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The Importance of Patient Sex in the Outcomes of Anterior Cruciate Ligament Reconstructions

A Systematic Review and Meta-analysis

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Background: One of the well-studied epidemiological phenomena of anterior cruciate ligament (ACL) injuries is the 2- to 9-fold increase in the relative risk of ACL rupture in female athletes compared with male athletes. However, the influence of patient sex on the outcome after ACL reconstruction remains unclear, with some authors reporting inferior outcomes in females and others noting no significant difference.

Purpose: To provide a comprehensive systematic review and meta-analysis to examine the possible association between patient sex and the subjective and objective outcomes after ACL reconstruction.

Methods: This study was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. All studies that reported clinical outcomes after ACL reconstruction in males and females independently were included in the review. A quantitative random-effects meta-analysis was performed to compare outcomes between sexes. For outcomes with considerable heterogeneity, meta-regression was used to identify potential moderators. Articles were evaluated qualitatively when quantitative data were not reported.

Results: A total of 135 publications were included in the review. Females had inferior outcomes in instrumented laxity (standardized mean difference [SMD], 0.24; 95% CI, 0.11-0.37), revision rate (relative risk [RR], 1.15; 95% CI, 1.02-1.28), Lysholm score (SMD, −0.33; 95% CI, −0.55 to −0.11), Tegner activity scale (SMD, −0.37; 95% CI, −0.49 to −0.24), and incidence of not returning to sports (RR, 1.12; 95% CI, 1.04-1.21), all of which were statistically significant. Other outcomes were comparable between sexes, including anterior drawer test, Lachman test, pivot-shift test, timed single-legged hop test, single-legged hop test, quadriceps testing, hamstring testing, extension loss, flexion loss, development of cyclops lesion, and International Knee Documentation Committee (IKDC) knee examination score. Females and males were equally likely to develop anterior knee pain and osteoarthritis after ACL reconstruction. The graft rupture and graft failure rates did not differ significantly between sexes.

Conclusion: There were comparable or inferior results for females compared with males in all outcomes analyzed. No statistically significant sex difference was identified in most of the objective parameters. However, subjective and functional outcomes, including Lysholm score, Tegner activity scale, and ability to return to sports, have been shown to be poorer in females.

Keywords: anterior cruciate ligament; anterior cruciate ligament reconstruction; sex; meta-analysis

The incidence of anterior cruciate ligament (ACL) reconstruction is steadily on the rise; recent reports indicate a 1½-fold increase in the rate of ACL reconstructions over the span of 12 years.[83,93] Multiple national databases have estimated that this incidence is around 30 to 45 per 100,000 person-years, and more than 120,000 ACL reconstructions are performed annually in the United States.[46,51,93,105]

One of the well-studied epidemiological phenomena of ACL injuries is the 2- to 9-fold increase in the relative risk of ACL rupture in female athletes compared with male athletes.[117,145] Multiple factors have been proposed to account for this variation in ACL rupture rates. These include increased general joint laxity, increased quadriceps angle, increased posterior tibial slope, decreased

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notch width, smaller ACL cross-sectional area, hormonal factors, and the tendency for female athletes to land with their knees in inadequate flexion and in a position of valgus and external rotation.[99,145]

Correspondingly, the rates of ACL reconstructions among females have increased over the years, especially with their increasing participation in sports activities.[93] However, despite recent advancements in the understanding of ACL injuries and ACL reconstruction, the influence of sex on outcome after ACL reconstruction remains unclear; some authors report inferior outcomes in females whereas others note no significant difference. These include both objective and subjective outcomes after ACL reconstruction.

The large amount of literature and research on ACL injury is telling of both the importance and the complexity of the condition. Yet, to date, there is a lack of comprehensive and conclusive studies investigating the role of sex in the objective and functional outcomes after ACL reconstruction. This article is one of the first attempts to consolidate the existing knowledge, in a bid to provide greater insight into the importance of sex on outcomes of ACL reconstruction.

METHODS

Systematic Review

The systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A search was conducted using PubMed, Medical Literature Analysis and Retrieval System Online (MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Library through April 25, 2014. The keywords used were “anterior cruciate ligament (ACL) reconstruction” and “gender or sex or male or female.” Inclusion criteria were all original studies that reported clinical outcomes after ACL reconstruction in males and females independently. Excluded were nonhuman studies, studies without clinical outcomes, studies in which ACL injuries were not treated with reconstruction, studies whose data could not be separately retrieved for males and females, studies with sample size fewer than 10 for each sex, review articles, non-English-language articles, and articles with no full-text version available.

The articles were selected in 2 stages. First, the abstracts of all citations identified by the above searches were downloaded and the list was narrowed using the inclusion and exclusion criteria stated. Second, the full-text versions of this short list were retrieved and similarly evaluated for eligibility. The reference lists of the identified publications were hand-searched for additional relevant studies. Figure 1 illustrates the selection process.

