TITLE: Obesity Management Interventions Delivered in Primary Care for Patients with Osteoarthritis: A Review of the Clinical Effectiveness

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CONTEXT AND POLICY ISSUES

Osteoarthritis (OA) is the most common joint disorder, affecting more than 10% of Canadian adults with symptoms in the hands, knees, hips, back, and neck.[1,2] In Canada, joint damage from osteoarthritis accounts for over 80% of hip and over 90% of knee replacements.[2] Obesity is recognized as the strongest modifiable risk factor in osteoarthritis.[3] It has been reported that obese women and men have nearly four times and greater than five times, respectively, the risk of knee arthritis compared to their non-obese counterparts.[1] The association between being overweight or obese and increased stress on weight-bearing joints like the knees and hips seem intuitive, but the exact manner in which excess weight influences OA is unclear. However, being overweight has been associated with higher rates of hand OA in some studies.[1] Thus, osteoarthritis is considered an active disease process with joint destruction driven by both biomechanical and pro-inflammatory factors.[4]

While effective weight management is a laudable health goal for all, it is especially important for obese patients with knee OA because being only 10 pounds overweight increases the force on the knee by 30 to 60 pounds with each step which exacerbates the OA and elevates the risk for future total knee replacement.[1,5] In addition to alleviating sheer pain, stiffness and risk of mobility disability, weight loss reduces the risk of vascular events which is reported to be higher in people with OA compared to people without OA.[5]

Substantial improvements in physical function in obese patients with OA have been reported with even modest weight loss (≥ 5% of baseline weight).[3] Some researchers have concluded that in elderly persons (mean age 70.5 years), if obese men lost enough weight to fall into the overweight category and men in the overweight category lost enough weight to move into the normal weight category, the risk of developing knee OA would decrease by 21.5%.[1] Similar changes in weight category by women would result in a 33% decrease.[1]

Even so, weight loss could potentially result in undesirable reductions in lean muscle and bone mass with the potential to aggravate age-related risk of disability and osteoporotic fractures which compromise quality of life and life expectancy.[3] The objective of this report is to review the evidence for clinical effectiveness of long-term primary care weight management interventions to halt or minimize the progression of osteoarthritis in obese patients.

RESEARCH QUESTION

What is the clinical effectiveness of long-term primary care obesity management interventions in halting or slowing the progression of osteoarthritis?

KEY FINDINGS

Dietary weight loss interventions, either alone or in combination with exercise produced greater reductions in the peak knee compressive force and plasma levels of interleukin-6 (IL-6) in knee OA patients compared with exercise-induced weight loss. Significantly greater reduction in pain and improvements in functions were reported in patients who received diet plus exercise interventions compared with either diet–only or exercise–only interventions. Regardless of group assignment, participants who lost 10% or more of baseline body weight had greater reductions in knee compressive force, systemic IL-6 concentrations, and pain, as well as gained greater improvement in function than those who lost less of their baseline weight. However, participants who lost the most weight also experienced greater loss of bone mass density at the femoral neck and hip, but not the spine, without a significant change of their baseline clinical classification with regards to osteoporosis or osteopenia. Findings from a cohort study suggest that patients with hip osteoarthritis could achieve weight loss associated with significant improvement in their physical function, mobility, and pain scores.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and June 24, 2014.

Selection Criteria and Methods

One researcher screened the citations and abstracts from the literature search; selected articles according to the selection criteria outlined in Table 1, and examined the full-text publications for the final study inclusion for this report.

Table 1: Selection Criteria

Population	Adults with body-mass-index (BMI) of 30 kg/m^2 or higher who have osteoarthritis.
Intervention	Non-surgical interventions for weight management that can be delivered in primary care or community care, including one or more of the following interventions: pharmacological, lifestyle (diet/healthy eating, exercise), or psychological therapy, applied for a duration of six months or longer.
Comparator	Osteoarthritis care that is not specialized on obesity/weight management
Outcomes	NSAID or medication change or functional improvement (if scored); mental health/illness – quality of life (QoL); depression severity index scores
Study Designs	Health Technology Assessments (HTA)/Systematic reviews/Meta-analysis; Randomized controlled trials (RCTs), and Non-randomized studies.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1. In particular, studies that focused on surgical interventions and interventions targeting osteoarthritis (without connection to obesity) or change in weight or body mass alone were not included. Studies were also excluded if they were published before 2009, if they were duplicate publications of an already selected study, or if they included in at least one of the selected HTAs or systematic reviews.

