Does sex affect second ACL injury risk? A systematic review with meta-analysis

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ABSTRACT

Objective To determine sex-based differences in risk of a second ACL injury (overall and by laterality) following primary ACL reconstruction in athletes who are attempting to return to sport.

Design Systematic review with meta-analysis.

Data sources Systematic search of five databases conducted in August 2019.

Eligibility criteria for selecting studies Studies reporting sex-based differences in the incidence of second ACL injury in athletes attempting to return-to-sports and who were followed for at least 1 year following primary ACL reconstruction.

Results Nineteen studies were included in this review, with seven studies excluded from the primary meta-analysis due to high risk of bias. The remaining 12 studies (n=1431 females, n=1513 males) underwent meta-analysis, with all 19 studies included in a sensitivity analysis. Total second ACL injury risk was 21.9% (females: 22.8%, males: 20.3%). Females were found to have 10.7% risk of an ipsilateral ACL injury and 11.8% risk of a contralateral ACL injury. Males were found to have 12.0% risk of an ipsilateral ACL injury and 8.7% risk of a contralateral ACL injury. No statistically significant differences were observed for total second ACL injury risk (risk difference=−0.6%, 95% CI −4.9 to 3.7, p=0.783, I^2=41%) or contralateral ACL injury risk (risk difference=1.9%, 95% CI −0.5% to 4.4%, p=0.113, I^2=15%) between sexes. Females were found to have a 3.4% absolute risk reduction in subsequent ipsilateral ACL injury risk compared with males (risk difference=−3.4%, 95% CI −6.7% to −0.02%, p=0.037, I^2=35%).

Conclusion Both sexes have >20% increased risk of experiencing a second ACL injury. Any difference in the absolute risk of either a subsequent ipsilateral or contralateral ACL injury between sexes appears to be small.

Registration PROSPERO (CRD42020148369)

INTRODUCTION

Female athletes are at two to four times greater risk of primary ACL injury compared with males, even when controlling for sport and competition level.[1–5] This difference has been attributed to anatomy, hormonal effects, neuromuscular control, biomechanics and sport participation.[6–19] Understanding the underlying risk factors and differences between sex has led to successful development of primary prevention programmes that have shown the ability to reduce the risk of sustaining an ACL injury by half in all athletes, with a decrease of non-contact ACL injuries in females by two-thirds.[20] These programmes are pivotal to the long-term health of athletes in reducing the risk of the initial ACL injury and in mitigating the risk of future complications associated with the injury, such as obesity, physical inactivity and osteoarthritis.[21–23] Unfortunately, not all athletes will be protected from a primary ACL injury, often requiring ACL reconstruction as part of the treatment plan. Following surgical reconstruction and rehabilitation, athletes expect to return to sport at their prior level.[24] Although returning to sport enhances the quality of life in athletes,[25] it does expose them to the possibility of a second ACL injury,[26 27] with 21%–23% of athletes experiencing either a re-tear of the ipsilateral graft or a new ACL injury to the contralateral knee.[28–30]

Age has been reported to be a risk factor for second ACL injury,[28 31–34] with athletes younger than 25 years old experiencing a combined second ACL injury risk of 23%.[28] Risk factors for second ACL injury also include allograft usage and lower self-reported confidence or psychological readiness.[33 35 36] However, the relationship between sex and second ACL injury risk is less clear. One study reports that female athletes have a greater second ACL injury risk in both knees compared with males.[29] Another study suggests that differences in risk of a second ACL injury are significantly higher in females when comparing contralateral ACL injuries (female=23.7%; male=10.5%), but no differences in ipsilateral ACL re-tear risk (female=8.5%; male=10.5%).[30] Other studies have found no sex differences.[37 38]

Understanding risk factors regarding second ACL injury is vital to the health and well-being of athletes. When compared with primary ACL injury and reconstruction, second ACL injury and reconstruction are associated with an increased likelihood of meniscal damage, reduced thigh muscle explosiveness and strength, increased pain, higher risk of post-traumatic knee osteoarthritis and future physical inactivity.[39–41] Similar to primary ACL injury, reducing the risk of second ACL injuries requires understanding if sex is a risk factor. The lack of consensus on which sex is most at risk for a second ACL injury may inhibit the rigorous development of effective second ACL injury screening and prevention programmes.

The purpose of this systematic review was to (1) determine the second ACL injury risk for patients included in studies followed for at least 12 months following their primary ACL reconstruction, (2) investigate the sex-based differences in risk of a second ACL injury following primary ACL reconstruction in active individuals attempting to return-to-sport, (3) determine the risk between sex and localisation of the second ACL injury (ipsilateral graft tear vs native contralateral ACL injury), and (4) determine if cohort age, percentage of cohort who return-to-sport, and pre-injury activity levels are moderators of the differences observed between male and female second ACL injury risk. We hypothesise that female athletes will demonstrate a higher second ACL injury risk compared with males, that female athletes will have a higher risk of contralateral ACL injuries compared with males and that younger age (<18 years) will modify sex-based differences in second ACL injury risk.

METHODS

Protocol, registration and critical appraisal

This systematic review and meta-analysis followed the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines.[42 43] The web-based platform for systematic review production, Covidence (Veritas Health Innovation), was used to manage all stages of the review process. AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews, version 2) was used to critically appraise this review.[44]

Literature search

A medical research librarian (JW) conducted a computerised literature search using a combination of keywords and database-specific controlled terminology related to 'ACL injuries', 'ACL surgeries' and 're-injury' in the following databases: MEDLINE via PubMed, Embase (Elsevier), CINAHL (EBSCO), SPORTDiscus (EBSCO) and Scopus (Elsevier). The search was conducted on 22 August 2019 and was not limited by date. Editorials and comments were removed as were animal-only studies. Results from all databases (n=3932) were uploaded to Covidence for screening. Following completion of full-text screening, a manual search of citation lists from included studies was performed to identify relevant citations that were missed, and a query of prominent journals related to sports medicine and orthopaedics was performed to capture citations published following the completion of the systematic search. A detailed search strategy can be found in online supplemental appendix 1.

Inclusion and exclusion criteria

Articles were included in this systematic review if they met the following criteria: (1) study cohort's average age was between 10 and 50 years; (2) undergoing any graft type ACL reconstruction; (3) attempting to return to sport, with a pre-injury or post-injury Tegner activity level of ≥7; (4) study reported second ACL injury incidence (ipsilateral graft rupture, native contralateral ACL injury or both); (5) ACL injuries were stratified by sex (or data were made available by authors); (6) study follow-up was at least 1 year following ACL reconstruction. Due to many studies not reporting activity levels using the Tegner scale, we used available information to determine equivalent activity levels appropriate for our cut-off including Marx activity score ≥8, International Knee Documentation Committee (IKDC) Level 1 or 2 sport determination, or descriptive information indicating Tegner ≥7. In addition, to ensure the majority of study participants were attempting to return-to-sport, we established that 55% of the entire sample must return-to-sport for the study to be included. This threshold was chosen based on previous work demonstrating 55% of athletes return to a competitive sport.[26]

Articles were excluded if (1) study participants had a prior knee surgery to either knee or bilateral ACL reconstruction; (2) underwent non-surgical management for their ACL injury; (3) underwent a revision ACL reconstruction at the start of the study; (4) had a grade 3 PCL, MCL or LCL injury; (5) not written in English; and (6) studies were systematic reviews, narrative reviews, meta-analysis, editorials, letters to the editor or clinical commentaries. When two or more different studies used the same named cohort of participants, the study with the larger overall sample size was included in this review.

Study selection

Two reviewers (ADP, JML) independently screened all relevant titles and abstracts retrieved from the database search against the selection criteria. Full-text manuscripts of remaining eligible studies were evaluated with the same selection criteria. Any discrepancies between the two reviewers were resolved by a third reviewer (GSB). If further data clarification was necessary to establish study eligibility, contact with the corresponding and/or senior listed author(s) was attempted via email with a 2-week follow-up email if no initial response.

Assessment of risk of bias and strength of the evidence

Two reviewers (ADP, JML) independently assessed risk of bias for each study. Any discrepancies were solved through discussion and consensus. A post hoc change was made to the study protocol to follow current systematic review best practice guidelines for assessing risk of bias using domain-based, study design–specific tools versus study methodological quality.[45]

We assessed risk of bias using three domain-based tools including the Cochrane Risk of Bias 2 tool for randomised controlled trials, the Risk of Bias Assessment tool for Non-Randomized Studies for observational studies including cohort, case–control and before–after studies,[46] and the Cochrane Risk Of Bias In Non-randomized Studies – of Interventions tool for studies assessing the effect of interventions between groups.[47] We assessed each tool for the primary outcome of second ACL injury only as this was most pertinent to this review. For the Risk of Bias 2 tool, risk of bias judgement per study is noted as 'low risk' when all domains are judged to be at 'low' risk of bias, 'some concerns' of bias when one or more domains are judged to be at 'some concerns', or 'high risk' of bias when at least one domain is judged to be at 'high' risk of bias or when multiple domains have 'some concerns' of bias. For the Risk of Bias Assessment tool for Non-Randomized Studies tool, risk of bias judgement per study is noted as 'high' risk if ≥2 domains were rated as 'high' risk, ≥2 'unclear' risk, or 1 'unclear' and 1 'high' risk. For the Risk Of Bias In Non-randomized Studies – of Interventions tool, risk of bias judgement per study is noted as 'low risk' when all domains are judged as 'low' risk of bias, 'moderate' risk when one domain is judged as 'moderate' risk of bias, 'serious' risk when one domain is judged as 'serious' risk of bias, or 'critical' risk of bias when one domain is judged as 'critical' risk of bias.

