Knee osteoarthritis risk is increased 4-6 fold after knee injury – a systematic review and meta-analysis

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ABSTRACT

Objective To estimate knee osteoarthritis (OA) risk following anterior cruciate ligament (ACL), meniscus or combined ACL and meniscus injury.

Design Systematic review and meta-analysis.

Data sources MEDLINE, Embase, SPORTDiscus, CINAHL and Web of Science until November 2018.

Eligibility criteria for selecting studies Prospective or retrospective studies with at least 2-year follow-up including adults with ACL injury, meniscal injury or combined injuries. Knee OA was defined by radiographs or clinical diagnosis and compared with the contralateral knee or non-injured controls.

Study appraisal and synthesis Risk of bias was assessed using the SIGN50 checklist. ORs for developing knee OA were estimated using random effects meta-analysis.

Results 53 studies totalling ~1 million participants were included: 185 219 participants with ACL injury, mean age 28 years, 35% females, 98% surgically reconstructed; 83 267 participants with meniscal injury, mean age 38 years, 36% females, 22% confirmed meniscectomy and 73% unknown; 725 362 participants with combined injury, mean age 31 years, 26% females, 80% treated surgically. The OR of developing knee OA were 4.2 (95% CI 2.2 to 8.0; I^2=92%), 6.3 (95% CI 3.8 to 10.5; I^2=95%) and 6.4 (95% CI 4.9 to 8.3; I^2=62%) for patients with ACL injury, meniscal injury and combined injuries, respectively.

Conclusion The odds of developing knee OA following ACL injury are approximately four times higher compared with a non-injured knee. A meniscal injury and a combined injury affecting both the ACL and meniscus are associated with six times higher odds compared with a non-injured knee. Large inconsistency (eg, study design, follow-up period and comparator) and few high-quality studies suggest that future studies may change these estimates.

Clinical relevance Patients sustaining a major knee injury have a substantially increased risk of developing knee OA, highlighting the importance of knee injury prevention programmes and secondary prevention strategies to prevent or delay knee OA development. PROSPERO registration number CRD42015016900

INTRODUCTION

Knee injury is one of the strongest risk factors for development of knee osteoarthritis (OA).[1 2] However, the relative importance of different types of knee injuries such as ACL injury and meniscal injury for knee OA risk is less clear. Previous systematic reviews report higher risk of knee OA in patients with combined ACL and meniscal injury compared with patients with isolated ACL injury.[3 4] Common for previous systematic reviews were that these did not quantitatively assess the risk of OA but relied on a narrative or 'best evidence synthesis' approach and did not include studies on patients with isolated meniscal injury, precluding any definitive conclusions about the relative importance of ACL injury and meniscal injury on subsequent risk of knee OA development.[3]

We performed an updated comprehensive systematic review and meta-analysis to ascertain the risk of knee OA development in adults following isolated ACL injury, isolated meniscal injury or combined ACL and meniscus injury.

MATERIALS AND METHODS

This systematic review was performed according to the guidelines from the Cochrane collaboration and followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[5 6] The study protocol is available online: http://www.crd.york.ac.uk/PROSPERO, CRD42015016900).

Literature search

The senior author (CBJ) developed a comprehensive search strategy, and a systematic search for published literature was performed in the electronic databases MEDLINE via PubMed, Embase via Ovid, SPORTDiscus, CINAHL via EBSCO and Web of Science up until 1 May 2015 by GHG. Two authors (GHG and EP) screened the titles, abstracts and full texts. An updated search was performed up to 1 November 2018. Furthermore, a supplementary manual search was performed based on the reference lists from the included studies and systematic reviews/meta-analyses by the first author (EP).

Where possible, all terms were searched as keywords (Medical Subject Headings (MeSH)) and text words in titles and abstracts to create three separate filters, which were then combined. These filters were: (1) knee injury: "menisc", "anterior cruciate ligament" or "knee injury", (2) knee OA: "radiographic", "radiological", "osteoarthritis", "degenerative arthritis" or "osteoarthrosis" and (3) risk factors: "causality", "risk factors" or "prognosis". The complete search strategy for all included databases is presented in detail in online supplementary appendix 1. No restriction on year of publication was applied, and only studies published in English, Norwegian, Swedish or Danish were included.

Eligibility criteria

We included studies meeting the following criteria: (1) *design*: prospective or retrospective designs with a follow-up time of a minimum of 2 years after knee injury/surgery. A minimum of 2 years was chosen as radiographic OA development has been demonstrated at 2 years following ACL reconstruction combined with meniscal surgery[7]; (2) *population*: participants having an ACL injury, meniscal injury, a combination of ACL injury and meniscal injury and a mean minimum age of 18 years at the time of injury. Studies including patients reported to have OA at time of injury were excluded; (3) *comparison*: risk of the injured knee needed to have been compared with either the contralateral leg or a non-injured control group; (4) *outcome*: development of knee OA defined as: (1) radiographic knee OA of the tibiofemoral joint according to either Kellgren & Lawrence classification ≥2, Ahlbäck grading scale ≥1, International Knee Documentation Committee (IKDC) radiographic scale C and D, Fairbank ≥2 or other radiographic scoring systems as well as reporting of total knee arthroplasty (TKA) due to OA, (2) symptomatic knee OA (ie, defined by criteria such as those developed by the American College of Rheumatology) or (3) self-reported knee OA.[8–10]

Selection of studies

Following the removal of duplicates from the initial search, two authors (GHG/EP) independently screened the articles by title and abstract to identify relevant studies. Full text of all abstracts considered relevant by either of these reviewers was obtained and screened independently for eligibility by both. The full-text studies were assessed independently by the same two authors and reasons for exclusion were listed. For the updated search, the authors EP and AB repeated these procedures.

Data extraction

The following data were extracted from the included studies: authors, publication year, country of origin, study design, number of participants at follow-up (with or without OA), participant characteristics (ie, age at time of injury/surgery, sex, body mass index (BMI) and activity level prior to injury), criteria for definition of symptomatic and/or radiographic OA, comparison group (ie, healthy control or contralateral leg), type of knee injury (ie, ACL injury, meniscal injury or combination of ACL and meniscal injury) and other knee injuries in addition (such as medial or lateral collateral ligament injury, posterior cruciate ligament and chondral injury and so on). When data could be extracted for more than one injury type, the OR for OA development was estimated for each injury type by comparing each injury group with the control group (eg, ACL injury vs control and combined vs control).[6] Hence, the reported ORs reflect the odds of developing knee OA after an ACL, meniscal or combined injury in comparison with a non-injured knee. Furthermore, data were extracted involving intervention (surgical, non-surgical or no intervention) and time to follow-up.

