AJSM PreView, published on November 8, 2013 as doi:10.1177/0363546513508376

Anterior Cruciate Ligament Injury and Radiologic Progression of Knee Osteoarthritis

A Systematic Review and Meta-analysis

Adil Ajuied,*† BSc(Hons), MSc, FRCS(Tr&Orth), Fabian Wong,† BSc(Hons), MRCS, Christian Smith,† MSc, MRCS, Mark Norris,† FRCS(Tr&Orth), Peter Earnshaw,† FRCS(Tr&Orth), Diane Back,† FRCS(Tr&Orth), and Andrew Davies,‡ FRCS(Tr&Orth)
Investigation performed at Guy's & St Thomas' Hospital NHS Foundation Trust, London, United Kingdom

Background: Knee osteoarthritis after anterior cruciate ligament (ACL) injury has previously been reported. However, there has been no meta-analysis reporting the development and progression of osteoarthritis.

Purpose: We present the first meta-analysis reporting on the development and progression of osteoarthritis after ACL injury at a minimum mean follow-up of 10 years, using a single and widely accepted radiologic classification, the Kellgren & Lawrence classification.

Study Design: Meta-analysis.

Method: Articles were included for systematic review if they reported radiologic findings of ACL-injured knees and controls using the Kellgren & Lawrence classification at a minimum mean follow-up period of 10 years. Appropriate studies were then included for meta-analysis.

Results: Nine studies were included for systematic review, of which 6 studies were further included for meta-analysis. One hundred twenty-one of 596 (20.3%) ACL-injured knees had moderate or severe radiologic changes (Kellgren & Lawrence grade III or IV) compared with 23 of 465 (4.9%) uninjured ACL-intact contralateral knees. After ACL injury, irrespective of whether the patients were treated operatively or nonoperatively, the relative risk (RR) of developing even minimal osteoarthritis was 3.89 ($P < .00001$), while the RR of developing moderate to severe osteoarthritis (grade III and IV) was 3.84 ($P < .0004$). Nonoperatively treated ACL-injured knees had significantly higher RR (RR, 4.98; $P < .00001$) of developing any grade of osteoarthritis compared with those treated with reconstructive surgery (RR, 3.62; $P < .00001$). Investigation of progression to moderate or severe osteoarthritis (grade III or IV only) after 10 years showed that ACL-reconstructed knees had a significantly higher RR (RR, 4.71; $P < .00001$) compared with nonoperative management (RR, 2.41; $P = .54$). It was not possible to stratify for return to sports among the patients undergoing ACL reconstruction.

Conclusion: Results support the proposition that ACL injury predisposes knees to osteoarthritis, while ACL reconstruction surgery has a role in reducing the risk of developing degenerative changes at 10 years. However, returning to sports activities after ligament reconstruction may exacerbate the development of arthritis.

Keywords: osteoarthritis; anterior cruciate ligament; knee injury; radiology; systematic review; meta-analysis

Anterior cruciate ligament (ACL) injury is the most common complete ligament injury of the knee. An ACL injury frequently occurs in fit and active patients, especially among those who engage in sporting pursuits.[6,33] Although acute symptoms of pain and swelling predominate, it is rotational instability that prevents return to function.[46,67] It has been proposed that ACL reconstruction (ACL-R) surgery prevents excessive torsional loading of the menisci by restoring rotational stability. Hence, ACL-R protects against subsequent damage to the menisci and articular cartilage, in turn preventing premature degenerative changes of the knee.[53,81]

*Address correspondence to Adil Ajuied, BSc(Hons), MSc, FRCS(Tr&Orth), Department of Trauma & Orthopaedic, Guy's & St Thomas' NHS Foundation Trust, Great Maze Pond, London Bridge, SE1 9RT, UK (e-mail: aajuied@doctors.org.uk).
†Department of Trauma & Orthopaedic, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom.
‡Fortius Clinic, London, United Kingdom.
The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

The American Journal of Sports Medicine, Vol. XX, No. X
DOI: 10.1177/0363546513508376

Search Number	Search Terms	Results
1	Anterior cruciate ligament [MeSH]	8894
2	Knee joint [MeSH]	39371
3	Ligaments, articular [MeSH]	22902
4	Knee joint OR Ligaments, articular	72587
5	Knee injuries [MeSH]	14679
6	Osteoarthritis, knee [MeSH]	8769
7	Osteoarthritis [MeSH]	39324
8	Epidemiologic studies [MeSH]	1480187
9	Epidemiology	1537967
10	2 OR 7	72318
11	1 OR 4 OR 5	76770
12	6 OR 10	72318
13	8 OR 9	2548320
14	11 AND 12 AND 13 (limits: humans, English)	8703

Figure 1. Search strategy and results from PubMed. MeSH, Medical Subject Headings.

Search Number	Search Terms	Results
1	ligaments/ or ligaments, articular	40790
2	Anterior Cruciate Ligament	17704
3	Knee Joint	85268
4	Knee Injuries	26642
5	Osteoarthritis	83380
6	Osteoarthritis, Knee	23967
7	Epidemiology	194644
8	epidemiologic studies	186430
9	7 or 8	200118
10	3 or 5	159349
11	1 or 3	121547
12	2 or 4 or 11	148576
13	6 or 10	176515
14	9 and 12 and 13	201
15	limit 14 to english language	185
16	limit 16 to humans	138

Figure 2. Search strategy and results from Medline, EMBASE, and AMED using OvidSP.

It is common for ACL-R patients to undergo surgery with the explicit aim of returning to sports that involve pivoting and cutting, while patients treated nonoperatively would be advised regarding sports and activities modification.[41,68] There is not a large amount of published high-quality evidence regarding the prevalence of successful return to, and maintenance of, sporting activities after ACL-R. The Multicenter Orthopaedic Outcomes Network (MOON) group has published in this area. They have reported that approximately 70% of athletes return to high-level sports after ACL-R, with fear of reinjury and risk of further damage commonly cited[5,36] as reasons for failure to do so. Maintenance of high-level sporting participation is not as encouraging, with the rate of participation dropping from approximately 70% to 30% by 5 to 4 years after ACL-R.[3,5] The findings of the MOON group have been echoed in previous studies.[14,29] Furthermore, Brophy et al[5] concluded from their multivariate analysis that advancing age and female sex were significant predictors of failure to return to sports.

Previous studies have attempted to assess the long-term risk of knee osteoarthritis after ACL injury with or without reconstruction surgery.[§] A comprehensive review by Øiestad et al[54] in 2009 concluded that the prevalence of osteoarthritis in knees after an isolated ACL injury was 0% to 13%. When associated with meniscal injuries, this figure increased to 21% to 48%.[54] The group also noted that 2 different, noninterchangeable radiologic grading systems were used by previous studies for the assessment of post–ACL injury osteoarthritis. As such, they concluded that results from some of these studies could not be combined or compared directly.

The Kellgren & Lawrence classification is a well-recognized radiologic grading system for assessing osteoarthritis of the knee.[17,25,30] This consists of 5 distinct grades based on osteophyte formation and evidence of joint space narrowing, where grades 0, I, II, III, and IV represent "normal," "doubtful significance," "minimal changes," "moderate changes," and "severe changes," respectively. A previous study has demonstrated a strong positive correlation between Kellgren & Lawrence grading and knee pain.[48]

The purpose of this study is to conduct a systematic review and meta-analysis of the published literature associated with the radiologic presence or progression of osteoarthritis after ACL injury, using the Kellgren & Lawrence classification system only. The radiologic appearances of ACL-reconstructed knees are also compared against those that are nonoperatively treated.

METHODS

A literature review was performed on the electronic databases PubMed, Medline, EMBASE, and AMED from the inception of the databases until September 31, 2012. MeSH terms and Boolean operators were used for journal articles related to ACL and osteoarthritis. This is a similar method to that used by the systematic review of Øiestad et al[54] in 2009. Figures 1 and 2 demonstrate the search terms and respective results using PubMed and OvidSP.

