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Clinically relevant subgroups exist among athletes who have ruptured their anterior cruciate ligaments: A Delaware-Oslo Cohort Study

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Abstract

Objective: Identify subgroups of ACL injured individuals based on patient characteristics, self-reported outcomes, and functional performance at baseline and to associate subgroups with long-term outcomes after ACL rupture.

Methods: 293 participants (45.7% male, 26.2 ± 9.4 years, 58 ± 35 days from injury) were enrolled after effusion, pain, and range of motion impairments were resolved and quadriceps strength was at least 70% of the uninvolved limb. Mixture modeling was used to uncover latent subgroups without a prior group classification using probabilistic assignment. Variables include demographics, functional testing, and self-reported outcome measures. Radiographic evidence of OA (i.e., Kellgren-Lawrence (KL) grade of ≥ 1) in the involved knee at 5 years after injury was the primary outcome of interest. Chi square tests assessed differences in involved knee radiographic OA presence between subgroups at 5 years after ACL rupture. Secondary outcomes of interest included radiographic OA in the uninvolved knee, return to preinjury sport by 2 years, operative status, and clinical OA (classified using Luyten et al. criteria) at 5 years.

Results: Four distinct subgroups exist after ACL rupture (*Younger good self-report*; *Younger poor self-report*; *Older, poor self-report*; *Older good self-report*) with 30%, 31%, 47%, and 53% having involved knee OA respectively. Percentage of radiographic OA was not significantly different between the groups (p=0.059).

Conclusion: The prevalence of OA in all subgroups is highly concerning. These results suggest there are unique subgroupings of individuals that may guide treatment after ACL rupture and reconstruction by providing support for developing a patient-centered approach.

Significance and Innovation

- While the *Older good self-report* group had the highest prevalence of OA at 5 years, the prevalence of OA at 5 years in the two younger subgroups is highly concerning.
- Using subgroup analyses to relate clinical characteristics to subsequent development of post-traumatic OA is an important step in identifying associations between subgroups and long-term outcomes and providing appropriate targets for rehabilitation.
- The four subgroups uncovered may assist in targeting clinical treatments that are individualized after ACL rupture.

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Introduction

Anterior cruciate ligament (ACL) ruptures are one of the most common traumatic knee joint injuries in adolescents and young adults. Post-traumatic osteoarthritis (PTOA) in the knee joint is one of many concerning long-term outcomes facing individuals who have torn their ACL. Recent data suggest that 50-80% of individuals develop PTOA within 10 years of ACL reconstruction (ACLR).[1–3] Most who undergo ACLR are young and active,[4] leaving them at a high risk of developing PTOA in young adulthood. These data also suggest there are some individuals who are successful in avoiding some of the most devastating long-term outcomes, suggesting a need for early identification of individuals who are most at risk. Identifying relevant clinical characteristics of patients who may be on a trajectory to developing PTOA is a critical step towards early detection of at-risk individuals and may provide insights into prevention.

Immediate and long-term outcomes after ACLR are highly variable. When considering metrics of return to sport, 65% of individuals return to their preinjury level of sport, with only 55% of athletes returning to competitive level of sport.[5] Overall reinjury rates are estimated at 15%, increasing to 23% for individuals younger than 25 who return to sport.[6] Previous work has identified individuals who are copers, those resuming prior activity level with dynamic knee stability, and noncopers, those who demonstrate dynamic knee instability and poor clinical presentation.[7] Copers have better outcomes after ACL rupture compared to noncopers across functional tests and patient-reported outcome measures.[8–10] Collectively, these differences suggest there may be homogenous subgroups that exist among ACL injured individuals that may help explain the heterogeneity seen in long-term outcomes.[11]

The objectives of rehabilitation after ACL injury are similar across patients: restore range of motion and minimize effusion, restore quadriceps strength, and when ready, return to sport or recreational activity. Clinical test batteries assist in ensuring patients do not return to sport or activity level until risk of re-rupture is minimized. However, there are no test batteries or clinical prediction rules to assist in identifying risk for PTOA or other long-term deficits. Further, the presence of subgroups may identify individuals who are at greater or lesser risk for negative long-term outcomes enabling insight into targeted treatments.

The primary purpose of this study was to identify if subgroups of ACL injured individuals exist based on personal characteristics, self-reported outcomes, and functional performance measures. The secondary purpose was to determine if associations exist between these latent subgroups and long-term outcomes including (1) development of radiographic PTOA of the involved knee as the primary long-term outcome, and (2) radiographic PTOA of the uninvolved knee, return to preinjury sport level by 2 years, operative status (i.e., has the participant undergone ACLR by 2 years), and clinical OA (classified using Luyten et al. criteria)[12] as additional outcomes. Identifying subgroups based on commonly measured clinical characteristics is an important step in pinpointing rehabilitation strategies for each group, moving ACL rehabilitation towards a more patient-centered approach.

Methods

This study was an analysis of 293 patients (Figure 1) enrolled in the Delaware-Oslo ACL prospective cohort study. Patients included were recruited between 2006 and 2012 from both the University of Delaware in Newark, Delaware, USA and the Norwegian

Sports Medicine Clinic in Oslo, Norway with previously reported the 5 years outcomes.[13,14] Individuals were screened for outliers among all variables using histograms and boxplots, and 7 individuals were removed (2 based on days from surgery, and 5 based on age).

