National Institute for Health and Care Excellence

Final

Osteoarthritis in over 16s: diagnosis and management

[D] Evidence review for the benefit of weight loss for the management of osteoarthritis for people living with overweight or obesity

NICE guideline NG226

Evidence reviews underpinning recommendation 1.3.5 in the NICE guideline

October 2022

Final

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1.1 Review question

What is the benefit of weight loss for the management of osteoarthritis in overweight and obese people?

1.1.1 Introduction

The benefits of weight loss in overweight and obese people are widely accepted. It is believed to help reduce the risk of a variety of conditions including type 2 diabetes, heart disease, stroke, some cancers and high blood pressure. While being overweight is thought to exacerbate lower limb osteoarthritis through extra pressure being placed on the joints, the interplay between weight and osteoarthritis is more complex than this alone, as people who are overweight and obese are more likely to get osteoarthritis in non-weight bearing joints such as the hand. While all the mechanisms are not completely understood, controlling weight to a healthy BMI is consistently advocated internationally both for osteoarthritis and general wellbeing.

Current practice for people with osteoarthritis is to advise them to lose weight. While most overweight and obese people with osteoarthritis will agree that losing weight would help their quality of life, they find it difficult to lose and sustain a weight loss. Currently, weight loss can occur in through one-to-one advice or within a group setting, in some areas of the country, dedicated weight loss programmes are commissioned, in others, osteoarthritis programmes are commissioned which include weight loss. There is no standard approach to how people with osteoarthritis should be supported to lose weight. This review aims to inform patients and healthcare professionals about the amount of weight loss needed to promote improvement in their osteoarthritis symptoms and joint functioning to then decide together how this may best be achieved.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Inclusion:
	• Adults (age ≥16 years) with osteoarthritis affecting any joint
	• People who are overweight (BMI of 25 or over) or obese (BMI of 30 or over)
	
	The population will be stratified by:
	• Overweight or obese classification (as defined above)
	• Site of osteoarthritis:
	  ○ Hip
	  ○ Knee
	  ○ Ankle
	  ○ Foot
	  ○ Toe
	  ○ Shoulder
	  ○ Elbow
	  ○ Wrist
	  ○ Hand

	○ Thumb ○ Finger ○ Temporomandibular joint (TMJ) ○ Multisite Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy). • Studies with an unclear population (e,g, proportion of participants with osteoarthritis unclear) • Spinal osteoarthritis
Prognostic variables under consideration	Weight loss by any means resulting in: • Weight loss <5% • 5-10% • >10%
Confounding factors	Confounding factors: • Baseline BMI (or weight in the absence of BMI) • Baseline symptoms such as pain and/or function • Intervention (if sample selected/were randomised to various interventions) • Age
Outcomes	Stratify by ≤/>3 months (longest time-point in each): Critical outcomes: • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] Important outcomes: • Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [validated patient-reported outcomes, continuous data prioritised]
Study design	Non-randomised evidence, including: 1. Secondary analyses of RCTs (stratified results by weight loss) 2. Prospective and retrospective cohort studies 3. Case control studies (if no other evidence identified) Studies will only be included if all of the key confounders have been accounted for in a multivariate analysis. In the absence of multivariate analysis, studies that account for key confounders with univariate analysis or matched groups will be considered.

For full details see the review protocol in Appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

were recorded according to NICE's conflicts of interest policy.

1.1.4 Prognostic evidence

1.1.4.1 Included studies

Two prospective cohort studies were included in the review[3, 55]; these are summarised in below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). These studies included people who were either obese[3] or where the proportion of people who were obese or overweight is unclear[55]. All studies included people with knee osteoarthritis. No relevant clinical studies investigated the effects on people with osteoarthritis of different joint sites. One study accounted for all confounders within a regression analysis[3], while the other accounted for some of these confounders in a regression analysis while other confounders were matched at baseline[55].

See also the study selection flow chart in Appendix A, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variable	Confounders	Outcomes	Limitations
Atukorala 2016[3]	**Knee osteoarthritis** People with knee osteoarthritis of whom the majority were obese (1130/81.7%) n=1383	Repeated-measures of analysis of variance, controlling for sex, age, body mass index and KOOS	Weight loss: Loss of ≤5% of baseline weight Loss of 5-10% of baseline weight Loss of ≥10% of baseline weight	Age Body mass index Baseline weight	Quality of life at >3 months Pain at >3 months Physical function at >3 months	Very high risk of bias (bias due to problems with study participation and study attrition)
Riddle 2013[55]	**Knee osteoarthritis** People with knee osteoarthritis of whom it is unclear what their baseline BMI category was. For the analysis this group is treated as if overweight. n=1410	Regression analysis adjusting for baseline symptoms, sex, depression and number of comorbidities	Weight loss: Loss of ≤5% of baseline weight Loss of 5-10% of baseline weight Loss of ≥10% of baseline weight	Regression analysis: Baseline symptoms Baseline values available and stated to be similar at baseline between different weight categories: Age Baseline weight	Pain at >3 months Physical function at >3 months	Very high risk of bias (bias due to problems with study participation and study confounding)

See Appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

Table 3: Clinical evidence summary: loss of 5-10% of baseline weight compared to loss of <5% of baseline weight for people with knee osteoarthritis who are obese (BMI ≥30)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality	MID
Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight Quality of life (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 3.40 (0.66 to 6.14) SMD 0.15 SD (0.01 to 0.29)	Not serious	LOW[b]	0.5 SD (SMD)
Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight Pain (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 3.70 (1.51 to 5.89) SMD 0.23 SD (0.09 to 0.37)	Not serious	LOW[b]	0.5 SD (SMD)
Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight Physical function (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 4.20 (2.16 to 6.24) SMD 0.27 SD (0.13 to 0.41)	Not serious	LOW[b]	0.5 SD (SMD)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if weight change is an independent risk factor. Key covariates included: sex, age, BMI, KOOS scores.
(b) Downgraded for risk of bias (see evidence table for additional information).

Table 4: Clinical evidence summary: >10% of baseline weight compared to loss of <5% of baseline weight for people with knee osteoarthritis who are obese (BMI ≥30)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality	MID
Loss of >10% of baseline weight compared to loss of <5% of baseline weight Quality of life (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 7.50 (4.89 to 10.11) SMD 0.42 SD (0.27 to 0.57)	Not serious	LOW[b]	0.5 SD (SMD)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality	MID
Loss of >10% of baseline weight compared to loss of <5% of baseline weight Pain (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 7.80 (5.44 to 10.16) SMD 0.42 SD (0.27 to 0.57)	Not serious	LOW[b]	0.5 SD (SMD)
Loss of >10% of baseline weight compared to loss of <5% of baseline weight Physical function (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 8.80 (6.56 to 11.04) SMD 0.57 SD (0.42 to 0.72)	Not serious	LOW[b]	0.5 SD (SMD)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if weight change is an independent risk factor. Key covariates included: sex, age, BMI, KOOS scores.
(b) Downgraded for risk of bias (see evidence table for additional information).

Table 5: Clinical evidence summary: >10% of baseline weight compared to loss of 5-10% of baseline weight for people with knee osteoarthritis who are obese (BMI ≥30)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality	MID
Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight Quality of life (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 4.10 (1.53 to 6.67) SMD 0.18 SD (0.06 to 0.30)	Not serious	LOW	0.5 SD (SMD)
Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight Pain (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 4.10 (2.13 to 6.07) SMD 0.25 SD (0.13 to 0.38)	Not serious	LOW	0.5 SD (SMD)
Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight Physical function (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks) (people with knee osteoarthritis who are obese)[a]	1	MD 4.60 (2.62 to 6.58) SMD 0.28 SD (0.16 to 0.41)	Not serious	LOW	0.5 SD (SMD)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if weight change is an independent risk factor. Key covariates included: sex, age, BMI, KOOS scores.
(b) Downgraded for risk of bias (see evidence table for additional information).

Table 6: Clinical evidence summary: loss of 5-10% of baseline weight compared to loss of <5% of baseline weight for people with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality	MID
Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 30 months) (people with knee osteoarthritis where their baseline BMI category is unclear)[a]	1	MD 0.10 (-0.60 to 0.80) SMD 0.03 SD (-0.14 to 0.19)	Serious[b]	VERY LOW[c]	0.5 SD (SMD)
Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight Physical function (WOMAC, 0-68, high is poor, change score) at >3 months (follow up: 30 months) (people with knee osteoarthritis where their baseline BMI category is unclear)[a]	1	MD -0.56 (-2.60 to 1.48) SMD -0.05 SD (-0.21 to 0.12)	Serious[b]	VERY LOW[c]	0.5 SD (SMD)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if weight change is an independent risk factor. Key covariates included: baseline symptoms, sex, depression, number of comorbidities. Factors with evidence to indicate they were matched between groups at baseline: baseline weight, age.
(b) 95% CI around the mean difference crosses null line.
(c) Downgraded for risk of bias (see evidence table for additional information).

