering the combined intervention programme has not increased their work load
5. Implementation and practicality	<10% missing data in each completed questionnaire (WOMAC and SF-36) ²⁸⁻³¹		They would not need any additional resources to implement the programme There are no factors that may affect the implementation, efficiency, speed or quality of delivery
6. Integration and expansion		Participants recommend the combined intervention programme to other patients	The programme could be applied in future The expansion of the programme would have a positive effect on the PT department and/or ROH The cost of the programme will be feasible for ROH and/or other hospital trusts

PT, Physiotherapy; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SF-36, Short Form-36; ROH, Royal Orthopaedic Hospital.

Storage and analysis of samples

Two blood samples (10 mL each) will be taken from each participant, one at baseline and one after completing 16 weeks of intervention to analyse the biomarkers of joint remodelling. If the participant has not given blood in the last 3 months, an extra sample will be taken during the first visit (20 mL) for safety testing. Blood samples for storage will be collected, coded and stored in SportExR for 6–12 months. They will be analysed in the Institute of Inflammation and Ageing, UoB under the supervision of a member of the study team. Collection, analysis, storage and destruction of blood samples will be according to local policy and standard operating procedures aligned to the UoB Quality Management System. Any safety bloods

(for those participants who may not have had a blood test within the past 3 months) will be taken from SportExR directly to the laboratories of Queen Elizabeth Hospital, Birmingham.

Monitoring and auditing

This study team will allow monitoring of the study, including access to source documents as requested. The UoB Clinical Research Compliance Team will review at intervals agreed with CI.

ETHICS AND DISSEMINATION

This study was approved.

All changes are documented in the trial site file and communicated with the Research Ethics Committee (REC), lead site, sponsor and funder. As stated in the procedure section, eligible participants will be provided with a participant information sheet and their informed consent form will be given at SportExR. Also, the participation information sheet will be given to the physiotherapy staff and their consent will be taken before completing the questionnaire.

The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high-quality peer-reviewed journals. The CI owns the data arising from the trial and will analyse, tabulate and prepare a final study report with guidance from the supervisory team. The full study report can be accessed 6 months after completing the trial.

DISCUSSION

The feasibility of the combined intervention programme will be assessed based on several areas of focus.²⁸ It will be considered feasible if the success criteria in table 3 are met.^{30 59 60} If the participants suggest major adaption to the study design, for example, cancelling the education session, the programme will be considered as unfeasible.

This feasibility study will answer the central question of whether a combined intervention programme is feasible and acceptable. It is hypothesised that a combined intervention programme of dietary restriction plus usual care for obese older adults with knee OA is feasible and acceptable to the ROH physiotherapists. Participants will experience benefits and the therapists will support the usual care programme plus weight loss in this specific sample. All outcome measures including WOMAC, body weight, WC, BMI, musculoskeletal function (knee ROM and muscle power), musculoskeletal function (stair climb and timed up-and-go), pain, QOL and markers of joint remodelling will show evidence of improvement due to reduction in the participants' body weight, inflammation and pain that which lead to overall improvement in function. It is hypothesised that there will be associations between changes in body weight, knee pain, BMI and markers of joint remodelling.

Participants may find that following designed plans of diet more useful than following general advice. This study has based on several factors to improve compliance with the exercise in the remaining 12 weeks of the intervention such as knowledge, providing facility to local gym and weekly phone call.^{61 62} The laboratory test will provide exploratory data for new biomarkers in knee OA. However, the results of this study will add clinical evidence to knee OA management in older adults with obesity and it may inform the provision of usual care of knee OA.

The qualitative component of the study will allow the participants to express their views and impressions about the combined intervention programme and this will

inform about the optimal body weight reduction methods and the best way of delivering exercise to achieve better outcomes. Also, the views of physiotherapy staff will be invaluable to confirm whether a combined intervention programme of dietary restriction and usual physiotherapy care is feasible in a hospital setting and could be incorporated into usual care.

Amendment

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor will submit a valid notice of amendment to the REC for consideration.

Author affiliations

¹School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK

²College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

³MRC-Arthritis Research UK Centre for Musculoskeletal Ageing and Health, University of Birmingham, Birmingham, UK

⁴The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK

⁵National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, Birmingham, UK

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Contributors ASA prepared the first draft of the manuscript that has been reviewed and approved by CAG before circulating it to all coauthors. ABR, GB and FP had critically revised the manuscript and provided their input before submission for publication. All the coauthors have been involved in the study design and developing the protocol.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study is approved by the West Midlands-Solihull Research Ethics Committee, REC ref: 17/WM/0122, protocol number ERN_16-1432; RG_17-024, and V.6.0 approved on 10 January 2018 by HRA and the ROH R&D Foundation Trust.

