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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 March 22nd, 2022. Studies in knee and hip OA reporting subgroup analyses in Randomized 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: 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 to 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

Keywords: hip osteoarthritis, knee osteoarthritis, effect modifier, moderator, modifier, sub-group analysis, diagnostic imaging.

Strengths and limitations of this study

- A rigorous risk of bias assessment and methodological quality appraisal of the subgroup analyses.
- Results are exclusively reported from studies that fulfill the methodological quality criteria for assessing effect modification.
- Only including OARSI-guideline-recommended interventions may exclude knee and hip OA treatments used in clinical practice.

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-Steroide Anti-Inflammatory Drugs (NSAIDs), 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-recognized method for identifying clinically relevant subgroups in a patient population is to analyze treatment effect modifiers using randomized controlled trial (RCT) data. Effect modifiers (also known as moderators) are patient characteristics, i.e., 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].

In order to improve targeting of non-surgical interventions and inform future research into treatment effect modification, we aimed to conduct a systematic review of the literature dealing with diagnostic imaging findings as effect modifiers of non-surgical interventions in knee and hip OA.

The specific objectives were to 1) summarize 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 March 19th, 2021, and updated the search on March 22nd, 2022. Search terms covered the following domains: knee OA, hip OA, and diagnostic imaging (radiography, ultrasound, magnetic resonance imaging (MRI) including MRI arthrography (MRIa), Computed Tomography (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]. (Supplementary file 1 for the complete search strategy). Reference

and citation tracking of included articles and related reviews within the topic was 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 recommended by Osteoarthritis Research Society International (OARSI) guidelines [2] on levels 1-3 and compare with either another OARSI recommended non-surgical intervention, placebo, or no treatment.

3) Include baseline diagnostic imaging findings as potential effect modifiers, e.g., structural, or inflammatory findings on radiographs, computed tomography (CT), Magnetic Resonance Imaging (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, i.e., excluding imaging findings and biochemical markers.

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

Study selection

Records returned from the search were screened using a two-stage process. One reviewer (SHC) 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 (SHC/JK/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). De-duplication and data extraction was conducted in Covidence [17].

Data extraction

Relevant data were extracted independently by two reviewers (SHC/JHe) using a standardized 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 and quality appraisal independently (SC, JHe). 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 in two steps. First, the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [18] was used to evaluate the design and conduct of the RCT. We used a "conservative summary risk of bias judgment" 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 randomization?* 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 (e.g., 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, categorization 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 is presented in Fig. 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).

Suggested position Figure 1.

Legend: Figure 1. The study selection process

Study characteristics

Study samples were recruited from communities [23, 24], primary health care [27], and secondary health care [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 sub-group analysis as a primary objective [20, 23], and in six studies, the sub-group 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], intraarticular hyaluronic acid injection [21, 22, 25, 26], intraarticular corticoid steroid injection (IACS) [26], and unloading shoes [24].

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 2016	Primary care (Physiotherapy and general practices)	The Netherlands	A) Exercise therapy + usual care (GP), n=101 B) Usual care (GP), n=102	A) 64 (8.5) B) 67 (9.6)	ACR	HOOS pain and function	6 weeks, 3, 6, 12 months	Radiographic OA severity (KL dichotomized 0-1 or ≥ 2)
Qvistgaard 2006	Secondary care (Rheumatology outpatient clinic)	Denmark	A) HA injection, n=33 B) IACS, n=32 C) Saline injection, n=36	A) 65 (14) B) 69 (9) C) 64 (11)	ACR	Pain on walking (VAS)	15, 45, 90 days	1) Radiographic OA severity (KL dichotomized 1-2 or ≥ 3) 2) Effusion (US) present/ absent
KNEE								
Beckwée 2017	Secondary care (Orthopedic outpatient clinic)	Belgium	A) Strength training, n=17 B) Walking training, n=18	A) 63.7 (8.1) B) 60.1 (9.5)	ACR	ICOAP The patient's global perceived effect	8 weeks	Bone marrow lesions dichotomized present/ absent (MRI)
Henderson 1994	Secondary care (Rheumatology outpatient clinics)	England	A) HA injection, n=45 B) Saline injection, n=46	A) Early OA: 63.9 (1.9) Advanced OA: 72.1 (1.7) B) Early OA: 60.0 (1.9) Advanced OA: 67.0 (1.7)	Knee pain and KL > 0	Pain (VAS) in the morning, evening, climbing stairs, rising from chair and nominated activity	2, 5 weeks, 3, 5 months	Radiographic OA severity (KL dichotomized 1-2 or ≥ 3)
Kawasaki 2009	Secondary care (no information on departments)	Japan	A) HA injection, n=42 B) Exercise therapy, n=45	A) 69.5 (8.4) B) 71.2 (7.1)	ACR	Pain (VAS) JKOM OMERACT–OARSI response	24 weeks	Radiographic OA severity (JSW dichotomized (< 3.0 mm, ≥ 3.0 mm))
Kudo 2013	Secondary care (Orthopedic outpatient clinic)	Japan	A) Group exercise, n=81 B) Home exercise, n=122	A) 63.8 (5.9) B) 65.6 (5.8)	Knee pain and KL > 0	Normalized WOMAC	4 months	1) Radiographic OA severity (KL dichotomized 1-2 or ≥ 3) 2) Meniscal pathology dichotomized into Mink grade 0-2 or grade 3 (MRI) 3) Bone marrow lesions dichotomized present/ absent (MRI)
Paterson 2018	Department of Physiotherapy, the University of Melbourne	Australia	A) Unloading shoes, n=83 B) Walking shoes, n=81	A) 65.2 (6.9) B) 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 2021	Medical University Hospital	China	A) CHAP-HA single-injection, n=71 B) Linear HA three-injection, n=69	A) 56.6 ± 12.6 B) 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)

SD: Standard deviation, GP: General practice, ACR: American College of Rheumatology criteria for hip OA, IACS: Intraarticular Corticosteroid Injection, HA: Hyaluronic Acid, HHS: Harris Hip Score, KL: Kellgren-Lawrence grade, US: ultrasound imaging, VAS: Visual analog scale, NRS: Numeric rating scale, ICOAP: The intermittent and constant osteoarthritis pain questionnaire, JKOM: The Japanese Knee Osteoarthritis Measure, Normalized WOMAC = (raw score out of 96) x 100/96, JSW: Joint space width.