Table 7: Clinical evidence summary: loss of >10% of baseline weight compared to loss of <5% of baseline weight for people with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality	MID
Loss of >10% of baseline weight compared to loss of <5% of baseline weight Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 30 months)	1	MD -0.96 (-1.99 to 0.07) SMD -0.24 SD (-0.47 to -0.02)	Serious[b]	VERY LOW[c]	0.5 SD (SMD)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality	MID
(people with knee osteoarthritis where their baseline BMI category is unclear)[a]					
Loss of >10% of baseline weight compared to loss of <5% of baseline weight Physical function (WOMAC, 0-68, high is poor, change score) at >3 months (follow up: 30 months) (people with knee osteoarthritis where their baseline BMI category is unclear)[a]	1	MD -4.72 (-7.68 to -1.76) SMD -0.40 SD (-0.62 to -0.17)	Not serious	LOW[c]	0.5 SD (SMD)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if weight change is an independent risk factor. Key covariates included: baseline symptoms, sex, depression, number of comorbidities. Factors with evidence to indicate they were matched between groups at baseline: baseline weight, age.

(b) 95% CI around the mean difference crosses null line.

(c) Downgraded for risk of bias (see evidence table for additional information).

Table 8: Clinical evidence summary: loss of >10% of baseline weight compared to loss of 5-10% of baseline weight for people with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality	MID
Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 30 months) (people with knee osteoarthritis where their baseline BMI category is unclear)[a]	1	MD -1.06 (-2.25 to 0.13) SMD -0.24 SD (-0.50 to 0.03)	Serious[b]	VERY LOW[c]	0.5 SD (SMD)
Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight Physical function (WOMAC, 0-68, high is poor, change score) at >3 months (follow up: 30 months) (people with knee osteoarthritis where their baseline BMI category is unclear)[a]	1	MD -4.16 (-7.59 to -0.73) SMD -0.32 SD (-0.59 to -0.06)	Not serious	LOW[c]	0.5 SD (SMD)

(a) Methods: multivariable analysis, including key covariates used in analysis to assess if weight change is an independent risk factor. Key covariates included: baseline symptoms, sex, depression, number of comorbidities. Factors with evidence to indicate they were matched between groups at baseline: baseline weight, age.
(b) 95% CI around the mean difference crosses null line.
(c) Downgraded for risk of bias (see evidence table for additional information).

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

There was no economic evidence found

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.11 Economic evidence statements

- No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The critical outcomes were quality of life, pain and physical function. These were considered critical due to their relevance importance to people with osteoarthritis. The Osteoarthritis Research Society International (OARSI) consider that pain and physical function were the most important outcomes for evaluating interventions. Quality of life gives a broader perspective on the person's wellbeing, allowing for examination of the biopsychosocial impact of interventions. Psychological distress and osteoarthritis flares were included as important outcomes.

The committee considered osteoarthritis flares to be important in the lived experience and management of osteoarthritis. However, these were also considered difficult to measure with no clear consensus on their definition. The Flares in OA OMERACT working group have proposed an initial definition and domains of OA flares through a consensus exercise; "it is a transient state, different from the usual state of the condition, with a duration of a few days, characterized by onset, worsening of pain, swelling, stiffness, impact on sleep, activity, functioning, and psychological aspects that can resolve spontaneously or lead to a need to adjust therapy". However, this has been considered to have limitations and has not been widely adopted. Therefore, the committee included the outcome accepting any reasonable definition provided by any studies discussing the event.

Mortality was included as treatment adverse events rather than as a discreet outcome and categorised as an important outcome. Osteoarthritis as a disease process is not considered to cause mortality by itself and mortality is an uncommon outcome from osteoarthritis interventions.

There was no evidence available for osteoarthritis flares and psychological distress. The committee acknowledged these as important outcomes rather than critical and agreed that they could make recommendations even though there was limited information for this outcome.

1.1.12.2 The quality of the evidence

Two studies were included in this review. The first (Atukorala 2016[3]) included people with knee osteoarthritis who were obese and investigated the effect of losing ≤5%, 5-10% and ≥10% of their baseline weight after participating in a weight loss management program. The second (Riddle 2013[55]) included people with knee osteoarthritis where it was unclear whether they were overweight or obese before entering the study. It also investigated the effect of losing ≤5%, 5-10% and ≥10% of their baseline weight after participating in two different weight loss management programs. These studies were not pooled for analysis as the populations were not comparable (one including only people who were obese, one comparing people who were overweight or obese) and different methods used to analyse the effect of confounders.

All outcomes were noted to be of very high risk of bias. The reasons for this included bias in study participation (as the inclusion and exclusion criteria are unclear), study attrition (as the proportion of baseline sample available for analysis was inadequate and there was insufficient information on why participants were lost to follow up) and study confounding (as not all confounding factors established in the protocol were accounted for in a multivariate analysis). No indirectness was noted in any outcomes. Imprecision was noted in four outcomes, including participants where their BMI classification before entering the study is unclear.

1.1.12.3 Clinical effects of weight loss

For people with knee osteoarthritis who were obese, the outcomes reported were quality of life, pain and physical function. For people with knee osteoarthritis where their BMI classification before the study was unclear, the outcomes reported were pain and physical function. All outcomes were reported at >3 months (18 weeks and 30 months respectively). In people who were obese, the results showed that people who have a >10% weight loss have a clinically important improvement in physical function at >3 months when compared to people with a loss of <5% of their baseline weight. Other outcomes did not show evidence of a clinically important effect using a standardised mean difference value of 0.5. However, in all outcomes participants achieved a beneficial effect to quality of life, pain and physical function at >3 months to lesser degrees (with standardised mean difference values between 0.15-0.27 for quality of life, pain and physical function for people losing 5-10% of their baseline weight compared to people with a <5% loss, and 0.42 in quality of life and pain for people losing >10% of their baseline weight compared to people with a <5% loss).

For people with knee osteoarthritis and an unclear BMI classification before the study no outcomes showed a clinically important change. The effects at >3 months with a loss of 5-10% of baseline weight had small effect sizes (for standardised mean differences where high is poor, pain = 0.03, physical function = -0.05) while the effects with a loss of >10% of baseline weight there were larger effect sizes indicating a possible benefit (pain = -0.24, physical function = -0.40). There was no evidence identified for the outcomes of osteoarthritis flares or psychological distress.

The committee acknowledged that there was a trend that increased weight loss led to better outcomes reflecting that the evidence indicated a dose-response gradient (with >10% weight loss group appearing to have a much more significant change than the <5% weight loss group). They acknowledged that the studies included achieved the higher amounts of weight loss through a formal weight loss programme, and so considered that support should be provided to people to help them to lose weight. However, the committee considered that the support required for people with osteoarthritis would be similar to from the support required for people with other conditions and so recommended to consider other relevant NICE guidance for this information (including: Weight management: lifestyle services for overweight or obese adults (PH53) and Obesity: identification, assessment and management (CG189)). Due to the observed benefits of weight loss the committee made a recommendation to advise people about weight loss and to support them to make meaningful weight loss goals. The committee noted that benefits were seen with all amounts of weight loss, with the most benefits being seen when ≥10% of their body weight was lost. To this end, they recommended that people lose as much weight as they can but wanted to encourage that losing any weight was likely to provide benefits for people with osteoarthritis who are overweight or obese.

Furthermore, the committee agreed that good practice should be used in supporting people to achieve this weight loss. This should include helping people to choose an achievable weight goal. The committee agreed that while there was limited evidence available, the evidence was sufficient to make a recommendation and therefore, no additional research was required in this area.

1.1.12.4 Cost effectiveness and resource use

No economic evaluations were identified for this question.

The clinical review showed a trend between greater weight loss and improved reported health outcomes. Conclusions could not be made regarding the cost effectiveness of structured weight loss programmes in osteoarthritis, however the committee agreed that some form of patient support should be indicated based on the clinical evidence, and motivational interviewing and health coaching techniques were suggested.