Provenance and peer review Not commissioned; externally peer reviewed.

Author note The protocol was developed by the CI and her supervisor and reviewed by the coinvestigators which include qualified medical staff at ROH. This is a low-risk study which has received peer review from the student supervisors plus independent peer review by ROH R&D Dept and an academic colleague (Dr Leigh Breen, SportExR).

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APPENDIX 4.1 TRANSCRIPT OF THE FOCUS GROUP DISCUSSION

Focus group discussion/ 02 May 2018 at SportExR

Dr Alison Rushton, Asma Alrushud, P1 and P2

Ali: Have you suffered from a long time.

P04: It developed very quick

Ali: and you (she looked to P01) is that so quick again

P01: No, I had pain from long time I've been tolerating my pain and then I can't take it anywhere and I went to my GP and my GP sent me to the orthopaedics and then to this programme.

Ali: OK and when you say from long time this sound number of years you suffered that

P01: Yes, because I've suffered from lymphedema from 20 years but then about 2 and half years

Ali: Ok so 2 and half years specifically pain was beginning

P01: I was tolerating and tolerating and tolerating because of my work consist walking and in one moment I can't tolerate the pain so I went to the GP and the GP referred me to the orthopaedics and had exercise done. I went couple of times and he said what would I want first before the operation (treat obesity or have injections), I had injections four times the he said it is a risk with injections so he said the only thing is go for physiotherapy and see how get on lose weight normal and then see how progress and then if you lose that amount of weight then can go ahead with the operation but I'm suffering a lot.

Ali: I will come back to that; P04 you just said how much was that is so quick

P04: I faced to experience a thing about a year ago. In May last year I went to the doctor and I was given an injection in my right knee but because I left my weight on my left knee it become more trouble soon than the right knee. The injection actually did not have much effect in my right knee at all and like you (she looked at P01) we put up with thing because life takes over work and family ..etc. and it was about October/ November when I went to the doctor because the building where I work its multi-purpose building , ground floor school. I need to cline up and downstairs and because I'm doing learning support the children didn't come to me I have to go to the children so up and down the stairs and I was finding it very very difficult on my knees hence I referred to the orthopaedic, I think it's November I had the appointment with the orthopaedic the x-ratation told me that very little cartilage left, had an injection in my left knee and it hard to say which one, I would say the left one is still more painful one to the right and I got here again lose weight, gentle exercise but I mean as Asma would tell you if I take something I go full head on and over did it and took myself backwards and that really really took me backward rather than doing thing slowly I jumped on too quickly too far and hurt myself too much.

Ali: OK and again think about the study, have you previously done any exercise classes or anything like that?

P01: I was in the gym anyway like I said before get a married it was part of my day 4-5 hours in the gym every day once I got married and have children just..

Ali: Yeah change does not?

P01: that took over and I developed active thyroid that made me low so much and I had the lymphedema anyway and from that you know just developed pains.

Ali: looked to P04 and say and you had doing the gym or exercise?

P04: No, I was very thin until I had my third pregnancy I had developed what they call it pre-claps isn't?

Ali: Oh yes, yes

P04: Since then 25 years I'm not able to lose the weight and never been in the gym and this this is an opportunity get braces too much too quickly so I now realised that gentle exercise just needed (she laughed).

Ali: Another question thinking about before you're involved with that when you had pain or stiffness did you find any strategies that help to improve the pain or relieve the stiffens is there anything you could do found in your own that help you?

P04: At night bracing on my knees it's so difficult to find suitable position but when you stablish that position in bed not moving to staying in that position but it is piece of stink, how long relief your pain.

P01: I used about 4-5 of ultra ...or Robison db on my legs.

Ali: Asked P01 did it help?

P01: Well, it did occasionally but sometimes it did not work at all. I wake up at morning and that pain not going that cause most of the pain in my leg.

Ali: You both can pick up with things aggravate it and made it worse but it hard to find something specifically made it better?

P04: Yes

P01: Yes

P04: I did actually bought something I can't remember is it fibro ..fibra! I can't remember what it is called and very cold and everybody but I found it.. I did not realistic any affect at all.

