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Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review

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▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bjsports-2013-093258).

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Accepted 2 March 2015
Published Online First 30 March 2015

ABSTRACT

Background Anterior cruciate ligament (ACL) injury is an important risk factor for development of knee osteoarthritis (OA). To identify those ACL injured patients at increased risk for knee OA, it is necessary to understand risk factors for OA.

Aim To summarise the evidence for determinants of (1) tibiofemoral OA and (2) patellofemoral OA in ACL injured patients.

Methods MEDLINE, EMBASE, Web of Science and CINAHL databases were searched up to 20 December 2013. Additionally, reference lists of eligible studies were manually and independently screened by two reviewers. 2348 studies were assessed for the following main inclusion criteria: ≥20 patients; ACL injured patients treated operatively or non-operatively; reporting OA as outcome; description of relationship between OA outcome and determinants; and a follow-up period ≥2 years. Two reviewers extracted the data, assessed the risk of bias and performed a best-evidence synthesis.

Results Sixty-four publications were included and assessed for quality. Two studies were classified as low risk of bias. Medial meniscal injury/meniscectomy showed moderate evidence for influencing OA development (tibiofemoral OA and compartment unspecified). Lateral meniscal injury/meniscectomy showed moderate evidence for no relationship (compartment unspecified), as did time between injury and reconstruction (tibiofemoral and patellofemoral OA).

Conclusions Medial meniscal injury/meniscectomy after ACL rupture increased the risk of OA development. In contrast, it seems that lateral meniscal injury/meniscectomy has no relationship with OA development. Our results suggest that time between injury and reconstruction does not influence patellofemoral and tibiofemoral OA development. Many determinants showed conflicting and limited evidence and no determinant showed strong evidence.

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is a common sports-related injury, with an annual incidence of approximately 5/10 000 persons in the general population.[1] Osteoarthritis (OA) is a well-known, long-term complication of ACL rupture, with a prevalence of 10–90% at 10–20 years post-injury.[2 3] It is important to identify the risk factors contributing to OA in patients with ACL rupture, because some risk factors may be modifiable as to prevent onset or early-stage progression of OA. At present, the only treatment options for OA are symptomatic relief, osteotomy, unicompartmental arthroplasty and, for end-stage disease, total knee arthroplasty. Early intervention is critical because patients with post-traumatic OA are typically young and it is important to postpone total knee arthroplasty.[4]

Numerous studies have evaluated the long-term consequences of ACL rupture. These studies are heterogeneous with regard to methodology, including treatments used, inclusion of additional intra-articular injuries, reported OA outcomes and descriptions of determinants (potential risk factors). Three previous systematic reviews of development of OA after ACL rupture were limited either because they considered OA only in the tibiofemoral compartment or because they focused on one type of treatment (ACL reconstruction). Oiestad *et al*[5] conducted a systematic review of the prevalence of OA in the tibiofemoral joint occurring more than 10 years after ACL injury. They included studies that used ACL reconstruction techniques, which are no longer used (eg, Leeds-Keio polyester ligament surgery or suturing of the ACL). Therefore, we did not include these techniques in this systematic review. To better evaluate newer and current techniques and rehabilitation methods, we included only studies which reported results based on current ACL reconstruction procedures. Magnussen and Spindler[6] reviewed patient factors affecting clinical and radiographic outcomes after ACL reconstruction in prospective studies with a 5-year minimum follow-up. Prospective study design was an inclusion criterion, so they missed the results of all retrospective studies. Claes *et al*[7] reviewed the literature on long-term radiographic outcome after autologous ACL reconstruction; studies with a mean follow-up of less than 10 years were excluded. They investigated only one predictor, namely the relationship between meniscal status and OA development in the reconstructed knee. Currently, there is no consensus about operative or non-operative treatment for preventing OA, and degenerative changes can develop in all knee compartments.

Culvenor *et al*[8] showed in their narrative literature review that patellofemoral OA after ACL reconstruction occurs as frequently as tibiofemoral OA. Different mechanisms, such as inflammation, concomitant injuries to the patellofemoral articular cartilage, meniscal injury, graft choice and changes of knee biomechanics, may play a role in the development of patellofemoral OA.[8]

The previous published reviews presented a part of the general question: Which determinants influence the development of degenerative changes after

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To cite: van Meer BL, Meuffels DE, van Eijsden WA, *et al. Br J Sports Med* 2015;**49**:975–983.

an ACL rupture? This systematic review will fill the gaps of the previous reviews and supplement recent published literature on both tibiofemoral and patellofemoral OA. We systematically reviewed the evidence for determinants of both (1) tibiofemoral OA and (2) patellofemoral OA in patients with an ACL injury treated operatively or non-operatively.

METHODS

The reporting in this systematic review was conducted according to the PRISMA statement.[9]

Data sources and searches

MEDLINE, EMBASE, Web of Science and CINAHL medical literature databases were searched up to 20 December 2013. Search terms included anterior cruciate ligament, synonyms for injury and synonyms for osteoarthritis. The full electronic search strategy for the MEDLINE database is presented in table 1. Similar search strategies were used in EMBASE, Web of Science and CINAHL. Additionally, the reference lists of all eligible studies were manually screened.

Study selection

Two reviewers (BLvM and MR) assessed the studies for the following inclusion criteria:

- The following study designs with at least 20 patients: randomised controlled trial, prospective follow-up study, matched case–control study and retrospective study;
- Subjects had to have an ACL injury consisting of:
  - Patients treated non-operatively or
  - Patients treated operatively; use of an arthroscopic or mini-arthrotomy technique and use of bone-patellar tendon-bone, hamstring tendon or allografts;
- Written in English, German, Dutch, Spanish, French, Swedish, Danish or Norwegian;
- Full text available;
- Measured one of the following OA outcomes:
  - Clinical OA: according to a clinician, self-reported or American College of Rheumatology (ACR) criteria[10]; osteotomy, unilateral knee arthroplasty or total knee arthroplasty (indirect measures for clinical knee OA);
  - Radiographic OA;
  - OA findings on MRI;
  - OA findings during arthroscopy;
- The relationship between outcome and determinant, defined as potential risk factors, must have been described or data must be available to calculate the relationship;
- Determinant studied in ≥2 studies;
- Determinant must be measured prior to the OA outcome;
- Follow-up period of at least 2 years.

Table 1 Search strategy for MEDLINE

(anterior cruciate*[tw] OR acl[tw])
AND
(rupture*[tw] OR tear*[tw] OR torn*[tw] OR lacerat*[tw] OR defici*[tw] OR injur*[tw] OR lesion*[tw] OR disrupt*[tw] OR trauma*[tw] OR reconstruct*[tw] OR repair*[tw])
AND
(osteoarthrit*[tw] OR osteo-arthrit*[tw] OR osteoarthro*[tw] OR osteo-arthro*[tw] OR arthrosis[tw] OR arthroses[tw] OR arthrot*[tw] OR gonarthro*[tw] OR degen*[tw]
NOT
(animals[mesh] NOT humans[mesh])

Animal studies and reviews were excluded. Disagreements on inclusions were resolved by discussion and, if necessary, a final decision was made by a third reviewer (JANV).

Data extraction and risk of bias assessment

Two reviewers (WAvE and BLvM) extracted the study characteristics, follow-up times, determinants, outcomes and the relationship between outcome and determinant.

The determinants were grouped into *patient characteristics* (age, body mass index (BMI), sex), *physical examination, activity level* and *intra-articular-related factors*. The determinant that was named laxity consisted of results of a pivot shift test, Lachman test, KT 1000 arthrometer or description of 'laxity'. The location of injury of the intra-articular determinants: chondral injury and meniscal injury/meniscectomy were presented when reported as such in the studies. For determining the influence of *tunnel placement* on OA development, we used the assessment of tunnel position when a study evaluated both femoral and tibial tunnel positions and graft inclination. If studies had the same population and determinant, but different follow-up times, we presented the results of the study with the longest follow-up time. When a determinant was measured in various ways and had different relationships with OA outcome in one study, all results were presented. For the analyses of the relationship between determinants and OA outcome, the distinction between patellofemoral and tibiofemoral OA was made. If the studies did not report a specific compartment for the OA outcome or if the studies reported the OA outcome for all compartments, then the study was classified as OA outcome in which the compartment was unspecified. Since the included studies presented the relationship between determinant and OA outcome in various ways, we reported the presence of a 'positive significant relationship' or 'negative significant relationship' or 'no significant relationship'. For presentation of the results, we distinguished the studies into two groups: (1) studies with inclusion of non-operatively treated patients and (2) studies with inclusion of both operatively and non-operatively or solely operatively treated patients.

