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The effect of physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese elders with knee osteoarthritis: a systematic review and mixed method data synthesis

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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 elders with knee OA.

Objective

To evaluate the effectiveness of combined physical activity and dietary restriction programmes on the musculoskeletal function of overweight and obese elders with knee OA.

Information sources

A detailed search strategy was applied to key electronic databases (Ovid, Embase, Web of Science and CINAHL) for randomised controlled trials (RCTs) published in English prior to 10th December 2015.

Participants

Participants with body mass index (BMI) ≥25kg.m^{-2}, aged ≥55 years of age and 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 (QoL).

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 2 trials with n=155 participants did not support the combined intervention programme. Narrative synthesis identified had higher scores for both body weight and the 6 minute walk test in the intervention groups. The physical component of the SF-36 was improved in the intervention group compared with usual care.

Conclusion

There was moderate evidence of no effect of the combined intervention programme on mobility, while the preliminary synthesis showed differences for changes in body weight, mobility and QoL.

Protocol was registered in PROSPERO (CDR42015019088).

Article summary

Strengths and limitations of the review

- This is the first systematic review of combined physical activity and dietary restriction interventions in overweight and obese older adults with knee OA.
- The protocol of this review was registered in PROSPERO and followed the PRISMA guidelines and the Cochrane handbook; GRADE was used to evaluate the quality of the included trials.
- The review included a mixed methods analytical approach.
- Few eligible studies were identified however important information is highlighted which could inform clinical practice.

Key messages

- The clinical recommendation for combined exercise and dietary intervention to manage knee OA is not well supported by the evidence.
- The quality of evidence of benefit of combining exercise and dietary interventions in older overweight/ obese adults with knee OA is unclear.
- High quality evidence is needed to investigate the effect of a combined intervention programme on musculoskeletal function and other important outcome measures such as body weight and QoL.

INTRODUCTION

Rational

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) [2-4]. Moreover, OA is the fourth predicted cause of women's health problems. In the United Kingdom (UK) there is approximately 4.7 million older adults aged 45 years or over experiencing knee OA symptoms [1, 5]. In addition, more than 20 million people seek treatment for knee OA in the United States (US) [6, 7]. 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 [5].

Unfortunately there is no specific treatment for knee OA. Most recommendations describe three treatment modalities: non-pharmacological, pharmacological and surgical [8, 9]. Most knee OA evidence-based guidelines recommend nonsurgical treatment [10, 11] and most general practitioners prefer the non-pharmacological and non-surgical interventions as the first line of treatment (recognised as 'usual care') [8]. 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) [1, 11]. Several studies recommend obesity control for decreasing knee OA burden, since a decrease in body weight will lead to a reduction of joint load and inflammation [3, 11, 12]. 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 [13]. Moreover, the appropriate percentage of body weight reduction has been investigated in a systematic review and meta-analysis of five randomised control trials (RCTs) [14]. The risk of bias of included RCTs was assessed using the Jadad score (an instrument designed to measure the possibility of bias, scoring 0 to 5 with low scores indicating high possibility of bias) [14,15]. The review authors assessed all trials as moderate risk of bias, with 3 RCTs scoring 3 and 2 RCTs scoring 2 [14]. The pooled effect sizes were 0.20 (95% CI 0 to 0.39) and 0.23 (0.04 to 0.42) for pain and physical disability respectively with a weight reduction of 6.1kg (4.7 to 7.6 kg). They 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 [14].

In addition to weight reduction, clinical guidelines for knee OA management and level 1 evidence recommend exercise therapy as the main intervention [14, 16-19]. Moderate intensity aerobic exercise (e.g. walking) is recommended to maintain musculoskeletal

function and reduce pain [14, 16, 17]. Combining a weight loss programme with exercise therapy may help overweight and obese elders 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 health care setting [20]. Moreover, for those who are eligible for unilateral TKR, non-surgical intervention may delay their surgical intervention for several months [21]. 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 elders 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 elders with BMI ≥25kg.m^{-2}, 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 the musculoskeletal function of overweight and obese elders with knee OA.

METHODS

Protocol and registration

A systematic review was conducted according to a pre-defined protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P guidelines [22] and the Cochrane handbook [23]. The review was registered on PROSPERO on 1/4/2015 (CDR42015019088), and is reported in accordance with the PRISMA statement [22].

Eligibility criteria

Inclusion criteria

- Older adults (aged ≥55 years, men and women).
- Overweight or obese with body mass index (BMI) ≥25 Kg.m^{-2} [3].
- Radiographic evidence of tibiofemoral OA (unilateral or bilateral), grade I-III (mild to moderate) [24].

Exclusion criteria

- Full article not written in English.

Studies

Randomised controlled trials.

Interventions

Combined physical activity and dietary restriction programmes.

Comparators

Usual care (constituting non-intervention care e.g. advice or intervention care which may include; physical activity alone, 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, (including: mobility, joint range of motion (ROM) and muscle strength).
Secondary outcome measures: pain and QoL.

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

- The Cochrane Library: Controlled Trials Register, NHS Economic Evaluation Database.
- 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, Organizational such as UK department of health, World Health Organization and NHS (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 13th February 2015). The definitive search strategy was run by two independent researchers (ASA/AMK, 10th December 2015). Endnote 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 (supplementary file 1).

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 [25].

Data collection
Using a standardised form (developed by ASA) based on the Cochrane Consumers and Communication Review Group's data extraction template [26], 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 tool [27] recommended by PRISMA [22]. 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 [27].

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-minute walk test at 6 months) using the random effects model [28, 29]. Ninety-five percent confidence intervals were reported for the summary statistics and the standard deviation was calculated from the standard errors and confidence interval [30, 31]. 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 [32, 33].

Synthesis of results

A mixed method analysis was required to synthesise the available data [28-33]. For the meta-analysis, no raw data were available, and therefore data analyses were conducted on the final summary statistics reports. Standard deviations were estimated from reported SE and CI for all available data [29]. 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 [29, 30]. For the modified narrative synthesis, change scores were used for trials when no other data were available [29-31]. 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 [32, 33].

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 standard errors or confidence intervals to SD [32, 33].

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 [32, 33].

Additional analyses

Grading the quality of evidence approach was used to evaluate the quality of evidence included in the meta-analysis [34, 35]. The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) software [36] was used to evaluate the quality of evidence included in the meta-analysis. This approach provided a system for rating the quality of evidence and determining the strength of recommendations for clinical practice guidelines [34, 35]. 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' [34, 35]. Each RCT evaluated as 'high' quality evidence was modified according to five negative and two positive factors [34, 35]. The Cochrane risk of bias assessment tool was used for this component [27]. 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 [34, 35]. 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% [35]. 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 [35]. Otherwise, the quality of evidence was downgraded by one or two levels if inconsistency of the results was classified as serious or very serious [35]. 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 [34]. 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 [35]. 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 [34, 35]. Publication of bias was undetectable or strongly suspected according to GRADE software [36]. The selective outcome reporting domain of the Cochrane risk of bias assessment tool was used to evaluate the publication bias [27, 35]. 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 [35].