Risk of bias assessment

Two of the authors (EP/CBJ) independently evaluated risk of bias of included studies using the SIGN50 checklists.[11] Authors EP and AB performed the same task for the updated search. The checklist evaluates internal validity with the domains: focused research question, selection of subjects, assessment, confounding and statistical analysis and an overall study assessment. The overall assessment of included studies was classified as high quality, acceptable quality or unacceptable quality.[11] Prior to risk of bias assessment, the evaluating authors familiarised themselves

with the guidelines for scoring each of the criteria as detailed in SIGN50. Disagreement was solved by discussion. The SIGN50 checklist is included in online supplementary appendix 2.

Strategy for data synthesis

As studies with 'clean' populations of isolated ACL tears are rare, we categorised study participants into three groups based on injury type: (1) the ACL group included studies with participants having isolated ACL injury and allowing for up to 20% of participants having a concurrent meniscal injury. (2) The meniscus group included studies with participants having an isolated meniscal injury and allowing for up to 20% of participants having a concurrent ACL injury. (3) The combined group included studies where more than 20% of participants were reported to have the combination of ACL and meniscus injury. Meta-analysis was applied based on the logarithmic transformed OR of developing knee OA in subjects with isolated ACL injury, meniscal injury and a combination of ACL and meniscal injury, respectively. Data from adjusted analyses of included studies were extracted if available. Meta-analysis using random effect models was applied as large clinical heterogeneity was expected in participant characteristics, comparator group, follow-up time and the definitions of knee OA. Between-study variance was estimated as Tau-squared,[12] and heterogeneity was calculated as the I-squared (I^2 statistics),[13] measuring the proportion of inconsistency in the combined estimates due to between-study heterogeneity.[14] An I^2 equal to 0% indicates minimal inconsistency, and an I^2 equal to 100% indicates maximal inconsistency between individual study results. Covariates are defined as variables able to reduce the Tau-squared when included in the analysis. Additional meta-regression analyses were performed to investigate the impact of physical activity level prior to injury and time to follow-up. Physical activity level was evaluated by dichotomising reported Tegner scores prior to injury (Tegner <7=low to moderate activity prior to injury and Tegner ≥7=high activity). Time to follow-up was used as a continuous variable (year) and also dichotomised into ≤10 years and >10 years. Risk of small study bias was assessed by visual inspection of funnel plots of included studies in the three groups.

Some studies, examining OA risk following ACL or meniscal injuries did not specifically report patient OA status at time of injury. Therefore, we performed a sensitivity analysis excluding studies with no information about baseline OA status and a mean patient age of 35 years or older as some of these patients could have OA at time of injury. In the analysis, we retained studies specifically reporting exclusion of patients with OA at time of injury and studies not reporting OA status at time of injury but a mean patient age under 35 years, as these patients are unlikely to have OA at time of injury. Furthermore, we performed a sensitivity analysis changing the cut-offs for isolated ACL and meniscal injury allowing only 10% concurrent meniscal or ACL injury and an analysis calculating the overall risk (OR) stratified by uninjured knee versus a healthy control group as comparator.

RESULTS

Following the initial literature search and after duplicates were removed, 8416 studies were reviewed by title and abstract, 341 studies were included for full-text screening and 53 papers were included in the meta-analysis. The updated search including 1 November 2018 revealed seven new studies for inclusion in the meta-analysis. The PRISMA flow chart including reason for full-text exclusion is attached in figure 1.
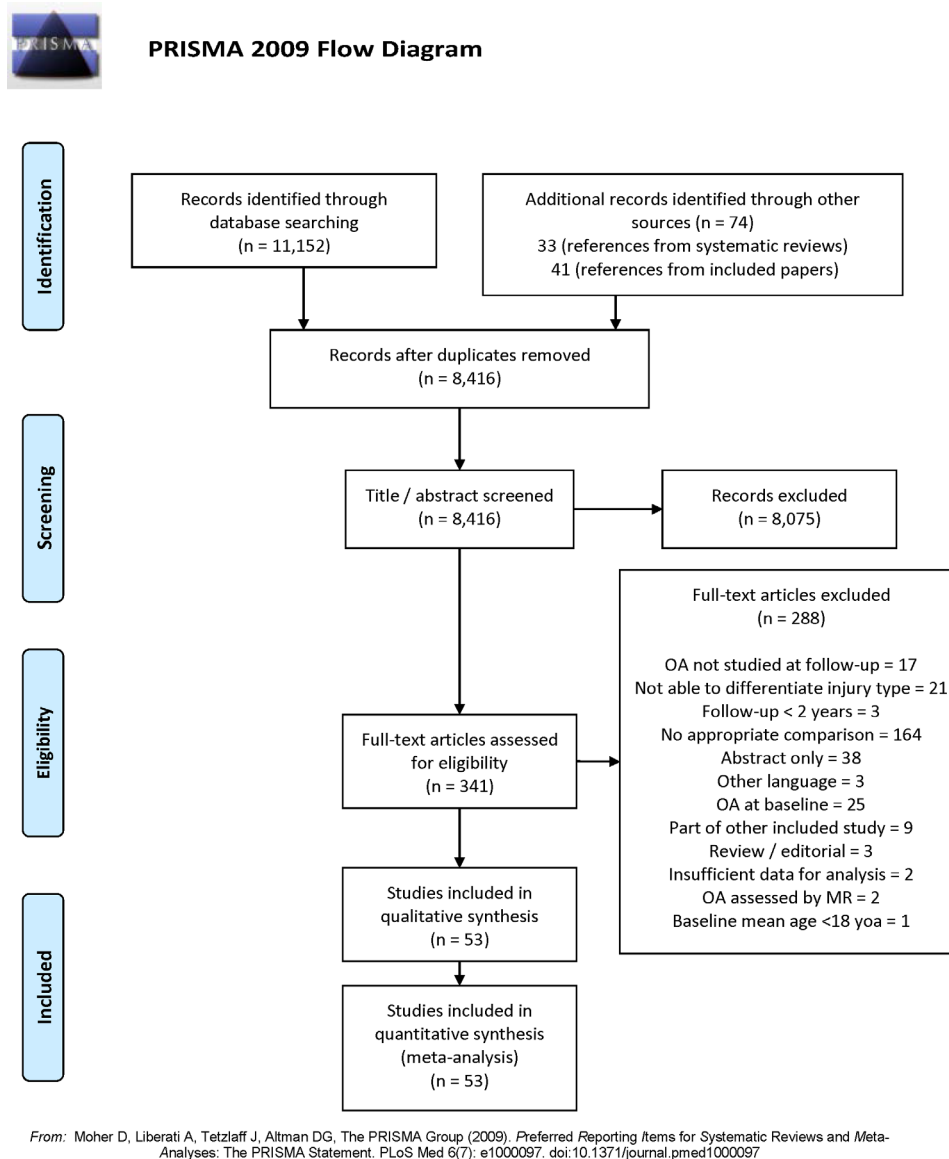
PRISMA 2009 Flow Diagram