Strength of the evidence included in this review was judged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale, which determines the overall certainty of the evidence per outcome that is statistically pooled and compared between groups.[48 49] The GRADE scale assesses five factors concerning risk of bias (see tool descriptions mentioned previously), imprecision (width of CIs) and publication bias (determined by funnel plot). These factors lead to a reported score of high, moderate, low or very low quality of the evidence. The GRADE scale was applied to assess the evidence regarding sex-based difference in total, ipsilateral and contralateral second ACL injury risk. The lead author (ADP)

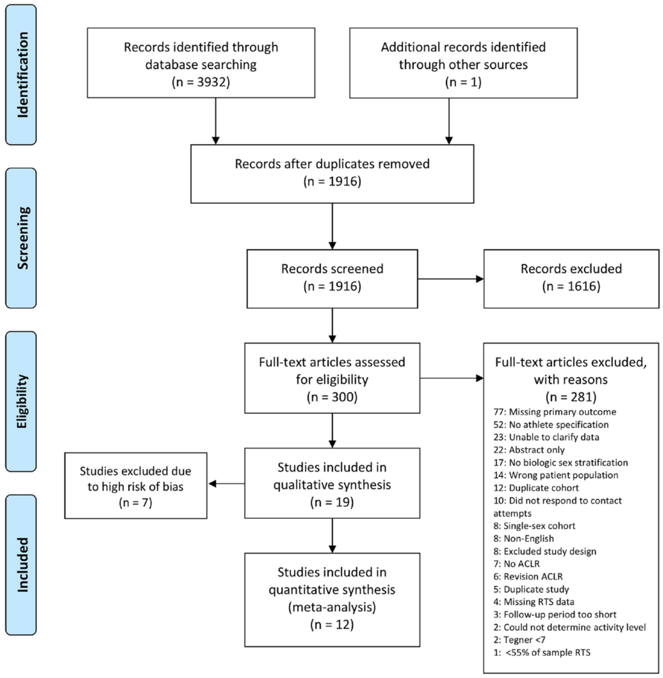

Figure 1 PRISMA flow diagram.

aggregated the necessary information for each GRADE domain and was reviewed by a second reviewer (JML) for accuracy and completeness. Any disagreements were settled through discussion and consensus.

Data extraction and primary outcome variables

Two reviewers (ADP, JML) independently extracted data from included studies using identical templates. Any discrepancies were solved through discussion and consensus. If further clarification on the reported data within included studies was necessary, contact with the listed corresponding authors was attempted. Study descriptive information including title, primary author, date of publication was recorded, as well as demographic information including sample size, participant age, participant sex, ACL reconstruction characteristics, pre-injury activity level, post-injury activity level, return-to-sport percentage and the diagnostic criteria used to determine a second ACL injury. To capture all possible second ACL injuries, diagnostic criteria used to determine a second ACL injury were not standardised in this review and determined via the methods used by each included study.

The primary outcome variables extracted were overall study incidence of a second ACL injury (graft rupture and native contralateral ACL injury), the incidence of a second ACL injury based on sex (male or female), incidence of second ACL injury based on which knee it occurred (contralateral or ipsilateral), and the incidence of a second ACL injury based on the interaction of sex and laterality of injury (contralateral or ipsilateral).

Statistical analyses

Per current meta-analyses best practice recommendations,[45 50] all studies assessed to be at high risk of bias were excluded from the primary meta-analyses to reduce compounding of bias,[45 50] but were included in our sensitivity analysis (described later).[45] Aggregated random effects incidence proportions with 95% CI were calculated for overall, ipsilateral and contralateral second ACL injuries for the total cohort and per sex. This calculation provides the cumulative incidence (expressed as a percentage) which is equivalent to the risk of experiencing a second ACL injury.[51] Heterogeneity bias was assessed through Begg-Mazumdar and Egger's calculations, with I^2 value reported (high heterogeneity: $I^2 \geq 50\%$, and p value <0.10).

To determine the relative and absolute risk of sustaining a second ACL injury between sexes, an inverse-weighted, DerSimonian and Laird random-effects risk ratio (RR) and risk difference meta-analysis were performed for overall, ipsilateral and contralateral second ACL injuries per sex at 95% CI. Both relative (RR) and absolute (risk difference) were reported to give a clear picture of the clinical relevance of the pooled estimates.[52] Pooled RR and risk difference statistics are reported with males as the reference population; thus, the calculations were RR=(female cumulative incidence/male cumulative incidence), risk difference=(female cumulative incidence–male cumulative incidence). Heterogeneity bias was assessed through Cochrane's Q and I^2, with high heterogeneity determined with an $I^2 \geq 50\%$ and a p value <0.10. Publication bias was assessed through funnel plots. Meta-regressions were then performed to determine the influence of age, pre-injury activity level and study return-to-sport percentage on overall, ipsilateral and contralateral second ACL injuries per sex. The variance explained through these confounders was assessed through R^2.

Sensitivity analyses were then performed to further understand the robustness of our results and the directions of biases. To determine if return-to-sport percentage introduced bias into our study, sensitivity analyses included studies that reported ≥85% return-to-sport. Further, to understand the direction and effect of bias in this literature, we performed a sensitivity analysis that included all studies, regardless of bias assessment (high risk of bias studies (n=7) included). Incidence proportion analyses were performed in StatsDirect (StatsDirect, Merceyside, UK) and all RR and risk difference meta-analyses and meta-regressions were performed in R V.5.042 (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) using the *meta* package.

RESULTS

Search results

The initial search resulted in 3932 potentially eligible studies, with one additional article discovered during the manual search that met our inclusion criteria (figure 1). After removal of duplicates, 1916 studies remained. Screening of title and abstracts yielded 300 studies for full-text analysis. Overall, 281 full-text articles were excluded for a variety of reasons as indicated in

Table 1A Risk of bias assessment: randomised controlled trials (Cochrane Risk of Bias 2 Tool)

Study	Sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessors	Incomplete data	Selective outcome reporting	Other sources	Overall
Fleming *et al*[55]	High	Low	Low	Some concerns	Some concerns	Low	Low	High
Mohtadi *et al*[68]	Low	Low	Low	Low	Low	Low	Low	Low

Table 1B Risk of bias assessment: non-randomised observational studies (Risk of Bias Assessment tool for Non-randomized Studies)

Study	Confounding	Participant selection	Blinding of outcome assessors	Missing data	Exposure measurement	Selective outcome reporting	Overall
Bak *et al*[60]	Low	Low	Low	Low	Low	Low	Low
Beischer *et al*[61]	Low	Low	Low	High	Low	Low	Low
Bourke *et al*[62]	Low	Low	Low	Low	Low	Low	Low
Cordasco *et al*[53]	Low	High	Unclear	Low	Low	Low	High
Dekker *et al*[63]	Low	Low	Low	High	Low	Low	Low
Demange *et al*[54]	Low	High	Unclear	Low	High	Low	High
Geffroy *et al*[56]	Low	Low	Unclear	Low	High	Low	High
Graziano *et al*[57]	Low	High	Low	Low	Unclear	Low	High
Gupta *et al*[58]	Low	Low	Unclear	Low	Low	High	High
Heath *et al*[65]	Low	Low	Low	Low	Low	Low	Low
Kamath *et al*[67]	Low	Low	Low	Low	Low	Low	Low
Laboute *et al*[59]	High	Low	Unclear	High	High	High	High
Paterno *et al*[30]	Low	Low	Low	Low	High	Low	Low
Shelbourne *et al*[38]	Low	Low	Low	Low	Low	Low	Low
Webster *et al*[69]	Low	Low	Low	Low	Low	Low	Low

figure 1. We contacted the corresponding authors of 49 studies via email and requested clarifying data (online supplemental appendix 2). Of these, 6 studies (12.2%) provided clarifying data that was used in this review (online supplemental appendix 2). The remaining 43 studies either provided clarifying data that excluded the study, did not provide clarifying data or the corresponding author did not respond (online supplemental appendix 2). Thus, 19 studies met the inclusion criteria for our qualitative synthesis (figure 1).

Risk of bias, GRADE and AMSTAR-2

Seven studies (36.8%) were found to be at high risk of bias.[53–59] The remaining 12 were determined to be at low (n=11, 57.9%) or moderate (n=1, 5.3%) risk of bias[30 38 60–69] (tables 1A–C).

The GRADE scale determined that the quality of evidence for the risk of sustaining a second ACL injury and ipsilateral ACL injury is 'very low quality', due to imprecision of the pooled RR and risk difference estimates and high levels of heterogeneity (online supplemental appendix 3). The quality of evidence for the risk of a contralateral ACL injury is 'low quality' because non-randomised studies were included (online supplemental appendix 3). This review met 15 of 16 reporting and quality items (94%) according to the AMSTAR-2 criteria (online supplemental appendix 4).

Study characteristics and demographics

Study demographic information, sample size, ACL reconstruction characteristics, activity levels, return-to-sport percentage and definition of a second ACL injury from all 19 included studies are available in table 2. From the 19 included studies, there were 4027 total participants (females=1715 (42.6%), males=2312 (57.4%))[30 38 53–69] (online supplemental appendix 5). Seven studies were excluded from our primary analysis due to high risk of bias.[53–59] Thus, 12 studies with 2944 participants (females=1431 (48.6%), males=1513 (51.4%)) were included in the primary meta-analyses.[30 38 60–69]

Second ACL injury risk

Primary meta-analysis estimated the pooled risk of a second ACL injury for the total cohort and by sex, which are presented in figure 2A–C. The pooled risk of a second ACL injury (either graft tear or contralateral ACL injury) for both males and females was 21.9% (95% CI 16.7% to 27.6%, I^2=92%).[30 38 60–69] Females were found to be at 22.8% (95% CI 16.6% to 29.6%, I^2=88%) risk for a second ACL injury. Males were found to be at 20.3% (95% CI 13.6% to 27.8%, I^2=91%) risk for a second ACL injury.