All returned articles were assessed against the following inclusion criteria:

1. All prospective and retrospective study designs
2. Surgically and nonsurgically treated ACL injuries
3. An ACL injury in isolation or in combination with meniscal and/or medial collateral ligament injury
4. Minimum mean 10-year follow-up
5. Radiologic assessment of ipsilateral knee after acute injury or contralateral knee at final follow-up, using Kellgren & Lawrence classification
6. Studies reported in English language

[§]References 12, 24, 27, 31, 38, 41, 42, 50, 70, 73, 74, 78.

Articles originally included by Øiestad et al were reviewed and included in this systematic review where they met our inclusion criteria.[||] These articles represent available publications from the inception of the relevant databases until August 2008.

All articles were screened and analyzed by 2 of the authors independently (F.W. and C.S.). Disagreement regarding inclusion and exclusion of any study was discussed between the 2 authors, and where required, a third author (A.A.) made the final decision.

Data Extraction and Statistical Analysis

Relevant data were extracted from all included studies for descriptive analysis, including patient demographics, associated injury, treatment modality for ACL injury, time to surgery, mean time to final follow-up, and rehabilitation regimen.

Studies that reported Kellgren & Lawrence grades for both ACL-injured knees and contralateral uninjured control knees were included for meta-analysis. The authors considered that inclusion of nonrandomized controlled trials for this meta-analysis would be appropriate due to the scarcity of published randomized controlled trials using a single appropriate radiologic classification system. A similar view was expressed previously by Shrier et al,[71] who concluded that a meta-analysis using both observational studies and randomized controlled trials could be advantageous.

The meta-analysis was conducted using Review Manager 5 (RevMan),[7] a software package developed by The Cochrane Collaboration. This package summarized data to create appropriate forest plots for graphical presentation. A random effect model was used to reduce bias from the potential systematic errors of the included studies, and an inverse variance method was used for the weighting of each study. Homogeneity across the studies was assessed and represented by I^2, with $P < .10$ being statistically significant.

RESULTS

Figure 3 demonstrates the results from the search strategy and the application of the PRISMA flow diagram.[44] A total of 8841 studies were identified using the search strategy from the inception of the databases until September 2012, of which 2703 studies were published between August 2008 and September 2012 inclusive. Removing all duplicates and application of our inclusion criteria resulted in 12 studies that were eligible for analysis.[¶]

Four studies used the same cohort of patients. Therefore, only the article with the largest number of patients was included. A further study with pair-matched subjects reported the mean follow-up of less than 10 years in one of the treatment arms[35]; this individual group of patients was excluded from analysis. As a result, a total of 9 studies were included in this systematic review,[#] and these articles are summarized in Table 1.

Descriptive Analysis

Patient Demographics. A total of 615 subjects were derived from 9 studies that fulfilled the inclusion criteria. This represented 422 male and 222 female subjects in total, with a range of mean ages from 22.3 to 41.0 years.

ACL and Associated Injuries. All 615 patients had their ACL injury diagnosed clinically, radiologically, arthroscopically, or by a combination of these 3 methods. Two hundred forty-eight patients were reported to have uninjured menisci, compared with 288 patients with injured menisci. For 98 patients from 2 studies, the articles did not have any comment on the status of the meniscus at the time of injury or during subsequent follow-up.[35,76]

Treatment of ACL Rupture. A total of 520 ACL-Rs were performed. The reported mean time from injury to reconstruction ranged from 0.5 to 31.1 months. Four hundred sixty-three (89.0%) ACL-Rs were performed using bone-patellar tendon-bone (BTB) grafts, and 29 (5.6%) ACL-Rs used hamstring (HS) tendon grafts. The remaining group of 28 (5.4%) patients was a mixture of both BTB and HS grafts, with the exact number being undisclosed by the authors. Of these 463 cases of BTB grafts, 444 (95.9%) used autograft, with the remaining 19 (4.1%) using allograft. All HS grafts were autografts.

Of the 95 patients who did not receive ACL-R, 25 (26.3%) received physiotherapy for HS- and quadriceps-strengthening exercises for a minimum period of 3 months. The remaining 70 (73.7%) patients received instruction on activity modification as well as lower extremity–strengthening exercises.

Radiologic Outcome. At the time of final follow-up, 613 of the 615 patients had radiologic assessment. The radiologic grades as described by the Kellgren & Lawrence classification system were available for 596 (97%) patients (Table 2).

Four hundred sixty-five (78.0%) of these 596 patients also underwent radiologic assessment of their contralateral ACL intact uninjured knee for use as a control.[20,41,55,68,76,79] The remaining 131 (22.0%) patients had the acute postinjury radiographs of their ACL-injured knees used as controls.[69,75] This demonstrated development and progression of osteoarthritis of the ipsilateral knee between index injury and final follow-up. However, as these controls did not take into account osteoarthritis developing as a natural process over time, these 131 knees were hence excluded from our statistical analysis.

Nineteen patients from one treatment arm in the study by Mascarenhas et al[35] fulfilled a mean follow-up period of 10 years and were included from this systematic review. Seventeen of these patients had radiologic grades at the final follow-up, with a mean follow-up period of 10.3 ±

[||] References 2, 8, 9, 11, 15, 16, 19, 26, 28, 32, 34, 37, 42, 43, 45, 47, 49, 51-53, 60, 63, 64, 66, 68, 69, 73, 79, 82-84.

[¶] References 20, 21, 35, 41, 55-57, 68, 69, 75, 76, 79.

[#] References 20, 35, 41, 56, 68, 69, 75, 76, 79.