We evaluated the selected studies on 12 aspects using modified questions of existing risk of bias assessment tools.[11–13] Our assessment tool contained questions about the aim of the study, description of inclusion and exclusion criteria, collection of data, validity and reliability of OA outcome measures, independent measure of determinants, valid and reliable measurement of determinants, follow-up period, loss to follow-up, and use of adequate statistical analyses. Four reviewers independently assessed the quality of the included studies. Disagreements were resolved by discussion. Studies were classified as low risk of bias when they scored 'adequate' on all the following topics: the authors reported inclusion of consecutive patients; there was unbiased assessment of the study outcome and determinants; the determinant measures were used accurately (valid and reliable); if there was a loss to follow-up of less than 20% and there was a description of the reasons, and if there was correction for confounding. The assessment tool used is given in online supplementary appendix table S1.

Data synthesis and analysis

Since the studies were considered clinically heterogeneous with regard to the outcome measures and determinants studied, it was not possible to pool the data for statistical analysis, and therefore we performed 'a best-evidence synthesis'.[14 15] With the use of the system developed by van Tulder *et al*,[16] the following ranking of levels of evidence was formulated: (1) Strong evidence is provided by two or more studies with low risk of bias and by generally consistent findings in all studies (≥75% of the studies reported consistent findings). (2) Moderate evidence is provided by one low risk of bias study and two or more high risk of bias studies and by generally consistent findings in all studies (≥75%). (3) Limited evidence is provided by one or more high risk of bias studies or one low risk of bias study and by generally consistent findings (≥75%). (4) Conflicting evidence is provided by conflicting findings (<75% of the studies reported consistent findings). (5) No evidence is provided when no studies could be found.[16 17]

RESULTS

Identification and selection of the literature

The search resulted in 2348 studies, for which all abstracts were reviewed. After screening of the abstracts, 157 were identified as possibly relevant, and full texts were retrieved. After review of the full texts, 56 met all the inclusion criteria (figure 1). There were no disagreements on inclusions. The references of all 56 studies were reviewed and 8 additional studies meeting the inclusion criteria were identified. Thus, 64 studies in total were included in this systematic review.

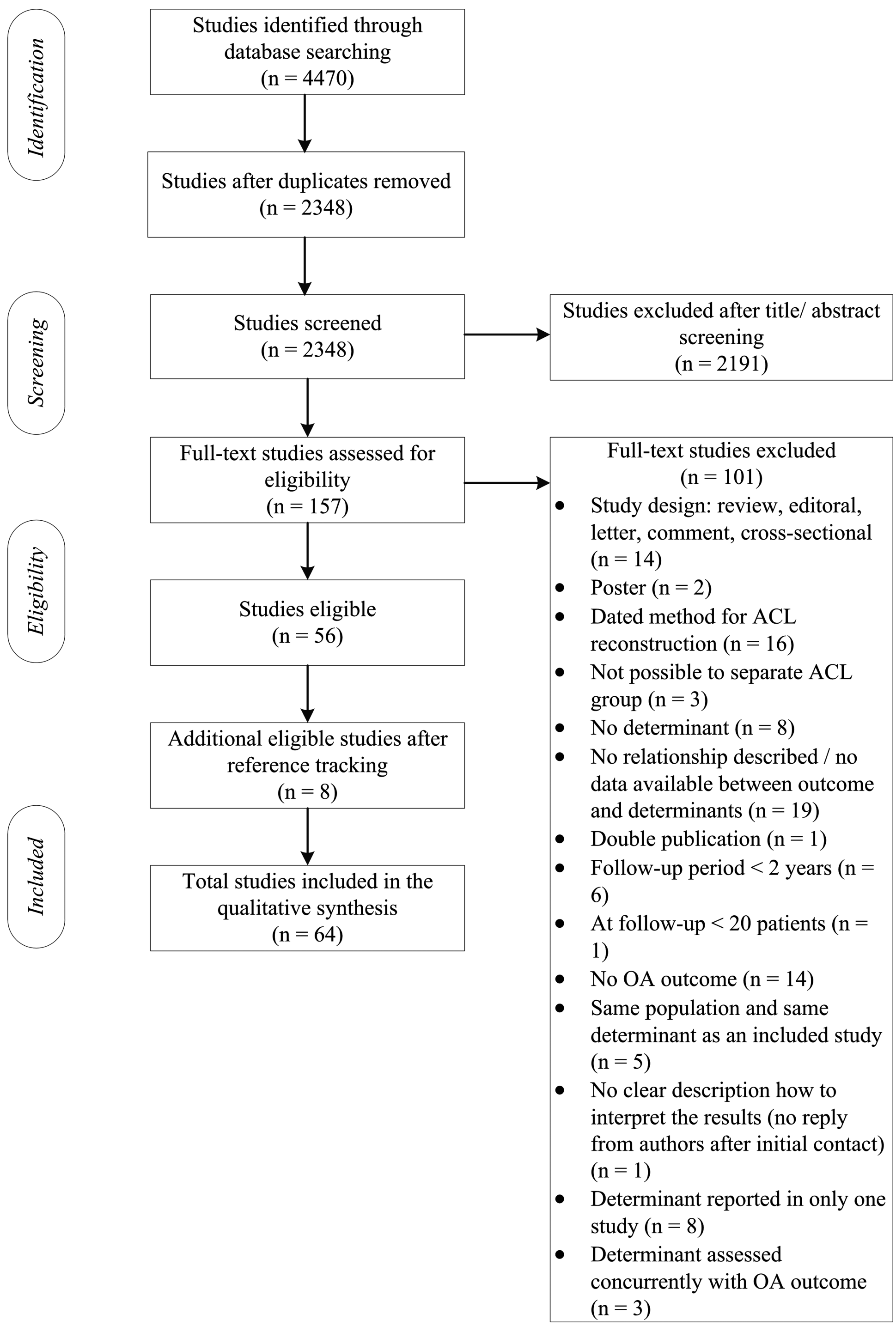

Figure 1 Study selection (ACL, anterior cruciate ligament; OA, osteoarthritis).

Description of the included studies

The characteristics of the included studies are presented in online supplementary appendix table S2. The studies had the following designs: randomised controlled trial (n=12),[18–29] prospective follow-up study (n=22),[30–51] matched case–control study (n=2)[52 53] and retrospective study (n=28).[54–81] The number of patients available for follow-up measurement in the studies ranged between 30 and 780. In 62 studies, the OA outcome was determined with radiographs, and in 2 studies by MRI assessment.[28 47] Only two studies[43 70] reported radiological OA and clinical OA as outcomes. Therefore, the findings of this systematic review address the influence of radiological OA. In 47 studies (4956 patients), the treatment strategy was ACL reconstruction, in 4 studies[22 64 71 76] (273 patients) non-operative treatment, and in 13 studies[19 30 31 40 41 47 53 65 70 72 77 79 80] (1169 patients) both reconstruction and non-operative treatment. The mean follow-up time varied between 3.9 and 20 years.

Risk of bias assessment

Two studies[35 56] were classified as 'low-risk of bias'. An overview of the quality assessment score of the included studies is presented in supplementary appendix table S3. The main aim of the two low risk of bias studies was to investigate risk factors for development of knee OA after ACL reconstruction. In these studies, the number of patients used for analyses was >50; Ahn *et al* had a sample size of more than 100 patients (n=117). Janssen *et al* used only hamstring tendon grafts, and Ahn *et al* bone-patellar tendon-bone grafts.

Influence of determinants in non-operatively treated patients

Four studies[22 64 71 76] included solely non-operatively treated patients. Limited evidence was found for a positive relationship between *meniscectomy* and development of knee OA in chronic ACL-deficient knees. Determinants *age*, *BMI* and *sex* were excluded because they were studied in only one study. The influence of *laxity* on OA development could not be presented because it was measured concurrently with the OA outcome.

