CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Body Weight Modification Interventions for Chronic Non-Cancer Pain: A Review of Clinical Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	March 27, 2020
Report Length:	39 Pages

CADTH

Authors: Yan Li, Charlene Argáez

Cite As: Body weight modification interventions for chronic non-cancer pain: a review of clinical effectiveness. Ottawa: CADTH; 2020 Mar. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **Requests@CADTH.ca**

Abbreviations

6MWT	6-minute walk test
AMSTAR	A Measurement Tool to Assess Systematic Reviews
BMI	Body mass index
CI	Confidence intervals
KOA	Knee osteoarthritis
KOOS	Knee Injury and Osteoarthritis Outcome Score
LBP	Lower back pain
NRS	Numerical rating scale
RCT	Randomized controlled trial
SMD	Standardized mean differences

Context and Policy Issues

In 2016, the World Health Organization estimated 1.9 billion adults (age ≥ 18 years) to be overweight (body mass index, BMI = 25-29.9 kg/m^2) and 650 million to be obese (BMI ≥ 30 kg/m^2).[1] Amongst other symptoms, individuals who are overweight are more likely to suffer from fatigue, depression, and chronic pain.[2,3] Chronic pain affects about one in five Canadian adults (age ≥ 18 years) and one in three seniors (age ≥ 65 years).[4] This has considerable economic implications as an estimated annual direct cost of $7.2 billion is associated with managing chronic pain in Canada.[5]

Chronic non-cancer pain is commonly caused by neuropathy, lower back issues, or arthritis.[6] Studies have shown obesity to be associated with knee and hip pain.[7] This link between chronic pain and obesity is related, in part, to the mechanical load on weight-bearing joints.[7] This is especially relevant in patients with knee osteoarthritis (KOA) as the knee joint is most commonly affected in the lower extremities.[8] As a chronic degenerative disease that could result in permanent damage to bone joints, osteoarthritis is the most common type of arthritis.[9]

With the goal of helping patients lose and maintain long-term weight loss, non-surgical treatments for obesity have been associated with benefits for obesity-related comorbidities.[10] Non-pharmacological options for pain and mobility include, but are not limited to, strength training, aerobic exercise, yoga, massage therapy, orthotics, and/or weight loss interventions.[11] Weight loss interventions can involve multidisciplinary teams consisting of dieticians, physiologists, and clinical psychologists.[8] Differences exist in weight management programs, which can incorporate diet (e.g., caloric restriction), exercise (e.g., aerobic and/or strength training), behavioural education (e.g., self-regulatory skills), or various combinations of these interventions.[8]

In February 2020, a CADTH Rapid Response Reference List report indicated the availability of relevant literature regarding the clinical effectiveness of body weight modification interventions for chronic non-cancer pain, as well as evidence-based guidelines regarding body weight modification for chronic, non-cancer pain.[12] The objective of this report is to review and summarize the relevant literature regarding the clinical effectiveness of body weight modification interventions for chronic non-cancer pain.

Research Question

What is the clinical effectiveness of body weight modification interventions for chronic non-cancer pain?

Key Findings

Three systematic reviews (that included 13 unique relevant primary studies) and two non-randomized studies were identified regarding the clinical effectiveness of body weight modification interventions (e.g., diet-only, exercise-only, combination diet and exercise) for the treatment of chronic non-cancer pain in adults with excess body weight (body mass index ≥ 25 kg/m^2). No evidence regarding the clinical effectiveness of body weight modification interventions in adults with body mass index < 18.5 kg/m^2 was identified.

The three systematic reviews were generally well-conducted, but there were methodological limitations in their included primary studies which provided low to moderate strength evidence. The identified literature revealed mixed conclusions regarding the clinical effectiveness of body weight modification interventions for chronic non-cancer pain for overweight adults. Specifically, in most studies, body weight modification interventions (i.e., diet or exercise) resulted in statistically significant weight reductions, and improvements in pain and physical function compared to no diet or exercise. However, in some studies, no statistically significant differences were detected in weight, pain, and physical function between diet and/or exercise groups and control groups (i.e., no diet and exercise). There were numerically more nonserious gastrointestinal issues associated with diet interventions compared to non-diet groups; however, specific numbers were not reported. Furthermore, no serious adverse events were reported for any intervention or control groups.

The limitations of the included studies (e.g., heterogeneity of interventions and outcome measures, variation in treatment durations, risk of performance bias due to unblinded participants, inconsistencies in study findings) should be taken into consideration when interpreting the findings of this report.

Methods

Literature Search Methods

This report made use of a literature search that was conducted for a previous CADTH report.[12] A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were weight change and chronic pain. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2015 and February 3, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults living with chronic non-cancer pain who are classified as either over- or under-weight (body mass index ≥ 25 or < 18.5), excluding pregnant adults
Intervention	Weight modification interventions (i.e., dietary and/or exercise interventions)
Comparator	Pharmacological interventions No treatment (no weight loss interventions) Usual care
Outcomes	Clinical effectiveness (e.g., pain, functional performance, quality of life, disability level, safety, global impression of recovery, adverse events)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, and non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using version two of A Measurement Tool to Assess systematic Reviews (AMSTAR 2)[13] and non-randomized studies were critically appraised using the Downs and Black checklist.[14] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 510 citations were identified in the literature search. Following screening of titles and abstracts, 503 citations were excluded and seven potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, four publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised three systematic reviews[8,11,15] (one with meta-analysis)[8] and two non-randomized studies.[7,10] Appendix 1 presents the PRISMA[16] flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Three systematic reviews[8,11,15] (one with meta-analysis)[8] and two non-randomized studies[7,10] were identified for inclusion in this review. Additional details regarding the characteristics of included publications are provided in Appendix 2, Table 2 and Table 3.

The three included systematic reviews[8,11,15] had broader inclusion criteria (i.e., wider in scope) than the current report. Specifically, all three systematic reviews[8,11,15] included primary studies that compared weight modification interventions (i.e., diet, exercise, or combination diet and exercise) with other weight modification interventions, in addition to

comparisons with usual care, or no treatment. Additionally, two systematic reviews[11,15] also included studies on the impact of pharmacological and surgical interventions for KOA. One systematic review[8] also included studies with indirect outcome measures (i.e., serum cytokines). Only the study characteristics and results of the subset of the relevant primary studies will be described and summarized in this report.

Study Design

Three systematic reviews[8,11,15] (one with meta-analysis)[8] were included in this report. The systematic review with meta-analysis was authored by Hall et al. (2019),[8] and included randomized controlled trials (RCTs) published from database inception to March 1, 2017 with language restricted to English, German, French or Dutch. The review[8] included a total of 16 articles; six RCTs[17-22] were relevant for the current report.

The systematic review authored by Charlesworth et al. (2019)[15]included systematic searches for relevant peer reviewed primary articles, systematic reviews, and meta-analyses published between 1990 and July 2017 with language restricted to English. A total of 34 articles were included in the systematic review[15] (two RCTs [17,23] were relevant for the current report). The systematic review authored by Newberry et al. (2017)[11]consisted of systematic searches for relevant RCTs and single-arm prospective observational studies published between 2006 and September 2016 with language restricted to English. A total of 107 articles were included in the systematic review[11] (five RCTs[18-20,24,25] and four single-arm studies[26-29] were relevant for the current report).

Two primary clinical studies not contained in the three aforementioned systematic reviews were included in this report.[7,10] Dunlevy et al. (2019)[10] conducted a single-arm retrospective analysis of anonymized patient data obtained from a multidisciplinary weight management service. Schrepf et al. (2017)[7] conducted a single-arm prospective longitudinal study of patients referred to a weight management program.

The two systematic reviews authored by Charlesworth et al. (2019)[15] and Newberry et al. (2017)[11] had one[17] and three[18-20] overlapping primary studies, respectively, with the aforementioned systematic review authored by Hall et al. (2019).[8] Thus, data from only two unique RCTs[21,22] were extracted from the systematic review authored by Hall et al. (2019).[8] A table of primary study overlap is provided in Appendix 5.

Country of Origin

The first authors of the systematic reviews were from Australia[8,15] and the US.[11] Charlesworth et al. (2019)[15] included primary studies conducted in the UK and the US; Hall et al. (2019)[8] included studies conducted in Denmark, UK, and US; and Newberry et al. (2017)[11] included studies conducted in Australia, Denmark, France, US, and Tunisia.

The first authors of the primary clinical studies by Dunlevy et al.[10] and Schrepf et al.[7] were from Ireland and the US, respectively.

Patient Population

All three systematic reviews involved patients with pain, who were diagnosed with KOA and had BMI ≥ 25 kg/m^2.[8,11,15] Two systematic reviews[11,15] included primary studies that recruited adults ≥ 18 years of age, and one systematic review[8] included studies that recruited adults ≥ 45 years of age. In the systematic review by Hall et al., the mean age and BMI of study participants ranged from 57.9 to 70.3 years of age and 32.8 to 45.0 kg/m^2, respectively, across the nine relevant primary studies.

The retrospective study authored by Dunlevy et al. included 806 adult patients (476 completed the program) with pain, and BMI > 40 or BMI of 35-40 kg/m^2 accompanied by a significant comorbidity.[10] Specific comorbid conditions were not reported.[10] Among those who completed the program, the mean age was 45.1 years, and mean baseline weight and BMI were 146.8 kg and 50.8 kg/m^2, respectively.[10]

In the prospective study conducted by Schrepf et al., 241 patients with pain and excess weight for height (BMI ≥ 30 kg/m^2 or ≥ 28 kg/m^2 for Asian Americans) were enrolled. Of these, 123 were included in the longitudinal analysis (the remainder were excluded from the analysis due to withdrawal, loss to follow-up, or weight gain).[7] The mean age of included patients was 51 years, and the mean weight and BMI at baseline were 116 kg and 40 kg/m^2, respectively.[7] In this study, 19% of participants were diagnosed with osteoarthritis, while the conditions of the remaining participants were not reported.[7]

Interventions and Comparators

The authors of the relevant primary studies within the three systematic reviews[8,11,15] and the two additional primary articles[7,10] investigated a variety of weight management interventions (including diet, exercise, diet plus exercise, and behavioural programs), compared to usual care (any non-pharmacological, non-surgical, and conventional diet treatment) or no treatment (advice pamphlet, placebo, or waitlist).

In the six relevant primary studies[17-22,30-32] included in the systematic review authored by Hall et al. (2019),[8] the diet interventions involved intake restriction to as low as 800 kilocalories/day, while the exercise regimens involved aerobic, strength, and/or stretching exercises. The intervention durations ranged from 8 to 96 weeks.[8] The two relevant primary studies[17,23] included in another systematic review[15] involved calorie restriction, and aerobic and/or resistance training for a duration of 18 to 24 months. In the nine relevant primary studies[18-20,24-29] included in the third systematic review,[11] the diet interventions involved intake restriction to as low as 415 kilocalories/day, while the exercise regimens involved aerobic and/or strength exercises. The intervention durations ranged from 8 to 52 weeks.[11] These interventions were compared to standard care (e.g., exercise only, or no diet and exercise).