Data Abstraction

Each study’s data were then retrieved individually for both the male and female subgroups. Outcomes evaluated included the anterior drawer test, Lachman test, pivot-

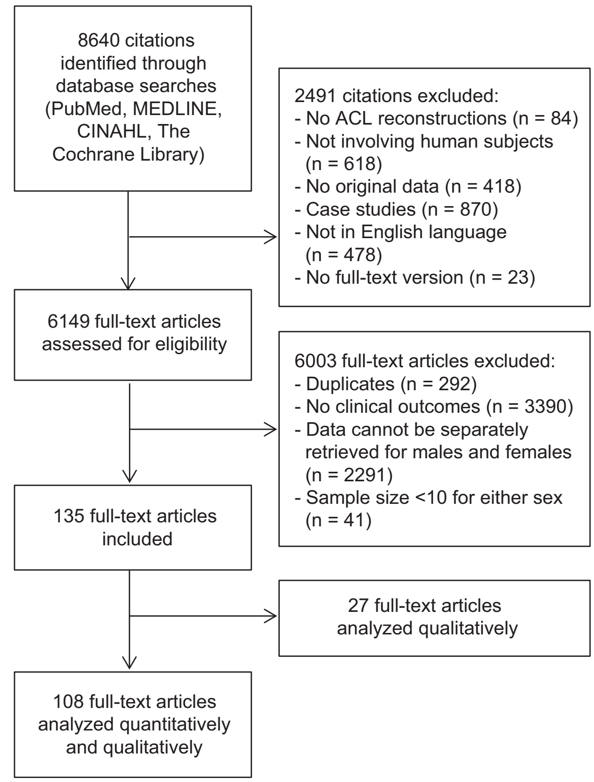

Figure 1. Flow diagram of the review and selection of cases. ACL, anterior cruciate ligament.

shift test, instrumented laxity, Lysholm score, International Knee Documentation Committee (IKDC) subjective and objective scores, Knee injury and Osteoarthritis Outcome Score (KOOS), patient satisfaction, Marx score, Tegner score, ability to return to sports, single-legged hop test, timed single-legged hop test, quadriceps peak torque, hamstring peak torque, extension loss, flexion loss, cyclops lesion, graft rupture, graft failure, revision surgery, anterior knee pain, and osteoarthritis.

Other demographic and surgical variables noted included age, type of surgeries (primary or revision), source of grafts (autograft or allograft), choice of grafts (hamstring or patellar tendon–bone), surgical techniques (single or double bundles), and duration of follow-up. Where subgroup analysis was performed within the study based on the source of graft, choice of graft, or surgical techniques, the results of each subgroup were entered separately.

Data Analysis

The random-effects model was used to obtain pooled estimates of sex differences for each outcome.[33] This assumes that the studies represented a random sample from the larger population of such studies, with each study having its own underlying effect size. Under this random-effects model, it is assumed that there is a mean population effect size about which the study-specific effect varies. As the random-effects model properly takes into account the interstudy heterogeneity such as differences in study design and definitions of outcomes, it thus provides a more conservative evaluation of the significance of the association than one based on fixed effects.[42]

The pooled relative risk (RR) or standardized mean difference (SMD) of the sex-based differences for each outcome is reported with the 95% confidence interval. Forest plots are provided for statistically significant sex differences. Other forest plots for statistically insignificant sex differences are provided in Appendix 1 (available online at http://ajsm.sagepub.com/supplemental).

Tests of heterogeneity were conducted with the Q statistic that is distributed as a chi-square variate under the assumption of homogeneity of effect sizes. The extent of between-study heterogeneity was assessed with the I^2 statistic[57,58] (Table 1).

If heterogeneity existed among studies, further analyses were performed using the random-effects meta-regression analysis technique, which allows the effect of multiple continuous or categorical characteristics to be investigated simultaneously. This identifies the moderators that might contribute to the heterogeneity of the effect sizes. Study identifiers were added in the model to control for the effect of any variations in study characteristics. The regression coefficient was calculated to indicate the percentage of variance explained by the moderators, and significant moderators were reported together with the associated adjusted pooled RR estimate and 95% CI.

Funnel plots of the sample sizes were plotted against the sex differences of each study. This was conducted together with the Egger test to evaluate the possibility of publication bias for the various outcomes analyzed.[156] Results for publication bias using the Egger test are depicted in Table 1, while funnel plots are provided for statistically significant pooled estimates in Appendix 2, available online.

All statistical evaluations were made assuming a 2-sided test at the 5% level of significance using Stata version 12 (Stata Corp). When quantitative data were not reported, the effects of sex on the outcomes were separately noted for each study when reported.

RESULTS

A total of 135 publications were identified and included in the review, of which 108 publications reported data quantitatively while 27 publications only reported the direction of sex effects without quantitative data. These included a total of 120,158 patients, with 49,860 females and 70,298 males. These are approximates, as similar cohorts might have been published repeatedly in several research groups, although attempts were made to eliminate cohorts with the same parameter being reported repeatedly. The results at the longest follow-up time point were used in these scenarios.

Anterior-Posterior Laxity

Four parameters were used in the assessment of anterior-posterior laxity: the anterior drawer test, Lachman test, pivot-shift test, and instrumented laxity. Anterior drawer tests were reported quantitatively in 3 studies.[40,100,159] Lachman tests were reported quantitatively in 6 studies,[2,39,98,104,129,148] and 6 studies only reported the effects of patient sex without quantitative data.[20,27,32,40,121,130] Pivot-shift tests were reported quantitatively in 10 studies[¶] and without quantitative data in 7 studies.[20,27,32,40,121,130,138] Instrumented laxity was reported quantitatively in 25 studies[#] and without quantitative data in 8 studies.[**]

No statistically significant difference was found when the parameters of anterior-posterior laxity on clinical examination were pooled. Females had pooled RR estimates of 0.94 (95% CI, 0.57-1.54), 1.17 (95% CI, 0.79-1.72), and 1.23 (95% CI, 0.94-1.62) for a positive anterior drawer test, Lachman test, and pivot-shift test compared with males, respectively. This lack of sex difference was reported in all studies for anterior drawer tests, 7 of 12 studies for Lachman tests, and 13 of 17 studies for pivot-shift tests. All studies that reported a sex difference showed an increased laxity in females.

