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Do imaging findings modify the effect of non-surgical treatment in patients with knee and hip osteoarthritis? A systematic literature review

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ABSTRACT

Objectives To review the available evidence on diagnostic imaging findings in knee and hip osteoarthritis (OA) as treatment effect modifiers in non-surgical OA interventions.

Methods MEDLINE, Embase and The Cochrane Central Register of Controlled Trials were searched from the earliest records published to 22 March 2022. Studies in knee and hip OA reporting subgroup analyses in randomised controlled trials with imaging findings as potential treatment effect modifiers were included. Studies were critically appraised using the Cochrane risk of bias tool and a subgroup analysis quality assessment.

Results Of 10 014 titles and abstracts screened, eight studies met the inclusion criteria, six on knee OA and two on hip OA. The studies investigated effect modifiers in exercise therapy, intra-articular injections and unloading shoes. Imaging findings assessed as potential treatment effect modifiers were radiographic OA severity, hip effusion (ultrasound), bone marrow lesions and meniscal pathology (MRI). Two studies fulfilled the methodological quality criteria for assessing effect modification. One reported that radiographic knee OA severity modified the effect of unloading shoes on walking pain. Those with more severe radiographic knee OA had a greater response to shoe inserts. One reported no interaction between radiographic OA severity or joint effusion and the effect of intraarticular injections of corticosteroid or hyaluronic acid in hip OA, indicating no difference in response in people with greater hip joint effusion or radiographic OA severity compared with those with less severe joint disease.

Conclusion Overall, methodological limitations and very few studies do not permit conclusions on diagnostic imaging findings as effect modifiers in non-surgical interventions in knee and hip OA.
Radiographic severity of knee OA potentially modifies the effect of unloading shoes.

PROSPERO registration number CRD42020181934.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The conduct and reporting of the review were guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 statement ensuring transparency in the methodology.
⇒ We performed a rigorous risk of bias assessment and methodological quality appraisal.
⇒ By only assessing studies on guideline-recommended non-surgical interventions, findings may not apply to all clinical situations.

INTRODUCTION

Clinical guidelines universally recommend patient education and exercise therapy as first-line treatments for knee and hip osteoarthritis (OA)[1–3] complemented by weight loss, non-steroidal anti-inflammatory drugs, corticosteroids or hyaluronic acid injections, and several adjunctive medications and interventions.[1 3] The common finding of relatively small treatment effects for many interventions has nourished the belief that subgroups showing larger effects may be identified in more homogenous groups of patients.[4–6] This belief has driven the interest in identifying subgroups of patients likely to respond better to specific interventions or respond poorly to an intervention where other approaches may be more efficacious.[7]

A well-recognised method for identifying clinically relevant subgroups in a patient population is to analyse treatment effect modifiers using randomised controlled trial (RCT) data. Effect modifiers (also known as moderators) are patient characteristics, that is, sociodemographic, clinical or other features, that interact with the treatment to influence clinical outcomes.[8] They are different from prognostic factors or predictors, which identify patients with different outcomes regardless of the intervention.[9] Thus, prognostic factors or predictors do not provide information about which patients will likely respond best to specific interventions.

Diagnostic imaging can detect a range of structural changes[10] that may have a bearing on function, pain, and disease progression

in knee and hip OA.[11–13] Likewise, diagnostic imaging findings may be potential treatment effect modifiers, either individually or as combined findings. Although the evidence on imaging findings as predictors or prognostic factors in knee and hip OA is relatively comprehensive, little is known about these findings as potential treatment effect modifiers.[14]

To improve the targeting of non-surgical interventions and inform future research into treatment effect modification, we aimed to systematically review of the literature on diagnostic imaging findings as modifiers of patient-reported outcome or function after non-surgical interventions in knee and hip OA.

The specific objectives were to (1) summarise the evidence on diagnostic imaging findings that modify the effect of non-surgical interventions for knee and hip OA and (2) determine the magnitude of effect modification reported for the individual imaging findings and interventions.