Influence of determinants in both operatively and non-operatively or solely operatively treated patients

Patient characteristics

Conflicting evidence was found for the influence of *age* on OA outcome in all compartments (tables 2–4). For the influence of *BMI* on OA outcome in the tibiofemoral compartment and compartment unspecified, conflicting evidence was found after ACL rupture. Limited evidence for no relationship was found for OA development in the patellofemoral compartment after ACL

Table 2 Influence of determinants on tibiofemoral radiological OA outcome in operatively and operatively/non-operatively treated cohorts

Group	Determinant	Number of studies	Significant relationship LR/HR: n studies	No significant relationship LR/HR: n studies	Best-evidence synthesis	Comments
Patient characteristics	Older age	6	Positive relationship: HR: 2[43 66]	LR: 1[56] HR: 3[37 40 60]	Conflicting evidence	
	Higher BMI	4	Positive relationship: LR: 1[56]* HR: 1[66]	HR: 2[40 43]	Conflicting evidence	*Ahn *et al*:[56] lateral OA
	Male sex	3	Positive relationship: HR: 1[43]	HR: 2[60 66]	Conflicting evidence	
Intra-articular-related factors	Additional injury	2	Positive relationship: HR: 1[44]	HR: 1[63]	Conflicting evidence	
	Chondral injury	3	Positive relationship: HR: 2[37 60]	HR: 1[66]	Conflicting evidence	
	Meniscal injury/ meniscectomy	11	Positive relationship: Medial meniscus injury/meniscectomy: LR: 1[56] HR: 2[20 57] Lateral meniscus injury/ meniscectomy: HR: 1[57] Location not reported: HR: 6[37 40 60 69 80 81]	Medial meniscus injury/ meniscectomy: None Lateral meniscus injury/ meniscectomy: LR: 1[56] HR: 1[20] Location not reported: HR: 2[48 66]	Medial meniscus injury/ meniscectomy: Moderate evidence positive relationship Lateral meniscus injury/ meniscectomy: Conflicting evidence Location not reported: Limited evidence positive relationship	
	Longer time between injury and reconstruction	6	Positive relationship HR: 1[61]	LR: 1[56] HR: 4[37 43 60 66]	Moderate evidence for no relationship	
	ACL reconstruction (vs non-operative treatment)	7	Positive relationship HR: 2[31 40] Negative relationship: HR: 1[47]	HR: 4[19 53 70 80]	Conflicting evidence	
	Graft type BPTB (vs HT)	8	Positive relationship HR: 4*[37 38 43 52]	HR: 6**[18 19 21 38 52 69]	Conflicting evidence	*Leys *et al*:[38] medial OA; Mascarenhas *et al*:[52] lateral OA **Leys *et al*:[38] lateral OA; Mascarenhas *et al*:[52] medial OA

*Refers to the comment in the last column in the same row.
ACL, anterior cruciate ligament; BMI, body mass index; BPTB, bone-patellar tendon-bone; HR, high risk of bias studies; HT, hamstring tendon; LR, low risk of bias studies; OA, osteoarthritis.

Table 3 Influence of determinants on patellofemoral radiological OA outcome in operatively and operatively/non-operatively treated cohorts

Group	Determinant	Number of studies	Significant relationship LR/HR: n studies	No significant relationship LR/HR: n studies	Best-evidence synthesis	Comments
Patient characteristics	Older age	3	Positive relationship: HR: 2[37 42]	LR: 1[56]	Conflicting evidence	
	Higher BMI	2		LR: 1[56] HR: 1[42]	Limited evidence for no relationship	
Intra-articular	Meniscal injury/meniscectomy	3	Positive relationship: HR: 1[41]	LR: 1[56] HR: 1[37]	Conflicting evidence	
	Longer time between injury and reconstruction	3		LR: 1[56] HR: 2[37 42]	Moderate evidence for no relationship	
	ACL reconstruction (vs non-operative treatment)	5	Positive relationship: HR: 2[31 41]	HR: 3[19 47 70]	Conflicting evidence	
	Graft type BPTB (vs HT)	6	Positive relationship: HR: 1[19]	HR: 5[18 37 38 52 69]	Limited evidence for no relationship	
	Tunnel placement	2		LR: 1[56] HR: 1[62]	Limited evidence for no relationship	

ACL, anterior cruciate ligament; BMI, body mass index; BPTB, bone-patellar tendon-bone; HR, high risk of bias studies; HT, hamstring tendon; LR, low risk of bias studies; OA, osteoarthritis.

rupture. Nine studies evaluated the relationship between *sex* and OA development after ACL rupture. For development of tibiofemoral OA, three high risk of bias studies[43 60 66] showed conflicting evidence. Moderate evidence was found for no relationship between male sex and OA development in compartment unspecified.[25 35 67 68 75 79]

Physical examination

One low risk of bias[35] and two high risk of bias[34 45] studies showed no relationship between *laxity* and development of OA in compartment unspecified (table 4). Thus, there is moderate evidence for no relationship between laxity and OA development.[34 35 45] Moderate evidence was also found for no relationship between range of motion and OA development in compartment unspecified.[34 35 45 50] Performance of a single-legged hop test was evaluated in three studies[34 35 45] and showed conflicting evidence.

Activity level

One low risk of bias study[35] and one high risk[68] of bias study found no significant relationship between activity level before reconstruction and OA development (compartment unspecified; table 4).

Intra-articular-related factors

Two high risk of bias studies[44 63] investigating *additional injuries in general* showed conflicting evidence (tables 2–4).

One high risk of bias study[68] evaluated patellar, medial and lateral chondral injury after ACL rupture and their influence on OA development in compartment unspecified. Medial and patellar chondral injury showed a positive significant relationship with development of knee OA and lateral chondral injury showed no relationship. There were ten other studies,[23 25 33 35 37 49 50 60 66 73] of which one low risk of bias study[35] showed conflicting evidence if the location of the chondral injury was not reported.

In nine studies,[20 35 49 55–57 67 68 75] of which two were low risk of bias studies, a distinction between medial and lateral *meniscus injury/meniscectomy* was made. We found moderate evidence for a positive relationship between medial meniscus injury/meniscectomy and development of OA (tibiofemoral and unspecified) in patients with an ACL rupture. Conflicting evidence was found for influence of lateral meniscus injury/meniscectomy on tibiofemoral OA development and moderate evidence for no significant relationship on OA development in compartment unspecified. Twenty-one high risk of bias studies did not report the location of the meniscus injury; these studies showed limited evidence for positive relationship with development of tibiofemoral OA and conflicting evidence if the compartment of OA development was unspecified. The studies did not report the extent of meniscectomy. Results of meniscus injury/meniscectomy showed conflicting evidence for a relationship with patellofemoral OA development. One low risk of bias study[56] and one high risk[37] of bias study reported no significant relationship, and in one high risk of bias study[41] meniscus injury/meniscectomy was related to patellofemoral OA development.

In seven studies,[37 42 43 56 60 61 66] one of them low risk of bias study, moderate evidence for no relationship was found for the influence of *time between injury and reconstruction* on development of tibiofemoral and patellofemoral OA. Seven studies did not specify the compartment of OA outcome and these studies showed conflicting evidence.[25 35 36 68 74 78 79]

In 13 studies investigating *ACL reconstruction* versus *non-operative treatment*, conflicting evidence was found with patellofemoral OA,[19 31 41 47 70] tibiofemoral OA[19 31 40 53 70 80] and if no specific compartment[30 65 72 77 79] was reported.

Fourteen studies reported outcomes on the relationship between *bone-patellar tendon-bone graft* versus *hamstring tendon graft* and development of tibiofemoral OA or OA in compartment unspecified. The studies gave conflicting findings. Mascarenhas *et al*[52] and Leys *et al*[38] reported opposite results for the development of medial and lateral tibiofemoral OA; Mascarenhas *et al* found a positive relationship between bone-patellar tendon-bone graft and development of lateral tibiofemoral OA, whereas Leys *et al* found a positive relationship between bone-patellar tendon-bone graft and development of medial tibiofemoral OA. In six studies,[18 19 37 38 52 69] the influence of graft type on patellofemoral OA was studied: limited evidence was found for no relationship. Conflicting evidence in two high risk of bias studies[26 68] was found for the influence of *allograft* on OA development in compartment unspecified.

One low risk of bias study and five high risk of bias studies reported on the influence of *tunnel placement* of the ACL reconstruction and OA development. Two studies showed no

Table 4 Influence of determinants on radiological OA outcome compartment unspecified in operatively and operatively/non-operatively treated cohorts