The I^2 statistics by the heterogeneity test showed homogeneity for anterior drawer and pivot-shift tests and heterogeneity for Lachman test. No significant moderators were identified for the heterogeneity between the studies for Lachman test. No publication biases were evident in these studies.

On instrumented testing, females had a statistically significant increase in pooled anterior tibial translation compared with males (pooled SMD estimate, 0.24; 95% CI, 0.11-0.37) (Figure 2). In total, increased laxity in females that reached statistical significance was reported in 8 of 33 studies, although the difference in 3 studies were minute and were not reflected in the forest plots when the 95% CIs were calculated from the raw data (Figure 2). Meta-analysis revealed significant heterogeneity; however, no significant moderators were identified. Publication bias was not evident in these studies.

Objective Knee Scores

The IKDC knee examination score was used to evaluate the objective parameters of the knee in totality. Seven studies reported the information quantitatively,[††] and 2 studies reported it without quantitative data.[40,116] The pooled RR estimate for females to have an abnormal or severely abnormal knee on IKDC scoring is 1.27 (95% CI, 0.95-1.69), which is not statistically significant. The only study that reported poorer outcomes in females only reported the information without quantitative data and could not be incorporated into the meta-analysis. The studies were homogeneous, and no publication biases were identified.

¶References 5, 12, 39, 45, 97, 98, 104, 129, 148, 149.

#References 2, 5, 12, 19, 20, 25-27, 39, 48, 59, 71, 78, 89, 97, 98, 104, 116, 118, 124, 129, 137, 148, 149, 157.

**References 13, 23, 45, 85, 101, 115, 130, 138.

††References 45, 71, 110, 129, 148, 149, 157.

TABLE 1
Meta-analysis, Tests for Heterogeneity, and Egger Test for Publication Bias[a]

	Meta-analysis		Tests for Heterogeneity			Egger Test
	Pooled Estimate	95% CI	Q	*P*	I^2, %	*P*
Objective Parameters						
Anterior-posterior laxity						
Anterior drawer test	RR = 0.94	0.57 to 1.54	4.25	.374	5.8	.930
Lachman test	RR = 1.17	0.79 to 1.72	14.48	.025	58.6	.440
Pivot-shift test	RR = 1.23	0.94 to 1.62	12.79	.464	0.0	.087
Instrumented laxity	SMD = 0.24	0.11 to 0.37	99.51	<.001	68.8	.236
Objective knee scores						
IKDC knee examination	RR = 1.27	0.95 to 1.69	5.68	.578	<0.01	.408
Neuromuscular testing						
Timed single-legged hop test	SMD = −0.54	–1.42 to 0.34	34.05	<.001	91.2	.418
Single-legged hop test	SMD = −0.21	–0.51 to 0.10	42.86	<.001	83.7	.102
Quadriceps testing	SMD = −0.20	–0.51 to 0.11	36.17	<.001	75.1	.546
Hamstrings testing	SMD = −0.01	–0.17 to 0.15	10.10	.342	10.9	.590
Extension loss	RR = 1.36	0.79 to 2.37	24.17	.001	71.0	.411
Flexion loss	RR = 1.02	0.54 to 1.91	13.88	.008	71.2	.552
Cyclops lesion	RR = 0.99	0.55 to 1.78	23.24	.002	69.9	.745
Graft rupture, failure, and revision						
Graft rupture	RR = 0.91	0.69 to 1.19	37.17	.115	24.7	.971
Graft failure	RR = 1.03	0.94 to 1.14	17.09	.517	<0.01	.050
Revision surgery	RR = 1.15	1.02 to 1.28	18.67	.478	<0.01	.103
Subjective Parameters						
Functional knee scores						
Lysholm score	SMD = −0.33	–0.55 to −0.11	42.85	<.001	74.3	.578
IKDC subjective score	SMD = −0.01	–0.25 to 0.24	29.32	<.001	79.5	.680
KOOS						
Sports and recreational activities	SMD = −0.03	–0.17 to 0.11	9.33	.097	46.4	.683
Quality of life	SMD = 0.02	–0.14 to 0.19	11.91	.036	58.0	.129
Daily living	SMD = 0.01	–0.05 to 0.07	3.07	.381	2.3	.795
Symptoms	SMD = 0.07	–0.10 to 0.24	9.10	.028	67.1	.305
Pain	SMD = 0.04	–0.12 to 0.19	0.04	.057	60.1	.637
Patient satisfaction	RR = 0.94	0.46 to 1.90	2.20	.333	9.0	.433
Sports and activity level						
Marx score	SMD = −0.05	–0.21 to 0.11	0.55	.768	<0.01	.580
Tegner score	SMD = −0.37	–0.49 to −0.24	52.06	<.001	65.4	.985
Return to sports	RR = 1.12	1.04 to 1.21	4.85	.848	<0.01	.838
Anterior knee pain and osteoarthritis						
Anterior knee pain	RR = 1.00	0.91 to 1.11	11.51	.645	<0.01	.427
Osteoarthritis	RR = 1.04	0.85 to 1.27	8.99	.174	33.3	.749

[a]IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; RR, relative risk; SMD, standardized mean difference.

