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Longitudinal MRI-defined Cartilage Loss and Radiographic Joint Space Narrowing Following Intra-Articular Corticosteroid Injection for Knee Osteoarthritis: A Systematic Review and Meta-analysis

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Abstract

Background: Intra-articular corticosteroid injections (IACS) are interventions which provide pain relief in knee osteoarthritis (OA). It remains unclear whether IACS have a deleterious effect on knee cartilage structure.

Purpose: To estimate the effect of IACS on cartilage structure in patients with knee OA, using joint space width (JSW) (in radiographic studies), and cartilage thickness (in magnetic resonance imaging).

Materials and methods: A literature search was performed to identify randomized control trials and observational studies published from inception to June 15, 2022. Studies were included if patients received IACS for knee OA, with a control arm. Given the different metrics used in reporting continuous variable outcomes among studies, pooled estimates for cartilage thickness change were assessed using standardized mean differences (defined as the difference between the means of the groups divided by a within-group standard deviation) to odds ratio transformation.

Author Contributions:

Hamza Ahmed Ibad : Study concept, Study design, Literature search, data extraction, statistical analysis and manuscript writing; Arta Kasaeian: Study design, Literature search, data extractions, and manuscript writing; Elena Ghotbi : Statistical analysis, manuscript editing and review, Frank Roemer: Manuscript editing and review; Mohamed Jarraya: Manuscript editing and review; Farzaneh Ghazi-Sherbaf: Manuscript editing and review; Mahsa Dolatshahi: Manuscript editing and review; Shadpour Demehri: Study concept, Manuscript editing and review; Ali Guermazi: Study concept, Manuscript editing and review.

Conflict of Interest:

Ali Guermazi is a shareholder of BICL. He is a consultant to Pfizer, TissueGene, Regeneron, Novartis, AstraZeneca, and Merck-Serono. Frank W Roemer is a shareholder of BICL. He is a consultant to Grünenthal GmbH and Calibr (past 36 months) None of the remaining authors have any conflicting personal or financial relationships that could have influenced the results of this study.

Sensitivity analyses were conducted based on outcome metric, imaging modality, and number of injections.

Results: Six studies (1437 participants) were identified. The estimated effect of IACS on cartilage structure revealed greater odds of cartilage structure worsening (Odds Ratio (OR): 2.01, 95% Confidence Interval (CI): 1.18,3.44). Sensitivity analyses revealed similar trends, with significant results for singular injections with preference to JSW (OR: 2.44, 95%CI: 1.23,4.82), radiographic outcomes with preference to KL grade (OR: 2.03, 95%CI: 1.01,4.10), binary outcomes with preference to KL grade (OR: 2.93, 95%CI: 1.18,7.25) and quantitative measures (Standardized Mean Differences (SMD): -0.34, 95%CI: -0.66, -0.02)

Conclusions: IACS use may contribute to imaging features of knee cartilage loss. Further studies are warranted to investigate the underlying pathogenesis.

Keywords

Osteoarthritis; Intra-articular; Corticosteroid; Cartilage; Joint Space

Introduction

Osteoarthritis (OA) is the most common form of arthritis, with knee OA accounting for an estimated 80% of OA burden worldwide¹. Global knee OA prevalence and incidence were recently estimated to be 16%². Knee OA is multifactorial, caused by biomechanical, biochemical, and metabolic derangements, ultimately leading to joint failure³. In the absence of disease modifying OA drugs, pharmacological treatment for the disease has been aimed at pain management and inflammatory control so far⁴.

Intra-articular injection is a common treatment choice that is considered a minimally invasive “bridging” intervention to delay surgical knee replacement in patients with advanced knee OA⁴. Particularly, intra-articular corticosteroid injections (IACS) are used for their anti-inflammatory and analgesic properties. IACS are strongly recommended by the American College of Rheumatology for short term pain relief (3–4 weeks) in patients with knee OA⁵, conditionally recommended by the Osteoarthritis Research Society International for short term pain relief⁶ and moderately recommended by the American Academy of Orthopedic Surgeons for IACS in knee OA treatment⁷.

A main emerging concern of IACS usage is its deleterious effects on knee cartilage structure including accelerated articular cartilage loss⁴. Studies have shown time and dose dependent adverse effects of high-dose corticosteroids on human and animal knee cartilage structure *in vitro* and *in vivo*⁸. In addition to accelerated cartilage loss, other potentially negative outcomes have been reported albeit causality to date has not been shown. Such safety events included accelerated OA progression, subchondral insufficiency fractures, complications of pre-existing osteonecrosis, and rapid joint destruction including bone loss^{9,10}. In addition, some studies have shown increased loss of joint space width (JSW) in patients receiving IACS¹¹.