Participants

Participants were included in the parent cohort study if they had an ACL rupture, achieved a quiet knee based on a clinical examination (i.e., minimal to no pain or effusion[15]), were between 13 and 60 years old, and participated in Level I and II[16] (e.g., cutting, jumping, pivoting) sports for ≥ 50 hours a year prior to injury. Injuries were verified using magnetic resonance imaging (MRI) and increased anterior knee joint laxity measured with a KT-1000 arthrometer (MED Metric). Participants with previous history of ACL rupture were included, but participants with any other previous injuries or surgeries to either knee, bilateral injuries, concomitant grade III ligament injuries, repairable menisci on MRI, full-thickness articular cartilage damage, or fracture were excluded. All participants provided informed consent and the study was approved by the Institutional Review Board at the University of Delaware or the Regional Committee for Medical Research Ethics South East Norway.

Treatment Algorithm

Participants underwent baseline testing when effusion was resolved, and they could hop on the involved knee without pain (58 ± 35 days from injury). Participants were classified as potential copers or non-copers at baseline based on previously established criteria.[7] They underwent a 5-week program of neuromuscular and strength training prior to the decision for ACLR or continued non-operative management.[17]

Patients who were managed non-operatively continued progressive rehabilitation for another 3-4 months and were assessed at follow-ups the same as the operative group.

Assessments and Outcome Variables

Variables selected for assessments and outcomes were collected in the parent cohort study and based on prior literature as those that predicted success after ACL rupture or had an association with PTOA.[18,19] Measures included in the model were baseline patient characteristics (age, sex, pre-injury level, concomitant injuries, and history of previous ACL rupture), days from injury to baseline evaluation and body mass index (BMI). Further variables included at baseline were quadriceps strength, single and triple hop for distance, Knee Outcome Survey- Activity of Daily Living Scale (KOS-ADLS), global rating scale of perceived function (GRS), and the International Knee Documentation Committee Subjective Knee Form (IKDC).

Quadriceps strength was measured differently at the two sites; in Delaware and in Oslo. In Delaware, strength was measured using an electromechanical dynamometer (Kin-com; DJO Global, Chula Vista, CA, USA or System 3; Biodex, Shirley, NY, USA) during a maximal voluntary isometric contraction (MVIC) knee extension test. Participants were seated with hips and knees flexed to 90 degrees, and the dynamometer's axis of rotation aligned with the axis rotation of the knee joint. The leg was strapped in at the upper thigh, pelvis, and shank to minimize accessory motion during testing. Participants completed 3 submaximal practice trials, followed by 3 maximal effort trials on the uninvolved limb first, then on the involved limb. In Oslo, strength was assessed using an isokinetic dynamometer (Biodex 6000; Biodex Medical Systems). Participants performed 4 submaximal practice trials, then 5 recorded maximal effort repetitions for the uninvolved limb first, then the involved limb. Due to this, quadriceps strength is reported as a limb symmetry index (LSI), calculated as the involved limb maximum torque divided by the uninvolved limb maximum torque expressed as a percentage.

Single-hop testing consisted of 4 hop tests (single, crossover, triple, 6-meter timed).[20,21] We only included the single hop for distance and triple hop for distance in the model, as hop scores for triple hop, crossover hop, and timed hop were highly correlated (all $r \varepsilon 0.95$). Each hop test consisted of 2 practice trials for familiarization, followed by 2 recorded trials. Uninvolved limbs were tested first, followed by the involved limbs. Hop tests were also reported using LSI scores, calculated from the average of 2 trials per limb (involved/uninvolved x 100).

A variety of valid, reliable, and responsive self-reported outcome measures were used to assess self-reported knee function at baseline. The KOS-ADLS assesses knee function during activities of daily living.[22] A higher number represents less limitation in knee function in daily life, with 100% indicating no limitation. GRS is a single item rating from 0 to 100% which rates overall knee function compared to knee function prior to injury.[23] A score closer to 100% indicates better perceived function. Finally, the IKDC measures knee specific symptoms, function, and sports activities. The IKDC is scored from 0-100, with scores closer to 100 indicating higher subjective reports of knee function.[24,25]

As participants were measured at 5-years from baseline, we wanted to capture individuals who are on the trajectory for early radiographic OA beyond those who already have the definite presence of osteophytes. Presence of joint characteristics consistent with the development of radiographic OA in the involved knee, therefore, was operationally defined as a KL grade of ≥ 1. Patients returned 5-years from baseline, after either ACLR or nonoperative management, for standardized bilateral posterior-anterior (PA) bent knee radiographs. Radiographs were taken at 5-years only, there were no radiographs collected at baseline. Participants in Delaware were assessed using the Lyon-Schuss protocol[26] where the x-ray beam was adjusted for each image to align with the medial tibial plateau. Participants were positioned with a 30-degree knee flexion angle with pelvis, thigh, and patella against the film cassette and coplanar with the tips of the great toes. In Oslo, a fixed flexion protocol was used with a 10-degree caudal bean angulation and a SynaFlexer Positioning Frame (Synarc, Inc, Denmark) to make knee alignment and angulation reproducible.[27,28] Levels of OA in the tibiofemoral joint were graded by an experienced radiologist with high intrarater reliability (kappa=0.77) using the Kellgren-Lawrence (KL) system in the tibiofemoral joint.[29]

Secondary outcomes included radiographic contralateral knee OA (KL ≥ 1) at 5 years. Presence of clinical knee OA was determined at 5 years using Luyten et al. criteria which require 2 of 4 KOOS subscales to score ≤85%, and consistent with our previous publications.[12,30] New injuries to the ipsilateral and contralateral knee were reported at the 5-year follow up. Return to preinjury sport level by 2 years was assessed using the question 'Has the subject returned to at least pre-injury level?' with a dichotomous yes/no, and operative status. Operative status was defined as undergoing ACLR or remaining nonoperatively managed by 2 years after baseline.

