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Review

Comparison of weight loss interventions in overweight and obese adults with knee osteoarthritis: A systematic review and network meta-analysis of randomized trials

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SUMMARY

Objective: To ascertain the comparative effectiveness of weight-loss strategies for osteoarthritis (OA) to develop rational treatment algorithms aimed at improving OA-related symptoms in overweight/obese individuals.
Design: Medline, Embase, CINAHL, Scopus, and Web of Science were searched from inception to June 2023 for observational studies and randomized trials. Network meta-analyses were performed using a frequentist approach. Effect sizes for pain and function were computed as standardized mean differences, while change in body weight was computed as mean differences.
Results: 13 RCTs on knee OA (KOA) (2800 participants) with 7 interventions: diet (D); exercise (E); diet and exercise (DE); pharmacological (L); psychological (P); psychological, diet, and exercise (PDE); and Mediterranean diets (M) were networked. For weight change (kg), all interventions significantly outperformed control comparators, with effect sizes ranging from −11.2 (95% CI, −16.0, −6.5 kg) for the most effective approach (PDE) to −4.7 (95% CI, −6.7, −2.7 kg) for the least effective approach (DE). In terms of pain (0–20 scale), only DE outperformed control comparators (−2.2, 95% CI: −4.1, −0.21), whereas PDE was not superior to control comparators (−3.9, 95% CI: −8.4, 0.5) in improving the pain. Regardless of the chosen intervention, prediction intervals from meta-regression analysis indicate that significant pain relief may be anticipated when patients achieve at least a weight reduction of 7%.
Conclusions: PDE and DE interventions may offer the most effective approach for weight loss, potentially leading to improvements in pain and physical function among overweight/obese individuals with KOA if they achieve more than 7% weight loss.
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Background

Osteoarthritis (OA), predominantly affecting the knee, hip, and spine joints, has a strong association with overweight and obesity. Obesity has long been touted as the most modifiable risk factor for OA, given the options to lose weight through diet, exercise, or surgery.[1] According to the Osteoarthritis Research Society International (OARSI) recommendations for knee OA (KOA), 13 different international guidelines suggest

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weight loss as a core treatment.[1] Every 1% weight loss is associated with a 3% reduced risk of hip replacement.[2] Nonetheless, it is still unclear which weight loss intervention is best for meaningful improvement of OA and OA-related symptoms in people with obesity. An unambiguous consensus about the optimal weight loss required for clinically meaningful improvement of OA symptoms does not exist. According to a prior meta-analysis, it is 5–10% [3]; however, a recent randomized controlled trial (RCT) suggests 10–20% may be required.[4]

This systematic review and network meta-analysis (NMA) sought to identify the most effective weight loss interventions or combinations of interventions for weight loss in people with symptomatic KOA and/or hip OA (HOA). A preliminary search of the literature has identified publications similar to this proposed review including the recent NMA by Panuzi et al.[5–7] The majority of the prior reviews only focused on exercise and/or diet interventions for weight loss for KOA. Our NMA adds to this previous work by covering a wider range of interventions, including pharmacological, physical, psychosocial, and surgical weight loss strategies, in addition to diet and exercise-based weight loss interventions for both KOA and HOA. We have also included longer follow-up periods, and included, more detailed analyses to help us identify the relationship between weight change, pain and physical activity, and indirectly infer a dose-response association.

Methods

We conducted a systematic review and NMA. We prospectively registered the protocol with PROSPERO (CRD42023430366) and reported the present manuscript in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA for NMA) statement.[8]

In this review, we have used the term 'exercise' as an umbrella term to include physical activity, which is used to refer to everyday exercise (e.g., walking or cycling to work) or general activities of daily living (e.g., housework), and therapeutic exercise which includes structured, planned, and repetitive activities undertaken for the improvement or maintenance of OA.

Search strategy

We searched five databases, MEDLINE (via OVID), Embase (via OVID), CINAHL, Scopus, and Web of Science, for published peer-reviewed literature from inception until June 2023. The protocol specified the inclusion of nine databases, which were reduced to five after consulting with an academic librarian. We used a predefined search strategy, developed from the literature and with the assistance of a University of Sydney Academic Librarian (Supplemental S1. Text). Conference proceedings or other published abstracts were included if data could be extracted for analysis. A manual search was also conducted to identify any missing studies.

Study selection

Eligibility criteria for studies were: (1) RCTs (minimum 3 months follow-up) or observational studies (minimum 1-year follow-up); (2) adults (≥18 years old) with KOA and/or HOA; (3) body mass index (BMI) of ≥25 kg/m^2; and (4) examining any weight loss intervention (e.g. physical activity or exercise, dietary, psychosocial, pharmacological or surgical), either alone or in combination; (5) published in English. The control comparators could include attention/non-attention group, usual diet, or a placebo (e.g. placebo medicine). Mixed population studies were eligible if data could be extracted for people with KOA/HOA. Exclusion criteria were studies that included participants with rheumatoid or other inflammatory arthritis; or targeted OA in other joints (e.g. hand, neck, or shoulder), and studies with < 20 participants. Detailed selection and exclusion criteria are provided in the protocol (Appendix 1).

Data extraction

Two reviewers (AS and AT) independently reviewed the titles and abstracts of retrieved studies for eligibility in Covidence [9] and removed duplicate records. Any disagreements were agreed by consensus, or with discussion with a third author (DJH or JLB). The primary outcome was weight change (kg). Secondary outcomes were pain, physical function, health-related quality of life (HRQoL), and the mandated core domain of adverse events, including mortality.[10] If data on multiple pain and physical function scales were available for a trial, we extracted data according to the hierarchy presented by Juhl et al. for pain and physical function outcomes.[11] For the trials that had more than one published study report, we selected the main report from each trial. For each study, we extracted data on study characteristics (number of participants, female ratio, number of participants who completed the study), comorbidities, length of follow-up, data on outcomes of interest, and adverse events.