P01: Well it did work on the other part of body, I have pain and when use it that pain went but on actual pain that not going, even now I use and use that as well other part of the leg it worked, in the main part did not work! I just use it at the night time to relief it and I could sleep.

Ali: OK and thinking about the intervention that you've been involved in so the first key question really do you gained any physical benefits from the intervention and this experience?

P01: A lot. My son was really pleased he said mum you did very well. It is four months does not matter but I got here, I tried very hard to lose that weight to have a good leg and walk properly.

Ali: (looked to P04 said) and you?

P04: I haven't lost weight but I think stress, family stress in my life but from healthy eating point of view I feel better in myself and "touch wood" my knees aren't too bad as I said I go down to work for only 2 days/ week so that's less impact on my knees and I do have 2 family members who are not very well at the moment. So it's very very stressful, so diet all the time is being very difficult especially if you just grapping the hospital sandwiches when you there but from a healthy eating point of view I feel I'm better in myself and my knees I mean I'm walking I'm not limping like I was. So I haven't lost any weight but I it's just doing gentle gentle exercise and going for walks it supposed to the other thing may impact. In fact on the 17th of May I think it's! I got an appointment at the Lacter clinic and is not far away from where I live to carry on with a programme like this and hopefully with working 2 day/week I can do more of it. But certainly I found

the advice that have been given and gentle exercise it supposed to go for it, I feel better! I feel better! And I'm not using anything on my knees the only thing is have a box of Proxin when they are very bad I talk one of those. I am not taking anything for them at all. No

Ali: fantastic! So it's a big difference

P04: It's a big difference

Ali: (looked to P01 and said) and you got that 4kg you lost which's brilliant, what about any other physical benefits. If you noticed any difference in your pain, your stiffness or ability to move

P01: Well, there is stiffness because I can't walk and stop working but because I work and I walk so I think that's pain! Whatever I lost that fine, my leg what is supposed to reduce pain on that it's not doing anything! gaining the pain

Ali: do you mean the pain is actually increased and is that in general area or in local area?

P01: just that knee part I mean I got,, I went to lymphedema clinic and she prescribed me the special socks to compressed the leg that works on the lymphedema but the knees aren't

Ali: Is that pain different before you started? Is it worse than before started programme or the same or you feel it is worse?

P01: Yes, it is worse

Ali: you got benefits from losing weight but not getting any benefits from the exercise side and what you have done

P01: Because when I went to the gym I explained to the gym person there I told that my problem is with my knee she showed me what exercise to do on leg but she said not over do it just do it slowly! I worked on that after I finish the exercise on the knee I got a lot of pain

Ali: how long does is that last?

P01: last when I go home and have a shower when I set down I can feel the pain.

Ali: So, that's in evening! And do you both notice any difference when exercises as you carried on is the exercise got easier, harder or the same?

P01: Easier

P04: Easier

Ali: So, both of you easier to do.

P01: I tried a new thing in the gym and feeling better

Ali: What do you describing here is the other parts of the body is feeling better from the exercise, even though the pain?

P01: yah

Ali: Ok brilliant! And you both talked about activities you're doing in your life like walking and work what about house work did you notice any difference in doing house work?

P01: I do the house work perfect, it's when I sit down relax ,,,,,,take ten minutes to start walking, climb stairs is terrible! I can't climb stairs at all.

P04: See I have the opposite I mean I can go up them, it is the coming down and that's always be my problem but it's easier again I think I don't know if weather affect it. I feel weather affect it.

P01: Oh yeah, some times

P04: (she continued) when it is warm day I go down stairs and gosh I didn't feel that but you know in those wet cold days it's still a little slower to walk down than to go up.

P04: Yah because I feel that in the other leg. When it's cold I can feel my knee big tense than that, but when it warm I feel fine, no problems either the whole month work

Ali: OK, then thinking specifically about the diet, did you feel satisfied with the diet? was that easy to follow?

P01: It was easy to follow but it was making me hungrier then I done it for a month and then I said let change so what I did was go back to what I was eating but reduce everything , the oils, the salt, the spices and then reduce the portions as well so that's worked fine for me. I'm not hungry, I'm satisfied, and I'm not snacking here and there and everywhere even my hair is growing back

Ali: You noticed a difference in your hair?

P01: Yes, my hair is growing and my nails are growing

Ali: Ok. So, generally feeling whole body feeling much healthier?