Critical Appraisal of Individual Studies

Two included studies[3,4] were appraised using the SIGN-50 Methodology Checklist 2 for Controlled Trials,[6] the other study[7] was assesses using SIGN-50 Methodology Checklist 3 for Cohort Studies.[8] The strengths and limitations of the individual studies have been summarized and presented in tabular form in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 119 citations of which 8 potentially relevant studies were selected upon screening of titles and abstracts. Grey literature searching identified additional 12 papers bringing the total pool of potential articles to 20 of which 3 studies were selected for inclusion in this report. The excluded did not meet the inclusion criteria listed in Table 1. The PRISMA flow chart in Appendix 1 outlines the selection process.

Summary of Study Characteristics

Further details of individual study characteristics have been summarized in Appendix 2

Country of origin

Two RCTs[3,4] were conducted in the United States of America (USA). The two reports were based on the same dataset as one of them[3] analyzed a subset of the population of the main

study (IDEA)[4] for outcomes which were not originally specified for investigation. The other study[7] was a prospective cohort study conducted in the Netherlands.

Study setting

The RCTs[3,4] were single-center studies conducted in a University setting. The cohort study[7] was conducted in a specialized department (Department of Orthopedic Surgery) in a University Medical Center.

Patient population

In the RCTs,[3,4] women represented 74% of the study sample and 86% self-identified as Caucasian. In the original study (IDEA),[4] 454 overweight and/or obese ($27.0 \leq BMI \leq 40.1$ kg/m^2) community-dwelling older adults (age ≥ 55 years) with pain and radiographic knee OA were enrolled into an 18 month study. Participants had to pass an initial symptom-limited, maximum exercise stress test which excluded anyone with severe manifestations of coronary heart disease. Patients were ineligible if they scored less than 70 on the Modified Mini-Mental State Exam screened for cognitive deficiencies at baseline. The second study[3] was based on data from 284 patients who completed the IDEA study,[4] and had dual energy X-ray absorptiometry (DXA) data for both baseline and 18 months.

In the cohort study,[7] 35 overweight or obese ($25 < BMI \leq 40$ kg/m^2) participants aged 25 years or older, who had clinical and radiological evidence of hip OA, were included. Patients were excluded if they had conditions that prevented safe participation in an exercise program, problems of the foot or ankle that could interfere with an exercise program, or rheumatoid arthritis. Other exclusion criteria included an inability to walk without a cane or other assistive device; participation in another research study; an inability to finish the study or a low likelihood of adhering to the instructions of the clinical staff because of frailty or illness; and an inability to complete a questionnaire because of language problems or dementia.

Interventions and comparators

The original RCT (IDEA)[4] randomized participants using a computer based permuted random block design into 1 of 3 groups: diet-induced weight loss plus exercise (D+E), diet-induced weight loss only (D), and exercise-only (E) interventions, with the exercise-only intervention designated as the comparator for the study. The other included RCT[3] was based on analysis of a subpopulation of patients who completed the IDEA study, and had similar patient characteristics.

All participants in the intervention arm received the same dietary intervention comprising up to two meal-replacement shakes per day with each shake providing 500 mg of calcium, and a third meal which was low in fat, high in vegetables, and provided 500 to 750 kcals/day.[4] Altogether, the dietary plan provided an energy-intake deficit of 800 to1000 kcals/day, with a calorie distribution goal of 15% to 20% from protein, less than 30% from fat, and 45% to 60% from carbohydrates.[4] Participants were offered weekly nutrition and behavior education sessions covering topics on problem solving, and goal-setting. Specific food topics including the opportunity to taste several well balanced, low-fat, nutritious foods prepared with easily available ingredients were also discussed. Participants attended biweekly group, and bimonthly individual behavioral sessions from the 7th to the 18th months, inclusive.[3]

Exercise consisted of walking (15 min), strength training (20 min), a second walking phase (15 min), and cool-down (10 min) 3 days per week for 18 months. For the first 6 months, exercises were done at the study center. After this period, participants could opt to continue at the facility, at home, or switch between the two venues.[4] The D + E group of the intervention arm received the same exercise program as the control arm (E).[4] Adherence data were reviewed regularly to identify participants who needed additional counseling.