Pooled risk of an ipsilateral ACL injury (for the total cohort and by sex) and contralateral ACL injury (for the total cohort and by sex) are presented in figure 3A–C (ipsilateral) and figure 4A–C (contralateral).

Of all male second ACL injuries, ipsilateral injuries accounted for 62.5% (95% CI 52.4% to 72.1%, I^2=64%) of those injuries, with contralateral injuries accounting for 37.5% (95% CI 27.9% to 47.6%, I^2=64%) of all male injuries (figure 5A,B). Of all female second ACL injuries, contralateral injuries account for 53.7% (95% CI 41.9% to 65.4%, I^2=74%) of those injuries, while ipsilateral injuries accounted for 46.3% (95% CI 34.6% to 58.1%, I^2=74%) of all female injuries (figure 6A,B).

Relative and absolute differences in second ACL risk by sex

Primary meta-analysis revealed there were no statistically significant differences between sexes in the relative risk of second ACL injury (RR=0.95, 95% CI 0.75 to 1.19, p=0.629, I^2=50%) (figure 7A) or in the absolute risk of second ACL injury (risk difference=−0.6%, 95% CI −4.9 to 3.7, p=0.783, I^2=41%). There was no statistically significant difference between sexes in ipsilateral ACL injury relative risk (RR=0.74, 95% CI 0.52 to 1.05, p=0.094, I^2=52%) (figure 7B). However, females were

Table 1C Risk of bias assessment: non-randomised studies (Cochrane Risk Of Bias In Non-randomized Studies – of Interventions Tool)

Study	Confounding	Participant selection	Classification of interventions	Deviation from intended intervention	Missing data	Outcome measurement	Selective outcome reporting	Overall
Everhart *et al*[64]	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Heijne *et al*[66]	Low	Low	Low	Low	Low	Low	Low	Low

Patel AD, *et al*. *Br J Sports Med* 2021;**55**:873–882. doi:10.1136/bjsports-2020-103408

Table 2 Study characteristics

Source	Year published	Study design	Sample size (n)	Mean age at ACLR (years)	Age variance (years, SD or range)*	Follow-up time (months, mean±SD or median* (range))	Activity level (Tegner or Marx)	Return-to-sport percentage (%)	Second ACL injuries (total)	Second ACL injuries (females)	Second ACL injuries (males)
Bak *et al*†‡[60]	2001	CS	132	23.0	16–39*	47* (24–92)	9	67	13	3	1
Beischer *et al*†[61]	2020	PC	159	21.5	4.4	15.5* (4–46.5)	8.5	64	18	11	7
Bourke *et al*†[62]	2012	CS	673	29.1	9.2	16.8* (15–18.9)	7§	73	156	48	108
Cordasco *et al*[53]	2017	CS	23	12.2	9.9–14.5*	32.1* (24–45)	13.4¶	95.7	1	0	1
Dekker *et al*†[63]	2017	RC	85	13.9	2.1	48.3±15.3	13.7¶	91	27	14	13
Demange *et al*[54]	2014	CS	12	10.7	8.3–12.4*	220* (180–264)	7§	83.3	3	1	2
Everhart *et al*†[64]	2019	RC	360	24.1	8.4	>24	7§	99	27	10	17
Fleming *et al*[55]	2013	RCT	85	23.5	2.5	36	7.6	100	7	5	2
Geffroy *et al***[56]	2018	PC	278	13.5	2.1	>24	7	77	29	10	13
Graziano *et al*[57]	2017	CS	42	12.0	10–15*	>24	23.2¶	95.2	6	2	4
Gupta *et al*[58]	2019	RC	340	26.0	5.5	>24	8.5	100	25	4	21
Heath *et al*†[65]	2019	CS	247	14.6	8–17.9*	54* (24–147)	7§	59.1	81	25	56
Heijne *et al*††[66]	2015	PC	68	29.5	8.1	61.5* (60–84)	7	100	11	9	2
Kamath *et al*†[67]	2014	CS	89	>18	N/A	48	8§	92.9	20	11	9
Laboute *et al*[59]	2010	RC	298	26.0	7.7	42* (36–48)	8§	86	26	5	21
Mohtadi *et al*†[68]	2016	RCT	322	28.5	9.8	>24	7.7	83	96	43	53
Paterno *et al*†[30]	2014	PC	78	17.1	3.1	>24	7§	100	23	19	4
Shelbourne *et al*†[38]	2009	PC	402	15.6	1.0	117.6±62.4	9	100	104	81	23
Webster *et al*†[69]	2019	RC	329	17.2	2.0	60 (36–108)	7§	100	95	36	59

*Median values.
†Included in primary meta-analysis.
‡Bak *et al* reported 9 contralateral ACL injuries that were not categorised by sex.
§Interpreted Tegner based on qualitative data.
¶Marx activity level.
**Geffroy *et al* reported 6 contralateral injuries that were not categorised by sex.
††Heijne *et al* reported two participants (1 male, 1 female) that experienced both an ipsilateral and contralateral ACL injury but did not report which occurred first, both injuries are included.
ACLR, ACL reconstruction; CS, case series; PC, prospective cohort; RC, retrospective cohort; RCT, randomised control trial.

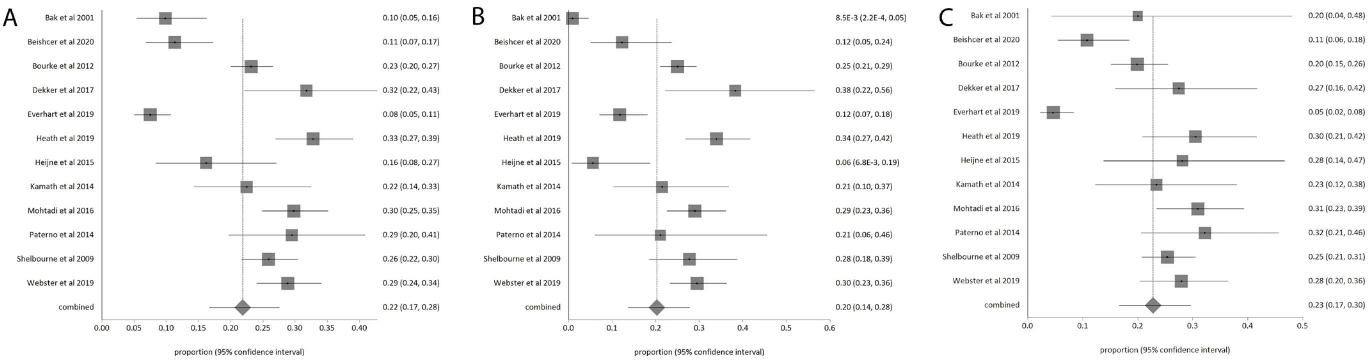

Figure 2 (A) Total cohort second ACL injury risk. Forest plot for the incidence proportion (risk) and 95% CI of experiencing a second ACL injury (ipsilateral and contralateral) in both male and female athletes combined. (B) Male second ACL injury risk forest plot for the incidence proportion (risk) and 95% CI of experiencing a second ACL injury (ipsilateral and contralateral) in male athletes. (C) Female second ACL injury risk forest plot for the incidence proportion (risk) and 95% CI of experiencing a second ACL injury (ipsilateral and contralateral) in female athletes.

found to have 3.4% reduced absolute risk of an ipsilateral ACL injury compared with males (risk difference=−3.4%, 95% CI −6.7% to −0.02%, p=0.037, I^2=35%). Females were found to have 1.27 times higher relative risk (95% CI 1.00 to 1.61, p=0.049, I^2=0%) of experiencing a contralateral ACL injury compared with males (figure 7C). Females were found to have a non-statistically significant, 1.9% increase in the absolute risk of experiencing a contralateral ACL injury compared with males (95% CI −0.5% to 4.4%, p=0.113, I^2=15%).

Funnel plot assessment did not indicate concern for publication bias (online supplemental appendix 6). Meta-regression performed using participant age, pre-injury activity level and study return-to-sport percentage as moderators of second ACL injury, ipsilateral ACL injury and contralateral ACL injury risk revealed these factors did not impact the pooled risk values (R^2=0.0% for all three analyses).

Sensitivity analysis

Sensitivity analysis performed including studies with a sample return-to-sport percentage ≥85% (n=6) showed no statistically significant differences in the relative risk of sustaining a second ACL injury between sexes (RR=0.86, 95% CI 0.66 to 1.12, p=0.273) or a native contralateral ACL injury (RR=1.26, 95% CI 0.83 to 1.90, p=0.281). However, females were found to be at a 41% reduced relative risk (RR=0.59, 95% CI 0.42 to 0.85, p=0.004) of an ipsilateral injury compared with males in studies with high return-to-sport percentage (≥85%).

High risk of bias studies were added back into the primary meta-analysis (n=7)[53–59] to determine the effect and direction of observed bias in the available literature. This sensitivity analysis found no statistically significant difference between sexes in the overall relative risk of sustaining a second ACL injury (RR=0.98, 95% CI 0.81 to 1.18, p=0.799, I^2=32%). However, females were found to be at 29% reduced relative risk of an ipsilateral ACL injury (RR=0.71, 95% CI 0.58 to 0.87, p=0.0008, I^2=0%) compared with males, and females were found to have 1.35 times greater relative risk of experiencing a native contralateral ACL injury compared with males (RR=1.35, 95% CI 1.07 to 1.70, p=0.011, I^2=0%).