The committee acknowledged that the recommendation would require the time of a healthcare professional but did not think it would lead to a substantial resource impact since this recommendation is intended to build upon likely unstructured conversations that are already occurring.

1.1.12.5 Other factors the committee took into account

Studies did not report if weight loss was maintained over this time period. The committee acknowledged the challenges of maintaining weight loss over a long period of time and that in order to maintain the benefits, maintained weight loss would be useful. They wanted to reinforce that good practice for supporting people with weight management should be used (such as those in other relevant NICE guidance) to help people maintain any weight loss that they achieve.

Overweight and obese people with osteoarthritis are often told to lose weight before they will be considered for joint replacement. However, losing weight may require exercise (for more information about exercise for osteoarthritis see evidence review C) and people report having difficulty exercising when they have joint pain, and it is uncertain whether losing weight before a joint replacement is required. The effect of people being in different BMI categories before joint replacement surgery is considered in evidence review 'Outcomes of joint replacement surgery dependent on body mass index', which investigates elements of this.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.3.5. Other evidence supporting this recommendation can be found in evidence review D.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for the benefit of weight loss for the management of osteoarthritis in people who are overweight or obese

ID	Field	Content
0.	PROSPERO registration number	CRD42021230518
1.	Review title	What is the benefit of weight loss for the management of osteoarthritis in overweight and obese people?
2.	Review question	What is the benefit of weight loss for the management of osteoarthritis in overweight and obese people?
3.	Objective	To assess the effect of weight loss (by any means) on outcomes in people with osteoarthritis who are overweight or obese people.
4.	Searches	The following databases will be searched: • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer.

		The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	People, aged 16 years and over, with osteoarthritis (of any joint)

6.	Population	Inclusion:
		• Adults (age ≥16 years) with osteoarthritis affecting any joint
		• People who are overweight (BMI of 25 or over) or obese (BMI of 30 or over)
		
		The population will be stratified by:
		• Overweight or obese classification (as defined above)
		• Site of osteoarthritis:
		  ○ Hip
		  ○ Knee
		  ○ Ankle
		  ○ Foot
		  ○ Toe
		  ○ Shoulder
		  ○ Elbow
		  ○ Wrist
		  ○ Hand
		  ○ Thumb
		  ○ Finger
		  ○ Temporomandibular joint (TMJ)
		  ○ Multisite

		Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy). • Studies with an unclear population (e,g, proportion of participants with osteoarthritis unclear) • Spinal osteoarthritis
7.	Intervention/Exposure/Test	Prognostic factors: Weight loss by any means resulting in: • Weight loss <5% • 5-10% • >10%
8.	Comparator/Reference standard/Confounding factors	Confounding factors: • Baseline BMI (or weight in the absence of BMI) • Baseline symptoms such as pain and/or function • Intervention (if sample selected/were randomised to various interventions) • Age
9.	Types of study to be included	Non-randomised evidence, including: 4. Secondary analyses of RCTs (stratified results by weight loss) 5. Prospective and retrospective cohort studies 6. Case control studies (if no other evidence identified) Studies will only be included if all of the key confounders have been accounted for in a multivariate analysis. In the absence of multivariate analysis, studies that account for key confounders with univariate analysis or matched groups will be considered.
10.	Other exclusion criteria	• Non-English language studies

		• Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] The COMET database was searched and several core outcome sets were identified for specific sites of osteoarthritis (including hand, knee and hip). The committee took these into account when defining outcomes: https://onlinelibrary.wiley.com/doi/full/10.1002/acr.22868 https://www.ncbi.nlm.nih.gov/pubmed/26136489 https://www.ncbi.nlm.nih.gov/pubmed/30647185 The committee did not include stiffness or global scores as Delphi discussions by the OMERACT group have found these to not be as important to people with osteoarthritis or clinicians. The outcomes included were universal for all groups allowing for broader comparisons.
13.	Secondary outcomes (important outcomes)	• Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flare-ups [validated patient-reported outcomes, continuous data prioritised]
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.

		Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual • The QUIPs checklist will be used to assess risk of bias of each individual study. For intervention reviews the following checklists will be used according to the study design being assessed: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.

		• WinBUGS will be used for network meta-analysis, if possible given the data identified. Heterogeneity between studies in the effect measures will be assessed using the I^2 statistic and visual inspection. We will consider an I^2 value great than 50% as indicative of substantial heterogeneity. If significant heterogeneity is identified during meta-analysis then subgroup analysis, using subgroups predefined by the GC, will take place. If this does not explain the heterogeneity, the results will be presented using a random-effects model.		
17.	Analysis of sub-groups	Study types (secondary analysis of RCTs, cohort studies, or case control studies)		
18.	Type and method of review	☐	Intervention	
		☐	Diagnostic	
		☒	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	23/08/2019		
22.	Anticipated completion date	25/08/2021		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☐

		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Julie Neilson [Senior systematic reviewer]		

		George Wood [Systematic reviewer] Emma Cowles [Senior health economist] Joseph Runicles [Information specialist] Amber Hernaman [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10127
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

32.	Keywords	Adults; Prognosis; Osteoarthritis; Overweight; Obese; Weight loss	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 9: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2005 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[45] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2005 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'.
- Studies published before 2005 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

- What is the benefit of weight loss for the management of osteoarthritis in overweight and obese people?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[45]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed by combining an Osteoarthritis population with prognostic/risk factor terms.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 17 November 2021	Exclusions (animals studies, letters, comments)
Embase (OVID)	1974 – 17 November 2021	Exclusions (animals studies, letters, comments)

Medline (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/

22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	weight loss/
28.	(weight adj2 (los* or reduc* or manag*)).ti,ab.
29.	exp overweight/
30.	(obese or obesity or overweight or over weight or overeat* or "over eat*").ti,ab.
31.	or/27-30
32.	26 and 31

Embase (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	body weight loss/
26.	(weight adj2 (los* or reduc* or manag*)).ti,ab.
27.	exp obesity/
28.	(obese or obesity or overweight or over weight or overeat* or "over eat*").ti,ab.
29.	or/25-28
30.	24 and 29

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updates after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies. Searches for quality of life studies were run for general information.

Table 11: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1 January 2014 – 17 November 2021	Health economics studies Quality of life studies Exclusions (animals studies, letters, comments)
Embase	1 January 2014 – 17 November 2021	Health economics studies Quality of life studies Exclusions (animals studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/

19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.

58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.