Patients in the cohort study[7] participated in an 8-month intervention program of exercise in combination with weight loss with diet. A physical activity specialist coordinated the exercise component and a certified dietitian provided consultations for the dietary aspects of the program. The exercise intervention consisted of individual and group sessions lasting 3 and 5 months, respectively. Both the individual and the group exercise sessions focused predominantly on improving aerobic capacity.[7] In general, a weekly session lasting approximately 1 hour was structured to have 10 minutes to 15 minutes warm-up, a moderate to intense aerobic exercise lasting 30 minutes, and a mobility and strength exercises for 15 minutes. The exercise intensity progressed as the participants improved. In addition, participants were encouraged to perform moderate-intensity aerobic exercise at home for a minimum of 30 minutes on most or preferably all days of the week throughout the program duration (8 months).[7]

The weight loss intervention portion of the cohort study[7] was divided into intensive, transition, and maintenance phases. Specifics of the diet were not described. The intensive phase lasted approximately 3 months and aimed to heighten awareness of the importance of and the need for changing eating habits. It consisted of a 1-hour intake consultation and 3 subsequent consultations of between 15 minutes and 30 minutes each every 4 weeks. Participants were encouraged to read and understand the diversity of labels on food products, and to set achievable weight loss goals.[7] The transition phase consisted of two 15-minute sessions over approximately 2 months period. It was used to discuss problems encountered by the participants and encourage them to apply insight gained to make food choices to prevent relapse. The maintenance phase lasted approximately 3 months and consisted of one 15-minute session every 6 weeks designed to preserve the participants' motivation to continue with healthful eating habits to sustain the achieved weight loss.[7]

All participants received a manual consisting of written information that focused on health education and OA. Throughout the program, focus was placed on teaching self-management, stimulating an active lifestyle, and eating a healthful diet.

Outcome Measures

The primary outcomes of the IDEA trial[4] were plasma interleukin-6 (IL-6) level and knee compressive force. Interleukin-6 is a pro-inflammatory cytokine implicated in the pathogenesis of OA and concentrations less than 2.5 pg/mL have been shown to reduce the risk of mobility disability and improve markers of metabolic syndrome.[3] All participants were assessed at baseline, 6 months, and 18 months for IL-6 levels, and knee-joint compressive force. Secondary outcomes were pain, function, mobility, and health-related quality of life (HRQoL). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to assess pain and function. Walking speed in meters per second (m/s); and walked distance in meters (m) were recorded as measures of mobility. Health related quality of life was assed using the physical and mental health components of the 36-item short-form (SF-36) scores.

The study[3] which analyzed a subset of data from the IDEA trial[4] had bone mineral density (BMD) and T-scores at the hip and spine, as well as relationships between change in BMD and change in body weight, composition, and adiposity as outcomes.[3] Osteoporosis and osteopenia were defined as location-specific T-scores of 2.5 and between 2.5 and 1, respectively.[3]

In the cohort study,[7] the primary outcome was self-reported physical function, as measured with a subscale of the Dutch version of the WOMAC Index. Secondary outcomes were pain and walking tests as quantitative measures of function. Pain was measured with a 10-point visual analog scale (VAS) score. Assessment of functional status and walking speed were obtained with the 6-minute walk test and the 20-metre walk test, while HRQoL was measured using the SF-36 instrument.[7]

Summary of Critical Appraisal

Appendix 3 provides further details of the critical appraisal of individual studies

In the IDEA study,[4] baseline characteristics were fairly evenly matched across study arms. Interventionists' responsibilities were limited to exercise and dietary therapy interactions with patients with no data collection duties. Independent personnel who were blinded to group assignment collected data without intervention responsibilities. A sample size calculation was performed to determine the power of study to detect differences among treatment groups for both primary and secondary outcomes. The statistical analysis was based on intention-to-treat (ITT) population which generally maintains prognostic balance generated from the original random treatment allocation and leads to conservative estimate of treatment effect.

The IDEA trial[4] had a high overall completion rate (88%) with no significant differences in retention among treatment groups. There was no detail reported of how missing data was handled except that, according to the investigators, missing data were "assumed missing at random".[3] However, sensitivity analyses performed using multiple imputations for all 454 randomized individuals to assess whether results were biased because of missing data, showed that primary outcomes were statistically unchanged between the intention-to-treat and multiple imputation analyses. The sensitivity analysis involved imputing data for all 454 participants in sets of 50 at 6- and 18-month visits, aggregating the results from each analyzed set and comparing the finding to analysis of data from participants who completed the program. Nonetheless, differences between D+E and E for some secondary outcomes (6-minute walk distance and SF-36 physical subscale) reached statistical significance only in the multiple imputation analysis.