Neuromuscular Testing

Neuromuscular testing included the timed single-legged hop, single-legged hop, peak torque for quadriceps and hamstrings, and loss of extension or flexion. Timed single-legged hop was reported in 4 studies.[39,84,119,120] Quantitative assessments of the single-legged hop were available in 8 studies,[‡‡] while quantitative data were not presented in 1 study.[45] Isokinetic testing was present quantitatively in 8 studies[§§] and without quantitative data in 5 studies for quadriceps[18,25,87,98,138] and 6 studies for hamstrings.[18,32,72,87,98,138] Extension losses were reported quantitatively in 8 studies[‖‖] and without quantitative data in 3 studies,[45,84,138] while flexion losses were reported quantitatively in 5 studies[2,12,129,148,157] and without quantitative data in 2 studies.[45,138]

Sex differences were not statistically significant in any of these parameters. The pooled SMD estimates for timed single-legged hop, single-legged hop, isokinetic quadriceps testing, and isokinetic hamstrings testing were −0.54 (95% CI, −1.42 to 0.34), −0.21 (95% CI, −0.51 to 0.10), −0.20 (95% CI, −0.51 to 0.11), and −0.01 (95% CI, −0.17 to 0.15), respectively. Only 1 study on timed single-legged

‡‡References 39, 66, 78, 84, 119, 120, 122, 157.

§§References 12, 19, 69, 122, 132, 148, 149, 160.

‖‖References 2, 12, 95, 104, 129, 148, 152, 157.

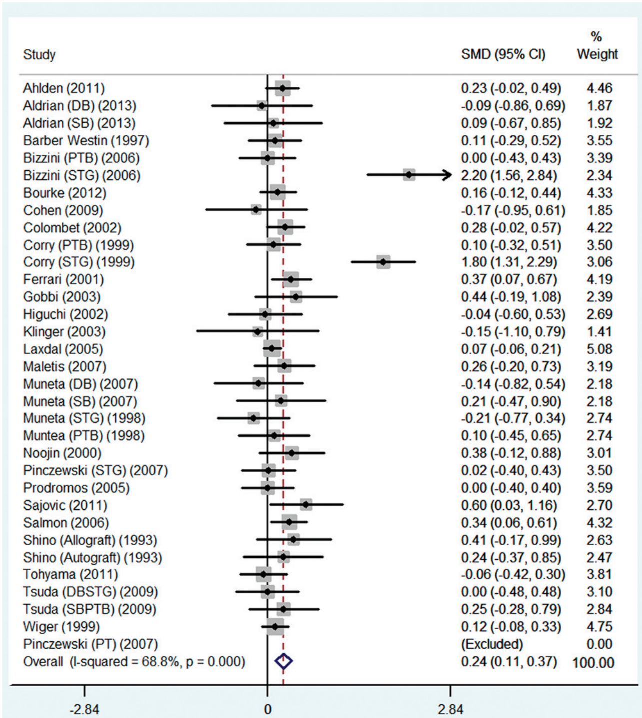

Figure 2. Forest plot for instrumented laxity for females compared with males. Weights are from random-effects analysis. DB, double bundle; SB, single bundle; PTB, patellar tendon–bone graft; SMD, standardized mean difference; STG, hamstring graft.

hop, 3 studies on single-legged hop, 1 study on quadriceps testing, and 2 studies on hamstring testing reported inferior outcomes in females. The pooled RR estimates of extension and flexion loss in females compared with males were not statistically significant, being 1.36 (95% CI, 0.79-2.37) and 1.02 (95% CI, 0.54-1.91), respectively.

The presence of cyclops lesion was reported quantitatively in 12 studies,[¶¶] and 2 studies only reported the sex effect without quantitative data.[29,138] These were defined as the presence of fibrous tissue located along the ACL graft that could result in extension loss, typically diagnosed after second-look arthroscopy. Four studies had no cyclops lesion in any of the patients. Three of 9 remaining studies showed significant sex differences, with 2 showing inferior results in females and 1 in males. Quantitatively, no significant sex difference was identified; the pooled RR estimate in females was 0.99 (95% CI, 0.55-1.78) compared with males.

Significant heterogeneity was present among all parameters except for hamstring testing. No statistically significant moderators were identified for flexion loss. Single-legged hop was most significantly correlated to the proportion of sexes (adjusted pooled RR estimate, 1.87; 95% CI, 1.68-2.08) and duration of follow-up (adjusted pooled RR estimate, 1.21; 95% CI, 1.17-1.25), with studies with lower female proportions and shorter follow-ups reporting inferior results among females. Recent publications also showed more comparable sex differences in quadriceps testing (adjusted pooled RR estimate, 1.87; 95% CI, 1.33-2.63) and extension loss (adjusted pooled RR estimate, 0.97; 95% CI, 0.95-0.99). The proportion of primary surgeries also mediated the sex effect, with primary surgeries having comparable sex differences in extension loss (adjusted pooled RR estimate, 0.95; 95% CI, 0.90-0.99) and inferior results among females for the development of cyclops lesion (adjusted pooled RR estimate, 0.98; 95% CI, 0.97-0.99). The choice of graft also affected the single-legged hop test, with females having inferior results more frequently if hamstrings grafts were used (adjusted pooled RR estimate, 0.93; 95% CI 0.91-0.96) compared with patellar tendon–bone grafts (adjusted pooled RR estimate, 1.11; 95% CI, 1.04-1.10). The use of autografts or allografts also mediated sex effect in the development of cyclops lesion (adjusted pooled RR estimate, 0.98; 95% CI, 0.97-0.99). All the meta-regression estimates reported were adjusted for study variation. No publication biases were noted in any of these studies.

Graft Rupture, Failure, and Revision

Rates of graft ruptures, failures, and revision surgeries were reported quantitatively in 29,[##] 17,[a] and 21[b] studies, respectively. Four studies,[47,81,92,116] one study,[138] and five studies[67,76,83,90,94] also reported the respective information without quantitative data. There were no ruptures in 2 studies and no revisions in 2 studies, and these were excluded from the meta-analysis.