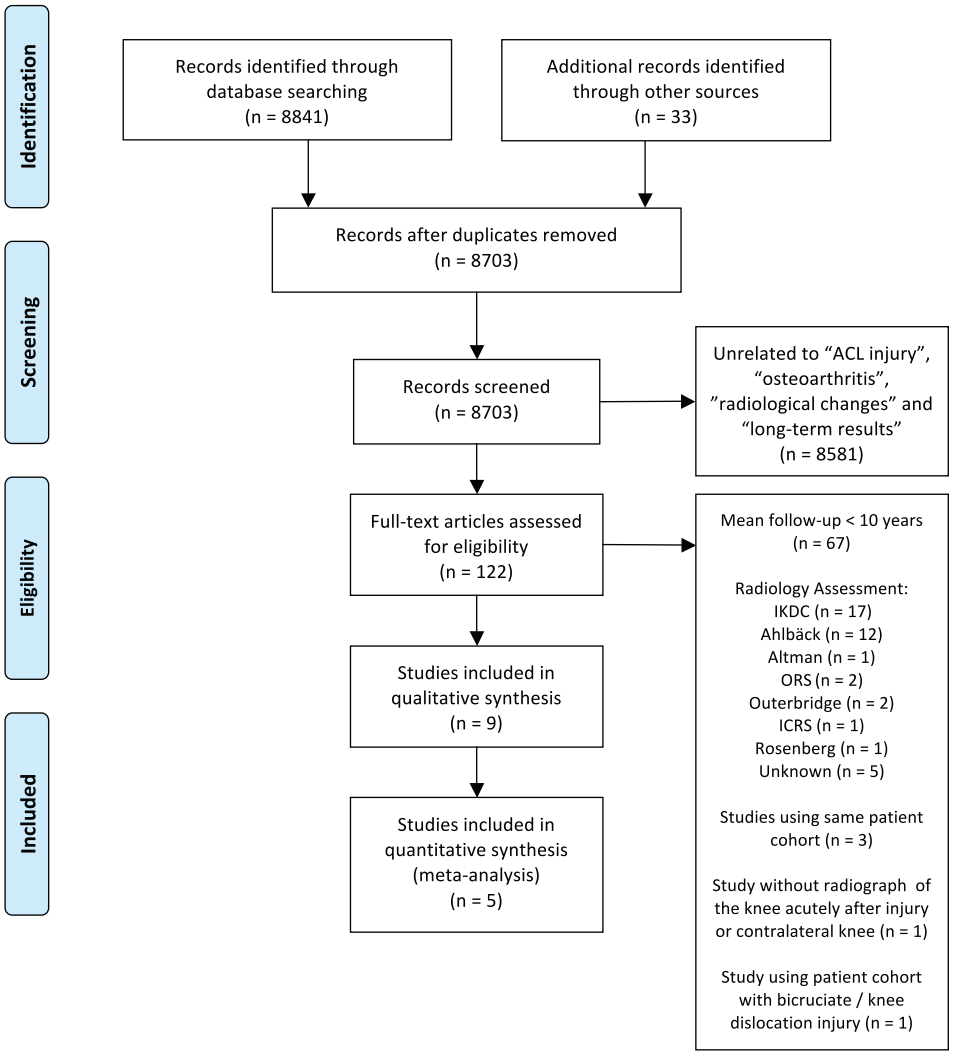

Figure 3. PRISMA flow diagram of the search strategy. ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; ORS, Osteoarthritis Research Society.

2.7 years. However, results were reported as the difference in Kellgren & Lawrence grades between the injured and uninjured knee. The actual assigned radiologic grades for each knee were not disclosed. This rendered it impossible to evaluate the proportion of each radiologic grade, so these 19 knees were hence excluded from our statistical analysis.

At the time of final follow-up, 202 of 596 knees (33.9%) with ACL injury demonstrated grade I radiologic changes, and 188 of 596 knees (31.5%) showed grade II changes. Only 14.3% of these knees were classified as grade 0, compared with 52.5% in the ACL-intact contralateral control group.

When grouped into minimal (grades 0, I, and II) versus moderate and severe (grades III and IV) radiologic changes, 475 of 596 knees (79.7%) with ACL injury had minimal changes regardless of treatment. Four hundred forty-two of 465 knees (95.1%) from the control group showed similar minimal radiologic changes. Thus "moderate" or "severe" radiologic changes account for 20.3% (121 knees) of the ACL injury group, compared with 4.9% (23 knees) of the control group. This represents a 4-fold increased risk of developing radiologic changes of moderate to severe osteoarthritis after ACL injury.

One hundred fifteen (115) of the 501 knees (23.0%) that underwent reconstruction (with or without a simultaneous meniscal procedure) had moderate or severe changes, compared with the 23 knees (4.9%) in the control group. Sixteen of the 101 (15.9%) ACL-reconstructed knees without meniscal injury demonstrated moderate or severe radiologic changes. Although radiologic osteoarthritic progression is less prevalent than in the group including meniscal injury, it is 3 times greater than the control group (15.9% vs 4.9%).

Three studies reported that 73 of 151 knees (48.3%) that received ACL-R within a mean time of 0.5 to 6.0 months from the initial injury had grade 0 or I radiologic changes after a minimum 10-year follow-up.[20,41,75] A further 3 studies reported that 187 of the 296 knees (63.2%) that had

TABLE 1
Summary of Included Studies[a]

Authors	Study Type	No. of Subjects	Description of Subjects	Additional Injuries and/or Reinjury at Follow-up	Mean Follow-up, (Range), y	Initial Treatment of ACL	Return to Sports	No. of Radiologically Assessed	Classification	Radiologic Findings
Struewer et al 2012[75]	Retrospective/ case series	73	Median age = 43 y (range, 24-63 y); 46 men, 27 women; isolated ACL injury at presentation without significant articular surface damage, meniscus lesions, osteoarthritic lesion (K/L grade I or higher) or concomitant MCL repair	Excluded from study	13.5	Isolated ACL-R using BTB graft within 2-3 wk of injury	High-demand, pivoting activities allowed after 6-9 mo	73	K/L	*Initial K/L* = 100% grade 0; *2-y K/L* = 17.5% grade 0, 46.8% grade I, 23.0% grade II, 11.9% grade III, 0.8% grade IV; *13.5-y* = 4.1% grade 0, 41.1% grade I, 32.9% grade II, 16.4% grade III, 5.5% grade IV
Hoffelner et al 2012[20]	Retrospective/ case series	28	*Skiers:* 6 males, 6 female; mean age = 21.9 ± 8.7 y at surgery; *Soccer players:* 15 males, 1 female, mean age = 22.6 ± 9.0 y at surgery	Excluded from study	9.6 (skiers); 10.15 (soccer players); 10 (overall)	Isolated ACL-R using BTB graft or double-looped single-bundle hamstring and gracilis graft	All athletes returned to previous sports competitively after 8 mo	28	K/L	*Uninjured knee K/L* = 14% grade I; *Injured knee K/L* = 18% grade I, 4% grade II
Øiestad et al 2011[56]	Cross-sectional study	210	90 females, 120 males; mean age = 39.1 ± 8.7 y at follow-up; isolated ACL or in combination with meniscus injury and/or chrondral lesion and/or MCL injury, with uninjured contralateral knee	Isolated ACL injury in 82 patients, medial meniscus injury in 39 patients, lateral meniscus injury in 19 patients, medial and lateral meniscus injury in 26 patients, meniscus and MCL in 5 patients, meniscus and MCL and chondral lesion in 3 patients, meniscus and chondral lesion in 29 patients, chondral lesion only in 7 patients	13.7 ± 4.4	ACL-R using BTB graft (n = 181) and hamstring tendon autograft (n = 29); 137 partial meniscal resections and 13 meniscal sutures performed	Allowed to return to full sports participation after 6 mo if full range of movement, no effusion, and good knee stability and strength	210	K/L	*Uninjured knee K/L* = 54% grade 0, 21% grade I, 19% grade II, 5% grade III, 1% grade IV; *Injured knee K/L* = 9% grade 0, 20% grade I, 47% grade II, 19% grade III, 5% grade IV
Sutherland et al 2010[76]	Retrospective/ case series	79	63 males, 16 females; mean age = 41 y (22-77 y) at review; unilateral ACL-R in the absence any identifiable injury in the contralateral knee	N/A	10 (8-15)	ACL-R using BTB graft	N/A	79	K/L	*Uninjured knee K/L* = 73/79 grade 0 or I, 6/79 grade II or III; *Injured knee K/L* = 43/79 grade 0 or I, 36 grade II or III
Mascarenhas et al 2010[35]	Case-control study	38	19 matched pairs previously participated in strenuous or very strenuous sporting activities 4-7 times per week; 36.8% female, 63.2% male; mean age = 27.86 ± 8.06 y (autograft), 28.11 ± 9.13 y (allograft); unilateral knee injury, without prior ipsilateral stablization procedure or PCL insufficiency or grade III medial/lateral/ posterolateral instability or previous revision ACL surgery	Associated lateral meniscus injury = 7 (autograft) and 11 (allograft); Associated medial meniscus injury = 9 (autograft) and 12 (allograft); Associated MCL injury = 1 (autograft) and 0 (allograft); chondral injury = 6 (autograft) and 10 (allograft)	9.14 ± 2.74 (autograft); 10.34 ± 2.64 (allograft)	ACL-R using harvested patellar autograft tendon with distal bone plug (n = 19) and fresh-frozen patellar allograft tendon with distal bone plug (n = 19); *Concomitant procedures:* n = 8 (autograft) and 12 (allograft); *Subsequent surgery:* n = 5 (autograft) and 3 (allograft)	Unrestricted return to sport or activities after 6 mo if full range of movement, no effusion, and muscle strength of at least 90% compared with uninjured side	34 (17 autograft, 17 allograft)	K/L	*Autograft:* 9/17 grade I side-to-side difference in ≥2 compartments or grade II in ≥1 compartments, 8/17 grade 0 side-to-side difference in all compartments or grade I side-to-side difference in only 1 compartment; *Allograft:* 9/17 grade I side-to-side difference in ≥2 compartments or grade II in ≥1 compartments, 8/17 grade 0 side-to-side difference in all compartments or grade I side-to-side difference in only 1 compartment
Meuffels et al 2009[41]	Case-control study	50	19 male matched pairs, 6 female matched pairs; mean age = 37.6 ± 6.2 y (operative) and 37.8 ± 6.8 y (nonoperative); ACL injury confirmed on MRI or arthroscopically, with no previous intra- or extra-articular knee ligament reconstruction	Operative (reconstructed) group: 68% had menisectomy; Nonoperative group (nonreconstructed): 80% had menisectomy	10	Patients had minimum 3 mo of a physical therapist–led rehabilitation program; patients to decide on either nonpivoting activity lifestyle (nonoperative) or ACL-R (operative)	Operative: return to sports after 6 mo; nonoperative: nonpivoting activity-lifestyle modification advised	50	K/L	*Operative group:* grade 0 = 4%, grade I = 9, grade II = 9, grade III = 3, grade IV = 0; *Nonoperative group:* grade 0 = 8, grade I = 10, grade II = 4, grade III = 3, grade IV = 0
van der Hart et al 2008[79]	Retrospective/ case series	28	17 males, 11 females; mean age at surgery = 30.5 y (range, 16-42 y); instability secondary to ACL rupture confirmed by clinical examination; exclusion: contralateral knee ligament surgery/ ipsilateral revision surgery/PCL or PCL injury/abnormal radiography of knee before reconstruction or subsequent total knee arthroplasty	13 medial meniscal injury, 7 medial and lateral meniscal injury; chondral injury: grade II = 1, grade III = 1, grade IV = 2; 3 lateral meniscal suturing, 1 medial meniscal suturing	10.3 (10-11)	Diagnostic arthroscopy ± meniscectomy or meniscal suturing, followed by planned ACL-R at 34 mo (range, 14-186 mo) from injury using BTB autograft	Return to competitive sport involving jumping, pivoting, or side stepping after formal clinical evaluation at 6-9 mo	28	K/L	*Uninjured knee K/L* = 71% grade 0, 26% grade I, 3% grade II, 0% grade III, 0% grade IV; *Injured knee K/L* = 10% grade 0, 45% grade I, 29% grade II, 10% grade III, 6% grade IV