Participants in the IDEA trial[4] reported relatively mild pain at baseline averaging 6.5 on a 0 to 20 scale. This relatively low score suggests that minimizing pain perception among this population required little intervention. Thus the contribution of the low baseline pain level to the significant reduction in pain at the end of the study could be substantial. In this sense, the generalizability of the findings to patients with a higher intensity of pain is uncertain.

The methodological strengths and limitations in the IDEA study are shared by the study[3] which investigated BMD in a subset of patients who completed the former.[4] However, it is noteworthy that the post hoc analysis conducted by the second study[3] was based on a smaller sample size than was used in the IDEA study and it is unclear if it had enough power to detect differences between treatment groups for the investigated outcomes. Though analyzing a subset has the

potential of breaking the randomization effect in the original population, the investigators reported that the analyzed subset was similar in characteristics to the overall original population and in terms of treatment arms.

In the prospective cohort study,[7] participants were recruited from several sources including outpatient OA clinics of Orthopedic Surgery department, general practitioners, patients who presented directly and were considered eligible, and participants recruited through newspaper and website advertising. The patients who were recruited through advertising had to be seen and certified by an orthopedic surgeon as eligible for the study. The wide spectrum of recruitment sources affords good generalizability for the average person who has hip OA.

Researchers in the cohort study[7] assessed baseline demographic and medical condition of the participants. Primary and secondary outcomes of the study were assessed at baseline and relevant endpoints using the same tools and instruments. Sample size was determined to provide power to detect approximately 25% improvement in the primary outcome from the baseline measurement to the last measurement at 8 months.

The cohort study[7] achieved high participant adherence rates and dropouts did not differ in age or BMI at baseline from those who completed the final measurements though they had lower percentage of body fat (31% versus 41%). Since dropped-out participants did not differ from those who completed the final measurements, the effect of dropouts on the outcome is not expected to be significant. However, considering that higher body fat was associated with worse outcomes,[7] it is probable that reported findings without data from dropouts may be conservative. Adherence to the home exercise portion of the program was self-reported and not registered formally, although it was discussed with the participants before the start of the next weekly session.

Though outcomes of the cohort study[7] were self-reported, generalized estimating equations (GEEs) were used to investigate whether the participants showed statistically significant changes over time in primary and secondary outcome measures while being exposed to the intervention. This helped to improve the reliability of the outcomes. Despite the small sample size (n = 35) and the number of dropout participants (n = 5), the investigators reported that a post hoc power calculation revealed that the power of the study was not adversely affected and it was possible to detect clinically relevant changes in the primary outcome measure. Even so, the findings need to be confirmed in a randomized controlled trial.

Summary of Findings

Appendix 4 provides further details of the findings and author's conclusions

In the IDEA study,[4] the completion rate was high (88%) and similar across treatment arms (E, 89%; D, 85%; D+E, 89%). Non-completers did not differ significantly from completers in terms of demographics, medical conditions, pain, or physical function.[4] Adherence to therapy (diet or exercise) was similar across all treatment groups. The mean weight losses at 18 months relative to baseline were 8.9kg (9.5%) and 10.6 kg (11.4%) in the D and D +E groups, respectively, compared with 1.8kg, or 2.0% in the E group ($P < 0.001$ in each comparison).[4]

The IDEA study[4] found that the IL-6 level was significantly lower in the intervention group at 18 months ($P = 0.008$). Pairwise between-group differences relative to E were as follows; 0.43 pg/mL (95% confidence interval [CI]: 0.01 to 0.85; $P = 0.006$) for the D intervention, and 0.39

pg/mL (95% CI: −0.03 to 0.81; *P* = 0.007) for the D+E intervention. The statistical significance of the latter finding is unclear as the reported confidence interval crosses zero, however the *P*-value suggests significance. Relative to the baseline values, the peak knee compressive force was reduced by 10% and 9% in the D and D + E groups, respectively compared with 5% in the exercise group. However, only the difference between D and E was statistically significant (*P* = 0.007).[4]