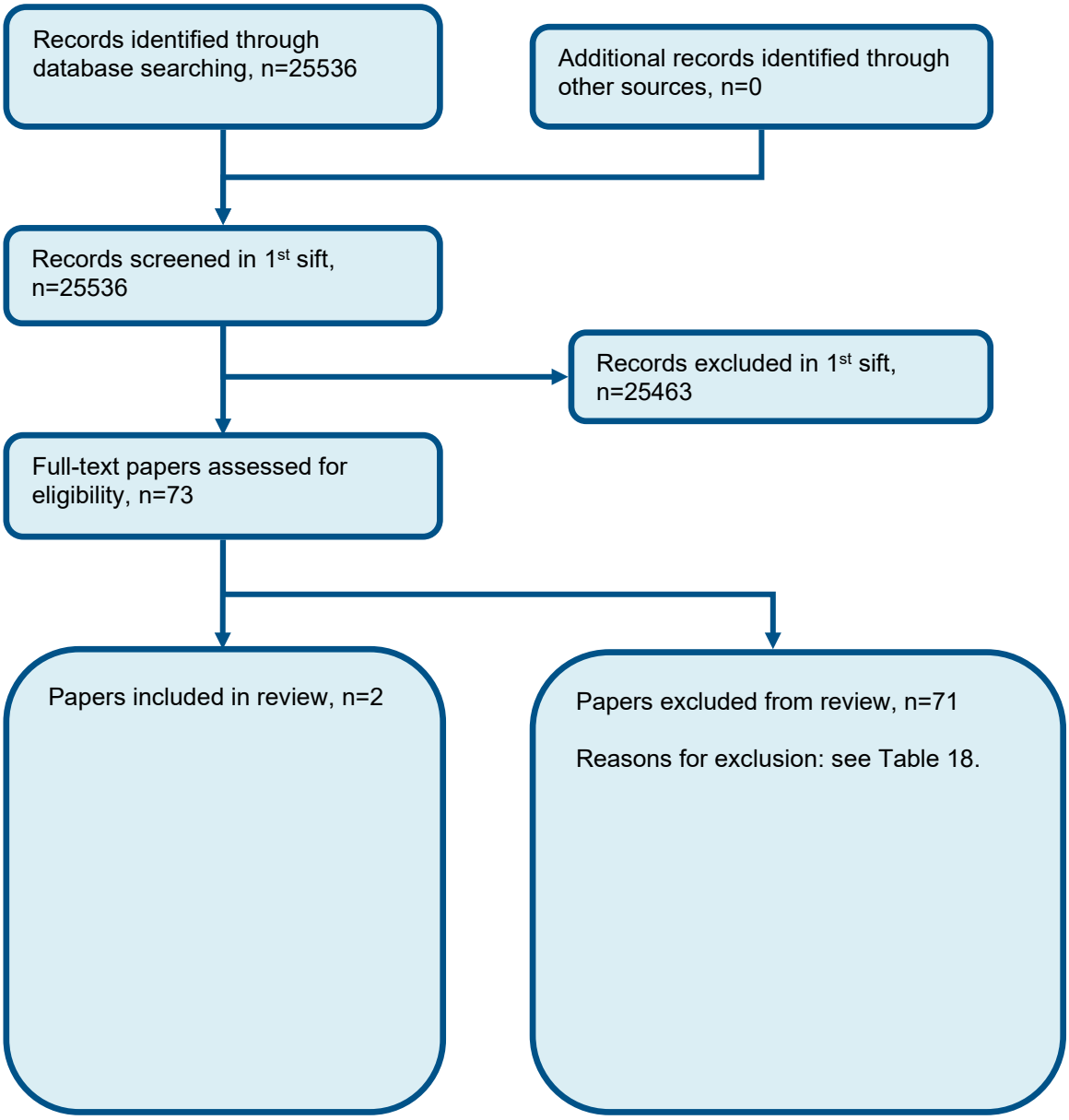
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	"quality of life index"/
41.	short form 12/ or short form 20/ or short form 36/ or short form 8/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.
44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.
54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/39-59
61.	24 and (38 or 60)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Osteoarthritis EXPLODE ALL TREES
#2.	((osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*))
#3.	((degenerative adj2 arthritis))
#4.	(coxarthrosis)
#5.	(gonarthrosis)
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(#6) IN NHSEED
#8.	(#6) IN HTA

Appendix C – Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of the benefit of weight loss for people with osteoarthritis who are overweight or obese



Appendix D – Prognostic evidence

Reference	Atukorala 2016[3]
Study type and analysis	Prospective cohort study Repeated-measures of analysis of variance, controlling for sex, age, body mass index and KOOS Australia, rural and urban settings
Number of participants and characteristics	N=3827 recruited, 2098 completed the follow up, 715 incomplete data or hip osteoarthritis, 1383 included Stable weight, n=110 (54 were obese) Loss of ≤5% of baseline weight (two groups) - Loss of ≤2.5% of baseline weight, n=79 - Loss of 2.5-5% of baseline weight, n=224 Loss of 5-10% of baseline weight (two groups) - Loss of 5-7.5% of baseline weight, n=332 - Loss of 7.5-10% of baseline weight, n=317 Loss of ≥10% of baseline weight, n=431 People with symptomatic knee osteoarthritis with a mean BMI of 34.39 (5.17) kg/m^2 (1130/81.7% were obese at baseline) who were enrolled in a specialized knee and hip osteoarthritis management program that focuses on weight loss (i.e., the Osteoarthritis Health Weight for Life Program). The OAHWFL program systematically implements a number of core nonsurgical osteoarthritis best practice treatment recommendations, including targeting >5% weight loss for overweight individuals, land- and water-based aerobic exercise (walking and swimming), muscle strengthening, and self-management and education strategies. The program utilizes a step-by-step approach that consists of 3 phases, carried out over 18 weeks. Each 6-week phase includes a portion control eating plan (including KicStart very low calorie diet meal replacements); an activity plan and physiotherapist-developed strength, balance and mobility exercises; a personalized online symptom, progress and satisfaction tracking (phone and mail alternatives also available) activity; and 2-way personal motivation, support and advice via phone, short message service/text message, e-mail, message board, and mail. **Inclusion criteria:** Participants in the OAHWFL program who fulfilled the 1986 American College of Rheumatology clinical criteria for classification of knee osteoarthritis. People had a current or historical diagnosis of knee osteoarthritis supported by radiology (e.g. on radiographs or magnetic resonance imaging) or by an incidental finding from a previous arthroscopy and a body mass index >28kg/m^2. In addition, all participants had, according to medical opinion, knee osteoarthritis symptoms that required (or were likely to in the foreseeable future)

Reference	Atukorala 2016[3]
	referral to an orthopaedic surgeon for evaluation for a knee joint replacement procedure. In these persons' weight loss, improved fitness and muscle strength prior to surgery was desirable. **Exclusion criteria:** No additional information. **Values listed below are presented as mean (SD) or number (%)** • Age: 64.0 (8.7) years • Male/female: 402/981 (29.1%/70.9%) • Weight: 95.12 (17.2) kg • Height: 1.66 (0.09) meters • BMI: 34.39 (5.17) kg/m^2 • Obesity (BMI ≥30kg/m^2) at baseline: 1130 (81.7%) • Obesity (BMI ≥30kg/m^2) at 18 weeks: 772 (56.3%) • Baseline KOOS pain subscale (0-100, high is good): 56.3 (16.8) • Baseline KOOS function in daily living subscale (WOMAC function) (0-100, high is good): 59.5 (18.3) • Baseline KOOS other symptoms subscale (0-100, high is good): 54.3 (17.7) • Baseline KOOS function in sport/recreation subscale (0-100, high is good): 27.6 (24.2) • KOOS knee related quality of life subscale (0-100, high is good): 35.1 (18.4) **Population source:** Consecutive persons enrolled in the OAHWFL program and fulfilling the eligibility criteria
Prognostic variable	Loss of ≤5% of baseline weight Loss of 5-10% of baseline weight Loss of ≥10% of baseline weight
Confounders	Repeated-measures of analysis of variance (beta-coefficient reported for one outcome) Factors included in adjusted analysis: Sex, age, BMI, KOOS scores.
Outcomes and effect sizes	Health-related quality of life (difference in KOOS quality of life subscale after weight loss) Pain (difference in KOOS pain subscale after weight loss) Physical function (difference in KOOS function in daily living subscale [WOMAC function score] after weight loss)

Reference	Atukorala 2016[3]
	<u>Health-related quality of life – Difference in KOOS quality of life subscale after weight loss (0-100, high is good)</u> **Loss of ≤5% of baseline weight (two groups) – mean (SD) – 8.7 (17.4)** - **Loss of ≤2.5% of baseline weight, n=79 – mean (SD) – 5.3 (17.6)** - **Loss of 2.5-5% of baseline weight, n=224 – mean (SD) – 9.9 (17.1)** **Loss of 5-10% of baseline weight (two groups) – mean (SD) – 12.1 (24.9)** - **Loss of 5-7.5% of baseline weight, n=332 – mean (SD) – 11.5 (25.1)** - **Loss of 7.5-10% of baseline weight, n=317 – mean (SD) – 12.7 (24.6)** **Loss of ≥10% of baseline weight, n=431 – mean (SD) – 16.2 (18.2)** **<u>Pain – Difference in KOOS pain subscale after weight loss (0-100, high is good)</u>** **Loss of ≤5% of baseline weight (two groups) – mean (SD) – 8.9 (16.0)** - **Loss of ≤2.5% of baseline weight, n=79 – mean (SD) – 6.1 (13.0)** - **Loss of 2.5-5% of baseline weight, n=224 – mean (SD) – 9.9 (16.8)** **Loss of 5-10% of baseline weight (two groups) – mean (SD) – 12.6 (16.2)** - **Loss of 5-7.5% of baseline weight, n=332 – mean (SD) – 12.0 (17.1)** - **Loss of 7.5-10% of baseline weight, n=317 – mean (SD) – 13.3 (15.1)** **Loss of ≥10% of baseline weight, n=431 – mean (SD) – 16.7 (16.1)** **<u>Physical function – Difference in KOOS function in daily living subscale [WOMAC function score] after weight loss (0-100, high is good)</u>** **Loss of ≤5% of baseline weight (two groups) – mean (SD) – 8.6 (14.4)** - **Loss of ≤2.5% of baseline weight, n=79 – mean (SD) – 7.8 (13.3)** - **Loss of 2.5-5% of baseline weight, n=224 – mean (SD) – 8.9 (14.7)** **Loss of 5-10% of baseline weight (two groups) – mean (SD) – 12.8 (16.1)** - **Loss of 5-7.5% of baseline weight, n=332 – mean (SD) – 12.0 (16.7)** - **Loss of 7.5-10% of baseline weight, n=317 – mean (SD) – 13.6 (15.5)** **Loss of ≥10% of baseline weight, n=431 – mean (SD) – 17.4 (16.3)** Follow up: 18 weeks
Comments	**<u>Health-related quality of life – Difference in KOOS quality of life subscale after weight loss (0-100, high is good)</u>**