(continued)

TABLE 1
(continued)

Authors	Study Type	No. of Subjects	Description of Subjects	Additional Injuries and/or Reinjury at Follow-up	Mean Follow-up, (Range), y	Initial Treatment of ACL	Return to Sports	No. of Radiologically Assessed	Classification	Radiologic Findings
Seon et al 2006[69]	Retrospective/ case series	58	55 males, 3 females; mean age at surgery = 30.4 y (range, 18-58 y); arthroscopically confirmed and reconstructed ACL ligament with/without concomitant meniscal procedure, with subsequent ligamentous surgery in any form	20 medial meniscectomy, 7 lateral meniscectomy, 6 medial and lateral meniscectomy	11.2 (8.6-13.8)	Arthroscopically assisted ACL-R using harvested BTB autograft with or without concomitant meniscal or chondral procedures, 31.1 mo (range, 0.5-180 mo) after injury	Low-impact sports allowed at 3 mo	58	K/L	*Injured knee K/L* = (presurgical) 2/58 grade II; (final follow-up) 20/58 grade II, 5/58 grade III
Segawa et al 2001[68]	Retrospective/ case series	70	28 males, 42 females; mean age at injury = 22.8 y (range, 12-50 y); isolated ACL deficiency with >5 y history, diagnosed on arthroscopy, declined ACLR or age >40 y, and without associated patellofemoral instability	38/65 medial meniscal tear, 22/65 lateral meniscal tear, 5/65 medial and lateral meniscal tear; 55/65 with arthroscopic partial meniscectomy	11.6 (5-27)	Nonoperative treatment with modification of athletic activity	Advised nature of the injury, the need of modification of athletic activity, and the importance of lower-extremity exercise	70	K/L	*Injured knee K/L* = 26/65 grade 0, 18/65 grade I, 23/65 grade II, 3/65 grade III; *Uninjured knee K/L* = 50/65 grade 0, 14/65 grade I, 2/65 grade II, 4/65 grade III

[a]ACL, anterior cruciate ligament; ACL-R, ACL reconstruction; BTB, bone–patellar tendon–bone; K/L, Kellgren & Lawrence classification; MCL, medial cruciate ligament; MRI, magnetic resonance imaging; OA, osteoarthritis; PCL, posterior cruciate ligament.

TABLE 2
Number and Percentage of Knees With Anterior Cruciate Ligament Injury According to the Reported Kellgren & Lawrence Classification From the Included Studies

	Kellgren & Lawrence Grade				
Studies	0	I	II	III	IV
Struewer et al 2012[75]	3	30	24	12	4
Hoffelner et al 2012[20]	22	5	1	0	0
Øiestad et al 2011[56]	19	42	99	40	10
Sutherland et al 2010[76]		43		36	
Meuffels et al 2009[41]	12	19	13	6	0
van der Hart et al 2008[79]	3	12	8	3	2
Seon et al 2006[69]		33	20	5	0
Segawa et al 2001[68]	26	18	23	3	0
Number of knees	85	202	188	105	16
Percentage of knees	14.3	33.9	31.5	17.6	2.7

reconstruction surgery at a mean time of 24.8 to 34.0 months after the index injury demonstrated grade II, III, or IV changes.[55,69,79] No studies reported a mean time to ACL-R surgery between 6.0 to 24.8 months from the index injury.

Meta-analysis

Of the 9 studies identified for systematic review, 3 were excluded from our meta-analysis. The study by Mascarenhas et al[35] reported the results of the differences in Kellgren & Lawrence grades instead of the actual score. Struewer et al[75] and Seon et al[69] used index radiologic appearance of the ACL-injured knee as a control and were hence also excluded.

A total of 6 studies were therefore suitable for meta-analysis.[20,41,56,68,76,79] They all reported Kellgren & Lawrence radiologic grades for knees after ACL injury using the opposite ACL-intact uninjured knee as a control, with a mean follow-up period of 10 years. Of these, 4 studies compared knees that underwent ACL-R against those ACL-intact knees without injury, 1 study looked at both ACL-R and nonoperatively treated ACL injury compared with the ACL-intact uninjured knee, and 1 study reported only ACL injuries treated with nonoperative management. There were insufficient data to perform a meta-analysis on ACL-R knees with confirmed uninjured menisci as a subgroup.

The relative risk (RR) of developing osteoarthritis (Kellgren & Lawrence grade II or greater), after an ACL injury, is 3.89 (range, 2.72-5.57; $P < .00001$) when compared with the contralateral uninjured control (Figure 4). This includes all ACL injuries with or without meniscal injury, whether treated by reconstructive surgery or nonoperatively.