Statistical Analysis

We identified the number of latent subgroups present at baseline using mixture modeling,[31,32] which can include both continuous and categorical variables (Appendix A, Mplus; Muthén and Muthén, Los Angeles, CA). The model included the 13 previously described variables for subgroup identification and the long-term outcome (radiographic knee OA) was included as auxiliary variables[33] using the automatic BCH (Bolck, Croon & Hagenaars)[34,35] procedure. Individuals were assigned to a latent class based on their highest posterior probability. Missing data were handled using Mplus' maximum-likelihood estimator.

The number of subgroups was determined based on multiple factors, including fit criteria Akaike Information Criteria (AIC),[36] Bayesian Information Criteria (BIC),[37] sample-size adjusted Bayesian Information Criteria (ABIC),[37] evaluating class homogeneity by examining entropy, and tests of model comparison.[38,39] Lower scores are better for AIC, BIC, and ABIC, while a higher entropy[40] (between 0 and 1) indicates a better separation of the classes with a high level of cohesion within classes. Vuong-Lo-Mendell-Rubin (VLMR), Lo-Mendell-Rubin (LMR) likelihood ratio and the bootstrap Likelihood ratio tests were used to determine whether a model with k classes fits better than a model with k-1 classes.[39] Significant values (i.e., $p \leq 0.050$) indicate that a model with k classes fits better than a model with one class less. Finally, clinical relevance and class sizes (≥5% of the cohort in each group)[41] were evaluated by expert opinion to ensure the differences in group membership were clinically meaningful.

Variables used to form the subgroups and the primary long-term outcome were compared across subgroups within the mixed model. Secondary long-term outcomes were compared using a chi-square test for categorical variables and ANOVAs for continuous variables, with a Bonferroni correction applied to post-hoc testing (SPSS, Version 26). These comparisons were done after subgroup enumeration to prevent any influence on class performance. All variables were assessed for normality using boxplots and histograms prior to comparison across subgroups.

Results

293 participants (45.7% male, 26.2 ± 9.4 years, 58 ± 35 days from injury) were included in this study.

Model Fit Statistics

The best fitting model identified four latent subgroups (Appendix B) based on information criteria, class size, and clinical relevance. While a 5-subgroup model had the highest entropy, and lowest AIC, BIC, sample-size adjusted BIC, one of the classes only consisted of 8 individuals (<5% of the sample).[40] Therefore, a 4-subgroup model was chosen as it's entropy (0.82) was nearly identical (0.83), and the AIC, BIC, sample-size adjusted BIC, and VLMR likelihood ratio test were all lower than 2 and 3 group models.[36–39] The VLRM p-value was only significant in a 2-group model, and uninformative in the other models.[39]

Group Formation

The specific patient demographics at baseline are reported as probability weighted results (Table 1). Subgroups primarily differed on age (p<0.001) and self-reported outcomes (i.e., IKDC, KOS-ADLS, Global Rating Score; Table 1, p<0.001) at baseline. Group 1 (*Younger good self-report*; n=99 (34%)) and 2 (*Younger poor self-*

report; n=119 (41%)) were on average <25 years old, and group 3 (*Older poor self-report*; n=48 (16%)) and 4 (*Older good self-report*; n=27 (9%)) were on average over 30.

Latent Subgroups

The two younger subgroups were significantly younger than the two older subgroups (22.7 ± 0.9 and 24.6 ± 1.3 vs. 31.3 ± 2.7 and 36.3 ± 3.0; p<0.001). The *Younger good self-report* group and *Older poor self-report* group had higher percentages of male participants (62% and 69% vs. 47% and 33%; p<0.03), the *Older good self-report* group had a higher percentage of female participants (67%; p<0.01), and the *Younger poor self-report* group was evenly split. The *Older poor self-report* group had a higher BMI than the other subgroups (26.2 ± 0.9; p=0.003). The *Younger good self-report* group had the best functional and self-reported outcomes (Table 1; p<0.02), while the *Older poor self-report* group had the poorest functional and self-reported outcomes. The *Younger poor self-report* group had the second-best functional outcomes, but the *Older good self-report* group had the second-best self-reported outcomes (Figure 2).

Long-Term Outcomes

The *Younger good self-report* group had the lowest percentage of involved knee radiographic OA (30%) while the *Older poor self-report* group and *Older good self-report* group had higher incidences (Table 2; Figures 2, 3).

Subgroups were statistically different in the development of uninvolved knee radiographic OA (Table 2). Pairwise comparisons revealed that the *Younger good self-report* group had a lower prevalence of uninvolved knee radiographic OA than both the *Older poor self-report* group (p=0.031) and the *Older good self-report* group (p=0.001).

Differences were also identified between the *Younger poor self-report* group and the *Older good self-report* group (p=0.006), where the *Younger good self-report* group had the lowest percentage of uninvolved radiographic OA (17%), and the *Older good self-report* group had the greatest.