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 fulfill the methodological quality criteria of the effect modifier analysis, all due to the lack of an interaction test between effect modifiers and treatment.

Table 2 Risk of bias in the randomized controlled trials

Study	Risk of bias in the five domains					
	1	2	3	4	5	Summary
HIP						
Teirlinck 2016	+	+	+	?	+	Some concerns
Qvistgaard 2006	+	+	?	+	+	Some concerns
KNEE						
Beckwée 2017	+	?	+	-	+	High
Henderson 1994	+	-	-	+	?	High
Kawasaki 2009	+	+	-	-	?	High
Kudo 2013	?	-	?	-	?	High
Paterson 2018	+	+	+	+	?	Low
Huang 2021	+	+	+	+	?	Some concerns

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

Table 3 Methodological quality in the effect modifier analysis

Study	1) Were effect modifiers measured prior to randomization*?	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 2016	yes	yes	no	no
Qvistgaard 2006	yes	yes	yes	yes
KNEE				
Beckwée 2017	yes	yes	no	no
Henderson 1994	yes	yes	no	no
Kawasaki 2009	yes	yes	no	no
Kudo 2013	yes	yes	no	no
Paterson 2018	yes	yes	yes	yes
Huang 2021	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.

Treatment effect modifiers

The study on knee OA [24] that fulfilled all three quality criteria for assessing effect modification 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 to those with mild OA (KL 2). The outcome was walking pain (Numeric Rating Scale 0-10) assessed at six months. People with KL grade 2 responded more favorably 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, -0.21) for KL 2, 0.98 (-0.44, 2.39) for KL 3, and 0.64 (-0.64, 1.93) for KL 4 (interaction term p=0.02).

The study of hip OA [26] compared the effect of IACS, intraarticular 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 intraarticular hip effusion (absent/present), or KL dichotomized (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 to 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 randomized 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 treatments targeting inflammation have a better effect in patients with signs of inflammation, e.g., effusion/synovitis diagnosed with MRI or ultrasound. Another belief revealed in

the literature is an expectation of structural OA severity to modify treatment effect. Radiographic OA severity was investigated in seven of the eight included studies.

We included several non-surgical treatment modalities and a variety of diagnostic imaging findings as potential 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 [31]. 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, 32, 33]. 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.

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 [34]. 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, 35]. 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 fulfill 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 recognized 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.

LIST OF ABBREVIATIONS

OA: Osteoarthritis

NSAIDs: Non-Steroide Anti-Inflammatory Drugs

RCT: Randomized Controlled Trial

PROSPERO: International prospective register of systematic reviews

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

MRI: Magnetic Resonance Imaging

MRIa: Magnetic Resonance Imaging arthrography

CT: Computed Tomography

OARSI: Osteoarthritis Research Society International

RoB 2: The revised Cochrane risk-of-bias tool for randomized trials

IACS: Intraarticular Corticoid Steroid injection

KL: Kellgren-Lawrence grade

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data used and/or analyzed and material used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

The protocol was drafted by SC with critical revisions from all authors. SC conducted the searches and the title abstract screening, SC, JK, BA the full-text screening. SC and JHe 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.

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Supplemental material

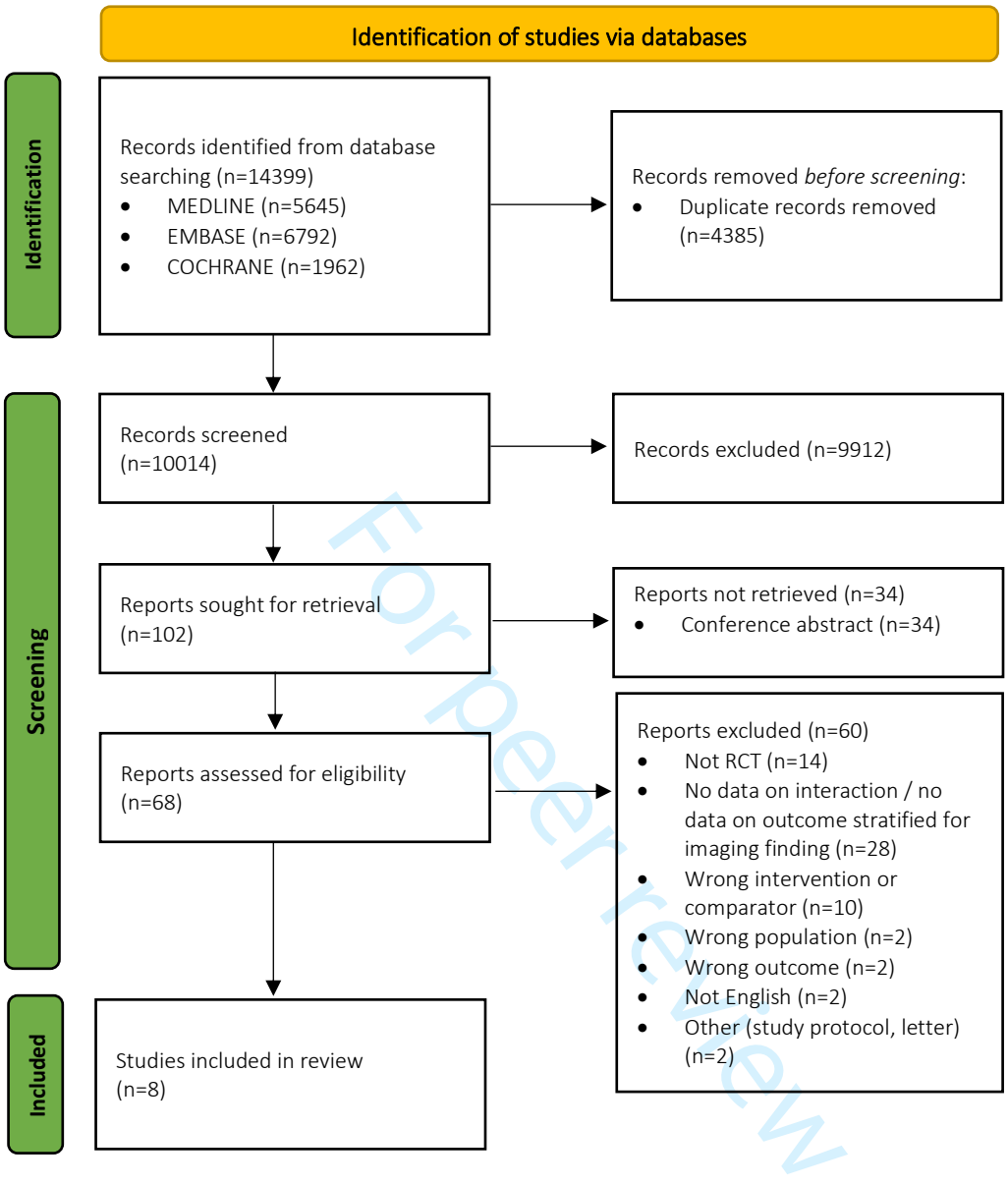
Supplemental file 1: Search strategy (.pdf)