The intervention in the retrospective study by Dunlevy et al.[10] was a 12-month multidisciplinary weight management service that consisted of individual and group counselling sessions with dieticians, psychologists, and physiotherapists. Specifically, dieticians developed patient-specific plans to promote healthy eating habits, psychologists evaluated participants for eating disorders, and physiotherapists prescribed exercise regimens to improve physical impairments.[10]

The intervention in the prospective study by Schrepf et al.[7] was a multidisciplinary behavioural lifestyle program that incorporated 12 to 16 weeks of a total liquid diet with 800 kilocalories/day, plus encouragement to walk 40 minutes daily for the first 12 weeks, and promotion of up to 90 minutes of moderate to vigorous activity for ≥ 4 days per week after the initial 12 weeks. Additional counselling was provided at each monthly follow-up visit to encourage participant adherence to the weight loss regimen.[7]

Outcomes

Outcomes in all three systematic reviews[8,11,15] were related to weight change, knee pain, functional status, and/or health-related quality of life. Self-reported safety data were

reported in two systematic reviews.[11,15] No information on the minimal clinically important difference for outcomes was available within the three included systematic reviews.[8,11,15]

The clinical outcomes in the retrospective study authored by Dunlevy et al. (2019)[10] were weight change, and severity and prevalence of knee and lower back (LBP) pain. The minimal clinically important difference in pain was reported to be a >30% change in this study.[10] The measured outcomes in the prospective study authored by Schrepf et al. (2017)[7] were weight change, pain, and health-related quality of life.

A brief description of the outcome assessment scales used in the included studies is provided in Appendix 2, Table 4. Various scores were used to evaluate pain (Knee injury and Osteoarthritis Outcome Score, Modified American College of Rheumatology score for fibromyalgia, Numeric Rating Scale for pain, Visual Analogue Scale for pain, Western Ontario and McMaster Universities Osteoarthritis Index pain score), functional status (6-minute walk test, Ontario and McMaster Universities Osteoarthritis Index physical function score),health-related quality of life (Short Form 12-Item Health Survey), or measures of anxiety and depression (Inventory of Depressive Symptomology, Hospital Anxiety and Depression Index).

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 5 and Table 6.

Systematic Reviews

The three included systematic reviews[8,11,15] were generally well-conducted as per AMSTAR II criteria. All three reviews[8,11,15] had clearly stated objectives, inclusion/exclusion criteria, searched multiple databases, provided a list of included studies, and evaluated the risk of bias in included primary studies with appropriate techniques. The literature search strategies of two systematic reviews[8,11] included grey literature searches, which decrease the risk of missing relevant, non-indexed studies. Additionally, Charlesworth et al. (2019) explicitly stated their justification for inclusion of only peer-reviewed articles, systematic reviews, and meta-analyses. Hall et al. (2019) and Newberry et al. (2017) conducted data extraction in duplicate, which decreases the risk for inconsistencies. All three systematic reviews had a priori protocols[8,11,15] (two review protocols[8,15] prospectively registered with PROSPERO). Key search terms and search strategies were described for all three reviews.[8,11,15] The systematic review authored by Hall et al. (2019)[8] used appropriate statistical methods (i.e., a random effects meta-analysis of standardized mean differences with assessment of heterogeneity using I^2 statistical and χ^2 tests). Hall et al. (2019) assessed the risk of publication bias using funnel plots, and publication bias was not identified or was considered low.[8] Finally, the authors of all three systematic reviews[8,11,15] stated that they did not have any funding or affiliations that would constitute conflicts of interest.

In terms of methodological limitations, the authors of one systematic review[15] did not include grey literature searches, which increased the risk of missing relevant, non-indexed studies. Charlesworth et al. (2019) performed data extraction by only one reviewer. Hall et al. (2019) extracted data on adverse events but did not report the findings. Authors of all three systematic reviews[8,11,15] provided reasons for excluding articles, but only Newberry et al. (2017) included a list of excluded studies in their appendix. Authors of two systematic reviews [11,15] did not report if publication bias was assessed. Hall et al. (2019) and Newberry

et al. (2017) limited eligible study designs to RCTs only, or RCTs or single-arm prospective studies, respectively, but there was no explicit justification for these decisions. Two systematic reviews[8,15] did not report the sources of funding for the included primary studies. Finally, the countries in which relevant primary studies were conducted were not reported in the three systematic reviews.[8,11,15] Upon close review of the relevant primary literature included in the three systematic reviews, these countries included Australia, Denmark, France, UK, US, and Tunisia; therefore, findings may not be generalizable to the Canadian setting.

In the systematic review authored by Hall et al. (2019),[8] I^2 statistics was used to quantify statistical heterogeneity across primary studies. With I^2 values ranging from 24% to 54% for WOMAC pain and physical function scores, the appropriateness of combining such heterogeneous data was unclear. Methodological limitations of primary studies included within the three systematic reviews[8,11,15] were incomplete adherence (especially for home-based exercise routines), inability to determine adequate concealment of participant allocation, unblinded participants and health care professionals, inadequate follow-up durations (as short as two months), and risk of attrition bias (especially in studies with unequal dropout rates across interventions). Inherent quality issues from the primary studies would cause uncertainty in the findings presented in the systematic reviews.

Non-Randomized Studies

The two single-arm non-randomized studies[7,10] shared some methodological strengths, including: 1) clearly stated objectives, inclusion criteria, outcome measures, interventions, and main findings; 2) reported estimates of random variability (e.g., confidence intervals, standard deviations); 3) planned data analysis at the outset of the study; and 4) all study authors disclosed funding sources and declared no potential conflicts of interest. Furthermore, study participants and health care settings in both non-randomized studies[7,10] appeared to be representative of the population and care settings of interest, which increased the external validity of the studies. Although both studies[7,10] outlined the methodology used to enroll participants, only the study authored by Dunlevy et al. explicitly stated the time period over which participants were recruited and described the characteristics of patients lost to follow-up or who did not complete the program.

These two non-randomized studies[7,10] also had some methodological limitations. In both studies,[7,10] specific exclusion criteria and sample size calculations were not reported. Although authors of both studies[7,10] reported P values for outcomes, Dunlevy et al. did not report exact P values for all outcomes. Since both single-arm studies[7,10] followed an open-label before-and-after design, they were at risk for several biases. For example, study participants may have over- or under-reported pain scores due to knowledge of the interventions received and beliefs about their potential effects. These studies were also prone to attrition bias due to patients lost to follow-up or who did not complete the program. Lastly, the generalizability of findings from these two non-randomized studies to the Canadian setting was unclear since they were conducted in Ireland[10] and the US.[7]

Summary of Findings

The overall findings of the included studies are highlighted below. Detailed summaries of the main findings are available in Appendix 4, Table 7 and Table 8.

Clinical Effectiveness of Body Weight Modification Interventions

Overweight Adults (BMI ≥ 25 kg/m^2)

Weight Change

Evidence regarding the clinical effectiveness of body weight modification interventions for weight change in participants with chronic non-cancer pain was available from 13 primary studies[17-32] within three systematic reviews[8,11,15] and two additional primary studies.[7,10] Two relevant RCTs[17,23] included in the systematic review authored by Charlesworth et al. (2019)[15] reported weight change as an outcome. In the primary study authored by Messier et al. (2004), the diet only (4.9% reduction) and diet plus exercise (5.7%) groups exhibited significantly greater (P < 0.05) weight reductions compared to the healthy lifestyle control group (1.2%).[17] However, there was no significant difference in weight reduction between the exercise only and control groups.[17] In the primary study authored by Jenkinson et al. (2009), there was a significant mean difference in weight reduction of 2.95 kg (1.44 to 4.46; P = 0.000) between the diet versus non-diet group, but no significant mean difference in weight reduction of 0.43 kg (-0.82 to 1.68; P = 0.501) between the exercise versus non-exercise group.[23]

Five relevant RCTs[18-20,24,25] and four relevant single-arm primary studies[26-29] included in the systematic review authored by Newberry et al. (2017)[11] reported weight change as an outcome. Three RCTs detected significant weight reductions in diet only and/or diet plus exercise interventions compared to control groups (no diet and exercise).[19,24,25] Compared to the standard care control group, Somers et al. (2012) detected significant weight reductions in participants receiving combination pain coping skills training and behavioural weight management, as well as behavioural weight management only interventions.[18] Compared to the exercise only group (considered standard care), Messier at al. (2013) detected significant weight reductions in the diet only (MD -6.00, 95% CI, -9.75 to -2.25) and diet plus exercise (MD -8.10, 95% CI, -11.92 to -4.28) group.[20] In two single-arm primary studies authored by Claes et al. (2015)[27] and Bartels et al. (2014),[28] significant weight reductions were detected from before to after a hospital-based weight program and low calorie diet intervention, respectively. Statistical analysis was not reported for the weight reductions compared to baseline in two other single-arm primary studies.[26,29]

Two relevant RCTs[21,22] included in the systematic review authored by Hall et al. (2019)[8] reported weight change as an outcome. In the study authored by Christensen et al. (2015), the diet only group achieved significantly greater weight reduction (11.0 kg, 95% CI, 9.0 to 12.8 kg) than the exercise only (6.2, 95% CI, 4.4 to 8.1 kg) and the usual care control group (8.2, 95% CI, 6.4 to 10.1 kg) (P = 0.002 by ANCOVA).[21] Furthermore, the diet group achieved significantly greater weight reduction (MD 6.8%, 95% CI, 5.5 to 8.1%; P < 0.0001) than the advice pamphlet group (control) in another study authored by Christensen et al. (2005).[22]

Two additional single-arm primary studies authored by Dunlevy et al. (2019)[10] and Schrepf et al. (2017)[7] not included in the three identified systematic reviews[8,11,15] also reported weight change. From before to after a 12-month multidisciplinary weight management program involving dieticians, psychologists, and physiotherapists, Dunlevy et al. reported a

significant mean weight reduction of 5.1 kg (P < 0.01) and BMI reduction of 1.8 kg/m^2 (P < 0.01).[10] From before to after a 2-year weight management program (involving 12-16 weeks of total liquid calorie-restricted diet combined with moderate to vigorous exercise), Schrepf et al. reported an average weight loss of 16.05% ± 6.54% (statistical analysis not reported).[7]

Pain

Overall, the impact of weight modification interventions on pain prevalence and severity was varied. Two relevant RCTs[17,23] included in the systematic review authored by Charlesworth et al. (2019)[15] reported WOMAC pain as an outcome. In the primary study authored by Messier et al. (2004), significant benefit (P < 0.05) was detected in WOMAC pain scores for participants in the diet plus exercise group compared to the healthy lifestyle control group.[17] However, no significant differences in WOMAC pain scores were detected in the diet only or exercise only groups compared to control.[17] In the primary study authored by Jenkinson et al. (2009), there was a significant improvement in WOMAC knee pain score (% risk difference = 1.61; 95% CI, 1.81% to 21.41%) in the exercise groups compared to non-exercise groups.[23] There was no significant difference in WOMAC pain scores in the diet only group compared to the control group (i.e., advice pamphlet only).[23]

Five relevant RCTs[18-20,24,25] and three relevant single-arm primary studies[27-29] included in the systematic review authored by Newberry et al. (2017)[11] reported pain as an outcome. Three RCTs detected significant improvements in pain scales (WOMAC or Visual Analogue Scale [VAS] pain scores) for diet only, exercise only, and/or diet plus exercise interventions compared to control groups (no diet and exercise).[19,24,25] Compared to the standard care control group, Somers et al. (2012) detected significant improvements in WOMAC pain scores in participants receiving combination pain coping skills training and behavioural weight management, but not those receiving the behavioural weight management only intervention.[18] Compared to the exercise only group (considered standard care), Messier et al. did not detect a significant difference in WOMAC pain scores for the diet only (MD 0.40, 95% CI, -0.31 to 1.11) or diet plus exercise (MD -0.70, 95% CI, -1.41 to 0.01) groups.[20] In three single-arm primary studies authored by Claes et al. (2015),[27] Bartels et al. (2014),[28] and Atukorala et al. (2016),[29] significant improvements in Knee Injury & Osteoarthritis Outcome Score (KOOS) for pain were detected following diet or exercise interventions compared to baseline.