The development of clinical OA was statistically different between subgroups (p=0.017). The *Younger good self-report* group had the lowest rate of clinical OA (11%), which was significantly lower than the *Younger poor self-report* group (25%; p=0.019) and the *Older poor self-report* group (33%; p=0.007). There was a significant difference among subgroups in operative status at 2 years. The *Older good self-report* group had a significantly lower percentage of individuals who underwent operative management (44%) compared to the *Older poor self-report* (79%; p=0.004), *Younger poor self-report* group (74%; p=0.011) and the *Younger good self-report* subgroups (72%; p=0.019). There was no significant difference between subgroups in new injuries at 5 years, including ipsilateral and contralateral ACL re-ruptures (p>0.31, Table 1).

Discussion

The purpose of this study was twofold: (1) to identify if latent subgroups of ACL injured individuals exist based on patient characteristics, self-reported outcome measures, and functional performance at baseline shortly after their ACL ruptures and (2) to determine associations between subgroups and PTOA and clinically relevant long-term outcomes 2-5 years after ACL injury. We identified four subgroups at baseline within our population of individuals after ACL rupture (Table 1, Figure 2): *Younger good self-report*; *Younger poor self-report*; *Older poor self-report*; *Older good self-report*. The latent subgroups found in this study demonstrated distinct characteristics that may provide insight into both variability in patient outcomes and clinical rehabilitation targets for patients within each subgroup. Each latent subgroup demonstrated differences in prevalence of uninvolved knee radiographic OA and clinical OA at 5-years, percentage undergoing operative management by 2-years, and potential coper status at baseline.

The *Younger good self-report* and *Younger poor self-report* subgroups were the largest subgroups (34% and 41% of the cohort, respectively). The *Younger good self-report* group was the highest performing group on all functional and self-reported outcome measures and were predominately classified as potential copers (88%) at baseline (Table 1). Both young subgroups had a comparable majority who underwent operative management (*Younger good self-report*: 72%, *Younger poor self-report*: 74%). Long-term, the *Younger good self-report* group had the lowest percentage of involved and uninvolved radiographic OA, and the lowest percentage of clinical OA.

The *Younger poor-self report* group was the closest to the group average in all baseline characteristics (Figure 2). The *Younger poor-self report* group had acceptable outcomes on all functional measures at baseline, ranging from 88.2 $\pm$ 1.6 LSI for quadriceps strength up to 93.5 $\pm$ 1.1 LSI for the triple hop. Self-reported outcome measures, however, were second-to-lowest in this group. The lowest mean score was 66.7 $\pm$ 1.7 for IKDC and highest mean score was 83.2 $\pm$ 1.8 for the KOS-ADLS. These data indicate that although the patients were on the cusp of 'normal' RTS values for function at baseline, they had substantial knee-related symptoms that may have ultimately hindered their successful return to pre-injury activity levels at 2 years after ACL rupture.

The *Older poor self-report* and *Older good self-report* subgroups made up smaller percentages (16 and 9%, respectfully) of the sample. Notably, the *Older poor self-report* group shared similar rates of individuals who chose operative management (79%) as the 2 younger subgroups. The *Older good self-report*, conversely, had the lowest percentage of individuals choosing operative management (44%). Like their larger, younger counterpart subgroups, the older subgroups differed primarily on self-reported outcome measures at baseline (Table 1). The *Older poor self-report* group had the lowest scores across all self-reported outcome measures, representing the group with the poorest self-assessed function and functional performance. The *Older poor self-report* group scored significantly lower on the self-reported outcomes than the *Older good self-report* group. Interestingly, the *Older poor self-report* group's functional test outcomes were not significantly different from the *Older good self-report* group. The *Older poor self-report* group also had the highest percentage of people who reported early clinical knee OA. Further, the *Older poor self-report* group had the highest percentage of individuals who chose operative management (79%) and the lowest percentage of potential copers (2%). The *Older poor self-report* group having the lowest self-reported outcome measures may partially explain the high percentage of operative management, as these individuals may have had knee-related symptoms preventing them from success with non-operative treatment.

The *Older good self-report* group had the highest percentage of both involved and uninvolved knee radiographic OA. The uninvolved knees in this group had a higher percentage of radiographic OA than the involved knee, suggesting the ACL injury may not be the main factor in this group. Further, all KL grades in the uninvolved knee for all groups were at a KL 1, suggesting a relatively early-stage disease process (Table 2). The *Older good self-report* group had no level I athletes to begin with and was predominately female compared to the other subgroups. They also had the highest percentage of individuals who chose nonoperative management (54%). The self-reported outcome measures of the *Older good self-report* group, however, exceeded those of the *Younger poor self-report* group and the *Older poor self-report* group and were the second highest in the sample, but also had the lowest quadriceps LSI at baseline. Clinically, this subgroup may represent individuals who may benefit from education on the risk of the development of PTOA at baseline, and the importance of maintaining quadriceps strength to support long-term knee joint health.[30,42] Future work assessing qualitative reason for selecting to reduce level of sport after ACL rupture is needed to confirm our speculation.

Though it may be expected that the oldest subgroup had the highest percentage of individuals with radiographic changes in both the involved and uninvolved knees, the percentages of individuals meeting our definition of knee OA in the younger subgroups is highly concerning. At a mean age of 22 years old, our youngest subgroup, the *Younger good self-report* group, demonstrated radiographic changes in 30% of ipsilateral and 17% of contralateral knees at 5 years after ACL rupture. These numbers are consistent with literature suggesting that anywhere from 30-90% of individuals develop knee OA within 10 years of ACL rupture.[1,43,44] The individuals in the older 2 subgroups that have radiographic OA data were an average of 38 and 43 years old at 5 years respectively, falling far below the age range of idiopathic OA, which ranges between 55-64 years old.[45] Our results stress the need for widespread patient education regarding the risk of developing OA after knee joint injury for all patients after ACL rupture, regardless of subgroup.[46] Properly understanding long-term risks may in turn affect decision-making with respect to return to activity.