REFERENCES

1. Bannuru RR, Osani MC, Vaysbrot EE et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019; 27: 1578-1589. doi:10.1016/j.joca.2019.06.011
2. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. JAMA 2021; 325: 568-578. doi:10.1001/jama.2020.22171
3. Kolasinski SL, Neogi T, Hochberg MC et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken) 2020; 72: 149-162. doi:10.1002/acr.24131
4. Teirlinck CH, Verhagen AP, Reijneveld EAE et al. Responders to Exercise Therapy in Patients with Osteoarthritis of the Hip: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2020; 17. doi:10.3390/ijerph17207380
5. Thorlund JB, Simic M, Pihl K et al. Similar Effects of Exercise Therapy, Nonsteroidal Anti-inflammatory Drugs, and Opioids for Knee Osteoarthritis Pain: A Systematic Review with Network Meta-analysis. J Orthop Sports Phys Ther 2022; 52: 207-216. doi:10.2519/jospt.2022.10490
6. Fransen M, McConnell S, Harmer AR et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med 2015; 49: 1554-1557. doi:10.1136/bjsports-2015-095424
7. Verhagen AP, Ferreira M, Reijneveld-van de Vendel EAE et al. Do we need another trial on exercise in patients with knee osteoarthritis?: No new trials on exercise in knee OA. Osteoarthritis Cartilage 2019; 27: 1266-1269. doi:10.1016/j.joca.2019.04.020
8. Corraini P, Olsen M, Pedersen L et al. Effect modification, interaction and mediation: an overview of theoretical insights for clinical investigators. Clin Epidemiol 2017; 9: 331-338. doi:10.2147/clep.S129728
9. Hancock M, Herbert RD, Maher CG. A guide to interpretation of studies investigating subgroups of responders to physical therapy interventions. Phys Ther 2009; 89: 698-704. doi:10.2522/ptj.20080351
10. Roemer FW, Guermazi A, Demehri S et al. Imaging in Osteoarthritis. Osteoarthritis Cartilage 2021. doi:10.1016/j.joca.2021.04.018. doi:10.1016/j.joca.2021.04.018
11. Bastick AN, Runhaar J, Belo JN et al. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Res Ther 2015; 17: 152. doi:10.1186/s13075-015-0670-x
12. Teirlinck CH, Dorleijn DMJ, Bos PK et al. Prognostic factors for progression of osteoarthritis of the hip: a systematic review. Arthritis Res Ther 2019; 21: 192. doi:10.1186/s13075-019-1969-9
13. Heidari P, Heidari B, Babaei M. Efficacy and predictive factors of response to intra-articular corticosteroids in knee osteoarthritis. Reumatologia 2020; 58: 424-435. doi:10.5114/reum.2020.102008
14. Sakellariou G, Conaghan PG, Zhang W et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. Ann Rheum Dis 2017; 76: 1484-1494. doi:10.1136/annrheumdis-2016-210815
15. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. doi:10.1136/bmj.n71

16. McKibbon KA, Wilczynski NL, Haynes RB. Retrieving randomized controlled trials from medline: a comparison of 38 published search filters. Health Info Libr J 2009; 26: 187-202. doi:10.1111/j.1471-1842.2008.00827.x
17. McKeown S, Mir ZM. Considerations for conducting systematic reviews: evaluating the performance of different methods for de-duplicating references. Syst Rev 2021; 10: 38. doi:10.1186/s13643-021-01583-y
18. Sterne JAC, Savović J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898. doi:10.1136/bmj.l4898
19. Pincus T, Miles C, Froud R et al. Methodological criteria for the assessment of moderators in systematic reviews of randomised controlled trials: a consensus study. BMC Med Res Methodol 2011; 11: 14. doi:10.1186/1471-2288-11-14
20. Beckwée D, Vaes P, Raeymaeckers S et al. Exercise in knee osteoarthritis: do treatment outcomes relate to bone marrow lesions? A randomized trial. Disabil Rehabil 2017; 39: 1847-1855. doi:10.1080/09638288.2016.1212110
21. Henderson EB, Smith EC, Pegley F et al. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: A randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. Ann Rheum Dis 1994; 53: 529-534. doi:http://dx.doi.org/10.1136/ard.53.8.529
22. Kawasaki T, Kurosawa H, Ikeda H et al. Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association 2009; 14: 182-191. doi:https://dx.doi.org/10.1007/s00776-008-1312-9
23. Kudo M, Watanabe K, Otsubo H et al. Analysis of effectiveness of therapeutic exercise for knee osteoarthritis and possible factors affecting outcome. J Orthop Sci 2013; 18: 932-939. doi:10.1007/s00776-013-0443-9
24. Paterson KL, Kasza J, Bennell KL et al. Moderators and mediators of effects of unloading shoes on knee pain in people with knee osteoarthritis: an exploratory analysis of the SHARK randomised controlled trial. Osteoarthritis Cartilage 2018; 26: 227-235. doi:10.1016/j.joca.2017.11.002
25. Huang TL, Tsai CH. Safety and efficacy of single CHAP Hyaluronan injection versus three injections of linear Hyaluronan in pain relief for knee osteoarthritis: a prospective, 52-week follow-up, randomized, evaluator-blinded study. BMC Musculoskelet Disord 2021; 22: 572. doi:10.1186/s12891-021-04467-3
26. Qvistgaard E, Christensen R, Torp-Pedersen S et al. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage 2006; 14: 163-170. doi:10.1016/j.joca.2005.09.007
27. Teirlinck CH, Luijsterburg PA, Dekker J et al. Effectiveness of exercise therapy added to general practitioner care in patients with hip osteoarthritis: a pragmatic randomized controlled trial. Osteoarthritis Cartilage 2016; 24: 82-90. doi:10.1016/j.joca.2015.07.023
28. Sun X, Briel M, Busse JW et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. BMJ 2012; 344: e1553. doi:10.1136/bmj.e1553
29. Saragiotto BT, Maher CG, Moseley AM et al. A systematic review reveals that the credibility of subgroup claims in low back pain trials was low. J Clin Epidemiol 2016; 79: 3-9. doi:10.1016/j.jclinepi.2016.06.003