RESULTS

Study selection

Three RCTs (n= 794) were included. One was a pilot trial [37] and two were definitive trials: the Arthritis, Diet and Activity Promotion Trial (ADAPT) [38] and the Intensive Diet and Exercise for Arthritis (IDEA) [3]. For the ADAPT trial, there was a main trial report, and two additional articles with further analyses of additional outcome measures [39, 40]. The trials used two comparators: An exercise programme in the pilot study and IDEA trial [3, 37], while usual care (healthy lifestyle) was the comparator in ADAPT [38]. 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 [25]. 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., (2000) [37] 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) [38]. The study flow diagram is presented in Figure1.

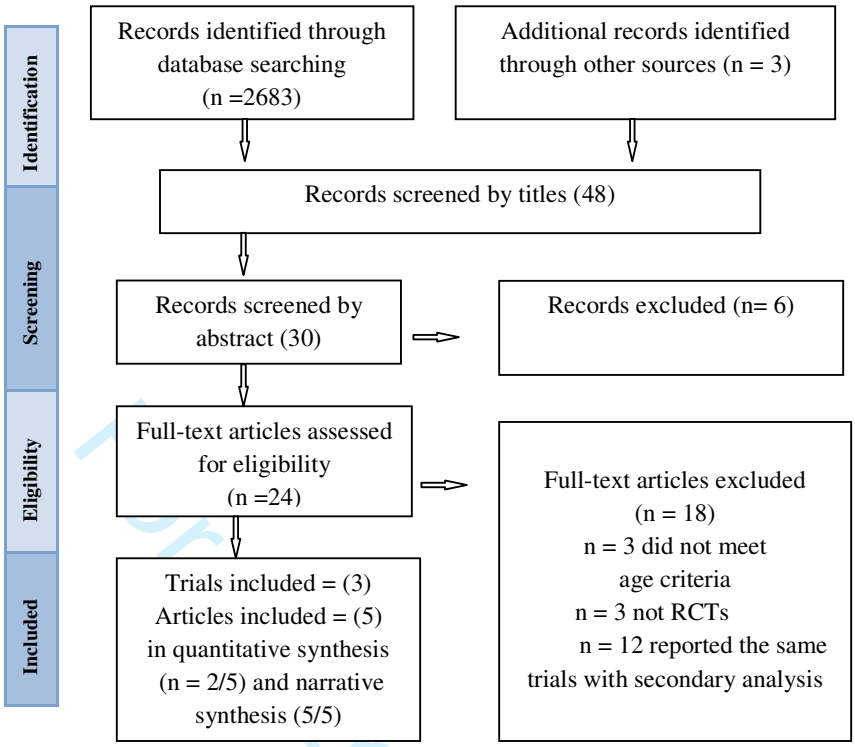

Figure1: Study selection flow diagram [22].

Study characteristics

The main characteristics of the included trials are presented in Table 2

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 et al., (2000) [37]**	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 Body mass index ≥ 28kg.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 420ft in 6 min 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 Center, USA **Exercise** Combined weight training and walking program 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 then3 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 sulphate proteoglycan (PG), keratan sulfate (KS) and interleukin-1β (1L-1)) 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 with (P=.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 =.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 =.03) and maximum braking force (P =.01) during gait No statistical differences were found between groups in knee pain scores Concentration level of keratan sulfate decreased similarly in both groups. The decrease in IL-1 correlated with joint pain (r = -0.77, P =.043)

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 Osteoarthritis **Messier et al., (2004) [38]**	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 ≥60years BMI ≥or =28 kg/m². 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 18months study Inability to walk without assistive device. Participation in another study 6-Reported alcohol consumption >14drinks per week ST segment depression of at least 2mm at an exercise level of 4 METS or less, hypotension, or complex arrhythmia during exercise Inability to complete the study protocol due to frailty, illness or other reason	**Participants** **N**=316community-dwelling obese older adults **Goal of weight loss** 5% of the total body weight over 18 months **Period of intervention** 18months **Setting** The Claude D. Pepper Older Americans Independence Center, 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 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 programs	Usual care healthy life style (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-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	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 IDEA Randomized Clinical Trial **Messier et al., (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 14grade 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 6months) Participants usual medications could be maintained or adjusted depending on physician advice **Exclusion** Significant co-morbid 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=454 **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 2meal-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 1000 kcal.day^{-1} as predicted by energy expenditure (estimated resting metabolism ×1.2 activity factor) **The Exercise Intervention** It 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 in the facility program, opt for a home-based program, or combine that two.The program consisted of aerobic walking (15 minutes), strength training (20minutes), a second aerobic phase (15minutes), and cool-down (10 minutes)	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 minute walk test between groups Significant pain reduction was observed in the diet plus exercise group at 18months compared with exercise group (mean score, 1.02; 95% CI, 0.33-1.71; P = .004) The difference in the SF-36 physical subscale was 2.81 units in diet plus exercise relative to exercise group (95% CI, −4.76 to −0.86; *P* = .005) No significant difference in the mental subscale between groups

Methods

In the pilot trial by Messier et al., (2000) participants were randomised into two groups, a combined intervention and control group [37]. The control group received an exercise programme similar to the intervention group [37]. Messier et al., (2004) [38] 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 [38]. Messier et al., (2013) [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 six for the pilot trial [37] and eighteen months for ADAPT [38] 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 trial [37] and two definitive trials [3, 38] were conducted by the same group from Wake Forest University, Winston-Salem, NC, USA. The goal of weight loss varied from 6.8kg over 6 months to 10-15% of total body weight over eighteen months of intervention. Outcomes were recorded at 3 time-points for the pilot trial (baseline, 3 months and 6 months) and for the two definitive trials (baseline, 6 months and eighteen months). Exercise duration and frequency were similar in all included trials (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 [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 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 to 1000 $Kcal.day^{-1}$, as predicted by an energy expenditure (estimated resting metabolism × 1.2 activity factor), of at least 1200kcal for men and 1100 for women [3].

Primary outcomes

No primary outcomes were specified for the pilot trial. The ADAPT primary outcome was self-reported physical function measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [38]. For the IDEA trial the primary outcomes were knee joint compressive force and plasma IL-6 concentration [3].

Secondary and additional outcomes

Secondary outcomes included weight loss; physical performance measured using the 6-minute walk distance and stair climb time; synovial fluid analysis for levels of total proteoglycan, keratan sulfate, and interleukin-1ß; physical disability and knee pain by WOMAC pain and stiffness; joint stiffness and joint space. Biomechanical testing included kinetic and kinematic analysis of gait and isokinetic strength testing and quality of life (SF-36).

Risk of bias within trials

Substantial inter-reviewer agreement was achieved on the risk of bias assessment (k= 0.73) [25]. All of the included trials were evaluated as unclear risk of bias [27]. Most of the key domains were assessed as unclear risk of bias within each trial (Table 3).