While age seems to be a differentiating factor among the subgroups, there may be other underlying mechanisms related to lifestyle that further affect the long-term outcomes. When considering the *Older poor self-report* and *Older good self-report* subgroups, the subgroups with the smallest number of individuals and older ages, lifestyle changes may explain some of the long-term outcomes. The *Older poor self-report* and *Older good self-report* subgroups had the lowest percentage of Level I athletes at baseline, which may explain why they also had the highest percentage of individuals returning to pre-injury sport level as the pre-injury level was inherently not as demanding on the knee. The individuals in these subgroups, being older, may want to balance knee limitations and an active lifestyle. Qualitative research on how goals change after ACLR has suggested a shift in some patients from return to sports participation as a primary goal to return to an active everyday life.[47] Even among young athletes, a common theme of ‘balancing physical activity and future knee health’ emerges as individuals consider their ACL injury in terms of long-term knee health.[48]

Clinically, it is important to continue to assess self-reported outcome measures throughout the course of rehabilitation. Not only does it give a snapshot of where the patients feel they are, but often there are cases where the self-reported outcome measures and functional performance do not line up. We do not know what caused individuals to report their knee outcomes as lower than their measured functional outcomes. This phenomenon was particularly evident in the *Younger poor self-report* group and *Older poor self-report* group. These subgroups had the lowest scores on self-reported outcome measures, however their means on functional testing were not the lowest of the 4 subgroups. In fact, the *Younger poor self-report* group functionally was the closest to the average of the total study sample (i.e., all subgroups combined) and had the second highest functional outcomes after the *Younger good self-report* group. This may be explained by recent data that suggests an association between psychological factors (e.g., kinesiophobia) and return to pre-injury sport after ACL reconstruction.[49] While psychological factors were not directly measured at baseline in the current study, literature does suggest a relationship between psychological factors and a number of functional outcomes including RTS[50,51] and second injury.[52] This literature, however, is conflicting with data suggesting both high and low fear have negative relationships with outcomes.[52,53] Self-reported function, specifically psychological factors, is an important next step in understanding the presence of subgroups in individuals after ACL rupture.

The results of our study suggest that there are subgroupings of individuals that may guide treatment after ACL rupture and reconstruction by providing support for developing a patient-centered approach. While returning to preinjury sport level may be a goal for some individuals, symptom management and returning a generally active lifestyle may be the goal for others as they transition away from previous sport participation. This analysis provides support for developing an individual-based approach, where all aspects of baseline evaluation are incorporated to inform treatment decisions. This includes assessing multiple domains of self-reported outcome measures, function, patient age, and most importantly patient goals. Treatment should also include education on long-term outcomes after ACL rupture (PTOA), but also on outcomes most relevant to themselves and their individual goals. Trajectories of self-reported function 5-years after treatment has been assessed in the Delaware-Oslo cohort using the IKDC score to assess factors relating to response after ACL injury and treatment.[11] The current paper differs as it uses a variety of demographics and functional and self-report outcomes to form baseline subgroups, and does not assess trajectories but rather determines baseline subgroup associations with 2-5 year outcomes.

There are limitations to consider when interpreting the data presented in this study. First, patients may fit into more than one subgroup clinically, and therefore treatment should continue to be multi-modal and not just target one specific area. Both participants and variables included in this analysis were limited by the inclusion criteria and study design of the parent study, so results may not be generalizable to the broader patient population. Strength testing did differ slightly between sites, so data were reported using limb symmetry measures to ensure strength data are comparable. Inclusion criteria were stringent, and individuals with more extensive concomitant injuries were excluded. Return to sport was defined as the first exposure to Level I or II sport and did not necessarily mean full match play. Only the self-reported outcome component of the Luyten et al.[12] criteria was applied to the sample, and the full criteria have not yet been validated. Similarly, the term ‘clinical knee OA’ was used to describe the partial application of the Luyten et al. [12] criteria in our sample to be consistent with previous published work from our cohort.[30] However, this may also be described as early knee OA symptoms and is consistent with the heterogeneity in early OA definitions for this population described by the most recent OPTIKNEE consensus.[54] Future research should work to develop a definition and classification criteria to best identify individuals with post-traumatic knee OA at early disease stage. Radiographs were only assessed at 5-years, therefore we do not know the KL grade of the knee joint at baseline. Finally, radiographic OA was defined as KL grade ≥1, which is not defined as 'definite osteophytes' like in grade 2. However, KL grade ≥1 has been proposed as an alternative cutoff due to the demonstration of early joint disease and association with the ultimate progression of radiographic features.[55,56] Finally, this study was a secondary analysis of a cohort study and was not originally powered to detect differences between subgroups within the larger group, therefore caution should be used when interpreting and applying results.