DISCUSSION

Currently, there is ambiguity regarding the relationship between sex and second ACL injury risk following primary ACL reconstruction. The results of this systematic review and primary meta-analysis determined that there is a negligible, non-statistically significant difference in the relative and absolute risk of experiencing a second ACL injury (both ipsilateral and contralateral combined) between sexes. Females may experience a small, 3.4% reduced absolute risk of a subsequent ipsilateral ACL injury compared with males. This review also found that females may

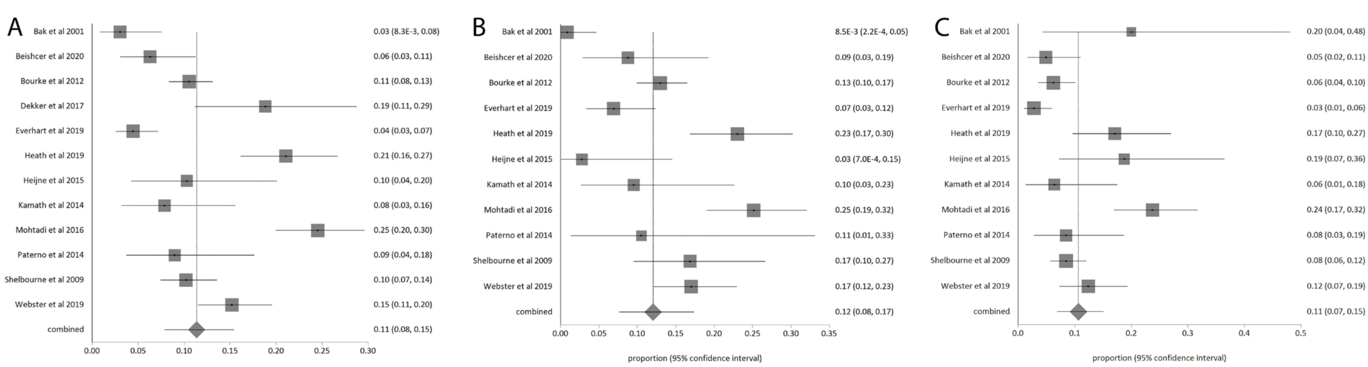

Figure 3 (A) Total cohort ipsilateral second ACL injury risk. Forest plot for the incidence proportion (risk) and 95% CI of experiencing an ipsilateral ACL injury in both male and female athletes combined. (B) Male ipsilateral second ACL injury risk. Forest plot for the incidence proportion (risk) and 95% CI of experiencing an ipsilateral ACL injury in male athletes. Dekker *et al*[63] was excluded from this analysis because data were not provided to quantify the number of male ipsilateral injuries. (C) Female ipsilateral second ACL injury risk. Forest plot for the incidence proportion (risk) and 95% CI of experiencing an ipsilateral ACL injury in female athletes. Dekker *et al*[63] was excluded from this analysis because data were not provided to quantify the number of female ipsilateral injuries.

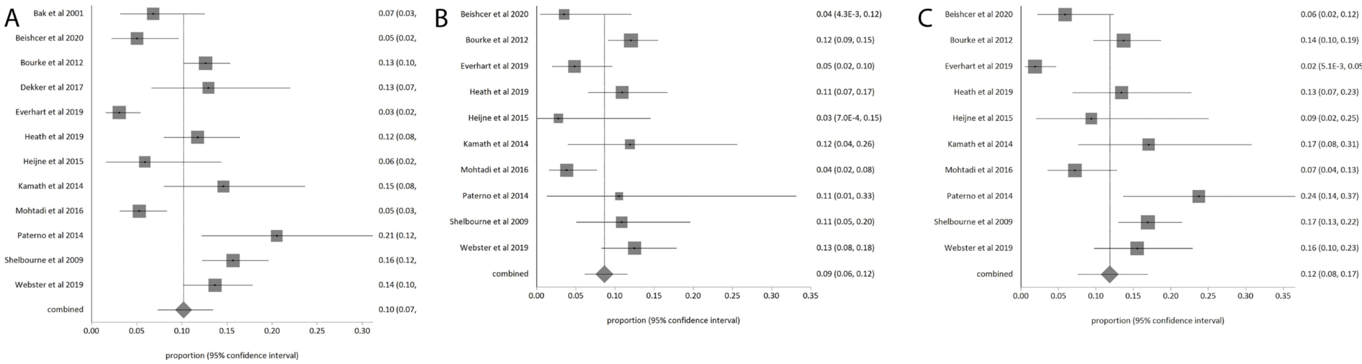

Figure 4 (A) Total cohort contralateral second ACL injury risk. Forest plot for the incidence proportion (risk) and 95% CI of experiencing an contralateral ACL injury in both male and female athletes combined. (B) Male contralateral second ACL injury risk. Forest plot for the incidence proportion (risk) and 95% CI of experiencing an ipsilateral ACL injury in male athletes. Bak *et al*[60] and Dekker *et al*[63] were excluded from this analysis because data were not provided to quantify the number of male contralateral injuries. (C) Female contralateral second ACL injury risk. Forest plot for the incidence proportion (risk) and 95% CI of experiencing an ipsilateral ACL injury in female athletes. Bak *et al*[60] and Dekker *et al*[63] were excluded from this analysis because data were not provided to quantify the number of female contralateral injuries.

experience 1.27 times higher relative risk of a subsequent contralateral ACL injury compared with males (95% CI 1.00 to 1.61, p=0.049). However, females were found to have only a small, non-statistically significant, absolute increase in subsequent contralateral ACL injury risk compared with males (risk difference=1.9%, 95% CI −0.5% to 4.4%, p=0.113). This suggests that any difference in subsequent contralateral ACL injury risk between sexes is minimal at best.

Risk of a second ACL injury

Males and females were found to be equally likely to experience a second ACL injury. Although a previous meta-analysis reported that females have higher odds of experiencing a second ACL injury than males,[70] this discrepancy is likely due to the absence of considering return-to-sport percentage in their inclusion criteria. This suggests that their findings might better reflect general populace ACL injury trends. Having considered return-to-sport percentage, the present review reflects active individuals attempting to return to their prior level of activity and exposing themselves to higher levels of ACL re-injury risk.

Although females have been considered to be at increased risk of a contralateral ACL injury compared with an ipsilateral ACL injury,[30] we found that females experience similar risk of sustaining an ipsilateral (11%) and contralateral (12%) ACL injury (figures 3C and 4C). However, differences between ipsilateral and contralateral ACL injury trends may occur at different rates.[4] When factoring in time from return-to-sport to injury, females demonstrate a considerably increased rate of a contralateral ACL injury compared with an ipsilateral ACL injury.[30] Our review did not factor in the rate of second ACL injuries because our focus was on determining the risk of second ACL injuries between sexes.

The primary analysis found that females demonstrated a small, 3.5% reduced absolute risk of experiencing an ipsilateral ACL injury compared with males. However, due to the number of statistical tests performed, this could be the result of type 1 error. Further, additive and multiplicative risks are not completely equal in analysis,[71] with additive risk potentially providing improved multivariable risk assessment for multiple exposures, time to event hazards, and overall public health impact.[71 72]

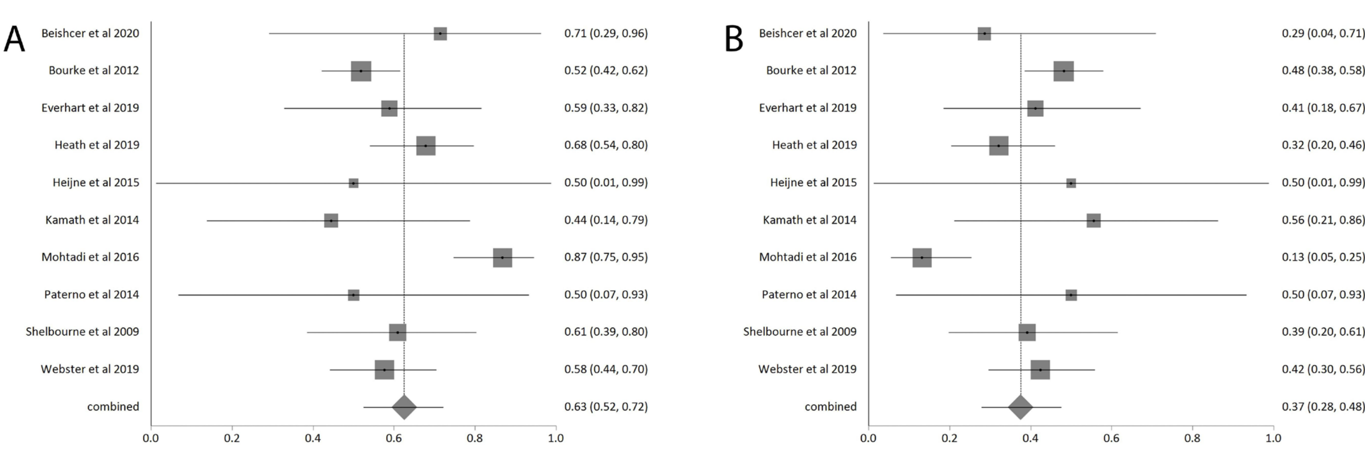

Figure 5 (A) Proportion of male second ACL injuries to the ipsilateral ACL. Forest plot for the proportion and 95% CI of ipsilateral ACL injuries experienced in male athletes. Bak *et al*[60] and Dekker *et al*[63] were excluded from this analysis because data were not provided to quantify the number of both ipsilateral and contralateral injuries in males. (B) Proportion of male second ACL injuries to the contralateral ACL. Forest plot for the proportion and 95% CI of contralateral ACL injuries experienced in male athletes. Bak *et al*[60] and Dekker *et al*[63] were excluded from this analysis because data were not provided to quantify the number of both ipsilateral and contralateral injuries in males.