After ACL-R in knees with or without meniscal injury, the RR of developing osteoarthritis is 3.62 (range, 2.40-

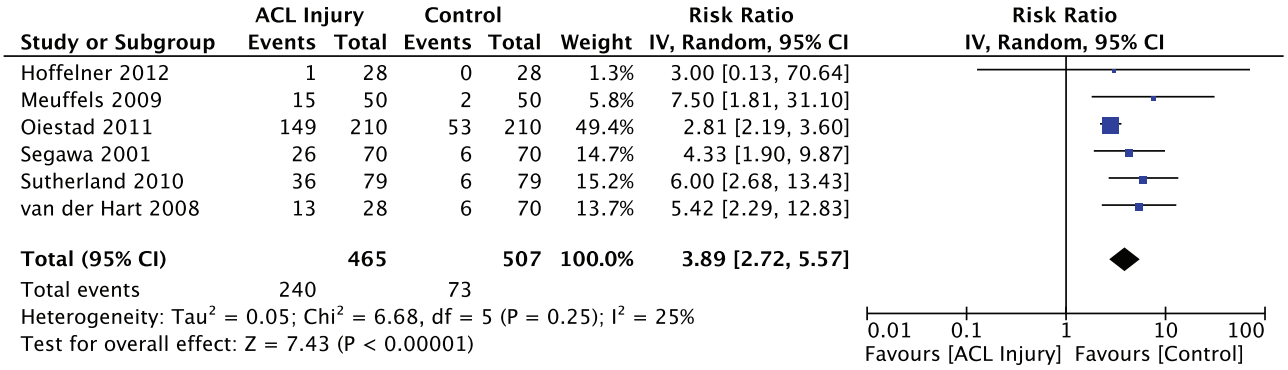

Figure 4. Forest plot of anterior cruciate ligament–injured knees versus contralateral knees (control) in developing osteoarthritis. Relative risk = 3.89 ($P < .00001$), with heterogeneity of 25% ($P = .25$).

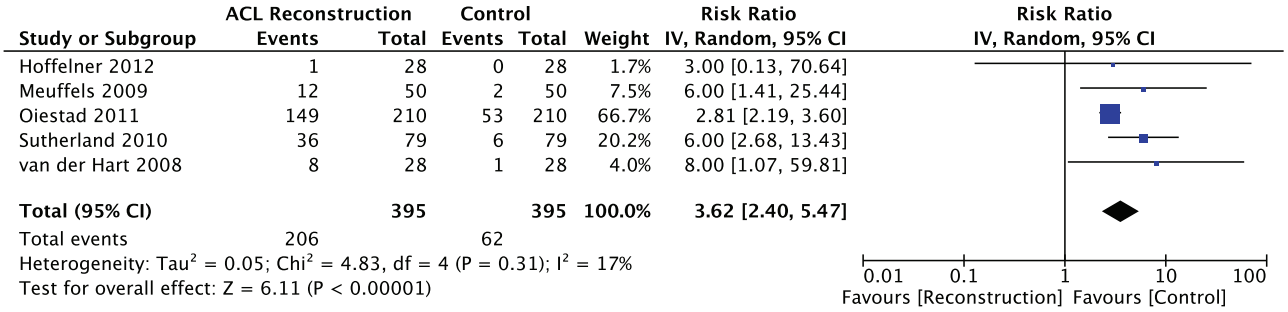

Figure 5. Forest plot of anterior cruciate ligament–reconstructed knees versus contralateral knees (control) in developing osteoarthritis. Relative risk = 3.62 ($P < .00001$), with heterogeneity of 17% ($P = .31$).

5.47; $P < .00001$) when compared with the uninjured control group at follow-up (Figure 5), whereas nonoperatively managed knees have an RR of 4.98 (range, 2.45-10.15; $P < .00001$; Figure 6).

With regard to the severity of osteoarthritis, the RR of developing moderate or severe (Kellgren & Lawrence grade III or IV) radiologic changes after an ACL injury is 3.84 (range, 1.84-8.01; $P < .0004$) when compared with the controls at a mean follow-up period of 10 years. The RR of developing the same progression of radiologic changes with ACL-R knees is 4.71 (range, 2.98-7.45; $P < .00001$). There is no significant difference in such risk between nonoperatively managed ACL-injured knees compared with the control group, with an RR of 2.41 (0.15-39.29; $P = .54$). The I^2 index of homogeneity ranged from 0% to 44%, with $P > .10$, in 5 of 6 meta-analyses, confirming that the outcomes reported within the included studies were homogeneous.

DISCUSSION

The purpose of this study was to perform a systematic review and meta-analysis of the published peer review literature assessing ACL injury and its association with the onset of radiologically defined osteoarthritis after a minimum mean follow-up of 10 years.

In our final data set consisting of 644 patients, there were 422 males and 222 females. An ACL rupture is more common among female patients within the general population due to several factors, including femoral structure,[59,80] increased quadriceps angle,[77] increased posterior tibial slope,[72] and genetic predisposition.[61,62] After searching the literature, we found that most outcome studies on ACL-R have heavily male-dominated sample groups. One of the largest studies was based on data from the Swedish National Ligament Register between 2005 and 2010. Examining almost 18,000 primary ACL reconstructions, this study showed that 57.5% were performed on male patients and 42.5% on female patients.[1] Janssen et al[23] also reported similar findings from the data compiled by the Australian Institute of Health and Welfare. They suggested that while females are at higher risk of sustaining ACL injuries compared with males participating in the same sport, there is a larger number of males who participate in high-risk sports compared with females, leading to participation bias. The study by Segawa et al[68] was the only one included in our work that had more females than males (42 vs 28) and examined nonoperatively treated ACL ruptures (this trend was not generally found in the literature, however). The fact that the samples of the included studies are not representative of the population may be considered a limitation of this study.

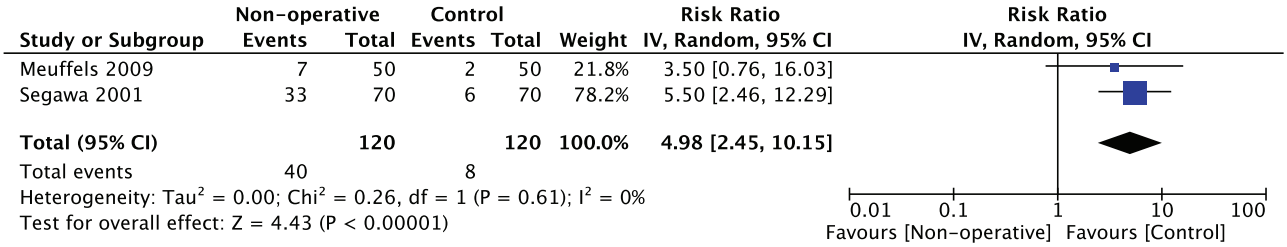

Figure 6. Forest plot of nonoperatively managed anterior cruciate ligament–injured knees versus contralateral knees (control) in developing osteoarthritis. Relative risk = 4.98 ($P < .00001$), with heterogeneity of 0% ($P = .61$).

Despite this, our results demonstrate that after an ACL injury, with or without associated meniscal injury, grade III or IV radiologic changes are nearly 5 times more likely than in the contralateral knees without history of an ACL injury. After ACL injury, regardless of the mode of management, our meta-analysis demonstrates an RR of 3.89 for developing any osteoarthritis and an RR of 3.84 for developing moderate or severe (grade III or IV) radiologic changes at a mean of 10 years of follow-up. After ACL-R, the RR was 3.62 for developing any osteoarthritis and 4.71 for moderate or severe (grade III or IV) radiologic changes, implying that if any osteoarthritic changes occur after ACL-R, they are likely to be moderate or severe as opposed to mild. Nonoperatively treated ACL-injured knees have a higher RR of developing grade II or greater radiologic changes (RR = 4.98) by 10 years, indicating that ACL-R surgery has a role in reducing the risk of developing osteoarthritis after ACL-R.

Previous studies and review articles have demonstrated the relationships between ACL injury and osteoarthritis.[24,75,76] However, no previous meta-analyses or systematic reviews have attempted to quantify the severity of radiologic changes in knees with ACL injury, owing to the wide range of established classification systems used by various authors. This fact was also acknowledged by Øiestad et al[54] in their comprehensive review article in 2009. Our decision to include only studies reporting results using the Kellgren & Lawrence grading system, a recognized and validated radiologic classification system for osteoarthritis,[17,25,30] has allowed for the first meta-analysis as well as a descriptive analysis.