Quality assessment and GRADE

The methodological quality of the included studies was assessed independently using the *Revised Cochrane Risk of Bias Tool for randomized trials*.[12] The overall risk of bias for each trial was considered low if the handling of four specific items (random sequence generation, allocation concealment, blinding of participants and personnel, and incomplete data) were adequately met (risk of bias considered low or unclear).[13] According to the registered protocol, we also assessed each trial for the risk of selective reporting. The overall quality of the evidence from the NMA was assessed using the CINEMA approach to Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) based on their published guidance.[14]

Statistical analysis

Data were extracted from the last follow-up timepoint reported where the study still respected the original study design, e.g., we did not extract data for longitudinal follow-up, open-label results, or similar that were reported in addition to the original design. Wherever available, we used estimates reported based on the intention-to-treat population. Continuous data were summarized as a mean difference for weight change (kg) and as standardized mean differences (SMDs) for symptomatic outcomes (from the initial to the longest follow-up) reported with 95% confidence interval (95% CIs).[10] When data were not directly reported in the article, estimates were derived from other available data where possible (e.g., 95% CIs, standard errors, or p-values). The pain data was converted to a 0–20 scale, and the data on physical function and HRQoL were converted to a 0–100 scale. The NMA was performed using the Frequentist framework in STATA, version 18, with the assistance of experienced biostatisticians (RC and VV).[15] Effect sizes as weighted mean difference (WMD) were computed for weight change (kg) and SMD for other core outcome set measures. Clinically, an effect size of < 0.2 is considered trivial, 0.2–0.5 as small, 0.5–0.8 as moderate and > 0.8 as large according to Cohen's quantified effect sizes.[16] Detailed descriptions of all statistical analyses are included in the supplementary data (S2. Text).

Results

A flow diagram showing the study selection is presented in Fig. 1. From a total of 3764 identified trials, 1892 duplicates were removed,

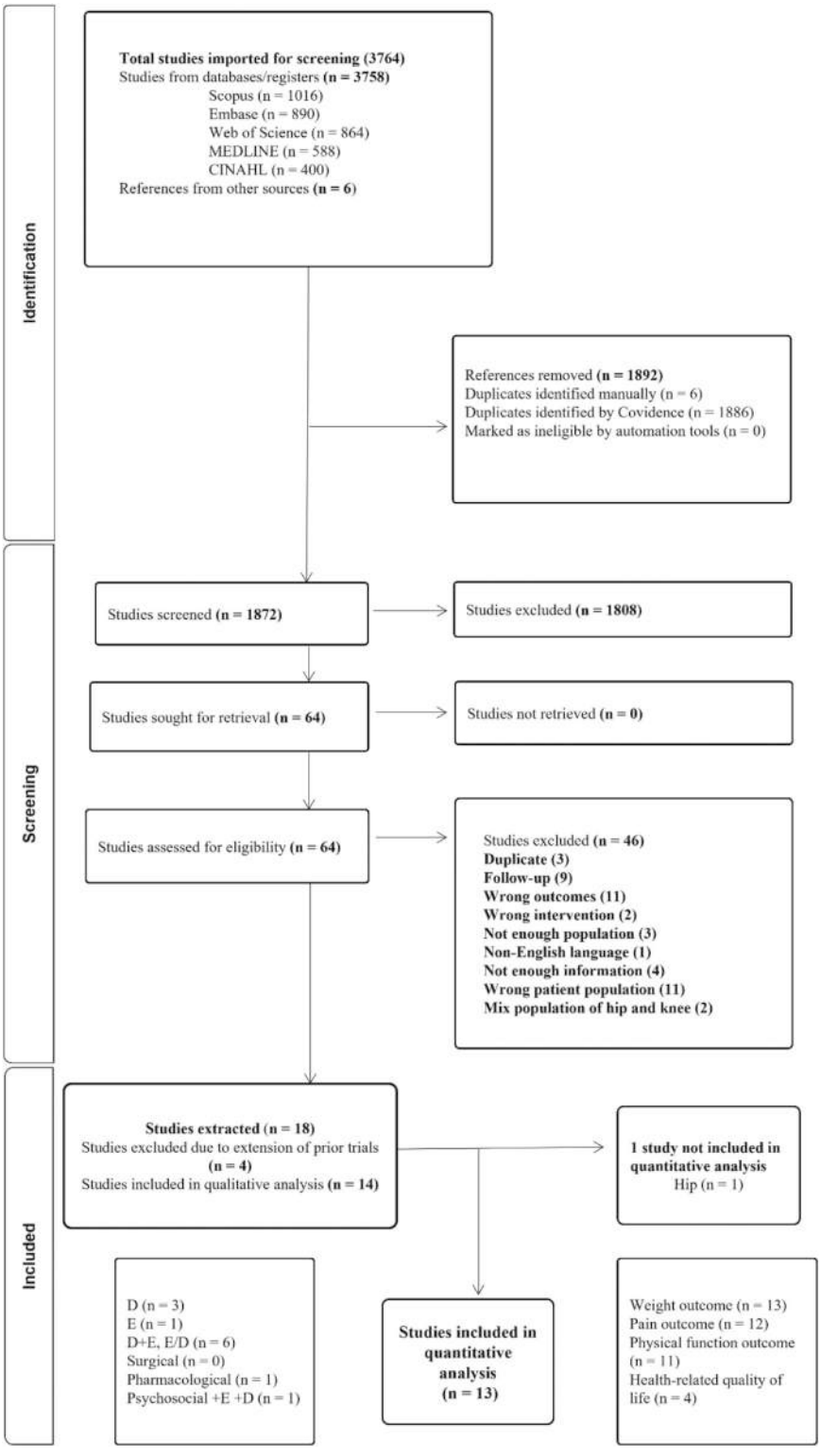

Fig. 1

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Prisma flow diagram. C: Control; D: Diet; E: Exercise; DE: Diet and exercise; L: Liraglutide; M: Mediterranean diet; P: Psychological; PDE: Psychological, diet, and exercise.

1808 trials were excluded at the initial abstract screening, and 64 full-length studies were assessed for eligibility. Of these, 50 studies, including all observational studies, were ultimately excluded. Of the 14 RCTs studies included, all 14 were included in the qualitative analysis (13 studies had KOA participants, and one study had HOA participants). All 13 KOA studies with 2865 enrolled participants [17–29] were included in the NMA. The single HOA study was excluded.[30] All 13 KOA studies reported weight change (kg), 12 reported pain outcomes, 11 reported physical function, and four provided HRQoL data. Eight studies were two-arm trials (57%), four (29%) were three-arm trials, and two studies (14%) were four-arm trials. Three trials were conducted in Denmark, five trials in the United States, and one each from Pakistan, Iran, Thailand, Australia, Italy, and Taiwan. The study length ranged between 3 and 24 months, and all trials were published between 2004 and 2022. The sample size varied between 21 and 289 participants, with most trials (57%) having more than 100 participants. The participants' mean age ranged between 53.8 and 69.7 years, their BMI was between 30.4 and 37.9 kg/m^2, and 74% were female.