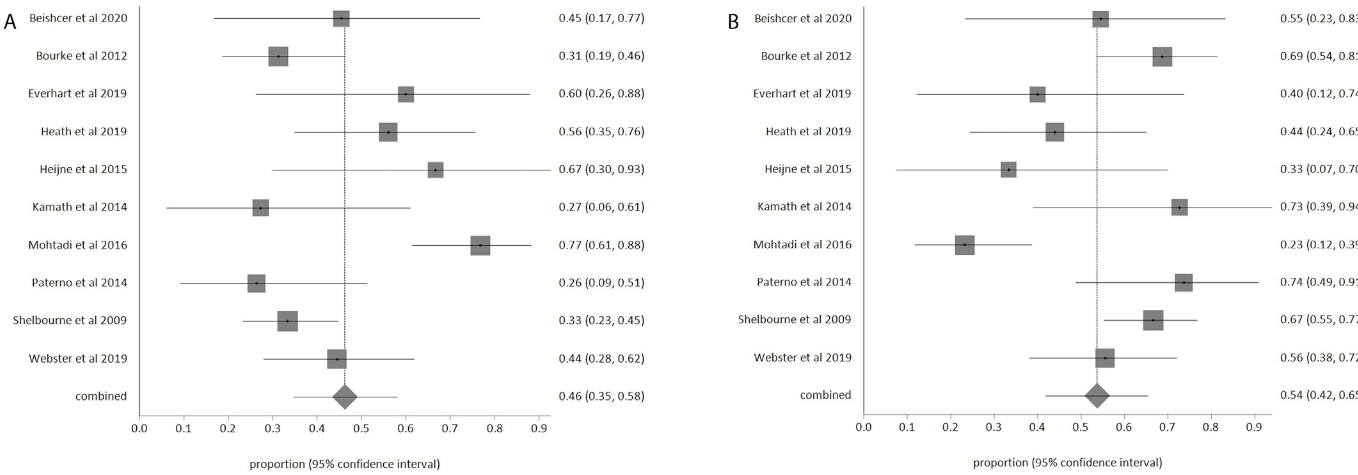

Figure 6 (A) Proportion of female second ACL injuries to the ipsilateral ACL. Forest plot for the proportion and 95% CI of ipsilateral ACL injuries experienced in female athletes. Bak *et al*[60] and Dekker *et al*[63] were excluded from this analysis because data were not provided to quantify the number of both ipsilateral and contralateral injuries in females. (B) Proportion of female second ACL injuries to the contralateral ACL. Forest plot for the proportion and 95% CI of contralateral ACL injuries experienced in female athletes. Bak *et al*[60] and Dekker *et al*[63] were excluded from this analysis because data were not provided to quantify the number of both ipsilateral and contralateral injuries in females.

While this review estimates there may be only negligible to small (and some not statistically significant) pooled sex-based differences in second ACL injury risk by injury laterality (ipsilateral vs contralateral), it is critical to note that both groups are still at >20% risk for either an ipsilateral or contralateral second ACL injury. Since both limbs remain at risk for a future ACL injury, this provides further evidence that suggests the contralateral limb may not be the most useful comparator when making rehabilitation and return to sport decisions.[36 73–76] There needs to be continued efforts towards optimising rehabilitation,[77] and standardising return-to-sport criteria and comparison metrics that limit reliance on the also at-risk contralateral limb.[73]

The primary analysis also found that males appear to experience a larger proportion of ipsilateral second ACL injuries (62.5%) compared with contralateral ACL injuries (37.5%). These findings may be explained by the already present differences in baseline primary ACL injury risk between sexes (one in 29 females sustains a primary ACL injury compared with one in 50 males).[4] One theoretical explanation for this second ACL injury trend is that both sexes may retain their baseline primary ACL injury risk following ACL reconstruction such that both limbs remain at elevated risk for an ACL injury in females, while males might have increased risk factors in the reconstructed (ie, ipsilateral) ACL, increasing injury risk compared with the uninjured (ie, contralateral) ACL. Because males are at much lower baseline risk of injury compared with females,[4] surgical reconstruction and subsequent reduction in strength and function (ie, knee joint loading, movement patterns, psychological aspects of recovery) of that limb may be the strongest factors affecting ipsilateral graft injuries in males.[78 79] This trend and its explanation require further research to understand the mechanism that underlies the higher proportion of male ipsilateral ACL injuries versus contralateral ACL injuries.

Age did not explain any variance within these findings. This may be due to the strict inclusion criteria used in the current study. The included studies demonstrated a homogenous age range and did not capture a substantial proportion of younger individuals (<18 years). Only 4 of the 12 studies in the primary meta-analysis had populations <18 years old, while 5 of the 7 studies excluded due to high risk of bias had populations <18 years old. Females have been shown in population-based studies to have a peak incidence of ACL injuries[80 81] and higher risk of a second ACL injury when they are <19 years old.[29 30 36] Males appear to experience peak incidence of primary ACL injury in their mid-20s.[80 81] A recent meta-analysis assessing second ACL injury differences between sexes following paediatric ACL reconstruction found that females experienced more contralateral injuries compared with males, but they did not calculate a meaningful measure of association that informs the magnitude and direction of the relationship.[82] Further methodological concerns include inappropriate statistical pooling and comparisons which indicate these results should be interpreted with caution. Recent evidence has challenged the notion of age as a risk factor for second ACL injury and concluded that functional readiness and returning to level 1 sport are the key factors associated with second ACL injury risk,[83] leading to continued ambiguity regarding the interaction between age and sex on second ACL injury risk.

Risk of bias

This review identified seven studies (36.8%) considered to be at high risk of bias and were removed from our primary analyses to not compound bias.(tables 1A–C) To assess the effect of high risk of bias studies on pooled second ACL injury estimates, a sensitivity analysis was performed which included the high risk of bias studies. These results suggest that including high risk of bias studies can exaggerate relative risk estimates away from the null; with the risk of females experiencing an ipsilateral ACL injury decreasing from RR=0.74 (95% CI 0.52 to 1.05) to RR=0.71 (95% CI 0.58 to 0.87). Similarly, female contralateral ACL injury risk increased from RR=1.27 (95% CI 1.00 to 1.60) to RR=1.34 (95% CI 1.07 to 1.70). The risk of bias concerns and noted high heterogeneity (I^2 >50%) seen in most analyses dictate that studies examining second ACL injury outcomes should ensure they adhere to established guidelines (eg, STROBE or CONSORT) in the design and execution of the final manuscript to ensure potential sources of bias are mitigated.[84–86] Of note, the Panther Symposium and Consensus Statements have been recently published and should provide an in-depth guide to

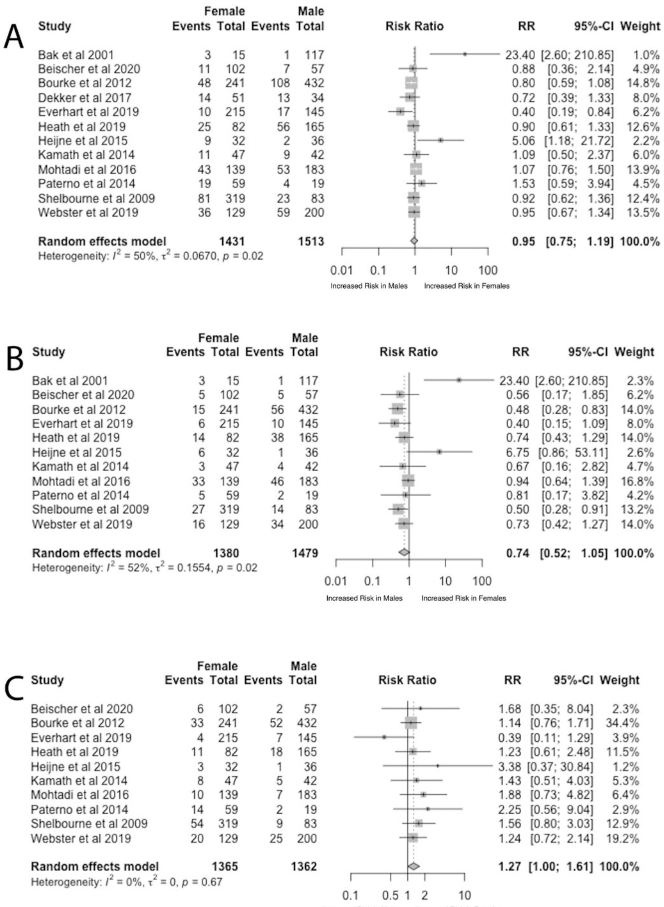

Figure 7 (A) Relative risk of a second ACL injury. Forest plot of the relative risk and 95% CI of experiencing a second ACL injury between sexes. Males are the reference population. Riski ratio (RR) >1: increased risk in females, RR <1: increased risk in males. (B) Relative risk of an ipsilateral ACL injury. Forest plot of the relative risk and 95% CI of experiencing an ipsilateral ACL injury between sexes. Males are the reference population. RR >1: increased risk in females, RR <1: increased risk in males. Dekker *et al*[63] was excluded from this analysis because data were not provided to quantify the number of female or male ipsilateral injuries. (C) Relative risk of a contralateral ACL injury. Forest plot of the relative risk and 95% CI of experiencing a contralateral ACL injury between sexes. Males are the reference population. RR >1: increased risk in females, RR <1: increased risk in males. Bak *et al*[60] and Dekker *et al*[63] were excluded from this analysis because data were not provided to quantify the number of female or male contralateral injuries.