Two relevant RCTs[21,22] included in the systematic review authored by Hall et al. (2019)[8] did not detect significant differences in VAS pain scores (P = 0.982 by ANCOVA)[21] and WOMAC pain scores (MD -27.2, 95% CI, -64.0 to 9.7; P = 0.15)[22] amongst diet only, exercise only, and/or control groups (usual care or advice pamphlet).

Two additional single-arm primary studies authored by Dunlevy et al. (2019)[10] and Schrepf et al. (2017)[7] not included in the three identified systematic reviews[8,11,15] also reported pain outcomes. From before to after a 12-month multidisciplinary weight management program involving dieticians, psychologists, and physiotherapists, Dunlevy et al. (2019) conducted a subgroup analysis of participants based on three weight loss categories: lost weight (≥ 5% loss), stable weight (less than 5% loss/gain), and gained weight (≥5% gain).[10] In the subgroup of participants who lost weight, Dunlevy et al. detected significant decrease in the prevalence of LBP (14.8%, P < 0.05) and knee pain (12.4%, P < 0.05).[10] In the overall group, 41% and 34% of participants with LBP and knee pain, respectively, exhibited minimal clinically important difference (i.e., > 30% change) in Numerical Rating Scale (NRS) pain scores.[10] From before to after a 2-year weight management program (involving

12 to 16 weeks of total liquid calorie-restricted diet combined with moderate to vigorous exercise), Schrepf et al. detected a significant improvement in the Modified American College of Rheumatology score for fibromyalgia (P = 0.004) in the subgroup of participants who lost ≥ 10% of their baseline weight (n = 99) compared to the subgroup who lost < 10% of their weight (n = 24).[7]

Functional Status

Overall, the impact of weight modification interventions on physical function was also varied. Two relevant RCTs[17,23] included in the systematic review authored by Charlesworth et al. (2019)[15] reported WOMAC physical function and/or 6-minute walk test (6MWT) as outcomes. In the primary study authored by Messier et al. (2004), significant benefit (P < 0.05) was detected in WOMAC physical function scores for participants in the diet plus exercise group compared to the healthy lifestyle control group.[17] However, no significant differences in WOMAC physical function scores were detected in the diet only or exercise only groups compared to control.[17] Furthermore, significant improvements (P < 0.05) in 6MWT scores were detected in the exercise only and diet plus exercise groups compared to control.[17] However, no significant difference in 6MWT scores was detected in the diet only group compared to control.[17] In the primary study authored by Jenkinson et al. (2009), there was no significant improvement in WOMAC physical function score (mean difference = −3.64; 95% CI, −6.01 to −1.27; P = 0.003) in the exercise groups compared to non-exercise groups.[23] There was no significant difference in WOMAC physical function scores in the diet only group compared to the control group (i.e., advice pamphlet only).[23]

Five relevant RCTs[18-20,24,25] and two relevant single-arm primary studies[28,29] included in the systematic review authored by Newberry et al. (2017)[11] reported WOMAC or KOOS physical function as outcomes. Two RCTs detected significant improvements in WOMAC physical function scales for diet only, exercise only, and/or diet plus exercise interventions compared to control groups (no diet and exercise).[19,24] Compared to the control group (i.e., moderate calorie restriction), Bliddall et al. (2011) did not detect a significant difference in WOMAC function scores for the low energy diet group (i.e., 810-1200 cal/day) (MD -3.60, 95% CI, -9.14 to 1.94).[25] Compared to the standard care control group, Somers et al. (2012) detected significant improvements in WOMAC physical function scores in participants receiving combination pain coping skills training and behavioural weight management, but not for the behavioural weight management only intervention.[18] Compared to the exercise only group (considered standard care), Messier et al. detected a significant difference in WOMAC physical function scores in the diet plus exercise group (MD -3.40, 95% CI, -6.02 to -0.78), but not in the diet only group (MD 0.10, 95% CI, -2.67 to 2.87).[20] In two single-arm primary studies authored by Bartels et al. (2014)[28] and Atukorala et al. (2016),[29] significant improvements in KOOS function score were detected following diet or exercise interventions compared to baseline.

Two relevant RCTs[21,22] included in the systematic review authored by Hall et al. (2019)[8] reported physical function as an outcome. In the study authored by Christensen et al. (2015), no significant differences were detected amongst the diet only, exercise only, and usual care control group (P = 0.910 by ANCOVA).[21] However, the diet group achieved significantly greater improvements in WOMAC physical function score (MD -166.9, 95% CI, -274.5 to -59.3; P = 0.003) than the advice pamphlet group (control) in another study authored by Christensen et al. (2005).[22]

Three relevant RCTs[19,20,24] and one relevant single-arm primary study[27] included in the systematic review authored by Newberry et al. (2017)[11] reported 6MWT as an outcome. In

the primary study authored by Ghroubi et al. (2008), significant improvements were detected in 6MWT scores for exercise only (MD -39.00, 95% CI, -46.47 to -31.53) and diet plus exercise (MD -53.00, 95% CI, -59.33 to -46.67) groups compared to control (no diet and exercise).[24] However, there was no significant difference in 6MWT scores for the diet only group (MD 2.00, 95% CI, -6.51 to 10.51) compared to control.[24] In the primary study authored by Miller at al. (2006), significant improvements were detected in 6MWT scores for the diet plus exercise group (MD -51.00, 95% CI, -96.03 to -5.97) compared to control (educational sessions only).[19] In the primary study authored by Messier et al. (2013), significant improvements were detected after 18 months in 6MWT scores for diet plus exercise interventions (MD -12.00, 95% CI, -33.93 to 9.93) compared to exercise only (considered to be part of the standard care).[20] However, there was no significant difference in 6MWT scores for the diet only group (MD 23.00, 95% CI, 3.15 to 42.85) compared to exercise only.[20] In one single-arm primary study authored by Claes et al. (2015), significant improvements in 6MWT scores were detected following 12 weeks of a hospital-based weight management program with unspecified interventions (MD 36.7, 95% CI, 27.2 to 46.2) and 26 weeks (MD 44.0, 95% CI, 31.5 to 56.5) when compared to baseline.[27]

Health-Related Quality of Life

In one relevant primary study authored by Makovey et al. (2015)[26] from the systematic review authored by Newberry et al. (2017),[11] a significant favourable dose-response relationship was observed between percentage weight loss and improvements in the Short Form (12-Item) Health Survey score (e.g., <2.5% weight loss: mean 3.16 [SD 8.24] versus > 10% weight loss: 8.60 [SD 8.18], P = 0.000).

Anxiety and Depression

In one relevant primary study authored by Jenkinson et al. (2009)[23] from the systematic review authored by Charlesworth et al. (2019),[15] weight loss was associated with a decrease in the Hospital Anxiety and Depression Index depression subscale (absolute effect size = 0.19) within the diet only group (depression scale for non-diet group and statistical analysis not reported).

In one additional primary study authored by Schrepf et al. (2017)[7] not included in the three systematic reviews,[8,11,15] there was a significant improvement in the Inventory of Depressive Symptomology score (P < 0.001) in the subgroup of participants who lost ≥ 10% of their baseline weight compared to the subgroup who lost < 10% of their weight.

Adverse Events

It was reported that there were no serious adverse events in two systematic reviews.[11,15] In the systematic review authored by Newberry et al. (2017),[11] there were numerically more nonserious gastrointestinal adverse events in diet intervention groups than non-diet intervention groups, but event rates, specific events, and statistical comparisons were not reported.[11] In one relevant primary study[17] included in the systematic review authored by Charlesworth et al. (2019),[15] one participant (out of a total of 252 participants) sustained a forehead laceration due to tripping during exercise.

Underweight Adults (BMI < 18.5 kg/m^2)

No evidence regarding the clinical effectiveness of body weight modification interventions for chronic non-cancer pain was identified for underweight adults (BMI < 18.5 kg/m^2); therefore, no summary can be provided.

Limitations

Numerous limitations were identified in the critical appraisal (Appendix 3, Table 5 and Table 6); however, additional limitations exist.

Although the three included systematic reviews[8,11,15] were generally well-conducted according to AMSTAR II criteria, the authors from two systematic reviews[8,11] rated the underlying evidence from relevant RCTs and single-arm studies as being "insufficient" to "moderate" in quality. Furthermore, the authors of the third systematic review[15] did not explicitly discuss the quality of evidence of included studies; however, they only included studies with a Downs and Black quality score ≥ 13. There was substantial clinical heterogeneity amongst included studies. The three systematic reviews[8,11,15] combined data from primary studies with differences in patient populations, types of diet and exercise regimens, frequencies of treatment, durations of treatment, and lengths of follow-up.

Two systematic reviews[8,11] and two additional primary studies[7,10] that reported demographic information on the sex of study participants enrolled a disproportionately higher number of female participants ranging from 62% to 100%. This disproportionate female representation should be considered when generalizing findings of included literature to male patients because women may report more pain than men.[33] Although two additional primary studies[7,10] evaluated pain sites other than knee (e.g., LBP, hip), all three systematic reviews[8,11,15] only included primary studies specific to osteoarthritis-related knee pain. Therefore, the clinical effectiveness of body weight modification interventions for chronic pain of other origins remains unclear. Furthermore, the assessed outcomes lacked standardization (i.e., scores for pain, physical function, and quality of life varied across primary studies), which may pose a challenge in interpreting global findings across studies.

Aside from the study authored by Dunlevy et al.,[10] there findings were not positioned in the context of minimal clinically important differences. In other words, statistically significant improvements in outcomes may not necessarily translate into clinically meaningful change from a patient's perspective.

No evidence regarding the clinical effectiveness of body weight modification interventions for chronic, non-cancer pain was identified for underweight adults (BMI < 18.5 kg/m^2).

Conclusions and Implications for Decision or Policy Making

This review was comprised of three systematic reviews[8,11,15] and two non-randomized studies[7,10] regarding the clinical effectiveness of body weight modification interventions for chronic non-cancer pain in adults with excess weight (BMI of greater than or equal to 25 kg/m^2). No evidence was identified for adults with BMI less than 18.5 kg/m^2. The identified literature revealed mixed conclusions (favourable and null) regarding the clinical effectiveness of body weight modification interventions for chronic non-cancer pain. This suggests that body weight modification interventions may have clinical benefit and are not likely to cause harm in this patient population.