Reference	Atukorala 2016[3]	
	Risk of bias:	
	1. Study participation	HIGH
	2. Study attrition	HIGH
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	LOW
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Pain – Difference in KOOS pain subscale after weight loss (0-100, high is good)	
	Risk of bias:	
	1. Study participation	HIGH
	2. Study attrition	HIGH
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	LOW
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Physical function – Difference in KOOS function in daily living subscale [WOMAC function score] after weight loss (0-100, high is good)	
	Risk of bias:	
	1. Study participation	HIGH
	2. Study attrition	HIGH
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	LOW
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH

Reference	Atukorala 2016[3]
	Indirectness: No indirectness noted

Reference	Riddle 2013[55]
Study type and analysis	Prospective cohort study Regression analysis adjusting for baseline symptoms, sex, depression and number of comorbidities. Baseline values of age and weight stated and reported to be similar at baseline between different weight categories. United States of America, data from two observational trial cohorts the Multicenter Osteoarthritis study (MOST) and Osteoarthritis Initiative (OAI). The MOST study is comprised of 4 cooperative grants (AG18820, AG18832, AG18947, AG19069) funded by the NIH. The OAI is a public-private partnership comprised of 5 contracts (N01-AR-2-2258, N01-AR-2-2250, N01-AR-2-2260, N01-AR-2-2261, N01-AR-2-2262) funded by the NIH. Private funding partners include Merck, Novartis, GlaxoSmithKline, and Pfizer. Private sector funding for the OAI is managed by the Foundation for the NIH.
Number of participants and characteristics	N=1785 combined baseline (OAI included 976, MOST included 809), 1410 complete weight data at baseline and follow up, 375 missing weight data at follow up Unclear if overweight or obese, will be considered as overweight for the analysis Stable weight (4.9% reduction to 4.9% gain), n=940 5-9.9% reduction, n=171 ≥10% reduction, n=82 5-9.9% gain (not included in the analysis), n=148 ≥10% gain (not included in the analysis), n=51 People enrolled in the OAI and MOST studies (studies looking at the development of knee osteoarthritis in high risk populations) who developed knee osteoarthritis. For the OAI study, people were between the ages of 45 and 79 years and were recruited from communities in and around 4 clinical sites: the University of Maryland School of Medicine in Baltimore, Maryland, the Ohio State University in Columbus, Ohio, the University of Pittsburgh in Pittburgh, Pennsylvania, and the Memorial Hospital of Rhode Island in Pawtucket, Rhode Island. For the MOST study people were aged 50-79 years and were recruited from communities in and around 2 clinical sites: the University of Iowa in Iowa City, Iowa, and the University of Alabama, Birmingham in Birmingham, Alabama. **Inclusion criteria:** Radiographic tibiofemoral knee osteoarthritis, defined as definite osteophytes (OARSI atlas grade 1-3 in the OAI or Kellgren Lawrence grade 2 or higher in the MOST study) as measured on a standardized fixed-flexion radiograph; a WOMAC pain scale score of 4 or higher; a WOMAC physical function score of 9 or higher; no knee replacement surgery during the follow up period. **Exclusion criteria:**

Reference	Riddle 2013[55]

	No additional information.
	
	Values listed below are presented as mean (SD) or number (%) (taken from complete weight data at baseline and followup)
	
	• Age: 62.73 (8.62) years
	• Male/female: 529/881 (37.5%/62.5%)
	• African American: 360 (25.5%)
	• Marital status:
	  ○ Married: 65.5%
	  ○ Widowed: 10.6%
	  ○ Divorced: 14.9%
	  ○ Separated: 1.9%
	  ○ Never married: 7.0%
	• Education:
	  ○ Less than high school diploma: 6.2%
	  ○ High school diploma: 23.2%
	  ○ At least some college: 70.6%
	• Comorbidity: 0.57 (0.95)
	• Weight: 89.62 (18.6) kg
	• Current smoker: 9.0%
	• Center for Epidemiologic Studies Depression Scale – Percent depressed: 17.7%
	• Baseline WOMAC pain score (0-20, high is poor): 7.83 (3.06)
	• Baseline WOMAC function score (0-68, high is poor): 25.12 (10.14)
	
	Population source: Participants in the MOST and OAI studies who developed osteoarthritis and fulfilling the eligibility criteria

Prognostic variable	Loss of ≤5% of baseline weight Loss of 5-10% of baseline weight Loss of ≥10% of baseline weight
Confounders	Two regression models were used to adjust for baseline symptoms, sex, depression and number of comorbidities. Reports that “the distributions of dependent variables approximated a normal distribution, and for each dependent variable, the variances among the % weight categories did not differ statistically”. The dependent variables included baseline weight and age.

Reference	Riddle 2013[55]
	Factors included in adjusted analysis: Baseline symptoms, sex, depression, number of comorbidities Factors with evidence to indicate they were matched between groups at baseline: Baseline weight, age
Outcomes and effect sizes	Pain (difference in WOMAC pain score after weight change) Physical function (difference in WOMAC function score after weight change) **<u>Pain – Difference in WOMAC pain score after weight change (0-20, high is poor)</u>** **Loss of 4.9% to gain of 4.9% of baseline weight – mean (SD) – -1.09 (3.86)** **Loss of 5-9.9% of baseline weight – mean (SD) – -0.99 (4.34)** **Loss of ≥10% of baseline weight, n=431 – mean (SD) – -2.05 (4.60)** **<u>Physical function – Difference in WOMAC function score after weight change (0-68, high is poor)</u>** **Loss of 4.9% to gain of 4.9% of baseline weight – mean (SD) – -2.78 (11.82)** **Loss of 5-9.9% of baseline weight – mean (SD) – -3.34 (12.62)** **Loss of ≥10% of baseline weight, n=431 – mean (SD) – -7.50 (13.24)** Follow up: 30 months
Comments	**<u>Pain – Difference in WOMAC pain score after weight change (0-20, high is poor)</u>** Risk of bias: 1. Study participation – LOW 2. Study attrition – HIGH 3. Prognostic factor measurement – LOW 4. Outcome Measurement – LOW 5. Study confounding – HIGH 6. Statistical analysis – LOW 7. Other risk of bias – LOW OVERALL RISK OF BIAS – VERY HIGH **<u>Physical function – Difference in WOMAC function score after weight change (0-68, high is poor)</u>** Risk of bias: 1. Study participation – LOW

Reference	Riddle 2013[55]	
	2. Study attrition	HIGH
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	LOW
	5. Study confounding	HIGH
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness: • Confounders: the analysis did not clearly adjust for baseline weight/BMI and age. However, they stated that the groups were matched therefore the study was included. This could be indirect evidence but will be adjusted for in risk of bias section instead to avoid reduction in quality twice for the same reason.	