help standardise the research on ACL reconstruction outcomes, including return-to-sport outcomes and second ACL injury definitions.[85]

Limitations

We removed 36 potentially eligible studies because data were unable to be clarified, thus the pooled estimates and conclusions from this study could have been different due to a selection bias. We acknowledge that all researchers/clinicians involved in those studies were experiencing unforeseen challenges due to the COVID-19 pandemic that could have decreased our response rate and their ability to facilitate our requests. We did not factor in return-to-sport testing or psychological readiness within this analysis. It is plausible there could have been a significant difference in the risk of a second ACL injury had participants received objective clearance based on commonly recommended assessments. We did not standardise the diagnostic criteria of a second ACL injury, which could explain the considerable heterogeneity seen in our per-sex risk estimates. However, we sought to capture all studies with potentially valuable data; and our approach factors in all possible diagnostic and treatment schemes one may experience following a second ACL injury (surgical revision, imaging, clinical examination without imaging, non-operative care and/or KT-1000 arthrometer testing). We only established a minimum follow-up period of 12 months following ACL reconstruction to ensure we captured the early phases of return-to-sport attempts and did not set a follow-up duration limit. We acknowledge there could potentially be studies with second ACL injury data but less than 12 months of follow-up that could have been missed in this review, leading to an underestimation of our estimates. Further, there may be a temporal factor (due to prolonged follow-up) that skewed our results due to continued (or reduced) exposure to risk, but previous literature refutes that association in primary ACL reconstruction.[4] We also recognise that mechanism of injury likely impacts the risk of injury and for some of the proposed mechanisms for sex-based differences. However, few studies reported this information, limiting our ability to factor this into our analysis.

What is already known

- Female athletes are at increased risk for sustaining a primary ACL injury compared with males when playing the same sport.

What are the new findings?

- Both sexes are at >20% risk of experiencing a second ACL injury.
- There is a negligible difference in the absolute risk of experiencing a second ACL injury between sexes (risk difference=−0.6%, 95% CI −4.9 to 3.7).
- Females may have a small reduction in the absolute risk of an ipsilateral second ACL injury compared with males (risk difference=−3.4%, 95% CI −6.7% to −0.02%).

CONCLUSION

Both sexes are at >20% increased risk of experiencing a second ACL injury. Overall, the magnitude of differences in the absolute risk of a subsequent ipsilateral or contralateral ACL injury between sexes appears small and potentially not clinically meaningful. Studies noting high return to sport percentages (>85%) demonstrate that males may be at increased risk of experiencing a subsequent ipsilateral ACL injury compared with females.

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Contributors AP was first author on this paper; he conducted the screening for articles, conducted the data gathering, wrote the paper and edited the paper. GSB conducted statistical analysis of the paper, helped to write the paper, edited the paper and provided expertise on the subject matter. JW conducted the search for articles for the paper. MP edited the paper and provided expertise on the subject matter. TS initiated the paper topic, edited the paper and provided expertise on the subject matter. JL was principal investigator on this paper; he conducted the screening for articles, conducted the data gathering, helped write the paper, edited

the paper and provided expertise on the subject matter. In addition, Leila Ledbetter, a contributor, provided guidance and assistance with generating the search and providing resources to optimise data management. All authors contributed to the writing, interpretation, critical revision and approval of the manuscript. AP, GSB, TS and JL conceived the research question. JW developed and executed the systematic literature search with input from JL, TS and GSB. AP, JL and GSB performed data extraction. GSB and JL performed statistical analysis and figure generation with input from TS and MP.

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APPENDIX

APPENDIX 1. Search Strategy
Date: 8/22/2019
Database (including vendor/platform): MEDLINE (via PubMed)

Set #		Results
1 ACL	"Anterior Cruciate Ligament"[Mesh] OR "Anterior Cruciate Ligament Injuries"[Mesh] OR "anterior cruciate"[tiab] OR ACL[tiab]	24,115
2 Surgery	"Anterior Cruciate Ligament Reconstruction"[Mesh] OR autograft[tiab] OR "auto-graft"[tiab] OR HTA[tiab] OR ACLR[tiab] OR surgery[tiab] OR surgeries[tiab] OR procedure[tiab] OR procedures[tiab] OR reconstruction[tiab] OR reconstructions[tiab] OR reconstructed[tiab]	2,204,124
3 Reinjury	"Recurrence"[Mesh] OR reinjury[tiab] OR "re-injury"[tiab] OR reinjured[tiab] OR "re-injured"[tiab] OR reinjuries[tiab] OR "re-injuries"[tiab] OR recurrence[tiab] OR recurring[tiab] OR recurrent[tiab] OR ((subsequent[tiab] OR second[tiab] OR secondary[tiab] OR multiple[tiab]) AND (injury[tiab] OR injuries[tiab]))	716,976
4	1 AND 2 AND 3	1,505
5	4 NOT (Editorial[ptyp] OR Comment[ptyp])	1,496
6	5 NOT (animals[mh] NOT humans[mh])	1,464

Database (including vendor/platform): EMBASE (via Elsevier)

Set #		Results
1 ACL	'anterior cruciate ligament'/exp OR 'anterior cruciate ligament injury'/exp OR 'anterior cruciate':ti,ab OR ACL:ti,ab	30,985
2 Surgery	'anterior cruciate ligament reconstruction'/exp OR autograft:ti,ab OR 'auto-graft':ti,ab OR HTA:ti,ab OR ACLR:ti,ab OR surgery:ti,ab OR surgeries:ti,ab OR procedure:ti,ab OR procedures:ti,ab OR reconstruction:ti,ab OR reconstructions:ti,ab OR reconstructed:ti,ab	2,991,980
3 Reinjury	'recurrence risk'/exp OR reinjury:ti,ab OR 're-injury':ti,ab OR reinjured:ti,ab OR 're-injured':ti,ab OR reinjuries:ti,ab OR 're-injuries':ti,ab OR recurrence:ti,ab OR recurring:ti,ab OR recurrent:ti,ab OR ((subsequent:ti,ab OR second:ti,ab OR secondary:ti,ab OR multiple:ti,ab) AND (injury:ti,ab OR injuries:ti,ab))	958,579
4	1 AND 2 AND 3	1,955
5	4 AND ([article]/lim OR [article in press]/lim OR [letter]/lim OR [review]/lim)	1,420
6	5 AND [humans]/lim	1,354

Database (including vendor/platform): CINAHL (via EBSCO)

Set #		Results
1 ACL	(MH "Anterior Cruciate Ligament" OR MH "Anterior Cruciate Ligament Injuries") OR TI ("anterior cruciate" OR ACL) OR AB ("anterior cruciate" OR ACL)	11,829
2 Surgery	(MH "Anterior Cruciate Ligament Reconstruction") OR TI (autograft OR "auto-graft" OR HTA OR ACLR OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed) OR AB (autograft OR "auto-graft" OR HTA OR ACLR OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed)	356,241
3 Reinjury	(MH "Recurrence" OR MH "Reinjury") OR TI (reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR recurrent OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries))) OR AB (reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries)))	113,076
4	1 AND 2 AND 3	839
5	4 AND Limiters - Publication Type: Clinical Trial, Journal Article, Letter, Meta Analysis, Meta Synthesis, Practice Guidelines, Randomized Controlled Trial, Review, Systematic Review	538

Database (including vendor/platform): SPORTDiscus (via EBSCO)

Set #		Results
1 ACL	(DE "ANTERIOR cruciate ligament" OR DE "ANTERIOR cruciate ligament injuries") OR TI("anterior cruciate" OR ACL) OR AB("anterior cruciate" OR ACL)	10,355
2 Surgery	(DE "ANTERIOR cruciate ligament surgery" OR DE "ANTERIOR cruciate ligament transplantation") OR TI(autograft OR "auto-graft" OR HTA OR ACLR OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed) OR AB(autograft OR "auto-graft" OR HTA OR ACLR OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed)	57,184
3 Reinjury	TI(reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR recurrent OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries))) OR AB(reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries)))	12,955
4	1 AND 2 AND 3	573

Database (including vendor/platform): Scopus (via Elsevier)

Set #		Results
1 ACL	TITLE-ABS ("anterior cruciate" OR acl)	30,854
2 Surgery	TITLE-ABS (autograft OR "auto-graft" OR hta OR aclr OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed)	4,099,026
3 Reinjury	TITLE-ABS (reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR recurrent OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries)))	857,866
4	1 AND 2 AND 3	1,708
5	4 AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re") OR LIMIT-TO (DOCTYPE , "le"))	1,563