Assessment at 18 months in the IDEA study[4] revealed that participants in the D+E group had significantly less pain relative to the E group (*P* = 0.004) and D (*P* = 0.001) groups. The D+E group also showed a significantly better WOMAC function score than the E group (*P* < 0.001), and the D group (*P* = 0.003) but no significant difference was observed between the E and D groups. Participants in the D+E group achieved a 0.04 m/s faster walk speed relative to the E group (*P* = 0.003). The differences in walk speed gained between groups E and D, and D and D+E were not significant.[4]. In terms of distance walked in 6 minutes, the D+E group walked 21.3 m, and 41.5 m farther than the E and D groups, respectively. The differences were significant in each pairwise comparison; E versus D+E, D versus D+E, and E versus D (*P* = 0.005, *P* = 0.005, *P* = 0.009, respectively). For HRQoL, a significant difference was observed only in the SF-36 physical component subscale for D+E group relative to the E group (*P* = 0.005). Changes in the SF-36 mental component subscale did not reach significance between any groups.[4]

Regardless of group assignment, participants who lost 10% or more of baseline body weight had greater reductions in knee compressive force, systemic IL-6 concentrations, and pain, as well as experienced greater improvement in function than those who lost between 5% and 9.9%, or less than 5% of their baseline weight, in that order.[4]

Investigators in the study[3] that analyzed a subset of patients who completed the IDEA trial[4] reported that the analyzed subset was similar to the main study population in terms of demographic and medical characteristics as well as group assignment and adherence to intervention, with no significant differences between treatment groups. A total of 9 (3.2%) participants across all groups had T-scores indicative of osteoporosis in any region. One participant (in D group) progressed from osteopenia to osteoporosis while two participants (one each in groups E and D) had baseline classification of osteoporosis changed to osteopenia at 18 months. Eleven participants (2 in E, 3 in D, and 6 in D + E) progressed from normal BMD to osteopenia in at least one region at 18 months.[3]

Changes in femoral neck and hip BMD correlated directly with changes in body weight (r = 0.21 and 0.54, both *P* ≤ 0.01) for the D and D+E groups. Analysis controlling for randomization group, gender, baseline BMI, and baseline outcome measures revealed that a 1 kg loss in body weight was associated with a 0.10 ± 0.03% reduction in femoral neck BMD and a 0.20 ± 0.03% reduction in hip BMD.[3]

Participants who lost the most weight and fat mass also lost the most hip and femoral neck BMD, regardless of baseline BMI, BMD, or exercise status. Significantly greater reductions of BMD at the femoral neck and hip, but not the spine were associated with the greatest weight loss (≥12.9% of initial weight). However, despite the significant loss in BMD, clinical classification of osteoporosis and osteopenia did not differ significantly.[3]

Adherence to the assigned intervention in the prospective cohort study[7] was high, with a rate of 94% in both individual and group exercise portion and 82% in the diet portion of the program. Participants who dropped out of the program (n=5) did not differ in age or BMI at baseline from

those who completed the final measurements. Reasons for not completing study included having too much pain (n=1), major depression (n=1), an ankle fracture (n=1), and inability to reach the study center every week (n=2).

Analysis revealed that over time participants exposed to the intervention in the cohort study,[7] achieved significant improvement in their physical function scores from a baseline value of 53.9 to 64.8 at 3 months, and 70.3 after 8 months. This represented a 32.6% improvement in self-reported physical function after 8 months.[7] WOMAC pain scores decreased by 25.4%, and the results of both walking tests (6-minute walk test and 20-m walk test) showed significant improvements after 8 months, with walked distance on the 6-minute walk test showing 11.6% improvement. Body mass also demonstrated significant reductions after 3 and 8 months, (2.8 kg $P < 0.05$; and 5.6 kg $P < 0.001$, respectively). The reduction reported at 8 months was equivalent to 5% of the baseline value.[7] Body fat, showed a significant reduction (3.3% $P = 0.000$) and SF-36 score for the perception of general health showed a significant improvement after 8 months.

Limitations

Limitations of included studies have been summarized in Appendix 3

A major limitation of this report is the paucity of available published literature that addresses the research question of interest. In addition, two of the included articles[3,4] were based on the same trial with one of them[3] being a post hoc analysis of a subset of the study population for outcomes which the original trial was not designed to investigate. Furthermore, the third included study was a prospective cohort study[7] designed to obtain preliminary evidence of the effect of a program of exercise in combination with weight loss in people who are overweight or obese and have hip OA. Thus an strong conclusion could not be drawn from its findings.

The investigators of the IDEA study[4] reported that the study patients had mild-to-moderate radiographic knee OA and mild-to-moderate levels of knee pain thus limiting the certainty of the reported benefits of the interventions in patients with more severe knee OA and higher levels of pain. A second limitation of the IDEA study[4] was that the musculoskeletal model used to calculate knee compressive forces excluded several knee ligaments and made assumptions about the hip flexors and hip abductors that may not be supported by anatomical evidence. Nonetheless, the researchers claim to have used the model to make previous predictions which were in agreement with those based on a variety of other models and from measured forces from instrumented knee joint prostheses.