The purpose of this systematic review and meta-analysis was to synthesize an estimate of longitudinal knee cartilage loss based on either direct assessment using quantitative MRI

or using radiographic loss in JSW as a surrogate for cartilage loss and meniscal changes in patients with knee OA who received IACS, compared to patients with knee OA who received placebo or no IACS.

Materials and Methods

Search Strategy and Study Selection

A comprehensive literature search was conducted to find eligible studies in the PubMed, Embase, and Cochrane Library databases (see Appendix 1 for search terms). No date restrictions were applied to include all published studies up to June 15, 2022. Peer-reviewed, original research on the effect of IACS on cartilage thickness and joint space width in patients with knee OA were identified. Screening of articles was performed independently by two authors (H.I. and A.K.). Randomized control trials and observational studies were screened for final eligibility based on the following inclusion criteria: 1) published as original research, 2) full-text was available in English, 3) intervention arm participants (or cases for observational studies) had received at least a single intra-articular administration of a corticosteroid agent in the knee joint, 4) no or placebo injections were administered in the control arm participants, 5) cartilage thickness or JSW were used as outcome measures for structural changes in cartilage, 6) participants of the study met the American College of Rheumatology's criteria for Knee Osteoarthritis or presented with KL grade 2. Exclusion criteria included 1) animal or cadaveric studies, 2) studies assessing non-cartilage measures (e.g., synovial thickness), 3) studies with the binary outcome but with insufficient data to reconstruct a 2x2 table (Not applicable to quantitative studies e.g., JSW in mm, cartilage thickness in mm), 4) studies that used data from the same overarching study (unless there was a different sub-sampling technique), and 5) studies that used a modality other than MRI or X-ray (such as ultrasound). In case of studies that used the same data from the same overarching study we chose the study that was the first to be published as an original research paper. Final eligibility of studies, study selection, and data extraction were reviewed by S.D (an attending musculoskeletal radiologist with 12 years of clinical experience).

Data Extraction

Data extraction was performed by two authors independently (H.I. and A.K.). The baseline clinical characteristics include age, gender, body mass index, time from diagnosis of OA, Kellgren-Lawrence (KL) grade, Western Ontario and McMaster Universities Osteoarthritis Index score, and non-steroidal anti-inflammatory drugs use. Data extracted on interventions included number of IACS injections performed and time intervals between administrations. The longitudinal outcome measurements extracted included follow-up time, imaging intervals, imaging modality, change in JSW or number of patients with change in JSW, change in cartilage volume and/or thickness (in the total, medial, or lateral compartment), and change in KL grade (available in one study). Changes in JSW and cartilage thickness were defined in both quantitative and qualitative (binary) terms in different studies whereas KL grade progression was defined in binary terms in one study. For our primary cumulative synthesis, in studies that reported both quantitative and qualitative measurements, quantitative measurements were preferentially used. In studies with quantitative measurements reporting changes in both cartilage thickness and JSW,

measurements of change in cartilage thickness were preferentially used due to their higher sensitivity regarding change over time (offered using MRI). In one study, cartilage thickness data was compartment-based, in which case, quantitative measurements of JSW loss were used after failed correspondence with the author. Preferential use of other measurements was explored in our sensitivity analyses (see below).

Quality Assessment

The Cochrane risk of bias tool for randomized trials (RoB2) was used to assess the methodological quality and risk of bias in four randomized trials and the Newcastle-Ottawa Quality Assessment Scale (NOSGEN) was used to qualitatively assess the two remaining case-control studies with nine being the maximum score. RoB 2's domains of bias focus on randomized trial design, conduct, and reporting. "Signaling questions" in each domain seek trial features relevant to the risk of bias. Based on signaling questions, an algorithm is generated which proposes a domain-specific risk of bias. The judgment about the risk of bias can be 'Low' or 'High' risk or 'Some concerns'¹². Using RoB2, five general domains including the randomization process, deviations from intended interventions, missing outcome data, measurements of the outcome, and selection of the reported results in the four randomized trials were independently evaluated for risk of bias. The remaining case-control studies were assessed and scored based on NOSGEN's three general domains including selection (of cases and controls), their comparability, and exposure. Two authors evaluated the RoB2 and NOSGEN domains and scores independently. In case of disagreement, a joint consensus was achieved through consultation.