30. Brookes ST, Whitley E, Peters TJ et al. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. Health Technol Assess 2001; 5: 1-56. doi:10.3310/hta5330
31. Quicke JG, Runhaar J, van der Windt DA et al. Moderators of the effects of therapeutic exercise for people with knee and hip osteoarthritis: A systematic review of sub-group analyses from randomised controlled trials. Osteoarthritis and Cartilage Open 2020; 2: 100113. doi:https://doi.org/10.1016/j.ocarto.2020.100113
32. Sun X, Briel M, Walter SD et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ (Clinical research ed) 2010; 340: c117-c117. doi:10.1136/bmj.c117
33. van Hoorn R, Tummers M, Booth A et al. The development of CHAMP: a checklist for the appraisal of moderators and predictors. BMC Med Res Methodol 2017; 17: 173. doi:10.1186/s12874-017-0451-0
34. Hancock MJ, Kjaer P, Korsholm L et al. Interpretation of subgroup effects in published trials. Phys Ther 2013; 93: 852-859. doi:10.2522/ptj.20120296
35. Brookes ST, Whitely E, Egger M et al. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol 2004; 57: 229-236. doi:10.1016/j.jclinepi.2003.08.009



Supplemental file 1: Complete search strategy

MEDLINE	
1	Osteoarthritis, Knee/
2	Osteoarthritis, Hip/
3	((Osteoarthr* adj3 knee) or (arthr* adj3 knee) or gonarthr* or gon arthr* or femorotibial arthr* or (osteoarthr* adj3 hip) or (arthr* adj3 hip) or coxarthr* or cox arthr*).ti,ab.
4	1 or 2 or 3
5	diagnostic imaging/
6	Magnetic Resonance Imaging/
7	Ultrasonography/
8	Ultrasonics/
9	exp Tomography/
10	X-Rays/
11	Radiography/
12	Ultrasonography/
13	(radiograph* or radiolog* or x ray* or mr* or magnetic resonance or ct* or computed tomography or sonograph* or echograph* or ultrasound or ultrasonography).ti,ab.
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	((((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)) or (allocated adj2 random)).tw. or (clin* adj25 trial*).ti,ab. or (clinic* adj trial*1).tw. or (double-blind* or random*).af. or clinical trial.pt. or clinical trials as topic.sh. or controlled clinical trial.pt. or double blind method.sh. or single blind method.sh. or double-blind method.sh. or single-blind method.sh. or drug therapy.fs. or exp clinical trials as topic/ or exp research design/ or placebo*.tw. or placebos.sh. or practice guideline.pt. or random allocation.sh. or random*.tw. or random.af. or randomized controlled trial.pt. or randomized controlled trials as topic.sh. or randomized.ab. or randomly allocated.tw. or randomly.ab. or single-blind method.sh. or trial.ab. or trial.ti.) not (case report.tw. or letter.pt. or historical article.pt. or review of reported cases.pt. or multicase review.pt.)
16	4 and 14 and 15
EMBASE	
1	knee osteoarthritis/
2	hip osteoarthritis/
3	knee arthritis/
4	((Osteoarthr* adj3 knee) or (arthr* adj3 knee) or gonarthr* or gon arthr* or femorotibial arthr* or (osteoarthr* adj3 hip) or (arthr* adj3 hip) or coxarthr* or cox arthr*).ti,ab.
5	1 or 2 or 3 or 4
6	diagnostic imaging/

7	exp nuclear magnetic resonance imaging/
8	exp knee arthrography/
9	echography/
10	ultrasound/
11	knee radiography/
12	hip radiography/
13	dual energy computed tomography/
14	X ray/
15	radiography/ or computer assisted radiography/ or digital radiography/ or joint radiography/
16	exp nuclear magnetic resonance/
1 7	computer assisted tomography/
18	exp x-ray computed tomography/
19	(radiograph* or radiolog* or x ray* or mr* or magnetic resonance or ct* or computed tomography or sonograph* or echograph* or ultrasound or ultrasonography).ti,ab.
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	(((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask$3)) or (allocated adj2 random)).tw. or (clin* adj25 trial*).ti,ab. or (clinic: adj trial$1).tw. or (double-blind* or random*).af. or exp "clinical trial (topic)"/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or placebo*.tw. or exp placebo/ or exp randomization/ or Random.af. or Random*.tw. or exp "randomized controlled trial (topic)"/ or randomized.ab. or randomly allocated.tw. or randomly.ab. or trial.ab. or trial.ti. or exp "controlled clinical trial (topic)"/ or randomized controlled trial/ or "randomized controlled trial (topic)"/ or exp "controlled clinical trial"/
22	5 and 20 and 21

COCHRANE

1	MeSH descriptor: [Osteoarthritis, Knee] explode all trees
2	MeSH descriptor: [Osteoarthritis, Hip] explode all trees
3	"Osteoarthr* NEAR/2 knee" or "arthr* NEAR/2 knee" or gonarthr* or "gon arthr*" or "femorotibial arthr*" or "osteoarthr* NEAR/2 hip" or "arthr* NEAR/2 hip" or coxarthr* or "cox arthr*"
4	#1 OR #2 OR #3
5	MeSH descriptor: [Diagnostic Imaging] this term only
6	MeSH descriptor: [Magnetic Resonance Imaging] this term only
7	MeSH descriptor: [Ultrasonography] this term only
8	MeSH descriptor: [Ultrasonics] this term only
9	MeSH descriptor: [Tomography] explode all trees
10	MeSH descriptor: [X-Rays] this term only
11	MeSH descriptor: [Ultrasonography] this term only

12	MeSH descriptor: [Radiography] this term only
13	(radiograph* or radiologic* or x-ray* or mr* or "magnetic resonance" or ct* or "computed tomography" or sonograph* or echograph* or ultrasound or ultrasonography):ti,ab,kw (Word variations have been searched)
14	#5 OR #6 OR #7 0R #8 OR #9 OR #10 0R #11 OR #12 OR #13
15	#4 AND #14

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	page 5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	page 5 and supplementary file 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	page 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	page 6, 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	page 6, 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	page 7, 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	page 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	page 8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	page 8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Table 1 p. 10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	page 8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	page 8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	page 9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 2 p. 11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	page 12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	page 13
	23b	Discuss any limitations of the evidence included in the review.	page 14
	23c	Discuss any limitations of the review processes used.	page 15
	23d	Discuss implications of the results for practice, policy, and future research.	page 13, 15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	page 17
Competing interests	26	Declare any competing interests of review authors.	page 17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	page 17

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

BMJ Open

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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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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Word count: main text 2894

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 March 22nd, 2022. Studies in knee and hip OA reporting subgroup analyses in Randomized 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 to 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

Keywords: hip osteoarthritis, knee osteoarthritis, effect modifier, moderator, modifier, sub-group analysis, diagnostic imaging.