Conclusion

Four distinct subgroups were identified at baseline with clinically meaningful differences in long-term outcomes: *Younger good self-report*; *Younger poor self-report*; *Older poor self-report*; *Older good self-report*. The *Younger good self-report* group had the highest function, self-reported outcomes, and number of potential copers at baseline, along with the lowest percentage of involved and uninvolved radiographic OA and clinical OA long-term. The *Younger poor self-report* group was the closest to the total sample average in all variables at baseline and had the second lowest percentage of involved and uninvolved knee radiographic OA. The *Older poor self-report* group had the lowest percentage of potential copers at baseline, highest percentage returning to preinjury sport level at 2 years, choosing operative management, and of clinical OA at 5 years. Finally, the *Older good self-report* group had the lowest percentage of individuals who chose operative management but the highest percentage of involved and uninvolved knee radiographic OA.

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Table 1. Comparisons of participant characteristics ((n) % or mean ± SD) and subgroup comparisons (1-4).

	Total Sample	**1 Younger good self-report** (n=99)	**2 Younger poor self-report** (n=119)	**3 Older poor self-report** (n=48)	**4 Older good self-report** (n=27)	P-Value	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Demographics at Baseline												
Age, years	26.2 ± 9.4	22.7 ± 0.9	24.6 ± 1.3	31.3 ± 2.7	36.3 ± 3.0	**<0.001**	0.30	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.020**
Sex, F:M	134:159	38:61	63:56	15:33	18:9	**0.004**	**0.03**	0.40	**0.01**	**0.01**	0.20	**0.003**
BMI, kg/m^2	24.7 ± 4.0	24.4 ± 0.5	24.4 ± 0.4	26.2 ± 0.9	24.7 ± 1.0	**0.040**	0.97	**0.03**	1.0	0.07	0.99	0.18
Days from Injury	56.6 ± 30.6	50.5 ± 3.1	56.4 ± 3.8	62.6 ± 7.2	69.3 ± 12.2	**0.020**	0.67	0.11	**0.04**	0.48	0.18	0.87
Pre-Injury Level, 1:2	203:90	86:13	87:32	30:18	0:27	**<0.001**	**0.01**	**<0.001**	**<0.001**	0.18	**<0.001**	**<0.001**
Concomitant Injury (y)	147 (50%)	46 (47%)	66 (55%)	29 (60%)	6 (22%)	**0.006**	0.19	0.11	**0.023**	0.56	**0.002**	**0.002**
Previous ACL Tear (y)	24 (8%)	11 (11%)	8 (7%)	5 (10%)	0 (0%)	0.24	--	--	--	--	--	--
Potential Coper (y)*	173 (59%)	87 (88%)	69 (58%)	1 (2%)	16 (59%)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.87	**<0.001**
Function at Baseline												
Quadriceps Strength	89.4 ± 11.0	94.0 ± 1.3	88.2 ± 1.6	85.1 ± 1.5	85.1 ± 2.1	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.22	0.22	0.99
Single Hop	89.7 ± 11.9	94.7 ± 1.1	89.8 ± 1.5	80.4 ± 3.23	85.0 ± 2.7	**<0.001**	**0.02**	**<0.001**	**<0.001**	**<0.001**	0.13	0.30
Timed Hop	94.0 ± 9.3	98.5 ± 1.0	93.5 ± 1.1	87.3 ± 2.8	88.8 ± 2.6	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.002**	**0.02**	0.99
Self-Reported Outcome Measures at Baseline												
IKDC	70.7 ± 12.55	81.6 ± 2.0	66.7 ± 1.7	53.6 ± 1.7	77.6 ± 2.3	**<0.001**	**<0.001**	**<0.001**	**0.01**	**<0.001**	**<0.001**	**<0.001**
KOS-ADLS	84.6 ± 10.6	93.3 ± 1.2	83.2 ± 1.8	66.9 ± 1.4	90.1 ± 1.4	**<0.001**	**<0.001**	**<0.001**	**0.02**	**<0.001**	**<0.001**	**<0.001**
Global Rating Score	78.4 ± 14.0	86.7 ± 1.7	75.8 ± 1.4	62.9 ± 4.1	86.0 ± 2.3	**<0.001**	**<0.001**	**<0.001**	1.0	**<0.001**	**<0.001**	**<0.001**
Secondary Outcomes at 5 Years: New Injuries												
Ipsilateral ACL tear (y)	23 (9.7%)	12 (12.2%)	8 (10.7%)	3 (7.5%)	0 (0%)	0.31	--	--	--	--	--	--
Contralateral ACL Tear (y)	15 (6.4%)	7 (9.3%)	6 (6.3%)	1 (2.5%)	1 (4.2%)	0.51	--	--	--	--	--	--
All second injuries (y)	54 (23.1%)	20 (24.2%)	23 (26.7%)	8 (20%)	3 (12.5%)	0.50	--	--	--	--	--	--

SD, standard deviation; F:M, female: male; BMI, Body Mass Index; ACL, Anterior Cruciate Ligament; IKDC, International Knee Documentation Committee; KOS-ADLS, Knee Outcome Survey-Activity of Daily Living Subscale.
*potential coper is defined as: Knee Outcome Survey-Activity of Daily Living Scale (KOS-ADLS) scores ≥ 80%, global rating scale of perceived function (GRS) scores ≥ 60%, symmetry on the timed hop ≥ 80%, and ≤1 episode of knee giving way during activities of daily living

Table 2. Long-term outcomes based on group membership (n/total sample available at timepoint (%yes)).