A total of seven different interventions (i.e., nodes) with a control/placebo group (C) were identified: diet (D), exercise (E), Mediterranean diet (M), pharmacological (L), psychological (P), diet plus exercise (DE), and psychological plus diet plus exercise (PDE). Only one psychological intervention was identified, and that was pain-coping skills training. Although we identified five surgical intervention studies with an observational design; four did not fulfill the required minimum of 1-year follow-up,[31–34] and one did not meet the minimum number of participants.[35]

The characteristics of studies eligible for the NMA are summarized in Table I. The network diagrams for weight change, pain, and physical function are represented in Fig. 2, with the total number of studies evaluating each direct comparison directly proportional to the width of the lines and the node size representing the number of participants. The direct and indirect evidence for weight (WMD) and pain (SMD) is shown in Table II (Supplemental S3. Figures) with 95%CI.

Weight change

A total of 13 trials (2800 participants) with 8 nodes contributed to the analysis of weight change (kg) outcomes. All interventions were significantly more effective at reducing weight compared to the control comparators. When comparing individual interventions with the control group, PDE was highly significant for weight loss (−11.2, 95%CI: −16.0, −6.5 kg), followed by P (−9.3, 95%CI: −14.2,−4.5 kg), D (−4.9, 95%CI: −6.9, −2.9 kg), and DE (−4.7, 95%CI: −6.7, −2.7 kg), respectively. The M (−4.3, 95%CI: −8.9, 0.3 kg), L (−4.0, 95%CI: −9.1, 1.1 kg), and E (−0.4, 95%CI: −2.7, 1.9 kg) interventions were not statistically better than control comparators for weight loss. The comparisons between different interventions suggested that PDE was significantly more effective for weight loss compared to E (−10.8, 95%CI: −15.9, −5.7 kg), M (−7.1, 95%CI: −13.5, −0.6 kg), DE (−6.6, 95%CI: −11.3, −1.8 kg), and D (−6.3, 95%CI: −11.3, −1.3 kg), while P was more effective than E (−8.9, 95% CI: −14.1, −3.7 kg) (Table II).

Pain

A total of 12 trials (2744 participants) where seven nodes with a control group contributed to the comparative pain analyses. Only the DE intervention was statistically significant compared to the control (SMD: −2.2, 95%CI: −4.1, −0.2). Neither the PDE (SMD: −3.9, 95%CI: −8.4, 0.5), M (SMD: −1.8, 95%CI: −6.2, 2.6), P (SMD: −1.5, 95%CI: −5.9,2.9), D (SMD: −0.9, 95%CI: −2.9, 1.1), E (SMD: −0.4, 95%CI: −2.9, 2.1), nor L (SMD: −0.2, 95%CI: −5.2, 4.8) were statistically superior to control comparators in improving the pain. Among the different intervention comparisons, there were no statistically significant differences between interventions for improving pain (Table II and Supplemental S4. Table).

Physical function

A total of 11 trials (2664 participants) with seven nodes with a control group contributed to the physical function analysis. However, out of all the interventions, only PDE (SMD: −15.8, 95%CI: −22.2, −9.3) and DE (SMD: −3.2, 95%CI: −6.3, −0.2) were statistically different from the control. M (SMD: −5.7, 95%CI: −12.2, 0.7), P (SMD: −4.2, 95%CI: −10.6, 2.3), L (SMD: −3.0, 95%CI: −10.2, 4.2), D (SMD: −2.1, 95%CI: −4.9, 0.8), and E (SMD: 0.18, 95%CI: −3.5, 3.8) alone were not effective in improving physical function compared to control. Comparisons between different intervention groups suggested that PDE significantly improved the physical function compared to E (SMD: −15.9), D (SMD: −13.7), DE (SMD: −12.6), and M (SMD: −10.2) (Supplemental S4. Table).

HRQoL

A total of 4 trials (1589 participants) with 4 nodes contributed to the HRQoL analysis. None of the interventions were superior to the control (DE: SMD: 3.8 (95%CI: −1.7, 9.4), E: SMD: 1.3 (95%CI: −5.7, 8.3), and D: SMD: 1.1 (95%CI: −5.9, 8.1)) or to the other intervention (D vs E: SMD: 0.1, 95%CI: −6.2, 6.5) (Supplemental S4. Table).

Rankograms

According to the rankograms, the PDE intervention ranked best for weight loss with 61.2% probability compared to other interventions. For secondary outcomes, PDE ranked best for pain reduction with 32.7% probability and 84.8% probability for physical function improvement compared to other approaches. For HRQoL, the DE intervention ranked best with a 60.4% probability (Supplemental S5. Figures). The side-splitting approach manifested no significant evidence of inconsistency for weight change, pain, physical function, or HRQoL. The network forest plot did not show the presence of inconsistency among the studies for weight change ($\chi^2(9) = 7.18$, $p = 0.62$), pain ($\chi^2(8) = 0.93$, $p = 0.99$), physical function ($\chi^2(8) = 5.58$, $p = 0.68$), or HRQoL ($\chi^2(2) = 0.71$, $p = 0.70$) (Supplemental S6. Figures).

Safety and withdrawal due to adverse events

A total of 2800 participants were randomized in 13 trials, out of which 82.46% (n = 2309) completed the study. Only nine trials reported adverse events that resulted in a loss of follow-up. The highest withdrawals due to adverse events were in the L (12.5%, n = 10), C (1.7%, n = 13), DE (0.9%, n = 7), E (0.63%, n = 2), and D intervention (0.27%, n = 1). Few studies provided detailed reports of the adverse events. Those that did were primarily related to exercise in the E or DE group, such as falls from the treadmill, tripping, muscle strain, or other body injuries. The overall-mortality rate was 0.25%, with a total of seven deaths reported by four trials.

Risk of bias and credibility of evidence

Out of 13 studies, 12 studies had a high risk of bias, and one had a low risk of bias. Concerning the specific items of the risk of bias assessment tool, 85% of the included studies indicated a low risk of bias for random sequence generation, 62% for allocation concealment, 92% for incomplete data outcome, 8% for blinding of participants and personnel, 77% for blinding outcome assessment and 85% for selective reporting (Supplemental S7. Table).

