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Review

Impact of anterior cruciate ligament surgery on the development of knee osteoarthritis: A systematic literature review and meta-analysis comparing non-surgical and surgical treatments

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ABSTRACT

Introduction: Context: The development of knee osteoarthritis (OA) after anterior cruciate ligament (ACL) injury is now widely recognized. The impact of surgical or non-surgical management on the development of post-traumatic osteoarthritis is still debated in the medical community.
Here, we present a meta-analysis comparing the impact of surgical or non-surgical management of ACL injuries on the development of knee OA.
Method: A systematic literature review was conducted using data from the PubMed, EMBASE, Medline, and Cochrane libraries from February to May 2019. Only randomized clinical trials published between 2005 and 2019 with a non-surgical group and a surgical group were included to explore the onset or progression of knee OA after ACL injury. Trials had to have at least one radiographic endpoint (Kellgren—Lawrence scoring system). Heterogeneity was assessed using the Cochrane's Q and I^2 statistical methods.
Results: Only three randomized controlled trials met the inclusion criteria and were selected for meta-analysis. Of the 343 injured knees included in the studies, 180 underwent ACL reconstruction and 163 underwent non-surgical treatment. The relative risk of knee osteoarthritis was higher after surgery than after non-surgical treatment (RR 1.72, CI 95% [1.18–2.53], $I^2 = 0\%$).
Conclusion: The results of this meta-analysis suggest a predisposition to knee osteoarthritis after ACL reconstruction surgery compared with non-surgical management. Due to the small number of good quality studies available, further well-conducted randomised studies are needed to confirm these findings.

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis worldwide and a major cause of disability in middle-aged and older adults [1]. OA is an important cause of disability, mainly in the knee, which is the most frequently affected joint [2].

Risk factors for OA can be broadly categorized as either systemic (age, sex, genetics, body mass index, and ethnicity), mechanical (joint structure/alignment, physical activity), or traumatic such as ligament injury [3–6]. In this article we will focus on the knee joint, and in particular the risk of developing knee osteoarthritis after anterior cruciate ligament injury. A decade after injury, half of the patients have radiographic OA [5,7,8]. The long-term consequences are significant; the frequency of total knee replacement for knee osteoarthritis 20 years after anterior cruciate ligament (ACL) injury is 7-fold greater than that in the sector of the population without injury [9].

To date, the management of an ACL injury is not codified. It can be surgical or not. The decision for surgery is often made based on the patient's previous level of fitness. Indeed, ACL injuries may be of greater concern for athletes than for the general population [10]. More than 200 000 ACL reconstructions are performed in the United States annually, with an annual estimated direct cost of 3 billion dollars [11]. Surgical reconstruction of the ACL has been regarded as critical for a positive long-term outcome, particularly in persons wishing to resume sporting activity [12–14].

Because the function of the ACL is to limit the anteroposterior translation of the tibia on the femur [15], some authors have suggested that early reconstruction of the ligament could limit instability of the

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femorotibial joint [4,5] and thus reduce the risk of development of osteoarthritis. Therefore, purely non-surgical management techniques are discussed in comparison with surgery.

A meta-analysis conducted in 2014 [15] was not limited to randomized controlled trials. Its main purpose was to find clinical and functional evidence for the choice between interventional and non-surgical management. One of the sub-objectives of this meta-analysis was to investigate the course of knee OA after ACL injury. The meta-analysis included studies of low level of evidence, the results of which showed that the presence of an ACL injury with conservative management could lead to the development or worsening of knee OA, whereas ACL surgery reduced this risk.

We aimed to systematically review the literature assessing the development of OA after surgical or non-surgical management of ACL injury and to provide a meta-analysis, including only randomized controlled trials, to compare the impact of surgical or non-surgical management of an ACL injury on the development and progression of knee osteoarthritis.

2. Method

2.1. Research strategy

This systematic review and meta-analysis was based on the guidelines of the Preferred Reporting Items for Symptomatic Reviews and Meta-Analysis statement [16]. We systematically reviewed articles written in English or French for studies evaluating the impact of anterior cruciate ligament reconstruction on the development of osteoarthritis. We searched articles published in Medline (via PubMed), Embase, the Cochrane Library, and databases for the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual meetings since May 2019. Search terms were: Knee Osteoarthritis, Osteoarthritis, Knee, Anterior Cruciate Ligament (ACL) Reconstruction, Anterior Cruciate Ligament Injuries, anterior cruciate ligament, anterior, cruciate, ligament, ACL, humans.