126 **APPENDIX 2.** Studies Contacted for Clarifying Data and Responses Received

Data clarification lead to inclusion		
Authors	Year	Title
Beischer et al	2020	Young athletes who return to sport before 9 months after anterior cruciate ligament reconstruction have a rate of new injury 7 times that of those who delay return
Bourke et al	2012	Survival of the anterior cruciate ligament graft and the contralateral ACL at a minimum of 15 years
Everhart et al	2019	Femoral nerve block at time of ACL reconstruction causes lasting quadriceps strength deficits and may increase short-term risk of re-injury
Fleming et al	2013	The effect of initial graft tension after anterior cruciate ligament reconstruction: a randomized clinical trial with 36-month follow-up
Kamath et al	2014	Anterior cruciate ligament injury, return to play, and reinjury in the elite collegiate athlete: analysis of an NCAA Division I cohort
Webster et al	2019	Clinical Tests Can Be Used to Screen for Second Anterior Cruciate Ligament Injury in Younger Patients Who Return to Sport
Data clarification lead to exclusion		
Authors	Year	Title
Herbst et al	2017	Impact of surgical timing on the outcome of anterior cruciate ligament reconstruction
Leys et al	2012	Clinical results and risk factors for reinjury 15 years after anterior cruciate ligament reconstruction: a prospective study of hamstring and patellar tendon grafts
McPherson et al	2019	Psychological readiness to return to sport is associated with second anterior cruciate ligament injuries
McRae et al	2013	Ipsilateral versus contralateral hamstring grafts in anterior cruciate ligament reconstruction: a prospective randomized trial
Schmale et al	2014	High satisfaction yet decreased activity 4 years after transphyseal ACL reconstruction
Paterno et al	2010	Biomechanical measures during landing and postural stability predict second anterior cruciate ligament injury after anterior cruciate ligament reconstruction and return to sport
Paterno et al	2017	Clinical factors that predict a second ACL injury after ACL reconstruction and return to sport: preliminary development of a clinical decision algorithm
Paterno et al	2018	Self-reported fear predicts functional performance and second ACL injury after ACL reconstruction and return to sport: a pilot study
Webster et al	2014	Younger patients are at increased risk for graft rupture and contralateral injury after anterior cruciate ligament reconstruction
Data could not be clarified		

Authors	Year	Title
Akada et al	2019	Partial meniscectomy adversely affects return-to-sport outcome after anatomical double-bundle anterior cruciate ligament reconstruction
Astur et al	2018	Increased incidence of anterior cruciate ligament revision surgery in paediatric verses adult population
Barrett et al	2010	Allograft anterior cruciate ligament reconstruction in the young, active patient: Tegner activity level and failure rate
Calvo et al	2015	Transphyseal anterior cruciate ligament reconstruction in patients with open physes: 10-year follow-up study
Dekker et al	2017	Return to sport after pediatric anterior cruciate ligament reconstruction and its effect on subsequent anterior cruciate ligament injury
Falciglia et al	2016	Anterior cruciate ligament reconstruction in adolescents (Tanner stages 2 and 3)
Gans et al	2018	Epidemiology of recurrent anterior cruciate ligament injuries in National Collegiate Athletic Association sports: the Injury Surveillance Program, 2004-2014
Geffroy et al	2018	Return to sport and re-tears after anterior cruciate ligament reconstruction in children and adolescents
Granan et al	2015	Associations between inadequate knee function detected by KOOS and prospective graft failure in an anterior cruciate ligament-reconstructed knee
Grindem et al	2012	A pair-matched comparison of return to pivoting sports at 1 year in anterior cruciate ligament–injured patients after a nonoperative versus an operative treatment course
Grindem et al	2014	Nonsurgical or surgical treatment of ACL injuries: knee function, sports participation, and knee reinjury: the Delaware-Oslo ACL Cohort Study
Grindem et al	2016	Simple decision rules can reduce reinjury risk by 84% after ACL reconstruction: the Delaware-Oslo ACL cohort study
Gupta et al	2018	Low re-rupture rate with BPTB autograft and semitendinosus gracilis autograft with preserved insertions in ACL reconstruction surgery in sports persons
Gupta et al	2019	Is anterior cruciate ligament graft rupture (after successful anterior cruciate ligament reconstruction and return to sports
Herbst et al	2017	Impact of surgical timing on the outcome of anterior cruciate ligament reconstruction
Imbert et al	2017	Midterm results of combined intra-and extra-articular ACL reconstruction compared to historical ACL reconstruction data
Ithurburn et al	2019	Knee function, strength, and resumption of preinjury sports participation in young athletes following anterior cruciate ligament reconstruction

Kaeding et al	2015	Risk factors and predictors of subsequent ACL injury in either knee after ACL reconstruction: prospective analysis of 2488 primary ACL reconstructions from the MOON cohort
Koga et al	2015	Effect of posterolateral bundle graft fixation angles on clinical outcomes in double-bundle anterior cruciate ligament reconstruction: a randomized controlled trial
Lebel et al	2008	Arthroscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone autograft: a minimum 10-year follow-up
Magnussen et al	2012	Graft size and patient age are predictors of early revision after anterior cruciate ligament reconstruction with hamstring autograft
Magnussen et al	2016	Effect of high-grade preoperative knee laxity on anterior cruciate ligament reconstruction outcomes
Nwachukwu et al	2017	Return to play and patient satisfaction after ACL reconstruction: study with minimum 2-year follow-up
Oates et al	1999	Comparative injury rates of uninjured, anterior cruciate ligament-deficient, and reconstructed knees in a skiing population
Pennock et al	2018	Use of a modified all-epiphyseal technique for anterior cruciate ligament reconstruction in the skeletally immature patient
Rousseau et al	2019	Complications after anterior cruciate ligament reconstruction and their relation to the type of graft: a prospective study of 958 cases
Siebold et al	2016	Anatomical “C”-shaped double-bundle versus single-bundle anterior cruciate ligament reconstruction in pre-adolescent children with open growth plates
Snaebjörnsson et al	2017	Adolescents and female patients are at increased risk for contralateral anterior cruciate ligament reconstruction: a cohort study from the Swedish National Knee Ligament Register
Sousa et al	2017	Return to sport: does excellent 6-month strength and function following ACL reconstruction predict midterm outcomes?
Takazawa et al	2013	ACL reconstruction preserving the ACL remnant achieves good clinical outcomes and can reduce subsequent graft rupture
Takazawa et al	2016	Anterior cruciate ligament injuries in elite and high school rugby players: a 11-year review
Wall et al	2017	Outcomes and complications after all-epiphyseal anterior cruciate ligament reconstruction in skeletally immature patients
Wernecke et al	2017	The diameter of single bundle, hamstring autograft does not significantly influence revision rate or clinical outcomes after anterior cruciate ligament reconstruction

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APPENDIX 3. Summary of Findings and Strength of the Evidence Using GRADE

GRADE Criteria	Total Second ACLI Risk	Justification	Ipsilateral ACLI Risk	Justification	Contralateral ACLI Risk	Justification
Study Design[$]	+2	RCT and non-RCT included	+2	RCT and non-RCT included	+2	RCT and non-RCT included
Risk of Bias*	0	Only low or moderate RoB included	0	Only low or moderate RoB included	0	Only low or moderate RoB included
Inconsistency*	-1	Inconsistency is present, (I^2=50%, p=0.02) and could be meaningful	-1	Inconsistency is present (I^2=52%, p=0.02) and could be meaningful.	0	Inconsistency is not present (I^2=0%, p=0.67)
Indirectness*	0	No concerns for indirectness	0	No concerns for indirectness	0	No concerns for indirectness
Imprecision*	-1	There is concern for imprecision of the estimate due to each end of the confi-dence intervals indicating an opposite effect	0	There is minimal concern for imprecision based on tight confidence intervals despite a null estimate for RR.	0	There is minimal concern for imprecision based on tight confidence intervals despite an estimate that includes the null estimate.
Publication Bias[&]	0	Not detected	0	Not detected	0	Not detected
Upgrading Factors[#]	0	No upgrading factors	0	No upgrading factors	0	No upgrading factors
GRADE Quality of Evidence Score[$$]	Very Low		Very Low		Low	
Summary of Findings	There was no difference in the relative or absolute risk of a second ACLI between males and females.		There was no difference in the relative risk, but females have a 3.5% reduced absolute risk of an ipsilateral ACLI compared to males.		Females were found to have 1.27 times higher relative risk of experiencing a contralateral ACL injury compared to males	

GRADE= Grading of Recommendations, Assessment, Development and Evaluation, RCT= randomized controlled trial, Non-RCT= nonrandomized controlled trail, ACLI= anterior cruciate ligament injury, RoB= Risk of Bias

$ RCT (+4, high quality), Non-RCT (+2, low quality)

*Judged as No (0), Serious (-1), Very Serious (-2)

&Undetected (0), Strongly Suspected (-1)

#Large Effect (+1 or +2), Dose Response (+1 or +2), No Plausible Confounding (+1 or +2)

$$Overall Quality of Evidence Score = sum of rating score given of all GRADE criteria

†High quality (score ≥ 4), moderate quality (score = 3), Low quality (score = 2), very low quality (score ≤ 1)

APPENDIX 4. A MeaSurement Tool to Assess systematic Reviews Version 2

Question	Criteria Met: Yes/No/Partial Yes	Justification
1	**Yes**	PICO established in research question and selection criteria.
2	**Yes**	Methods were established prior to conducting this review.
3	**Yes**	Explanation provided for inclusion of RCTs and NRSI
4	**Yes**	Searched 5 databases, considered grey literature in search design, provided all searches for reviewers, and searched within 12 months of submission.
5	**Yes**	Two reviewers independently performed study selection.
6	**Yes**	Two reviewers independently performed data extraction.
7	**Partial Yes**	A list of reasons for excluded studies provided, but not a complete list of references.
8	**Yes**	Adequate description of included studies provided.
9	**Yes**	RoB was assessed, reported and used to factor into GRADE scoring.
10	**Yes**	Funding sources of included studies were reported.
11	**Yes**	Appropriate decision to perform statistical analysis provided, methods and justification described in detail. Appropriate weighting performed with meta-regression to determine influence of confounders.
12	**Yes**	High RoB studies were excluded from meta-analysis, and sensitivity analyses reported.
13	**Yes**	RoB was reported for each study, influenced meta-analysis inclusion and considered during GRADE scoring.
14	**Yes**	Yes, heterogeneity was discussed, and limitations were noted that could have contributed.
15	**Yes**	Publication bias was reported, discussed and considered during GRADE scoring.
16	**Yes**	We report that one listed author of the present study (MVP) was the first author of one study included in this review. However, we

		declare no other competing interests.