P01: Yes

Ali: That's lovely. That's really good.

P04: It's the portion size increasing the vegetables I'm a salad person not vegetable person but I'm eating vegetables now the one thing I did not like and I did say very early I don't like smoothies I need the crunches so it's the whole fruits that I'm eating that supposed to eating, I need the crunches. Yes reducing portion size I started of using the 3 suggested new portions then I started to use the way which receipts book just for variety and reducing how much I'm eating and also maintaining recipes as well to suit the family because I have to cook for the family. When you get an ill person at home and sometimes these days made me think I can't do that. Because I think stress make you hungry so I don't know whether of be your fairy cases but I'm not strictly adhere to it through the full 4 months. However, the time that I have done it or before the time I have to done it (looked to P01) like you say it's interesting to thin about my hair I have not thought about that but it is not as bold my hair grow back I feel its fuller than than it was but in myself I feel healthier and not hungry my feeling always before to go to bed and eat apiece of food but I don't do that at all.

Ali: OK, so we got a nice description there both of you how was the programme easy or difficult to stick to. What do you think in particular things that helped you stick to the programme?

P01: the determination

Ali: Internally within you have determination to do it!

P01: Yes

P04: Thinking that this will help to ease the pain because when the pain was bad you seeking anything to make the pain less and something like this will possibly work keeping it to go. When she said it could be beneficial as she said running from one hospital to another, downstairs and trying to find departments. Where I think going back to November OMG I can't do this anymore but whether adrenaline or something it catch you going and I have to be onset what is the additional exercise of walking or something it made the joints movable I don't know I'm not medical! I'm just

Ali: You're giving a great description, which is lovely.

P01: For me I mean I did use walk but now, it's getting better the movement but the pain getting worse. Mine is getting slow and started to use stick; it's my balance.

Ali: So the stick specifically..

P01: Stick it just to help my balance because from one terminal to the other terminal so difficult walk

Ali: Any other things that help to stick with the programme so I'm wondering about family around you things like this

P01: Of course

Ali: So that's being important?

P01: Yes, my sons are supporting me, very supporting. Encouraging me to carry on, carry on Mom! Because they said mum you only young you're not old yet so because my mom was the same. I think when she was 57 she got arthritis as well she had operations but they did not work. She had car accident! My sons said don't go that rotten you only young

Ali: so they is giving you good opportunity, then she looked at P04 and said your family encouraging you as well?

P04: They have but from selfish point (laughs). No, I mean I'm just joking. Yes family support is important and it's for your self-steam as well you know rather than you can't keep it if you out of company I can't keep up with you I have to go this way because she's not able to manage the stairs or something like that so you know it make you feel better but another time being helpful but always keep up with them, so yes.

Ali: Was the weekly contact with the study team member helpful for the motivation point for you?

P04: Yes, sometimes I was big short with you because it depends on what is happening at home! I most apologies. Sometimes, I don't have time to speak to you!

P01: Yes, for me coming here in my days off so OK

Ali: Access to the gym did that work OK so if you need to access anywhere or that being barrier?

P01: At one time I had wait for car park honestly but always early. I know the hospital car park noticing that, the blue card! Come little bit early.

Ali: you talked little bit about things difficult with the intervention but any other specific barriers things stopped you doing it, you said few thing already work, family, stress and things some time interfer?

P04: It was not expensive thing to do I already buy food but I need to modify it so it was not expensive to doing anything at all.

P01: No, everything was bought already in house just to use what was there and just carried on normal food

Ali: Very good. Just going back to the initial question when you talking about the pain that you experienced before you started this was pain affecting or weather was easy to do the intervention or not? Or not really? (she looked to P04 said) you just describing good days and bad days..

P04: yes, on bad days I think with me I think I am a different case really in the way home life was being a big part as well and so feeling miserable because things were not going well I did some exercise but it's just so low because you know how much spend time in hospital driving home, grabbing sandwiches or something at

the hospital set other factors that take these factors away I think my answer would be different so when I describe good and bad days those possibly days when I faced these, it was not depression but it was

P01: I have a problem at work because I was walking and the pain you know but as soon I walked out the door everything just cleared. So it's half and half for me I just let everything go. Once I walked out the door I can.

Ali: It sounds when you had days more difficult and prevent you from doing the intervention, did that last?

P01: No

P04: No

Ali: Ok, we talked about the intervention as a whole quite a bit, the exercise and the weight lost combined together, was one easier than the other or would they be the same to do?