Statistical Analysis

For each study, data extraction yielded several different outcome measures: numerical cartilage thickness change, numerical JSW change, binary cartilage thickness change, binary JSW change, and binary KL grade change. Log odds ratios were used as the outcome effect-size measure for the cumulative synthesis of all studies and for studies of binary outcomes (Binary JSW or KL grade change). Standardized mean differences were used as the outcome effect-size measure for the synthesis of studies of numerical scale outcomes (Numerical JSW and cartilage thickness change). Statistical transformation of the standardized mean differences to an estimate of log odds ratio assuming logistic distributions was performed for the cumulative synthesis of all identified studies.¹³⁻¹⁵

The amount of heterogeneity for all syntheses was estimated using the restricted maximum-likelihood estimator. The Cochrane's Q-test for heterogeneity and the I^2 statistic are reported. To account for the heterogeneity test result and provide generalizable results from the six studies with varying sample sizes included in the meta-analysis, a random effects model using a restricted maximum likelihood estimator was used to synthesize the results^{16,17}. Funnel plots of extracted outcome measures were created to evaluate the presence of publication bias. Egger's funnel plot asymmetry tests were performed, and P-values less than 0.1 indicated statistically significant coefficients. The trim-and-fill method was used to obtain adjusted funnel plots. The analysis was carried out using R (version 4.2.0) and the metafor package (version 3.4.0)

Due to several eligible outcomes being reported by some studies, sensitivity analyses were performed giving preference to one outcome measure over another (e.g., separate analyses for JSW binary change and KL-grade binary change for the same set of studies). In the case of one study (Pelletier et al), compartment-wise cartilage thickness change and cumulative JSW change were reported. The authors were contacted to acquire whole cartilage thickness change, but no response was received. Hence, we chose to report the cumulative JSW loss as the measure of choice at our discretion.

Results

Study Selection

The literature search identified 270 studies from PubMed, 151 studies from Embase, and 281 studies from the Cochrane Library. Twenty-three duplicated studies were excluded, and the remainder of studies were assessed based on the previously described inclusion criteria. Only one study which did not strictly meet the inclusion criterion of presence of KL 2 was included. In this study participants of the case arm stated a positive response to the following question: ‘During the past 6 months, have you had a treatment with injections of steroids (cortisone, corticosteroids) in either of your knee(s) for your arthritis?’. However, 72.1% of the participants in the case arm of this study and 50.8% of the control arm presented with baseline radiographic KL grade 2. Forty-one studies which met the inclusion criteria were evaluated at the full text level. Thirty-four of these studies were excluded after full-text evaluations due to use of wrong interventions (n=1), wrong outcome (n=15), lack of control arm (n=4), wrong study design (n=6), wrong language (n=4), or being reports of studies already included in our analysis (n=4). One additional study was excluded in which the association between IACS use and OA outcomes were assessed only using a cross-sectional design, which did not allow the longitudinal assessment of IACS vs. no IACS on the OA outcomes. The resulting six studies containing measurements of joint space width change, cartilage thickness change, or KL grade change in either quantitative or binary metrics were included in our meta-analysis. The exclusion chart demonstrating the literature review as well as the screening and selection of studies is shown in Figure 1.

Study Characteristics and Methodological Quality

A total of six studies were included in the meta-analysis including 1437 participants. Dosage of IACS administration included 40 milligrams(mg) of triamcinolone acetonide, 32 mg of FX006 (a microsphere-based, extended-release triamcinolone acetonide) and 12 and 18 mg of dexamethasone sodium phosphate. The dosage information for IACS is available in Supplementary Table 4. Out of the six studies, three studies measured cartilage thickness changes (derived from MRI) and four studies measured changes in JSW (derived from X-ray). In addition, one study described changes in KL grade in addition to changes in JSW. Three of the studies provided numerical measurement data (e.g., change in cartilage thickness (in mm) or meniscal thickness (mm) or JSW (mm)) and the remaining three studies provided binary measurement data (e.g., JSW or KL grade worsening). Four studies were randomized controlled trials and the other two were case-control studies derived from the Osteoarthritis Initiative (OAI) database. One study was limited to an abstract. The characteristics of the included studies are summarized in Table 1.

