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Improvement Trajectories in Patient-Reported Outcomes Between Males and Females After Anterior Cruciate Ligament Reconstruction

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Context: Patient-reported outcomes (PROs) are used to track recovery and inform clinical decision-making after anterior cruciate ligament reconstruction (ACLR). Whether sex influences the trajectory of improvements in PROs over time post-ACLR remains unclear.

Objectives: To (1) examine the effect of sex on the association between months post-ACLR and Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL) scores in individuals with ACLR and (2) assess sex differences in the KOOS QOL score at selected timepoints post-ACLR.

Design: Cross-sectional study.

Setting: Laboratory.

Patients or Other Participants: A total of 133 females (20 ± 3 years) and 85 males (22 ± 4 years) within 6 to 60 months of primary, unilateral ACLR.

Main Outcome Measure(s): The KOOS QOL was completed at a single follow-up timepoint post-ACLR. A multivariate linear regression model was calculated to assess the interaction of sex on the association between months post-ACLR and KOOS QOL score. Sex-specific linear regression models were then used to predict KOOS QOL estimated marginal means at each clinical timepoint (6, 12, 24, 36, 48, and 60 months post-ACLR) and compare the sexes.

Results: In the primary model ($R^2 = 0.16$, $P < .0001$), a significant interaction existed between sex and time post-ACLR ($\beta = -0.46$, $P < .01$). Greater months post-ACLR were associated with better KOOS QOL scores for males ($R^2 = 0.29$, $\beta = 0.69$, $P < .001$); months post-ACLR was a weaker predictor of KOOS QOL scores for females ($R^2 = 0.04$, $\beta = 0.23$, $P < .02$). Estimated marginal means for KOOS QOL scores were greater for males than females at 36 months ($t_{210} = 2.76$, $P < .01$), 48 months ($t_{210} = 3.02$, $P < .01$), and 60 months ($t_{210} = 3.09$, $P = .02$) post-ACLR.

Conclusions: Males exhibited PRO improvement post-ACLR as the months post-ACLR increased, whereas females did not demonstrate the same magnitude of linear increase in KOOS QOL score. Females may require extended intervention to improve clinical outcomes post-ACLR and address a plateau in QOL score.

Key Words: self-reported outcomes, Knee injury and Osteoarthritis Outcome Quality of Life score, sex differences

Key Points

- Males displayed better improvement trajectories on the Knee injury and Osteoarthritis Outcome Score Quality of Life subscale than females after anterior cruciate ligament reconstruction (ACLR).
- Females reported worse quality-of-life scores than males at 36, 48, and 60 months after ACLR.
- To improve long-term quality of life after ACLR, females may require extended clinical intervention to address worse patient-reported outcomes than males in the first 5 years after ACLR.

Patient-reported outcomes (PROs) are critical for monitoring recovery and the effectiveness of an intervention for improving pain, symptoms, function, and quality of life (QOL) after joint injury.[1] Worse PROs after anterior cruciate ligament reconstruction (ACLR) have been associated with deleterious biological joint tissue changes,[2,3] suggesting that PROs are an easily implemented and important clinical indicator of the underlying development of posttraumatic osteoarthritis (PTOA), which is a common long-term condition in those with ACLR.[4] Therefore, understanding the factors related to changes in PROs after ACLR is important for developing the most effective interventions to maximize long-term clinical outcomes. Previous authors have demonstrated that females were at higher risk of sustaining anterior cruciate ligament (ACL) injury,[5] and recent health insurance data suggested that females were also more likely than males to be diagnosed with PTOA within 5 years of ACLR.[6]

Table 1. Descriptive Statistics by Sex (Mean ± SD)

Variable	Males (n = 85)	Females (n = 133)	*P* Value
Age, y	22.48 ± 4.41	20.20 ± 2.80	<.0001[a]
Body mass index, kg/m^2	25.57 ± 3.63	23.74 ± 3.38	<.001[a]
Months since anterior cruciate ligament reconstruction	17 ± 16	20 ± 16	.13
Knee injury and Osteoarthritis Outcome Score Quality of Life subscale score	67.07 ± 20.55	66.85 ± 17.54	.93

[a] Significant sex difference.

Females differed in their symptomatic presentation and overall response to musculoskeletal diseases compared with males[7]; therefore, sex should be considered a factor in clinical rehabilitation outcomes, including self-reported progress. Further, whether sex influences improvements in PROs over time after ACLR remains unclear. Thus, understanding the effect of sex on changes in PROs after ACLR is important for developing sex-specific rehabilitation strategies to maximize long-term health outcomes after ACLR.