Overall, weight reductions were significantly greater following diet only,[17,21-23,25] exercise only,[18] and/or diet plus exercise[17,19,24] interventions compared to control groups (i.e., no diet or exercise). Three single-arm primary studies reported statistically significant weight reductions compared to baseline weight in participants who completed a hospital-based weight management program (unspecified intervention),[27] a low calorie diet,[28] or a

multidisciplinary weight management program.[10] However, two RCTs[17,23] did not detect significant weight reductions in the exercise versus non-exercise groups.

Compared to control groups (i.e., no diet or exercise), improvements in pain were significantly greater or not significantly different following body weight modification interventions. Specifically, findings were favourable[24,25] (or not significantly different[17,21-23]) following diet only, favourable[23,24] (or not significantly different[17,21]) following exercise only, and favourable following diet plus exercise[17,19,24] compared to control groups (i.e., no diet or exercise). Three single-arm primary studies reported statistically significant improvements in pain compared to baseline in participants who completed a hospital-based weight management program (unspecified intervention),[27] low calorie diet,[28] or internet-based weight loss program.[29] Compared to the standard care control group, a significant improvement in pain was detected in participants receiving combination pain coping skills training and behavioural weight management, but not those receiving the behavioural weight management only intervention.[18] In the two additional single-arm primary studies investigating the impact of a multidisciplinary weight management program[10] or diet plus exercise,[7] statistically significant differences were detected in pain prevalence[10] and pain severity[7] from before to after interventions in the weight loss subgroups.

Compared to control groups (i.e., no diet or exercise), improvements in physical function were significantly greater[22,24] (or not significantly different[17,21,23,25]) following diet only, significantly greater[24] (or not significantly different[17,21,23]) following exercise only, and significantly greater following diet plus exercise[17,19,24] interventions. Two single-arm primary studies reported statistically significant improvements in pain compared to baseline in participants who completed a low calorie diet intervention[28] or internet-based weight loss program.[29] Compared to the standard care control group, there were significant improvements in physical function in participants receiving combination pain coping skills training and behavioural weight management, but not in those who received the behavioural weight management intervention alone.[18]

There was a significantly favourable dose-response relationship between percentage weight loss and improvements in quality of life from before to after a diet only intervention.[26] Weight loss was associated with improvements in depression within the diet only group (statistical analysis not reported).[23] Furthermore, there was a significant improvement in depression in the subgroup of participants who lost ≥ 10% of their baseline weight compared to those that lost < 10%.[7]

Overall, information on adverse events was sparsely reported, but in the two systematic reviews that did document adverse events there were no serious adverse events reported for any intervention or groups.[11,15] A numerically higher incidence of nonserious gastrointestinal adverse events was reported in participants in diet interventions compared to non-diet interventions in one systematic review, but specific numbers and statistical comparisons were not reported,[11] and in one primary study[17] included in another systematic review[15] a single participant (out of 252 participants) sustained a forehead laceration due to tripping while exercising.

The limitations of the included literature[7,10,17-29] (e.g., heterogeneity of interventions and outcome measures, variation in treatment durations, risk of performance bias due to unblinded participants, inconsistencies in study findings) should be considered when interpreting these results. Overall, low to moderate strength evidence helped inform the results of this report. Further research investigating the clinical effectiveness of body weight modification interventions, especially with large clinical trials with long-term follow-up and

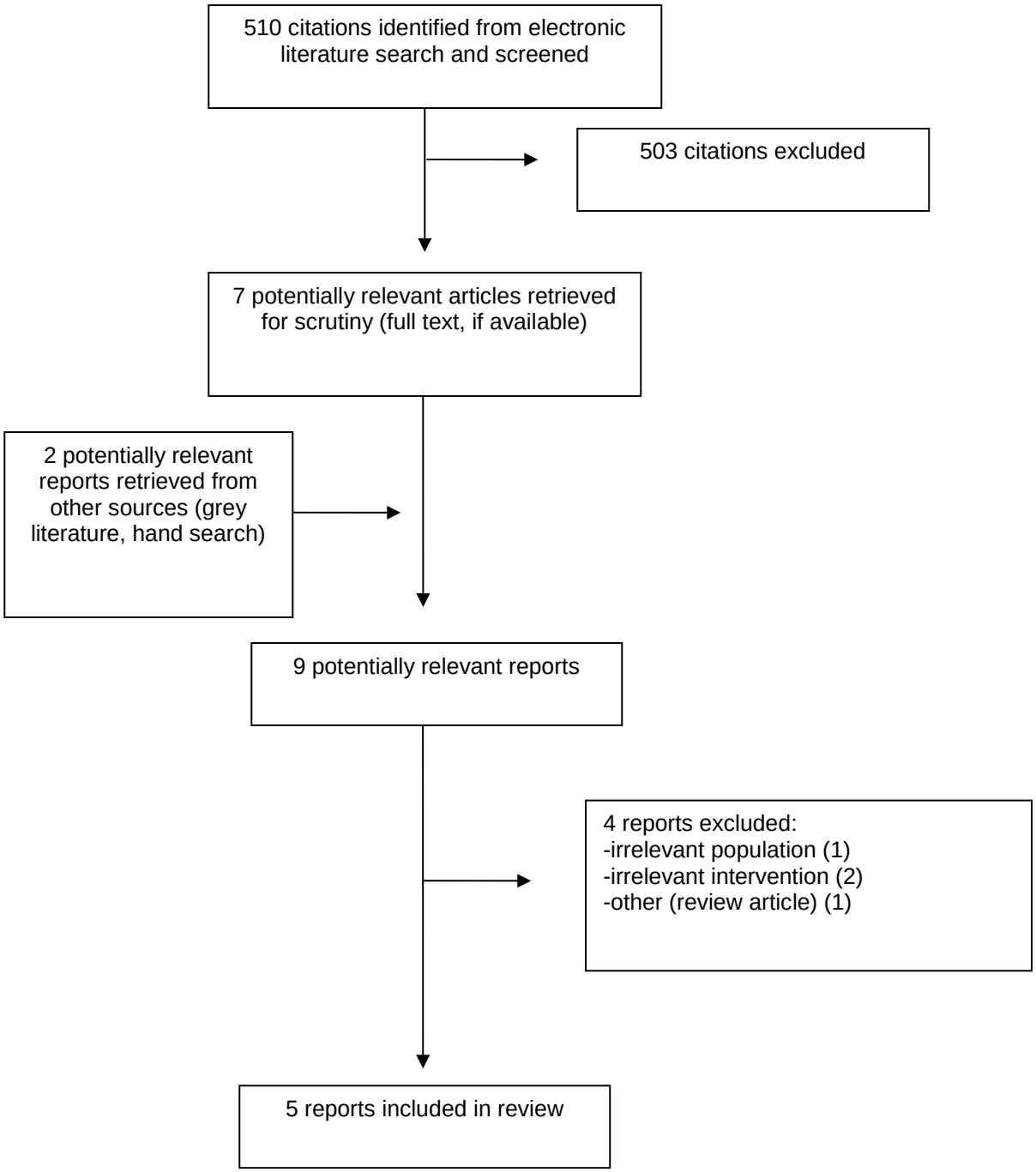
measures to increase methodological quality, would provide additional knowledge base for clinicians providing care to adults living with chronic non-cancer pain.

References

1. World Health Organization. Obesity and overweight fact sheet. 2020 Mar; https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 2020 Mar 09.
2. Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab.* 2005;90(8):4510-4515.
3. Kennedy J, Roll JM, Schraudner T, Murphy S, McPherson S. Prevalence of persistent pain in the U.S. adult population: new data from the 2010 national health interview survey. *J Pain.* 2014;15(10):979-984.
4. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. *Pain Res Manag.* 2011;16(6):445-450.
5. Hogan ME, Taddio A, Katz J, Shah V, Krahn M. Incremental health care costs for chronic pain in Ontario, Canada: a population-based matched cohort study of adolescents and adults using administrative data. *Pain.* 2016;157(8):1626-1633.
6. Michael G. DeGroote National Pain Centre, McMaster University. Epidemiology of chronic non-cancer pain. In: *Canadian guideline for safe and effective use of opioids for chronic non-cancer pain*; 2010 Apr: http://nationalpaincentre.mcmaster.ca/opioid/cgop_a07_epidemiology_of_chronic_non_cancer_pain.html. Accessed 2020 Mar 09.
7. Schrepf A, Harte SE, Miller N, et al. Improvement in the spatial distribution of pain, somatic symptoms, and depression after a weight loss intervention. *J Pain.* 2017;18(12):1542-1550.
8. Hall M, Castelein B, Wittoek R, Calders P, Van Ginckel A. Diet-induced weight loss alone or combined with exercise in overweight or obese people with knee osteoarthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum.* 2019;48(5):765-777.
9. Arthritis Society. The truth about arthritis. 2020; https://arthritis.ca/about-arthritis/what-is-arthritis/the-truth-about-arthritis. Accessed 2020 Mar 09.
10. Dunlevy C, MacLellan GA, O'Malley E, et al. Does changing weight change pain? Retrospective data analysis from a national multidisciplinary weight management service. *Eur J Pain.* 2019;23(8):1403-1415.
11. Newberry SJ, FitzGerald J, SooHoo NF, et al. AHRQ Comparative Effectiveness Reviews. *Treatment of Osteoarthritis of the Knee: An Update Review*. Rockville (MD): Agency for Healthcare Research and Quality; 2017.
12. Freige C, Argáez C. Body weight modification interventions for chronic, non-cancer pain: clinical effectiveness and guidelines. [*CADTH rapid response report reference list*]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Feb: https://cadth.ca/sites/default/files/pdf/htis/2020/RA1085-%20Weight%20Change%20Pain%20Final.pdf. Accessed 2020 Mar 09.
13. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2020 Mar 09.
14. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2020 Mar 09.
15. Charlesworth J, Fitzpatrick J, Perera NKP, Orchard J. Osteoarthritis- a systematic review of long-term safety implications for osteoarthritis of the knee. *BMC Musculoskelet Disord.* 2019;20(1):151.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
17. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: The arthritis, diet, and activity promotion trial. *Arthritis Rheum.* 2004;50(5):1501-1510.
18. Somers TJ, Blumenthal JA, Guilak F, et al. Pain coping skills training and lifestyle behavioral weight management in patients with knee osteoarthritis: a randomized controlled study. *Pain.* 2012;153(6):1199-1209.
19. Miller GD, Nicklas BJ, Davis C, Loeser RF, Lenchik L, Messier SP. Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. *Obesity.* 2006;14(7):1219-1230.
20. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. *JAMA.* 2013;310(12):1263-1273.
21. Christensen R, Henriksen M, Leeds AR, et al. Effect of weight maintenance on symptoms of knee osteoarthritis in obese patients: a twelve-month randomized controlled trial. *Arthritis Care Res.* 2015;67(5):640-650.
22. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthritis Cartilage.* 2005;13(1):20-27.
23. Jenkinson CM, Doherty M, Avery AJ, et al. Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: randomised controlled trial. *BMJ.* 2009;339:b3170.
24. Ghroubi S, Elleuch H, Kaffel N, Echikh T, Abid M, Elleuch MH. [Contribution of exercise and diet in the management of knee osteoarthritis in the obese]. *Ann Readapt Med Phys.* 2008;51(8):663-670.