The Kellgren & Lawrence classification was chosen because of its well-documented validity in assessing plain radiographs of the joint for the diagnosis of osteoarthritis and related symptoms.[48] Other classification systems include the International Knee Documentation Committee (IKDC) radiologic assessment and the Ahlbäck classification, used by 18 and 12 studies, respectively (as identified by our literature review strategy).

However, the radiologic grading of the IKDC system is defined as the lowest grade (A to D, representing changes from none, mild, moderate, to severe, respectively) observed from a total of 5 components on plain radiographs: anterior, posterior, medial, and lateral joint spaces, as well as the patellofermoral joint.[18,22,40] Consequently, the IKDC system can result in overreporting of the severity of osteoarthritis.[4] Furthermore, it has been suggested that the Ahlbäck classification system has a poor inter- and intraobserver agreement.[13]

Our results support the proposition that ACL-R has a role to play in preventing the development of post–ACL injury osteoarthritis. The principle of ACL-R is to restrain anterior tibial translation and restore rotational stability as would be expected for a functional ACL,[10,85] thus preventing excessive torsional force acting on the menisci and articular cartilages. The ACL-deficient knees that were nonoperatively treated were therefore expected to develop osteoarthritis more rapidly. It is therefore surprising to find that ACL-reconstructed knees tended toward a higher proportion of moderate and severe osteoarthritic changes (grades III and IV; RR = 4.71, $P < .00001$) when compared with ACL-injured knees managed nonoperatively (RR = 2.41, $P = .54$).

One explanation for this was that the heterogeneity of the included studies for nonoperative treatment was statistically significant ($I^2 = 67\%$, $P = .08$). An alternative explanation is differing patient expectations and activity modification between the ACL-R and nonoperatively treated groups. For ACL injuries that were managed nonoperatively, Segawa et al[68] and Meuffels et al[41] advised their patients on the importance of activity modification. Conversely, ACL-R patients would frequently undergo surgery with the explicit aim of returning to sport, which often would include pivoting and cutting. Although some of these patients would invariably report at their final follow-up that they had failed to return to sport or had to adopt activity modification after ACL-R, most patients remained very active after postoperative rehabilitation.[20,35,69,75,79] Four studies included within our meta-analysis reported that patients were "allowed" to return to sports[20,41,56,68,76,79]; however, they do not report the numbers of patients actually achieving this goal, and as such, it is not possible to ascertain whether return to sport accelerates or protects against osteoarthritis progression within the ACL-R group. The increased relative risks in the ACL-R group for developing grade III or IV changes may be explained by this group's return to sports and further secondary injury to the joint or may be a consequence of their reconstructive surgery and nonnative ACL biomechanics.

As such, the observed difference in relative risks would suggest the importance of patient- and injury-specific rehabilitation regimens and expectation management after

ACL injury and that there is still a role for nonoperative treatment.

We acknowledged there are limitations in this systematic review and meta-analysis. There were variations in surgical technique, tunnel placement, and rehabilitation across the patient groups assessed. Limiting inclusion to those studies using a single radiologic classification system would have excluded high-quality published literature that adopted other forms of radiologic assessment. However, as the aim of this study has been to perform a meta-analysis on the progression and the severity of osteoarthritis, we believe that the methodology of using a single, validated, and well-recognized radiologic grading system provides the best means of addressing the research question. In addition, the rationale to include non–randomized controlled trials for the meta-analysis was previously presented by other researchers,[71] and although the authors acknowledge there would be potential systematic error and contributing bias, there are great potential benefits to this approach.

We note also the preponderance of BTB graft use within the studies, which may not be representative of current contemporary practice. Overtightening of the BTB graft has been implicated in the premature onset of knee osteoarthritis after ACL-R and as such represents a possible confounder.[60]

We were unable to ascertain the number of patients who were able to return to sporting activities after ACL-R. The origins of post–ACL-R knee osteoarthritis remain unclear; however, participation in cutting and twisting sports, with repeated secondary injury, may play a role.

It is likely that other intra-articular injury, such as meniscal tears or chondral damage, will have acted as confounders. Previous studies have suggested that intact menisci are critical in the protection of the articular cartilage.[39,58,65] Based on the available literature, it is not possible to stratify for these differing groups within our study.

We believe that the adoption of soft-tissue sports injuries databases, for the prospective collection of data, will allow future researchers to stratify patients based on the degree and location of intra-articular derangement and limb alignment. This will allow for the correlation of different patterns of joint derangement (meniscal injury, chondral injury, etc) with patient outcomes and prognosis.

CONCLUSION

After an ACL injury, the RR for developing any osteoarthritis (Kellgren & Lawrence grades II, III, and IV) at a mean of 10 years is 3.89, while the RR for developing moderate or severe (grades III and IV) radiologic changes is 3.84.

Returning to pivoting and cutting sports after ACL-R may lead to an increased risk of developing moderate or severe radiologic changes, with a relative risk of 4.71, when compared with nonoperatively managed knees for which patients were advised activity modification. There is also an argument that returning to sport signifies good surgical outcome, and patients who do not achieve this goal after ACL-R have a poorer outcome and may be given an increased risk of osteoarthritis progression due to abnormal biomechanical forces. There are no data at present to link returning to sports after ACL-R and the development of osteoarthritis.

The wide adoption of the soft-tissue knee databases with prospective data collection will facilitate future studies and allow stratification of patients based on the presence of internal joint derangement (meniscal deficit, chondral injury, etc) and limb alignment. This would remove this significant confounder and allow for separate analysis of these arthritic high-risk groups.

There should also be an emphasis on the use of a single validated radiologic grading system when assessing evidence of osteoarthritis at follow-up.

REFERENCES

1. Ahlden M, Samuelsson K, Sernert N, Forssblad M, Karlsson J, Kartus J. The Swedish National Anterior Cruciate Ligament Register: a report on baseline variables and outcomes of surgery for almost 18,000 patients. *Am J Sports Med*. 2012;40(10):2230-2235.
2. Ait Si Selmi T, Fithian D, Neyret P. The evolution of osteoarthritis in 103 patients with ACL reconstruction at 17 years follow-up. *Knee*. 2006;13(5):353-358.
3. Ardern CL, Webster KE, Taylor NF, Feller JA. Return to the preinjury level of competitive sport after anterior cruciate ligament reconstruction surgery: two-thirds of patients have not returned by 12 months after surgery. *Am J Sports Med*. 2011;39(3):538-543.
4. Beard DJ, Knezevic K, Al-Ali S, Dawson J, Price AJ. The use of outcome measures relating to the knee. *Orthop Trauma*. 2010;24(4):309-316.
5. Brophy RH, Schmitz L, Wright RW, et al. Return to play and future ACL injury risk after ACL reconstruction in soccer athletes from the Multicenter Orthopaedic Outcomes Network (MOON) group. *Am J Sports Med*. 2012;40(11):2517-2522.
6. Clayton RA, Court-Brown CM. The epidemiology of musculoskeletal tendinous and ligamentous injuries. *Injury*. 2008;39(12):1338-1344.
7. Cochrane Collaboration. *Review Manager (RevMan)* [computer program]. Version 5.2. Copenhagen: The Cochrane Collaboration; 2012.
8. Cohen M, Amaro JT, Ejnisman B, et al. Anterior cruciate ligament reconstruction after 10 to 15 years: association between meniscectomy and osteoarthrosis. *Arthroscopy*. 2007;23(6):629-634.
9. Drogset JO, Grontvedt T, Robak OR, Molster A, Viset AT, Engebretsen L. A sixteen-year follow-up of three operative techniques for the treatment of acute ruptures of the anterior cruciate ligament. *J Bone Joint Surg Am*. 2006;88(5):944-952.
10. Duthon VB, Barea C, Abrassart S, Fasel JH, Fritschy D, Menetrey J. Anatomy of the anterior cruciate ligament. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(3):204-213.
11. Fink C, Hoser C, Hackl W, Navarro RA, Benedetto KP. Long-term outcome of operative or nonoperative treatment of anterior cruciate ligament rupture: is sports activity a determining variable? *Int J Sports Med*. 2001;22(4):304-309.
12. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med*. 2010;363(4):331-342.
13. Galli M, De Santis V, Tafuro L. Reliability of the Ahlback classification of knee osteoarthritis. *Osteoarthritis Cartilage*. 2003;11(8):580-584.
14. Gobbi A, Francisco R. Factors affecting return to sports after anterior cruciate ligament reconstruction with patellar tendon and hamstring graft: a prospective clinical investigation. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(10):1021-1028.
15. Hanypsiak BT, Spindler KP, Rothrock CR, et al. Twelve-year follow-up on anterior cruciate ligament reconstruction: long-term outcomes of prospectively studied osseous and articular injuries. *Am J Sports Med*. 2008;36(4):671-677.