Two of the randomized trials had a moderate risk of bias in their deviations from the intended interventions, and one of the trials had a high risk of bias in its deviations from the intended interventions and missing outcome data while also demonstrating a moderate risk of bias in its measurements of the outcome and its selection of the reported results. The results of the RoB 2 tool are shown in Figure 2. Both studies derived from the OAI database were considered to have acceptable methodological quality with NOS scores of 5 but lacked the required quality metrics for their case definition and selection of controls as measured in the NOS selection domain, as well as the information about their ascertainment of exposure and non-response rate as measured in the NOS exposure domain. The results of the NOSGEN tool are shown in Figure 2.

Meta-analysis

The effect-size odds-ratio and 95% confidence intervals for knee cartilage structure worsening including all six studies is shown in Table 2. Analysis was stratified into two subgroups to preferentially report two valid outcomes (JSW and KL grade) separately. Forest plots of all included studies with individual study results are provided in Figures 3 and 4 for JSW and KL grade subgroups, respectively.

Overall, effect sizes for the primary syntheses showed a significant odds ratio (OR) signifying knee cartilage structure worsening, both when preferentially considering JSW and KL grade outcomes (OR: 2.01 and 1.99, respectively; 95% Confidence Interval: 1.18,3.44 and 1.21,3.28 respectively).

Visual funnel plot assessment for both subgroups showed missing studies in the bottom right-hand corner of the plot (Figures 5 and 6). Egger's regression test for funnel plot asymmetry supported the presence of publication bias for both subgroups (p-values <0.01). Trim-and-fill method for bias correction showed an odds ratio of 2.71 (95% Confidence Interval: 1.54–4.77) for the JSW subgroup and 2.89 (95% Confidence Interval: 1.68–4.97) for the KL grade subgroup.

Several sensitivity analyses were performed to account for different outcome measures of reported outcomes (cartilage thickness, JSW, and KL grade), different metrics of outcomes (numerical or binary), different imaging modalities (MRI or radiography), and number of IACS administrations (single or multiple injections). The summary the syntheses conducted using different imaging modalities is reported in Table 3. Additional syntheses are reported in the supplemental material (Supplementary Table 1). Overall, effect sizes of the sensitivity analyses also trended towards signifying knee cartilage structure worsening, with significance in syntheses of quantitative measurements (effect size: -0.34, 95% Confidence Interval: -0.66, -0.02), radiographic outcomes preferentially reporting KL grade (OR: 2.03, 95% Confidence Interval: 1.01, 4.10), binary outcomes with preference to KL grade (OR: 2.93, 95% CI: 1.18,7.25), and singular injection studies (both preferentially reporting JSW or KL grade) (OR: 2.44 and 2.40 respectively; 95% Confidence Interval: 1.23,4.82 and 1.30, 4.43 respectively).

The forest plots of all included studies in each synthesis and the respective funnel plots are provided in Supplementary File 1.

Discussion

In this meta-analysis, we summarized the available literature regarding potential adverse effects of IACS injections on either progression of cartilage thickness or JSW loss and found that individuals who received IACS were around twice as likely (OR: 1.99 and 2.01 depending on preferential outcome) to experience deleterious effects on knee cartilage structure than individuals who received no or placebo treatment. Our study also found a significant negative estimate (expressed in standardized mean differences) when synthesizing quantitative reports of changes in JSW and cartilage thickness further demonstrating knee cartilage structure deterioration in the context of IACS injections. These pooled data on the available human studies are in line with findings from a systematic review demonstrating significant cartilage damage with higher doses of corticosteroids in in-vitro animal and human models¹⁸.

The primary endpoints of the study were changes in JSW and cartilage thickness and were included in the primary cumulative synthesis, whereas KL grade change data was available in one study in tandem with JSW change and used for sensitivity analysis purposes and an initial subgroup of the primary cumulative synthesis. Interestingly, the worsening of the described endpoints was shown to decrease long-term pain-relief and gain-of-function responses to IACS injections by Maricar et al¹⁹. A meta-analysis by Jüni et al. on the effect of IACS on pain, function, and quality of life showed unclear benefits in the short-term and non-existent benefits in the long term and posed that this is partially due to the high risk of bias and low methodological quality²⁰.

Some studies included in our analysis suggested a protective effect of IACS injections against radiological OA outcomes. For instance, Shih et al., demonstrated that long-term use of TLC599 (a liposomal formulation of dexamethasone sodium phosphate) intra-articular injections provide pain-relief, increased function, and protection of articular cartilage with long-term usage. However, these findings are questionable and could raise concern in multiple domains in risk of bias assessment²¹. McAlindon et al. suggested flaws in the outcome measures of previous studies demonstrating deleterious effects of IACS injections leading to potential biases in reporting treatment complications²². Our meta-analysis attempts to address these concerns by including all such studies that provided well-defined radiographic evidence of change as compared to baseline measurements.