Author	Acronym	Country	Intervention	Brief name (node)	Age (Mean)	Female (N)	Randomized participants	Analyzed participants	Participants completed the study	Joint	Comorbidities	Co-intervention	Time point (Weeks)	Outcomes of interest	Weight MD (95% CI)
Christensen 2015[17]	CAROT	Denmark	Usual care	C	61.7	51	64	64 (ITT)	52	Knee	-	-	68	Weight (kg) *KOOS pain	−8.23 (−10.9 to −6.36)
			Formula products diet	D	63.0	52	64	64 (ITT)	55			-		KOOS Function in daily living	−10.96 (−12.83 to −9.09)
			Exercise	E	62.9	52	64	64 (ITT)	52			-		SF−36 for mental and physical health OMERACT_OARSI response	−6.24 (−8.11 to −4.38)
Bliddal 2011[18]	-	Denmark	Conventional diet program	C	64.1	40	45	45 (ITT)	23	knee	-	-	52	*Weight (kg) *WOMAC pain	−3.60 (−5.22 to −1.98)
			Intensive diet	D	61.1	39	44	44 (ITT)	33			-		*WOMAC physical function	−10.90 (−12.52 to −9.28)
^Cannata 2021[30]	-	Italy	Normal diet	C	72	13	-	25	25	Hip	-	-	13	Weight (kg) OHS	−0.2 (−1.4 to 1.7)
			Fiber enriched diet	D	74	23	-	36	36			-		HOOS WOMAC questionnaire	−3.7 (−4.4 to −2.5)
Gudbergsen 2021[19]	-	Denmark	Placebo	C	59.3	49	76	76 (ITT)	63	Knee	-	-	52	Weight (kg) *KOOS pain	1.20 (−1.20 to 3.60)
			Liraglutide	L	59.2	52	80	80 (ITT)	66			-		KOOS function in daily living OMERACT-OARSI	−2.80 (−5.30 to −0.20)
Hsu 2021[20]	-	Taiwan	Diet	D	66	12	22	21	21	Knee	-	-	12	*Weight (kg) *WOMAC pain	−3.41 (−7.22 to 0.40)
			Exercise	E	64.2	13	22	21	21			-		*WOMAC physical function	−0.36 (−5.21 to 4.49)
			Diet+ exercise	DE	65.6	15	22	21	21			-			−3.50 (−8.02 to 1.02)
Messier 2022[21]	WE-CAN	US	Attention group	C	64.7	317	409	316	316	Knee	Arthritis in other joints	Pain medications	78	Weight (kg) WOMAC pain	−1.70 (−2.50 to −0.80)
			Formula product diet + exercise	DE	64.5	320	414	329	329		Diabetes CVD Hypertension	Pain medications		*WOMAC physical function SF−36 for mental and physical health	−7.70 (−8.70 to −6.70)
Messier 2004[23]	ADAPT	US	Healthy lifestyle	C	69	53	78	67	67	Knee	Arthritis in other joints Coronary heart disease	Cognitive-behavioral modification strategies	78	Weight (kg) WOMAC pain *WOMAC function score	−1.10 (−5.20 to 3.00)
			Caloric restriction diet	D	68	59	82	63	63		Hypertension Diabetes	Cognitive-behavioral modification strategies		Lateral and medial joint space	−4.61 (−8.84 to −0.38)
			Exercise	E	69	59	80	64	64			Cognitive-behavioral modification strategies			−3.46 (−7.69 to 0.77)
			Caloric restriction diet + Exercise	DE	69	56	76	58	58			Cognitive-behavioral modification strategies			−5.20 (−9.55 to −0.85)

(*continued on next page*)

Table I (*continued*)

Author	Acronym	Country	Intervention	Brief name (node)	Age (Mean)	Female (N)	Randomized participants	Analyzed participants	Participants completed the study	Joint	Comorbidities	Co-intervention	Time point (Weeks)	Outcomes of interest	Weight MD (95% CI)
Messier 2013[22]	IDEA	US	Exercise	E	66	108	150	134	134	Knee	Arthritis in other joints Coronary heart disease	Group counseling, social support, Incentives	78	Weight (kg) *WOMAC pain *WOMAC physical function score	−1.80 (−4.29 to 0.69)
			Formula product caloric deficit diet	D	66	108	152	129	129		Hypertension Diabetes	Group counseling, social support, Incentives		*SF−36 for mental and physical health	−8.90 (−11.28 to −6.52)
			Formula product caloric deficit diet + Exercise	DE	65	109	152	136	136			Group counseling, social support, Incentives			−10.60 (−12.98 to −8.22)
Miller 2006[24]	-	US	Weight stable	C	69.3	26	43	41	41	Knee	Angina Congestive heart failure Heart surgery	2-month supply of meal replacement products	26	*Weight (kg) *WOMAC pain *WOMAC physical function	1.40 (−3.64 to 6.44)
			Intensive weight loss	D	69.7	28	44	38	38		Hypertension Myocardial infarction Cancer Diabetes, Lung disorder Kidney disease Leg cramp Transient ischemic attack	Exercise, behavioral and educational session an			−8.30 (−13.59 to −3.01)
O'Brien 2018[25]	-	Australia	Usual care	C	60.2	35	60	60	60	Knee	-	Medication of knee pain	26	*Weight (kg) *WOMAC pain	−0.20 (−3.92 to 3.52)
			Telephone weight loss support with diet and exercise	DE	63	39	60	59	59			Medication of knee pain Telephone weight loss support		*WOMAC physical function *SF12v2 physical and mental components	−0.40 (−3.95 to 3.15)
Rafiq 2021[26]	-	Pakistan	Usual care	C	54.56	8	28	23	23	Knee	-	-	12	Weight (kg)	−0.26 (−4.28 to 3.76)
			Exercise	E	53.78	9	28	23	23			-			−1.65 (−4.96 to 1.66)
Sadeghi 2022[27]	-	Iran	Regular diet	C	57.98	37	43	42	42	Knee	-		12	*Weight (kg) *WOMAC pain	0.40 (−2.57 to 3.37)
			Low fat diet	D	55.98	40	43	43	43					*WOMAC physical function	−2.80 (−6.18 to 0.58)
			Mediterranean diet	M	59.1	37	43	40	40						−3.00 (−6.42 to 0.42)
Somers 2012[28]	-	US	Pain coping skills training+ behavior weight management with diet and exercise	PDE	57.47	57	62	47	47	Knee	-	-	104	*Weight (kg) *WOMAC pain *WOMAC physical function/disability	−7.00 (−14.41 to 0.41)
			Behavior weight management with diet and exercise	DE	58.27	47	59	40	40			-			−0.20 (−8.01 to 7.61)
			Pain coping skills training	P	58.13	40	60	39	39			-			−5.10 (−13.46 to 3.26)
			Usual care	C	57.94	40	51	37	37			-			4.00 (−5.10 to 13.10)