25. Bliddal H, Leeds AR, Stigsgaard L, Astrup A, Christensen R. Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomised controlled trial. *Ann Rheum Dis.* 2011;70(10):1798-1803.
26. Makovey J, Lawler L, Bennell KL, Hunter DJ. Dose response relationship between weight loss and improvement in quality of life in persons with symptomatic knee osteoarthritis. *Osteoarthritis Cartilage.* 2015;23:A386.
27. Claes B-EA, Leung HWC, Matters K, Williams MJ, Hunter DJ. Interim analysis: an interdisciplinary team approach in facilitating weight reduction and improving function for people with knee or hip osteoarthritis. the Osteoarthritis Chronic Care Program at Royal North Shore Hospital. *Nutr Diet.* 2015;72(3):232-239.
28. Bartels EM, Christensen R, Christensen P, et al. Effect of a 16 weeks weight loss program on osteoarthritis biomarkers in obese patients with knee osteoarthritis: a prospective cohort study. *Osteoarthritis Cartilage.* 2014;22(11):1817-1825.
29. Atukorala I, Makovey J, Lawler L, Messier SP, Bennell K, Hunter DJ. Is there a dose-response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? *Arthritis Care Res.* 2016;68(8):1106-1114.
30. Messier SP, Loeser RF, Mitchell MN, et al. Exercise and weight loss in obese older adults with knee osteoarthritis: a preliminary study. *J Am Geriatr Soc.* 2000;48(9):1062-1072.
31. Gudbergsen H, Boesen M, Christensen R, Astrup A, Bliddal H. Radiographs and low field MRI (0.2T) as predictors of efficacy in a weight loss trial in obese women with knee osteoarthritis. *BMC Musculoskelet Disord.* 2011;12(1):56.
32. U.S. Department of Veteran Affairs. NCT00126737: Home-based exercise and weight control program for pain control in overweight elderly with osteoarthritis of the knee. [*ClinicalTrials.gov*]. Bethesda (MD): U.S. National Library of Medicine; 2015 Jan: https://clinicaltrials.gov/ct2/show/NCT00126737. Accessed 2020 Mar 26.
33. Keogh E. Sex Differences in Pain. *Rev Pain.* 2008;2(2):4-7.
34. Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews Rockville (MD): AHRQ; 2008-: https://www.ncbi.nlm.nih.gov/books/NBK47095/. Accessed 2020 Mar 05.
35. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes.* 2003;1:64-64.
36. Wolfe F, Clauw DJ, Fitzcharles M-A, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR preliminary diagnostic criteria for fibromyalgia. *J Rheumatol.* 2011;38(6):1113.
37. Rodriguez CS. Pain measurement in the elderly: a review. *Pain Manag Nurs.* 2001;2(2):38-46.
38. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res.* 2011;63 Suppl 11:S240-252.
39. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Care Res.* 2001;45(5):453-461.
40. Balke B. A simple field test for the assessment of physical fitness. *[Report 63-6] Civil Aeromedical Research Institute (US).* 1963:1-8.
41. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996;34(3):220-233.
42. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med.* 1996;26(3):477-486.
43. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Charlesworth et al., 2019[15] Australia	**Study design**: systematic review of relevant peer reviewed primary articles, systematic reviews, and meta-analyses that met PICO criteria and had a Downs and Black score > 13 **Literature search strategy**: Authors performed literature searches in Cochrane Database of systematic reviews, Medline, and PubMed from 1990 to July 2017 inclusive (a priori study protocol was registered on PROSPERO: CRD42017072809) **Number of studies included**: Out of 34 included studies, two RCTs were relevant for this report **Quality assessment tool**: Authors used Downs and Black checklist **Objective**: To assess long-term safety (≥ 12 months) of various therapies for KOA including lifestyle modifications (e.g., weight loss and exercise)	Adult patients ≥ 18 years of age and BMI ≥ 25 kg/m^2 with KOA-associated pain	**Interventions:** - Surgical and non-surgical treatment options for KOA (with a focus on treatment safety) - Interventions relevant to this report were weight modification interventions such as diet and/or exercise **Comparators:** - Healthy lifestyle - Educational pamphlet	**Relevant Outcomes:** - Weight loss - Pain (self-reported via WOMAC pain score) - Physical function (6MWT, self-reported WOMAC physical function score) - Quality of life (HADS) - Adverse events (self-reported) **Follow-up:** Studies of any follow-up duration ≥ 12 months were included
Hall et al., 2019[8]	**Study design**: systematic review with	Adult patients ≥ 45 years old and BMI ≥ 25	**Interventions:** - Diet and/or exercise, behavioural therapy	**Relevant Outcomes:** - Weight loss

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Authors from Australia and Belgium	meta-analysis of relevant RCTs **Literature search strategy**: Authors performed literature searches in MEDLINE, EMBASE, the Cochrane Library Online, CINAHL and PEDRO from inception to March 1, 2017 (a protocol was registered prospectively on PROSPERO: CRD42017056125). Grey literature was also searched. **Number of studies included**: Out of 16 included studies, nine RCTs were relevant to this report **Quality assessment tool**: To evaluate each included study, two authors used the Cochrane Risk of Bias tool. To evaluate pooled outcomes of the meta-analysis, the authors used GRADE. **Objective**: To assess the impact of diet-only and combined diet and exercise treatments on pain, physical function, and inflammatory biomarkers in patients with KOA	kg/m^2 with KOA-associated pain	**Comparators:** - Usual care (any non-pharmacological, non-surgical, or non-diet treatment) - No treatment (placebo or waitlist)	- Pain (self-reported WOMAC pain score, VAS pain score) - Physical function (self-reported WOMAC physical function score) **Follow-up:** Follow-up times ranged from 2 to 24 months
Newberry et al., 2017[11] US	**Study design**: systematic review with of relevant RCTs and single-arm prospective observational studies	Adult patients (≥ 18 years old) with KOA-associated pain	**Interventions:** - Pharmacological and non-pharmacological treatment options for KOA	**Relevant Outcomes:** - Weight loss - Pain (self-reported WOMAC pain score, VAS pain score, KOOS pain score)

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Literature search strategy: Authors performed literature searches in PubMed, Embase, the Cochrane Collection, Web of Science, and PEDRO from 2006 to September 2016. Authors also searched ClinicalTrials.gov and 2015 American College of Rheumatology annual meeting proceedings. **Number of studies included**: Out of 107 included studies, nine studies (five RCTs and four single-arm studies) were relevant for this report **Quality assessment tool**: To evaluate each included study, pairs of reviewers used GRADE to assess the strength of evidence as per the AHRQ Methods Guide[34] **Objective**: To assess the effectiveness of various therapies for KOA including weight loss diets		- Interventions relevant to this report were weight loss modifications such as diet and/or exercise **Comparators:** - Usual care - No treatment (placebo or waitlist)	- Quality of life (SF-12 score) - Adverse events (self-reported) **Follow-up:** Follow-up times ranged from 4-12 weeks (short-term), 12-26 weeks (medium-term), or > 26 weeks (long-term)

6MWT = 6-minute walk test; AHRQ = Agency for Healthcare Research and Quality; BMI = body mass index; CRD = Centre for Reviews and Dissemination; GRADE = Grades of Recommendation, Assessment, Development and Evaluation; HADS = Hospital Anxiety and Depression Index; KOA = knee osteoarthritis; KOOS = Knee Injury & Osteoarthritis Outcome Score; NRS = numerical rating scale; PEDRO = Physiotherapy Evidence Database; PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial; SF-12 = Short Form (12-Item) Health Survey; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WORMS = Whole-Organ Magnetic Resonance Imaging Score.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Dunlevy et al., 2019[10] Ireland	**Study design:** Single-arm retrospective analysis of anonymized data from patients who underwent multidisciplinary team weight management systems (MDT WMS) between January 2011 and February 2015 **Setting:** Teaching hospital in Dublin **Objective:** To assess the effects of the MDT WMS program on weight, BMI, and pain	Adults patients with pain and BMI > 40 or BMI of 35-40 kg/m^2 accompanied by a significant comorbidity (unspecified) **Number of patients:** N = 806 (476 completers; 330 non-completers who did not stay in the program) **Age (years) (mean ± SD):** 45.1 ± 12 (completers); 44.2 ± 12.3 (non-completers) **% female:** 62% (completers); 71% (non-completers) **Baseline weight (kg) and BMI (kg/m^2) (mean ± SD):** 146.8 ± 29 and 50.8 ± 8.1 (completers); 143.8 ± 30.0 and 50.5 ± 9.1 (non-completers)	**Intervention:** This MDT WMS program was based on behavioural change interventions involving dieticians, psychologists, and physiotherapists **Comparator:** No treatment	**Outcomes:** - Weight change, pain prevalence, pain severity (NRS) **Follow-up:** - This 12-month program incorporates one initial group-based education session with follow-up individual assessments and nine visits - Individual assessments are conducted at baseline and after a minimum of 6 months in the program
Schrepf et al., 2017[7] US	**Study design:** Single-arm prospective longitudinal study involving patients who were referred to the Weight Management Program **Setting:** Michigan **Objective:** To evaluate the impact of weight loss induced by low caloric diet on pain and somatic symptoms associated with pain	Adult patients with pain and BMI ≥ 30 kg/m^2 or ≥ 28 kg/m^2 for Asian Americans **Number of patients:** N = 123 (out of 241 enrolled participants, only 123 participants were included in the longitudinal study due to withdrawal, lost to follow-up, or weight gain) **Age (years) (mean ± SD):** 51 ± 10.96 **% female:** 67%	**Intervention:** - This Weight Management Program was a multidisciplinary behavioural lifestyle program that incorporated 12-16 weeks of total liquid diet replacement with 800kcal/day - The program also encouraged participants to walk 40 minutes daily for the first 12 weeks, and engage in up to 90 minutes of moderate to vigorous activity for ≥ 4	**Outcomes:** - Weight loss - Modified ACR score for fibromyalgia was used to evaluate pain and comorbid symptoms (consists two scales: WPI for reporting pain in 19 body sites and SS which measures multiple symptoms such as fatigue and depressed mood) - IDS (self-report of depression symptoms) **Follow-up:**

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Baseline weight (kg) and BMI (kg/m^2) (mean ± SD): 116 ± 23.27 and 40 ± 6.45	days weekly after the initial 12 weeks **Comparator:** No treatment	- During this 2-year program, BMI was calculated at each monthly visit

ACR = American College of Rheumatology; BMI = body mass index; IDS = Inventory of Depressive Symptomology; kcal = kilocalorie; MDT = multidisciplinary team; NRS = numerical rating scale; SS = Symptom Severity; WMS = weight management services; WPI = widespread pain index.