Lack of sensitivity of radiography in the detection of longitudinal knee cartilage structure deterioration in knee OA patients have been raised by several studies, especially in comparison to MRI which can quantitatively measure changes in cartilage morphology and thickness via 3D direct cartilage visualization^{23,24}. To address these concerns, we conducted sensitivity analyses on identified studies based on the used imaging modality (i.e., plain radiograph vs. MRI) and found similar trends in odds ratios as our primary analysis, though some results were found not significant.

Proposed underlying mechanisms of IACS leading to short-term positive outcomes in knee cartilage are related to the steroids' anti-inflammatory effects, decreasing C-reactive protein and erythrocyte sedimentation rates, and allowing for chondrocyte growth²⁵. Yet factors

contributing to the negative effects of IACS injections on knee cartilage structure remain to be investigated in future studies. In-vivo animal models have demonstrated decreased thickness and elasticity of the cartilage as well as inhibited cell maturation and increased fibrillation of the articular surface²⁶. In line with the dose-dependent and time-dependent efficacy of treatment with IACS, the relationships between treatment and negative knee cartilage structure outcomes in knee OA patients may be confounded by both the elevated rate of radiographic knee cartilage volume loss in late stage and symptomatic osteoarthritic knees²⁷. In addition, there may be an increased necessity for receiving injections in individuals with higher pain levels. On the other hand, the analgesic effects of the steroid injections in these patients may accentuate harmful gait patterns due to lack of pain feedback and therefore, lead to accelerated knee articular cartilage deterioration. Our study does not include a risk evaluation regarding potential factors that may or may not increase the likelihood of accelerated progression as defined by our structural outcomes.

In summary, our meta-analysis showed that IACS administration increases the likelihood of knee cartilage structure deterioration as measured by JSW and cartilage thickness (both binary and numerical variables). Given that this meta-analysis included studies investigating MRI-defined cartilage loss and radiographic joint space narrowing and given that JSW may be affected by numerous factors, e.g., swelling and extra fluid in the synovium, this could be considered as a limitation of our results given the available relevant literature. Future trials can be designed to compare the effect of IACS Injection on “MRI-defined Cartilage Loss” vs “Radiographic Joint Space Narrowing”. Further high-quality investigations, including randomized controlled trials are urgently needed to gain further insights in cartilage structure deterioration in knee OA patients undergoing IACS injections to establish guidance for physicians performing IACS by careful selection and screening of candidates prior to intervention. In addition, risk profiles are desirable to avoid potential adverse outcomes including but not limited to cartilage loss and decrease in JSW.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

OA	Osteoarthritis
IACS	Intraarticular Corticosteroids
MRI	Magnetic Resonance Imaging

JSW	Joint Space Width
KL	Kellgren- Lawrence
NOSGEN	Newcastle-Ottawa Quality Assessment Scale