Figure 1 PRISMA flow chart of study selection. OA, osteoarthritis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Study characteristics

Of the 53 included studies, 11 investigated isolated ACL injury (185 219 participants, 35% females, mean age 28.1 years at time of injury), 22 meniscal injury (83 267 participants, 36% females, mean age 38.1 years at time of injury) and 25 combined injury (725 362 participants, 26% females, mean age 30.5 years at time of injury). One study reported both ACL and meniscal injuries separately, two papers reported isolated ACL and combined injuries separately and two studies reported isolated meniscal and combined injuries separately. Additional details of included studies are listed in table 1.

Forty-two studies used the opposite knee as a control, and 11 studies involved an age-matched, and sex-matched control group or a reference population of similar mean age and sex distribution. The knee OA outcome was based on knee radiographs for 91% of the studies (n=48), one study used self-reported OA, two studies used physician-diagnosed OA and two studies reported TKA due to knee OA. Radiographic OA defined by a cut-off of Kellgren & Lawrence grade ≥2 was reported in 19 studies, by Albäck score ≥1 in 10 studies, by IKDC score (C

and D) in 9 studies and by Fairbank score ≥2 in 6 studies. Four studies used other radiographic grading systems.

The risk of OA development was assessed regardless of treatment strategy (surgery/non-surgery/not reported) in all three groups. For the isolated ACL injury group, 98% of participants had arthroscopic ACL reconstruction and for the remaining 2%, the treatment was not specified. For the meniscal injury group, 22% had meniscal surgery, the treatment strategy was not reported for 73% of participants, and treatment was non-surgical for 5% of participants. In the combined injury group, 26% of participants had received ACL reconstruction as the primary surgery, meniscectomy was reported as the primary surgery for 54% of participants and for 20% of participants treatment was not specified.

Risk of knee OA

The OR for developing knee OA in comparison with a non-injured knee following ACL injury and meniscal injury were 4.2 (95% CI 2.2 to 8.0; I^2=92%) and 6.3 (95% CI 3.8 to 10.5; I^2=95%), respectively. The odds of developing OA following a combined

Table 1 Characteristics of study participants, study characteristics and risk of bias assessment of included studies

Author, year Country (reference)	Participants n, age, (female%)*	Type of injury and (intervention)†	Activity level‡	OA classification (radiographic/self-reported/clinical)	Comparison (n and type)§	Years of follow-up (mean, SD/range)	Risk of bias assessment (Total and ratio score)¶
Ait Si Selmi, 2006 France[21]	n=89, 22.0 (11%)	Combined (ACL reconstr.)	Not reported	IKDC	n=89 Opposite knee	17.4	+ (8/13)
Andersson-Molina, 2002 Sweden[22]	n=36, 29.0 (0%)	Meniscus (APM - medial)	1	Ahlbäck	n=18 Matched controls	14.0	+ (11/13) retrospective
	n=36, 28.0 (0%)	Menisc (total meniscect.)	1	Ahlbäck	n=18 Matched controls	14.0	+ (11/13)
Barenius, 2014 Sweden[23]	n=69, 24.0 (49%)	Combined (ACL reconstr. BTPB)	0	KL	n=69 Opposite knee	15.2	++ (10/13)
	n=65, 26.1, (32%)	Combined (ACL reconstr.)	0	KL	n=65 Opposite knee	15.5	++ (10/13)
Bonneaux, 2002 Belgium[24]	n=29, 25.0 (31%)	Meniscus (APM lateral)	1	Fairbank	n=29 Opposite knee	8.0 (SD 1.5)	+ (7/13)
Bulgheroni, 2015 Italy[25]	n=34, 31.0 (76%)	Combined (ACL reconstr. – meniscect./CMI impl.)	0	KL	n=34 Opposite knee	11.8 (SD 2.4)	+ (5/13)
Chatain, 2001 France[26]	n=218, 38.0 (19%)	Menisc (medial meniscect.)	1	IKDC	n=218 Opposite knee	11.5 (10–15)	+ (6/13)
Chatain, 2003 France[27]	n=64, 35.0 (18%)	Meniscus (lateral meniscect.)	1	IKDC	n=64 Opposite knee	11.0 (SD 1.4)	+ (6/13)
Chen, 2017 China[28]	n=59, 28.6 (14%)	Combined (ACL reconstr.-ham.)	1	KL	n=59 Opposite knee	11.7 (SD 1.0)	+ (9/13)
	n=30, 27.6, (36%)	Combined ACL reconstr.-syn.)	1	KL	n=30 Opposite knee	11.6 (SD 2.3)	+ (9/13)
Englund, 2009 USA[17]	n=405, 61.6, (62%)	Meniscus tear (no intervention)	0	KL	n=294 Matched controls	2.5	+ (12/13) retrospective
Faunø, 1992 Denmark[29]	n=136, 33.8, (26%)	Meniscus (arthroscop. resec.)	0	Fairbank	n=136 Opposite knee	8.5 (8–12)	+ (7/13)
Golightly, 2009 USA[30]	n=2511, 53.8 follow-up, (0%)	ACL (not reported)	1	Self-reported	n=1390 Matched controls	More than 10 years	- (3/13)
	n=2511, 53.8 follow-up, (0%)	Meniscus (not reported)	1	Self-reported	n=1315 Matched controls	More than 10 years	- (3/13)
Hart, 2005 UK[31]	n=16, 27.8, (32%)	Combined (PBTB +meniscect.)	0	Ahlbäck	n=16 Opposite knee	10 (9–13)	+ (6/13)
	n=15, 27.8, (32%)	ACL (PBTB reconstruct.)	0	Ahlbäck	n=15 Opposite knee	10 (9–13)	+ (6/13)
Hoffelner, 2012 Austria[32]	n=28, 22.4, (25%)	ACL (PBTB/hamstring)	1	KL	n=28 Opposite knee	10.0	+ (6/13)
Hulet, 2015 France[33]	n=89, 35.0 (37%)	Meniscus (APM lateral)	0	IKDC	n=89 Opposite knee	22.0 (SD 3.0)	+ (9/13)
Inderhaug, 2013 Norway[34]	n=78, 28.0 (34%)	Combined (ACL autograft)	1	IKDC	n=78 Opposite knee	11.0 (SD 0.6)	+ (6/13)
Jackson, 1968 UK[35]	n=382, 35.8 (11%)	Meniscus (meniscect.)	Not reported	other (radiographic)	n=382 Opposite knee	11.0	+ (5/13)