16. Hart AJ, Buscombe J, Malone A, Dowd GS. Assessment of osteoarthritis after reconstruction of the anterior cruciate ligament: a study using single-photon emission computed tomography at ten years. *J Bone Joint Surg Br*. 2005;87(11):1483-1487.
17. Hart DJ, Spector TD. The classification and assessment of osteoarthritis. *Baillière's Clin Rheumatol*. 1995;9(2):407-432.
18. Hefti F, Muller W, Jakob RP, Staubli HU. Evaluation of knee ligament injuries with the IKDC form. *Knee Surg Sports Traumatol Arthrosc*. 1993;1(3-4):226-234.
19. Hertel P, Behrend H, Cierpinski T, Musahl V, Widjaja G. ACL reconstruction using bone-patellar tendon-bone press-fit fixation: 10-year clinical results. *Knee Surg Sports Traumatol Arthrosc*. 2005;13(4):248-255.
20. Hoffelner T, Resch H, Moroder P, et al. No increased occurrence of osteoarthritis after anterior cruciate ligament reconstruction after isolated anterior cruciate ligament injury in athletes. *Arthroscopy*. 2012;28(4):517-525.
21. Holm I, Øiestad BE, Risberg MA, Aune AK. No difference in knee function or prevalence of osteoarthritis after reconstruction of the anterior cruciate ligament with 4-strand hamstring autograft versus patellar tendon-bone autograft: a randomized study with 10-year follow-up. *Am J Sports Med*. 2010;38(3):448-454.
22. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the international knee documentation committee subjective knee form. *Am J Sports Med*. 2001;29(5):600-613.
23. Janssen KW, Orchard JW, Driscoll TR, van Mechelen W. High incidence and costs for anterior cruciate ligament reconstructions performed in Australia from 2003-2004 to 2007-2008: time for an anterior cruciate ligament register by Scandinavian model? *Scand J Med Sci Sports*. 2012;22(4):495-501.
24. Keays SL, Newcombe PA, Bullock-Saxton JE, Bullock MI, Keays AC. Factors involved in the development of osteoarthritis after anterior cruciate ligament surgery. *Am J Sports Med*. 2010;38(3):455-463.
25. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16(4):494-502.
26. Kessler MA, Behrend H, Henz S, Stutz G, Rukavina A, Kuster MS. Function, osteoarthritis and activity after ACL-rupture: 11 years follow-up results of conservative versus reconstructive treatment. *Knee Surg Sports Traumatol Arthrosc*. 2008;16(5):442-448.
27. Kullmer K, Letsch R, Turowski B. Which factors influence the progression of degenerative osteoarthritis after ACL surgery? *Knee Surg Sports Traumatol Arthrosc*. 1994;2(2):80-84.
28. Lebel B, Hulet C, Galaud B, Burdin G, Locker B, Vielpeau C. Arthroscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone autograft: a minimum 10-year follow-up. *Am J Sports Med*. 2008;36(7):1275-1282.
29. Lee DY, Karim SA, Chang HC. Return to sports after anterior cruciate ligament reconstruction: a review of patients with minimum 5-year follow-up. *Ann Acad Med Singapore*. 2008;37(4):273-278.
30. Lethbridge-Çejku M, Scott WW, Reichle R, et al. Association of radiographic features of osteoarthritis of the knee with knee pain: data from the Baltimore longitudinal study of aging. *Arthritis Rheum*. 1995;8(3):182-188.
31. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med*. 2007;35(10):1756-1769.
32. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis Rheum*. 2004;50(10):3145-3152.
33. Majewski M, Susanne H, Klaus S. Epidemiology of athletic knee injuries: a 10-year study. *Knee*. 2006;13(3):184-188.
34. Maletius W, Messner K. Eighteen- to twenty-four-year follow-up after complete rupture of the anterior cruciate ligament. *Am J Sports Med*. 1999;27(6):711-717.
35. Mascarenhas R, Tranovich M, Karpie JC, Irrgang JJ, Fu FH, Harner CD. Patellar tendon anterior cruciate ligament reconstruction in the high-demand patient: evaluation of autograft versus allograft reconstruction. *Arthroscopy*. 2010;26(9 suppl):S58-S66.
36. McCullough KA, Phelps KD, Spindler KP, et al. Return to high school- and college-level football after anterior cruciate ligament reconstruction: a Multicenter Orthopaedic Outcomes Network (MOON) cohort study. *Am J Sports Med*. 2012;40(11):2523-2529.
37. McDaniel WJ Jr, Dameron TB Jr. The untreated anterior cruciate ligament rupture. *Clin Orthop Relat Res*. 1983;172:158-163.
38. McDaniel WJ Jr, Dameron TB Jr. Untreated ruptures of the anterior cruciate ligament: a follow-up study. *J Bone Joint Surg Am*. 1980;62(5):696-705.
39. McNicholas MJ, Pengas IP, Assiotis A, Nash W, Hatcher J, Banks J. Total meniscectomy in adolescents: a 40-year follow-up. *J Bone Joint Surg Br*. 2012;94(12):1649-1654.
40. Mehta VM, Paxton LW, Fornalski SX, Csintalan RP, Fithian DC. Reliability of the International Knee Documentation Committee radiographic grading system. *Am J Sports Med*. 2007;35(6):933-935.
41. Meuffels DE, Favejee MM, Vissers MM, Heijboer MP, Reijman M, Verhaar JA. Ten year follow-up study comparing conservative versus operative treatment of anterior cruciate ligament ruptures: a matched-pair analysis of high level athletes. *Br J Sports Med*. 2009;43(5):347-351.
42. Meunier A, Odensten M, Good L. Long-term results after primary repair or non-surgical treatment of anterior cruciate ligament rupture: a randomized study with a 15-year follow-up. *Scand J Med Sci Sports*. 2007;17(3):230-237.
43. Meystre JL, Vallotton J, Benvenuti JF. Double semitendinosus anterior cruciate ligament reconstruction: 10-year results. *Knee Surg Sports Traumatol Arthrosc*. 1998;6(2):76-81.
44. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2700.
45. Murray AW, Macnicol MF. 10-16 year results of Leeds-Keio anterior cruciate ligament reconstruction. *Knee*. 2004;11(1):9-14.
46. Nakamura S, Kobayashi M, Asano T, Arai R, Nakagawa Y, Nakamura T. Image-matching technique can detect rotational and AP instabilities in chronic ACL-deficient knees. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(suppl 1):S69-S76.
47. Nakata K, Shino K, Horibe S, et al. Arthroscopic anterior cruciate ligament reconstruction using fresh-frozen bone plug-free allogeneic tendons: 10-year follow-up. *Arthroscopy*. 2008;24(3):285-291.
48. Neogi T, Felson D, Niu J, et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ*. 2009;339:b2844.
49. Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE. Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. *Am J Sports Med*. 2008;36(9):1717-1725.
50. Neuman P, Kostogiannis I, Friden T, Roos H, Dahlberg LE, Englund M. Patellofemoral osteoarthritis 15 years after anterior cruciate ligament injury: a prospective cohort study. *Osteoarthritis Cartilage*. 2009;17(3):284-290.
51. Neyret P, Donell ST, DeJour D, DeJour H. Partial meniscectomy and anterior cruciate ligament rupture in soccer players: a study with a minimum 20-year followup. *Am J Sports Med*. 1993;21(3):455-460.
52. Noyes FR, Matthews DS, Mooar PA, Grood ES. The symptomatic anterior cruciate-deficient knee. Part II: the results of rehabilitation, activity modification, and counseling on functional disability. *J Bone Joint Surg Am*. 1983;65(2):163-174.
53. O'Brien WR. Degenerative arthritis of the knee following anterior cruciate ligament injury: role of the meniscus. *Sports Med Arthrosc Rev*. 1993;1(2):114-118.
54. Øiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. *Am J Sports Med*. 2009;37(7):1434-1443.
55. Øiestad BE, Holm I, Aune AK, et al. Knee function and prevalence of knee osteoarthritis after anterior cruciate ligament reconstruction: a prospective study with 10 to 15 years of follow-up. *Am J Sports Med*. 2010;38(11):2201-2210.
56. Øiestad BE, Holm I, Engebretsen L, Risberg MA. The association between radiographic knee osteoarthritis and knee symptoms,