(*continued on next page*)

Table I (*continued*)

Author	Acronym	Country	Intervention	Brief name (node)	Age (Mean)	Female (N)	Randomized participants	Analyzed participants	Participants completed the study	Joint	Comorbidities	Co-intervention	Time point (Weeks)	Outcomes of interest	Weight MD (95% CI)
[#]Aree-Ue 2017[29]	Quasi-experimental Study	Thailand	OA-related information	C	67.08	34	40	36	36	knee	-	-	52	*Weight (kg) *VAS pain	2.50 (−0.43 to 5.43) −2.80 (−5.68 to 0.08)
			Exercise + weight management program	DE	68.11	34	40	38	38			-			

A negative sign with values indicates the decrement. ^This single hip OA study was not included in the qualitative evidence synthesis. [#]uses Asian BMI criteria for participants (23 kg/m^2 to 29.9 kg/m^2). *The estimates derived from available data. ITT: Intention to treat, C: Control; D: Diet; E: Exercise; DE: Diet and exercise; L: Liraglutide; M: Mediterranean diet; P: Psychological; PDE: Psychological, diet, and exercise; N: number; MD: Mean difference; 95% CI: 95% confidence interval; KOOS: knee injury and osteoarthritis outcome score; SF-36: 36-item short form health survey; OHS: Oxford hip score; HOOS: Hip disability and osteoarthritis outcome score; OARSI: Osteoarthritis research society international; WOMAC: Western Ontario and McMaster Universities Arthritis index; SF12v2: Short-form 12-item survey-version 2; VAS: Visual analog scale.

Table I

Characteristics of trials eligible studies for qualitative evidence synthesis.

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According to GRADE evaluation, certainty of evidence for weight was rated as high to very low (except for D vs M, DE vs M, and M vs P, evidence was rated low), moderate to very low for pain and physical function, and very low for HRQoL (primary outcomes in Table II and secondary outcomes in Supplemental S8. Table). Serious risk of bias was mainly related to the blinding of participants and personnel, unclear reporting of allocation concealment, random sequence, and/or imprecision.

Sensitivity and subgroup analyses

Sensitivity analysis including only studies with low risk of bias was not possible to conduct due to low number of studies (n = 1).[19] The planned subgroup analyses for the BMI > 35 kg/m^2 and age ≤59-year cohorts were also not possible to conduct since only four studies were included with these parameters. Likewise, only four studies reported comorbidities. However, subgroup analyses on the no-comorbidities and ≤35 BMI cohorts were performed and confirmed the primary analysis results by showing that the PDE intervention still ranked best for weight change, pain, and physical function. While the result of the subgroup analysis included people ≥60 years of age, it was inconsistent with the primary analysis as no study with PDE intervention was present for that cohort. Moreover, for that cohort, the D intervention ranked best for weight and physical function, and DE ranked best for pain.

The relationship between weight change and pain is shown in Fig. 3A and B. A clinically significant reduction in pain would be predicted (Adj R-squared=40.13%, β = 0.044, SE=0.015, and Adj R-squared=27.93%, β = 1.60, SE=0.53, respectively) if the magnitude of weight reduction was at least 7% or the intensity at least 0.20% within a 35-week duration, as calculated from an efficacy equation (upper prediction limit ≤0). Similarly, as shown in Fig. 3C and D our results suggested a substantial improvement in physical function when the magnitude of weight change or intensity of weight change were used as independent variables (Adj R-squared=41.55%, β = 0.041, SE=0.01 and Adj R-squared=25.71%, β = 1.44, SE=0.55, respectively). If the magnitude of weight reduction was at least 8.34% or the intensity of weight reduction was 0.26% per week, within a 32-week duration, it would predict a significant improvement in physical function.

Assessing the risk of publication bias

The visual representation of publication bias for no-comorbidities and ≤35 BMI cohorts was assessed by funnel plots (Supplemental S9. Figures). The Egger test suggested no publication bias, but the trim and fill analysis indicated the publication bias for ≤35 BMI.

Discussion

This NMA provides evidence-based estimates of the relative efficacy of widely used weight loss approaches for people with OA and their effect on pain, physical function, and HRQoL. Overall, our results supported previous evidence that weight loss is beneficial for improving symptoms in people with KOA. However, we did not identify any eligible observational studies or any relevant studies to examine the impact of weight loss on HOA, except for one study that was not part of the quantitative evidence synthesis.[30] We found that a combined intervention of psychological, diet, and exercise (PDE) resulted in the highest weight loss of 11.2 kg for people with KOA and ranked best with 61.2% probability but had a low confidence rating. With 19% probability, the psychological (P) intervention was the second most effective, resulting in a 9.3 kg weight loss. Notably,