No statistical significance was found between sexes for the rates of graft rupture or failure. Females had pooled RR estimates of 0.91 (95% CI, 0.69-1.19) for graft ruptures and 1.03 (95% CI, 0.94-1.14) for graft failures. The pooled RR estimates for revision surgeries were 1.15 (95% CI, 1.02-1.28) for revision surgeries, with females having a higher risk (Figure 3). A total of 28 of 33 studies for graft rupture, 17 of 18 studies for graft failure, and 23 of 26 studies for revision surgeries also reported no significant sex difference. All studies were homogeneous, and no publication biases were noted in the analysis.

Functional Knee Scores

The Lysholm score, IKDC subjective knee evaluation, and KOOS, together with patient satisfaction, were used to evaluate patient symptoms and knee function.

The Lysholm score was reported quantitatively in 11 studies,[c] and 7 studies only reported the effects of sex without quantitative data.[10,23,38,40,98,118,129] IKDC subjective knee evaluation score was reported quantitatively in 7 studies[5,25,36,55,120,133,140] and without quantitative data in

[¶¶]References 3, 12, 25, 28, 34, 39, 44, 69, 106, 125, 129, 152.

[##]References 4, 11, 20, 21, 25, 39, 45, 49, 50, 56, 60, 63, 77, 111, 112, 118, 125, 127-129, 130, 134, 148, 149, 154, 155, 157-159.

[a]References 11-14, 16, 45, 68, 70, 86, 88, 104, 109, 110, 126, 129, 142, 149.

[b]References 25, 37, 39, 45, 49, 60, 86, 88, 91, 104, 109, 110, 114, 118, 125, 142, 148, 149, 153, 158, 159.

[c]References 2, 5, 25, 39, 71, 78, 84, 104, 140, 148, 157.

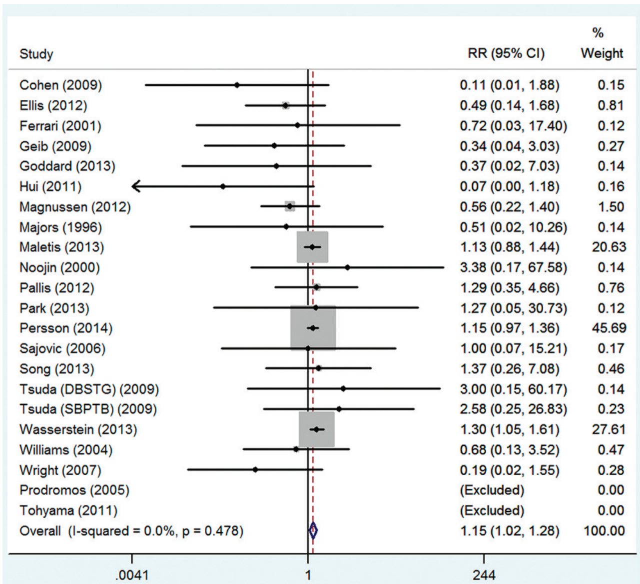

Figure 3. Forest plot for revision surgery rates for females compared with males. Weights are from random-effects analysis. DBSTG, double bundle hamstring graft; RR, relative risk; SB, single-bundle patellar tendon–bone graft.

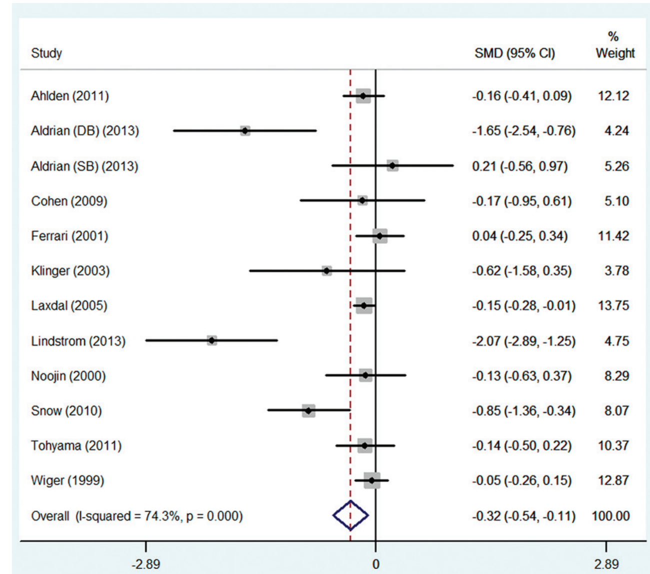

Figure 4. Forest plot for Lysholm scores for females compared with males. Weights are from random-effects analysis. DB, double bundle; SB, single bundle; SMD, standardized mean difference.

7 studies.[1,10,23,24,40,79,143] KOOS was reported quantitatively in 6 studies[1,43,55,56,84,133]; 2 studies reported only the "sports and recreational activities" and "quality of life" domains,[42,46] while the other 4 studies reported all 5 KOOS domains.[1,36,43,75] KOOS was also reported without quantitative data in 6 other studies.[10,17,35,38,76,143] Subjective patient satisfaction was reported in 3 studies each with[2,39,157] and without quantitative data.[38,80,138]

The pooled SMD estimate revealed a statistically significant, inferior score in females compared with males in Lysholm score (pooled SMD estimate −0.33; 95% CI, −0.55 to −0.11) (Figure 4). Significant heterogeneity was present between the studies, although no significant moderators were identified. No publication bias was evident between the studies. Of the 11 studies that reported the Lysholm score, 3 studies reported statistically significant, lower Lysholm scores in females compared with males.