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 (PRISMA) 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 (NSAIDs), 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-recognized method for identifying clinically relevant subgroups in a patient population is to analyze treatment effect modifiers using randomized controlled trial (RCT) data. Effect modifiers (also known as moderators) are patient characteristics, i.e., 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) summarize 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 March 19th, 2021, and updated the search on March 22nd, 2022. Search terms covered the following domains: knee OA, hip OA, and diagnostic imaging (radiography, ultrasound, magnetic resonance imaging (MRI) including MRI arthrography (MRIa), Computed Tomography (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]. (Supplementary file 1 for the complete search strategy). Reference and citation tracking of included articles and related reviews within the topic was 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, e.g., structural, or inflammatory findings on radiographs, computed tomography (CT), Magnetic Resonance Imaging (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, i.e., excluding imaging findings and biochemical markers.

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

Study selection

Records returned from the search were screened using a two-stage process. One reviewer (SHC) 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 (SHC/JK/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). De-duplication and data extraction was conducted in Covidence [17].

Data extraction

Relevant data were extracted independently by two reviewers (SHC/JHe) using a standardized 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, JHe). 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, JHe) 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 randomized trials (RoB 2) [18] was used to

evaluate the design and conduct of the RCT. We used a "conservative summary risk of bias judgment" 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 randomization?* 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 (e.g., 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, categorization 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 is presented in Fig. 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).

Suggested position Figure 1.

Legend: Figure 1. The study selection process

Study characteristics

Study samples were recruited from communities [23, 24], primary health care [27], and secondary health care [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 sub-group analysis as a primary objective [20, 23], and in six studies, the sub-group 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], intraarticular hyaluronic acid injection [21, 22, 25, 26], intraarticular corticoid steroid injection (IACS) [26], and unloading shoes [24].

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 2016	Primary care (Physiotherapy and general practices)	The Netherlands	A) Exercise therapy + usual care (GP), n=101 B) Usual care (GP), n=102	A) 64 (8.5) B) 67 (9.6)	ACR	HOOS pain and function	[illegible]s, 6, 12 months	Radiographic OA severity (KL dichotomized 0-1 or ≥ 2)
Qvistgaard 2006	Secondary care (Rheumatology outpatient clinic)	Denmark	A) HA injection, n=33 B) IACS, n=32 C) Saline injection, n=36	A) 65 (14) B) 69 (9) C) 64 (11)	ACR	Pain on walking (VAS)	30, 90 days	1) Radiographic OA severity (KL dichotomized 1-2 or ≥ 3) 2) Effusion (US) present/ absent
KNEE								
Beckwée 2017	Secondary care (Orthopedic outpatient clinic)	Belgium	A) Strength training, n=17 B) Walking training, n=18	A) 63.7 (8.1) B) 60.1 (9.5)	ACR	ICOAP The patient's global perceived effect	8 weeks	Bone marrow lesions dichotomized present/ absent (MRI)
Henderson 1994	Secondary care (Rheumatology outpatient clinics)	England	A) HA injection, n=45 B) Saline injection, n=46	A) Early OA: 63.9 (1.9) Advanced OA: 72.1 (1.7) B) Early OA: 60.0 (1.9) Advanced OA: 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, 3, 6 months	Radiographic OA severity (KL dichotomized 1-2 or ≥ 3)
Kawasaki 2009	Secondary care (no information on departments)	Japan	A) HA injection, n=42 B) Exercise therapy, n=45	A) 69.5 (8.4) B) 71.2 (7.1)	ACR	Pain (VAS) JKOM OMERACT–OARSI response	24 weeks	Radiographic OA severity (JSW dichotomized (< 3.0 mm, ≥ 3.0 mm))
Kudo 2013	Secondary care (Orthopedic outpatient clinic)	Japan	A) Group exercise, n=81 B) Home exercise, n=122	A) 63.8 (5.9) B) 65.6 (5.8)	Knee pain and KL > 0	Normalized WOMAC	3 months	1) Radiographic OA severity (KL dichotomized 1-2 or ≥ 3) 2) Meniscal pathology dichotomized into Mink grade 0-2 or grade 3 (MRI) 3) Bone marrow lesions dichotomized present/ absent (MRI)
Paterson 2018	Department of Physiotherapy, the University of Melbourne	Australia	A) Unloading shoes, n=83 B) Walking shoes, n=81	A) 65.2 (6.9) B) 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 2021	Medical University Hospital	China	A) CHAP-HA single-injection, n=71 B) Linear HA three-injection, n=69	A) 56.6 ± 12.6 B) 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)

SD: Standard deviation, GP: General practice, ACR: American College of Rheumatology criteria for hip OA, IACS: Intraarticular Corticosteroid Injection, HA: Hyaluronic Acid, HHS: Harris Hip Score, KL: Kellgren-Lawrence grade, US: ultrasound imaging, VAS: Visual analog scale, NRS: Numeric rating scale, ICOAP: The intermittent and constant osteoarthritis pain questionnaire, JKOM: The Japanese Knee Osteoarthritis Measure, Normalized WOMAC = (raw score out of 96) x 100/96, JSW: Joint space width.

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 fulfill the methodological quality criteria of the effect modifier analysis, all due to the lack of an interaction test between effect modifiers and treatment.