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 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)

Risk of bias across trials

Risk of bias across trials was evaluated as unclear [27] 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 minute walk test (metres) after 6 months of intervention. Only two trials [3, 37] 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).

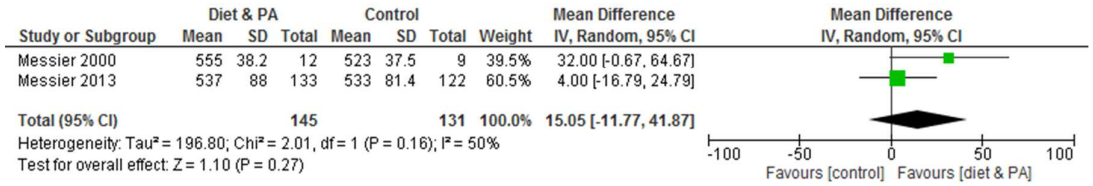

Figure 2: 6 minute walk test (metres) at 6 months.

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 [32, 33].

Developing a preliminary synthesis

Tabulation was used to present primary and secondary outcome measures that were not included in the meta-analysis; body weight, BMI, musculoskeletal function, (including; mobility, joint range of motion (ROM) and muscle strength) pain and QoL. Studies including a comparison of the combined intervention programme with an exercise intervention are presented in Tables 4-5 (supplementary files 2).

Tabulation was used to compare the effect of the combined intervention programme compared with usual care (healthy life style) on primary and secondary outcome measures; body weight, BMI, musculoskeletal function, (including; mobility, joint range of motion (ROM) and muscle strength) pain and QoL (Tables 6 &7) (supplementary files 3).

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/3 times per week) was the same across the included trials. Further details about the design of the trials are presented above.

Tables 4 &6 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 consistent with the results from the included trials. The diet plus exercise group in the pilot study [37] lost weight compared with the control group ($p=0.01$) after 6 months of intervention [37] and 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 [3]. However, in ADAPT [38] both groups (intervention and healthy lifestyle) lost weight ($p<0.05$) after 18 months of intervention [38] although there was a significant difference in the 6 minute walk result in favour of the diet plus exercise group ($p<0.05$) [38]. Also, there was a significant difference ($p=0.005$) in the 6 minute 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 [36]. Both trials included in the meta-analysis [3, 37] were evaluated as 'high' quality evidence before being downgraded as they were RCTs, before being modified according to five negative and two positive factors [34, 35]. The quality of evidence for a combined intervention programme of physical activity and diet on walking distance (metres) within 6 minutes after a period of 6 months of intervention was evaluated as moderate (Table 8).

Table 8: Factors determining the quality of evidence according to GRADE

Factor	Judgment	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 1 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.

DISCUSSION

Summary of evidence

This is the first systematic review and mixed methods analysis investigating the effectiveness of combining dietary restriction and physical activity interventions for musculoskeletal function in older overweight/ obese elders with knee OA. One pilot trial [37] and two definitive trials [3, 38] (794 participants) conducted by the same research group (Wake Forest University, Winston-Salem, NC, USA) were included. The intervention programme was compared with exercise training in one definitive trial (IDEA) [3] and the pilot trial [37], while usual care was the comparator in the ADAPT [38]. Two additional articles [39, 40] which reported further outcomes of the ADAPT were identified [38].

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. 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 [3, 37] with 155 participants did not support the combined intervention program (15.05, 95% CI -11.77 to 41.87). Although the meta-analyses showed substantial heterogeneity I^2=50%, this was classified as not serious using the GRADE evaluation tool [34, 35] 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 [36]. All included trials were reported as having an unclear risk of bias which was mainly due to unclear reporting of some information [27]. 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., [37] 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 ofIL-1) after 6 months of intervention. Findings from Messier et al., [38] 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., [3] indicated a significant improvement in the 6 minute walk test and walking speed in the intervention group. Moreover, there was a significant reduction ($p<0.05$) 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 within each trial was good. For example, in the pilot study [37] 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 difference between groups.

The cost-effectiveness of the combined intervention programme in overweight or obese elderly people with knee OA in the ADAPT [38] was reported by Servick et al., [41] which is not included in this review. The main findings showed that the intervention programme was considered as an expensive approach [41]. The minimal cost was 5460$ for the diet plus exercise, 2415$ for the diet and 2731$ for the exercise group with a cost of $24 for each percentage point improvement in subjective function, $20 for each percentage point improvement in self-reported pain, and $56 for each percentage point improvement in self-reported stiffness [41]. Cost of the intervention may increase in certain circumstances, for example, with disability, population suffering severe or complex medical conditions and even with transportation difficulty [41]. Despite the high cost of the intervention programme the required use of health services for the consequences of knee OA such as hospitalizations, nursing home care, home care, and medications may cost more [41].

In addition to diet and exercise two current trials MEDIC1 [21] and MEDIC2 [20] have reported that a multimodal approach of education, neuromuscular exercise, insoles and, if indicated, a dietary weight loss program 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. MEDIC 1 [21] included 9 participants and MEDIC2 [20] included 12 participants below the age of 55 years and there was no sub-group analysis of older participants. In MEDIC1 [21] the participants were eligible for total knee replacement (TKR) and were randomized to nonsurgical 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 nonsurgical treatment alone. However, only 26% of the patients who were assigned to receive nonsurgical treatment alone underwent TKR in the following year [21]. In MEDIC2 [20] participants had radiographic confirmation of OA (Kellgren-Lawrence grade ≥ 1), but were not eligible for a TKR. The 12-week non-surgical treatment program consisted

of individualized 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 nonsurgical treatment program 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 OA patients [20].

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

This systematic review has shown that, based on current evidence from trials, a combined programme of diet and physical activity is not effective with respect to an improvement in body weight, BMI and musculoskeletal function. However the included number of trials and participants was low. The narrative synthesis suggests that interventions with a focus on reduction of body weight and/or improved mobility are worthy of further evaluation. Only moderate quality evidence was available to investigate the intervention programmes. An adequately powered RCT is required following work to optimise diet and exercise interventions using a multimodal approach.

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Contributorship statement

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 GRADE 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 a PRISMA 2009 checklist and approved the final manuscript.

Competing interests

There are no competing interests.

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Data sharing statement

There are no additional unpublished data from the review.

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Table 1: Example of Medline Ovid search strategy 1948- 10th 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 or3 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 hypocloric 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

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	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 min walk test (meters)	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*	13	7.4 (0.32)	12	9.81*	11	8.7 (0.36)	9

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

Table 6: Preliminary synthesis for 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 min walk test (meters)	6 months	Messier et al., 2004	416.2 (98.7)	76	482.3 (100)	63	434.6 (96.4)	78	429 (108)	70
	6 min walk test (meters)	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 min walk test (meters)	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= Participants number at baseline, M1 (SD1)= Mean and standard deviation after intervention, N1= Participants number after intervention, N/A= Data not available.