function and quality of life 10-15 years after anterior cruciate ligament reconstruction. *Br J Sports Med*. 2011;45(7):583-588.
57. Øiestad BE, Holm I, Gunderson R, Myklebust G, Risberg MA. Quadriceps muscle weakness after anterior cruciate ligament reconstruction: a risk factor for knee osteoarthritis? *Arthritis Care Res (Hoboken)*. 2010;62(12):1706-1714.
58. Papalia R, Del Buono A, Osti L, Denaro V, Maffulli N. Meniscectomy as a risk factor for knee osteoarthritis: a systematic review. *Br Med Bull*. 2011;99:89-106.
59. Park JS, Nam DC, Kim DH, Kim HK, Hwang SC. Measurement of knee morphometrics using MRI: a comparative study between ACL-injured and non-injured knees. *Knee Surg Relat Res*. 2012;24(3):180-185.
60. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J. A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. *Am J Sports Med*. 2007;35(4):564-574.
61. Posthumus M, Collins M, van der Merwe L, et al. Matrix metalloproteinase genes on chromosome 11q22 and the risk of anterior cruciate ligament (ACL) rupture. *Scand J Med Sci Sports*. 2012;22(4):523-533.
62. Posthumus M, September AV, O'Cuinneagain D, van der Merwe W, Schwellnus MP, Collins M. The COL5A1 gene is associated with increased risk of anterior cruciate ligament ruptures in female participants. *Am J Sports Med*. 2009;37(11):2234-2240.
63. Pritchard JC, Drez D Jr, Moss M, Heck S. Long-term followup of anterior cruciate ligament reconstruction using freeze-dried fascia lata allografts. *Am J Sports Med*. 1995;23(5):593-596.
64. Reid JS, Hanks GA, Kalenak A, Kottmeier S, Aronoff V. The Ellison iliotibial-band transfer for a torn anterior cruciate ligament of the knee: long-term follow-up. *J Bone Joint Surg Am*. 1992;74(9):1392-1402.
65. Roos EM, Ostenberg A, Roos H, Ekdahl C, Lohmander LS. Long-term outcome of meniscectomy: symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls. *Osteoarthritis Cartilage*. 2001;9(4):316-324.
66. Salmon LJ, Russell VJ, Refshauge K, et al. Long-term outcome of endoscopic anterior cruciate ligament reconstruction with patellar tendon autograft: minimum 13-year review. *Am J Sports Med*. 2006;34(5):721-732.
67. Scanlan SF, Chaudhari AM, Dyrby CO, Andriacchi TP. Differences in tibial rotation during walking in ACL reconstructed and healthy contralateral knees. *J Biomech*. 2010;43(9):1817-1822.
68. Segawa H, Omori G, Koga Y. Long-term results of non-operative treatment of anterior cruciate ligament injury. *Knee*. 2001;8(1):5-11.
69. Seon JK, Song EK, Park SJ. Osteoarthritis after anterior cruciate ligament reconstruction using a patellar tendon autograft. *Int Orthop*. 2006;30(2):94-98.
70. Sherman MF, Warren RF, Marshall JL, Savatsky GJ. A clinical and radiographical analysis of 127 anterior cruciate insufficient knees. *Clin Orthop Relat Res*. 1988;227:229-237.
71. Shrier I, Boivin JF, Steele RJ, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *Am J Epidemiol*. 2007;166(10):1203-1209.
72. Sonnery-Cottet B, Archbold P, Cucurulo T, et al. The influence of the tibial slope and the size of the intercondylar notch on rupture of the anterior cruciate ligament. *J Bone Joint Surg Br*. 2011;93(11):1475-1478.
73. Strand T, Molster A, Hordvik M, Krukhaug Y. Long-term follow-up after primary repair of the anterior cruciate ligament: clinical and radiological evaluation 15-23 years postoperatively. *Arch Orthop Trauma Surg*. 2005;125(4):217-221.
74. Streich NA, Zimmermann D, Bode G, Schmitt H. Reconstructive versus non-reconstructive treatment of anterior cruciate ligament insufficiency: a retrospective matched-pair long-term follow-up. *Int Orthop*. 2011;35(4):607-613.
75. Struewer J, Frangen TM, Ishaque B, et al. Knee function and prevalence of osteoarthritis after isolated anterior cruciate ligament reconstruction using bone-patellar tendon-bone graft: long-term follow-up. *Int Orthop*. 2012;36(1):171-177.
76. Sutherland AG, Cooper K, Alexander LA, Nicol M, Smith FW, Scotland TR. The long-term functional and radiological outcome after open reconstruction of the anterior cruciate ligament. *J Bone Joint Surg Br*. 2010;92(8):1096-1099.
77. Sutton KM, Bullock JM. Anterior cruciate ligament rupture: differences between males and females. *J Am Acad Orthop Surg*. 2013;21(1):41-50.
78. Taylor DC, Posner M, Curl WW, Feagin JA. Isolated tears of the anterior cruciate ligament: over 30-year follow-up of patients treated with arthrotomy and primary repair. *Am J Sports Med*. 2009;37(1):65-71.
79. van der Hart CP, van den Bekerom MP, Patt TW. The occurrence of osteoarthritis at a minimum of ten years after reconstruction of the anterior cruciate ligament. *J Orthop Surg Res*. 2008;3:24.
80. van Diek FM, Wolf MR, Murawski CD, van Eck CF, Fu FH. Knee morphology and risk factors for developing an anterior cruciate ligament rupture: an MRI comparison between ACL-ruptured and non-injured knees. *Knee Surg Sports Traumatol Arthrosc*. 2013. doi: 10.1007/s00167-013-2588-7
81. Vasara AI, Jurvelin JS, Peterson L, Kiviranta I. Arthroscopic cartilage indentation and cartilage lesions of anterior cruciate ligament-deficient knees. *Am J Sports Med*. 2005;33(3):408-414.
82. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. *Ann Rheum Dis*. 2004;63(3):269-273.
83. Wu WH, Hackett T, Richmond JC. Effects of meniscal and articular surface status on knee stability, function, and symptoms after anterior cruciate ligament reconstruction: a long-term prospective study. *Am J Sports Med*. 2002;30(6):845-850.
84. Yamaguchi S, Sasho T, Tsuchiya A, Wada Y, Moriya H. Long term results of anterior cruciate ligament reconstruction with iliotibial tract: 6-, 13-, and 24-year longitudinal follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(11):1094-1100.
85. Zantop T, Petersen W, Sekiya JK, Musahl V, Fu FH. Anterior cruciate ligament anatomy and function relating to anatomical reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(10):982-992.