METHODS

The protocol for this systematic review was registered in the PROSPERO database: International prospective register of systematic reviews (CRD42020181934). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement[15] was used to guide the conduct and reporting of the study.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Database search strategy

The literature search was performed with no restrictions on publication type or language within the following databases: MEDLINE and Embase (via OVID) and The Cochrane Central Register of Controlled Trials, from the earliest records published to 19 March 2021, and updated on 22 March 2022. Search terms covered the following domains: knee OA, hip OA and diagnostic imaging (radiography, ultrasound, MRI including MRI arthrography (MRIa), CT). Search terms and database-specific variations and synonyms were used as keywords and Medical Subject Headings. Database-specific filters for RCTs were used in MEDLINE and EMBASE[16] (online supplemental file 1 for the complete search strategy). Reference and citation tracking of included articles and related reviews within the topic were performed to identify further studies.

Eligibility criteria

To be included, studies had to be RCTs and meet the following criteria:

1. Include people aged >18 years with hip/knee pain suspected or confirmed to be caused by OA (radiographic, clinical criteria, or self-reported).
2. Include non-surgical interventions strongly or conditionally recommended by Osteoarthritis Research Society International (OARSI) guidelines[2] and compare with either another OARSI recommended non-surgical intervention, placebo, or no treatment.
3. Include baseline diagnostic imaging findings as potential effect modifiers, for example, structural, or inflammatory findings on radiographs, CT, MRI/MRIa or diagnostic ultrasound. As an exception for baseline assessment, imaging findings could be retrieved from radiographs from the previous 12 months.
4. Report the outcome stratified by imaging finding(s) or report an interaction test between treatment and the imaging finding(s). The outcome had to be patient-reported outcome measures or functional measures collected via tests, that is, excluding imaging findings and biochemical markers.

Studies of patients with hip/knee pain of other specific pathological origins (eg, fracture, avascular necrosis, tumour, infection) or prior knee or hip arthroplasty and studies that were not available in English or full text (eg, conference abstracts) were excluded.

Study selection

Records returned from the search were screened using a two-stage process. One reviewer (SC) screened titles and abstracts against the eligibility criteria in the first stage. In the second screening stage, full-text versions of the potentially relevant studies were independently screened by two reviewers (SC/JLK/BA). When necessary, discrepancies were resolved through discussion.

Reasons for exclusion of full-text articles were recorded. All references identified in the database search were managed using Endnote X9 (Clarivate Analytics, Philadelphia, USA) and Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Deduplication and data extraction were conducted in Covidence.[17]

Data extraction

Relevant data were extracted independently by two reviewers (SC/JoshuaH) using a standardised form including clinical settings, population (knee or hip OA), age, diagnostic criteria for OA, intervention(s), comparator, outcome(s), follow-up time points and imaging findings(s) assessed as effect modifier(s). Data on potential treatment effect modifiers and associated analysis of treatment effect modification were also extracted. If the study was a secondary analysis from an RCT, the primary study article was consulted to get further information if necessary. Two reviewers completed data extraction independently (SC, JoshuaH). In cases of disagreement, a joint review of the original article was performed until consensus was reached, with a third reviewer (BA) resolving questions of doubt and disagreements if necessary.

Critical appraisal

The critical appraisal was performed by two of the authors independently (SC, JoshuaH) and the results discussed

during a joint review of the original article. The critical appraisal was performed in two steps. First, the revised Cochrane risk-of-bias tool for randomised trials (RoB 2)[18] was used to evaluate the design and conduct of the RCT. We used a 'conservative summary risk of bias judgement' based on the lowest rating for any individual domain. Second, a methodological quality appraisal for assessing effect modification was carried out using the criteria suggested by Pincus *et al*.[19] The assessment was based on the three criteria:

1. *Were effect modifiers measured prior to randomisation?* We modified this to include all assessor-blinded baseline assessments of the imaging finding(s) since there is no risk of the findings being influenced by the tested intervention by this modification.
2. *Was the quality of measurement of the effect modifiers (imaging findings) adequate (reliable and valid)?*
3. *Was there a relevant subgroup analysis? (Identification of treatment effect modifiers should be based on statistical tests of interactions).*

The methodological quality criteria for the effect modifier analysis were fulfilled if a study met all three criteria.