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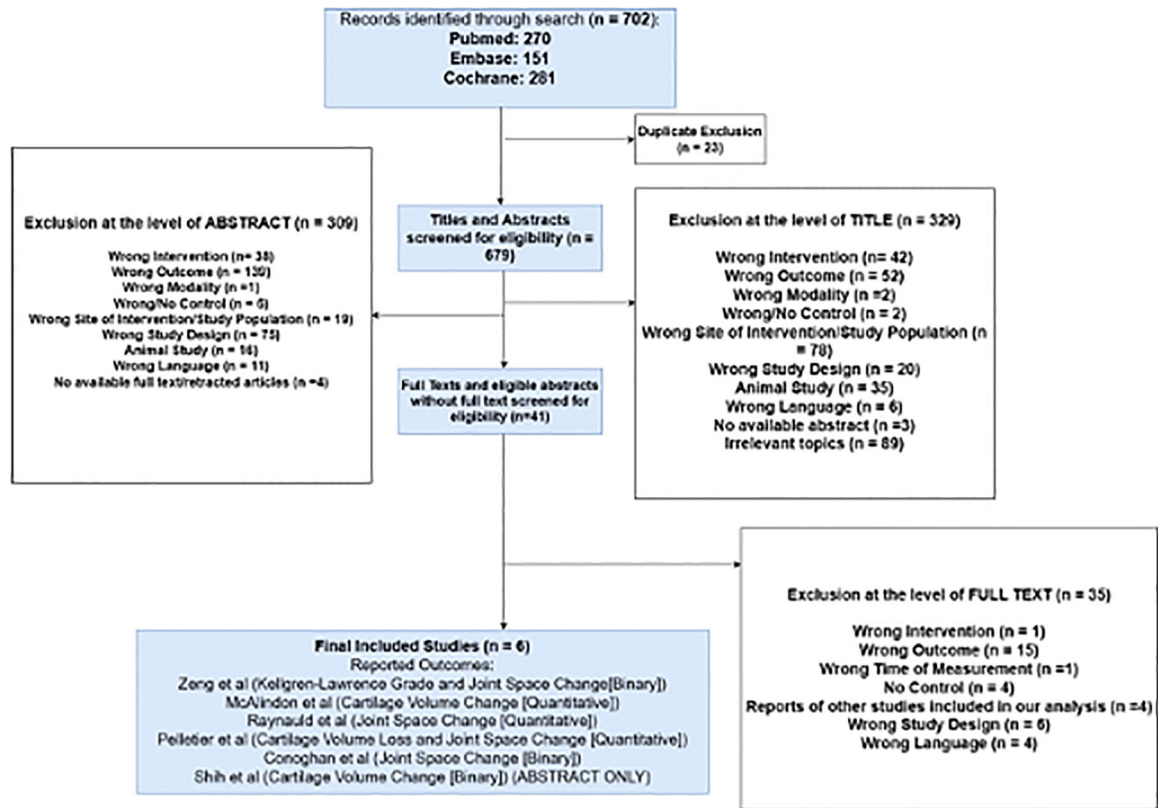


Figure 1: Flowchart summary of literature search and study selection. A more detailed version may be found in Appendix 2.

Cochrane risk-of-bias tool for randomized trials.

<u>Author</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>	
Raynauld							Low risk
Conaghan							Some concerns
McAlindon							High risk
Shih							

D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

Newcastle - Ottawa Quality Assessment Scale.

<u>Author</u>	<u>Selection Domain</u>	<u>Comparability Domain</u>	<u>Exposure Domain</u>	<u>Total</u>
Pelletier	2	2	1	5
Zeng	2	2	1	5

Figure 2: Methodological quality assessment of randomized control trials using the Cochrane Risk of Bias assessment tool for randomized trials and assessment of case-control studies using the Newcastle-Ottawa Quality assessment scale.

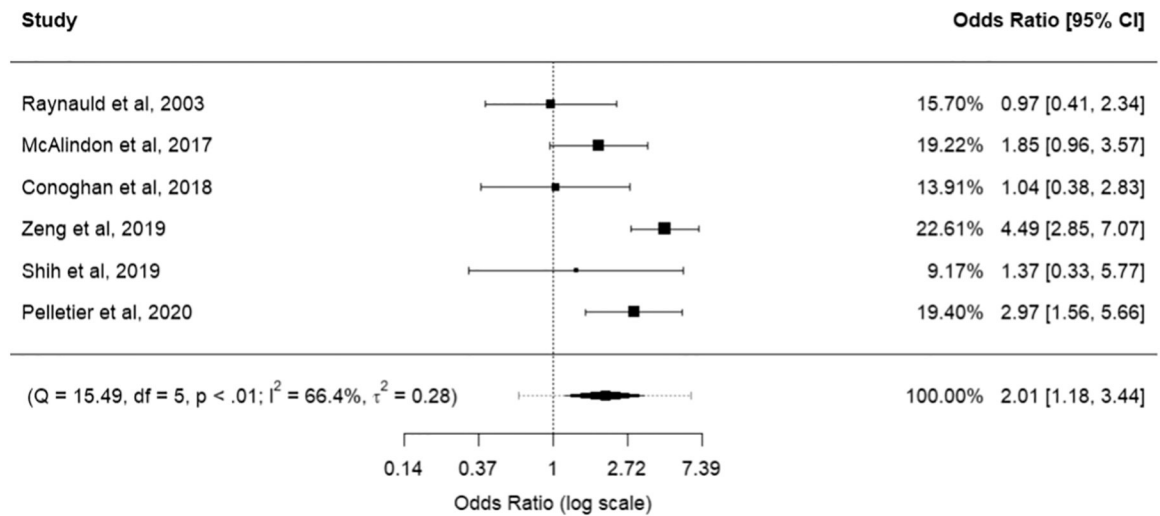


Figure 3:

Forest plot for synthesis of all studies identified through literature search. Results from quantitative studies were transformed into standardized mean differences and subsequently into odds ratios for cumulative synthesis with qualitative outcomes. Preference was given to outcomes reporting JSW.