In addition, the reference lists of the articles detected were manually searched to identify additional relevant articles. The trials were selected based on their titles and abstracts and then on their full text. Duplicates were then removed.

2.2. Study selection

The population of interest included all patients with ACL rupture. We included studies comparing ACL reconstruction and non-operative treatment for known modifiable factors of knee osteoarthritis. Knee osteoarthritis was defined by a Kellgren–Lawrence radiographic score of >2 [17]. Only randomized controlled trials (RCTs) were eligible for inclusion.

We included RCTs of adults aged >18 years with ACL injury who had undergone either surgical or non-surgical management. X-rays were performed and classified using the Kellgren–Lawrence scoring system, both at baseline and at the end of the study.

The primary endpoint was the trigger or increase in knee OA after one of the two procedures between the baseline and the end of the study.

Articles that related to high level athletes and that included a meniscal reconstruction were excluded.

2.3. Data extraction and quality assessment

Two independent investigators (SF and ML) collected data using a predetermined form. Data were collected on the study design, sample size, treatments received, patient and control group characteristics (age, sex, study duration, year of publication, recruitment duration, mean participant age, and definition of the outcome measure (radiologic or MRI)). Comparisons were performed between the data collected by the two investigators, and disagreements were resolved by a third investigator (CHR). The quality of the studies suitable for meta-analysis was evaluated.

The Cochrane Bias Risk Assessment Tool was used to determine the methodological quality of the RCTs. A total of seven areas were assessed: random sequence generation, concealment of allocation, participant blinding, outcome assessor blinding, incomplete outcome data, selective reporting, and other biases [18].

Each domain was assigned a judgment of low risk of bias, high risk of bias, or unclear risk of bias by two reviewers.

The authors or patients of the selected studies were not contacted.

2.4. Subgroup analysis

A secondary analysis was performed, which included articles initially excluded from the study design. They were finally retained in a subgroup analysis because their results met our primary endpoint and allowed us to increase the total sample of patients analyzed. To avoid distorting the results of the main meta-analysis, this subgroup study was conducted in parallel. These studies were open [19,20] or retrospective [21].

2.5. Data analysis

Qualitative data, expressed as percentages in each study, were compiled by estimating the relative risk and its 95% confidence interval by meta-analysis using the inverse variance method. Statistical heterogeneity was assessed using the Cochrane Q test and the I^2 value. I^2 value of <25% indicates low statistical heterogeneity, $25\% \leq I^2 < 50\%$ indicates moderate statistical heterogeneity, and $50\% \leq I^2 < 75\%$ indicates high statistical heterogeneity. For moderate or high levels of heterogeneity, a random effect model was used. Statistical analyses were performed using RevMan software (version 5.3; Cochrane Collaboration), and a $P < 0.05$ was considered significant.

3. Results

3.1. Literature research

Searches in the various databases resulted in the selection of 958 articles. A total of 877 studies were excluded based on their titles, and 69 based on the content of their abstracts. Fig. 1 illustrates the selection process. Of the remaining 12 articles; six were deemed eligible and six were excluded because there was (i) insufficient information to calculate the outcome measure of interest, (ii) no discernible surgical or non-surgical treatment group for comparison, (iii) study design details were not available or invalid, or (iv) meniscal surgery was included. Of these, only three RCTs [4,22,23] were retained as relevant and meeting the selection criteria after reading of the full article. The three other articles [19–21] assessed the relative risk of developing osteoarthritis but had exclusion criteria.

3.2. Study characteristics

Table 1 sums up the main characteristics of the 3 studies included in the analysis. All three studies were randomized controlled trials, with a total of 343 participants overall, 180 in the surgery group versus 163 in the non-surgical-only group.

All three studies were conducted in Europe, namely in Sweden [4,21] and Switzerland [22]. Follow-up averaged 2–11.1 years, and the radiographic score was determined using the Kellgren–Lawrence scoring system (KL).