Since the other included RCT[3] presents analysis based on a portion of data from the IDEA study,[4] it is, in the minimum, inherently subject to the same limitations as described for the IDEA study. Furthermore, the IDEA study was not designed to investigate difference across study groups with regards to bone mineral density (BMD) and T-scores at the hip and spine, as well as relationships between change in BMD and change in body weight, composition, and adiposity which were the focus of this study.[3] This limitation is further increased by the fact that the analysis involved data from only a subsection of participants who completed the IDEA study. Thus it is unclear to what extent the reported findings may be due to chance, or where a significant difference was not detected between groups, whether an increase in sample size to investigate the same question among comparable patients would result in a difference between groups.

The major limitation of the cohort study[7] is that it lacks the ability to rule out placebo effects. In addition, adherence to the home exercise portion of the program was self-reported. Thus, a further research in a randomized controlled setting is needed to confirm the finding. Moreover, it is not known whether the positive effect will be longer-term than 8 months.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

An 18 month study employing diet-induced, or exercise-induced, or diet and exercise-induced interventions among overweight and obese adults with knee OA demonstrated that diet-based interventions achieved more weight loss and greater reductions in IL-6 levels and knee compression force than those in the exercise group. Reductions in IL-6 levels knee compression force and pain, as well as improvements in function correlated positively with the extent of weight loss irrespective of the assigned treatment group. Participants who lost the most weight and fat mass also had significantly greater reductions in bone mass density at the femoral neck and hip at 18 months without a significant difference in the clinical classification of osteoporosis and osteopenia from baseline. The longer term implication of this tradeoff between loss of bone mass density and the reported benefits in other domains is not clear. A cohort study demonstrated reductions in weight with concomitant improvements in self-reported physical function scores and mobility as well as reduction in pain after 8 months. This resonates with findings of the RCTs. However, in view of the limitations of cohort studies in general, these findings may be considered exploratory awaiting confirmation from further studies in a randomized controlled setting.

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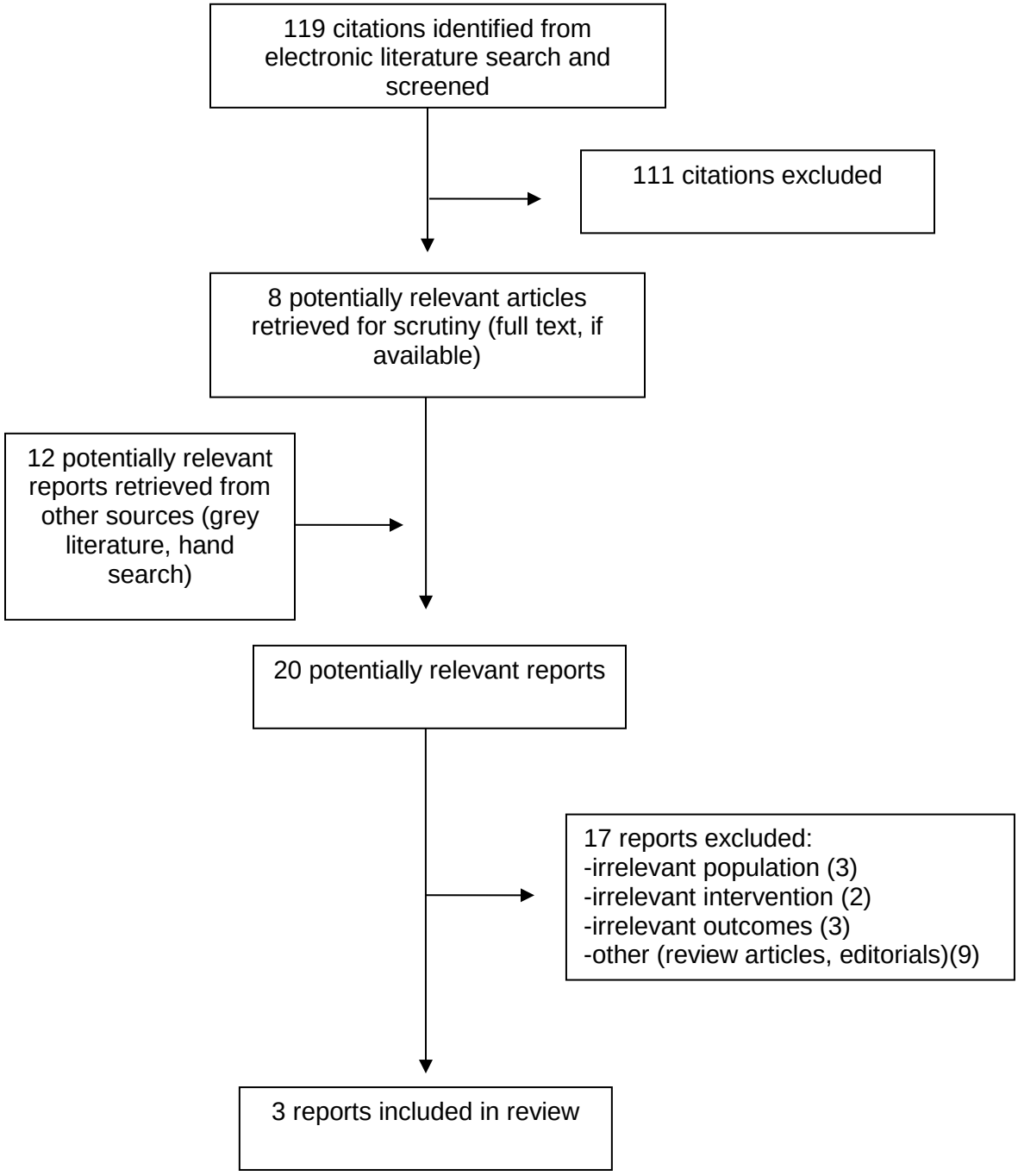
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