Table 4: Description of Outcome Assessment Scales/Tests

Outcome Assessment Scale/Tests	Description
Pain and Functional Status	
Knee injury and Osteoarthritis Outcome Score (KOOS)	As a measure of symptoms and function in patients with knee osteoarthritis or injury, this score consists of five subscales (i.e., pain, other symptoms such as swelling, disability in activities of daily living, disability in sport and recreation, and quality of life measures), each with nine, seven, 17, five, and four items, respectively. Scores for individual items range from 0 to 4, with higher scores indicating greater symptom levels. Total scores from each of the five subscales is converted to a 0-100 scale, with 100 indicating no knee issues.[35]
Modified American College of Rheumatology (ACR) score for fibromyalgia	As a measure of diffuse pain and comorbid symptoms in patients with fibromyalgia, this score consists of two subscales: the WPI and SS scale. Containing 19 body sites where participants can indicate presence of pain (i.e. 0 for no pain, 1 for pain), the WPI can range from 0 to 19. Ranging from a score of 0 to 12, the SS scale consists of multiple pain continuum symptoms (e.g., fatigue, depression, headache). Scores for each of these individual symptoms range from 0 to 3, with higher scores indicating severe issues.[36]
Numeric Rating Scale (NRS) for Pain	A single-item measure of pain level in which participants select a whole number ranging from 0 (no pain) to 10 (maximal pain) that best reflects their pain level.[37]
Visual Analogue Scale (VAS) for Pain	A single-item continuous measure consisting of a horizonal or vertical line on which participants select a point between 0 (no pain) and 100 (maximal pain) that reflects their pain level.[38]
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)	As a measure of symptoms and function originally developed for patients with osteoarthritis, this score consists of three subscales (i.e., pain, stiffness, and physical function), each with five, two, and 17 questions, respectively. Scores for individual questions range from 0 to 4, with higher scores indicating greater symptom levels. Each subscale can have a maximum score of 20, 8, and 68, respectively, which add up to a global score. A higher global score indicates greater symptoms.[39]
6-Minute Walk Test (6MWT)	Originally designed to assess functional capacity in frail elderly patients, the 6-minute walk test is a measure of the distance a participant can walk in six minutes on a flat surface.[40]
Health-Related Quality of Life	
Short Form (12-Item) Health Survey (SF-12)	A Short Form (12-Item) Health Survey is condensed from SF-36, which provides an evaluation of physical functions and health-related quality of life. Survey responses are weighted between 0 (lowest health level) and 100 (highest health level), which are combined to result in separate composite scores for physical health and mental health.[41]

Outcome Assessment Scale/Tests	Description
Inventory of Depressive Symptomology (IDS)	As a 30-item self-reported measure of depression symptoms (e.g., sleep, anxiety, appetite), each item has a score range of 0 to 3, with 3 indicating severe symptoms. The total score can range from 0 to 84, with 84 being the most severe.[42]
Hospital Anxiety and Depression Index (HADS)	Designed to be used for hospital outpatients, the hospital anxiety and depression index is a self-reported scale used to detect states of depression and anxiety and evaluate the severity of emotional disorders. The summation of the depression and anxiety scores yields a total score ranging from 0 (normal) to 21 (abnormal).[43]

6MWT = 6-minute walk test; ACR = American College of Rheumatology; HADS = Hospital Anxiety and Depression Index; IDS = Inventory of Depressive Symptomology; KOOS = Knee Injury and Osteoarthritis Outcome Score; NRS = Numerical Rating Score; SF = short form; SS = symptoms severity; VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WPI = widespread pain index.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[13]

Strengths	Limitations
Charlesworth et al., 2019[15]	
• The objectives and inclusion/exclusion criteria were clearly stated, and timeframe for follow-up was stipulated • Components of PICO that were described were population, intervention, and outcomes • Multiple databases were searched (Cochrane Database of Systematic Reviews, MEDLINE and PubMed) • Search terms and time frames were provided (1990 to July 2017, inclusive) • A priori study protocol was registered on PROSPERO (CRD42017072809) • The details of study selection and extraction were explicitly reported • The choice of included study designs and exclusion of non-English publications was justified • A list of included studies was provided, and the characteristics of included studies were described in detail • To minimized risk of bias, the quality of included studies was assessed using Downs and Black checklist and only studies with a score ≥ 13 were included • Authors reported no source of funding was provided to conduct this review • The authors stated that they had no conflicts of interest related to this review	• The comparator component of PICO was not explicitly stated • Grey literature search was not conducted • Apart from listing the exclusion criteria, a list of excluded studies was not provided • Data extraction was performed by one reviewer • Assessment of publication bias was not reported • The three relevant primary studies were conducted in the UK or US; findings may not be generalizable to the Canadian setting
Hall et al., 2019[8]	
• The objectives and inclusion/exclusion criteria were clearly stated, and timeframe for follow-up was stipulated • Components of PICO that were described were population, intervention, comparator, and outcomes • Multiple databases were searched (MEDLINE, EMBASE, the Cochrane Library Online, CINAHL and PEDro) • Search terms and time frames were provided (from inception to March 1, 2017) • Grey literature search was conducted • A study protocol was prospectively registered on PROSPERO (CRD42017056125) • The details of study selection and extraction was explicitly reported (e.g., duplicate reviewers) • A list of included studies was provided, and the characteristics of included studies were described in detail • The methodological quality of included studies was assessed using the Cochrane Risk of Bias tool • Conducted a random effects meta-analysis by pooling standardized mean differences of outcomes • Assessed for heterogeneity using the I^2 statistic and χ^2test • Publication bias was assessed using funnel plots • Authors reported sources of funding to conduct this review	• Apart from listing the exclusion criteria, a list of excluded studies was not provided • Data on adverse events were extracted, but not reported in systematic review • Justification was not provided for the choice of included study design, and the exclusion of publications in languages other than English, German, French or Dutch • Primary study and investigator funding information was not reported • The included primary studies were conducted in Denmark, UK or US; findings may not be generalizable to the Canadian setting

Strengths	Limitations
• The authors stated that they had no conflicts of interest related to this review	
Newberry et al., 2017[11]	
• The objectives and inclusion/exclusion criteria were clearly stated, and timeframe for follow-up was stipulated • Components of PICO that were described were population, intervention, comparator, and outcomes • Multiple databases were searched (PubMed, EMBASE, the Cochrane Collection, Web of Science, and PEDro) • Search terms and time frames were provided (from 2006 to September 2016) • Grey literature search was conducted (i.e., ClinicalTrials.gov and 2015 American College of Rheumatology annual meeting proceedings) • A priori study protocol was developed • The details of study selection and extraction was explicitly reported (e.g., duplicate reviewers) • A list of included studies was provided, and the characteristics of included studies were described in detail • A list of excluded studies was provided in the appendix • The methodological quality of included studies was assessed using GRADE to evaluate the strength of evidence • Primary study and investigator funding information was extracted • The authors stated that they did not have any funding or affiliations that conflict with findings of this systematic review	• Justification was not provided for the choice of included study design, and the exclusion of publications in languages other than English • Assessment of publication bias was not reported • The included primary studies were conducted in Australia, Denmark, France, US, Tunisia; findings may not be generalizable to the Canadian setting

CINAHL = Cumulative Index to Nursing and Allied Health Literature; CRD = Centre for Reviews and Dissemination; EMBASE = Excerpta Medica database; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MEDLINE = Medical Literature Analysis and Retrieval System Online; PEDro = Physiotherapy Evidence Database; PICO = population, intervention, comparator, and outcome; PubMed.

Table 6: Strengths and Limitations of Clinical Studies using Downs and Black checklist[14]

Strengths	Limitations
Dunlevy et al., 2019[10]	
• The study's objective, intervention, and main findings were clearly stated • The main outcomes to be measured were clearly described in the Methods section • The inclusion criteria were clearly described • Estimates of random variability were reported • The statistical tests used to assess the main outcomes were described and appropriate • Patient data were retrieved from a database at a hospital offering WMS, which would be representative of the population of interest • Characteristics of patients lost to follow-up or who did not complete the program were described • Data analyses were planned at the outset of the study	• This was not a randomized controlled trial, but a retrospective single-arm study using anonymized patient data • The exclusion criteria were not reported • A sample size calculation was not conducted a priori • Potential adverse events relating to the intervention were not discussed • Exact P values were not reported for all outcomes • Study was conducted in Ireland; findings may not be generalizable to the Canadian setting

Strengths	Limitations
• The main outcome measures used were valid and reliable • The time period over which patients were recruited was specified • The authors disclosed no conflicts of interest and no funding support for this study	
Schrepf et al., 2017[7]	
• The study's objective, intervention, and main findings were clearly stated • The main outcomes to be measured were clearly described in the Methods section • The inclusion criteria were clearly described • Estimates of random variability were reported • The statistical tests used to assess the main outcomes were described and are appropriate • Exact P values were reported for outcomes • The participants were referred to the weight management program by hospital and community physicians, which would be representative of the population of interest • Data analyses were planned at the outset of the study • The main outcome measures used were valid and reliable • The authors disclosed no conflicts of interest • The authors disclosed funding support	• This was not a randomized controlled trial, but a prospective single-arm study following participants enrolled in a weight management program • The exclusion criteria were not reported • A sample size calculation was not conducted a priori • Characteristics of patients lost to follow-up or who did not complete the program were not reported, although common reasons of drop out were described • The time period over which patients were recruited was not specified • Potential adverse events relating to the intervention were not discussed • Study was conducted in the US; findings may not be generalizable to the Canadian setting

PICO = population, intervention, comparator, and outcome; WMS = weight management services.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Charlesworth et al., 2019[15]	
Systematic review that evaluated the long-term clinical effectiveness and safety (≥ 12 months) of surgical and non-surgical treatment options for adult patients (≥ 18 years old) with pain, BMI > 25 kg/m^2, and diagnosed with KOA. **Findings:** **RCTs:** **Messier et al., 2004[17]** - Participants were randomized into four groups: diet only, exercise only, diet plus exercise, healthy lifestyle group (control) - Relative to the control group which had a 1.2% weight loss, weight loss was significantly greater (P < 0.05) in the diet only (4.9%) and diet plus exercise (5.7%) groups - The diet plus exercise group exhibited significant benefit in WOMAC knee pain scale (P < 0.05), WOMAC physical function scale (P < 0.05), and 6MWT score (P < 0.05) compared to the control group - The exercise only group exhibited significant benefit in 6MWT score (P < 0.05) compared to the control group. There was no significant difference in WOMAC pain or physical function scores relative to the control group. - The diet only group was not significantly different in WOMAC pain or physical function scores, or 6MWT relative to the control group - One participant (out of 252 participants) sustained a forehead laceration due to tripping during exercise **Jenkinson et al., 2009[23]** - Participants were randomized into four groups: diet only, exercise only (quadriceps strengthening), diet plus exercise, and advice pamphlet only (control) - After 24 months, there was a significant mean difference in weight reduction of 2.95 kg (1.44 to 4.46; P = 0.000) between the diet versus non-diet group - There was a non-significant mean difference in weight reduction of 0.43 kg (-0.82 to 1.68; P = 0.501) between the exercise versus non-exercise group - The exercise groups experienced significant decrease in WOMAC knee pain score (% risk difference = 1.61; 95% CI, 1.81% to 21.41%) and significant increase in WOMAC physical function score (mean difference = −3.64; 95% CI, −6.01 to −1.27; P = 0.003) relative to non-exercise groups - The diet only group was not significantly different in WOMAC pain or physical function scores relative to the control group, but weight loss was associated with a decrease in HADS depression score (absolute effect size = 0.19) within the diet only group	"Our results indicate that nonpharmacological treatment such as exercise [10–13] and weight management [12, 14] are effective in management of KOA with minimal adverse effects. Primary care settings provide a great platform to support lifestyle interventions effective in treatment and management of KOA. Therefore, weight loss and exercise should be advocated as part of the treatment in all patients due to the low risk of harm, cost effectiveness as well as associated health benefits."[15] (*pp7*)