P01: the same

P04: I think the exercise for me was more difficult, the eating was not too bad when you get in your mind said this is for your own good which over that pressure this is feeling benefit then it becomes unequal balance really

Ali: OK, and again thinking particularly for the study going forward do you think there is anything we need to change about the intervention so two of you know experience of doing it. Is there anything that needs to be adapted to make it even easier to adhering?

P04: I think from my point personal of view, someone hadn't exercise for 50 years do tell them the exercise need to build up as supposed to just going in because I worked from body have not moved too much and sat myself back but for diet point I mean it always in terms of understandable, for me not understanding the exercises but I think

P01: Just to let you know that to going from point A to point B it's not worry about it what do we want first and what do we feeling.

Ali: And things like the timing the classes and help you to have the diet plan

P01: To me because I coming to the classes on my days off but some people who can't get time go so it depends on them, you know!

P04: I got time from work to attend the classes so it's fine.

Ali: You said really you both satisfied with the results of the programme but interestingly in different ways slightly difference some areas

P01: I mean I'm Asian race as well doing this programme a lot of people my sister as well she is waiting for her GP to referred her what I'm telling she suffered the same thing like me I told her I am going the classes and I am doing physio then going to the gym I told her that. She said I just wait to my GP to tell me so education, educating

Ali: sensible interesting that she is waiting for someone to tell her she can do it programme so this programme you can do in your own but sounds she definitely needs motivation

P01: She is that kind of person who not listen to me, because I'm the younger she won't listen to me. But if somebody with authority telling she's recently had an injection in her knee pain feel but most fine go to the gym come with me because I'm in a lady's gym getting her education so is difficult talk

P04: What I think, going to the gym together

P01: Yeah, make friends, even in my gym he first its achievable 2-3 months ease the symptoms that you feeling. Exercise and diet.....baby steps.

Ali: I like what you said about the social interaction between it obviously motivation as well and also you said in the lady's gym so are these ladies exercising together was that important to you? Interesting the interaction between you

P01: I think the distraction men distract women once you do that its done just taking to another person. Just relax then moving to something els

Ali: (looked to participant P04) and said any preferences in the type of gym as well?

P04: I prefer a ladies only as well but trouble it's I don't have anyone to go with but I'm determined to go and start this programme in May whatever it would be I don't know and hopefully it will be a ladies only but to be with someone. I think being with someone helps you because when you in your own.. I don't know

Ali: A lot of people describe that when something do collectively would be easier and could be motivating!

P01: Well I go to gym I go to work but if I preferred is taking somebody with me

Ali: we talked about this programme is there any area we did not talk about as useful the different types of exercise you are doing any exercise you would like to move from this or any exercise modifying?

P01: For me I found the bicycle was the most difficult because you know turning the peddles it's hurting my knees because I can't bending so I found that difficult but any others exercise is fine.

Ali: is bicycle get easier every time or not change?

P01: No change.

P04: I found that easy which I found difficult is the squat or aerobic exercise where I'm.....my knees, my legs I find that very very difficult walking but the squat or anything I find it very difficult

Ali: Did they get easier when go through or no changed?

P04: I think ..to much so I have not tried the proper squat and I am not lunges properly, like baby lunches and baby squat because I'm too scared to does..so yeas. If there is something I want to say is lifting the knees col that all fine if the knee position basically afraid of

Ali: was that before the study or because specifically from doing the exercise cold weather or

P04: I t was one time in the gym when I really week 3 or 4 I can't remember now I over worked it and stiff and I have not attended it since.

Ali: Any other comments about the exercise?

P01: Make sense

P04: Just do gentle exercise rather than taking yourself down after work and I feel difficult at the morning in the feeling of stiffness I recognised that but I don't have I can stand-up quickly where is before

P01:.....even get up from chair I can't put pressure on my knees done all these exercise but weight on my knee and the leg fine now just the knee when I'm working and collecting money from the.....then the other part of the leg hurt because put pressure on knee from here (ant aspect of her knee)

Ali: If I try to pull all that discussion overall do you think the study was successful?

P01: Yah

P04: Yes

Ali: lovely and both of you describing how the intervention has affected you in a positive way I think I may right?

P01: Yeah

P04: Yeah

Ali: Thinking from things you just said which is nice and also both of you saying you are going continue do you think will be easy to continuo or difficult to continuo?