Table 2 Risk of bias in the randomized controlled trials

Study	Risk of bias in the five domains					
	1	2	3	4	5	Summary
HIP						
Teirlinck 2016	+	+	+	?	+	Some concerns
Qvistgaard 2006	+	+	?	+	+	Some concerns
KNEE						
Beckwée 2017	+	?	+	-	+	High
Henderson 1994	+	-	-	+	?	High
Kawasaki 2009	+	+	-	-	?	High
Kudo 2013	?	-	?	-	?	High
Paterson 2018	+	+	+	+	?	Low
Huang 2021	+	+	+	+	?	Some concerns

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

Table 3 Methodological quality in the effect modifier analysis

Study	1) Were effect modifiers measured prior to randomization*?	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 2016	yes	yes	no	no
Qvistgaard 2006	yes	yes	yes	yes
KNEE				
Beckwée 2017	yes	yes	no	no
Henderson 1994	yes	yes	no	no
Kawasaki 2009	yes	yes	no	no
Kudo 2013	yes	yes	no	no
Paterson 2018	yes	yes	yes	yes
Huang 2021	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.

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 to those with mild OA (KL 2). The outcome was walking pain (Numeric Rating Scale 0-10) assessed at six months. People with KL grade 2 responded more favorably 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, -0.21) for KL 2, 0.98 (-0.44, 2.39) for KL 3, and 0.64 (-0.64, 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, intraarticular 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 intraarticular hip effusion (absent/present), or KL dichotomized (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 to 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 randomized 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, e.g., effusion/synovitis visualized 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 osteoarthritis 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 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.

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 fulfill 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 recognized 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.

LIST OF ABBREVIATIONS

OA: Osteoarthritis

NSAIDs: Non-Steroide Anti-Inflammatory Drugs

RCT: Randomized Controlled Trial

PROSPERO: International prospective register of systematic reviews

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

MRI: Magnetic Resonance Imaging

MRIa: Magnetic Resonance Imaging arthrography

CT: Computed Tomography

OARSI: Osteoarthritis Research Society International

RoB 2: The revised Cochrane risk-of-bias tool for randomized trials

IACS: Intraarticular Corticoid Steroid injection

KL: Kellgren-Lawrence grade

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing not applicable as no datasets generated and/or analysed for this study.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

The protocol was drafted by SC and JH with critical revisions from all authors. SC conducted the searches and the title abstract screening, SC, JK, BA the full-text screening. SC and JHe 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.

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Supplemental material

Supplemental file 1: Search strategy (.pdf)

REFERENCES

1. Bannuru RR, Osani MC, Vaysbrot EE et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019; 27: 1578-1589. DOI: 10.1016/j.joca.2019.06.011
2. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. JAMA 2021; 325: 568-578. DOI: 10.1001/jama.2020.22171
3. Kolasinski SL, Neogi T, Hochberg MC et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken) 2020; 72: 149-162. DOI: 10.1002/acr.24131
4. Teirlinck CH, Verhagen AP, Reijneveld EAE et al. Responders to Exercise Therapy in Patients with Osteoarthritis of the Hip: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2020; 17. DOI: 10.3390/ijerph17207380
5. Thorlund JB, Simic M, Pihl K et al. Similar Effects of Exercise Therapy, Nonsteroidal Anti-inflammatory Drugs, and Opioids for Knee Osteoarthritis Pain: A Systematic Review with Network Meta-analysis. J Orthop Sports Phys Ther 2022; 52: 207-216. DOI: 10.2519/jospt.2022.10490
6. Fransen M, McConnell S, Harmer AR et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med 2015; 49: 1554-1557. DOI: 10.1136/bjsports-2015-095424
7. Verhagen AP, Ferreira M, Reijneveld-van de Vendel EAE et al. Do we need another trial on exercise in patients with knee osteoarthritis?: No new trials on exercise in knee OA. Osteoarthritis Cartilage 2019; 27: 1266-1269. DOI: 10.1016/j.joca.2019.04.020
8. Corraini P, Olsen M, Pedersen L et al. Effect modification, interaction and mediation: an overview of theoretical insights for clinical investigators. Clin Epidemiol 2017; 9: 331-338. DOI: 10.2147/clep.S129728
9. Hancock M, Herbert RD, Maher CG. A guide to interpretation of studies investigating subgroups of responders to physical therapy interventions. Phys Ther 2009; 89: 698-704. DOI: 10.2522/ptj.20080351
10. Roemer FW, Guermazi A, Demehri S et al. Imaging in Osteoarthritis. Osteoarthritis Cartilage 2021. DOI: 10.1016/j.joca.2021.04.018
11. Bastick AN, Runhaar J, Belo JN et al. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Res Ther 2015; 17: 152. DOI: 10.1186/s13075-015-0670-x
12. Teirlinck CH, Dorleijn DMJ, Bos PK et al. Prognostic factors for progression of osteoarthritis of the hip: a systematic review. Arthritis Res Ther 2019; 21: 192. DOI: 10.1186/s13075-019-1969-9
13. Heidari P, Heidari B, Babaei M. Efficacy and predictive factors of response to intra-articular corticosteroids in knee osteoarthritis. Reumatologia 2020; 58: 424-435. DOI: 10.5114/reum.2020.102008
14. Sakellariou G, Conaghan PG, Zhang W et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. Ann Rheum Dis 2017; 76: 1484-1494. DOI: 10.1136/annrheumdis-2016-210815
15. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. DOI: 10.1136/bmj.n71