Group	Determinant	Number of studies	Significant relationship LR/HR: n studies	No significant relationship LR/HR: n studies	Best-evidence synthesis	Comments
Patient characteristics	Older age	9	Positive relationship: HR: 3[50 65 78]	LR: 1[35] HR: 5[25 67 68 75 79]	Conflicting evidence	
	Higher BMI	5	Positive relationship: HR: 2[65 68]	LR: 1[35] HR: 2[67 79]	Conflicting evidence	
	Male sex	6	Positive relationship: HR: 1[68]	LR: 1[35] HR: 4[25 67 75 79]	Moderate evidence for no relationship	
Physical examination	Laxity	3		LR: 1[35] HR: 2[34 45]	Moderate evidence for no relationship	
	Range of motion loss	4	Positive relationship: HR: 1[50]	LR: 1[35] HR: 2[34 45]	Moderate evidence for no relationship	
	Performance single-legged hop test	3	Negative relationship: HR: 1[45]	LR: 1[35] HR: 1[34]	Conflicting evidence	
Activity	Activity level before reconstruction	2		LR: 1[35] HR: 1[68]	Limited evidence for no relationship	
Intra-articular	Chondral injury	8	*Medial chondral injury:* Positive relationship: HR: 1[68] *Lateral chondral injury:* None *Patellar chondral injury:* Positive relationship: HR: 1[68] *Location not reported* Positive relationship: LR: 1[35] HR: 3[33 50 73]	*Medial chondral injury:* None *Lateral chondral injury:* HR: 1[68] *Patellar chondral injury:* None *Location not reported* HR: 3[23 25 49]	*Medial chondral injury:* Limited evidence for positive relationship *Lateral chondral injury:* Limited evidence for no relationship *Patellar chondral injury:* Limited evidence for positive relationship *Location not reported* Conflicting evidence	
	Meniscal injury/meniscectomy	19	Positive relationship: Medial meniscus injury/meniscectomy: LR: 1[35] HR: 5 (49, 55, 67, 68: concurrent*, 75) Lateral meniscus injury/meniscectomy: None Both meniscectomy: 1[49] Location not reported: HR: 9[36 39 50 51 54 70 73 74 78]	Medial meniscus injury/meniscectomy: HR: 1 (68: prior*) Lateral meniscus injury/meniscectomy: LR: 1[35] HR: 4 (49, 67, 68: prior and concurrent, 75) Both meniscectomy None Location not reported: HR: 4[23 32 59 79]	Medial meniscus injury/meniscectomy: Moderate evidence positive relationship Lateral meniscus injury/meniscectomy: Moderate evidence no relationship Both meniscectomy: Limited evidence for positive relationship Location not reported: Conflicting evidence	*Li *et al*;[68] concurrent: meniscectomy concurrent with ACL reconstruction; prior: meniscectomy prior to ACL reconstruction
	Longer time between injury and reconstruction	7	Positive relationship HR: 4[36 68 74 78]	LR: 1[35] HR: 2[25 79]	Conflicting evidence	
	ACL reconstruction (vs non-operative treatment)	5	Positive relationship: HR: 1[65] Negative relationship: HR: 2[72 77]	HR: 2[30 79]	Conflicting evidence	
	Graft type BPTB (vs HT)	7	Positive relationship: HR: 5[24 29 38 45 68]	HR: 2[23 28]	Conflicting evidence	
	Graft type allograft (vs autograft)	2	Positive relationship: HR: 1[68]	HR: 1[26]	Conflicting evidence	
	Tunnel placement	4	Positive relationship: HR: 1[68]	HR: 3[38 46 58]	Limited evidence for no relationship	
	Single bundle (vs double bundle)	2		HR: 2[25 27]	Limited evidence for no relationship	

*Refers to the comment in the last column in the same row.
ACL, anterior cruciate ligament; BMI, body mass index; BPTB, bone-patellar tendon-bone; HT, hamstring tendon; HR, high risk of bias studies; LR, low risk of bias studies; OA, osteoarthritis.

significant relationship between tunnel placement and patellofemoral OA development.[56 62] Four high risk of bias studies[38 46 58 68] evaluated the influence on development of OA in compartment unspecified; three studies[38 46 58] found no significant relationship, resulting in limited evidence for no relationship.

Two studies with high risk of bias reported on the influence of double-bundle and single-bundle ACL reconstruction and OA development in compartment unspecified.[25 27] These studies showed limited evidence for no relationship with development of OA.

DISCUSSION

We summarised the available evidence concerning which determinants influence the risk of OA after ACL rupture. Sixty-four studies were included, but 62 were classified as high risk of bias.

Key clinically relevant findings

There was moderate evidence for:

- Medial meniscal injury/meniscectomy influencing OA development (tibiofemoral OA and compartment unspecified).
- No relationship with time between injury and reconstruction and OA development in patellofemoral and tibiofemoral compartments.
- No relationship between OA development in unspecified compartments and the following determinants was found: sex, laxity, range of motion and lateral meniscal injury/meniscectomy.

There was limited evidence for influencing OA development by the following determinants:

- Medial and patellar chondral injury (compartment unspecified).
- Meniscal injury/meniscectomy if the location was not reported (tibiofemoral OA).
- Meniscectomy of both menisci (compartment unspecified).
- Meniscectomy in non-operatively treated patients.

The following determinants showed limited evidence for no relationship with OA development:

- BMI (patellofemoral OA).
- Graft type (patellofemoral OA).
- Activity level pre-reconstruction (compartment unspecified).
- Lateral chondral injury (compartment unspecified).
- Tunnel placement (patellofemoral OA and compartment unspecified).
- Single-bundle versus double-bundle ACL reconstruction technique (compartment unspecified).

Outcome measure—OA

Notably, most studies reported only radiological OA. Only two studies[43 70] reported both radiological OA and clinical OA as outcomes for evaluating the influence of determinants. Thus, the findings of this systematic review address the influence on radiological OA but not on clinical OA. We were also interested in determinants that influence early degenerative changes; however, the majority of the included studies reported mid-term or long-term follow-up. A mean follow-up time ≤5 years was reported in only eight studies.

The role of the meniscus: keep or cut?

Many studies evaluated the influence of the meniscus on the development of OA. The majority of studies did not report the location of the tear, the extent of meniscectomy, and in which compartment the OA was developing. We had no information about the influence of the time of the meniscus injury, also a possible confounder.

Although more extended, our results are in line with the findings of the previous reviews concerning meniscal injury and meniscectomy as risk factors for tibiofemoral OA development. However, these previous reviews did not distinguish between medial and lateral meniscal injuries/meniscectomies.

Our review provides important data that medial meniscal injury/meniscectomy showed a relationship with the development of OA, but lateral meniscal injury/meniscectomy did not. Anatomically, the medial meniscus is more rigid with less anterior posterior mobility than the more mobile lateral meniscus; this could have an effect on the secondary OA changes of the affected compartment.[82]

These findings contradict the results of a systematic review concerning clinical outcome and risk of OA development in patients undergoing meniscectomy. In that review, Salata *et al*[83] found four studies with a higher rate of OA in the lateral meniscectomy group, two studies reporting no significant difference, and one study in which medial meniscectomy was more related with OA. These results were not included in our systematic review because the meniscus studies did not meet the inclusion criteria. Moreover, most studies did not report the location (medial or lateral compartment) of the meniscal resection, making it difficult to discern the specific influence of medial/lateral meniscectomy.

A possible explanation for conflicting evidence for development of OA (compartment unspecified) and limited evidence for a positive relationship with development of tibiofemoral OA is the heterogeneity of the location of meniscectomy. Also, the included studies did not report the extent of meniscectomy, except the study of Fink *et al*,[30] which found in patients treated non-operatively for their ACL rupture a significant correlation between the degree of OA and the amount of meniscal resection that was performed at the time of the initial arthroscopy. For the ACL reconstructed group, there was no significant correlation.

A focus on patellofemoral OA

Patellofemoral OA is gaining consideration as an important clinical entity.[84] Regarding OA of the patellofemoral joint, two studies[37 56] found no relationship with meniscal injury/meniscectomy in an ACL reconstructed population. However, in the study of Keays *et al*,[37] the relationship was close to significant and in another study meniscal injury/meniscectomy was significantly associated with patellofemoral OA.[41] Furthermore, in a population without ACL injury, meniscectomy was related to development of patellofemoral OA.[85] An explanation for this relationship could be the influence of altered biomechanics in the knee, or the meniscal tear was a feature of the already existing early knee OA.

The results of this systematic review confirm the thoughts about the importance of preservation of the meniscus for preventing development of OA. Our advice for future studies is to document the location and extent of meniscectomy as well as which knee compartments, medial, lateral or patellofemoral, were used for assessing OA development.

Three key clinical questions and our findings

In clinical practice, three questions are important with regard to choice of treatment for ACL injuries and the development of knee OA.

1. *What is the influence of operative versus non-operative treatment on OA development?* On the basis of our results, we

cannot answer this question because there was conflicting evidence. However, we should note that, in the operatively treated patients, the graft type was mostly bone-patellar tendon-bone.[30 31 40 41 47 53 65 70 72 77 79 80] So, there is less information on hamstring tendon reconstructed patients versus non-operatively treated patients and development of OA, despite both graft types being commonly used for ACL reconstruction.[86]

2. *When operative treatment is chosen, what is the influence of graft choice?* On the basis of this systematic review, we cannot recommend one graft type to reduce OA risk.
3. *Is early reconstruction necessary for preventing OA development?* The aim of early timing of reconstruction after ACL rupture is to prevent new meniscal and cartilage damage. Our results indicate that early or late reconstruction is not related to greater risk of patellofemoral or tibiofemoral OA.

However, for OA development in unspecified compartment, we cannot give any indication which time point, early or late after injury, is best for reconstruction with regard to preventing OA development. A possible explanation for these conflicting results is the heterogeneity of additional injuries in the included studies and differences in the definition of early reconstruction. Furthermore, Smith *et al*[87] found in their meta-analysis no significant difference in the incidence of chondral and meniscal injuries between early and delayed reconstruction groups (the latter was defined as a minimum of 6 weeks postinjury). Another explanation might be that degenerative changes develop after the initial trauma caused by, for example, traumatic bone marrow lesions and activation of proinflammatory cytokines, independently of the choice of treatment.[3] Besides, ACL reconstruction is a new trauma with additional damage such as bone marrow lesions, haemarthrosis and inflammation-related factors, for example, inflammatory cytokines.