Table 7: Preliminary synthesis for 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= Participants number at baseline, M1 (SD1)= Mean and standard deviation 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.

Effect of physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese elders with knee osteoarthritis: protocol for a systematic review

Asma Alrushud, Alison Rushton, Carolyn Anne Greig

Citation
Asma Alrushud, Alison Rushton, Carolyn Anne Greig. **Effect of physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese elders with knee osteoarthritis: protocol for a systematic review.**

Review question(s)
What is the effect of combined physical activity and dietary restriction programmes on the musculoskeletal function of overweight and obese elders with knee osteoarthritis?

Searches
Cochrane databases Ovid (MEDLINE), EMBASE Web of science and CINAHL will be searched with a search strategy comprising comprehensive keyword combinations for each of the concepts of interest: 1) knee osteoarthritis, 2) physical activity, 3) dietary restriction, 4) ageing 5) musculoskeletal function. There will be no language, publication status or publication year limitations.

Types of study to be included
Randomised control trials.

Condition or domain being studied
Musculoskeletal function of overweight and obese elders with knee osteoarthritis.

Participants/ population
Older men or women aged ≥55 years with BMI ≥25Kg/m² and diagnosed (radiographically) with either unilateral or bilateral knee osteoarthritis.

Intervention(s), exposure(s)
Physical activity combined with dietary restriction programmes.

Comparator(s)/ control
Usual care.

Usual care may constitute non intervention e.g. advice, or an intervention which may include physical activity alone or dietary restriction alone.

Outcome(s)
Body weight, Body Mass Index, musculoskeletal function (mobility, knee range of movement, muscle strength), pain and quality of life.

Data extraction, (selection and coding)
A customised data extraction form including: demographic information, methodology, interventions details and all specified reported outcomes has been designed and will be used by the reviewers. Two reviewers will independently extract data. The accuracy and clarity of the extracted data will be checked by a third reviewer.

Risk of bias (quality) assessment
The Cochrane risk of bias assessment tool will be used to appraise the internal validity of each included trial. All domains of the bias tool will be assessed independently. The blinding domain will be divided into 2 items, one for the blinding of participants and personnel and the other for blinding of the outcome assessors. Two independent reviewers will assess the risk of bias and in case of disagreement a third reviewer will be consulted.

Strategy for data synthesis
Data synthesis is anticipated to be narrative based on a scoping search of the literature.

If possible, a meta-analysis will be conducted (if included trials are of sufficient number, with comparable interventions and outcomes, and of acceptable risk of bias.

Analysis of subgroups or subsets

Not anticipated.

Dissemination plans

A poster of progress will be presented in MRC Arthritis Research UK Centre for Musculoskeletal Ageing Research (CMAR/CIMA) Conference on 15th – 16th April and the University of Birmingham's Research Poster Conference on 16th June 2015. After completing the work, an article will be submitted for publication in peer reviewed journal.

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Anticipated or actual start date

1 November 2014

Anticipated completion date

30 April 2015

Funding sources/sponsors

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Conflicts of interest

None.

Language

English

Country

United Kingdom

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Knee osteoarthritis, elders, overweight, obese, musculoskeletal function, dietary restriction, physical activity.

Stage of review

Continuous.

Date of registration in PROSPERO

31 March 2015

Date of publication of this revision

Not applicable

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No

Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

PRISMA 2009 Checklist

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PRISMA 2009 Checklist

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BMJ Open

The effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese elders with knee osteoarthritis: a systematic review and mixed method data synthesis

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Date Submitted by the Author:	20-Feb-2017
Complete List of Authors:	Alrushud, Asma; School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK Rushton, Alison; School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK; MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research Kanavaki, Archontissa; School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK; MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research Greig, Carolyn; School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK; MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research
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The effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese elders with knee osteoarthritis: a systematic review and mixed method data synthesis

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Keywords
Exercise, diet, elderly, obesity, randomised controlled trials

Word count
4,591

Number of figures: 2

Number of tables: 8 within the text

Number of references: 50

Number of supplementary files 4 (SR protocol, PRISMA 2009 checklist, cover letter, BMJ response letter).

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 elders 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 elders with knee OA.

Information sources

A detailed search strategy was applied to key electronic databases (Ovid, Embase, Web of Science and CINAHL) for randomised controlled trials (RCTs) published in English prior to 15th January 2017.

Participants

Participants with BMI ≥25kg.m^{-2}, aged ≥55 years of age and 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 (QoL).

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 2 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 minute 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. Protocol was registered in PROSPERO (CRD42015019088).

Article summary

Strengths and limitations of the review

- This is the first systematic review of combined physical activity and dietary restriction interventions in overweight and obese older adults with knee OA.
- The protocol of this review was registered in PROSPERO and followed the PRISMA guidelines and the Cochrane handbook; GRADE was used to evaluate the quality of the included trials.
- The review included a mixed methods analytical approach.
- Few eligible studies were identified however important information is highlighted which could inform clinical practice.

INTRODUCTION

Rational

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 United Kingdom (UK) there is approximately 4.7 million older adults aged 45 years or over experiencing knee OA symptoms [1, 8]. In addition, more than 20 million people seek treatment for knee OA in the United States (US) [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 nonsurgical 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) [1, 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 control 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 (e.g. 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 obese patients 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 elders 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 health care 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 elders 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 elders with BMI ≥25kg.m^{-2}, 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 elders with knee OA.

METHODS

Protocol and registration

A systematic review was conducted according to a pre-defined protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P guidelines [29] and the Cochrane handbook [30]. The review was registered on PROSPERO on 1/4/2015 (CRD42015019088), and is reported in accordance with the PRISMA statement [29].

Eligibility criteria

Inclusion criteria

- Older adults (aged ≥55 years, men and women).
- Overweight or obese with BMI ≥25 Kg.m^{-2} [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.

Information sources

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

- The Cochrane Library: Controlled Trials Register, NHS Economic Evaluation Database.
- 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, Organizational such as UK department of health, World Health Organization and NHS (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 13th February 2015). The definitive search strategy was run by two independent researchers (ASA/AMK, 10th 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 (15th January 2017) to include studies published in 2016 by (ASA/AMK) and no eligible studies were identified.

Table 1: Example of Medline Ovid search strategy 1948- 10th 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 or3 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 hypocloric 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

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 tool [34] 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-minute walk test at 6 months) using the random effects model [35, 36]. Ninety-five percent confidence intervals were reported for the summary statistics and the standard deviation was calculated from the standard errors and confidence interval [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. Standard deviations 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 standard errors or confidence intervals to SD [39, 40].

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 trial [44] 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 trial, 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., (2000) [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 (Messier et al., 2004) [45]. The study flow diagram is presented in Figure1[48].