Of the studies in the secondary analysis (Appendix B) that did not meet all inclusion criteria due to study design, one study was based on the Taiwanese health insurance registry [21] with 9769 eligible cases (1374 surgical vs. 7395 non-surgical). Another study was based on the Swedish national registry [20], including 64 614 cases (30 919 surgical vs. 33 695 non-surgical) and one study [19] by the formation of two

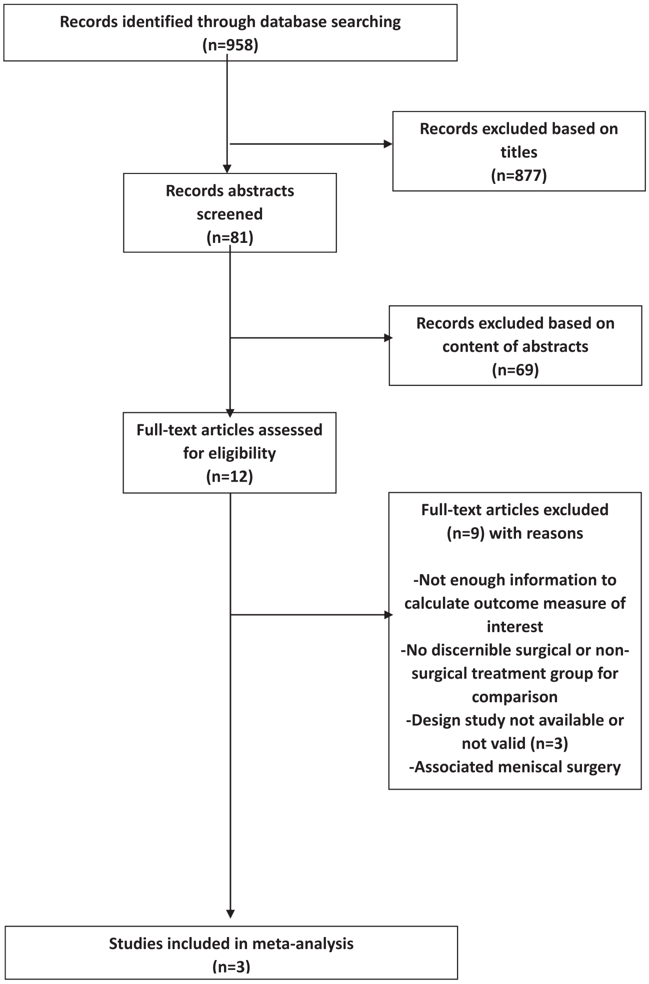

Fig. 1. Flowchart.

cohorts of a clinic without specifying the modalities, including 50 patients (25 surgical vs. 25 non-surgical). The mean follow-up period ranged from 9 to 17 years.

A table including studies that were not included because they did not use KL is presented in a (Appendix A).

3.3. Main analysis

Based on the KL scores among the three RCTs [4,22,23], the analysis suggests a higher risk of developing knee osteoarthritis after ACL surgery than after non-surgical management. The relative risk was based on an M–H fixed effect model of 1.72, 95% CI (1.18–2.53), with a statistically significant difference between the two groups (Fig. 2). In addition, all the selected studies found a higher risk of developing osteoarthritis after surgery (Frobell et al., 1.80, 95% CI (0.92–3.52) [4]; Harris et al. 1.67, 95% CI (0.75–3.68) [23]; Kessler et al. 1.70, 95% CI (1.18–2.53) [22]).

Surgery was not a protective factor for osteoarthritis in any of the three studies.

3.4. Subgroup analysis

We repeated the analyses with the three excluded items [19–21] (Appendix A). The relative risk of developing osteoarthritis in the surgery group was 1.51 times higher than in the non-surgical group, with a 95% CI (1.21–1.90).

3.5. Sensitivity analysis

3.5.1. Main analysis

Statistical heterogeneity tests showed minimal heterogeneity between studies of 0% ($Chi^2 = 0.003$, df = 2 (P = 0.99), $I^2 = 0\%$). A test for overall effects Z = 2.79 (P = 0.005) (Fig. 2).

3.5.2. Secondary analysis

When repeating the analysis with all studies included, the heterogeneity tests found significant heterogeneity, with $I^2 = 76\%$ (Tau2 = 0.04; $Chi^2 = 20.59$; df = 5; P = 0.001) (Appendix B).

3.6. Risk of bias and quality of evidence

This presents the quality assessment of the studies included in the meta-analysis using the Cochrane Library evaluation tool (Table 2).

3.6.1. Allocation (selection bias)

Two trials [4,23] were described as randomized and assessed as low risk. One trial [22] did not describe the method used, and we assessed it as being of uncertain risk. We assessed the concealment of allocation as a low risk.

Table 1
Table of study characteristics.