Approximately 43% of patients continued to describe clinically relevant knee-related symptoms at 2 years after ACLR, and the prevalence of knee-related symptoms at the 6-year follow-up examination was relatively similar to that at the 2-year follow-up (ie, 39%).[8] Similarly, QOL assessed with the Knee injury and Osteoarthritis Outcomes Score (KOOS) improved between the preoperative and 2 years post-ACLR timepoints, yet KOOS scores remained stable at the 2-, 6-, and 10-year post-ACLR follow-up examinations.[9] Overall, these data suggest that the greatest improvements in PROs occurred in the first 2 years after ACLR and then plateaued after the 2-year post-ACLR follow-up examination. Still, whether males and females demonstrate similar trajectories of improvement after ACLR is unknown.

Conclusions drawn from earlier studies evaluating sex differences in PROs after ACLR are ambiguous. Researchers[10] who conducted a systematic review of 13 studies found no clinically meaningful PROs differences between the sexes; nonetheless, the included studies were performed at various timepoints between 2 and 7 years post-ACLR, and the authors used inconsistent survey measures. Similarly, investigators[11] of a separate systematic review observed no conclusive sex differences for health-related QOL in a subanalysis of 5 studies examining data collected from cross-sectional studies between 5 and 16 years post-ACLR. However, these systematic reviews included cross-sectional studies of various sample sizes and a variety of PROs to measure QOL at different timepoints post-ACLR, which may have limited the ability to detect sex differences in the trajectories over time. Conversely, others[12,13] have determined that females consistently scored worse on the KOOS Sport and Recreation subscale preoperatively and at 1, 2, and 5 years post-ACLR, indicating that sex may influence changes in PROs over time. Hence, we need to evaluate the influence of sex on the association between PROs and time post-ACLR at clinically relevant timepoints post-ACLR using a consistent PRO measure. Understanding the influence of sex on the trajectory of improvement in PROs over time is important to identify patients who are at risk of long-term, suboptimal QOL and develop personalized intervention strategies to optimize their outcomes.

The purpose of our study was to assess the effect of sex on the association between months post-ACLR and KOOS QOL scores in a cross-sectional sample of individuals with ACLR. We hypothesized that sex would influence the association between the KOOS QOL score and time post-ACLR, with males demonstrating a stronger association between a better KOOS QOL score at more months post-ACLR than females. The secondary purpose was to characterize sex differences in the KOOS QOL score at 6, 12, 24, 36, 48, and 60 months post-ACLR. We proposed that females would report lower mean KOOS QOL scores than males at each timepoint.

METHODS

Study Design

We retrospectively combined data from multiple projects conducted in the same laboratory that collected PROs and time post-ACLR in both males and females for a single, cross-sectional analysis. If multiple responses were available from a single participant as part of a longitudinal trial, only the earliest timepoint post-ACLR was used to ensure that no duplicated responses were included (ie, no within-person correlation would be present). We focused on the KOOS QOL score collected at a single timepoint occurring within 6 to 60 months post-ACLR. All participants provided written informed consent, and all methods were approved by the university's biomedical institutional review board.

Participants

Participants were recruited from a variety of sources, including the community, recreational clubs, intercollegiate athletics, and a local orthopaedic clinic, to maximize the generalizability of our cohort. We included all participants from the aforementioned studies who were between 16 and 35 years of age and within 6 to 60 months of primary, unilateral ACLR. Excluded were individuals with a history of lower extremity orthopaedic surgery before or after ACLR and those who required multiligament reconstruction at the time of ACLR, were pregnant or planned to become pregnant, or had radiographic evidence of knee OA at the time of testing. All participants had completed formal physical therapy and returned to unrestricted physical activity at the time of study enrollment. Demographic information including age, sex, body mass index (BMI), and months post-ACLR are provided in Table 1. Bins were created to visualize sex-specific frequencies of months post-ACLR at common clinical timepoints (Figure 1).