	1 Younger good self-report group (n=99)	**2 Younger poor self-report group (n=119)**	**3 Older poor self-report (n=48)**	**4 Older good self-report (n=27)**	**P-value***
Radiographic OA- Involved N (%)	19/64 (30%)	24/77 (31%)	17/36 (47%)	10/19 (53%)	0.073
KL1	9	15	1	3	
KL2	9	8	13	7	
KL3	1	1	3	0	
Radiographic OA- Uninvolved N (%)	11/65 (17%)	18/76 (24%)	13/36 (36%)	11/19 (58%)	**0.004**
KL1	11	18	13	11	
KL2	0	0	0	0	
KL3	0	0	0	0	
Clinical OA	8/71 (11%)	24/95 (25%)	13/39 (33%)	6/24 (25%)	**0.017**
Return to Preinjury Sport Level	45/73 (62%)	53/91 (58%)	25/38 (66%)	13/20 (65%)	**0.013**
Operative Status	68/95 (72%)	86/117 (74%)	37/47 (79%)	12/26 (44%)	**0.039**

*Adjusted P-value reported; P-value is for chi-square analysis between presence of radiographic OA and subgroup, it does not take KL level into account. OA, osteoarthritis

Figure 1. Delaware-Oslo ACL Cohort Study Consort Diagram for data available at baseline subgroup formation and long-term outcomes.

Figure 2. Comparison of functional performance and self-reported outcomes among subgroups (colored lines) and the group average (dotted black line). Variables have been standardized and adjusted so that closer to the center represents better function or outcome. IKDC, international knee documentation committee; KOS-ADLS, knee outcome survey-activity of daily living subscale.

Figure 3. Group differences at baseline in function and self-reported outcomes (mean ± SD), primary outcome at 5 years, and secondary outcomes at 2 and 5 years between Subgroups**.** OA, osteoarthritis; ACLR, anterior cruciate ligament reconstruction**;** SD, standard deviation; IKDC, international knee documentation committee; KOS-ADLS, knee outcome survey-activity of daily living subscale**.**

Figure 1.

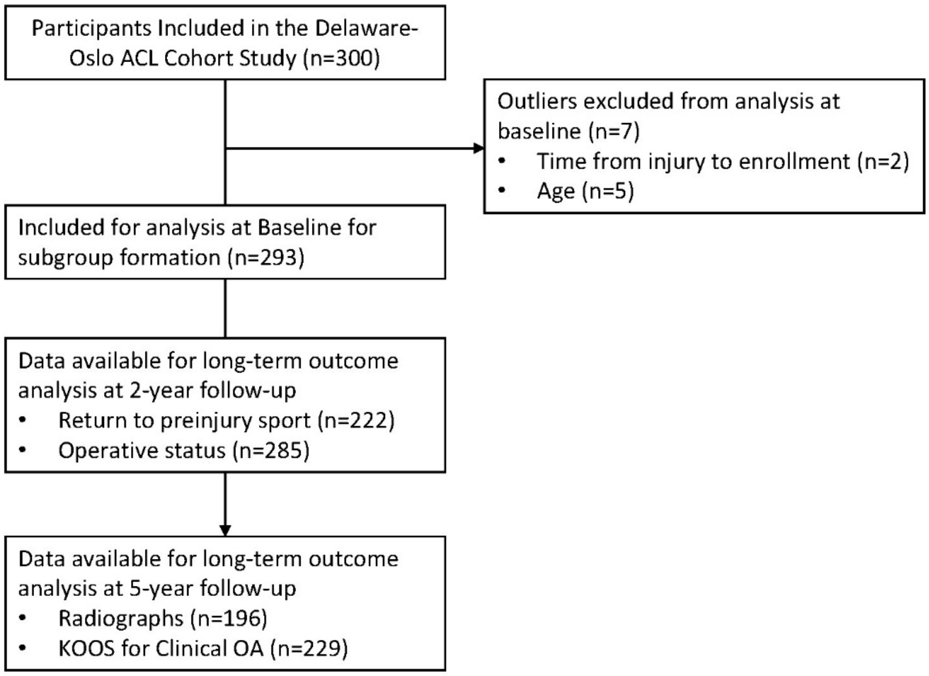


Figure 2.