Study	Design	Origin	N (op vs. non op)	Mean age	Diagnosis/score	Concomitant injury	Mean follow up period (year)	Sex (M/F)
Kyle Harris et al.	RCT	Sweden	121 (62 vs. 59)	18–35	MRI/KL	51% meniscal injury; 31% chondral lesion	5	88/32
Kessler et al.	nRCT	Switzerland	109 (60/49)	30.7	Arthroscopy/KL	35% MM/cartilage injury	11.1	68/11
Frobell et al.	RCT	Sweden	121 (62 vs. 59)	26.3 ± 5.1 vs. 25.8 ± 4.7	MRI/KL	51% meniscal injury; 31% chondral lesion	2	88/32

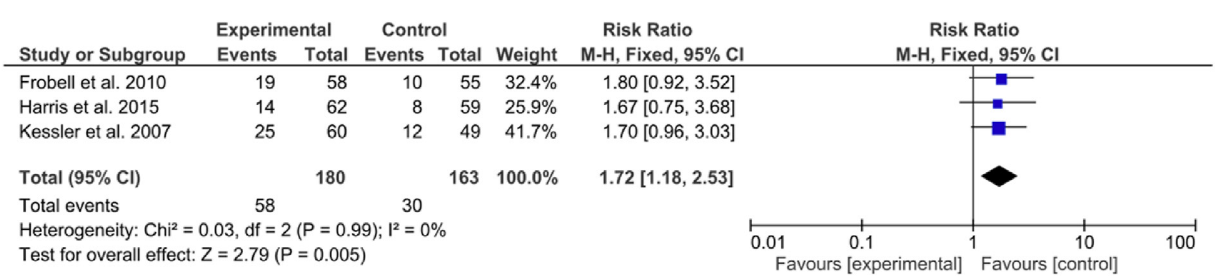

Fig. 2. Main analysis.

Table 2
Bias risk assessment tool (Cochrane library).

Bias risk assessment tool (cochrane library)	Allocation concealment?	Random sequence generation?	Blinding (participants and personnel)	Blinding (outcome assessment)	Selective reporting?	Incomplete outcome?	Other biases?
Frobell et al. [4]	L	L	H	H	L	U	L
Harris et al. [23]	L	L	H	H	L	U	L
Kessler et al. [22]	U	U	H	H	L	U	H

3.6.2. Blinding (outcome assessment, and participants and personnel)

We assessed a high risk of blinding bias in all three studies.

3.6.3. Incomplete outcome (attrition bias)

The risk of attrition bias was considered uncertain for all papers with missing or undescribed data.

3.6.4. Selective reporting (reporting bias)

The overall trials were judged to have a low risk of bias in the face of detailed protocols.

3.6.5. Other biases

We did not find any other sources of bias in two of the studies [4,23], but there was a high risk of other sources of bias in one of the trials [22].

4. Discussion

The results of our meta-analysis suggest that in patients with ACL injury, ACL reconstruction surgery is associated with the knee to the development of osteoarthritis, than non-surgical management is.

These results are consistent with those of Smith et al. [24], who reported that the current literature was insufficient to provide a basis for clinical decision-making regarding treatment indications for people who have experienced ACL rupture.

Based on our review, there is limited evidence to suggest the need for a change in management strategies in the development of osteoarthritis in the first few years following index management strategies. However, the methodological evidence is limited, as it is based on only three RCTs, one of which [23] followed the methodology of Frobell [4] in 2007.

This is all the more important because there is a variety of approaches to the choice of ACL treatment, both in terms of the surgical technique itself (which are not detailed in this meta-analysis), and in terms of choice of whether to perform an intervention or to promote rehabilitative management.

To date, there are no clear recommendations regarding the management of ACL lesions. Recommendations may depend on the patient's joint instability after the injury, age, gender, socioeconomic profile, and, above all, on the patient's level of sportsmanship and radiographic lesions [25]. In a study by Kapoor et al. [25], the authors surveyed 192 orthopedic surgeons using a questionnaire; 58% said they would recommend ACL reconstruction for a 22-year-old man with a recent ACL rupture, compared to 24% who would manage such a rupture in the patient conservatively. The remaining 18% would treat the patient conservatively first and then reassess their clinical status 5–12 weeks later, to consider surgery at a later stage.