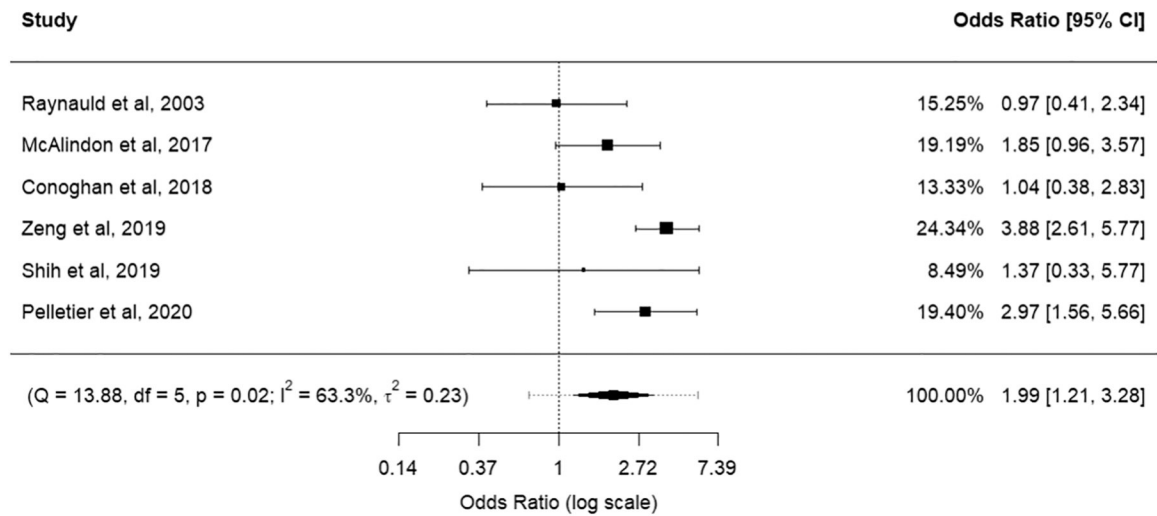


Figure 4: Forest plot for synthesis of all studies identified through literature search. Results from quantitative studies were transformed into standardized mean differences and subsequently into odds ratios for cumulative synthesis with qualitative outcomes. Preference was given to outcomes reporting KL grade.

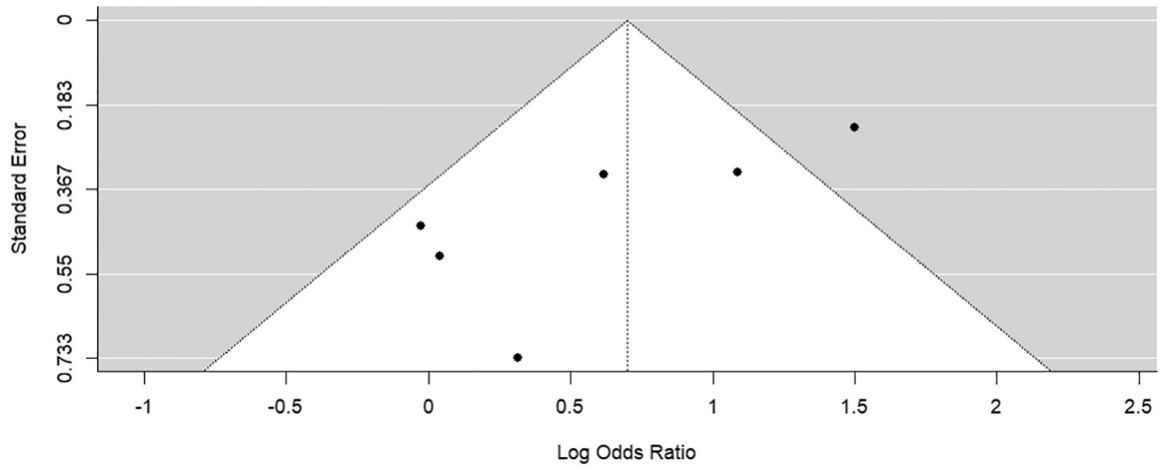


Figure 5: Funnel plot of synthesis of all studies identified through literature search. Preference was given to outcomes reporting JSW.