Data synthesis

Results on treatment effect modification (eg, mean difference and interaction term) are exclusively reported only from the studies that had a risk of bias of 'low' or 'some concerns', excluding studies with a high risk of bias. Moreover, all three methodological quality criteria for assessing effect modification had to be fulfilled.

Due to the methodological quality and heterogeneity between the included trials in terms of imaging findings assessed, categorisation of potential effect modifiers, interventions and outcomes, it was impossible to perform a meta-analysis, and the results are presented descriptively.

RESULTS

Search results and study selection

The search identified 14 399 papers. No additional studies were identified through previous reviews and citation tracking of included articles. The study selection process

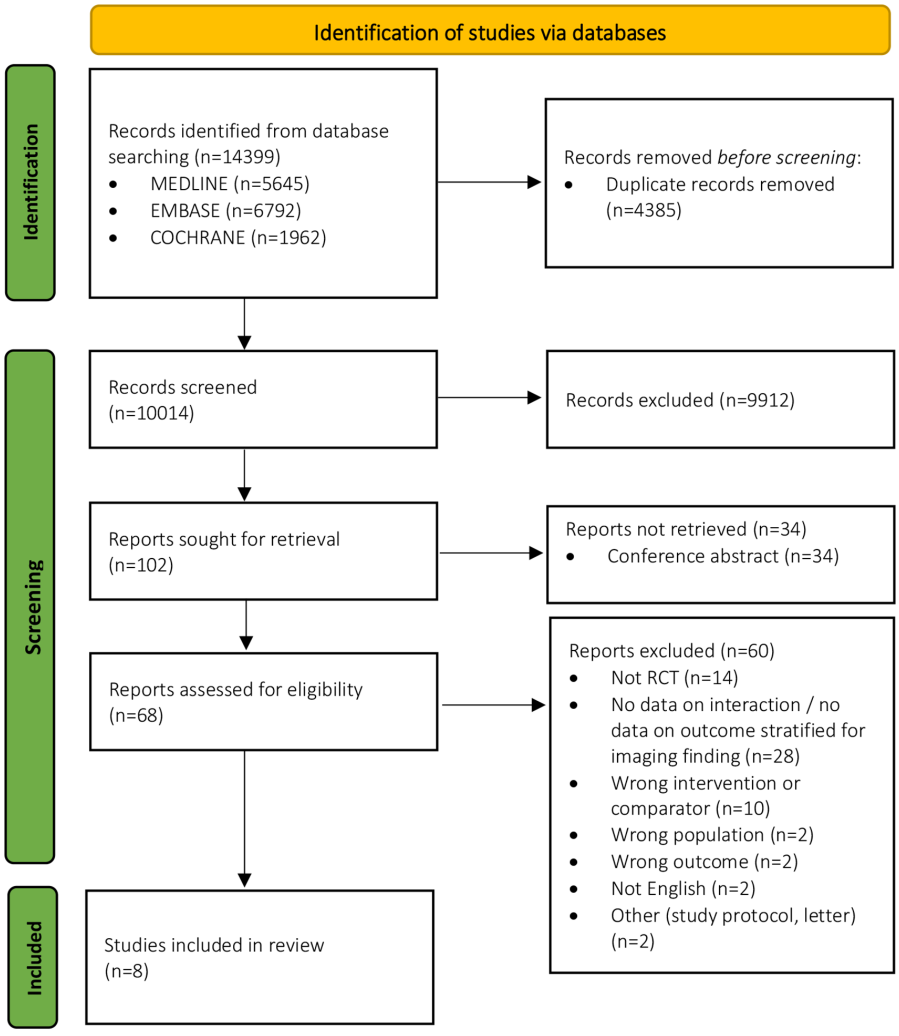

Figure 1 The study selection process. RCT, randomised controlled trial.

is presented in figure 1. After removing duplicates, 10 014 titles and abstracts were screened, and 102 records were deemed relevant for full-text screening. After the full-text screening, eight studies, six studies on knee OA[20–25] and two on hip OA,[26 27] met the eligibility criteria for this review (table 1).