Study characteristics

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

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 et al., (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 Body mass index ≥ 28kg.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 420ft in 6 min 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 Center, USA **Exercise** Combined weight training and walking program 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 then3 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 sulphate proteoglycan (PG), keratan sulfate (KS) and interleukin-1β (1L-1)) 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 with (P=.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 =.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 =.03) and maximum braking force (P =.01) during gait No statistical differences were found between groups in knee pain scores Concentration level of keratan sulfate decreased similarly in both groups. The decrease in IL-1 correlated with joint pain (r = -0.77, P =.043)

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 Osteoarthritis **Messier et al., (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 ≥60years BMI ≥or =28 kg/m². 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 18months study Inability to walk without assistive device. Participation in another study 6-Reported alcohol consumption >14drinks per week ST segment depression of at least 2mm at an exercise level of 4 METS or less, hypotension, or complex arrhythmia during exercise Inability to complete the study protocol due to frailty, illness or other reason	**Participants** **N**=316community-dwelling obese older adults **Goal of weight loss** 5% of the total body weight over 18 months **Period of intervention** 18months **Setting** The Claude D. Pepper Older Americans Independence Center, 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 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 programs	Usual care healthy life style (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-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	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 IDEA Randomized Clinical Trial Messier et al., (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 14grade 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 6months) Participants usual medications could be maintained or adjusted depending on physician advice **Exclusion** Significant co-morbid 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=454 **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 2meal-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 1000 kcal.day^{-1} as predicted by energy expenditure (estimated resting metabolism ×1.2 activity factor) **The Exercise Intervention** It 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 in the facility program, opt for a home-based program, or combine that two. The program consisted of aerobic walking (15 minutes), strength training (20minutes), a second aerobic phase (15minutes), and cool-down (10 minutes)	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 minute walk test between groups Significant pain reduction was observed in the diet plus exercise group at 18months compared with exercise group (mean score, 1.02; 95% CI, 0.33-1.71; P = .004) The difference in the SF-36 physical subscale was 2.81 units in diet plus exercise relative to exercise group (95% CI, −4.76 to −0.86; *P* = .005) No significant difference in the mental subscale between groups

Methods

In the pilot trial by Messier et al., (2000) 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 [44]. Messier et al., (2004) [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., (2013) [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 six for the pilot trial [44] and eighteen months for ADAPT [45] 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 trial [44] and two definitive trials [3, 45] were conducted by the same group from Wake Forest University, Winston-Salem, NC, USA. The goal of weight loss varied from 6.8kg over 6 months to 10-15% of total body weight over eighteen months of intervention. Outcomes were recorded at 3 time-points for the pilot trial (baseline, 3 months and 6 months) and for the two definitive trials (baseline, 6 months and eighteen months). Exercise duration and frequency were similar in all included trials (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 [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 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 to 1000 $Kcal.day^{-1}$, as predicted by an energy expenditure (estimated resting metabolism × 1.2 activity factor), of at least 1200kcal for men and 1100 for women [3].

Outcome measures

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

Messier et al., (2000): No primary or secondary outcomes were specified [44].

Messier et al., (2004): 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, 6-minute walk distance, stair-climb time, WOMAC pain and stiffness scores, and joint space width [45].

Messier et al., (2013): In the IDEA trial the primary outcomes were knee joint compressive force and plasma IL-6 concentration. Secondary outcome measures included WOMAC pain,

WOMAC function, gait speed, 6 minute walk test, quality of life, 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).

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 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)

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 minute 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.

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	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 min walk test (meters)	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*	13	7.4 (0.32)	12	9.81*	11	8.7 (0.36)	9

Abbreviations: M0 (SD0)= Mean and standard deviation at baseline, N0= Participants number at baseline, M1 (SD1)= Mean and standard deviation 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	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= Participants number at baseline, M1 (SD1)= Mean and standard deviation after intervention, N1= Participants number after intervention, N/A= Data not available.

Tabulation was used to compare the effect of the combined intervention programme compared with usual care (healthy life style) on primary and secondary outcome measures; body weight, , physical function, mobility, pain and QoL (Tables 6-7).

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	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 min walk test (meters)	6 months	Messier et al., 2004	416.2 (98.7)	76	482.3 (100)	63	434.6 (96.4)	78	429 (108)	70
	6 min walk test (meters)	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 min walk test (meters)	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= Participants number at baseline, M1 (SD1)= Mean and standard deviation after intervention, N1= Participants number after intervention, N/A= Data not available.

Table 7: Preliminary synthesis for the secondary outcome measures at baseline and after intervention; body weight, 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= Participants number at baseline, M1 (SD1)= Mean and standard deviation 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.

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/3 times per week) was the same across the included trials. Further details about the design of the trials are presented above.

Tables 4 &6 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 included trials. The diet plus exercise group in the pilot study [44] lost weight compared with the control group ($p=0.01$) after 6 months of intervention [44] and 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 [3]. However, in ADAPT [45] 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 minute 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 minute 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 minutes after a period of 6 months of intervention was evaluated as moderate (Table 8).

Table 8: Factors determining the quality of evidence according to GRADE

Factor	Judgment	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 1 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.

DISCUSSION

Summary of evidence

This is the first systematic review and mixed methods analysis investigating the effectiveness of combining dietary restriction and physical activity interventions for musculoskeletal function in older overweight/ obese elders with knee OA. One pilot trial [44] and two definitive trials [3, 45] (794 participants) conducted by the same research group (Wake Forest University, Winston-Salem, NC, USA) 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 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 [3, 44] with 155 participants did not support the combined intervention program (15.05, 95% CI -11.77 to 41.87) (albeit with a total effect of 15 m deemed not clinically significant according to previous literature) [49, 50]. Although the meta-analyses showed substantial heterogeneity 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 ofIL-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 minute walk test, stair climb and knee pain. The findings from Messier et al., [3] indicated a significant improvement in the 6 minute walk test and walking speed in the intervention group. Moreover, there was a significant reduction ($p<0.05$) 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 within each trial was good. For example, 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 difference between groups.

In addition to diet and exercise two current trials MEDIC1 [28] and MEDIC2 [27] have reported that a multimodal approach of education, neuromuscular exercise, insoles and, if indicated, a dietary weight loss program 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. MEDIC 1 [28] included 9 participants and MEDIC2 [27] included 12 participants below the age of 55 years and there was no sub-group analysis of older participants. In MEDIC1 [28] the participants were eligible for total knee replacement (TKR) and were randomized to nonsurgical 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 nonsurgical treatment alone. However, only 26% of the patients who were assigned to receive nonsurgical 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 program consisted of individualized 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 nonsurgical treatment program 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 OA patients [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 RCT testing the effects of a combined intervention against each component individually are required to optimise diet and exercise interventions using a multimodal approach.

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Contributorship statement

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 GRADE 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 a PRISMA 2009 checklist and approved the final manuscript.

Competing interests
There are no competing interests.

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

Figure1: Study selection flow diagram [48].
Figure 2: 6 minute walk test (metres) at 6 months.