First Author, Publication year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcome
Beavers,[3] 2014 USA	RCT	284 overweight and obese, older adults with OA	Dietary (D) and Dietary plus exercise (D +E)	Exercise (E) involving walking and strength training	Weight loss; BMD and T-scores at the hip and spine; Relationships between change in BMD and change in body weight, composition, and adiposity
Messier,[4] 2013 USA	RCT	454 overweight or obese persons (27 ≤ BMI ≤ 41 kg/m^2), aged 55 years or older with mild or moderate OA of one or both knees, pain on most days due to knee OA and a sedentary lifestyle	Dietary (D) and Dietary plus exercise (D +E)	Exercise (E) involving walking and strength training	Primary: IL-6 level and knee-joint compressive force. Secondary: weight loss, pain, function, mobility, and HRQoL
Paans,[7] 2013 The Netherlands	Prospective cohort study	35 overweight or obese (25 < BMI ≤ 40 kg/m^2) patients, 25 years or older, with clinical and radiological evidence of hip OA.	Exercise plus diet	NA	Primary: Self-reported physical function. Secondary: Pain and function.

BMD = bone mineral density; **D** = dietary intervention; **D + E** = dietary plus exercise intervention; **E** = exercise; **IL-6** = interleukin 6 **HRQoL** = intervention; **NA** = not applicable; **OA** = osteoarthritis; **RCT** = randomized controlled trial