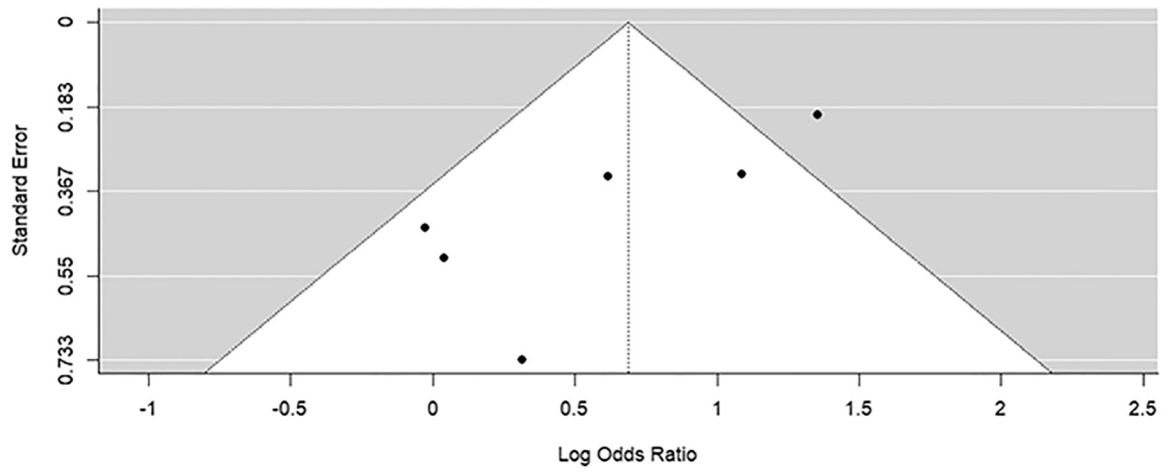


Figure 6: Funnel plot of synthesis of all studies identified through literature search. Preference was given to outcomes reporting KL grade.

Table 1:

Summary characteristics of all studies identified through literature search

First Author	Year of Publication	Journal	Type of Study	Imaging Modality	Reported Outcomes	Control Subjects (n)	IACS Subjects (n)	Mean Age (years)	Sex (% Female)
Raynauld	2003	Arthritis and Rheumatism	Randomized Control Trial	Radiography	JSW (Numerical)	34	34	63.1–63.3	61–74
McAlindon	2017	Journal of the American Medical Association	Randomized Control Trial	Magnetic Resonance Imaging	Cartilage Thickness (Numerical)	70	70	57.2–59.1	52.9–54.3
Conaghan	2018	Journal of Bone and Joint Surgery	Randomized Control Trial	Radiography	JSW (Binary)	162	322	62.1	83.7
Shih	2018	American College of Rheumatology (Abstract)	Randomized Control Trial	Magnetic Resonance Imaging	Cartilage Thickness (Binary)	22	45	NA	NA
Zeng	2019	Osteoarthritis and Cartilage	Case-Control	Radiography	JSW (Binary) & KLG(Binary)	148 (KLG) 104 (JSW)	536 (KLG) 388 (JSW)	64.4 (KLG) 63.4–63.8 (JSW)	64.2–66.8 (KLG) 70.2–73.7 (JSW)
Pelletier	2020	Scientific Reports	Case-Control	Magnetic Resonance Imaging & Radiography	JSW (Numerical) & Compartment-wise cartilage volume / thickness (Numerical)	93	93	66.2–66.6	51.6–62.4

KLG = Kellgren-Lawrence Grade; JSW = Joints Space Width

Summary of random-effects models of all studies identified through literature search. Two subgroups were created, each synthesizing all studies with preference to JSW and KL grade reporting, respectively.

Table 2:

Analysis	Outcome	Confidence Interval	Cochrane's Q-test p-value	I ²	τ^2
All studies, preferentially JSW	2.01	1.18,3.44	<0.01	66.4%	0.28
All studies, preferentially KL grade	1.99	1.21,3.28	0.02	63.3%	0.23

Summary of random-effects models of sensitivity analyses conducted based on imaging modality (MRI or radiography)

Table 3:

Analysis	Outcome	Confidence Interval	Cochrane's Q-test p-value	I ²	τ ²
Radiographic outcomes – preferentially JSW	2.08*	0.98, 4.45	<0.01	78.3%	0.45
Radiographic outcomes – preferentially KL grade	2.03 *	1.01, 4.10	<0.01	78.3%	0.45
MRI outcomes	1.76*	0.97, 3.20	0.71	0.0%	0.00

* Odds Ratios