The KOOS QOL Measure

We used the KOOS QOL subscale to assess PROs, as previous investigators[14] have demonstrated its validity and reliability for assessing knee-related patient outcomes. Further, the KOOS QOL is the most responsive KOOS

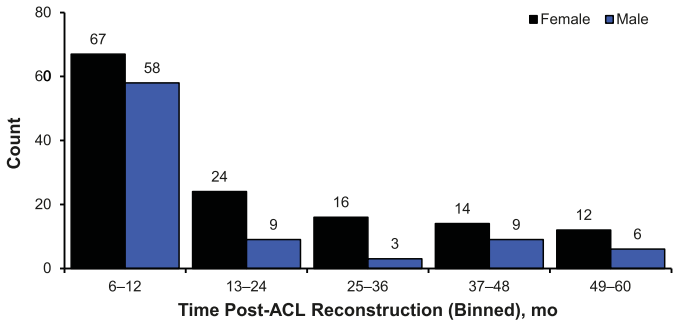

Figure 1. Sex-specific frequencies of months post-anterior cruciate ligament reconstruction (ACLR). Bins were created to display the distribution of males and females represented at common clinical timepoints within the cross-sectional sample (6–12, 13–24, 25–36, 37–48, and 49–60 months).

subscale to changes over time.[14] The QOL subscale consists of 4 knee-specific questions answered on a 5-point Likert scale, with the final score transformed into a score of 1% to 100%, with lower scores indicating clinical concern.[15] All participants answered the KOOS QOL subscale electronically at a single timepoint between 6 and 60 months post-ACLR; therefore, no within-person correlation is present in these data.

Statistical Analyses

Descriptive statistics are supplied by sex for age, BMI, months post-ACLR, and KOOS QOL score (Table 1). Between-sexes differences were assessed using independent *t* tests for each predictor.

Primary Analysis: Linear Regression Model to Predict KOOS QOL Scores

We generated a multiple linear regression model to evaluate the interaction between sex and time post-ACLR (months), modeled continuously, on KOOS QOL scores. The model was constructed with main effects for both explanatory variables of interest (ie, time post-ACLR and sex), as well as the interaction between time post-ACLR and sex, modeled to predict the criterion variable KOOS QOL score. Additionally, sex-specific simple linear regression models were fitted to measure the association between months post-ACLR and KOOS QOL score. We provide R^2, the unstandardized β coefficients, and corresponding 95% CIs for the primary model. A 2-sided α level of .05 was set a priori, and statistical analyses were performed in R Studio (version 1.3.1056; The R Project for Statistical Computing).

Sensitivity Analysis

Greater BMI and age are recognized as risk factors for the development of chronic poor knee-related outcomes.[16] A preliminary analysis showed that these outcomes differed by sex in our sample. Therefore, we assessed BMI and age as demographic covariates using hierarchically structured multiple linear regression models. The primary explanatory variables of interest (ie, time post-ACLR, sex, and the interaction between time post-ACLR and sex) were included in each model along with age and BMI—separately as well as simultaneously—in models for KOOS QOL scores. Changes in R^2 and β coefficients were supplied for the additional models in reference to the primary model.

Secondary Analysis: Sex Differences in the KOOS QOL Score at Clinical Timepoints

Linear combinations of the coefficients produced by the multiple linear regression equations from the primary analysis were specified to produce sex-specific model-estimated marginal means for the KOOS QOL score at selected clinically relevant timepoints (6, 12, 24, 36, 48, and 60 months post-ACLR). Between-sexes differences were identified through a statistical contrast at each clinical timepoint, recognizing a 2-sided α level of .05 (ie, no adjustment was performed for multiple comparisons). Model-estimated marginal means and standard errors will be reported by sex at each clinical timepoint. Only statistically significant differences will appear in the narrative.

Post Hoc Analysis: Time Post-ACLR and Sex on All Other KOOS Subscale Scores

In our primary analysis, males and females displayed differences in KOOS QOL trajectories after ACLR. Hence, the primary and secondary analyses were replicated for the remaining 4 KOOS subscales (Activities of Daily Living, Sport and Recreation, Pain, and Symptoms) to supply a comprehensive appraisal of sex differences in all other subscale scores post-ACLR. Multiple linear regression models were used to determine the interaction between time post-ACLR (months) and sex, modeled continuously, on the Activities of Daily Living, Sport and Recreation, Pain, and Symptoms KOOS subscale scores. The models were constructed with the main effects of time post-ACLR and sex, as well as the interaction between time post-ACLR and sex, modeled separately to predict each KOOS subscale score. We reported unstandardized β coefficients and corresponding *P* values for each model. Secondly, linear regression equations for each KOOS subscale were specified to provide model-estimated marginal means by sex at the following timepoints: 6, 12, 24, 36, 48, and 60 months post-ACLR. Statistical contrasts assessed between-sexes differences at each clinical timepoint, using a 2-sided α level of .05 (ie, no adjustment was performed for multiple comparisons). Both model-estimated marginal means and standard errors are given by sex at each clinical timepoint.