Main Study Findings	Authors' Conclusion
- Adverse events were not reviewed in this study	
Hall et al., 2019[8]	
Systematic review with meta-analysis that assessed the impact of diet-only and combined diet and exercise treatments on pain, physical function, and inflammatory biomarkers in adult patients (≥ 45 years old) with pain, BMI > 25 kg/m^2, and diagnosed with KOA. **Findings:** **<u>Diet only:</u>** **Christensen et al., 2015[21]** - Participant were randomized into three groups: diet only, exercise only, and usual care/no attention (control group) **Weight change:** - Diet only group achieved significantly greater weight reduction (11.0 kg, 95% CI, 9.0 to 12.8 kg) than exercise only (6.2, 95% CI, 4.4 to 8.1 kg) and control (8.2, 95% CI, 6.4 to 10.1 kg) (P = 0.002 by ANCOVA) **Pain severity:** - No significant difference in VAS pain score amongst three groups (P = 0.982 by ANCOVA) **Physical function:** - No significant difference in VAS disability score amongst three groups (P = 0.910 by ANCOVA) **Christensen et al., 2005[22]** - Participant were randomized into two groups: low energy diet versus advice pamphlet (control group) **Weight change:** - Diet group achieved significantly greater weight reduction (MD 6.8%, 95% CI, 5.5 to 8.1%; P < 0.0001) than control group **Pain severity:** - No significant difference in WOMAC pain score in the diet group (MD -27.2, 95% CI, -64.0 to 9.7; P = 0.15) compared to control group **Physical function:** - There was a significant difference in WOMAC function score in the diet group (MD -166.9, 95% CI, -274.5 to -59.3; P = 0.003) compared to control group **<u>Diet and exercise:</u>** **Messier et al., 2013[20]** - Participants were randomized into three groups: diet plus exercise, diet only, and exercise only (considered to be part of the standard care) **Weight change:** - Compared to the exercise only group (i.e., standard care), there were significant weight reductions in the diet only (MD -6.00, 95% CI, -9.75 to -2.25) and diet plus exercise (MD -8.10, 95% CI, -11.92 to -4.28) groups after 18 months **Pain severity:**	"This meta-analysis quantitatively synthesized the effects of D and D + EX treatments on symptoms and inflammation in overweight and obese adults with knee OA. Overall moderate quality evidence supports no effect of D on pain and low-quality evidence supports a moderate effect of D + EX treatment on pain. Moderate quality evidence supports a moderate effect of both D and D + EX on physical function improvement. However, treatment effects appear dependent on treatment duration, such that improvements in pain from D + EX and physical function from D and D + EX were only observed for treatments<12 months in duration."[8] (*pp770*)

Main Study Findings	Authors' Conclusion
- Long-term: Compared to the exercise only group, there were no significant differences in the WOMAC pain scores in the diet only (MD 0.40, 95% CI, -0.31 to 1.11) or diet plus exercise (MD -0.70, 95% CI, -1.41 to 0.01) groups after 18 months **Physical function:** - Medium-term: Compared to the exercise only group, there were no significant differences in the 6MWT scores in the diet only (MD 28.00, 95% CI, 8.90 to 47.10) or diet plus exercise (MD -4.00, 95% CI, -24.52 to 16.52) groups after six months - Long-term: Compared to the exercise only group after 18 months, participants in the diet plus exercise group exhibited significantly greater improvements in WOMAC function scores (MD -3.40, 95% CI, -6.02 to -0.78), but the diet only group did not (MD 0.10, 95% CI, -2.67 to 2.87) - Long-term: Compared to the exercise only group after 18 months, participants in the diet plus exercise group exhibited significantly greater improvements in the 6MWT score (MD -12.00, 95% CI, -33.93 to 9.93), but the diet only group did not (MD 23.00, 95% CI, 3.15 to 42.85) **Somers et al., 2012[18]** - Participants were randomized into four groups: PCST plus BWM, PCST only, BWM only, standard care (control) **Weight change:** - Compared to the control group, PCST plus BWM and BWM only groups achieved significant weight reductions (specific numbers NR) **Pain severity:** - Medium-term: Compared to the control group, participants in the PCST plus BWM group achieved significant improvements in WOMAC pain scores (MD -10.80, 95% CI, -15.77 to -5.83), but those in the BWM only group did not (MD -2.50, 95% CI, -7.67 to 2.67) - Long-term: Compared to the control group after 18 months, participants in the PCST plus BWM group continued to exhibit significantly less pain (MD -14.00, 95% CI, -24.77 to -3.23) **Physical function:** - Medium-term: Compared to the control group, participants in the PCST plus BWM group achieved significant improvements in WOMAC function scores (MD -12.40, 95% CI, -17.29 to -7.5), but those in the BWM only group did not (MD-1.50, 95% CI, -6.46 to 3.46) **Miller et al., 2006[19]** - Participants were randomized into two groups: weight loss group (diet plus exercise) versus control group (educational sessions only) **Weight change:** - Compared to the control group, the weight loss group achieved significant weight reductions (MD -9.10, 95% CI, -16.87 to -1.33) after six months **Pain severity:** - Compared to the control group, the weight loss group exhibited a significant improvement in WOMAC pain scores (MD -2.00, 95% CI, -3.25 to -0.75)	

Main Study Findings	Authors' Conclusion
Physical function: - Compared to the control group, the weight loss group exhibited a significant improvement in WOMAC function scores (MD -8.60, 95% CI, -13.50 to -3.70) - Compared to the control group, the weight loss group also exhibited a significant improvement in the 6MWT score (MD -51.00, 95% CI, -96.03 to -5.97) **Messier et al., 2004[17]** - Participants were randomized into four groups: diet only, exercise only, diet plus exercise, healthy lifestyle group (control) - Relative to the control group which had a 1.2% weight loss, weight loss was significantly greater (P < 0.05) in the diet only (4.9%) and diet plus exercise (5.7%) groups - The diet plus exercise group exhibited significant benefit in WOMAC knee pain scale (P < 0.05), WOMAC physical function scale (P < 0.05), and 6MWT score (P < 0.05) compared to the control group - The exercise only group exhibited significant benefit in 6MWT score (P < 0.05) compared to the control group. There was no significant difference in WOMAC pain or physical function scores relative to the control group. - The diet only group was not significantly different in WOMAC pain or physical function scores, or 6MWT relative to the control group - One participant (out of 252 participants) sustained a forehead laceration due to tripping during exercise **Adverse Events** - The systematic review authors reported having extracted data on adverse events, but these data were not reported in systematic review	
Newberry et al., 2017[11]	
Systematic review that assessed the effectiveness of various therapies for KOA including weight loss diets in adult patients (≥ 18 years old) with pain and diagnosed with KOA, categorized by short- (4-12 weeks), medium- (12-26 weeks), or long-term (> 26 weeks) effects. **Findings:** **<u>RCTs:</u>** **Ghroubi et al., 2008[24]** - Participants were randomized into four groups: control group (no diet and exercise), exercise only, diet plus exercise, and diet only **Weight change:** - Diet plus exercise group lost significantly more weight relative to diet only and control groups (specific numbers NR) **Pain severity:** - Compared to the control group, the diet plus exercise group (MD -4.56, 95% CI, -5.82 to -3.30), diet only group (MD -2.10,	"Weight loss with or without exercise has a beneficial effect on medium-term pain and function and on long-term pain but inconsistent effects across studies on long-term function and quality of life. - Evidence was insufficient to assess short-term effects of dieting, with or without exercise on pain and function. - Weight loss had a significant beneficial effect on medium-term pain, based on two RCTs and four single-arm trials. One single-arm trial assessed and reported a dose-response effect between weight and outcomes of interest (moderate-level evidence). - Weight loss had a significant beneficial effect on medium-term function, based on two RCTs and three single-arm trials (low strength of evidence). - Weight loss had a significant long-term beneficial effect on pain based on three RCTs and one single-arm trial (low level of evidence) but inconsistent effects on function and quality of life, based on two RCTs (low strength of evidence)."[11] (*pp58-59*)

Main Study Findings	Authors' Conclusion
95% CI, -3.32 to -0.88) and exercise only group (MD -2.90, 95% CI, -4.52 to -1.28) exhibited significant improvement in VAS pain score (1 to 10 cm scale) **Physical function:** - Compared to control, all three active intervention groups exhibited significant improvements in WOMAC function scores (diet: MD -2.34, 95%, CI -3.71 to -0.97; exercise: MD -3.09, 95% CI, -4.46 to -1.72; diet plus exercise: MD -4.01, 95% CI, -5.56 to -2.46) - Compared to control, exercise only (MD -39.00, 95% CI, -46.47 to -31.53) and diet plus exercise groups (MD -53.00, 95% CI, -59.33 to -46.67) significantly increased 6MWT scores. Diet only did not significantly improve 6MWT scores (MD 2.00, 95% CI, -6.51 to 10.51). **Miller et al., 2006[19]** - Participants were randomized into two groups: weight loss group (diet plus exercise) versus control group (educational sessions only) **Weight change:** - Compared to the control group, the weight loss group achieved significant weight reductions (MD -9.10, 95% CI, -16.87 to -1.33) after six months **Pain severity:** - Compared to the control group, the weight loss group exhibited a significant improvement in WOMAC pain scores (MD -2.00, 95% CI, -3.25 to -0.75) **Physical function:** - Compared to the control group, the weight loss group exhibited a significant improvement in WOMAC function scores (MD -8.60, 95% CI, -13.50 to -3.70) - Compared to the control group, the weight loss group also exhibited a significant improvement in the 6MWT score (MD -51.00, 95% CI, -96.03 to -5.97) **Somers et al., 2012[18]** - Participants were randomized into four groups: PCST plus BWM, PCST only, BWM only, standard care (control) **Weight change:** - Compared to the control group, PCST plus BWM and BWM only groups achieved significant weight reductions (specific numbers NR) **Pain severity:** - Medium-term: Compared to the control group, participants in the PCST plus BWM group achieved significant improvements in WOMAC pain scores (MD -10.80, 95% CI, -15.77 to -5.83), but those in the BWM only group did not (MD -2.50, 95% CI, -7.67 to 2.67) - Long-term: Compared to the control group after 18 months, participants in the PCST plus BWM group continued to exhibit significantly less pain (MD -14.00, 95% CI, -24.77 to -3.23) **Physical function:** - Medium-term: Compared to the control group, participants in the PCST plus BWM group achieved significant improvements in WOMAC function scores (MD -12.40, 95% CI, -17.29 to -	