Study characteristics

Study samples were recruited from communities,[23 24] primary healthcare[27] and secondary healthcare[20–22 25 26] settings. The number of participants varied from 35 to 203, and the mean age ranged from 60.1 to 72.1 years. Two studies had subgroup analysis as a primary objective,[20 23] and in six studies, the subgroup analysis was applied post hoc.[21 22 24–27] The potential effect modifiers were radiographic OA severity in seven studies.[21–27] Other potential effect modifiers reported were joint effusion assessed using ultrasound,[26] bone marrow lesions on MRI[20 23] and meniscal pathology on MRI[23] (see table 1 for details). The interventions investigated were exercise therapy,[20 23 27] intra-articular hyaluronic acid injection,[21 22 25 26] intra-articular corticoid steroid injection (IACS)[26] and unloading shoes.[24]

Critical appraisal

Table 2 lists the risk of bias for each study, and table 3 the methodological quality of effect modifier analyses. One study had a low risk of bias,[24] three studies had some concerns[25–27] and four studies had a high risk of bias.[20–23] Two studies, one on knee OA[24] and one on hip OA,[26] fulfilled all three methodological quality criteria of the effect modifier analysis. Of these, one had a low risk of bias,[24] and one had a risk of bias with some concerns.[26] The remaining six studies[20–23 25 27] did not fulfil the methodological quality criteria of the effect modifier analysis, all due to the lack of an interaction test between effect modifiers and treatment.

Treatment effect modifiers

The study on knee OA[24] that fulfilled all three quality criteria for assessing effect modification included 164 participants and found that participants with moderate to severe radiographic knee OA (Kellgren-Lawrence grade (KL) 3–4) had additional symptomatic benefits of wearing unloading shoes compared with those with mild OA (KL 2). The outcome was walking pain (Numeric Rating Scale 0–10) assessed at 6 months. People with KL grade 2 responded more favourably to the conventional walking shoes (control intervention). The difference in adjusted mean change (unloading shoes – conventional shoes) in walking pain were −1.64 (95% CI: −3.07 to −0.21) for KL 2, 0.98 (−0.44 to 2.39) for KL 3 and 0.64 (−0.64 to 1.93) for KL 4 (interaction term p=0.02).

The study of hip OA[26] included 101 patients and compared the effect of IACS, intra-articular hyaluronic acid injections and isotonic saline (control group) over three follow-up time points: 14 days, 28 days and 92 days. The study reported the average effect size in the subgroups and found no interaction between intra-articular hip effusion (absent/present), or KL dichotomised (1–2/3–4) and the average effect on walking pain (registered on a 100 mm visual analogue scale) in any of the interventions.

DISCUSSION

In this systematic review of subgroup analyses from RCTs, we included results from eight RCTs where diagnostic imaging findings as treatment effect modifiers for non-surgical interventions in knee and hip OA was assessed. Only two studies, one on knee OA[24] and one on hip OA,[26] fulfilled the methodological quality criteria for assessing effect modification, highlighting analysis limitations that are frequent in subgroup analyses in RCTs.[28 29] From these two studies, it appears that those with more severe radiographic knee OA have a greater response to shoe inserts, while there was no difference in response to IACS or hyaluronic acid injections in people with greater hip joint effusion or radiographic OA severity compared with those with less severe joint disease.