RESULTS

Participants

A total of 218 participants were included in the cross-sectional study: 133 females (61.0%) and 85 males (39.0%; Table 1). No individuals were excluded due to radiographic evidence of knee OA. Further, no outliers were detected for any of the predictor variables. Male participants were older (22.48 ± 4.41 versus 20.20 ± 2.80 years, respectively; $P < .0001$) and had greater BMI (25.57 ± 3.63 versus 23.74 ± 3.38 kg/m^2, respectively; $P < .001$; Table 1) than females. No between-sexes differences were found in the time post-ACLR (males $= 17 \pm 16$ versus females $= 20 \pm 16$ months post-ACLR, $P = .13$). Overall, no differences in KOOS

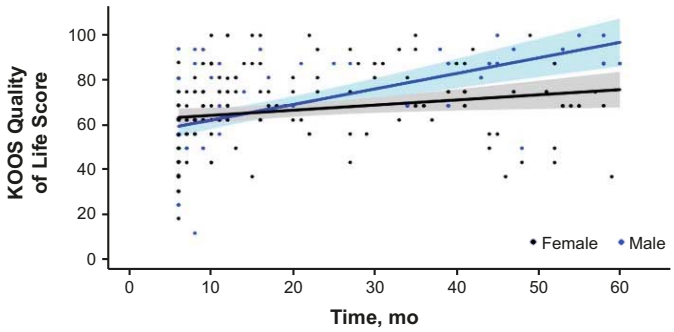

Figure 2. Predicted regression lines for time, sex, and time × sex on Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QOL). Shaded regions represent the 95% CI surrounding the association between months post-anterior cruciate ligament reconstruction (ACLR) and KOOS QOL for males (blue) and females (gray).

QOL scores were present between sexes (males = 67.07 ± 20.55 versus females = 66.85 ± 17.54, $P = .93$).

Primary Analysis: Time Post-ACLR and Sex

In the primary model, a significant interaction existed between time post-ACLR and sex ($\beta = -0.46$, $P < .01$). More months post-ACLR were moderately associated with a better KOOS QOL score for males ($R^2 = 0.29$, $\beta = 0.69$, $P < .001$), whereas females exhibited a weaker association ($R^2 = 0.04$, $\beta = 0.23$, $P = .02$; Figure 2). The interaction between time post-ACLR and sex remained associated with the KOOS QOL score after controlling for age ($P = .004$) and BMI ($P = .003$; Table 2).

Secondary Analysis: Sex Differences in the KOOS QOL Score at 6, 12, 24, 36, 48, and 60 Months Post-ACLR

Males demonstrated greater estimated KOOS QOL scores at 36 months (80.37 ± 2.94 versus 70.47 ± 2.11, respectively; $P < .01$), 48 months (88.63 ± 4.13 versus 73.20 ± 3.01, respectively; $P < .01$), and 60 months (96.90 ± 5.42 versus 75.93 ± 4.03, respectively; $P < .01$) post-ACLR than females (Table 3; Supplemental Figure 2). No differences were observed at 6, 12, or 24 months post-ACLR, but it is noteworthy that females had greater estimated KOOS QOL scores than males at 6 months (females = 63.64 ± 2.00 versus 59.71 ± 2.26, respectively; $P = .19$) and 12 months (65.01 ± 1.68 versus 63.84 ± 1.96, respectively; $P = .65$; Table 3). Males displayed greater estimated KOOS QOL scores than females at 24 months (72.10 ± 2.06 versus 67.74 ± 1.54, respectively; $P = .09$; Table 3).