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Table 1 Continued

Author, year Country (reference)§	Participants n, age, (female%)*	Type of injury and (intervention)†	Activity level‡	OA classification (radiographic/self-reported/clinical)	Comparison (n and type)§	Years of follow-up (mean, SD/range)	Risk of bias assessment (Total and ratio score)¶‖
Jarvela, 2017 Finland[36]	n=24, 34.0, (30%)	Combined (ACL – DB auto.)	Not reported	KL	n=24 Opposite knee	13.1 (SD 0.3)	+ (8/13)
	n=23, 30.0, (30%)	Combined (ACL – SB bio.)	Not reported	KL	n=23 Opposite knee	13.1 (SD 0.3)	+ (8/13)
	n=23, 33.0, (37%)	Combined (ACL – SB metal)	Not reported	KL	n=23 Opposite knee	13.1 (SD 0.3)	+ (8/13)
Jauregito, 1995 USA[37]	n=18, 30.0, (not reported)	Meniscus (part. lat. menisect.)	Not reported	Fairbank	n=18 Opposite knee	8.0 (6–11)	+ (6/13)
Johnson, 1999 USA[38]	n=34, 18.9, (11%)	Meniscus (meniscal repair)	Not reported	Fairbank	n=34 Opposite knee	10.9 (8–13)	+ (7/13)
Johnson, 2015 USA[39]	n=710, 56.0, (67%)	ACL (not reported)	0	KL	n=355 Matched controls	4	+ (5/13)
Karikis, 2018 Sweden[40]	n=29, 26.0, (50%)	Combined (ACL reconstr. early)	1	KL	n=29 Opposite knee	10.5 (SD 2.6)	+ (8/13)
	n=29, 27.0, (39%)	Combined (ACL reconstr. late)	1	KL	n=29 Opposite knee	13.3 (SD 2.7)	+ (8/13)
Khan, 2018 UK[41]	n=154 076, 57.3, (27%)	Combined (TKA)	Not reported	Clinical	n=104 353 Matched controls	More than 20 years	++ (11/13)
	n=154 076, 65.1, (37%)	Meniscus (TKA)	Not reported	Clinical	n=104 353 Matched controls	More than 20 years	++ (11/13)
Leiter, 2014 Canada[42]	n=68, 31.2, (37%)	ACL (autograft)	1	KL	n=68 Opposite knee	14.6 (SD 1.9)	+ (7/13)
Leroux, 2014 Canada[43]	n=181 451, 28.0, (35%)	ACL (TKA)	Not reported	Clinical	n=151 362 Matched controls	15	+ (10/13) retrospective
Li, 2011 USA[44]	n=249, 26.4, (39%)	ACL (single bundle)	1	KL	n=249 Opposite knee	9.5 (4–22)	+ (8/13)
Lohmander, 2004 Sweden[45]	n=41, 19.0, (100%)	Combined (ACL reconstr.)	1	KL	n=41 Opposite knee	12	+ (8/13)
	n=26, 19.0, (100%)	Combined (no surgery)	1	KL	n=26 Opposite knee	12	+ (8/13)
Majewski, 2006 Switzerland[46]	n=64, 29.8, (39%)	Meniscus (suture repair)	1	Fairbank	n=64 Opposite knee	10.0 (5–17)	+ (9/13)
Maletius, 1997 Sweden[47]	n=52, 25.4, (34%)	Combined (ACL reconstruct.)	0	Ahlbäck	n=52 Opposite knee	9.0 (7–11)	+ (7/13)
Maletius, 1996 Sweden[48]	n=21, 28.0, (24%)	Meniscus (APM)	0	Ahlbäck	n=21 Opposite knee	13.0 (12–15)	+ (9/13)
Meuffels, 2009 Netherlands[49]	n=50, 27.7, (24%)	Combined (BPTB reconstruct.)	1	KL	n=50 Opposite knee	10.0	+ (6/13)
Meunier, 2007 Sweden[50]	n=93, 22.0, (32%)	Combined (ACL repair)	Not reported	Ahlbäck	n=93 Opposite knee	15.0 (14–19)	+ (7/13)
Murray, 2004 UK[51]	n=18, 28.4, (6%)	ACL (allograft)	0	IKDC	n=18 Opposite knee	13.0 (11–16)	+ (5/13)