Other considerations

We did not distinguish between partial and complete ACL tears. Partial or complete tears need to be diagnosed by arthroscopic evaluation, the reference for diagnosing ACL rupture. We may assume that the studies that included operatively treated patients enrolled patients with complete ACL tears. However, most studies did not describe their arthroscopic findings. Of the four studies which included non-operatively treated patients, one[64] reported the inclusion of both partial and complete tears, two[22 76] reported the inclusion of only complete tears and one [71] did not describe the type of the ACL tear. Thus, it is difficult to draw conclusions about the difference between the influence of partial and complete tears on OA development. Besides, in long-term follow-up studies, it is possible that partial tears progress to complete ACL tears[88] and then it is difficult to distinguish the contribution of the partial and complete tears to the development of OA.

A determinant, which was not included in the results, is the altered knee biomechanics after ACL injury. The possible explanation for no information about this determinant is that studies researching the altered knee biomechanics include fewer patients (n≤20, exclusion criteria of this systematic review) and that these studies have a cross-sectional design (exclusion criteria of this systematic review). Chaudari *et al*[89] suggest that the observed changes in the knee biomechanics result in altered loading patterns and influence metabolic changes in the underlying cartilage. Reduced internal tibial rotation was found in patients after ACL reconstruction compared with the contralateral knee and healthy controls.[90] In addition to this finding, a recently published cross-sectional study showed that after ACL reconstruction, patients with patellofemoral OA and valgus alignment had significantly less internal knee rotation during walking and running than patients with valgus alignment and no patellofemoral OA.[91] However, this study had a cross-sectional design; prospective studies are required to evaluate if the altered knee rotation is a result of patellofemoral OA or influences the development of patellofemoral OA.

Limitations

This systematic review has some limitations. First, of the 64 included studies, only 14[23 26 34 35 38 42 43 46 47 56 65 67 68 70] corrected for the influence of confounders. Consequently, the reported influence of determinants on the development of OA may be partly or completely explained by other factors. By presenting the data, one of the criteria to be classified as a low risk of bias study was controlling for confounding. A prospective observational study design is the best way to determine predictors for development of OA after an ACL rupture. However, prospective collected data and retrospective analyses (research question defined after data collection) were also useful for our research question. Therefore, we also included retrospective study designs.

Second, the number of patients available for analysis at follow-up in the included studies was small. Only 18 of the 64 (28%) included studies had more than 100 patients available for analysis at follow-up.

Third, the included studies were heterogeneous with regard to study design, determinant assessment, additional intra-articular injuries, reported OA outcome, definition of OA and the statistical methods used. For these reasons, comparison between the included studies was difficult and pooling of the data was not possible. Therefore, we used the second best option for presenting the results: best-evidence synthesis.

Best-evidence synthesis is appropriate for summarising the available evidence. All the 64 included studies were classified as low risk or high risk of bias; however, only two studies met the criteria for low risk of bias. This means that reporting of inclusion of consecutive patients, measurement of determinants and outcomes independently, using accurate measures for the determinants and description of loss to follow-up with a maximal 20% and correction for confounding were poorly performed and described in the included studies.

Finally, we attempted to evaluate the influence of determinants on the development of tibiofemoral and patellofemoral OA separately. However, we should note that some studies did not use a valid tool for the compartmental assessment of OA, (eg, Kellgren and Lawrence score for assessment of patellofemoral OA). In some studies, the compartment was not described (compartment unspecified). The evaluation of the correctly used classification system for compartmental OA assessment was not included in the quality assessment tool.

Strengths

The strengths of this systematic review are that we summarised the evidence for tibiofemoral OA and patellofemoral OA outcomes after ACL injury separately. Moreover, we summarised these outcomes in patients who had had ACL reconstruction and those who had been managed with conservative treatment. Additionally, we evaluated determinants that influence early degenerative changes because we included studies with relatively short follow-ups (a minimum of 2 years). To be comprehensive, we chose to include both prospective and retrospective study designs having at least 20 patients. In addition to previously published systematic reviews,[5–7] we included 21 studies published after the search dates of those systematic reviews.

Studies that used outdated surgery techniques were excluded, which resulted in exclusion of many older studies. However, our oldest study included was published in 1989[64] and newer studies might be of better quality as our two low risk of bias studies were published in 2012[56] and 2013.[35] The best-evidence synthesis considers the quality of the studies and accounts for a possible bias. When we analysed the results of studies only published during the past 10 years, the results differed minimally. The only aspects that changed were the influence of chondral injury (location not reported) on OA development (compartment unspecified), and of the graft type bone-patellar tendon-bone; both would change from conflicting evidence to limited evidence for a positive relationship with development of OA. These results of limited evidence still need more high-quality studies in order to make firm recommendations.

Overall, we can conclude that despite the inclusion of many new studies in this comprehensive systematic review, including two low risk of bias studies,[35 56] more low risk of bias studies are required to evaluate determinants and their role in OA development. Many determinants showed conflicting and limited evidence. The following determinants should be further studied in large prospective studies, which could be used for meta-analysis: knee function and activity level, both examined in the first period after ACL rupture, patients characteristics, such as age, BMI and sex, meniscal injury/meniscectomy specified in medial and lateral compartments, meniscus repair, chondral injury, choice of treatment, graft type and reconstruction technique. We strongly recommend specifying the compartment of OA development.

In summary, medial meniscal injury/meniscectomy after ACL rupture influences the development of OA (tibiofemoral OA and compartment unspecified). In contrast, it seems that lateral meniscal injury/meniscectomy has no relationship with OA development. Our results also suggest that time between injury and reconstruction does not influence the development of patellofemoral and tibiofemoral OA. However, we found limited or conflicting evidence for many determinants.

What are the new findings?

In patients with an anterior cruciate ligament rupture:

- Moderate evidence was found that medial meniscus injury/meniscectomy had influence on osteoarthritis (OA) development; in contrast, lateral meniscus injury/meniscectomy showed moderate evidence for no relationship with development of OA.
- Time between injury and reconstruction showed moderate evidence for no relationship with patellofemoral and tibiofemoral OA development.
- It is still unclear which treatment option is the best for preventing OA development; conflicting evidence was found between treatment choice (operative vs non-operative treatment) and development of knee OA.

Acknowledgements The authors would like to thank Louis Volkers for his help with the literature search.

Contributors All authors were involved in designing this systematic review, interpreting the data and have contributed to the writing and editing of the manuscript. BLvM and MR assessed the studies for inclusion. BLvM and WAvE performed the data extraction. MR, SMAB-Z, DEM, JANV and BLvM performed the risk of bias assessment.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix Table 1

Quality Assessment

Paper ID: Reviewer:

Study design:

Question	Response	Scoring
1. A clearly stated aim	Did they have a “study question” or “main aim” or “objective”? The question addressed should be precise and relevant in light of available literature. To be scored *adequate* the aim of the study should be coherent with the “Introduction” of the paper.	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
2. Inclusion of consecutive patients	Did the authors say: “consecutive patients” or “all patients during period from … to….” or “all patients fulfilling the inclusion criteria”.	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
3. A description of inclusion and exclusion criteria	Did the authors report the inclusion and exclusion criteria?	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
4. Inclusion of patients	Did the authors report how many eligible patients agreed to participate (i.e. gave consent)?	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
5. Prospective collection of data. Data were collected according to a protocol established before the beginning of the study.	Did they say “prospective” or “follow-up”? The study is NOT PROSPECTIVE when: • chart review, or database review • “retrospective”	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
6. Outcome measures	Did they report the OA outcome; clinical OA, osteotomy, total knee arthroplasty, unilateral knee arthroplasty, radiographic OA, OA findings on MRI, OA findings during arthroscopy?	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
7. Was the used OA classification shown to be valid and reliable?	To be scored as *adequate*, the following classifications or indications could be used: • Clinical: ACR criteria, osteotomy, total knee arthroplasty, unilateral knee arthroplasty • Radiographic OA: Kellgren & Lawrence, Fairbank, Ahlback, IKDC grading system, OARSI grading system. • MRI: use of description of definite osteophyte formation <u>and</u> cartilage loss • Arthroscopic: Outerbridge classification • Combination of above-mentioned classifications/ indications.	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported

	To be scored as *inadequate*: • Use of self-formulated classifications • Use of modified classifications	
8. Unbiased assessment of the study outcome and determinants	To be judged as *adequate* the following 2 aspects had to be positive: • Outcome and determinants had to be measured independently • Both for cases and controls the outcome and determinants had to be assessed in the same way	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
9. Were the determinant measures used accurate (valid and reliable)?	For studies where the determinant measures are shown to be valid and reliable, the question should be answered *adequate*. For studies which refer to other work that demonstrates the determinant measures are accurate, the question should be answered as *adequate*. For example: a meniscus rupture had to be scored during arthroscopy or on MRI; activity level had to be measured with a validated questionnaire.	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
10. Follow-up period appropriate to the aim of the study	Did they report the follow-up period? To be judged as *adequate*: • the follow-up should be sufficiently long to allow the assessment of the main outcome: for radiographic OA a minimum of 4 years and for OA findings on MRI or during arthroscopy a minimum of 2 years.	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
11. Loss to follow-up	To be judged as *adequate* the following 2 aspects had to be positive: • Did they report the losses to follow-up? • Was the loss to follow-up less than 20%	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
12. Adequate Statistical analyses	To be judged as *adequate* the following 3 aspects had to be positive: • There must be a description of the relationship between the determinant and OA outcome or a description of the comparison (with information about the statistical significance) • Was there adjustment for the following confounders: a. Age b. Gender c. BMI If the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses, the question should be answered *inadequate*. • Did they show variance in the reported outcome (for example SD, CI)	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported

Abbreviations: ACR: American College of Rheumatology; BMI: body mass index; CI: confidence interval; IKDC; International Knee Documentation Committee; MRI: magnetic resonance imaging; OA: osteoarthritis; SD: standard deviation

Appendix Table 2
Characteristics of included studies (n=64)

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex, % male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Aglietti 1994 (54)	retrospective study	57	not reported	not reported	meniscus repair group: mean 55 (range 36-71) months; meniscectomy group: mean 52 (range 36-90) months; normal meniscus group: mean 57 (range 37-77) months	radiographic: the Hospital for Special Surgery(HSS) radiographic score	tibiofemoral (medial and lateral) and patellofemoral	< 26 points	HR
Aglietti 1997 (55)	retrospective study	77	mean 23 (range 15-40)	81	mean 7 (range 5.4-8.6) years	radiographic: JSN (no specific definition)	not reported	not reported	HR
Ahlden 2009 (18)	RCT	44	BPTB group: median 26 (range 14-48); hamstring group: median 29 (range 15-40)	68	BPTB group: median 89 (range 77-110) months hamstring group: median 86 (range 69-109) months	radiographic: Ahlbäck and Fairbank score / presence of osteophytes	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Ahn 2012 (56)	retrospective study	117	mean 29.2 (SD 8.8)	75.2	mean 10.3 (SD 1) years	radiographic: IKDC grading system	tibiofemoral (medial and lateral) and patellofemoral	grade C and D	LR
Cohen 2007 (57)	retrospective study	62	mean 27 (range 15-46)	76	mean 11 years 2 months (range 10-15 years)	radiographic; Fairbank score	tibiofemoral (medial and lateral)	not reported	HR
Fink 2001 (30)	prospective follow-up study	84	ACL reconstruction group: mean 33.6 (SD 8.0); non-operative group: mean 32.3 (SD 9.9)	ACL reconstruction group: 80; non-operative group: 72	ACL reconstruction group: mean 74.2 months; non-operative group: mean 84.2 months	radiographic: modified Fairbank score	tibiofemoral	not reported	HR
Fithian 2005 (31)	prospective follow-up study	209	mean 39 (range 16 - 69)*	48	mean 6.6 (range 3 - 10) years	radiographic: IKDC grading system	tibiofemoral (medial and lateral) and	not reported	HR

							patellofemoral		
Frobell 2013 (19)	RCT	113	early ACL reconstruction group: mean 26.4 (SD 5.1); delayed optional ACL reconstruction group: mean 25.8 (SD 4.7)	early ACL reconstruction group: 80; delayed optional ACL reconstruction group: 66	early ACL reconstruction group: mean 60 (95% CI 59 to 61) months; delayed ACL reconstruction group: mean 59 (95% CI 57 to 60) months; rehabilitation alone group: mean 58 (95% CI 55 to 61) months	radiographic: grading according to atlas of OARSI	tibiofemoral and patellofremoral	JSN ≥2 in compartment, a sum of osteophyte grades ≥ 2 in the same compartment or grade 1 JSN combined with grade 1 osteophyte in same compartment	HR
Gerhard 2013 (58)	retrospective study	63	mean 27 (SD 7)	86	mean 16 (SD 1) years	radiographic: Kellgren and Lawrence score	not reported	not reported	HR
Giron 2005 (32)	prospective follow-up study	38	mean 29 (range 17-53)	79	5 years†	radiographic: IKDC grading system	not reported	not reported	HR
Hanypsiak 2008 (33)	prospective follow-up study	44	39*	70	mean 12.7 (range 11.8-13.8) years	radiographic: Rosenberg	not reported	JSN ≥ 2 mm compared to uninvolved contralateral compartment	HR
Harilainen 2006 (20)	RCT	71	not reported	not reported	median 5 years (range 3 years 11months-6 years 7 months)	radiographic: IKDC grading system	tibiofemoral (medial and lateral)	not reported	HR
Hart 2005 (59)	retrospective study	31	mean: 27.8 (range 18-47)	68	mean 10 years (range 9-13)	radiographic: Ahlbäck score	tibiofemoral (medial and lateral) and patellofemoral	Ahlbäck grade ≥ 1	HR
Holm 2010 (21)	RCT	57	hamstring group: mean 27 (SD 9); BPTB group: 25 (SD 7)	hamstring group 52; BPTB group: 64	hamstring group: mean 10.7 (SD 0.4) years; BPTB group: 10.2 (SD 0.4) years	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR

Hui 2011 (34)	prospective follow-up study	59	mean 25 (range 15-42)	51	mean 184 (range 169-199) months	radiographic: IKDC grading system	not reported	not reported	HR
Ichiba 2009 (60)	retrospective study	46	mean 26 (range 13-39)	26	mean 3.9 (range 2-8) years	radiographic: Kawakubo method	tibiofemoral	Increase OA score: differences between preoperative OA score and at follow-up	HR
Janssen 2013 (35)	prospective follow-up study	86	mean 31.2 (SD 8.0)	66	mean 10 (SD 0.7) years	radiographic: Ahlbäck and Kellgren and Lawrence score	not reported	Ahlbäck grade 1 and Kellgren and Lawrence grade 3	LR
Jarvela 1999 (61)	retrospective study	91	early reconstruction group: 32 (range 15-61); late reconstruction group: 30 (range 16-46)	69	mean 7 (range early reconstruction group 5.9-8.5; late reconstruction group range 4.6-8.8) years	radiographic: IKDC grading system	medial tibiofemoral	IKDC grade ≥ nearly normal‡	HR
Jarvela 2001 (62)	retrospective study	86	mean 31 (range 15-61)	70	mean 7 (range 4.6-8.8) years	radiographic: IKDC grading system	patellofemoral	IKDC evaluation system ≥ mild	HR
Jarvela 2001 (63)	retrospective study	72	isolated ACL rupture group: mean 29 (SD 9); ACL tear accompanying injuries group: mean 34 (SD 12)	67	isolated ACL rupture group: mean 7.1 (SD 0.7) years; ACL tear accompanying injuries group: mean 6.9 (SD 0.7) years	radiographic: IKDC grading system	tibiofemoral and patellofemoral	not reported	HR
Jomha 1999 (36)	prospective follow-up study	53	acute ACL tears group: mean 27; chronic ACL tear group: mean 28	70	7 years†	radiographic: IKDC grading system	not reported	presence of osteophytes, subchondral sclerosis, change of articular surface, or JSN	HR

Kannus 1989 (64)	retrospective study	77	mean 30 (SD 11)*	75.3	mean 7.8 (SD 2.0) years	radiographic: classification according to Kannus (0-100 point scale)	tibiofemoral (medial and lateral) and patellofemoral	score 95-99: good; score 90-94: fair; ≤ 89: poor	HR
Keays 2010 (37)	prospective follow-up study	56	mean 27 (range 18-38)	71	6 years†	radiographic: modified Kellgren and Lawrence score (grade 0-3)	tibiofemoral and patellofemoral	Modified Kellgren & Lawrence score ≥ 1	HR
Kessler 2008 (65)	retrospective study	109	mean 30.7 (range 12.5-54.0)	62.4	mean 11.1 (range 7.5-16.3) years	radiographic: Kellgren and Lawrence score	not reported	Kellgren & Lawrence score > 1	HR
Lebel 2008 (66)	retrospective study	98	mean 28.8 (SD 8.3)	77	mean 11.6 (SD 0.8) years	radiographic: IKDC grading system	tibiofemoral	not reported	HR
Leiter 2013 (67)	retrospective study	68	mean 31.2 (SD 9.1)	63	mean 14.6 (SD 1.9) years	radiographic: Kellgren and Lawrence score	not reported	not reported	HR
Leys 2012 (38)	prospective follow-up study	109	BPTB group: median 25 (range 15-42); hamstring group: median 24 (range 13-52)	53	15 years†	radiographic: IKDC grading system	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Li 2011 (68)	retrospective study	249	mean 26.4 (SD 10.2)	61.4	mean 7.9 (range 2.1-20.3) years	radiographic: Kellgren and Lawrence score	not reported	2 grade difference between index and contralateral in at least 2 compartments or 1 grade difference between knees in at least 2 compartments	HR