Post Hoc Analysis: Effects of Time Post-ACLR and Sex on All Other KOOS Subscale Scores

A significant interaction was evident between sex and time post-ACLR for the KOOS Sport and Recreation ($\beta = -0.19$, $P < .0001$) and Symptoms ($\beta = -0.51$, $P < .0001$) subscale scores (see Supplemental Table 1, available online at https://doi.org/10.4085/1062-6050-0093.22.S1; see Supplemental Figure 1, available online at https://doi.org/10.4085/1062-6050-0093.22.S2). No differences in timepoint estimated marginal means were identified between males and females for the Activities of Daily Living, Sport and Recreation, or Pain KOOS subscale scores. However, KOOS Symptoms scores were higher for males than females at 36 months (88.67 ± 2.26 versus 79.24 ± 1.62, respectively; $P < .0001$), 48 months (92.51 ± 3.16 versus 74.79 ± 2.31, respectively; $P < .0001$), and 60 months (96.36 ± 4.16 versus 72.57 ± 3.09, respectively; $P < .0001$) post-ACLR (see Supplemental Table 1).

DISCUSSION

Consistent with our primary hypothesis, males showed greater improvements in KOOS QOL with increasing time post-ACLR, whereas females demonstrated a weak association between improvements in KOOS QOL score with increasing time post-ACLR, suggesting a plateau in QOL score over time. Furthermore, females exhibited lower KOOS QOL scores at 36 months post-ACLR, indicating that these data were collected well after most individuals had completed formal rehabilitation and returned to unrestricted activity.[17] We chose to focus our primary analysis on KOOS QOL score, as KOOS QOL is the most responsive subscale,[14] yet our post hoc findings provided overall support for the results of the primary analysis. Specifically, males displayed greater improvements than females on the KOOS Sport and Recreation and Symptoms subscales with more time post-ACLR. These differences in PROs suggest that males and females had different long-term recovery trajectories after ACLR. Previous researchers[18] assessing PROs in patients with arthroscopic meniscal repair noted the minimally important clinical difference for the KOOS QOL score was 16.9. Our model-estimated marginal means indicated sex differences of 15.43 and 20.67 on the KOOS QOL subscale at 48 and 60 months post-ACLR, respectively. Therefore, the KOOS QOL sex differences in our study tended to be most clinically meaningful at the later timepoints post-ACLR. This cross-sectional analysis is important in justifying the need to evaluate sex differences using longitudinal studies and to understand the unique combination of biological and functional mechanisms that may contribute to these sex

Table 2. Regression Model Comparison for Sensitivity Analysis β (Standard Error)

Predictor Variable	Primary Model	Model Adjusted for Age	BMI	Age and BMI
Sex	6.70 (3.63)	5.39 (3.78)	6.68 (3.66)	5.38 (3.81)
Months post-ACLR	0.69 (0.12)[a]	0.66 (0.12)[a]	0.69 (0.12)[a]	0.66 (0.12)[a]
Sex × months post-ACLR	−0.46 (0.15)[a]	−0.44 (0.15)[a]	−0.46 (0.15)[a]	−0.44 (0.15)[a]
Age	NA	−0.42 (0.34)	NA	−0.42 (0.34)
BMI	NA	NA	−0.02 (0.34)	−0.01 (0.34)
Change in R^2	NA	0.006	<0.0001	0.006

Abbreviations: ACLR, anterior cruciate ligament reconstruction; BMI, body mass index; NA, not applicable.
[a] $P < .01$.

Table 3. Model-Estimated Marginal Means (Standard Error) for Knee injury and Osteoarthritis Outcome Score Quality of Life Scores at Selected Timepoints

Months Post-Anterior Cruciate Ligament Reconstruction	Males	Females	Mean Difference	*P* Value
6	59.71 (2.26)	63.64 (2.00)	−3.93 (3.02)	.19
12	63.84 (1.96)	65.01 (1.68)	−1.18 (2.58)	.65
24	72.10 (2.06)	67.74 (1.54)	4.37 (2.58)	.09
36	80.37 (2.94)	70.47 (2.11)	9.90 (3.62)	<.01[a]
48	88.63 (4.13)	73.20 (3.01)	15.43 (5.11)	<.01[a]
60	96.90 (5.42)	75.93 (4.03)	20.96 (6.75)	<.01[a]

[a] $P < .01$.

differences. Our results signal that the biological variable of sex must be considered in future analyses of PROs after ACLR. Finally, future researchers may seek to develop specific interventions to optimize long-term QOL and improve women's health after ACL injury and ACLR.