Continued

Table 1 Continued

Author, year Country (reference)§	Participants n, age, (female%)*	Type of injury and (intervention)†	Activity level‡	OA classification (radiographic/self-reported/clinical)	Comparison (n and type)§	Years of follow-up (mean, SD/range)	Risk of bias assessment (Total and ratio score)¶
Murray, 2012 Australia[52]	n=84, 30.0, (not reported)	Combined (ACL autograft)	1	IKDC	n=84, Opposite knee	13.0	+ (7/13)
Neyret, 1993 France[53]	n=29, 30.0, (not reported)	ACL (autograft)	1	IKDC	n=29, Opposite knee	13.0	+ (7/13)
	n=92, 32.5, (22%)	Meniscus (partial meniscect.)	0	Other (radiographic)	n=92, Opposite knee	26.0 (20–34)	+ (6/13)
	n=88, 24.0, (22%)	Combined (partial meniscect.)	1	Other (radiographic)	n=88, Opposite knee	27.0 (20–34)	+ (6/13)
Oiestad, 2011 Norway[54]	n=210, 25.4, (43%)	Combined (ACL autograft)	Not reported	KL	n=210, Opposite knee	13.7 (SD 4.4)	++ (10/13)
Persson, 2018 Sweden[55]	n=645 967, 30.5, (26%)	Combined (Repair/part. menisc.)	Not reported	Clinical	n=643 480 Matched controls	10.5 (median, range 5–18)	++10/13
Reid, 1992 USA[56]	n=32, 22.0, (16%)	Combined (ACL reconstruc.)	1	other (radiographic)	n=32, Opposite knee	11.0 (7–15)	+ (7/13)
Rockborn, 1995 Sweden[57]	n=33, 19.0, (14%)	Meniscus (meniscect.)	1	Ahlbäck	n=33, Opposite knee	13.0 (11–15)	+ (6/13)
Rockborn, 2000 Sweden[58]	n=62, 25.0, (16%)	Meniscus (open meniscect.)	1	Ahlbäck	n=31, Matched controls	13.5 (11–19)	+ (7/13)
Roos, 2008 Sweden[59]	n=291, 34.4, (19%)	Meniscus (isolated meniscect.)	Not reported	KL	n=50, Matched controls	18.2 (SD 2.3)	+ (10/13) retrospective
Sanders, 2017 USA[60]	n=728, 31.5, (40%)	Combined (none)	Not reported	Clinical	n=364, Matched controls	14.3 (SD 7.4)	+ (7/13)
Scheller, 2001 Germany[61]	n=23, 39.9, (42%)	Meniscus (partial meniscect.)	Not reported	Jäger-Wirth	n=23, Opposite knee	12.3 (10–15)	+ (7/13)
	n=35, 42.5, (42%)	Meniscus (partial meniscect.)	Not reported	Jäger-Wirth	n=35, Opposite knee	7.1 (5–9)	+ (7/13)
Segawa, 2001 Japan[62]	n=70, 22.8, (40%)	Combined (no surgery)	0	KL	n=70, Opposite knee	11.9 (5–27)	+ (7/13)
Sommerlath, 1991 Sweden[63]	n=38, 28.0, (20%)	Combined (ACL repair)	0	Ahlbäck	n=38, Opposite knee	12.0 (9–16)	+ (6/13)
Sonne Holm, 1980 Denmark[64]	n=131, 25.0, (14%)	Meniscus (total menicectomy)	1	Ahlbäck	n=131, Opposite knee	4.25 (median, range 2.3–11)	+ (9/13)
Stein, 2010 Germany[65]	n=26, 31.1, (38%)	Meniscus (repair)	1	Fairbank	n=26, Opposite knee	9.0	+ (9/13)
	n=20, 30.4, (31%)	Meniscus (partial meniscect.)	1	Fairbank	n=20, Opposite knee	9.0	+ (9/13)
Strand, 2005 Norway[66]	n=61, 28.0, (not reported)	ACL (open repair)	0	IKDC	n=61, Opposite knee	23.0	+ (7/13)
Sun, 2009 China[67]	n=76, 29.8, (20%)	Combined (BPTB autograft)	0	KL	n=76, Opposite knee	5.6	+ (6/13)
	n=80, 30.7, (21%)	Combined (BPTB allograft)	0	KL	n=80, Opposite knee	5.6	+ (6/13)

Continued

Table 1 Continued

Author, year Country (reference)	Participants n, age, (female%)*	Type of injury and (intervention)†	Activity level‡	OA classification (radiographic/self-reported/clinical)	Comparison (n and type)§	Years of follow-up (mean, SD/range)	Risk of bias assessment (Total and ratio score)¶
Sun, 2011 China[68]	n=31, 28.5 (23%)	Combined (hamstring allograft)	0	KL	n=31 Opposite knee	3.6	+ (5/13)
	n=38, 29.6 (18%)	Combined (hamstring allograft)	0	KL	n=38 Opposite knee	3.6	+ (5/13)
Sutherland, 2010 UK[69]	n=79, 31.0 (20%)	ACL (reconstruc - BPLB)	0	KL	n=79 Opposite knee	11.0 (8–15)	+ (8/13)
Thelin, 2006 Sweden[18]	n=631, 62.6 follow-up, (0%)	Meniscus	0	Ahlbäck	n=293 Matched controls	More than 10 years	+ (5/13)
	n=842, 62.6 follow-up, (100%)	Meniscus	0	Ahlbäck	n=402 Matched controls	More than 10 years	+ (5/13)
van der Hart, 2008 Netherlands[70]	n=28, 27.6 (39%)	Combined (ACL autograft)	0	KL	n=28 Opposite knee	10.3 (10–11)	+ (7/13)
Yamaguchi, 2006 Japan[71]	n=24, 21.0 (31%)	Combined (ACL reconstruc.)	1	IKDC	n=24 Opposite knee	24.0	+ (7/13)

*n = number of participants included in analysis, age reported as mean years and gender as % females.
†ACL, meniscus, combined ACL and meniscus.
‡Pre-operative Tegner score ≥7 = 1, <7 = 0.
§n = number of controls in analysis, type = opposite knee or matched controls.
¶Total assessment score (++ high quality, + acceptable, - unacceptable), ratio score = number of items assessing bias in study/total number of items available for bias assessment.

ACL and meniscal injury was 6.4 (95% CI 4.9 to 8.3; I^2=62%) times higher compared with a non-injured knee (figure 2).

Sensitivity analyses lowering the threshold for overlap between study types from 20% to 10%, excluding studies with patient mean age of 35 years or older and not reporting OA status at time of injury as well as using the opposite knee versus using an uninjured control did not markedly change the estimates (online supplementary appendix 3).

Physical activity

Overall, 40 studies (75%) reported activity levels primarily using the Tegner score. Activity level (low-moderate vs high) prior to injury did not influence the risk of knee OA development, OR 0.85 (95% CI 0.51 to 1.41).

Length of follow-up

For 80% of the studies, the follow-up period was more than 10 years. The analysis indicated that studies with a longer time to follow-up had a significantly higher probability of reporting OA development (slope 1.049, 95% CI 1.009 to 1.090) (figure 3). Furthermore, categorising into follow-up periods into less than or more than 10 years, longer follow-up time (ie, 10 years or more) was associated with higher risk of developing knee OA (OR 1.46 (95% CI 0.95 to 2.26)).