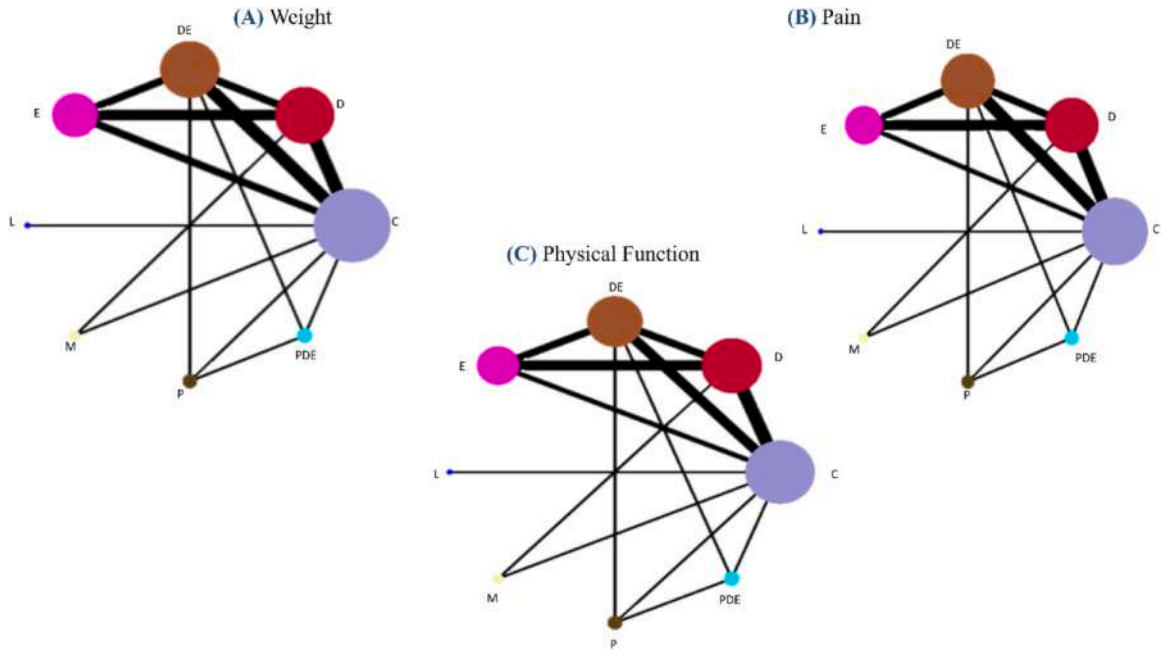

Fig. 2

Osteoarthritis and Cartilage

Network diagrams for weight change (trials:13, participants: 2800), pain (trials: 12, participants: 2744), and physical function (trials: 11, participants: 2664). The width of the lines presents the number of studies evaluating each direct comparison and the size of the node presents the population size allocated to each study. C: Control; D: Diet; E: Exercise; DE: Diet and exercise; L: Liraglutide; M: Mediterranean diet; P: Psychological; PDE: Psychological, diet, and exercise.

the weight loss differences between diet in combination with exercise (DE) and diet alone (D) were minimal (4.6 kg to 4.9 kg).

The credibility of the evidence was low for C vs PDE, C vs P, C vs D, and C vs DE. For pain reduction, PDE ranked best with a 32.7% probability, improved pain non-significantly by 3.9 units, and had a very low confidence rating. DE significantly reduced the pain by 2.2 units, but the confidence in the evidence was very low. For physical function, PDE was ranked best with 84.8% probability and improved the physical function by 15.8 units. The confidence rating for PDE was low. DE ranked second with 5.8% probability with low quality of evidence and improved the physical function by 3.2 units. The confidence rating for M vs C was very low. Although a previous meta-analysis [36] demonstrated that exercise can improve physical function, our analysis contradicted these findings and showed that exercise decreased physical function by 0.2 units, albeit with low-quality evidence. For HRQoL, DE ranked best with 60.4% probability and improved HRQoL non-significantly by 3.8 units, followed by E (1.3 units) and D (1.1 units) with very low confidence.

Another important finding of this NMA was the association between weight loss and significant improvement in pain and physical function, indicating that pain and physical function improvements can be predicted from weight loss. A previous meta-analysis [37] suggested that weight loss was not associated with pain reduction; however, those results were only based on four studies.

The meta-regression models allowed us to indirectly infer the dose-response associations that are applicable for clinical practice when recommending weight reduction to KOA patients. Based on the estimates, to experience a significant reduction in pain, people with KOA should aim to attain at least 7% weight loss (SMC=0.308), or approximately 0.20% weight loss per week (SMC=0.32), within a 35-week duration (Fig. 3A). Our findings fit with a previous meta-analysis that showed 5–10% weight loss was required to significantly improve disability, pain, and quality of life in KOA.[3] Similarly, we were able to predict the effect of weight reduction on improvements in physical function (Fig. 3C, D). Based on our estimates, people with KOA should aim to achieve at least 8.3% weight loss (SMC=0.34), or approximately 0.26% weight loss per week (SMC=0.37), within a 32-week duration to experience a significant improvement in physical function. Again, these findings are consistent with a previous meta-analysis,[37] which indicated a minimum of 7.5% weight loss was required to reduce disability significantly. Similarly, a recent NMA suggested that a 25% weight reduction was necessary to obtain a 50% improvement in physical function, pain, and joint stiffness, according to meta-regression analyses.[7]

Strengths and limitations

Overall, the results of this NMA support the use of weight loss approaches for adults above a healthy weight to improve knee pain and physical function in the clinical management of OA. However, it is important to consider the strengths and limitations of this study when interpreting the results. The strength of our systematic review includes a comprehensive literature search on five databases, that has identified seven weight loss approaches delivered over a minimum of three months. We have combined direct and indirect evidence through the application of NMA and meta-analysis methodology, risk of bias assessment, quality of evidence by the GRADE approach, subgroup analysis, meta-regression with a 95% prediction interval, and employed different approaches to identify inconsistencies and heterogeneity. Another strength is the