No statistically significant sex difference was found in the IKDC subjective knee evaluation score (pooled SMD estimate, −0.01; 95% CI, −0.25 to 0.24), KOOS, or patient satisfaction (pooled RR estimate, 0.94; 95% CI, 0.46 to 1.90). The pooled SMD estimates for the domains of the KOOS were as follows: −0.03 (95% CI, −0.17 to 0.11) for sports and recreational activities, 0.02 (95% CI, −0.14 to 0.19) for quality of life, 0.01 (95% CI, −0.05 to 0.07) for daily living, 0.07 (95% CI, −0.10 to 0.24) for symptoms, and 0.04 (95% CI, −0.12 to 0.19) for pain. Four studies indicated that IKDC subjective scores had statistically significant sex differences: 2 of these studies favored females, 1 study favored males, and 1 study did not report the precise difference. Four of 12 studies reported lower KOOS in females than males, although 3 of the 4 studies did not report the data quantitatively and thus could not be incorporated into the meta-analysis. Similarly, none of the studies reported a difference in patient satisfaction quantitatively, although 1 study without quantitative data reported greater satisfaction among males.

No publication biases were evident between these studies. Studies reporting patient satisfaction and the KOOS daily living domain were homogeneous, while the other KOOS domains and IKDC subjective knee evaluation score were heterogeneous. After adjustment for study variation, age (adjusted pooled RR estimate, 0.18; 95% CI, 0.05-0.64) and the type of surgery (adjusted pooled RR estimate, 0.32; 95% CI, 0.15-0.68) were the only significant moderators identified for the KOOS sports and recreational activities domain: Older patients and patients undergoing primary surgeries had lower scores among females compared with males. The choice of graft was a significant moderator for IKDC subjective scores after adjustment for study variation: Hamstrings graft had lower scores in females (adjusted pooled RR estimate, 0.87; 95% CI, 0.82-0.95) and patellar tendon–bone grafts had lower scores in males (adjusted pooled RR estimate, 1.28; 95% CI, 1.10-1.50). No other moderators were statistically significant.

Sports and Activity Level

The Marx activity scale, Tegner activity scale, and ability to return to sports are used to assess the activity level of patients postoperatively. Three studies reported the Marx activity scale quantitatively,[36,39,120] while 1 study reported only the effect of sex without quantitative data.[143] Eighteen studies reported Tegner activity scale quantitatively,[d]

[d]References 2, 5, 14, 39, 52-54, 71, 78, 84, 100, 104, 108, 140, 144, 147, 148, 157.

whereas 5 studies reported without quantitative data.[10,38,47,92,98] Ten studies reported the ability to return to sports quantitatively,[e] whereas 2 studies reported without quantitative data.[85,135]

Meta-analysis revealed females to have a lower Tegner score (pooled SMD estimate, −0.37; 95% CI, −0.49 to −0.24) (Figure 5) and an increased pooled RR estimate of 1.12 (95% CI, 1.04-1.21) to be unable to return to sports compared with males (Figure 6). Nine of 23 studies and 2 of 12 studies reported inferior outcomes in females for Tegner score and ability to return to sports. None of the studies reported a difference in Marx activity scale, and pooled estimate was not significantly different between sexes (pooled SMD estimate, −0.05; 95% CI, −0.21 to 0.11).

Significant heterogeneity was identified among studies reporting Tegner scores, with the only significant moderator being the year of the study, which was significant even after adjustment for study variation (adjusted pooled RR, 0.94; 95% CI, 0.89-0.98). Studies conducted at an earlier year did not reveal as much sex difference compared with studies conducted recently. Marx activity level and the ability to return to sports were homogeneous across studies. No publication biases were evident among the studies.

Anterior Knee Pain and Osteoarthritis

The incidences of anterior knee pain and osteoarthritic changes were reported quantitatively in 13[f] and 8[g] studies, respectively. Sex effects were also reported without quantitative data in 6 studies for anterior knee pain[2,10,24,35,104,138] and in 6 studies for osteoarthritic changes.[15,61,92,116,121,130] Females were reported to have a statistically significant, increased incidence of anterior knee pain in 4 of 18 studies and osteoarthritic knee changes in 1 of 14 studies. One other study reported a statistically significant increase in the incidence of osteoarthritic changes in males. Meta-analysis did not reveal any statistically significant differences with the pooled RR estimates in females, being 1.00 (95% CI, 0.91-1.11) for anterior knee pain and 1.04 (95% CI, 0.85-1.27) for osteoarthritic changes. These studies were homogeneous with no publication bias.

DISCUSSION

This study is the first comprehensive systematic review and meta-analysis of sex differences in the outcome of ACL reconstructions. To date, only 2 other reviews on this subject have been published. Both reviews, however, included only a limited number of studies that were specifically designed to compare sex differences in the outcomes of ACL reconstruction.[113,123] A plethora of other studies have included patient sex as one of the variables in the outcome analysis, although these studies were not represented in the reviews. The authors of both reviews acknowledged the possibility of underdetection or overinterpretation of these sex differences owing to the lack of sufficient power and sample size in their reviews. Our review included all studies that reported clinical outcomes after ACL reconstruction so long as the outcomes were separately reported for each sex. This yielded a total of 135