Although the mechanisms causing sex differences in PROs after ACLR remain unclear, authors[19–23] have described differences in the functional, psychological, and biological responses to ACLR between the sexes, which may contribute to the sex differences we identified in PROs. Adequate quadriceps function is critical for physical performance, as diminished quadriceps function impairs function in daily activities and complex, sport-specific tasks after ACLR.[24] Quadriceps weakness is also associated with worse PROs[25,26] and deficits in clinical outcomes such as hop testing[27,28] after ACLR. Females had poorer quadriceps function than males in the first 12 months post-ACLR,[19,20] and their performance on the single-legged hop in the ACLR limb between 1 and 2 years post-ACLR was worse than in males.[21] Increased difficulty for females in regaining sufficient quadriceps strength at the same clinical timepoints as males and possible sex differences in the psychological response post-ACLR[22] may contribute to greater interlimb asymmetries in functional performance and influence the ability to return to sport.[29] Therefore, future investigators may pursue methods to specifically optimize strength in females after ACLR to ensure that they achieve similar functional performance benchmarks as males. Additionally, biological responses to ACL injury and ACLR differ between males and females, which may also contribute to worse KOOS QOL scores after ACLR for females. In particular, higher urinary concentrations of biomarkers of type II cartilage breakdown (CTX-II) are associated with the development and progression of knee OA.[30] Higher concentrations of urinary CTX-II in females at the time of ACLR are more strongly associated with worse KOOS QOL scores at 2 years post-ACLR than in males.[23] Further, we should continue to evaluate differences in the biological response to injury between sexes to determine if sex-specific biological factors may improve outcomes after ACLR in females. Sex-specific progressions have been advocated in functional rehabilitation for patients with total knee arthroplasty[31]; similarly, females may benefit from extended rehabilitation post-ACLR to address persistent KOOS QOL deficits.

Our cross-sectional study was unique, as we assessed sex differences in KOOS QOL scores at different timepoints throughout the first 60 months post-ACLR; however, several limitations should be noted to inform future research. The KOOS was initially validated in a sample of 9 men and 12 women who underwent ACLR.[14] To our knowledge, no inherent sex biases have been reported for the KOOS QOL subscale; nonetheless, earlier authors[3] suggested that the biological process of pain and experience of pain differs between the sexes[2] and may contribute to the sex differences in self-reported KOOS QOL scores we identified. Differences in how males and females experience and report pain after ACLR are understudied and would benefit from additional examination. Males exhibited greater BMI than females (Table 1); yet when included as a covariate, BMI did not influence the relationship between months post-ACLR and KOOS QOL scores. Male participants (22.48 ± 4.41 years) were older than females (20.20 ± 2.80 years), and younger age has been associated with a greater risk of reinjury within 5 years.[33] The age difference between the sexes was consistent with prior literature[34] that supported males typically being older at the time of ACL injury; after controlling for age, no change in the interaction effect was found. Further, earlier investigators determined that females participated in less physical activity after ACLR than healthy control individuals.[35] Future authors should assess the sex-specific effect of physical activity on PROs after ACLR. Finally, our study was cross-sectional, and we did not longitudinally evaluate how the KOOS QOL score changed over time in each person. We also acknowledge that our sample consisted of 61% female ACLR patients, and the sample was specifically skewed toward more female participants in the range of 25 to 36 months post-ACLR. A longitudinal cohort is needed if we are to understand sex differences in long-term QOL that may be time dependent. Future researchers should identify mechanisms that influence sex-specific recovery progress post-ACLR.

A higher KOOS QOL score was more strongly associated with greater months post-ACLR in males than in females. Females had lower KOOS QOL scores between 3 and 5 years post-ACLR. These differences in PROs suggest that males and females have different trajectories for recovery after ACLR, with males more likely to continue to improve over time, whereas females may tend to plateau. Clinicians should consider that rehabilitation progress may differ between males and females, with the possibility that females require extended rehabilitation or different clinical interventions after ACLR to maximize improvements in long-term QOL.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Interaction Effect and Estimated Marginal Means for Knee injury and Osteoarthritis Outcome Score (KOOS) Subscales at Selected Timepoints.

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Supplemental Figure 1. Predicted regression lines for time, sex, and time × sex on Knee injury and Osteoarthritis Outcome Score (KOOS) Subscales. Shaded regions represent the 95% CI surrounding the association between months post-anterior cruciate ligament reconstruction and KOOS (A) Activities of Daily Living, (B) Sport and Recreation, (C) Pain, and (D) Symptoms subscales for males (blue) and females (gray).

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Supplemental Figure 2. Model-estimated marginal means by sex for Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life at selected timepoints for males (blue) and females (black). An asterisk represents a statistically significant sex difference at a single timepoint ($P < .01$).

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