To clinicians, this finding could indicate it is pointless giving shoe inserts to people with mild radiographic knee OA but worthwhile in more severe radiographic knee OA. In hip OA, the severity of imaging findings should not influence whether to give someone an injection. However, even when treatment effect modifiers are investigated in high-quality randomised trials, they are still prone to spurious findings.[30] They should be interpreted with caution, and this systematic review finds the evidence is too limited to inform questions on imaging findings as treatment effect modifiers. Hence, the use of imaging findings for guiding treatment decisions in recommended non-surgical knee and hip OA interventions remains to be explored.

For several years, investigating diagnostic imaging findings as treatment effect modifiers has been a research agenda in OA.[14] The belief that diagnostic imaging findings in OA may identify subgroups showing different effects on specific treatments has driven this interest. One example is the belief that therapies targeting inflammation better affect patients with signs of inflammation, for example, effusion/synovitis visualised with MRI or ultrasound. However, this study's results revealed that there is currently no evidence to support this theory. Another belief exposed in the literature is an expectation of structural OA severity to modify treatment effects. While radiographic OA severity was investigated in seven of the eight included studies in the current review, only one high-quality study reported OA severity as an effect modifier (to unloading shoes). It is, moreover, essential to acknowledge that radiographic OA severity and patient symptom severity do not correlate well.[31] Therefore, the diagnosis of OA is clinical,[32] and radiographs provide little value in addition to the clinical assessment in primary care.[14 33] Currently, no evidence supports using imaging to guide non-surgical treatment decisions.

We included several non-surgical treatment modalities and a variety of diagnostic imaging findings as potential

Table 1 Individual study characteristics in the eight included RCT studies

Study	Clinical setting	Country	Intervention and control groups and number of participants	Participants mean age in the group(s), years (SD)	OA criteria for inclusion	Primary outcome(s)	Follow-up time points	Imaging feature assessed as effect modifier
Hip								
Teirlinck *et al* 2016[27]	Primary care (physiotherapy and general practices)	The Netherlands	1. Exercise therapy + usual care (GP), n=101 2. Usual care (GP), n=102	1. 64 (8.5) 2. 67 (9.6)	ACR	HOOS pain and function	6 weeks, 3, 6, 9, 12 months	Radiographic OA severity (KL dichotomised 0–1 or ≥2)
Qvistgaard *et al*[26] 2006	Secondary care (rheumatology outpatient clinic)	Denmark	1. HA injection, n=33 2. IACS, n=32 3. Saline injection, n=36	1. 65 (14) 2. 69 (9) 3. 64 (11)	ACR	Pain on walking (VAS)	14, 28, 90 days	1. Radiographic OA severity 2. (KL dichotomised 1–2 or ≥3). 3. Effusion (US) present/ absent.
Knee								
Beckwée 2017[20]	Secondary care (orthopaedic outpatient clinic)	Belgium	1. Strength training, n=17 2. Walking training, n=18	1. 63.7 (8.1) 2. 60.1 (9.5)	ACR	ICOAP The patient's global perceived effect	18 weeks	Bone marrow lesions dichotomised present/ absent (MRI)
Henderson *et al* 1994[21]	Secondary care (rheumatology outpatient clinics)	England	1. HA injection, n=45 2. Saline injection, n=46	1. Early OA: 63.9 (1.9) Advanced OA: 72.1 (1.7) 2. Early OA: 60.0 (1.9) Advanced OA: 3. 67.0 (1.7)	Knee pain and KL >0	Pain (VAS) in the morning, evening, climbing stairs, rising from chair and nominated activity	1–2–3–4–5 weeks, 1–3–5 months	Radiographic OA severity (KL dichotomised 1–2 or ≥3)
Kawasaki *et al* 2009[22]	Secondary care (no information on departments)	Japan	1. HA injection, n=42 2. Exercise therapy, n=45	1. 69.5 (8.4) 2. 71.2 (7.1)	ACR	Pain (VAS) JKOM OMERACT–OARSI response	24 weeks	Radiographic OA severity (JSW dichotomised (<3.0 mm, ≥3.0 mm))
Kudo *et al*[23] 2013	Secondary care (orthopaedic outpatient clinic)	Japan	1. Group exercise, n=81 2. Home exercise, n=122	1. 63.8 (5.9) 2. 65.6 (5.8)	Knee pain and KL >0	Normalised WOMAC	3 months	1. Radiographic OA severity (KL dichotomised 1–2 or ≥3) 2. Meniscal pathology dichotomised into Mink grade 0–2 or grade 3 (MRI) 3. Bone marrow lesions dichotomised present/ absent (MRI)