Appendix 3: Summary of Critical Appraisal of Included Studies

First Author, Publication year	Strengths	Limitations
Beavers,[3] 2014	1. Randomized controlled trial design, with relatively large sample size and serial measures of BMD at clinically important sites of osteoporotic fracture. 2. Baseline characteristic were balanced across treatment arms. 3. All outcome measures were assessed by blinded study staff. 4. Adherence to the study programs (diet and exercise) was comparable across study arms without a significant difference	In addition to the limitations of the IDEA study[4] which was the source of data for this study, the following are noted: 1. Data for analysis were from a subset of participants from another study (the IDEA trial)[4], and there is not enough information on how the subset was selected. 2. The IDEA study was not designed to evaluate outcomes of this investigation; therefore findings could not be confirmatory. 3. Only data from participants who complete the IDEA study were included in analysis; therefore the findings may not by representative of all the randomized participants.
Messier,[4] 2013	1. Randomized controlled trial design with a relatively large sample size. 2. Being a single-center study reduces the probability of variations in how study protocol was implemented. 3. Investigators with responsibilities for interventions and/or comparator did not collect data and personnel responsible for data collection were blinded to group assignment without intervention responsibilities. Such separation of duties helps to minimize reporting bias. 4. Sample size calculation was done to determine power of study to detect differences among treatment groups for both primary and secondary outcomes.	1. Important pieces of medical and medication use information (osteoporosis, bone medication use, calcium/vitamin D use) with potential to affect reported findings were self-reported at baseline and raise questions about reliability. 2. Participants continued on their usual medications during the study so it is unclear if the protective effect of pharmacotherapy might have compromised the ability to observe lifestyle-based differences. 3. Information on how missing data was handled is very scanty and it is unclear how this may impact the reported findings.
Paans,[7] 2013	1. The participants originated from diverse sources which strengthens the probability that findings may be generalizable to the average hip OA patients. 2. Participants' adherence to the study protocol was high: 94% in both individual and group exercise portions of the program and 82% in the diet portion. 3. Participants who dropped out before completion (n=5) had comparable characteristics to those who completed the study, and their reasons for discontinuation were not related to these characteristics. Therefore, the effect of these dropouts on the reported outcomes is likely to be negligible.	1. This was a prospective cohort study and thus placebo effect cannot be ruled out. 2. The sample size (n=35) seem relatively small though an *a priori* power calculation determined it was sufficient to determine approximately 25% difference in primary outcome, and *a post hoc* power calculation indicated that it was possible to detect clinically relevant changes in the primary outcome measure. 3. It is not known whether the positive effect will be long-term. 4. Adherence to the home exercise portion of the program was self-reported. 5. Details of what participants actually did to reduce weight are not enough to facilitate reproducibility.

Appendix 4: Main Study Findings and Authors' Conclusions

First Author, Publication year	Main Study Findings	Authors' Conclusions
Beavers,[3] 2014	1. Participants in the dietary and dietary plus exercise groups lost significantly greater weight than those in the exercise group ($P < 0.01$). 2. The hip and femoral neck regions demonstrated significant treatment effects for BMD with the D and D + E groups showing similar relative losses compared to E (both $P < 0.01$). 3. At 18 months, fewer participants had T-scores indicative of osteoporosis compared to baseline (9 versus 10, respectively). 4. Changes in BMD in the hip and femoral neck, but not spine, correlated with changes in body weight among participants in the D and D + E groups ($P \leq 0.01$ in all cases).	"Weight loss via an intensive dietary intervention, with or without exercise, results in bone loss at the hip and femoral neck in overweight and obese, older adults with OA. Although the exercise intervention did not attenuate weight loss-associated reductions in BMD, classification of osteoporosis and osteopenia remained unchanged."[3] page 726
Messier,[3] 2013	1. Both diet groups (D and D+E) lost significantly more weight than the exercise (E) group ($P < 0.001$). 2. Regardless of group assignment, participants who lost 10% or more of baseline body weight had greater reductions in knee compressive force, systemic IL-6 concentrations, and pain, as well as greater improvement in function than those who lost between 5% and 9.9%, or less than 5% of their baseline weight, in that order. 3. Compared with the E group, the D+E group had less inflammation, less pain, better function, faster walking speed, and better physical HRQoL.	"The findings from the IDEA trial data suggest that intensive weight loss may have both anti-inflammatory and biomechanical benefits; when combining weight loss with exercise, patients can safely achieve a mean long-term weight loss of more than 10%, with an associated improvement in symptoms greater than with either intervention alone." Page 1271
Paans,[7] 2013	1. After 3 and 8 months, there were significant decreases in body mass— 2.8 kg (95% CI:-4.4 to -1.2, $P < 0.05$) and 5.6 kg (95% CI: -7.7 to --3.4, $P < 0.001$), respectively.. 2. Body fat showed a significant reduction from baseline after 8 months (-.3%; 95% CI: -4.6 to -2.1; $P = 0.000$). 3. Participants improved their physical function scores to 64.8 and 70.3 after 3 and 8 months, respectively, compared with their baseline score of 53.0; an improvement of 32.6% after 8 months. 4. There was a decrease in pain indicated by 25.4% reduction in WOMAC pain score after 8 months. 5. A significant improvement in walking ability was demonstrated with a 11.1% increase in distance walked in the 6-minute walk and a reduction in time it took to walk 20 meters (-1.2; 95% CI: -1.8 to 0.6).	"Overall, we concluded that the cohort study provided preliminary evidence of the effectiveness of a program of exercise in combination with weight loss. Our findings should be confirmed in a randomized controlled trial." Page 144

BMD = bone mineral density; **CI** = confidence interval; **D** = dietary intervention; **D + E** = dietary plus exercise intervention; **E** = exercise intervention, **OA** = osteoarthritis