P01: It will be easy for me to continuo I think just swap my knees sorted and yes it would be fine

P04: See I'm going to continuo but it's the fact I know that I'm not losing any weight and now been suggested to me not lay on medical where I got thyroid problem Because I recently notice my nails are I'm eating sensibly but the time not losing any weight but I'm going to continuo and I'm going to procsi that thyroid problem.

P01: I got under active thyroid problem which slow metabolism I mean 4months I should lose little bit more than 4 kilos. It is good to lose 4 kilos over 4 months but should be more because the thyroid slow. I am not gonna complaining you know but it's gonna take time and I accept that.

Ali: It's interesting to listening both of you because you gave a nice description there analysing weight loss alongside other potential problems in your case or exciting problems. So you recognising you should lose weight from what you done and there may be something else preventing that so that quite interesting to listen to you both and do you think you will continuo both equally it similar to the question that I asked you but is it easy to keep be able to continue both of them equally. It is similar to the last question that I asked you but will be easy to keep the diet and exercise. Are they equal or one easier than the other?

P01: To me they are equal

P04: To me both of them the sensible eating and doing..., I can see the benefits from the exercises simply because I don't have the pain that I'm experiencing before and the fact that I am not reaching out of the tablet, the fact I can't remember the last time I had at tablet probably Jan/ Feb was so it's obviously have an effect.

Ali: You said the cost early on I think both said the cost was not higher for diet component of the programme what about the exercise did you have any cost that needed for exercise? Did you pay anything to the gym or..?

P01: Well I paid to the gym because I have paid to monthly membership pay for every session that I go to and paid for new trainers (laugh)

Ali: And is that an acceptable cost to you not barrier to you?

P01: Yes.

Ali: (she looked to P04) any cost linked to the exercise?

P04: I haven't joint the gym and I don't know what is going to be like (she looked to P01 I have to speak to you where to go, linked up with you but no, no at all because I mean if anything cheaper.

P01: and also with me my sons are helping, they are on the diet as well whatever I eat they eating the same thing because they trying to improve their selves as well

Ali: and did they feel benefit?

P01: Yah, they said mom always buy broccoli buy always buy vegetables get chicken, get fish then once I cocked they watching me how I cock food they do it for their selves when they want to eat. My elder son day his portion is small as well my portion is once or twice a day

Ali: and is that extended to the exercise? Do they exercise as well?

P01: Yen, they go to the gym. My oldest go to the gym and my youngest son walks to work go and back

Ali: Do they start when see you do this or they're starting from a while?

P01:

Ali: (then looked to P04) any impact on your family?

P04: Not really. Because...my husband can't joining this programme and no.

Ali: and final question then do you think the intervention worth to offering to other people with knee OA?

P01: Yes, because I know that I'm suffering a lot and obviously the other person suffering you know if this helping me it should help them as well.

P04: definitely yes

Ali: As long you said something you can see it benefits you said that good reason to offer it. I'm just picking the pain is better then you saying your pain is worse but you think the other benefits may still make it worth. OK, lovely. Anything opportunity to say hopefully these questions or comments from your experience is there anything else.....with these question?

P04: It covered everything I expected really, I don't know.

P01: I think work with people to get more physio doctors referred other people to go weather they do it or not but they need to be educated about that physiotherapy is good you know

Ali: So we can hear ourselves about things that motivate you.....big issues in this area, how motivate people and hoe check they don't have barriers from doing this and hoe to motivate

P01: Sometimes

P04: I think one of the barriers from going to physio is the time of work person does weather they got the time off to go. I mean the four sessions but depending on the employer weather they allow the person time off. So it difficult depends on the time of their work it depends on their job for me I would recommend it for anyone.

I don't know whether arthritis is heredity or it would lifestyles, I am not qualified to say this. But from my point of view I can see what I was doing was wrong you know we say Oh yes will have this this look nice will get that we don't need that.

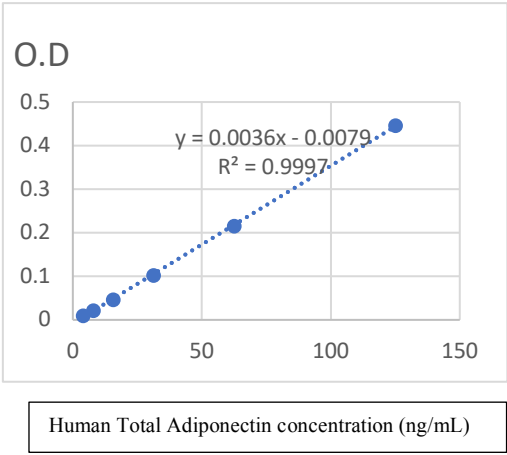
P01: You know in my family it's started from my Mom and my sisters they all got the same problem as me but is not the knee is the legs with my other sisters. So to me I think ..from my mom to me I think that so I don't know it's heredity or not you know

Ali: So it's important to family to understand that when you described that nicely when you talking about your sisters.