PICO= Patient/problem, Intervention, Comparison, Outcome; framework for development of research questions, RoB= risk of bias, GRADE= Grading of Recommendations, Assessment, Development and Evaluation, RCTs= Randomized controlled trials, NRSI= Non-randomized studies of healthcare interventions

1=research question and inclusion criteria include PICO? 2= Was review methods/protocol established prior to conduct of review? 3= Explain selection criteria based on study design? 4= Comprehensive literature search? 5= Study selection in duplicate? 6= Data extraction in duplicate? 7= List of excluded studies provided? 8= Describe included studies in adequate detail? 9= Satisfactory technique to assess RoB? 10= Report sources of funding for included studies? 11= Appropriate statistical methods used for meta-analysis? 12= Assess for impact of RoB on results of meta-analysis? 13= RoB accounted for when discussing results? 14= Discussion of heterogeneity? 15= Investigation into publication bias? 16= Any conflict of interest report

Potential Sources of Conflict and Sources of Funding for Included Studies

INCLUDED STUDIES	Potential Sources of Support (if reported in study)
Bak *et al*[†](58)	No reported conflict of interest statement or statement of funding provided
Beischer *et al*[†]*(59)*	The authors report no conflicts of interest. Funding: Grants from the Swedish Research Council for Sport Science, by the Local Research and Development Board of Gothenburg and Sodra Bohuskan, and by the Unit of Physiotherapy, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg.
Bourke *et al*[†](60)	**“**One or more of the authors has declared the following potential conflict of interest or source of funding: Dr. Pinczewski has received research funds from Smith & Nephew in the past 5 years. No funding was received for the current study.”
Cordasco *et al(51)*	“One or more of the authors has declared the following potential conflict of interest or source of funding: FAC is a consultant for Arthrex and receives royalties from Conmed Linvatec and Arthrex. DWG is a consultant for and receives royalties from Arthrex.”
Dekker *et al*[†](61)	The authors report no conflicts of interest or external sources of funding for this study.
Demange *et al*(52)	“The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.”
Everhart *et al*[†](62)	The authors report no funding for this study and declare no conflicts of interest
Fleming *et al*(53)	Funding: This study was funded by grants from the National Institues of Health (RO1-AR047910; RO1-AR047910S1. No conflict of interest statement provided.
Geffroy *et al*(54)	Funding: None Conflicts of Interest: NL is a consultant for developing logicielwebsurvey.fr® software.
Graziano *et al*(55)	The authors declare no conflicts of interest
Gupta *et al*(56)	The authors declare no conflicts of interest or funding for this study
Heath *et al*[†] (63)	The authors declare no conflicts of interest. “AOSSM has not conducted an independent investigation on the Open Payments Database (OPD) and disclaims any liability or responsibility relating therto.”
Heijne *et al*[†](64)	No conflict of interest statement or statement of funding provided
Kamath *et al*[†](65)	“One or more of the authors has declared the following potential conflict of interest or source of funding: This study was paid for by the University of North Carolina at Chapel Hill, Department of Orthopaedic Surgery, Sports Medicine Research Fund.”
Laboute *et al*(57)	Authors declare no conflicts of interest. Funding statement not provided.
Mohtadi *et al*[†](66)	“NM and DC are currently receiving a research grant to support this trial, from the Workers’ Compensation Board, Alberta, and received prior funding from the Calgary Orthopaedic Research and Education Fund (COREF). The remaining authors report no conflicts of interest.”
Paterno *et al*[†](31)	“One or more of the authors has declared the following potential conflicts of interest or source of funding: The study was supported by the National Football League Charities and the National Institute of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases grants RO1-AR049735, RO1-AR049735, RO1-AR056259, and F32-AR055844.”
Shelbourne *et al*[†](36)	No potential conflicts of interest declared.
Webster *et al*[†](67)	The authors declare no conflicts of interest. “AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating therto.”

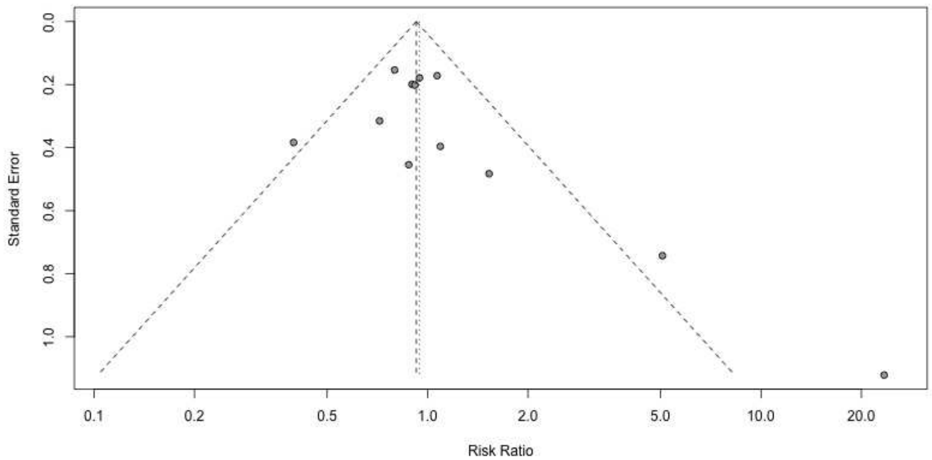
[†]Included in meta-analysis

APPENDIX 5. Incidence Numbers by Sex and Laterality

Source	Whole Cohort			Second ACL Injuries			Ipsilateral Injuries			Contralateral Injuries		
	Total	*Females*	*Males*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*
Bak *et al*†(61)	132	15	117	13*	3	1	4	3	1	9*	-	-
Beischer *et al*†*(62)*	159	102	57	18	11	7	10	5	5	8	6	2
Bourke *et al*†(63)	673	241	432	156	48	108	71	15	56	85	33	52
Cordasco *et al(51)*	23	6	17	1	0	1	1	0	1	0	0	0
Dekker *et al*†(64)	85	51	34	27	14	13	16	-	-	11	-	-
Demange *et al*(52)	12	5	7	3	1	2	3	1	2	-	-	-
Everhart *et al*†(65)	360	215	145	27	10	17	16	6	10	11	4	7
Fleming *et al*(53)	85	48	42	7	5	2	4	3	1	3	2	1
Geffroy *et al*(54)	278	123	155	29*	10	13	14	3	11	15*	7	2
Graziano *et al*(55)	42	12	30	6	2	4	4	1	3	2	1	1
Gupta *et al*(56)	340	26	314	25	4	21	7	1	6	18	3	15
Heath *et al*† (67)	247	82	165	81	25	56	53	14	39	30	11	19
Heijne *et al*†(68)**	68	32	36	11	9	2	7	6	1	4	3	1
Kamath *et al*†(69)	89	47	42	20	11	9	7	3	4	13	8	5
Laboute *et al*(57)	298	64	234	26	5	21	26	5	21	0	-	-
Mohtadi *et al*†(72)	322	139	183	96	43	53	79	33	46	17	10	7
Paterno *et al*†(36)	78	59	19	23	19	4	7	5	2	16	14	2
Shelbourne *et al*†(38)	402	319	83	104	81	23	41	27	14	63	54	9
Webster *et al*†(74)	329	129	200	95	36	59	50	16	34	45	20	25
Totals	4027	1715	2312	771	337	418	420	147	257	351	176	148

†Included in meta-analysis; *Contralateral injuries were not classified by sex. **2 participants (1 male, 1 female) experienced 2 subsequent ACL injuries (1 ipsilateral and 1 contralateral injury each) that could not be clarified which occurred first and are still included

205 **APPENDIX 6**. Funnel Plot



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Multiple Choice Questions

1. According to previous literature, what is the relationship between biologic sex and primary ACL injury in athletes?
   a. Males are more likely than females to incur a primary ACL injury.
   b. **Females are more likely than males to incur a primary ACL injury.**
   c. Males and females are equally likely to incur a primary ACL injury.
   d. This is an area of debate and requires significant more research.

2. According to previous literature, which one of the following is not a reason that is believed to contribute to females incurring more primary ACL injuries than males?
   a. Anatomy
   b. Hormonal effects
   c. Biomechanics
   d. Sport participation
   e. **All of the above are possible reasons**

3. According to this systematic review, what is the relationship between biologic sex and overall second ACL injury in athletes?
   a. Males are more likely than females to incur a second ACL injury.
   b. Females are more likely than males to incur a second ACL injury.
   c. **Males and females are equally likely to incur a second ACL injury.**
   d. This systematic review did not address this issue.

4. According to this systematic review, what is one relationship between biologic sex and laterality of second ACL injury in athletes?
   a. **Males are more likely to incur a second ACL injury to the ipsilateral knee.**
   b. Females are more likely to incur a second ACL injury to the ipsilateral knee.
   c. Males are more likely to incur a second ACL injury to the contralateral knee.
   d. Females are more likely to incur a second ACL injury to the contralateral knee.

5. According to this systematic review, what is another relationship between biologic sex and laterality of second ACL injury in athletes?
   a. Only males are equally likely to incur a second ACL injury to either knee.
   b. **Only females are equally likely to incur a second ACL injury to either knee.**
   c. Both males and females are equally likely to incur a second ACL injury to either knee.
   d. Neither males nor females are equally likely to incur a second ACL injury to either knee.