Comparison	Weight WMD (95% CI)			Pain SMD (95% CI)		
	Direct evidence	Network meta-analysis	Confidence rating	Direct Evidence	Network meta-analysis	Confidence rating
D vs E	−5.28 (−7.85 to −2.70)	4.54 (2.21 to 6.89)	Low[$]	−1.51 (−1.85 to −1.18)	0.47 (−1.88 to 2.82)	Very low[$#]
D vs M	−2.90 (−5.30 to −0.49)	0.68 (−3.89 to 5.26)	Very low[$#]	−1.79 (−2.86 to −0.71)	−0.89 (−5.30 to 3.52)	Very low[$#]
D vs PDE	_	−6.28 (−11.3 to −1.26)	Low[#]	_	−3.01 (−7.67 to 1.66)	Very low[$#]
D vs P	_	−4.38 (−9.46 to 0.70)	Very low[$#]	_	−0.57 (−5.23 to 4.09)	Very low[$#]
D vs L	_	0.96 (−4.54 to 6.45)	Low[$#]	_	0.69 (−4.59 to 5.98)	Low[$#]
E vs M		−3.85 (−8.78 to 1.08)	Low[$#]	_	−1.33 (−6.12 to 3.46)	Very low[$#]
E vs PDE	_	−10.80 (−15.92 to −5.68)	Low[$]	_	−3.44 (−8.25 to 1.36)	Very low[$]
E vs P	_	−8.90 (−14.09 to −3.72)	Low[$#]	_	−1.00 (−5.81 to 3.80)	Very low[$#]
E vs L	_	−3.56 (−9.17 to 2.05)	Moderate[$#]	_	0.27 (−5.18 to 5.72)	Low[$#]
DE vs E	−4.37 (−7.51 to −1.22)	4.24 (1.78 to 6.70)	Low[$]	−2.04 (−2.80 to −1.28)	1.69 (−0.79 to 4.16)	Very low[$]
DE vs D	−6.43(−9.04 to −3.82)	−0.316 (−2.62 to 1.99)	Low[$]	−2.21 (−2.79 to −1.62)	1.21 (−0.99 to 3.41)	Very low[$#]
DE vs M	_	0.37 (−4.49 to 5.23)	Very low[$#]	_	0.31 (−4.37 to 4.99)	Very low[$#]
DE vs PDE	−3.72 (−10.38 to 2.95)	−6.57 (−11.32 to −1.83)	Low[$#]	−2.75 (−5.38 to −0.12)	−1.79 (−6.21 to 2.64)	Very low[$#]
DE vs P	−2.48 (−8.19 to 3.22)	−4.67 (−9.48 to 0.13)	Very low[$#]	−1.52 (−2.17 to −0.88)	0.65 (−3.77 to 5.08)	Very low[$#]
DE vs L	_	0.66 (−4.84 to 6.15)	Moderate[$#]	_	1.88 (−3.42 to 7.18)	Low[$#]
C vs E	−3.85 (−6.54 to −1.16)	−0.42 (−2.73 to 1.89)	Low[$]	−1.20 (−1.74 to −0.66)	−0.42 (−2.89 to 2.05)	Very low[$#]
C vs D	−5.07 (−7.90 to −2.24)	−4.98 (−6.98 to −2.98)	Low[$]	−1.21 (−1.64 to −0.78)	−0.89 (−2.86 to 1.07)	Very low[$#]
C vs DE	−1.84 (−4.06 to 0.39)	−4.69 (−6.67 to −2.67)	Low[$]	−2.19(−4.21 to −0.18)	−2.15 (−4.08 to −0.21)	Very low[$#]
C vs M	−1.19 (−4.51 to 2.14)	−4.29 (−8.87 to 0.30)	Low[#]	−1.51 (−3.07 to 0.06)	−1.79 (−6.23 to 2.64)	Very low[$#]
C vs PDE	−1.83 (−12.59 to 8.93)	−11.24 (−16.00 to −6.48)	Low[$]	−2.60 (−5.56 to 0.36)	−3.92 (−8.36 to 0.51)	Very low[$]
C vs P	−0.73 (−9.65 to 8.18)	−9.34 (−14.16 to −4.52)	Low[$#]	−1.39 (−2.11 to −0.67)	−1.48 (−5.92 to 2.95)	Very low[$#]
C vs L	−0.78 (−4.70 to 3.14)	−4.00 (−9.13 to 1.13)	High[#]	0.01 (−0.52 to 0.54)	−0.2 (−5.19 to 4.79)	Moderate[#]
M vs PDE	_	−7.05 (−13.51 to −0.59)	Low[$#]	_	−2.37 (−7.98 to 3.23)	Very low[$#]
M vs P	_	−5.15 (−11.65 to 1.35)	Very low[$#]	_	0.07 (−5.54 to 5.67)	Very low[$#]
M vs L	_	0.18 (−6.59 to 6.96)	Low[$#]	_	1.33 (−4.74 to 7.39)	Low[$#]
PDE vs P	−6.15 (−11.59 to −0.72)	1.57 (−3.75 to 6.90)	Very low[$#]	−2.88 (−5.27 to −0.49)	1.87 (−2.83 to 6.57)	Very low[$#]
PDE vs L	_	6.72 (−0.17 to 13.62)	Moderate[$#]	_	2.80 (−3.32 to 8.93)	Low[$#]
P vs L	_	4.92 (−2.01 to 11.85)	Low[$#]	_	1.09 (−4.97 to 7.17)	Low[$#]

A negative sign with value indicates the reduction. $: within study bias, #: imprecision. WMD: Weighted mean difference; SMD: Standardized mean difference; 95% CI: 95% confidence interval; C: Control; D: Diet; E: Exercise; DE: Diet and exercise; L: Liraglutide; M: Mediterranean diet; P: psychological; PDE: Psychological, diet, and exercise.

Table II

Osteoarthritis and Cartilage

Direct and network meta-analysis evidence and quality ratings for comparison of weight loss interventions effect on weight and pain.

stringent inclusion criteria for follow-up (3 months for RCTs and 1-year for observational studies) that are paramount in enhancing clinical trial validity and quality. However, due to our strict inclusion criteria for follow-up, we excluded four bariatric surgery observational studies with a follow-up of < 1 year. Therefore, we were unable to comment on the effectiveness of surgical weight loss interventions for OA. Furthermore, data at multiple time points was not extracted, limiting our ability to determine at which time point the weight and pain reduction were highest. Another major constraint was that the supposedly most effective intervention (PDE) was supported by only one trial with imprecise estimates. The lack of classification of diets into different categories (e.g., high-intensity diet, low-calorie diet), limited the interpretation of our results to determine which specific dietary interventions would work better. We only report trials related to KOA, and our results may not be generalizable to other joints. Only four studies reported HRQoL outcomes, which precluded us from reaching a meaningful conclusion on this outcome. In addition, there was inadequate reporting of ethnicity and adverse event data, which halted the quantitative analysis of those outcomes. Moreover, meta-regression analysis provided us with dose-response associations between weight change and pain or physical function, but this type of analysis based on aggregate data has a risk of methodological pitfalls (e.g., ecological fallacy), which can impact the found associations.[38] Finally, the authors are also aware of additional GLP-1 clinical trials nearing completion that are not included in the current review (e.g., the STEP 9 Trial [39]); however, given the rapidly changing evidence in this space, we recommend a future systematic review of this topic.