16. McKibbon KA, Wilczynski NL, Haynes RB. Retrieving randomized controlled trials from medline: a comparison of 38 published search filters. Health Info Libr J 2009; 26: 187-202. DOI: 10.1111/j.1471-1842.2008.00827.x
17. McKeown S, Mir ZM. Considerations for conducting systematic reviews: evaluating the performance of different methods for de-duplicating references. Syst Rev 2021; 10: 38. DOI: 10.1186/s13643-021-01583-y
18. Sterne JAC, Savović J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898. DOI: 10.1136/bmj.l4898
19. Pincus T, Miles C, Froud R et al. Methodological criteria for the assessment of moderators in systematic reviews of randomised controlled trials: a consensus study. BMC Med Res Methodol 2011; 11: 14. DOI: 10.1186/1471-2288-11-14
20. Beckwée D, Vaes P, Raeymaeckers S et al. Exercise in knee osteoarthritis: do treatment outcomes relate to bone marrow lesions? A randomized trial. Disabil Rehabil 2017; 39: 1847-1855. DOI: 10.1080/09638288.2016.1212110
21. Henderson EB, Smith EC, Pegley F et al. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: A randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. Ann Rheum Dis 1994; 53: 529-534. DOI: http://dx.doi.org/10.1136/ard.53.8.529
22. Kawasaki T, Kurosawa H, Ikeda H et al. Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association 2009; 14: 182-191. DOI: https://dx.doi.org/10.1007/s00776-008-1312-9
23. Kudo M, Watanabe K, Otsubo H et al. Analysis of effectiveness of therapeutic exercise for knee osteoarthritis and possible factors affecting outcome. J Orthop Sci 2013; 18: 932-939. DOI: 10.1007/s00776-013-0443-9
24. Paterson KL, Kasza J, Bennell KL et al. Moderators and mediators of effects of unloading shoes on knee pain in people with knee osteoarthritis: an exploratory analysis of the SHARK randomised controlled trial. Osteoarthritis Cartilage 2018; 26: 227-235. DOI: 10.1016/j.joca.2017.11.002
25. Huang TL, Tsai CH. Safety and efficacy of single CHAP Hyaluronan injection versus three injections of linear Hyaluronan in pain relief for knee osteoarthritis: a prospective, 52-week follow-up, randomized, evaluator-blinded study. BMC Musculoskelet Disord 2021; 22: 572. DOI: 10.1186/s12891-021-04467-3
26. Qvistgaard E, Christensen R, Torp-Pedersen S et al. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage 2006; 14: 163-170. DOI: 10.1016/j.joca.2005.09.007
27. Teirlinck CH, Luijsterburg PA, Dekker J et al. Effectiveness of exercise therapy added to general practitioner care in patients with hip osteoarthritis: a pragmatic randomized controlled trial. Osteoarthritis Cartilage 2016; 24: 82-90. DOI: 10.1016/j.joca.2015.07.023
28. Sun X, Briel M, Busse JW et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. BMJ 2012; 344: e1553. DOI: 10.1136/bmj.e1553
29. Saragiotto BT, Maher CG, Moseley AM et al. A systematic review reveals that the credibility of subgroup claims in low back pain trials was low. J Clin Epidemiol 2016; 79: 3-9. DOI: 10.1016/j.jclinepi.2016.06.003

30. Brookes ST, Whitley E, Peters TJ et al. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. Health Technol Assess 2001; 5: 1-56. DOI: 10.3310/hta5330

31. Kim C, Nevitt MC, Niu J et al. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. BMJ 2015; 351: h5983. DOI: 10.1136/bmj.h5983

32. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet (London, England) 2019; 393: 1745-1759. DOI: 10.1016/S0140-6736(19)30417-9

33. Skou ST, Thomsen H, Simonsen OH. The value of routine radiography in patients with knee osteoarthritis consulting primary health care: a study of agreement. Eur J Gen Pract 2014; 20: 10-16. DOI: 10.3109/13814788.2013.818132

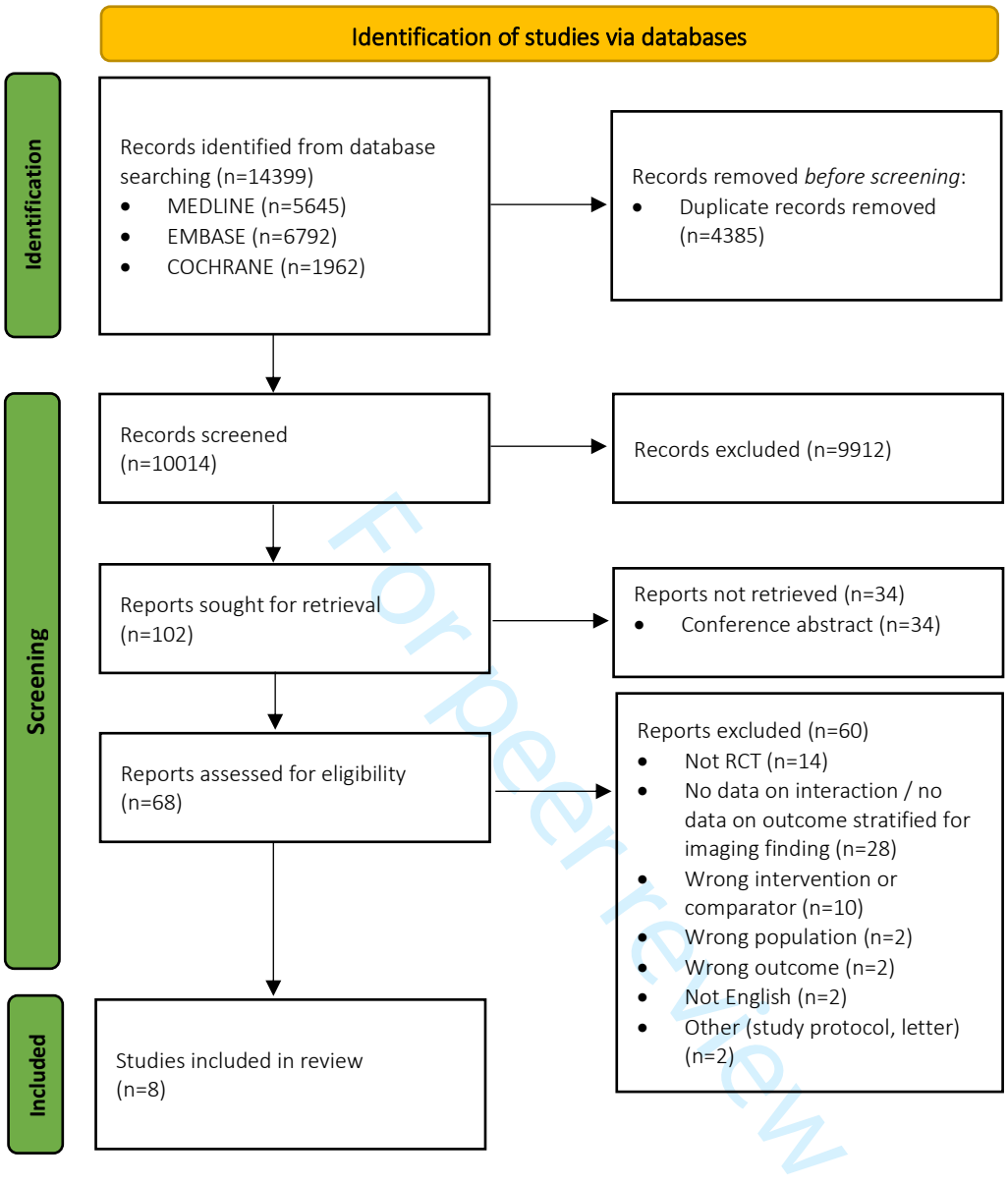
34. Quicke JG, Runhaar J, van der Windt DA et al. Moderators of the effects of therapeutic exercise for people with knee and hip osteoarthritis: A systematic review of sub-group analyses from randomised controlled trials. Osteoarthritis and Cartilage Open 2020; 2: 100113. DOI: https://doi.org/10.1016/j.ocarto.2020.100113