Risk of bias

Four studies were rated as having low risk of bias, 48 (91%) studies as having moderate risk of bias and 1 study as having high risk of bias. Ten studies were prospective and 43 were retrospective. Risk of bias assessments of individual studies are given in table 1.

Visual inspection of funnel plots of included studies (figure 4A–C) indicated no risk of small study bias for the ACL or meniscal groups, whereas a risk of small study bias was present in the combined injury group.

No subgroup analyses were performed for BMI, baseline pain, surgery versus no surgery and additional injury due to insufficient data. BMI was reported in only 11 studies (21%), of which six reported BMI at follow-up. Additional injuries (collateral ligament and/or chondral) were reported for nine studies (17%). Pain level at baseline were reported for only one study.

DISCUSSION

In comparison with previous studies, this study provides pooled estimates of the additional risk of knee OA following different types of knee injuries in comparison with a non-injured knee. The results of the current synthesis confirm that both ACL and meniscal injuries are strong individual risk factors for the development of knee OA at 10 or more years following injury. At the same time, the results indicate that a meniscal lesion, isolated or in combination with an ACL injury is an even more important risk factor than an isolated surgically reconstructed ACL injury. Our results suggest that OA risk after knee injury is time dependent and increases with longer follow-up time.

This is the first systematic review to provide pooled estimates of OA risk following three different types of knee injuries. However, it should be noted that the populations sustaining these different types of injuries differ with regard to age. Individuals sustaining an injury involving the ACL were on average 28 and 31 years of age, while those with an isolated meniscal injury were on average 38 years. The difference in age indicates that individuals sustaining an injury involving the ACL
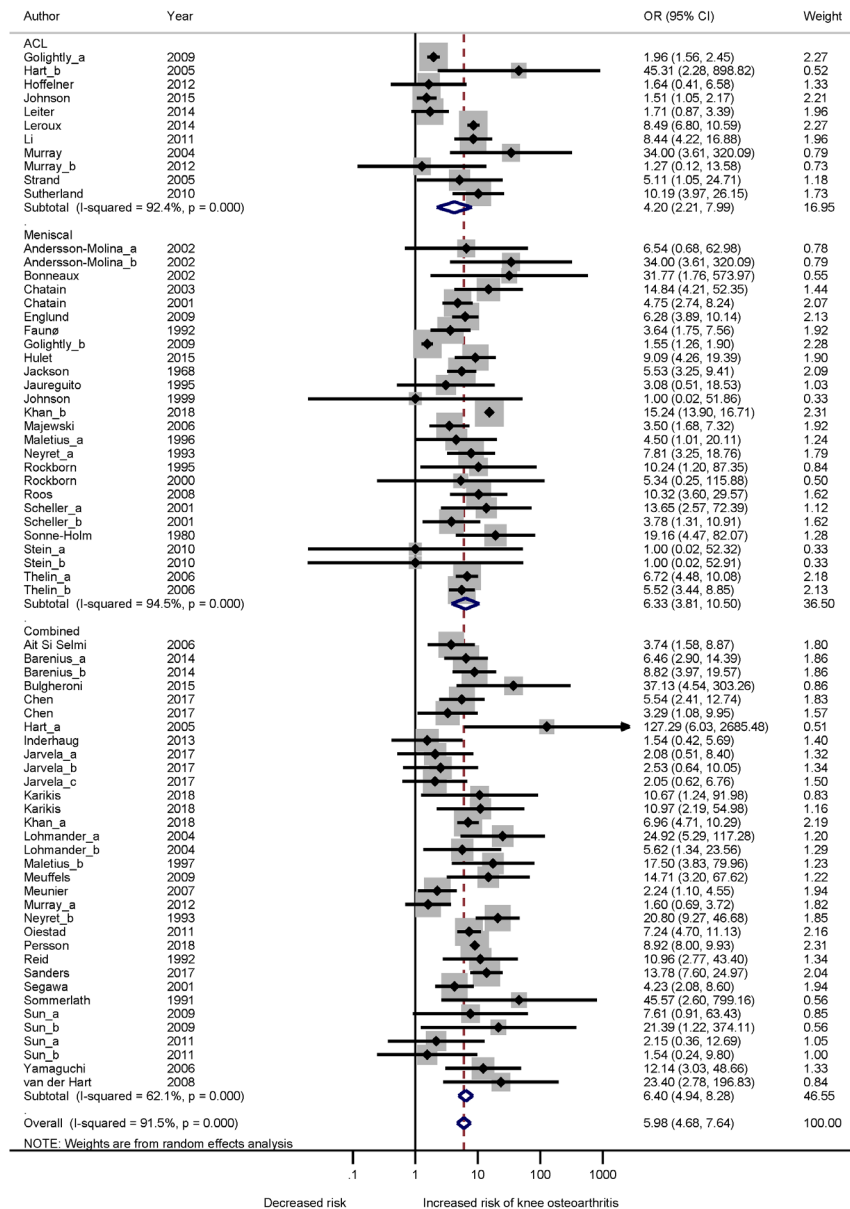
Author	Year	OR (95% CI)	Weight
ACL			
Golightly_a	2009	1.96 (1.56, 2.45)	2.27
Hart_b	2005	45.31 (2.28, 898.82)	0.52
Hoffelner	2012	1.64 (0.41, 6.58)	1.33
Johnson	2015	1.51 (1.05, 2.17)	2.21
Leiter	2014	1.71 (0.87, 3.39)	1.96
Leroux	2014	8.49 (6.80, 10.59)	2.27
Li	2011	8.44 (4.22, 16.88)	1.96
Murray	2004	34.00 (3.61, 320.09)	0.79
Murray_b	2012	1.27 (0.12, 13.58)	0.73
Strand	2005	5.11 (1.05, 24.71)	1.18
Sutherland	2010	10.19 (3.97, 26.15)	1.73
Subtotal (I-squared = 92.4%, p = 0.000)		4.20 (2.21, 7.99)	16.95
Meniscal			
Andersson-Molina_a	2002	6.54 (0.68, 62.98)	0.78
Andersson-Molina_b	2002	34.00 (3.61, 320.09)	0.79
Bonneaux	2002	31.77 (1.76, 573.97)	0.55
Chatain	2003	14.84 (4.21, 52.35)	1.44
Chatain	2001	4.75 (2.74, 8.24)	2.07
Englund	2009	6.28 (3.89, 10.14)	2.13
Faunø	1992	3.64 (1.75, 7.56)	1.92
Golightly_b	2009	1.55 (1.26, 1.90)	2.28
Hulet	2015	9.09 (4.26, 19.39)	1.90
Jackson	1968	5.53 (3.25, 9.41)	2.09
Jaureguito	1995	3.08 (0.51, 18.53)	1.03
Johnson	1999	1.00 (0.02, 51.86)	0.33
Khan_b	2018	15.24 (13.90, 16.71)	2.31
Majewski	2006	3.50 (1.68, 7.32)	1.92
Maletius_a	1996	4.50 (1.01, 20.11)	1.24
Neyret_a	1993	7.81 (3.25, 18.76)	1.79
Rockborn	1995	10.24 (1.20, 87.35)	0.84
Rockborn	2000	5.34 (0.25, 115.88)	0.50
Roos	2008	10.32 (3.60, 29.57)	1.62
Scheller_a	2001	13.65 (2.57, 72.39)	1.12
Scheller_b	2001	3.78 (1.31, 10.91)	1.62
Sonne-Holm	1980	19.16 (4.47, 82.07)	1.28
Stein_a	2010	1.00 (0.02, 52.32)	0.33
Stein_b	2010	1.00 (0.02, 52.91)	0.33
Thelin_a	2006	6.72 (4.48, 10.08)	2.18
Thelin_b	2006	5.52 (3.44, 8.85)	2.13
Subtotal (I-squared = 94.5%, p = 0.000)		6.33 (3.81, 10.50)	36.50
Combined			
Ait Si Selmi	2006	3.74 (1.58, 8.87)	1.80
Barenius_a	2014	6.46 (2.90, 14.39)	1.86
Barenius_b	2014	8.82 (3.97, 19.57)	1.86
Bulgheroni	2015	37.13 (4.54, 303.26)	0.86
Chen	2017	5.54 (2.41, 12.74)	1.83
Chen	2017	3.29 (1.08, 9.95)	1.57
Hart_a	2005	127.29 (6.03, 2685.48)	0.51
Inderhaug	2013	1.54 (0.42, 5.69)	1.40
Jarvela_a	2017	2.08 (0.51, 8.40)	1.32
Jarvela_b	2017	2.53 (0.64, 10.05)	1.34
Jarvela_c	2017	2.05 (0.62, 6.76)	1.50
Karikis	2018	10.67 (1.24, 91.98)	0.83
Karikis	2018	10.97 (2.19, 54.98)	1.16
Khan_a	2018	6.96 (4.71, 10.29)	2.19
Lohmander_a	2004	24.92 (5.29, 117.28)	1.20
Lohmander_b	2004	5.62 (1.34, 23.56)	1.29
Maletius_b	1997	17.50 (3.83, 79.96)	1.23
Meuffels	2009	14.71 (3.20, 67.62)	1.22
Meunier	2007	2.24 (1.10, 4.55)	1.94
Murray_a	2012	1.60 (0.69, 3.72)	1.82
Neyret_b	1993	20.80 (9.27, 46.68)	1.85
Oiestad	2011	7.24 (4.70, 11.13)	2.16
Persson	2018	8.92 (8.00, 9.93)	2.31
Reid	1992	10.96 (2.77, 43.40)	1.34
Sanders	2017	13.78 (7.60, 24.97)	2.04
Segawa	2001	4.23 (2.08, 8.60)	1.94
Sommerlath	1991	45.57 (2.60, 799.16)	0.56
Sun_a	2009	7.61 (0.91, 63.43)	0.85
Sun_b	2009	21.39 (1.22, 374.11)	0.56
Sun_a	2011	2.15 (0.36, 12.69)	1.05
Sun_b	2011	1.54 (0.24, 9.80)	1.00
Yamaguchi	2006	12.14 (3.03, 48.66)	1.33
van der Hart	2008	23.40 (2.78, 196.83)	0.84
Subtotal (I-squared = 62.1%, p = 0.000)		6.40 (4.94, 8.28)	46.55
Overall (I-squared = 91.5%, p = 0.000)		5.98 (4.68, 7.64)	100.00