More specifically, we were interested in the development of OA in these ACL lesions. A consistent conclusion from the literature review is that reports of OA are often poor, with heterogeneous clinical studies. The development of OA in injured joints is caused by intra-articular pathogenic processes initiated at the time of injury, combined with long-term changes in the dynamic loading of the joint. The variation in outcomes is reinforced by additional individual variables similar to those determining the choice of management, to which genetics, obesity, and muscle strength may be added [3].

4.1. Importance of the choice of measurement tool

Several previous studies could not be included in our analysis in view of the tools used to measure osteoarthritis of the chosen knee, which could not be combined or compared between the different articles, having not all selected the gold standard Kellgren—Lawrence scoring system [24,26]. Diestad et al. had, moreover, in their 2009 systematic review, attempted to compare the different scoring systems, finding them extremely difficult to compare [27].

4.2. Associated meniscal disease

Some authors have questioned whether there is an increased risk of osteoarthritis in the presence or absence of a meniscal lesion, combined with ACL rupture [27]. Indeed, in this study, we found that there is greater incidence of osteoarthritis when there is a combined ACL lesion compared to an isolated lesion; this study confirmed older data in the literature [7,28,29]. Thus, we focused on isolated ACL lesions. Here again, the results diverge in the literature, as Diester and colleagues demonstrated an increased risk of OA after surgical management of LCA, regardless of whether a meniscal lesion was present [30].

4.3. Surgery or non surgery for development osteoarthritis?

Concerning the development of knee osteoarthritis:

The current literature suggests that an ACL lesion in the general working population could be conservatively managed (non surgical) if well-managed rehabilitative care is in place. In a 2004 systematic review, no superiority was found in the surgical management of knee osteoarthritis development [7]. It revealed an increase in postoperative pain with a rebound of secondary osteoarthritis. In addition, Nordenvall et al. [20] in 2014, as well as Luc et al. [31], do not seem to find any protective effect of ACL surgery on knee osteoarthritis.

In another study conducted in 2017, no protective effect was found on the development of knee osteoarthritis in patients with an operated ACL injury compared to unoperated patients [21].

Conversely, data from discordant literature can be found in the study by Meuffels et al. [19], who found an identical rate of osteoarthritis between the surgical and non-surgical groups. However, these results should be taken with caution in view of the sample of patients analyzed (excluding the entire active general population) who benefitted from an adapted rehabilitation protocol.

Also, these results should be taken with caution as the indication for surgical management of ACL injury depends on the patients' previous physical activity. Athletes are more likely to benefit from surgery. However, it is now recognized that high levels of physical activity predispose to greater knee osteoarthritis than in the general active population. As the resumption of sport is carried out following ACL surgery, it is therefore likely that the results we present in this review, with a higher prevalence of osteoarthritis in this group, are not solely due to the surgery itself. The risks described could be increased by the addition of the activity of these patients [32].

4.4. Development of osteoarthritis in athletes?

Our meta-analysis should be taken with caution as it only concerns ACL injury in the general population, excluding studies of young athletes. However, young athletes represent a large majority of ACL injuries.

In high-level athletes, ACL reconstruction is more frequently performed to allow a quicker return to sport, to the detriment of joint degeneration. In 2020, Wang et al. described the notion of post-traumatic osteoarthritis (PTOA) which would develop after a joint injury.

Specifically, patients with an anterior cruciate ligament (ACL) injury are at high risk of developing (PTOA) [31,33].

It is hypothesized that the surgery itself may result in trauma to the knee joint, and that post-surgical hemarthrosis may result in prolonged inflammation of the joint [34].

Postoperative inflammation can damage synovial stem cells and lead to a compromised joint environment, affecting the ability of tissues to heal.

4.5. Limitations

This systematic review of the literature has some limitations, such as selection bias regarding the study participants. In addition, the weak methodology of the studies and the heterogeneity of the selection criteria, especially for the radiological score, contribute to the limitations of the study.

The radiographic analyses used to diagnose OA in different types of sub-samples is generally poorly described.

It is also possible that patients who were managed surgically had severe ACL injuries with associated meniscal damage. Poor outcome selection could partly explain these results.

The small number of articles in our meta-analysis remains a very important limitation; however, we made this choice in order to include only well-conducted RCTs for which one of the judging criteria was the development of post-surgical OA, comparing a surgical versus a non-surgical group.

For this reason, at the end of our literature search, we included articles published before 2014, since the results of the meta-analysis of Smith et al. [24] are based on clinical studies of varying quality, for which osteoarthritis was not the primary endpoint, most often including an associated meniscal lesion.