Appendix E – Forest plots

E.1 People with knee osteoarthritis who are obese – Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight

Figure 2: Quality of life (KOOS, 0-100, high is good, change score) at >3 months

	5-10% weight loss			<5% weight loss			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Atukorala 2016	12.1	24.9	649	8.7	17.4	303	3.40 [0.66, 6.14]	

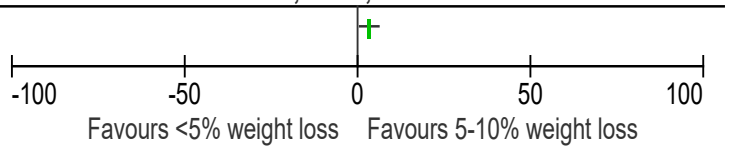


Figure 3: Pain (KOOS, 0-100, high is good, change score) at >3 months

	5-10% weight loss			<5% weight loss			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Atukorala 2016	12.6	16.2	649	8.9	16	303	3.70 [1.51, 5.89]	

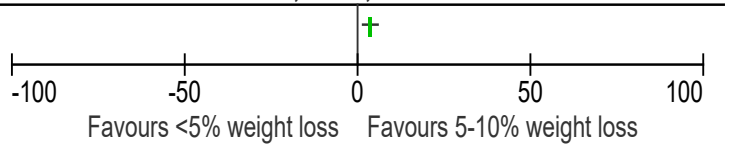
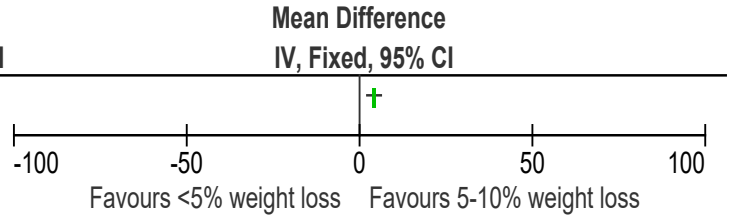


Figure 4: Physical function (KOOS, 0-100, high is good, change score) at >3 months

Study or Subgroup	5-10% weight loss Mean	SD	Total	<5% weight loss Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Atukorala 2016	12.8	16.1	649	8.6	14.4	303	4.20 [2.16, 6.24]



E.2 People with knee osteoarthritis who are obese – Loss of >10% of baseline weight compared to loss of <5% of baseline weight

Figure 5: Quality of life (KOOS, 0-100, high is good, change score) at >3 months

Study or Subgroup	>10% weight loss Mean	SD	Total	<5% weight loss Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Atukorala 2016	16.2	18.2	431	8.7	17.4	303	7.50 [4.89, 10.11]

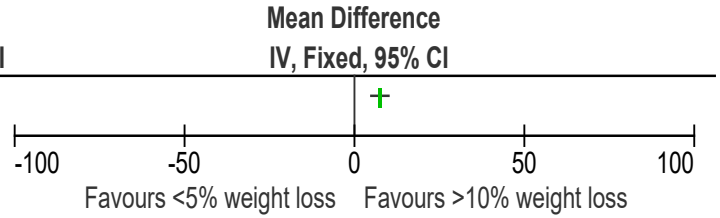


Figure 6: Pain (KOOS, 0-100, high is good, change score) at >3 months

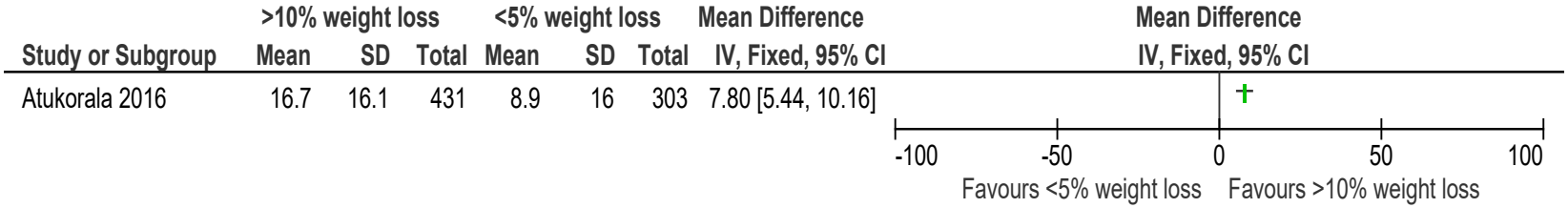
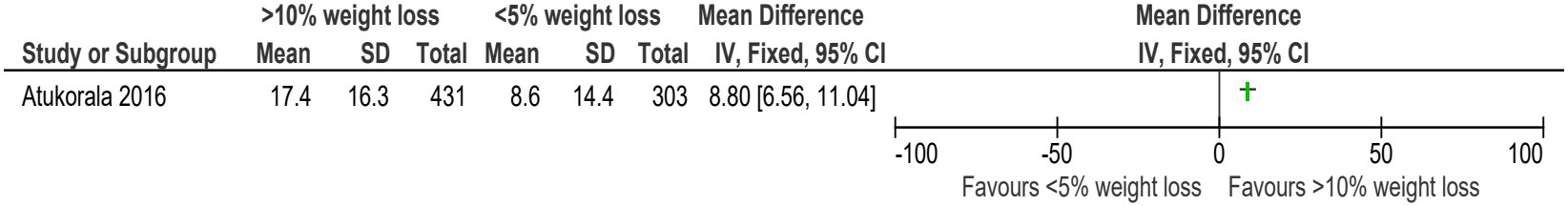


Figure 7: Physical function (KOOS, 0-100, high is good, change score) at >3 months



E.3 People with knee osteoarthritis who are obese – Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight

Figure 8: Quality of life (KOOS, 0-100, high is good, change score) at >3 months

	>10% weight loss			5-10% weight loss			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Atukorala 2016	16.2	18.2	431	12.1	24.9	649	4.10 [1.53, 6.67]

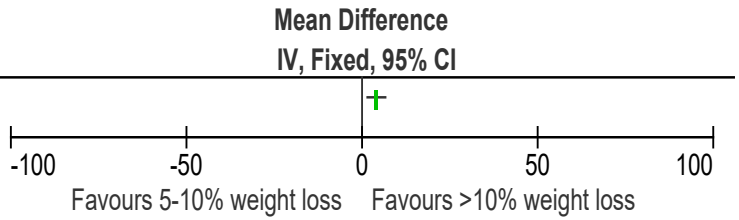


Figure 9: Pain (KOOS, 0-100, high is good, change score) at >3 months

	>10% weight loss			5-10% weight loss			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Atukorala 2016	16.7	16.1	431	12.6	16.2	649	4.10 [2.13, 6.07]

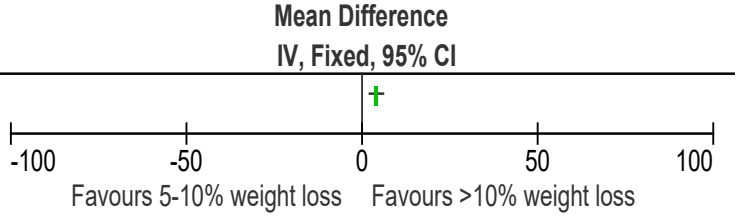
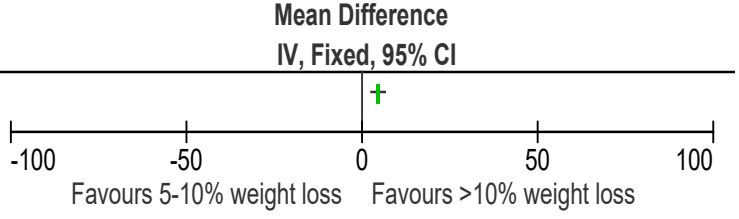


Figure 10: Physical function (KOOS, 0-100, high is good, change score) at >3 months

	>10% weight loss			5-10% weight loss			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Atukorala 2016	17.4	16.3	431	12.8	16.1	649	4.60 [2.62, 6.58]



E.4 People with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis) – Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight

Figure 11: Pain (WOMAC, 0-20, high is poor, change score) at >3 months

	5-10% weight loss			<5% weight loss			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Riddle 2013	-0.99	4.34	171	-1.09	3.86	940	0.10 [-0.60, 0.80]

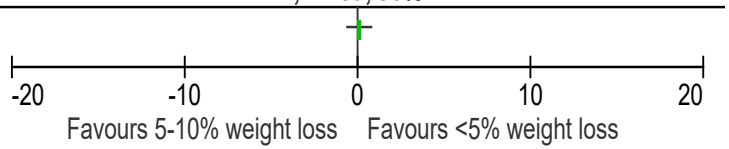
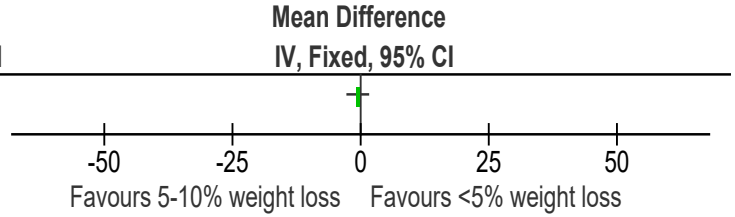


Figure 12: Physical function (WOMAC, 0-68, high is poor, change score) at >3 months

	5-10% weight loss			<5% weight loss			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Riddle 2013	-3.34	12.62	171	-2.78	11.82	940	-0.56 [-2.60, 1.48]



E.5 People with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis) – Loss of >10% of baseline weight compared to loss of <5% of baseline weight