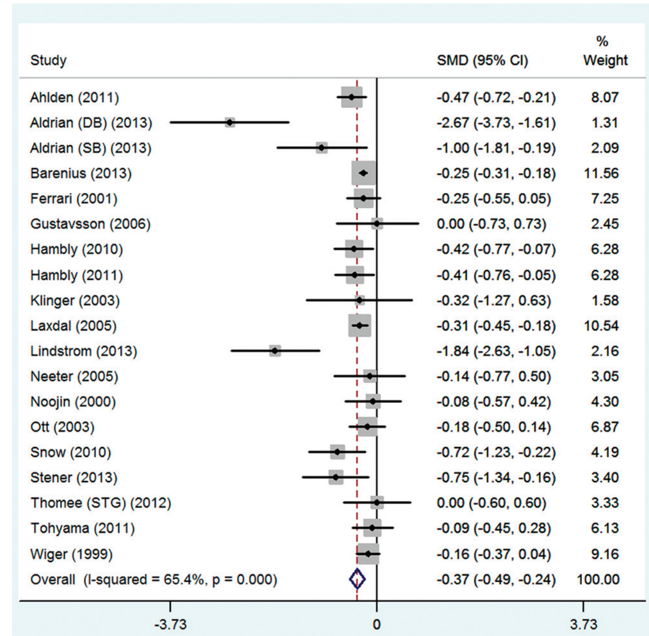

Figure 5. Forest plot for Tegner activity scale, with females compared with respect to males. Weights are from random-effects analysis. DB, double bundle; SB, single bundle; SMD, standardized mean difference.

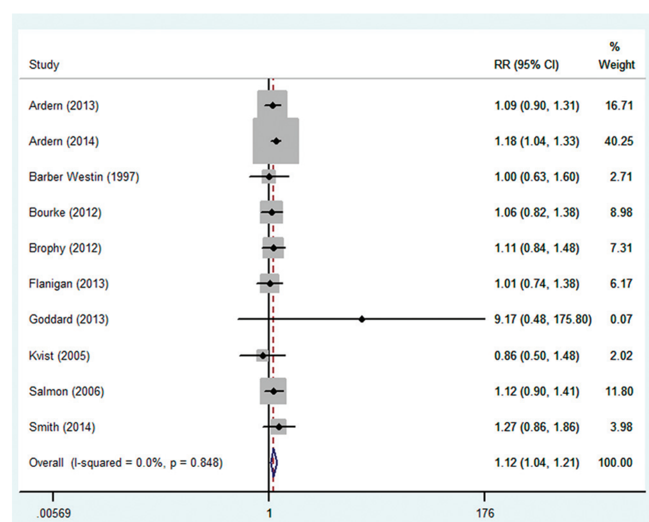

Figure 6. Forest plot for incidence of not returning to sports, with females compared with respect to males. Weights are from random-effects analysis. RR, relative risk.

[e]References 7, 8, 12, 21, 22, 41, 49, 75, 129, 139.

[f]References 12, 39, 72, 98, 99, 102, 103, 107, 108, 129, 149, 150, 157.

[g]References 9, 62, 64, 79, 82, 107, 136, 142.

publications, with more than 120,000 patients being included in the review, minimizing the reporting and publication biases among the studies included.

Statistically significant sex differences in the outcomes of ACL reconstruction identified in this study included instrumented laxity, rates of revision surgeries, Lysholm scores, Tegner scores, and the ability to return to sports. Females showed comparable or inferior results in all outcomes analyzed. In none of the outcomes were males shown to have poorer results compared with females.

The result of an increased instrumented laxity in females is mirrored in the review by Paterno et al,[113] in which the authors analyzed 6 studies qualitatively and concluded that increased anterior-posterior laxity was present after ACL reconstruction in females for both clinical examination and instrumented testing. In the current review, quantitative meta-analysis similarly showed statistically significant, increased instrumented laxity of 0.21 mm in females when compared with males. However, while this is statistically significant, the clinical significance of this difference is brought into question in this scenario. Daniel et al[31] were the first to analyze anterior-posterior knee laxity in ACL-deficient knees using instrumented testing. When comparing between healthy and ACL-deficient knees, the authors noticed a greater than 2-mm difference for knees with ACL injuries that was not recognized in healthy knees. This 2-mm cutoff has been used to date in the assessment for abnormal laxity. When this is used as a reference, the magnitude of sex difference in instrumented laxity found in the current review is considered to be minimal. Understandably, this minute difference could be not detected in any of the parameters performed on clinical examination. Similar to the meta-analysis performed by Ryan et al,[123] our study detected no statistically significant differences in anterior drawer tests, Lachman tests, and pivot shift tests.

Likewise, we found no statistical significance when analyzing sex differences for other objective parameters, including neuromuscular testing, range of motion, and objective knee examination scores. The rates of graft ruptures and graft failures were also found to have no significant sex differences on meta-analysis. While the rates of revision surgeries were statistically significant (95% CI, 1.02-1.28), 23 of 26 of the studies actually did not report any statistical significance.

Despite our findings regarding statistical significance, subjective and functional outcomes have both been demonstrated to be inferior in females when compared with males. Previous studies analyzing the effect of objective knee examination findings on subjective and functional outcomes have echoed this lack of correlation.[30,141,151] In fact, it has been reported that only 36% of patients moderated their activity levels after ACL reconstruction based on knee function alone.[74,75] This highlights the presence of multiple other factors that have been attributed to the successful return to sports after ACL reconstruction. Some of the many factors include the presence of other associated injuries, preoperative knee self-efficacy, presence of rehabilitation goals, degree of self-motivation, athletic confidence, fear of reinjury, negativity in the athlete's outlook regarding the injury, readiness to return to sports, hedonic tone, level of preinjury sports participation, duration between injury and surgery, and other psychosocial support.[6,24,30,65,96,131] It is thus important for surgeons to assess and optimize these factors before surgery in order for patients to obtain best functional outcome after ACL reconstruction.