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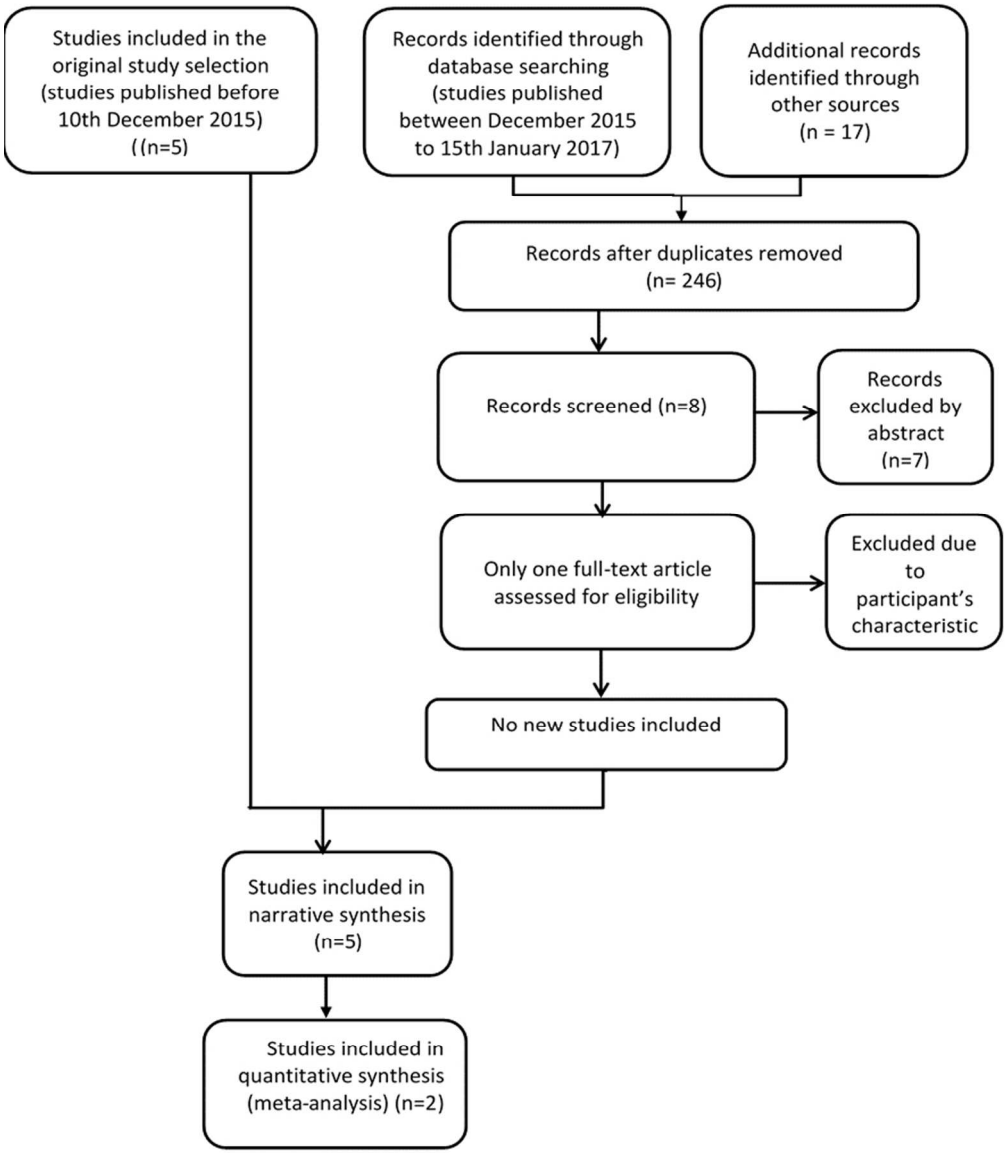

Figure1: Study selection flow diagram [48].

Figure 2: 6 minute walk test (metres) at 6 months.

6x1mm (300 x 300 DPI)

Effect of physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese elders with knee osteoarthritis: protocol for a systematic review

Asma Alrushud, Alison Rushton, Carolyn Anne Greig

Citation
Asma Alrushud, Alison Rushton, Carolyn Anne Greig. **Effect of physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese elders with knee osteoarthritis: protocol for a systematic review.**

Review question(s)
What is the effect of combined physical activity and dietary restriction programmes on the musculoskeletal function of overweight and obese elders with knee osteoarthritis?

Searches
Cochrane databases Ovid (MEDLINE), EMBASE Web of science and CINAHL will be searched with a search strategy comprising comprehensive keyword combinations for each of the concepts of interest: 1) knee osteoarthritis, 2) physical activity, 3) dietary restriction, 4) ageing 5) musculoskeletal function. There will be no language, publication status or publication year limitations.

Types of study to be included
Randomised control trials.

Condition or domain being studied
Musculoskeletal function of overweight and obese elders with knee osteoarthritis.

Participants/ population
Older men or women aged ≥55 years with BMI ≥25Kg/m² and diagnosed (radiographically) with either unilateral or bilateral knee osteoarthritis.

Intervention(s), exposure(s)
Physical activity combined with dietary restriction programmes.

Comparator(s)/ control
Usual care.

Usual care may constitute non intervention e.g. advice, or an intervention which may include physical activity alone or dietary restriction alone.

Outcome(s)
Body weight, Body Mass Index, musculoskeletal function (mobility, knee range of movement, muscle strength), pain and quality of life.

Data extraction, (selection and coding)
A customised data extraction form including: demographic information, methodology, interventions details and all specified reported outcomes has been designed and will be used by the reviewers. Two reviewers will independently extract data. The accuracy and clarity of the extracted data will be checked by a third reviewer.

Risk of bias (quality) assessment
The Cochrane risk of bias assessment tool will be used to appraise the internal validity of each included trial. All domains of the bias tool will be assessed independently. The blinding domain will be divided into 2 items, one for the blinding of participants and personnel and the other for blinding of the outcome assessors. Two independent reviewers will assess the risk of bias and in case of disagreement a third reviewer will be consulted.

Strategy for data synthesis
Data synthesis is anticipated to be narrative based on a scoping search of the literature.

If possible, a meta-analysis will be conducted (if included trials are of sufficient number, with comparable interventions and outcomes, and of acceptable risk of bias.

Analysis of subgroups or subsets

Not anticipated.

Dissemination plans

A poster of progress will be presented in MRC Arthritis Research UK Centre for Musculoskeletal Ageing Research (CMAR/CIMA) Conference on 15th – 16th April and the University of Birmingham's Research Poster Conference on 16th June 2015. After completing the work, an article will be submitted for publication in peer reviewed journal.

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Anticipated or actual start date

1 November 2014

Anticipated completion date

30 April 2015

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Conflicts of interest

None.

Language

English

Country

United Kingdom

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Knee osteoarthritis, elders, overweight, obese, musculoskeletal function, dietary restriction, physical activity.