Clinical implications and future research

Existing clinical practice guidelines consistently recommend weight loss for the management of OA in people above a healthy weight. However, guidelines are typically vague on the relative effectiveness of the various weight loss interventions that should be recommended to OA patients to optimize health outcomes and lack reliable information to assist individuals with OA and health professionals to select the most effective weight loss approach. This systematic review bridges an important research gap by ascertaining the comparative effectiveness of a wide variety of weight loss interventions with quality evidence. Our study shows that the integrated delivery of a psychological (e.g., pain coping skills training), diet and exercise approach (PDE) provides better outcomes than exercise, diet only, or diet and exercise combined. Findings from our study should be considered when developing or updating KOA clinical practice guidelines, particularly the support for PDE intervention in overweight/obese people. By delineating the relationship between weight loss and improvements in pain and physical function, we sought to provide health professionals with specific weight loss targets to improve pain and function in OA patients. Future research should focus on conducting high-quality RCTs testing the effectiveness of PDE intervention, particularly in people with KOA and/or HOA, to provide the quality evidence needed to develop a personalized approach for managing KOA and HOA in overweight/obese individuals. Observational studies of surgical interventions with a follow-up of > 1 year may also be warranted. The results of this systematic review could be beneficial to people who have OA in different joints or with different types of arthritis where weight loss

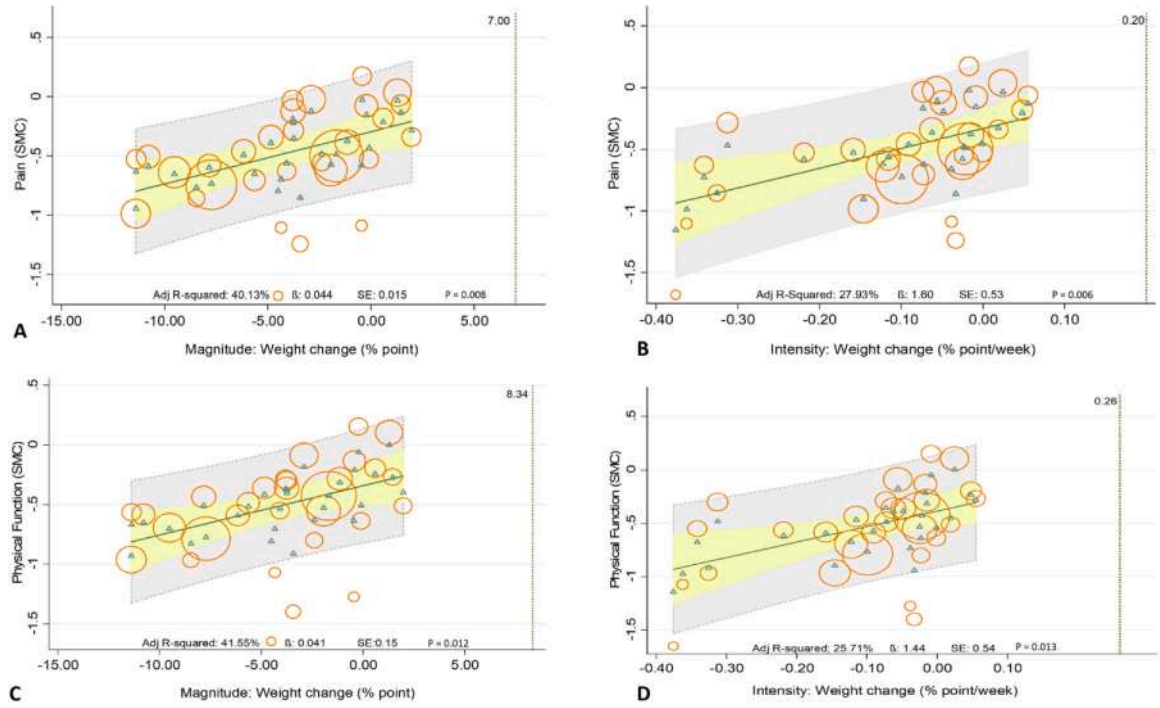

Fig. 3 Osteoarthritis and Cartilage

Weighted random effects meta-regression analysis: Standardized mean change (SMC) of pain (A, B), and physical function (C, D) of each study at different intensities (B, D); a decrement in SMC represents a clinical improvement in pain and physical function. The linear prediction line is shown with a 95% prediction interval and represents the variance projected by weight change magnitude and intensity. The colored triangle represents the prediction, including random effects, and the dark orange colored circle represents the SMC- an area of each circle is inversely proportional to the random effects variance. A dotted vertical line is shown with its corresponding values representing the point where the 95% prediction interval indicates a clinically significant improvement.

plays an important role (e.g., rheumatoid arthritis);[40,41] however, more work is needed to ascertain the effects in these populations.

Conclusion

The results from this NMA suggest that the combined interventions of psychological, diet, and exercise (PDE) and diet and exercise (DE) may be the most effective approaches for substantial weight loss, leading to pain reduction, and improved physical function in KOA individuals. Meanwhile, psychological (P) and diet (D) interventions are effective for only weight loss. The result of that study supports the practice of recommending PDE or DE for a significant weight reduction to improve pain and physical function, at least 7% weight loss within 35 weeks for pain reduction and 8.34% weight loss within 32 weeks for physical function improvement.

Ethical approval

Ethical approvals are not required for this systematic review.

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Author contributions

Arashi Shahid: Conception and design, acquisition of data, data analysis and interpretation, drafting and final approval of the article. **Aricia Jieqi Thirumaran:** Acquisition of data, data preparation, and review and final approval of the article. **Robin Christensen:** Conception and design, data analysis and interpretation, critical revision, and final approval of the article. **Venkatesha Venkatesha:** Data preparation, data analysis and interpretation, final approval of the article. **Marius Henriksen:** Conception and design, interpretation, critical review and final approval of the article. **Jocelyn L Bowden:** Conception and design, drafting and critical revision of the article, final approval of the article. **David J. Hunter:** Conception and design, critical revision of the article, final approval of the article.

Declaration of competing interest

AS declares no competing interests.

AJT declares no competing interests.

RC declares no financial conflicts of interest; he is the statistical editor of 'Osteoarthritis and Cartilage' and 'Acta Orthopaedica'.

VV declares no competing interests.

MH provides consulting advice on scientific advisory boards for Thuasne and Contura International.

JLB declares no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2024.08.012.

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