Continued

Table 1 Continued

Study	Clinical setting	Country	Intervention and control groups and number of participants	Participants mean age in the group(s), years (SD)	OA criteria for inclusion	Primary outcome(s)	Follow-up time points	Imaging feature assessed as effect modifier
Paterson *et al* 2018[24]	Department of Physiotherapy, the University of Melbourne	Australia	1. Unloading shoes, n=83 2. Walking shoes, n=81	1. 65.2 (6.9) 2. 63.3 (7.9)	Knee pain and KL >1	Average knee pain on walking over the previous week (NRS)	6 months	Radiographic OA severity (three groups) KL 2, KL 3, KL 4
Huang and Tsai 2021[25]	Medical University Hospital	China	1. CHAP-HA single-injection, n=71 2. Linear HA three-injection, n=69	1. 56.6±12.6 2. 56.0±9.7	Knee pain and KL 2 or 3	VAS pain at 26 weeks	4–12–26–39–52 weeks	Radiographic OA severity (KL 2 or 3)

Normalised WOMAC = (raw score out of 96) × 100/96.
ACR, American College of Rheumatology criteria for hip OA; GP, general practice; HA, hyaluronic acid; HHS, Harris Hip Score; IACS, intra-articular corticosteroid injection; ICOAP, The intermittent and Constant Osteoarthritis Pain Questionnaire; JKOM, The Japanese Knee Osteoarthritis Measure; JSW, joint space width; KL, Kellgren-Lawrence grade; NRS, Numeric Rating Scale; OARSI, Osteoarthritis Research Society International ; OMERACT, Outcome Measures in Reumatology; RCT, randomised controlled trial; US, ultrasound imaging; VAS, visual analogue scale.

Table 2 Risk of bias in the randomised controlled trials

Study	Risk of bias in the five domains 1	2	3	4	5	Summary
Hip						
Teirlinck *et al* 2016[27]	+	+	+	?	+	Some concerns
Qvistgaard *et al* 2006[26]	+	+	?	+	+	Some concerns
Knee						
Beckwée *et al* 2017[20]	+	?	+	–	+	High
Henderson 1994[21]	+	–	–	+	?	High
Kawasaki *et al* 2009[22]	+	+	–	–	?	High
Kudo *et al* 2013[23]	?	–	?	–	?	High
Paterson *et al* 2018[24]	+	+	+	+	?	Low
Huang and Tsai 2021[25]	+	+	+	+	?	Some concerns

The five domains in Revised Cochrane risk-of-bias tool for randomised trials.
1. Randomisation process (allocation sequence concealed and random?)
2. Deviations from the intended interventions.
3. Missing outcome data influencing the results.
4. Measurement of the outcome (eg, appropriate, and blinded).
5. Selective of the reported result.
+: low risk of bias; –: high risk of bias; ?: unclear risk of bias.

effect modifiers. However, despite beliefs in interventions that theoretically should provide better outcomes in specific subgroups, we found few studies on this issue. Quicke *et al* reviewed all potential effect modifiers of therapeutic exercise for knee and hip OA.[34] They report limited evidence supporting varus knee malalignment, obesity, cardiac problems, varus thrust, knee laxity and instability, and upper leg strength as effect modifiers of therapeutic exercise. Consistent between the two reviews was the lack of consensus about potential effect modifiers, subgroup analysis limitations and an absence of evidence, particularly for hip OA. These findings reveal that further well-designed, adequately powered studies, including investigation of treatment effect modifiers in the planning of the study, are needed to determine if imaging findings (such as radiographic severity or joint effusion) identify subgroups with different treatment effects.