P01: Yah I mean my elder sister she died last year she had the operation but she developed an infection in her lung. I don't know the operation would bad or good she developed an infection in her lungs and she passed away from that so there are so many factors you know she have operation or she haven't operation even my sister worried because the next to her is her and the other sister she had an operation and she went abroad but her job left when she developed an infection so taking care of yourself parents and says to them we should take care of yourself id you have other take care.

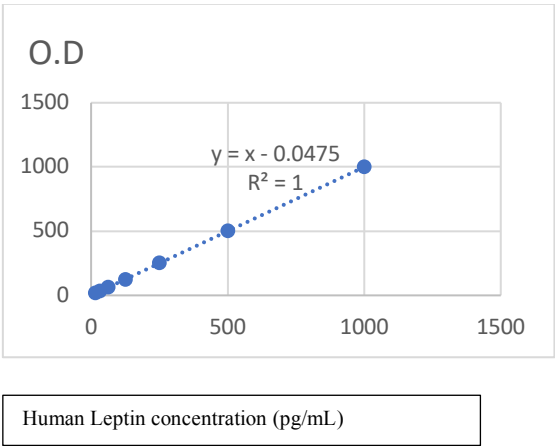
APPENDIX 4.2 CALCULATION OF ELISA KIT TEST FINDINGS

1. Adiponectin



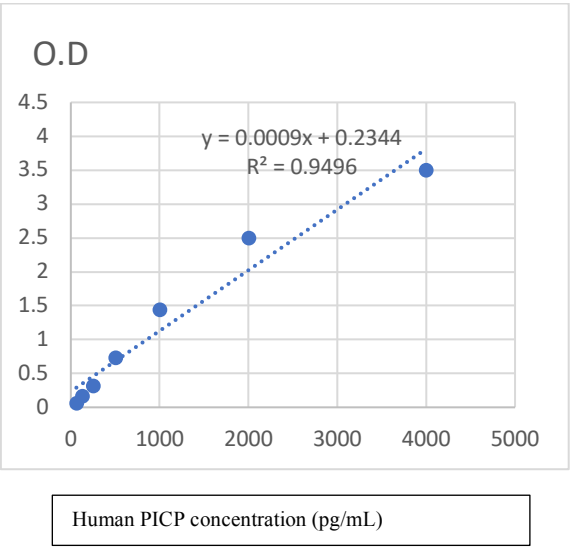
WL:450	WL:540	Corrected 450-540	CONC. (ng/mL)
0.158	0.005	0.153	44.6944444
0.0975	0.003	0.0945	28.4444444
0.229	0.0065	0.2225	64
0.167	0.002	0.165	48.0277778
0.2055	0.0165	0.189	54.6944444
0.1825	0.0305	0.152	44.4166667
0.048	0.002	0.046	14.9722222
0.293	0.0065	0.2865	81.7777778
0.5675	0.0145	0.553	482.1818
0.7515	0.012	0.7395	651.7273
1.114	0.0195	1.0945	974.4545

2. Leptin



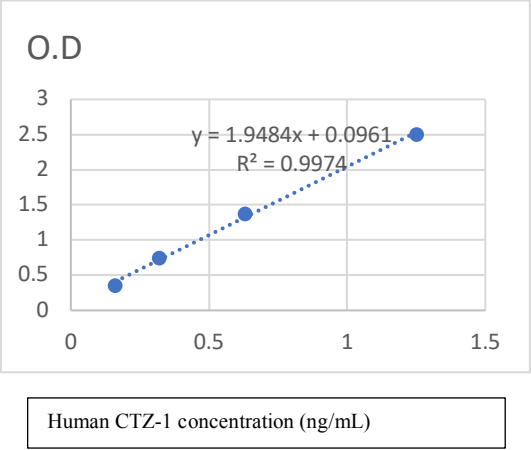
WL:450	WL:540	Corrected 450-540	CONC (pg/ML)
0.114	0.002	0.112	81.27273
0.583	0.0025	0.5805	507.1818
0.4365	0.002	0.4345	374.4545
0.8255	0.008	0.8175	722.6364
0.645	0.0075	0.6375	559
0.472	0.0035	0.4685	405.3636
1.4505	0.0435	1.407	1258.545
0.0215	-0.003	0.0245	1.727273
0.5675	0.0145	0.553	482.1818
0.7515	0.012	0.7395	651.7273
1.114	0.0195	1.0945	974.4545