Stage of review

Continuous.

Date of registration in PROSPERO

31 March 2015

Date of publication of this revision

Not applicable

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No

Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

PRISMA 2009 Checklist

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PRISMA 2009 Checklist

BMJ Open

The effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese elders with knee osteoarthritis: a systematic review and mixed method data synthesis

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The effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese elders with knee osteoarthritis: a systematic review and mixed method data synthesis

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Keywords
Exercise, diet, elderly, obesity, randomised controlled trials

Word count
4,600

Number of figures: 2

Number of tables: 8 within the text

Number of references: 50

Number of supplementary files 4 (SR protocol, PRISMA 2009 checklist, cover letter, BMJ response letter).

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 elders 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 elders with knee OA.

Information sources

A detailed search strategy was applied to key electronic databases (Ovid, Embase, Web of Science and CINAHL) for randomised controlled trials (RCTs) published in English prior to 15th January 2017.

Participants

Participants with BMI ≥25kg.m^{-2}, aged ≥55 years of age and 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 (QOL).

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 2 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 minute 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. Protocol was registered in PROSPERO (CRD42015019088).

Article summary

Strengths and limitations of the review

- This is the first systematic review of combined physical activity and dietary restriction interventions in overweight and obese older adults with knee OA.
- The protocol of this review was registered in PROSPERO and followed the PRISMA guidelines and the Cochrane handbook; GRADE was used to evaluate the quality of the included trials.
- The review included a mixed methods analytical approach.
- Few eligible studies were identified however important information is highlighted which could inform clinical practice.

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 United Kingdom (UK) there is approximately 4.7 million older adults aged 45 years or over experiencing knee OA symptoms [1, 8]. In addition, more than 20 million people seek treatment for knee OA in the United States (US) [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 nonsurgical 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) [1, 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 control 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 (e.g. 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 obese patients 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 elders 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 health care 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 elders 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 elders with body mass index (BMI) ≥25kg.m^{-2}, 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 elders with knee OA.

METHODS

Protocol and registration

A systematic review was conducted according to a pre-defined protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P guidelines [29] and the Cochrane handbook [30]. The review was registered on PROSPERO on 1/4/2015 (CRD42015019088), and is reported in accordance with the PRISMA statement [29].

Eligibility criteria

Inclusion criteria

- Older adults (aged ≥55 years, men and women).
- Overweight or obese with BMI ≥25 Kg.m^{-2} [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.

Information sources

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

- The Cochrane Library: Controlled Trials Register, NHS Economic Evaluation Database.
- 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, Organizational such as UK department of health, World Health Organization and NHS (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 13th February 2015). The definitive search strategy was run by two independent researchers (ASA/AMK, 10th 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 (15th January 2017) to include studies published in 2016 by (ASA/AMK) and no eligible studies were identified.

Table 1: Example of Medline Ovid search strategy 1948- 10th 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 or3 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 hypocloric 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

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 tool [34] 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-minute walk test at 6 months) using the random effects model [35, 36]. Ninety-five percent confidence intervals were reported for the summary statistics and the standard deviation was calculated from the standard errors and confidence interval [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. Standard deviations 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 standard errors or confidence intervals to SD [39, 40].

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 trial [44] 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., (2000) [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 (Messier et al., 2004) [45]. The study flow diagram is presented in Figure1 [48].

Study characteristics

The main characteristics of the included trials are presented in Table 2

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 et al., (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≥ 28kg.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 420ft 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 then3 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 sulphate (KS) and interleukin-1β (1L-1)) 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 with (P=.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 =.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 =.03) and maximum braking force (P =.01) during gait No statistical differences were found between groups in knee pain scores Concentration level of keratan sulphate decreased similarly in both groups. The decrease in IL-1 correlated with joint pain (r = -0.77, P =.043)

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 Osteoarthritis **Messier et al., (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 ≥60years BMI ≥or =28 kg/m². 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 18months study Inability to walk without assistive device. Participation in another study 6-Reported alcohol consumption >14drinks per week ST segment depression of at least 2mm at an exercise level of 4 METS or less, hypotension, or complex arrhythmia during exercise Inability to complete the study protocol due to frailty, illness or other reason	**Participants** **N**=316community-dwelling obese older adults **Goal of weight loss** 5% of the total body weight over 18 months **Period of intervention** 18months **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 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) 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-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	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 IDEA Randomized Clinical Trial Messier et al., (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 14grade 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 6months) Participants usual medications could be maintained or adjusted depending on physician advice **Exclusion** Significant co-morbid 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=454 **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 2meal-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 1000 kcal.day^{-1} as predicted by energy expenditure (estimated resting metabolism ×1.2 activity factor) **The Exercise Intervention** It 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 in the facility programme, opt for a home-based programme, or combine that two. The programme consisted of aerobic walking (15 minutes), strength training (20minutes), a second aerobic phase (15minutes), and cool-down (10 minutes)	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 minute walk test between groups Significant pain reduction was observed in the diet plus exercise group at 18months compared with exercise group (mean score, 1.02; 95% CI, 0.33-1.71; P = .004) The difference in the SF-36 physical subscale was 2.81 units in diet plus exercise relative to exercise group (95% CI, −4.76 to −0.86; *P* = .005) No significant difference in the mental subscale between groups

Methods

In the pilot trial by Messier et al., (2000) 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 [44]. Messier et al., (2004) [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., (2013) [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 six for the pilot trial [44] and eighteen months for ADAPT [45] 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 trial [44] and two definitive trials [3, 45] were conducted by the same group from Wake Forest University, Winston-Salem, NC, USA. The goal of weight loss varied from 6.8kg over 6 months to 10-15% of total body weight over eighteen months of intervention. Outcomes were recorded at 3 time-points for the pilot trial (baseline, 3 months and 6 months) and for the two definitive trials (baseline, 6 months and eighteen months). Exercise duration and frequency were similar in all included trials (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 [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 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 to 1000 Kcal.day-1, as predicted by an energy expenditure (estimated resting metabolism × 1.2 activity factor), of at least 1200kcal for men and 1100 for women [3].

Outcome measures

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

Messier et al., (2000): No primary or secondary outcomes were specified [44].

Messier et al., (2004): 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, 6-minute walk distance, stair-climb time, WOMAC pain and stiffness scores, and joint space width [45].

Messier et al., (2013): In the IDEA trial the primary outcomes were knee joint compressive force and plasma IL-6 concentration. Secondary outcome measures included WOMAC pain,

WOMAC function, gait speed, 6 minute 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).

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 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)

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 minute 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.

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	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 min walk test (meters)	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*	13	7.4 (0.32)	12	9.81*	11	8.7 (0.36)	9

Abbreviations: M0 (SD0)= Mean and standard deviation at baseline, N0= Participants number at baseline, M1 (SD1)= Mean and standard deviation 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	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= Participants number at baseline, M1 (SD1)= Mean and standard deviation after intervention, N1= Participants number after intervention, N/A= Data not available.