Methodological limitations in subgroup analyses

No formal guideline for quality appraisal in subgroup analyses exists. However, at least three methodological quality criteria for assessing the credibility of subgroup analysis are suggested.[19 35 36] The criteria by Pincus *et al* distinguish between a set of criteria (five) for studies confirming subgroup effects and a reduced set of criteria (three) for hypothesis-generating studies exploring subgroup effects.[19] We found this guideline was most suitable since all included studies were hypothesis-generating studies exploring modifier effects.

Table 3 Methodological quality in the effect modifier analysis

Study	(1) Were effect modifiers measured prior to randomisation*?	(2) Was the quality of measurement of baseline factors adequate?	(3) Was there explicit test of the interaction between effect modifiers and treatment?	Were methodological quality criteria fulfilled?
Hip				
Teirlinck *et al* 2016[27]	Yes	Yes	No	No
Qvistgaard *et al* 2006[26]	Yes	Yes	Yes	Yes
Knee				
Beckwée *et al* 2017[20]	Yes	Yes	No	no
Henderson *et al* 1994[21]	Yes	Yes	No	No
Kawasaki *et al* 2009[22]	Yes	Yes	No	No
Kudo *et al* 2013[23]	Yes	Yes	No	No
Paterson *et al* 2018[24]	Yes	Yes	Yes	Yes
Huang and Tsai 2021[25]	Yes	Yes	No	No

*Assuming that the assessment of baseline imaging findings could not be influenced by the tested intervention in the case of blinding, this criterion was modified to include all blinded baseline assessments regardless of assessment time.

Reporting interaction analyses is one of the methodological quality criteria in the assessment[19] since evidence of treatment effect modification requires a test of interaction between the potential effect modifier(s) and treatment.[37] Only two included studies reported a test of the interaction, and insufficient statistical tests were a significant limitation in six studies.

The sample size is another critical issue in the included studies as most RCTs are powered only to test the main effect of treatment. Applying an interaction test requires a significantly larger sample size to achieve the same statistical power or precision level as the overall effect test.[9 38] The sample size is not a specific item in the methodological quality criteria we used.[19] However, a minimum sample size of 20 in the smallest subgroup of the modifier has been recommended.[19] Four included studies[20 21 25 26] did not fulfil this recommendation. Thus, in the study by Qvistgaard *et al*, potentially significant interactions could be undiscovered due to insufficient sample size.[26]

Strengths and limitations

Strengths of this review include a rigorous risk of bias assessment and methodological quality appraisal of the subgroup analyses, which strengthens our confidence in the results. Further, we adhered to and reported our study according to the PRISMA recommendations. By only including guideline-recommended non-surgical interventions in knee and hip OA (OARSI-guidelines), we may have excluded treatments used in treating knee and hip OA in clinical practice. However, despite minor differences, OARSI guidelines follow OA treatment guidelines from major professional societies and include a variety of treatments.[2] Thus, we believe the most recognised and relevant interventions are included. Another limitation is that relevant articles might not have been included because of the limited number of databases used in the search or limitations in the search and screening strategy. However, no additional studies were identified from previous reviews and citation tracking of included articles, indicating a comprehensive and complete search.

CONCLUSION

Methodological limitations and few studies do not permit conclusions on diagnostic imaging findings as effect modifiers in non-surgical interventions in knee and hip OA. One study indicated that radiographic severity of knee OA potentially modifies the effect of unloading shoes. This review identifies a knowledge gap and frequently occurring limitations in subgroup analyses.

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Contributors The protocol was drafted by SC and JanH with critical revisions from all authors. SC conducted the searches and the title abstract screening. SC, JLK and BA performed the full-text screening. SC and JoshuaH carried out the data extraction and critical appraisal. SC and BA did the data analysis and interpretation of results. SC drafted the manuscript with critical revisions from all authors and takes full responsibility for the work and/or the conduct of the study, and controlled the decision to publish.

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Competing interests None declared.

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