In our study, we did not perform a subgroup analysis comparing different ACL impairments (partial or total), which in some previous studies showed the importance of this knowledge [35].

Another limitation of our study may be the length of the studies included in this meta-analysis. Osteoarthritis is known to be a disease that is usually slow to progress. In a study conducted on microRNA in 2022, arthroscopy was identified as a rapid progressor of knee osteoarthritis [36]. However, in the literature, rapid progressors are evaluated over defined periods of 5 years with little superiority of MRI to assist in structural diagnosis [37].

In our meta-analysis, although one study was 2 years in duration, it used MRI to assess osteoarthritic progression. The other studies had a duration of 10 and 11 years, which seems relevant for studying the evolution of post-traumatic osteoarthritis pathology.

4.6. Conclusion

In conclusion, the results of this meta-analysis suggest that ACL reconstruction surgery predisposes patients to knee OA compared to non-surgical management. Due to the small number of good quality studies available, further well-conducted randomised studies are needed to confirm these findings.

Scientific contributions of each author

Stephanie Ferrero, MD: First author, main contributor to conception, draft of the article, and critical revision of the article for important intellectual content; final approval of the version to be published.

Marion Louvois, MD: Second author, substantial contributions to critical revision of the article, and final approval of the version to be published.

Thomas Barnetche: Third author, substantial contributions to critical revision of the article, and final approval of the version to be published.

Veronique Breuil MD, PhD: author, substantial contributions to critical revision of the article, and final approval of the version to be published.

Christian Roux, MD, PhD: Last author, substantial contributions to the design of the work, critical revision of the article, and final approval of the version to be published.

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Declaration of competing interest

None declared.

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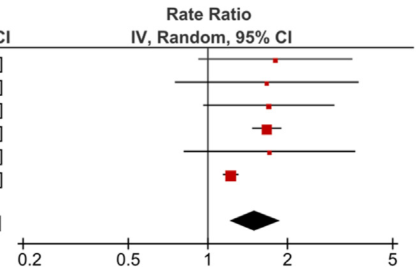
Appendix A. Table characteristics of all studies.

Study	Design	Origin	N (op vs. non op)	Mean age	Diagnosis/ score	concomitant injury	Mean follow up period (year)	Sex (M/F)
Kyle Harris et al.	RCT	Sweden	121 (62 vs. 59)	18–35	MRI/KL	51% meniscal injury; 31% chondral lesion	5	88/32
Kessler et al.	nRCT	Switzerland	109 (60/49)	30.7	Arthroscopy/ KL	35% MM/cartilage injury	11.1	68/11
Frobell et al.	RCT	Sweden	121 (62 vs. 59)	26.3 ± 5.1 vs. 25.8 ± 4.7	MRI/KL	51% meniscal injury; 31% chondral lesion	2	88/32
Meuffels et al.	Case control study	Netherlands	50 (25/25)	Op: 37.6 38/ 12.6 No op: 37.8	MRI	74% meniscal injury; 38% chondral lesion	10	38/12
Nordenvall et al.	Open cohort	Sweden	64614 (30,919 vs. 33,695)	26.01 vs. 32.03	Radiographic/ KL	Not precise	1987–2009	Not precise
Lin et al.	Retrospective cohort study	Taiwan	8769 (1374 vs. 7395)	30.46 vs. 40.3	Radiographic	Not precise	January 1996 and December 2013	4968/ 3800

Appendix B. Secondary analysis.

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Frobell et al. 2010	0.5878	0.3424	8.6%	1.80 [0.92, 3.52]
Harris et al. 2015	0.5128	0.4084	6.5%	1.67 [0.75, 3.72]
Kessler et al. 2007	0.5306	0.2916	10.8%	1.70 [0.96, 3.01]
Lin et al. 2017	0.5128	0.0651	32.1%	1.67 [1.47, 1.90]
Meuffels et al.	0.5365	0.3812	7.3%	1.71 [0.81, 3.61]
Nordenvall et al. 2014	0.1989	0.0346	34.7%	1.22 [1.14, 1.31]
Total (95% CI)			**100.0%**	**1.51 [1.21, 1.90]**

Heterogeneity: Tau² = 0.04; Chi² = 20.59, df = 5 (P = 0.0010); I² = 76%
Test for overall effect: Z = 3.60 (P = 0.0003)



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