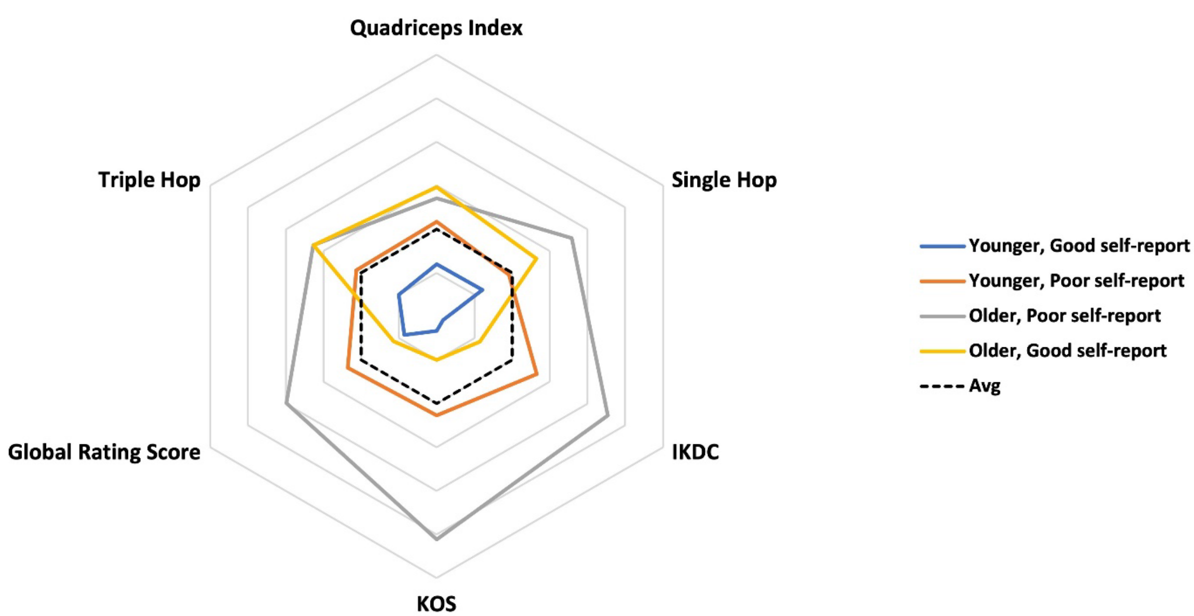
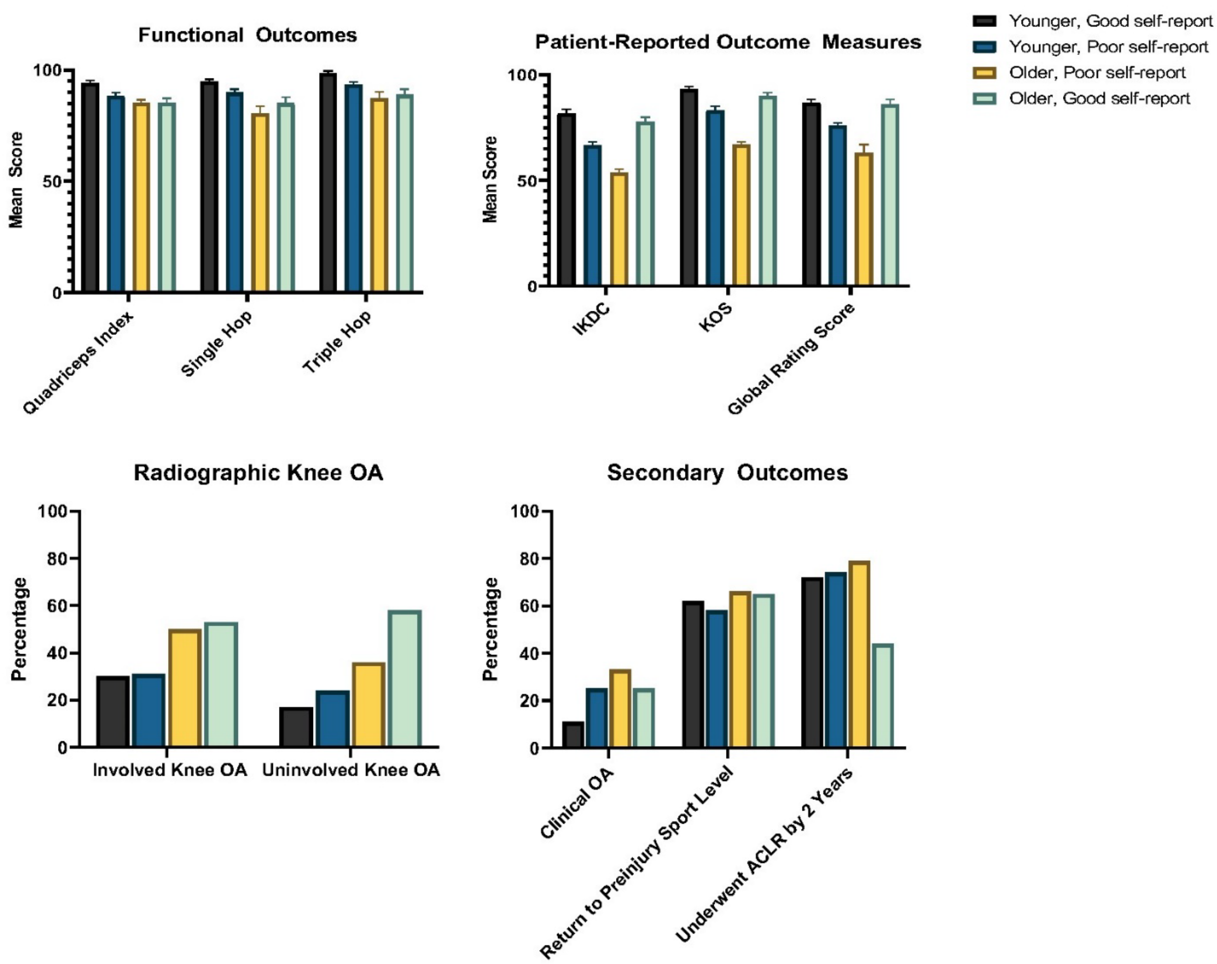


Figure 3.


Functional Outcomes
Mean Score
100
50
0
Quadriceps Index
Single Hop
Triple Hop
Patient-Reported Outcome Measures
Mean Score
100
50
0
IKDC
KOS
Global Rating Score
Younger, Good self-report
Younger, Poor self-report
Older, Poor self-report
Older, Good self-report
Radiographic Knee OA
Percentage
100
80
60
40
20
0
Involved Knee OA
Uninvolved Knee OA
Secondary Outcomes
Percentage
100
80
60
40
20
0
Clinical OA
Return to Preinjury Sport Level
Underwent ACLR by 2 Years