NOTE: Weights are from random effects analysis

.1   1   10   100   1000

Decreased risk ← | → Increased risk of knee osteoarthritis

Figure 2 Forest plot showing ORs for OA development following ACL, meniscal and combined knee injury compared with a non-injured control knee.

are representative of young adults sustaining a trauma, typically during sport, whereas the group with isolated meniscal injury is more diverse.

Meniscal injury can be traumatic, for example, commonly a vertical longitudinal tear sustained to a healthy meniscus, or degenerative, for example, commonly horizontal and complex tears having a sudden or insidious onset. Both types of injury are associated with an increased risk of OA,[15] but the mechanisms may differ. For the traumatic tear, it has been suggested to be the tear itself or the frequent loss of tissue from surgical removal and the (resulting) change in joint loading and biomechanics that drive OA development, while the degenerative tear in the middle-aged and older individual has been suggested to be part of the OA process itself.[16] In our synthesis, one population-based study from the USA[17] and one study where cases were systematically identified from radiology departments in one geographical area in Sweden,[18] both with mean ages slightly over 60 years, contribute to the higher mean age in the meniscal subgroup. In the US population-based study, meniscal injury was confirmed by MRI at a mean age of 61 years, indicating the meniscal tears were degenerative by nature. In the Swedish study reporting a physician-confirmed meniscal injury, the presence of meniscus injury was self-reported retrospectively, and the age at time of injury and the most likely type of meniscal tear (traumatic or degenerative) are therefore unknown.