Statistically significant sex-based differences in subjective and functional outcomes include a lower Lysholm score, lower Tegner score, and lower rates of return to sports in females compared with males. Significantly, the Lysholm and the Tegner are the most frequently reported subjective knee score and activity scale, respectively. Other scores, such as the KOOS and Marx scores, have only been quantitatively reported in a small number of papers (including 4 papers for the KOOS scores and 3 papers for the Marx scores) for all domains and could thus be underpowered for the analysis. Notably, 3 of 4 of the studies that reported significant sex differences in KOOS did not report the information quantitatively. As a result, these studies could not be incorporated into the meta-analysis, possibly causing an underestimation of the effect of the sex difference.

Intrinsic differences within the different questionnaires and activity scales could account for the variation in sex differences. Particularly, the Lysholm score and the Tegner activity scale were originally designed to assess for ligament injuries of the knee. This is in contrast to the IKDC subjective knee evaluation and the KOOS, which were designed for all knee conditions.[73,146] Compared with the IKDC subjective knee evaluation and the KOOS, the Lysholm questionnaire is more directed toward the function of the ACL, with 40% of the score being allocated to the sensation of giving way or locking of the knee. Differences also exist between the Tegner activity scale and the Marx activity scale, where the Tegner is targeted to the level of sports participation while the Marx reports the frequency of sports participation regardless of the level of competitiveness. This difference allows the Tegner activity scale to be more reflective of the actual rates of return to preinjury sports after ACL reconstruction, which is a function of multiple factors as illustrated previously.

Although we did not analyze the effects of these factors on subjective and functional sex differences, meta-regression in this study did identify several significant moderators for the heterogeneity across the studies incorporated. Regarding the choice of graft, the use of hamstring versus patellar tendon served as a significant moderator for sex differences in the single-legged hop test. Studies that had a higher proportion of hamstring grafts tended to report inferior results in female patients. This is similar to multiple other studies that have reported inferior results in females when hamstring grafts are used compared with patellar tendon grafts, although this effect has yet to be reported for neuromuscular function.[19,27,48] No other outcomes were moderated by the choice of hamstring or patellar tendon grafts. The proportions of autografts and primary surgeries performed were also significant moderators for sex differences. Further subgroup analysis for each of these surgeries could be performed to analyze for the variations in sex differences between grafts and types of surgeries.

Other significant moderators for sex differences include patient and study characteristics. Interestingly, age appeared to be a significant moderator. Studies with a lower mean age tended to report inferior results in males, whereas studies with a higher mean age tended to report inferior results in females. To our knowledge, this effect has yet to be studied in any other published literature and could benefit from further research. Additionally, the year of publication affects the degree of sex differences reported in the literature and was found to be a significant moderator of both subjective and objective parameters. Significantly, recent publications have found comparable objective parameters such as extension loss and quadriceps testing when comparing between sexes. This was in contrast to earlier publications, where females were reported to have greater incidences of extension loss and deficits in quadriceps testing compared with males. However, recent publications also showed more significant sex differences, with females having inferior results compared with males as detected in Tegner scores. The comparable objective findings could reflect the evolution of ACL reconstruction techniques, with recent techniques being equally effective in both males and females,[104] whereas the subjective difference could have arisen due to greater research efforts in postoperative functional level of patients and also the increase in the number of studies that controlled for other variables in the investigation of sex differences.

Indeed, although this study is the first comprehensive meta-analysis and systematic review of all the available literature on sex differences after ACL reconstructions, this study faces several limitations. Although the reporting and publication bias is minimized in the study, as evident by the Egger test, the inclusion of all available studies with sex-specific outcomes on ACL reconstructions could have introduced certain confounders that were not controlled in the original studies. However, these effects should have been minimized with the large number of studies as well as sample sizes. Additionally, the relative heterogeneity in the assessment and reporting of outcomes precluded more rigorous and robust analysis. Multiple definitions have been used for the various outcome variables throughout the literature. In this review, results of the outcome variables have been extracted according to each study's definition, and that could have introduced other sources of variability that could not be detected in this meta-analysis. Rigorous analysis and the development of definitions to standardize each of these variables would be beneficial in future assessment and reporting of outcomes in ACL studies. The level of evidence of this review is limited by the presence of adequately powered trials investigating the effect of sex in the current literature. The number of studies for each level of evidence, as per the primary objectives of the studies, were as follows: level 1 (n = 10), level 2 (n = 42), level 3 (n = 38), and level 4 (n = 45).

This systematic review and meta-analysis indicates that the current knowledge regarding sex differences is still in its infancy. More research is needed to analyze factors that could influence the effect of sex in ACL reconstructions, such as graft choice, other variables affecting subjective and functional outcomes, and the precise components of the functional scoring systems in which patient sex exerts an effect. The need for research is highlighted by the fact that this meta-analysis is the first that has reviewed and highlighted sex differences in the subjective and functional outcomes.

CONCLUSION

This comprehensive systematic review and meta-analysis is the first available in the current literature that has included all available studies with reported sex-specific clinical outcomes after ACL reconstruction. Females showed comparable or inferior results in all outcomes analyzed. No statistically significant sex difference was identified in most of the objective parameters. However, subjective and functional outcomes were shown to be poorer in females, including lower Lysholm scores, lower Tegner scores, and reduced ability to return to sports. Further investigation is required to ascertain the cause of inferior functional scores in females, as we did not find any difference in objective parameters.

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