Liden 2008 (69)	retrospective study	113	median 28 (range 15-59)	69	median 86 (range 67-111) months	radiographic: Ahlbäck and Fairbank score / unknown system	tibiofemoral and patellofemoral	not reported	HR
Lohmander 2004 (70)	retrospective study	67	mean 19 (range 14-28)	0	12 years†	radiographic: grading according to atlas of OARSI	tibiofemoral and patellofemoral	JSN grade of ≥ 2 or a sum of ≥ 2 for the 2 marginal osteophyte grades from the same compartment, or a JSN grade of at least 1 in combination with an osteophyte grade of at least 1 in the same compartment	HR
Mascarenhas 2012 (52)	matched case control study	46	mean 18 (SD 3)	43	BPTB group: mean 5 (SD 2) years; hamstring group: mean 4 (SD 2) years	radiographic: Kellgren and Lawrence score	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Menke 1990 (71)	retrospective study	90	not reported	94	5 to 12 years	radiographic: Tapper and Hoover grading system	not reported	not reported	HR
Meuffels 2009 (53)	matched case control study	50	operative group: mean 37.6 (SD 6.2); non-operative group: mean 37.8 (SD 6.8)*	76	10 years†	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR
Meunier 2007 (22)	RCT	36	non-operative group: mean 21 (range 14-30)	62.5	mean 15 (SD 1) years	radiographic: Ahlbäck and Fairbank score	not reported	Ahlbäck and Fairbank grade > 0	HR

Mihelic 2011 (72)	retrospective study	54	reconstruction group: mean 25.3; non-operative group: mean 25.5	81	range 17-20 years	radiographic: IKDC grading system	not reported	not reported	HR
Moisala 2007 (39)	prospective follow-up study	66	mean 34 (range 16-64)	64	mean 57 months (range 3-8 years)	radiographic: IKDC grading system	not reported	IKDC grading system > A	HR
Murray 2012 (73)	retrospective study	83	mean 30 (SD 10)	not reported	mean 13 years	radiographic: IKDC grading system	not reported	IKDC grade C and D	HR
Neuman 2008 (40)	prospective follow-up study	79	mean 26 (SD 8)	58	mean 15.7 (SD 1.4) years	radiographic: grading according to atlas of OARSI	tibiofemoral	JSN ≥ grade 2, sum of the 2 marginal osteophyte scores from the same compartment ≥2, or grade 1 JSN in combination with grade 1 osteophyte in the same compartment.	HR
Neuman 2009 (41)	prospective follow-up study	75	mean 26 (SD 8)	58	mean 15.7 (SD 1.4) years	radiographic: grading according to atlas of OARSI	patellofemoral	JSN of grade 2 or higher in either the medial or lateral compartment, sum of marginal osteophyte grades ≥ 2, or grade 1 JSN in combination with a grade 1 marginal osteophyte.	HR

Oiestad 2013 (42)	prospective follow-up study	181	mean 39.1 (SD 8.7)*	58	mean 12.3 (SD 1.2) years	radiographic: Kellgren and Lawrence score	patellofemoral	Kellgren and Lawrence grade ≥ 2	HR
Oiestad 2010 (43)	prospective follow-up study	164	mean 27.4 (SD 8.5)	57	mean 12.1 (SD 1.4) years	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR
Oiestad 2010 (44)	prospective follow-up study	181	mean 39.5 (8.6) *	57	mean 12.4 (SD 1.2) years	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR
O'Neill 2001 (23)	RCT	225	not reported	not reported	mean 102 months (range 6-11 years)	radiographic: IKDC grading system	not reported	not reported	HR
Otto 1998 (74)	retrospective study	62	mean 27 (range15-46)	72	minimum 5 years	radiographic: IKDC grading system	not reported	not reported	HR
Pinczewski 2007 (45)	prospective follow-up study	128	BPTB group median 25 (range 15-42); hamstring group: median 24 (range 13-52)	not reported	10 years†	radiographic: IKDC grading system	not reported	not reported	HR
Pinczewski 2008 (46)	prospective follow-up study	184	not reported	not reported	7 years†	radiographic: IKDC grading system	not reported	not reported	HR
Potter 2012 (47)	prospective follow-up study	40	mean 37.2 (SD 9.1)	40	maximum 11 years	MRI: modified Outerbridge assessment	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Ruiz 2002 (48)	prospective follow-up study	30	not reported	93	mean 7 years (range 64-114 months)	radiographic: JSN	tibiofemoral	not reported	HR
Sajovic 2011 (24)	RCT	52	hamstring group: mean 36 (range 25-54); BPTB group: mean 38 (range 27-58)*	58	11 years†	radiographic: IKDC grading system	not reported	worst grading compartment was used as overall grade	HR
Salmon 2006 (75)	retrospective study	43	median 27(95% CI 25-28)	70	minimum 13 years	radiographic: IKDC grading system	not reported	not reported	HR

Segawa 2001 (76)	retrospective study	70	mean 22.8 (range 12-50)	40	mean 11.6 (range 5-27) years	radiographic: Kellgren and Lawrence score	not reported	Kellgren & Lawrence score ≥ 1	HR
Seitz 1994 (77)	retrospective study	87	operative group: mean 27 (range 15-42); non-operative group: mean 28 (range 18-56)	51	mean 8.5 (range 5-12) years	radiographic: Jäger and Wirth grading system	not reported	not reported	HR
Seon 2006 (78)	retrospective study	58	mean 30.4 (range 18-58)*	95	mean 11.2 (range 8.6-13.8) years	radiographic: Kellgren and Lawrence score	not reported	Kellgren and Lawrence > 2	HR
Shelbourne 2000 (49)	prospective follow-up study	range 45-282	women: mean 21 (range 13.2-50.1); men: mean 23.7 (range 11.8-53)	73	mean 7.6 (SD 2.3) years	radiographic: IKDC grading system	not reported	IKDC grade ≥ nearly normal‡	HR
Shelbourne 2012 (50)	prospective follow-up study	780	mean 25.4 (SD 9.2)	not reported	mean 10.5 (SD 4.5) years	radiographic: IKDC grading system	tibiofemoral (medial and lateral) and patellofemoral	IKDC evaluation system > grade A	HR
Song 2013 (25)	RCT	112	DB group: mean 30.3 (range 17-50); SB group: mean 35.5 (range 19-58)	DB group: 85; SB group: 63	DB group: mean 5.3 (range 4.1-6.1) years; SB group: mean 5.7 (range 4.1-6.2) years	radiographic: Kellgren and Lawrence score	not reported	≥ 1 grade progression compared with pre-operative condition	HR
Streich 2011 (79)	retrospective study	80	mean 25.8 (range 17-39)	70	operative group: mean 15.4 (SD 0.8) years; non-operative group: mean 15.2 (SD 0.7) years	radiographic: IKDC grading system	not reported	IKDC evaluation system > grade A	HR
Sun 2009 (26)	RCT	156	autograft group: mean 31.7 (SD 6.3); allograft group: mean 32.8 (SD 7.1)*	79	mean 5.6 (autograft group: SD 1.2; allograft group: SD 1.3) years	radiographic: Kellgren and Lawrence score	not reported	not reported	HR
Suomalainen 2012 (27)	RCT	65	Double-bundle with bioabsorbable screw group: mean 34 (SD 10); single-bundle with bioabsorbable screw	Double-bundle with bioabsorbable screw group: 30;	5 years†	radiographic: Kellgren and Lawrence score	tibiofemoral and patellofemoral	not reported	HR

			group: mean 30 (SD 8); single-bundle with metallic screw group: mean 33 (SD 10)	single-bundle with bioabsorbable screw group: 30; single-bundle with metallic screw group: 37					
von Porat 2004 (80)	retrospective study	122	mean 38 (SD 5.2)	100	14 years†	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR
Wang 2004 (81)	retrospective study	44	mean 31 (range 19-57)	73	mean 70 (range 46-86) months	radiographic: Ahlbäck rating system	tibiofemoral	not reported	HR
Wipfler 2011 (28)	RCT	54	BPTB: mean 29.87 (range 25 to 55); HT: 34.23 (range 26 to 64)	BPTB: 62; HT: 60	mean 8.8 (SD 0.55) years	MRI: International Cartilage Repair Society evaluation	not reported	not reported	HR
Wu 2002 (51)	prospective follow-up study	34	mean 24 (15-45)	57	mean 10.4 (range 9-13) years	radiographic: Fairbank system	not reported	not reported	HR
Zaffagnini 2011 (29)	RCT	79	BPTB group: mean 26 (SD 9.5); hamstring group: mean 27 (SD 9)	53	mean 8.6 (range 8-10) years	radiographic: IKDC grading system	not reported	not reported	HR

*Age at follow-up

†Median or mean of follow-up time not reported

‡For calculation of the relationship between determinant and OA development, we chose a cut-off point.