Comparison with previous literature

Several systematic reviews and meta-analyses have reported on the risk of developing knee OA following a knee injury, but
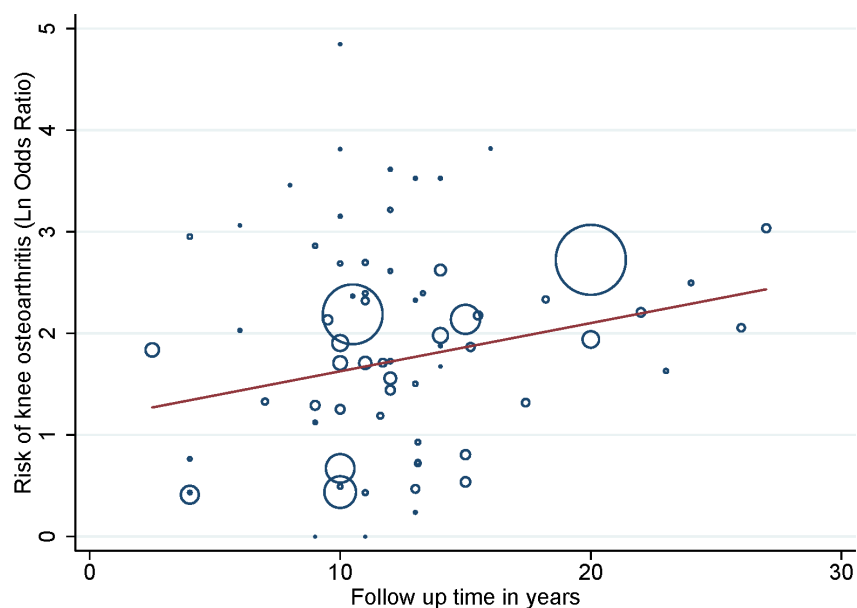
Figure 3 Metaregression analysis of impact of follow-up time on the OR of OA development. Weight of individual studies is indicated by the size of the circles, a study with high precision (typically more participants – larger circle) has greater weight. OA, osteoarthritis.

direct comparison is restricted by difference in eligibility criteria such as primary study aim, pooling of injury types, intervention investigated, comparator, follow-up time, outcomes and type of analyses. However, overall an increased risk of knee OA is reported following major knee injuries. Pooling all knee injury types, Silverwood *et al.* and Muthuri *et al.* found three and four times higher odds of developing knee OA after knee injury in comparison ith an uninjured knee but with large heterogeneity in estimates.[1][2] Claes *et al.*[19] included ACL reconstructed knees with or without meniscectomy and found an almost four times higher odds of OA development when the surgery included both the ACL and the meniscus in comparison with ACL reconstruction alone, but there was no comparison to an uninjured knee. Similar to the present study, the OA risk increased with time to follow-up. We only identified one recent systematic review reporting on long-term prevalence of radiographic OA (>10 years) after arthroscopic partial meniscectomy; however, no estimate for comparison was available as no meta-analysis was performed.[20]

Limitations

An important limitation is that some of the included studies did not specifically report patient knee OA status at time of injury/

surgery. We decided to include these studies in this systematic review and only exclude studies specifically reporting presence of OA at time of injury/surgery. Thus, some studies may have included patients with pre-existing OA at time of inclusion. To take this into account, we performed a sensitivity analysis including only studies specifically reporting no OA at time of injury/surgery and studies with patient mean age lower than 35 years (these patients would not be expected to have pre-existing OA). The estimates from this sensitivity analysis only slightly reduced the risk in the meniscal and combined group.

Few studies were restricted to isolated ACL or meniscal injury. We allowed up to 20% overlap between injury types but conducted a sensitivity analysis allowing only up to 10% overlap between injury types, which yielded similar estimates of OA risk. Another limitation is that comparison between surgery and non-surgical treatment strategies was not possible, since treatment strategy was unknown for 73% and 20%, respectively, of the meniscal and combined groups. For the ACL group, 98% had had ACL reconstruction surgery, and the results are generalisable to those having had surgical reconstruction but not those treated without surgery. The variation in participant characteristics, study size, type of study (retrospective vs prospective and case–control vs randomised
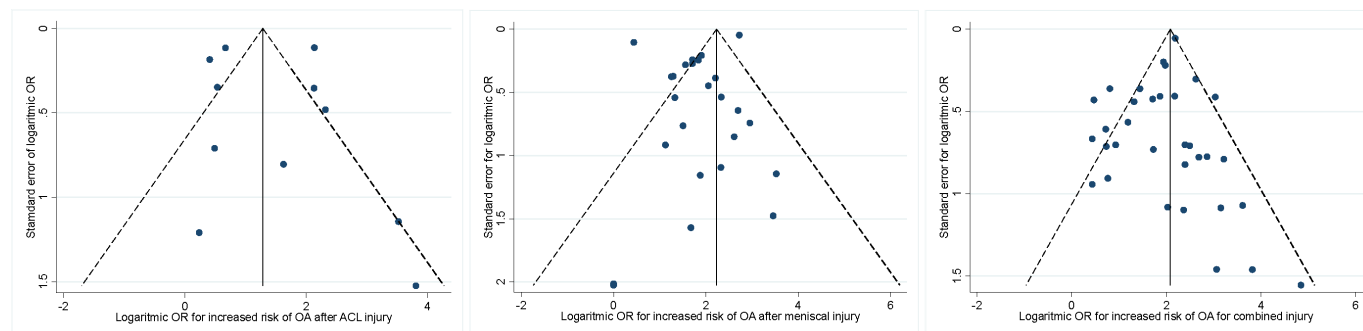

Figure 4 Funnel plots for OA development of included studies investigating risk of small study bias stratified by injury type. OA, osteoarthritis.

controlled trial), type of intervention and outcomes contribute to the high inconsistencies seen in the meta-analyses. However, different sensitivity analyses showed consistent results, indicating a high risk of knee OA development following the three types of injury.

Implications for research

Within the last year, several large high-quality registry studies have been published investigating the risk of OA development following meniscal and ACL injuries but using different definitions of OA. To further improve the quality in this area, future research should focus on large prospective cohorts with high follow-up rates reporting both patient-reported outcomes, imaging and the combination thereof to allow for comparison across studies using different OA definitions. Increased implementation of primary and secondary prevention programmes is urgently needed to reduce the number of knee injuries and the future increasing burden of OA.

CONCLUSIONS

This meta-analysis provides estimates for the risk of knee OA development following three knee injury types compared with a non-injured knee. An isolated ACL injured knee is associated with a four times higher odds of subsequent knee OA development compared with a non-injured knee. When sustaining an isolated meniscal injury or an injury affecting both the ACL and meniscus, the odds increase to sixfold compared with a non-injured knee, indicating the injured meniscus plays an important role in OA development. However, due to great between-study variation in design and outcomes collected and the lack of prospective studies with high-follow up rates, future high-quality studies may change the estimates.

What is already known

▶ Major knee injury such as ACL or meniscus injury are important risk factors for developing osteoarthritis (OA), but their relative importance is unknown.

What are the new findings

▶ Compared with an uninjured knee, patients with a meniscal injury, isolated or combined with an ACL injury have a higher relative risk for development of knee OA than patients with an isolated ACL injury.

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