Figure 13: Pain (WOMAC, 0-20, high is poor, change score) at >3 months

Study or Subgroup	>10% weight loss Mean	SD	Total	<5% weight loss Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Riddle 2013	-2.05	4.6	82	-1.09	3.86	940	-0.96 [-1.99, 0.07]

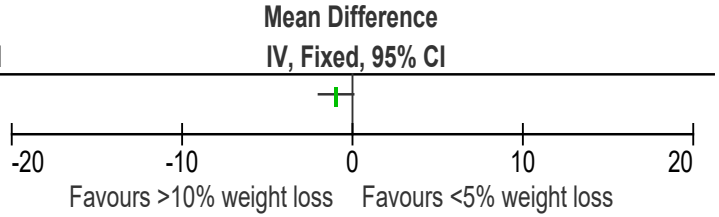
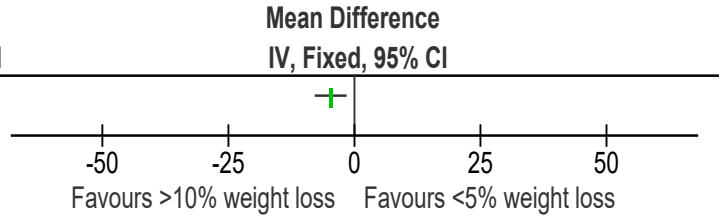


Figure 14: Physical function (WOMAC, 0-68, high is poor, change score) at >3 months

Study or Subgroup	>10% weight loss Mean	SD	Total	<5% weight loss Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Riddle 2013	-7.5	13.24	82	-2.78	11.82	940	-4.72 [-7.68, -1.76]



E.6 People with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis) – Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight

Figure 15: Pain (WOMAC, 0-20, high is poor, change score) at >3 months

	>10% weight loss			5-10% weight loss			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Riddle 2013	-2.05	4.6	82	-0.99	4.34	171	-1.06 [-2.25, 0.13]	

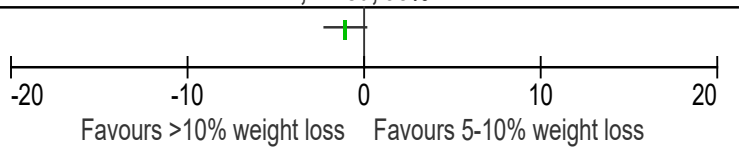
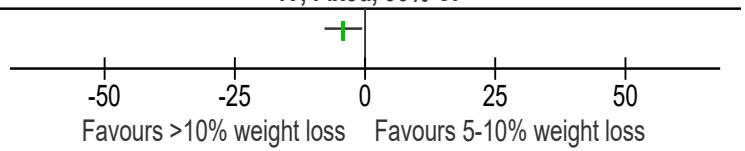


Figure 16: Physical function (WOMAC, 0-68, high is poor, change score) at >3 months

	>10% weight loss			5-10% weight loss			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Riddle 2013	-7.5	13.24	82	-3.34	12.62	171	-4.16 [-7.59, -0.73]	



Appendix F – GRADE tables

F.1 People with knee osteoarthritis who are obese – Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight

Table 12: Clinical evidence profile: loss of 5-10% of baseline weight compared to loss of <5% of baseline weight in people with knee osteoarthritis who are obese

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	loss of 5-10% of baseline weight	loss of <5% of baseline weight	Relative (95% CI)	Absolute (95% CI)		
Quality of life (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	649	303	-	MD **3.4 higher** (0.66 higher to 6.14 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	649	303	-	**3.7 higher** (1.51 higher to 5.89 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	649	303	-	**4.2 higher** (2.16 higher to 6.24 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

F.2 People with knee osteoarthritis who are obese – Loss of >10% of baseline weight compared to loss of <5% of baseline weight

Table 13: Clinical evidence profile: loss of >10% of baseline weight compared to loss of <5% of baseline weight in people with knee osteoarthritis who are obese

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	loss of >10% of baseline weight	loss of <5% of baseline weight	Relative (95% CI)	Absolute (95% CI)		
Quality of life (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	431	303	-	MD **7.5 higher** (4.89 higher to 10.11 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	431	303	-	MD **7.8 higher** (5.44 higher to 10.16 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	431	303	-	MD **8.8 higher** (6.56 higher to 11.04 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

F.3 People with knee osteoarthritis who are obese – Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight

Table 14: Clinical evidence profile: loss of >10% of baseline weight compared to loss of 5-10% of baseline weight in people with knee osteoarthritis who are obese

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	loss of >10% of baseline weight	loss of 5-10% of baseline weight	Relative (95% CI)	Absolute (95% CI)		
Quality of life (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	431	649	-	MD **4.1 higher** (1.53 higher to 6.67 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	431	649	-	**4.1 higher** (2.13 higher to 6.07 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (KOOS, 0-100, high is good, change score) at >3 months (follow up: 18 weeks; assessed with: KOOS; Scale from: 0 to 100)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	431	649	-	**4.6 higher** (2.62 higher to 6.58 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

F.4 People with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis) – Loss of 5-10% of baseline weight compared to loss of <5% of baseline weight

Table 15: Clinical evidence profile: loss of 5-10% of baseline weight compared to loss of <5% of baseline weight in people with knee osteoarthritis and an unclear BMI classification

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	loss of 5-10% of baseline weight	loss of <5% of baseline weight	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 30 months; assessed with: WOMAC; Scale from: 0 to 20)												
1	cohort studies	very serious [a]	not serious	not serious	serious [b]	none	171	940	-	MD **0.1 higher** (0.6 lower to 0.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, 0-68, high is poor, change score) at >3 months (follow up: 30 months; assessed with: WOMAC; Scale from: 0 to 68)												
1	cohort studies	very serious [a]	not serious	not serious	serious [b]	none	171	940	-	MD **0.56 lower** (2.6 lower to 1.48 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.5 People with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis) – Loss of >10% of baseline weight compared to loss of <5% of baseline weight

Table 16: Clinical evidence profile: loss of >10% of baseline weight compared to loss of <5% of baseline weight in people with knee osteoarthritis and an unclear BMI classification

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	loss of >10% of baseline weight	loss of <5% of baseline weight	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 30 months; assessed with: WOMAC; Scale from: 0 to 20)												
1	cohort studies	very serious [a]	not serious	not serious	serious [b]	none	82	940	-	MD **0.96 lower** (1.99 lower to 0.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 30 months; assessed with: WOMAC; Scale from: 0 to 68)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	82	940	-	MD **4.72 lower** (7.68 lower to 1.76 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.6 People with knee osteoarthritis where their BMI classification before the study is unclear (assumed overweight [BMI 25-30] for the analysis) – Loss of >10% of baseline weight compared to loss of 5-10% of baseline weight

Table 17: Clinical evidence profile: loss of >10% of baseline weight compared to loss of 5-10% of baseline weight in people with knee osteoarthritis and an unclear BMI classification

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	loss of >10% of baseline weight	loss of 5-10% of baseline weight	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 30 months; assessed with: WOMAC; Scale from: 0 to 20)												
1	cohort studies	very serious [a]	not serious	not serious	serious [b]	none	82	171	-	MD **1.06 lower** (2.25 lower to 0.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, 0-68, high is poor, change score) at >3 months (follow up: 30 months; assessed with: WOMAC; Scale from: 0 to 68)												
1	cohort studies	very serious [a]	not serious	not serious	not serious	none	82	171	-	MD **4.16 lower** (7.59 lower to 0.73 lower)	⨁⨁◯◯ LOW	CRITICAL