Abbreviations: BPTB, bone-patellar tendon-bone; CI, confidence interval; HR, high-risk of bias; IKDC, International Knee Documentation Committee; JSN, joint space narrowing; LR, low-risk of bias; OARSI, Osteoarthritis Research Society International; RBA, risk of bias assessment; RCT, Randomized Controlled Trial; SD, standard deviation; WORMS, Whole Organ Magnetic Resonance Imaging Score.

Appendix Table 3 Quality Assessment Score

	RBA*	Quality Assessment questions												
		2	**8**	**9**	**11**	**12[a]**	**1**	**3**	**4**	**5**	**6**	**7**	**10**	**12[a,b,c]**
Aglietti 1994 (54)	HR	0	0	1	1	0	1	1	0	0	1	0	0	0
Aglietti 1997 (55)	HR	0	0	1	0	0	1	1	0	0	1	0	1	0
Ahlden 2009 (18)	HR	0	0	1	0	0	1	1	0	1	1	1	1	0
Ahn 2012 (56)	**LR**	**1**	**1**	**1**	**1**	**1**	1	1	0	0	1	1	1	0
Cohen 2007 (57)	HR	1	1	1	0	0	1	1	0	0	1	1	1	0
Fink 2001 (30)	HR	1	0	1	0	0	1	1	1	1	1	1	1	0
Fithian 2005 (31)	HR	0	0	1	0	0	1	1	0	1	1	1	0	0
Frobell 2013 (19)	HR	1	0	1	1	0	1	1	1	1	1	1	1	0
Gerhard 2013 (58)	HR	1	0	1	1	0	1	0	1	0	1	1	1	0
Giron 2005 (32)	HR	0	0	1	1	0	1	1	0	1	1	1	1	0
Hanypsiak 2008 (33)	HR	1	1	1	1	0	1	1	0	1	1	0	1	0
Harilainen 2006 (20)	HR	0	1	1	0	0	1	1	0	1	1	1	0	0
Hart 2005 (59)	HR	1	1	1	0	0	1	1	1	1	1	1	1	0
Holm 2010 (21)	HR	0	0	1	0	0	1	0	1	1	1	1	1	0
Hui 2011 (34)	HR	1	0	1	0	1	1	1	0	1	1	1	1	0
Ichiba 2009 (60)	HR	0	0	1	0	0	1	1	0	0	1	0	0	0
Janssen 2013 (35)	**LR**	**1**	**1**	**1**	**1**	**1**	1	1	1	1	1	1	1	1
Jarvela 1999 (61)	HR	0	0	1	0	0	1	0	0	0	1	0	1	0
Jarvela 2001 (62)	HR	1	0	0	0	0	1	0	1	0	1	1	1	0
Jarvela 2001 (63)	HR	1	0	1	0	0	1	0	0	0	1	1	1	0

Jomha 1999 (36)	HR	1	1	1	0	0	1	1	0	1	1	1	1	0
Kannus 1989 (64)	HR	0	0	1	0	0	1	1	0	0	1	0	1	0
Keays 2010 (37)	HR	1	1	1	1	0	1	1	1	1	1	0	1	0
Kessler 2008 (65)	HR	0	0	1	1	1	1	1	0	0	1	1	1	0
Lebel 2008 (66)	HR	1	0	1	0	0	1	1	0	1	1	1	1	0
Leiter 2013 (67)	HR	1	1	1	0	1	1	1	0	0	1	1	1	1
Leys 2012 (38)	HR	1	0	1	0	1	1	1	0	1	1	1	1	0
Li 2011 (68)	HR	0	0	1	0	1	1	1	0	0	1	1	1	1
Liden 2008 (69)	HR	1	0	1	1	0	1	1	1	0	1	1	1	0
Lohmander 2004 (70)	HR	1	0	1	0	1	1	1	1	0	1	1	1	1
Mascarenhas 2012 (52)	HR	0	0	1	0	0	1	1	0	0	1	1	0	0
Menke 1990 (71)	HR	0	0	1	0	0	0	0	0	0	1	0	1	0
Meuffels 2009 (53)	HR	0	1	1	0	0	1	1	0	0	1	1	1	0
Meunier 2007 (22)	HR	0	1	1	1	0	1	0	0	1	1	1	1	0
Mihelic 2011 (72)	HR	0	1	1	0	0	1	1	0	0	1	1	1	0
Moisala 2007 (39)	HR	1	0	1	0	0	1	1	0	0	1	1	0	0
Murray 2012 (73)	HR	0	1	1	0	0	1	1	0	0	1	1	1	0
Neuman 2008 (40)	HR	1	0	1	1	0	1	1	1	1	1	1	1	0
Neuman 2009 (41)	HR	1	1	1	0	0	1	0	0	1	1	1	1	0
Oiestad 2013 (42)	HR	0	0	1	1	1	1	1	0	1	1	1	1	1
Oiestad 2010 (43)	HR	1	0	1	1	1	1	1	1	1	1	1	1	1
Oiestad 2010 (44)	HR	1	0	1	1	0	1	1	1	1	1	1	1	0

O'Neill 2001 (23)	HR	0	0	1	0	1	0	0	0	0	1	1	1	0
Otto 1998 (74)	HR	1	0	1	1	0	1	0	0	0	1	1	1	0
Pinczewski 2007 (45)	HR	1	0	1	0	0	1	1	0	1	1	1	1	0
Pinczewski 2008 (46)	HR	1	1	0	1	1	1	1	0	1	1	1	1	0
Potter 2012 (47)	HR	0	1	1	1	1	1	1	0	1	1	0	1	0
Ruiz 2002 (48)	HR	0	0	1	0	0	1	0	0	1	1	0	1	0
Sajovic 2011 (24)	HR	0	0	1	1	0	1	1	1	1	1	1	1	0
Salmon 2006 (75)	HR	1	1	1	0	0	1	1	0	0	1	1	1	0
Segawa 2001 (76)	HR	0	0	1	0	0	1	1	1	0	1	1	1	0
Seitz 1994 (77)	HR	0	0	1	0	0	1	0	0	0	1	0	1	0
Seon 2006 (78)	HR	1	0	1	1	0	1	0	0	0	1	1	1	0
Shelbourne 2000 (49)	HR	0	0	1	0	0	1	1	0	0	1	1	1	0
Shelbourne 2012 (50)	HR	0	0	1	0	0	1	1	0	1	1	1	1	0
Song 2013 (25)	HR	0	0	1	1	0	1	1	0	1	1	1	1	0
Streich 2011 (79)	HR	1	0	1	1	0	1	1	1	0	1	1	1	0
Sun 2009 (26)	HR	0	0	1	1	1	1	1	1	1	1	1	1	0
Suomalainen 2012 (27)	HR	0	0	1	0	0	1	1	0	1	1	1	1	0
von Porat 2004 (80)	HR	1	0	0	0	0	1	1	1	0	1	1	1	0
Wang 2004 (81)	HR	1	0	1	0	0	1	0	0	0	1	1	0	0
Wipfler 2011 (28)	HR	0	0	1	1	0	1	1	0	1	1	1	1	0
Wu 2002 (51)	HR	0	0	1	0	0	1	0	0	1	1	1	1	0
Zaffagnini 2011 (29)	HR	1	0	1	1	0	1	1	0	1	1	1	1	0

Abbreviations: HR, high-risk of bias; LR, low-risk of bias; RBA, risk of bias assessment.

The following quality assessment questions were scored as adequate (1), inadequate (0) or not reported (0):

1. A clearly stated aim
2. Inclusion of consecutive patients
3. A description of inclusion and exclusion criteria
4. Inclusion of patients: did the authors report how many eligible patients agreed to participate (i.e. gave consent)?
5. Prospective collection of data. Data were collected according to a protocol established before the beginning of the study.
6. Outcome measure: did they report the OA outcome?
7. Was the used OA classification shown to be valid and reliable?
8. Unbiased assessment of the study outcome and determinants?
9. Were the determinant measures used accurate (valid and reliable)?
10. Follow-up period appropriate to the aim of the study
11. Loss to follow-up: did they report the losses to follow-up? Was the loss to follow-up less than 20%?
12. Adequate statistical analyses: a) correction for confounding; b) there must be a description of the relationship between the determinant and OA outcome or a description of the comparison (with information about the statistical significance); c) reporting variance in the outcome (for example SD, CI))

*Studies were classified as low-risk of bias when they scored adequate (1) on questions 2, 8, 9, 11 and 12a.
Low-risk of bias studies are printed in bold.