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

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	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 min walk test (meters)	6 months	Messier et al., 2004	416.2 (98.7)	76	482.3 (100)	63	434.6 (96.4)	78	429 (108)	70
	6 min walk test (meters)	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 min walk test (meters)	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= Participants number at baseline, M1 (SD1)= Mean and standard deviation after intervention, N1= Participants number after intervention, N/A= Data not available.

Table 7: Preliminary synthesis for the secondary outcome measures at baseline and after intervention; body weight, 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= Participants number at baseline, M1 (SD1)= Mean and standard deviation 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.

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/3 times per week) was the same across the included trials. Further details about the design of the trials are presented above.

Tables 4 &6 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 included trials. The diet plus exercise group in the pilot study [44] lost weight compared with the control group ($p=0.01$) after 6 months of intervention [44] and 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 [3]. However, in ADAPT [45] 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 minute 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 minute 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 minutes after a period of 6 months of intervention was evaluated as moderate (Table 8).

Table 8: Factors determining the quality of evidence according to GRADE

Factor	Judgment	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 1 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.

DISCUSSION

Summary of evidence

This is the first systematic review and mixed methods analysis investigating the effectiveness of combining dietary restriction and physical activity interventions for musculoskeletal function in older overweight/ obese elders with knee OA. One pilot trial [44] and two definitive trials [3, 45] (794 participants) conducted by the same research group (Wake Forest University, Winston-Salem, NC, USA) 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 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 [3, 44] with 155 participants did not support the combined intervention program (15.05, 95% CI -11.77 to 41.87) (albeit with a total effect of 15 m deemed not clinically significant according to previous literature) [49, 50]. Although the meta-analyses showed substantial heterogeneity 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 sulphate and level ofIL-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 minute walk test, stair climb and knee pain. The findings from Messier et al., [3] indicated a significant improvement in the 6 minute walk test and walking speed in the intervention group. Moreover, there was a significant reduction ($p<0.05$) 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 study [44] 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 MEDIC1 [28] and MEDIC2 [27] 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. MEDIC 1 [28] included 9 participants and MEDIC2 [27] included 12 participants below the age of 55 years and there was no sub-group analysis of older participants. In MEDIC1 [28] the participants were eligible for total knee replacement (TKR) and were randomised to nonsurgical 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 nonsurgical treatment alone. However, only 26% of the patients who were assigned to receive nonsurgical 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 nonsurgical 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 OA patients [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 multimodal approach.

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Contributorship statement
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 GRADE 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 a PRISMA 2009 checklist and approved the final manuscript.

Competing interests
There are no competing interests.

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

Figure1: Study selection flow diagram [48].
Figure 2: 6 minute walk test (metres) at 6 months.

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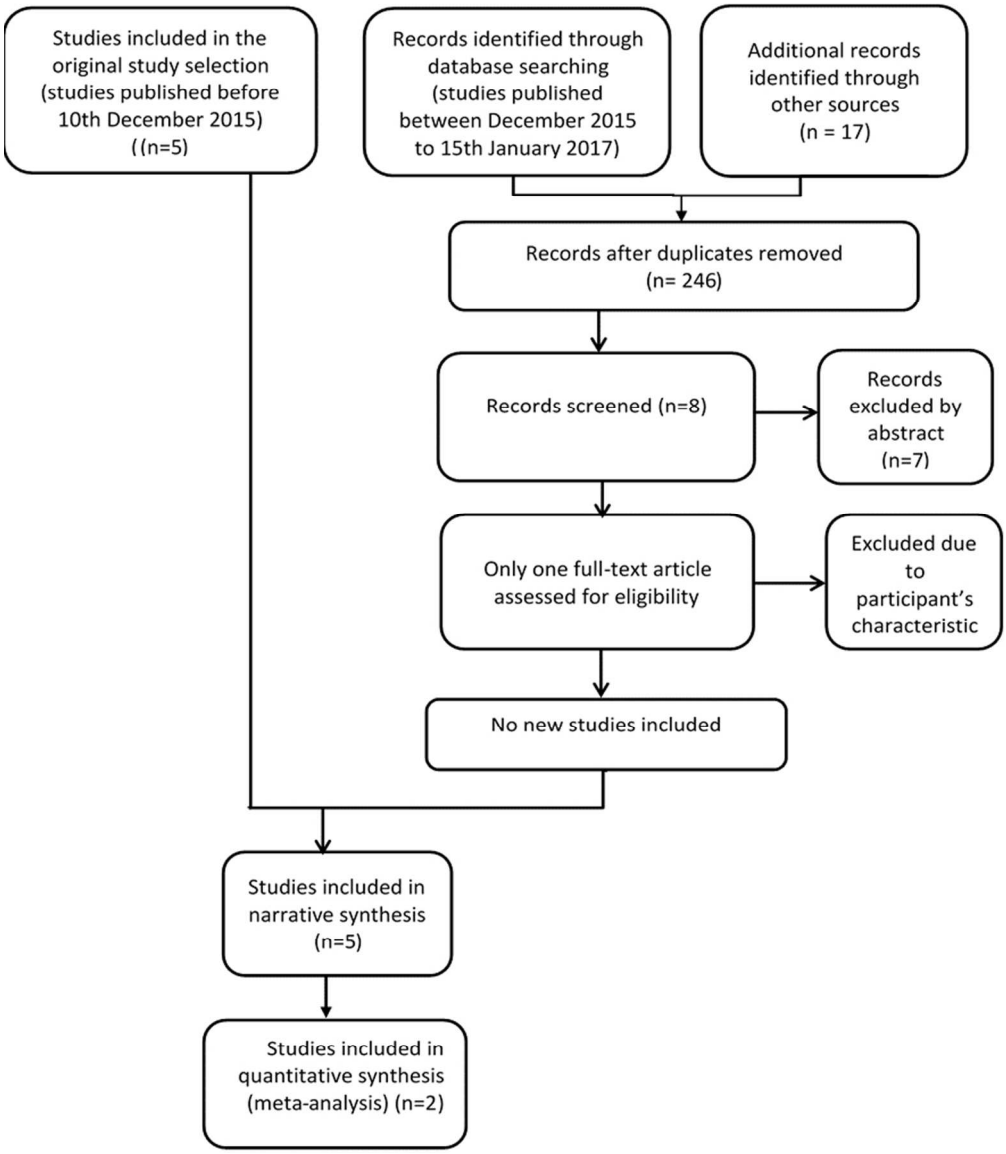

Figure1: Study selection flow diagram [48].

Figure 2: 6 minute walk test (metres) at 6 months.

6x1mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			2
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.	2-3
INTRODUCTION			3
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			4
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.	4
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.	4
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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).	5
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.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
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.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			7
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.	7
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.	8-11
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).	13
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.	13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			15
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).	15-17
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).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			17
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.	17

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