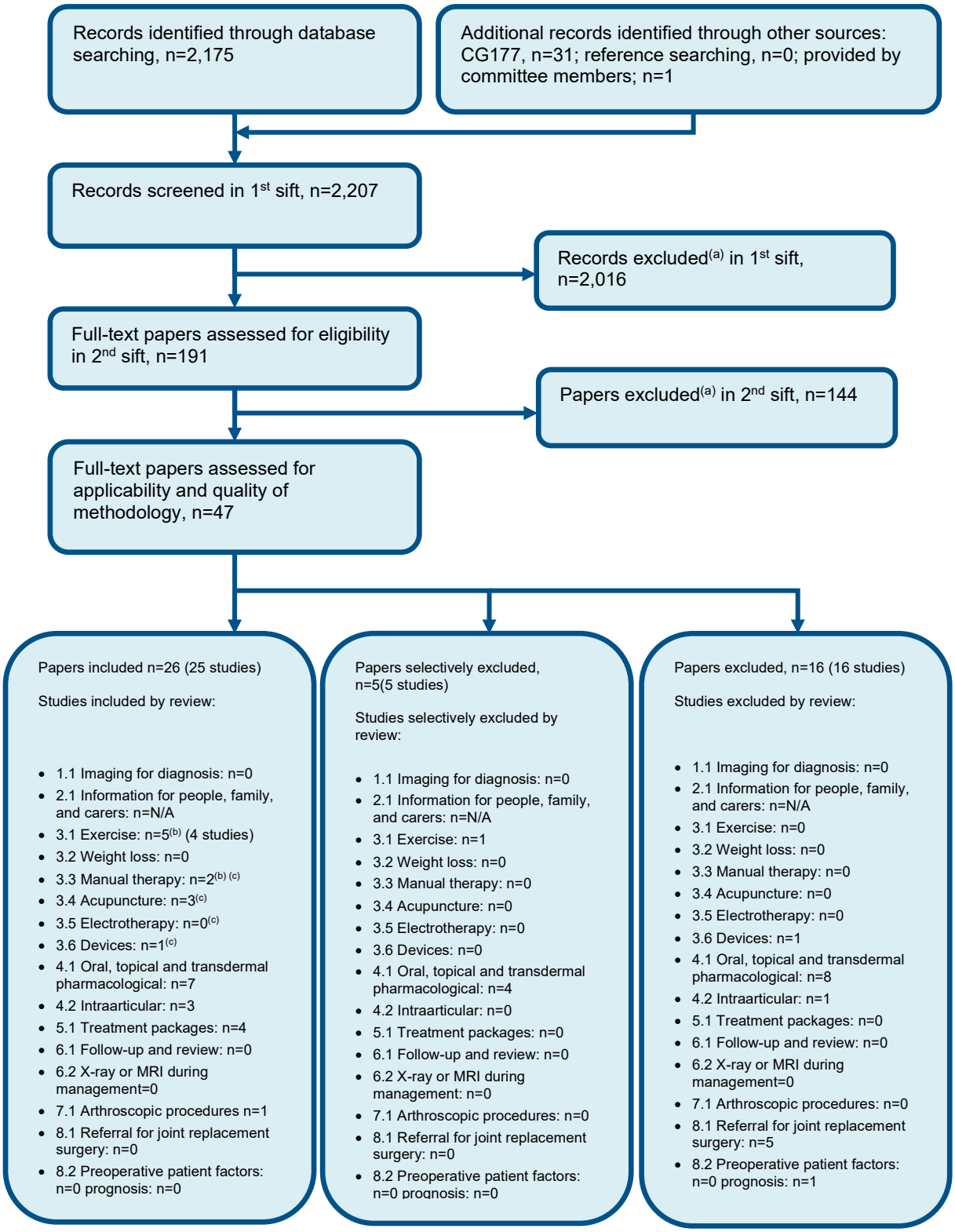
CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G – Economic evidence study selection



(a) Non-relevant population, intervention, comparison, design or setting; non-English language.
(b) Two articles identified were applicable to Q3.1 and Q3.3, for the purposes of this diagram they have been included under Q3.1 only.
(c) One article identified was applicable to Q3.3, Q3.4, Q3.5 and Q3.6, for the purposes of this diagram it has been included under Q3.3 only.

Appendix H – Economic evidence tables

There were no health economic studies found in the review.

Appendix I – Health economic model

No original economic modelling was undertaken.

Appendix J – Excluded studies

Clinical studies

Table 18: Studies excluded from the clinical review

Reference	Reason for exclusion
Aaboe 2011[1]	Non-comparative study
Anandacoomarasamy 2012[2]	No usable outcomes (reported radiographic parameters only)
Bartels 2014[5]	Non-comparative study
Bliddal 2011[4]	Commentary only
Brennan 2010[6]	Wrong population (studies the effects of weight gain)
Chu 2018[7]	Systematic review (inadequate quality assessment, includes study designs not included in the protocol for this review)
Cuzdan Coskun 2017[8]	Wrong population (includes healthy participants)
Daugaard 2020[9]	Results not stratified by weight loss
de Luis 2012[10]	Does not report a regression analysis and baseline values for confounders were not comparable at baseline (specifically baseline values for symptoms)
DeClercq 2017[11]	Wrong population (includes people with rheumatoid arthritis)
Edwards 2012[12]	Does not account for confounding factors adequate and outcomes not usable (reported medians and interquartile ranges)
Felson 1996[14]	Systematic review (methodology inadequate for inclusion in this review)
Felson 2004[15]	Results not stratified by weight loss
Felson 2021[13]	Incorrect prognostic variable (not stratified by amount of weight loss)
Fonseca Mora 2020[16]	Studies different types of surgical weight loss procedures and does not stratify results by amount of weight loss
Gersing 2016[19]	No usable outcomes (reported biomechanical parameters only)
Gersing 2019[17]	No usable outcomes (reported biomechanical parameters only)
Gersing 2019[18]	No usable outcomes (reported radiographic outcomes only)
Gorsky 1996[20]	Wrong study type (economic study using hypothetical cohorts)
Gudbergsen 2013[21]	No usable outcomes (reported biomechanical parameters only)
Guimaraes 2018[22]	No usable outcomes (reported biomechanical parameters only)
Hacken 2019[23]	Results not stratified by amount of weight loss
Hall 2019[24]	Results not stratified by amount of weight loss
Hamdi 2018[25]	Non-comparative study
Hawker 2014[26]	Results not stratified by amount of weight loss
Inacio 2014[27]	Wrong population (people who had total joint arthroplasty surgery)
Jafarzadeh 2018[28]	No usable outcomes (reported radiographic parameters only)
Jin 2021[29]	No usable outcomes (reported rates of surgery only)
Kallchman 2007[30]	Non-comparative study
Kannus 1988[31]	Wrong population/study type of interest (study investigates people after acute ligament injury and investigates whether they develop osteoarthritis)
Kim 2020[32]	Wrong study type (cross-sectional study)
King 2015[33]	Wrong population (people without osteoarthritis)

Reference	Reason for exclusion
King 2016[34]	Wrong population (people without osteoarthritis)
Larsen 1980[35]	Wrong comparison (compares people being given surgery to people being told to lose weight before surgery is attempted)
Li 2019[36]	Non-comparative study
Magnusson 2015[37]	Results not stratified by amount of weight loss
Martin 2001[38]	Stratifies by BMI category. However, the amount of weight loss was the same category for both groups. Inadequate data adjustment for confounding factors.
Messier 2007[39]	Commentary only
Messier 2021[40]	Wrong prognostic variable (study weight regain rather than weight loss)
Messier 2021[41]	Duplicate reference (Messier 2021[40])
Moss 2016[42]	Non-comparative study
Munugoda 2020[43]	No usable outcomes (reported radiographic outcomes only)
Murphy 2016[44]	Non-comparative study
Nicholls 2012[46]	Non-comparative study
Nuesch 2011[47]	Non-comparative study
Paans 2013[48]	Non-comparative study
Pellegrini 2016[49]	Non-comparative study
Pi-Sunyer 1996[50]	Systematic review (methodology inadequate for inclusion in this review)
Pogacnik Murillo 2017[51]	Results not stratified by amount of weight loss
Ravikumar 2020[52]	Results not stratified by amount of weight loss
Reyes 2016[53]	Results not stratified by amount of weight loss
Richette 2011[54]	Results not stratified by amount of weight loss
Rishi 2018[56]	Results not stratified by amount of weight loss
Rosemann 2008[57]	Results not stratified by amount of weight loss
Sarumathy 2016[58]	Results not stratified by amount of weight loss
Serebrakian 2015[59]	No usable outcomes (reported radiographic parameters only)
Shin 2014[60]	Results not stratified by amount of weight loss
Tanamas 2013[61]	Wrong population (includes healthy participants)
Teichtahl 2015[62]	Wrong population (people without osteoarthritis)
Trofa 2014[63]	Wrong population (people after arthroplasty surgery)
Ustun 2019[64]	Results not stratified by amount of weight loss
Veronese 2018[65]	Non-comparative study
Vincent 2012[66]	Systematic review (methodology inadequate for inclusion in this review)
Visser 2014[67]	Results not stratified by amount of weight loss
White-O'Connor 1989[68]	No usable outcomes (studies dietary choices between people in different BMI categories)
Wluka 2013[69]	Systematic review (methodology inadequate for inclusion in this review)
Yoshimura 2012[70]	Non-comparative study
Zeng 2021[71]	Wrong prognostic variable (whether a person had bariatric surgery or not)

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.