3. PICP



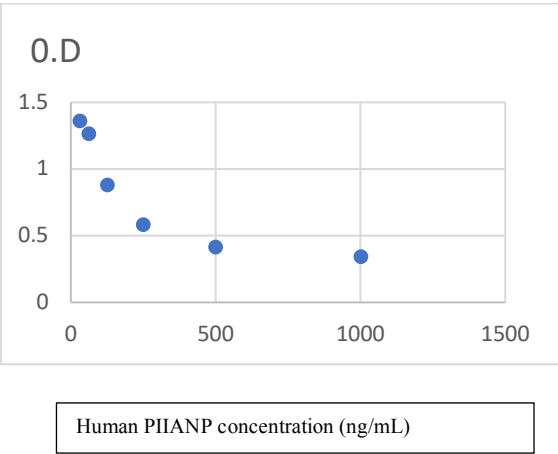
AVERAGE	CORRECTED	CONC. (pg/mL)
3.9375	3.842	3886.171
3.2295	3.134	3134.712
3.3055	3.21	3215.377
3.366	3.2705	3279.591
3.076	2.9805	2971.79
3.2135	3.118	3117.73
2.289	2.1935	2136.481
1.9125	1.817	1736.87
3.606	3.5105	3534.323
3.2775	3.182	3185.658
3.613	3.5175	3541.752

4. CTX-1



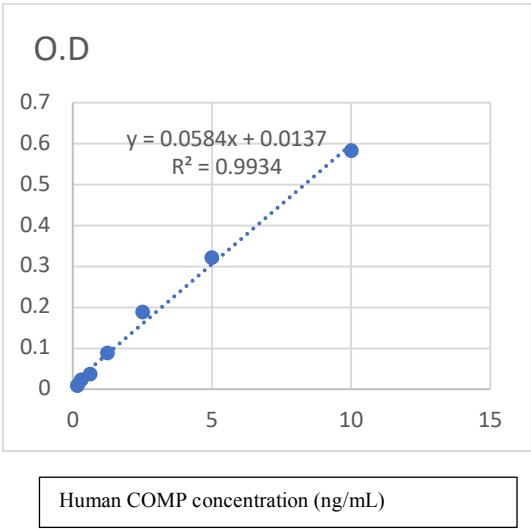
AVERAGE	CORRECTED	CONC. (ng/mL)
0.329	0.243	0.075395
0.2345	0.1485	0.026894
0.3455	0.2595	0.083864
0.152	0.066	-0.01545
0.1795	0.0935	-0.00133
0.3365	0.2505	0.079245
0.2335	0.1475	0.026381
0.2975	0.2115	0.059228
AVERAGE	CORRECTED	conc.(ng/ml)
0.3515	0.2655	0.086943
0.2515	0.1655	0.035619
0.186	0.1	0.002002

5. PIIANP



AVERAGE	CORRECTED	CONC. (ng/mL)
0.045	0.377	631.6059
0.0515	0.1995	756.3
0.0815	0.254	718.0136
0.0595	0.263	711.6911
0.0465	0.461	572.5957
0.0495	0.268	708.1786
0.069	0.763	360.4401
0.0495	0.5685	497.0767
0.0525	0.3065	681.132
0.0645	0.1635	781.59
0.074	0.783	346.39

6. COMP



WL:450	WL:540	Corrected 450-540	CONC. (ng/mL)
0.1165	0.0005	0.116	1.751712
0.014	-0.001	0.015	0.02226
0.0945	0.0065	0.088	1.27226
0.019	0	0.019	0.090753
0.1375	-0.0005	0.138	2.128425
0.0245	-0.003	0.0275	0.236301
0.144	-0.0015	0.1455	2.256849
0.2485	0.004	0.2445	3.952055
0.1505	0.001	0.1495	2.325342
0.192	0.003	0.189	3.001712
0.1025	0.003	0.0995	1.469178