Main Study Findings	Authors' Conclusion
7.5), but those in the BWM only group did not (MD-1.50, 95% CI, -6.46 to 3.46) **Messier et al., 2013[20]** - Participants were randomized into three groups: diet plus exercise, diet only, and exercise only (considered to be part of the standard care) **Weight change:** - Compared to the exercise only group (i.e., standard care), there were significant weight reductions in the diet only (MD -6.00, 95% CI, -9.75 to -2.25) and diet plus exercise (MD -8.10, 95% CI, -11.92 to -4.28) groups after 18 months **Pain severity:** - Long-term: Compared to the exercise only group, there were no significant differences in the WOMAC pain scores in the diet only (MD 0.40, 95% CI, -0.31 to 1.11) or diet plus exercise (MD -0.70, 95% CI, -1.41 to 0.01) groups after 18 months **Physical function:** - Medium-term: Compared to the exercise only group, there were no significant differences in the 6MWT scores in the diet only (MD 28.00, 95% CI, 8.90 to 47.10) or diet plus exercise (MD -4.00, 95% CI, -24.52 to 16.52) groups after six months - Long-term: Compared to the exercise only group after 18 months, participants in the diet plus exercise group exhibited significantly greater improvements in WOMAC function scores (MD -3.40, 95% CI, -6.02 to -0.78), but the diet only group did not (MD 0.10, 95% CI, -2.67 to 2.87) - Long-term: Compared to the exercise only group after 18 months, participants in the diet plus exercise group exhibited significantly greater improvements in the 6MWT score (MD -12.00, 95% CI, -33.93 to 9.93), but the diet only group did not (MD 23.00, 95% CI, 3.15 to 42.85) **Bliddall et al., 2011[25]** - Participants were randomized into two groups: low energy diet (810-1200 cal/day plus education) versus control group (moderate calorie restriction plus education) **Weight change:** - Compared to the control group, the low energy diet plus counselling group exhibited significantly greater reduction in weight (MD -7.30, 95% CI, -9.52 to -5.08) **Pain severity:** - Compared to the control group, the low energy diet plus counselling group exhibited significantly greater improvements in WOMAC pain scores (MD -7.20, 95% CI, -13.30 to -1.10) **Physical function:** - No significant differences were detected in WOMAC function scores between the two groups (MD -3.60, 95% CI, -9.14 to 1.94) **<u>Single-Arm Studies:</u>** **Claes et al., 2015[27]** **Weight change:**	

Main Study Findings	Authors' Conclusion
- **Short-term:** After 12 weeks in a hospital weight loss program, study completers exhibited significant reduction in BMI (MD 0.50, 95% CI, 0.3 to 0.7) compared to baseline **Pain severity:** - Medium-term: At 26 weeks, participants that remained in the program had significant improvements in KOOS pain score (MD 5.6, 95% CI, 1.6 to 9.6) compared to baseline **Physical function:** - Short-term and medium-term: Participants at 12 weeks (MD 36.7, 95% CI, 27.2 to 46.2) and 26 weeks (MD 44.0, 95% CI, 31.5 to 56.5) exhibited significant improvements in 6MWT scores compared to baseline **Bartels et al., 2014[28]** **Weight change:** - After 16 weeks in the CAROT weight loss study (Influence of weight loss or exercise on CARtilage in Obese knee osteoarthriTis patients), program completers exhibited significant weight loss (MD 14.00, 95% CI, 13.3 to 14.7) compared to baseline **Pain severity:** - Compared to baseline, program completers exhibited significant KOOS pain score improvements (MD 10.7, 95% CI, 8.5 to 12.9) **Physical function:** - Compared to baseline, program completers exhibited significant KOOS function score improvements (MD 12.1, 95% CI, 10.0 to 14.2) **Atukorala et al., 2016[29]** **Weight change:** - Overall, the mean weight reduction was 7.9 ± 4.2 kg with a weight loss of 8.3% from baseline (statistical analysis NR) **Pain severity:** - In an 18-week weight loss program, investigators detected a significant dose-response relationship between percentage weight loss from baseline and KOOS pain score improvements (e.g., >10% weight loss: MD 16.7, 95% CI, 15.2 to 18.2 versus <2.5% weight loss: MD 6.1, 95% CI, 3.2 to 9.0) **Physical function:** - There was a significant dose-response relationship between percentage weight loss from baseline and KOOS function score improvements (e.g., >10% weight loss: MD 17.4, 95% CI, 15.9 to 18.9 versus <2.5% weight loss: MD 7.8, 95% CI, 4.8 to 10.8) **Makovey et al., 2015[26]** **Weight change:** - Percentage of participants according to percentage weight loss from baseline (statistical analysis NR): 7.2% (<2.5% weight loss), 16.2% (2.5-4.9%), 25.0% (5-7.4%), 22.1% (7.5-9.9%), 29.2% (≥10%) **Quality of life:** - There was a significant dose-response relationship between percentage weight loss from baseline and SF-12 quality of life	

Main Study Findings	Authors' Conclusion
score improvements (e.g., <2.5% weight loss: mean 3.16 [SD 8.24] versus > 10% weight loss: 8.60 [SD 8.18], P = 0.000) **Adverse Events:** - Diet interventions were associated with numerically more nonserious gastrointestinal adverse events (event rates, specific events, and statistical analysis not reported) than non-diet interventions	

6MWT = 6-minute walk test; ANCOVA = analysis of covariance; BMI = body mass index; BWM = behavioural weight management; CI = confidence interval; D = diet; EX = exercise; HADS = Hospital Anxiety and Depression Index; KOA = knee osteoarthritis; KOOS = Knee Injury & Osteoarthritis Outcome Score; MD = mean difference; NR = not reported; NRS = numerical rating scale; PCST = pain coping skills training; RCT = randomized controlled trial; SF-12 = Short Form (12-Item) Health Survey; SMD = standard mean difference; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WORMS = Whole-Organ Magnetic Resonance Imaging Score.

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Dunlevy et al., 2019[10]	
Single-arm retrospective analysis of data from adult patients, with pain and BMI > 40 or BMI of 35-40 kg/m^2 accompanied by a significant comorbidity, who underwent a 12-month MDT WMS program based on behavioural change interventions involving dieticians, psychologists, and physiotherapists. **Weight change** • After the intervention, overall weight reduction of 5.1 kg (P < 0.01) and BMI reduction of 1.8 kg/m^2 (P < 0.01) was achieved in the program completers (n = 476) • Of these completers, 37.3% (n = 177) lost weight (i.e., ≥ 5% reduction), 58.7% (n = 279) maintained stable weight (i.e., less than 5% loss/gain in weight) **Baseline data** • Baseline: 70% (n = 281) reported LBP with NRS = 7.3 ± 2.5; 59% (n = 234) reported knee pain with NRS = 6.9 ± 2.4 **Pain prevalence** • Post-WMS (overall): significant decrease by 9.7% in LBP prevalence (P = 0.001) and NRS; no significant change in knee pain prevalence or NRS • Post-WMS (subgroup who lost weight): significant decrease by 14.8% in LBP (P < 0.05) and by 12.4% in knee pain (P < 0.05) prevalence **Pain scale** • Post-WMS (LBP): 41% (n = 92) of patients with LBP exhibited minimal clinically significant difference (i.e., > 30% change) in NRS; no significant differences amongst weight loss groups (i.e., lost weight, stable weight, gained weight)	"Overall this WMS was effective for clinical weight loss. For those who lost most weight prevalence of knee and LBP reduced. Imbedding pain management strategies within WMS's may provide a more holistic approach to obesity management." [10] (*pp1403*)

Main Study Findings	Authors' Conclusion
• Post-WMS (knee pain): 34% (n = 63) of patients with knee pain exhibited minimal clinically significant difference in NRS; no significant differences amongst weight loss groups	
Schrepf et al., 2017[7]	
Single-arm prospective longitudinal study involving adult patients, with pain and BMI ≥ 30 or ≥ 28 kg/m^2 for Asian Americans, who were referred to the Weight Management Program. This behavioural lifestyle program incorporated 12-16 weeks of total liquid diet replacement with 800kcal/day, 40 minutes daily of walking for the first 12 weeks, and up to 90 minutes of moderate to vigourous activity for ≥ 4 days weekly after the initial 12 weeks. **Weight change and physical activity** • Study participants lost an average of 16.05% of their baseline weight (SD = 6.54%; range = 2% to 30% loss) • 80% (n = 99) lost ≥ 10% of their baseline weight • No significant differences in BMI or weight loss were detected between male and female participants **Somatic symptoms and depression** • Post-intervention and after weight loss, there was a significant decrease in the modified ACR score for fibromyalgia (P = 0.004), SS score (P = 0.002), and IDS (P < 0.001) • Compared to women, men exhibited a greater decrease in the modified ACR score for fibromyalgia (P = 0.002) and SS score (P = 0.009)	"The spatial distribution of pain, symptom severity (eg, fatigue, sleep difficulties), depression, and total fibromyalgia scale scores were measured before and after weight loss. Pain (P = .022), symptom severity (P = .004), depression (P < .001), and fibromyalgia scores (P = .004) improved after weight loss; men showed greater improvement than women on somatic symptoms and fibromyalgia scores (both P < .01). Those who lost at least 10% of body weight showed greater improvement than those who lost <10%. […] Weight loss may improve diffuse pain and comorbid symptoms commonly seen in chronic pain participants."[7] (*pp1*)

ACR = American College of Rheumatology; BMI = body mass index; IDS = Inventory of Depressive Symptomology; kcal = kilocalorie; LBP = lower back pain; MDT = multidisciplinary team; NRS = numerical rating scale; RCT = randomized controlled trial; SS = Symptom Severity; WMS = weight management services; WPI = widespread pain index.

Appendix 5: Overlap between Included Systematic Reviews

Table 9: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Charlesworth et al., 2019[15]	Hall et al., 2019[8]	Newberry et al., 2017[11]
Jenkinson et al., 2009[23]	▪		
Messier et al., 2004[17]	▪	▪	
Christensen et al., 2015[21]		▪	
Messier et al., 2013[20]		▪	▪
Somers et al., 2012[18]		▪	▪
Miller et al., 2006[19]		▪	▪
Christensen et al., 2005[22]		▪	
Atukorala et al., 2016[29]			▪
Claes et al., 2015[27]			▪
Makovey et al., 2015[26]			▪
Bartels et al., 2014[28]			▪
Bliddal et al., 2011[25]			▪
Ghroubi et al., 2008[24]			▪

▪ = the primary study was included in the systematic review.

Appendix 6: Additional References of Potential Interest

Systematic Review – Alternative Intervention

Narouze S, Souzdalnitski D. Obesity and chronic pain: systematic review of prevalence and implications for pain practice. *Reg Anesth Pain Med*. 2015 Mar-Apr;40(2):91-111.
PubMed: PM25650632

Non-Randomized Study – Alternative Population

White DK, Neogi T, Rejeski WJ, et al. Can an intensive diet and exercise program prevent knee pain among overweight adults at high risk? *Arthritis Care Res*. 2015 Jul;67(7):965-971.
PubMed: PM25692781