35. Sun X, Briel M, Walter SD et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ (Clinical research ed) 2010; 340: c117-c117. DOI: 10.1136/bmj.c117

36. van Hoorn R, Tummers M, Booth A et al. The development of CHAMP: a checklist for the appraisal of moderators and predictors. BMC Med Res Methodol 2017; 17: 173. DOI: 10.1186/s12874-017-0451-0

37. Hancock MJ, Kjaer P, Korsholm L et al. Interpretation of subgroup effects in published trials. Phys Ther 2013; 93: 852-859. DOI: 10.2522/ptj.20120296

38. Brookes ST, Whitely E, Egger M et al. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol 2004; 57: 229-236. DOI: 10.1016/j.jclinepi.2003.08.009



Supplemental file 1: Complete search strategy

MEDLINE	
1	Osteoarthritis, Knee/
2	Osteoarthritis, Hip/
3	((Osteoarthr* adj3 knee) or (arthr* adj3 knee) or gonarthr* or gon arthr* or femorotibial arthr* or (osteoarthr* adj3 hip) or (arthr* adj3 hip) or coxarthr* or cox arthr*).ti,ab.
4	1 or 2 or 3
5	diagnostic imaging/
6	Magnetic Resonance Imaging/
7	Ultrasonography/
8	Ultrasonics/
9	exp Tomography/
10	X-Rays/
11	Radiography/
12	Ultrasonography/
13	(radiograph* or radiolog* or x ray* or mr* or magnetic resonance or ct* or computed tomography or sonograph* or echograph* or ultrasound or ultrasonography).ti,ab.
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	((((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)) or (allocated adj2 random)).tw. or (clin* adj25 trial*).ti,ab. or (clinic* adj trial*1).tw. or (double-blind* or random*).af. or clinical trial.pt. or clinical trials as topic.sh. or controlled clinical trial.pt. or double blind method.sh. or single blind method.sh. or double-blind method.sh. or single-blind method.sh. or drug therapy.fs. or exp clinical trials as topic/ or exp research design/ or placebo*.tw. or placebos.sh. or practice guideline.pt. or random allocation.sh. or random*.tw. or random.af. or randomized controlled trial.pt. or randomized controlled trials as topic.sh. or randomized.ab. or randomly allocated.tw. or randomly.ab. or single-blind method.sh. or trial.ab. or trial.ti.) not (case report.tw. or letter.pt. or historical article.pt. or review of reported cases.pt. or multicase review.pt.)
16	4 and 14 and 15
EMBASE	
1	knee osteoarthritis/
2	hip osteoarthritis/
3	knee arthritis/
4	((Osteoarthr* adj3 knee) or (arthr* adj3 knee) or gonarthr* or gon arthr* or femorotibial arthr* or (osteoarthr* adj3 hip) or (arthr* adj3 hip) or coxarthr* or cox arthr*).ti,ab.
5	1 or 2 or 3 or 4
6	diagnostic imaging/

7	exp nuclear magnetic resonance imaging/
8	exp knee arthrography/
9	echography/
10	ultrasound/
11	knee radiography/
12	hip radiography/
13	dual energy computed tomography/
14	X ray/
15	radiography/ or computer assisted radiography/ or digital radiography/ or joint radiography/
16	exp nuclear magnetic resonance/
1 7	computer assisted tomography/
18	exp x-ray computed tomography/
19	(radiograph* or radiolog* or x ray* or mr* or magnetic resonance or ct* or computed tomography or sonograph* or echograph* or ultrasound or ultrasonography).ti,ab.
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	(((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask$3)) or (allocated adj2 random)).tw. or (clin* adj25 trial*).ti,ab. or (clinic: adj trial$1).tw. or (double-blind* or random*).af. or exp "clinical trial (topic)"/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or placebo*.tw. or exp placebo/ or exp randomization/ or Random.af. or Random*.tw. or exp "randomized controlled trial (topic)"/ or randomized.ab. or randomly allocated.tw. or randomly.ab. or trial.ab. or trial.ti. or exp "controlled clinical trial (topic)"/ or randomized controlled trial/ or "randomized controlled trial (topic)"/ or exp "controlled clinical trial"/
22	5 and 20 and 21

COCHRANE

1	MeSH descriptor: [Osteoarthritis, Knee] explode all trees
2	MeSH descriptor: [Osteoarthritis, Hip] explode all trees
3	"Osteoarthr* NEAR/2 knee" or "arthr* NEAR/2 knee" or gonarthr* or "gon arthr*" or "femorotibial arthr*" or "osteoarthr* NEAR/2 hip" or "arthr* NEAR/2 hip" or coxarthr* or "cox arthr*"
4	#1 OR #2 OR #3
5	MeSH descriptor: [Diagnostic Imaging] this term only
6	MeSH descriptor: [Magnetic Resonance Imaging] this term only
7	MeSH descriptor: [Ultrasonography] this term only
8	MeSH descriptor: [Ultrasonics] this term only
9	MeSH descriptor: [Tomography] explode all trees
10	MeSH descriptor: [X-Rays] this term only
11	MeSH descriptor: [Ultrasonography] this term only

12	MeSH descriptor: [Radiography] this term only
13	(radiograph* or radiologic* or x-ray* or mr* or "magnetic resonance" or ct* or "computed tomography" or sonograph* or echograph* or ultrasound or ultrasonography):ti,ab,kw (Word variations have been searched)
14	#5 OR #6 OR #7 0R #8 OR #9 OR #10 0R #11 OR #12 OR #13
15	#4 AND #14

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	page 5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	page 5 and supplementary file 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	page 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	page 6, 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	page 6, 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	page 7, 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	page 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	page 8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	page 8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Table 1 p. 10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	page 8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	page 8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	page 9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 2 p. 11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	page 12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	page 13
	23b	Discuss any limitations of the evidence included in the review.	page 14
	23c	Discuss any limitations of the review processes used.	page 15
	23d	Discuss implications of the results for practice, policy, and future research.	page 13, 15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	page 17
Competing interests	26	Declare any competing interests of review authors.	page 17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	page 17

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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