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Prognostic factors for tibiofemoral and patellofemoral osteoarthritis 32–37 years after anterior cruciate ligament injury managed with early surgical repair or rehabilitation alone

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S U M M A R Y

Objective: Explore prognostic factors for tibiofemoral (TFJ) and patellofemoral (PFJ) radiographic osteoarthritis (ROA) and 'symptoms plus ROA' (SOA), 32–37 years following anterior cruciate ligament (ACL) injury.
Design: Exploratory analysis, longitudinal cohort.
Methods: In 1980–1985, 251 patients aged 15–40 years with acute ACL rupture were allocated to early augmented or non-augmented repair (5 ± 4 days post-injury) plus rehabilitation, or rehabilitation alone. 127 of 190 participants who completed follow-up questionnaires were eligible. We classified ROA as TFJ/PFJ K&L Grade ≥2, and SOA as ROA plus pain and/or symptoms. Multivariable age-adjusted logistic regression investigated potential prognostic factors (assessed at 4 ± 1 year follow-up: ACL treatment, isokinetic quadriceps/hamstrings strength, single-leg-hop for distance, knee flexion/extension deficit, knee laxity, Tegner Activity Scale, Lysholm Scale; sex, baseline meniscus status).
Results: 127 patients were aged 58 ± 6 years; BMI 27 ± 4 kg/m^2; 28% female; 59% had TFJ-ROA, 48% had TFJ-SOA (including $n = 9$ knee-arthroplasties), 36% had PFJ-ROA; 27% had PFJ-SOA. Baseline meniscus surgery was a prognostic factor for TFJ-ROA (multivariable age-adjusted odds ratio (95% CI): 3.0 (1.2, 7.8)). A single-leg-hop limb symmetry index (LSI) < 90% was a prognostic factor for PFJ-ROA (5.1 (1.4, 18.7)) and PFJ-SOA (4.9 (1.2, 19.7)). Hamstrings strength LSI <90% was a prognostic factor for PFJ-SOA (5.0 (1.3, 19.3)). ACL treatment with rehabilitation-alone was associated with an 80% reduction in the odds of PFJ-SOA (0.2 (0.1–0.7)), compared with early ACL-repair.
Conclusions: These findings are hypothesis generating, research is needed to determine whether ACL-injured individuals with these characteristics benefit from interventions to prevent or delay the onset of osteoarthritis.

Introduction

Anterior cruciate ligament (ACL) injury is associated with an increased risk of tibiofemoral joint (TFJ) and patellofemoral joint (PFJ) osteoarthritis (OA)[1,2], and a 7-fold increased odds of total knee arthroplasty (TKA)[3]. Since ACL injury is most common in youth, people who develop OA after ACL injury are typically young or middle aged, and can experience prolonged disability with few effective treatment options[4,5]. People who develop knee OA in young or middle adulthood report difficulties participating in work and parenting roles, psychological distress and quality of life impairment[6–8]. Additionally, living with knee symptoms and radiographic OA (ROA) more than five years after ACL injury is associated with a lack of confidence in the knee, fear during exercise and limitations participating in desired recreational activities[8]. Individuals exposed to ACL injury represent an 'at-risk' population,

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who would benefit from targeted interventions to prevent the onset and progression of knee OA. To inform the design of such interventions, prospective studies investigating prognostic factors for TFJ and PFJ OA after ACL injury are needed.

A recent systematic review found that only two studies that investigated prognostic factors for TFJ ROA after ACL injury had an adequate sample size and drop-out rate, and adjusted for confounding factors[1]. Oiestad *et al.*, 2010 identified increased age and meniscal and/or chondral injury as prognostic factors for TFJ ROA 10–15 years after ACL surgery[9]. Shelbourne *et al.*, 2012 found that a postoperative knee flexion deficit, partial medial meniscectomy and chondral damage were prognostic factors for TFJ ROA 5–21 years after ACL surgery[10]. Only two studies assessed prognostic factors for PFJ ROA after ACL injury[1,11]. These studies identified increased age as a prognostic factor for PFJ ROA at 12-year follow-up[11] and no prognostic factors for PFJ ROA at a mean 10-years following ACL surgery[12]. Thus, the evidence assessing prognostic factors for ROA after ACL injury is limited, and many potential prognostic factors have not been investigated.

The evidence investigating prognostic factors for knee ROA plus self-reported symptoms (referred to as 'symptoms plus ROA (SOA)' from hereon) after ACL injury is even more limited. Only one study investigated prognostic factors for TFJ SOA and found that worse self-reported knee function 2 years after ACL surgery, and a loss of quadriceps strength between early and mid-term follow-up, were related to a higher odds of TFJ SOA[9]. No studies had assessed prognostic factors for PFJ SOA[1]. The limited research that is available suggests that approximately 50% of people with TFJ or PFJ ROA after ACL injury have knee symptoms[1]. There is strong evidence of the discord between ROA and patient-reported symptoms, and our ability to predict which people will develop SOA after ACL injury is poor.

Further research is needed to determine whether the choice of ACL treatment (ACL surgery vs non-surgical management) is related to the risk of OA, beyond 30 years of injury. A recent meta-analysis of five studies with 10–20 year follow-up, found a higher risk of ROA following ACL surgery compared to non-surgical management of ACL injury[13]. However, systematic reviews on this topic are limited by poor methodological quality studies, and retrospective designs subject to confounding and selection bias[13]. Short-term follow-up studies have identified greater cartilage loss and increased pro-inflammatory markers following early ACL surgery compared to non-operative management[14–16], however, prospective studies with longer-term follow-up are needed to determine whether ACL surgery is associated with an increased risk of osteoarthritis.

The purpose of this exploratory study was to identify prognostic factors for ROA and SOA of the TFJ and PFJ, 32–37 years following acute ACL injury. Our hypothesis was that we would identify prognostic factors for OA 32–37 years after ACL injury. Additionally, considering the poor association between ROA and SOA[1], we hypothesised that prognostic factors would differ for ROA and SOA.

Methods

Participants and design

This is an exploratory, secondary analysis of a prospective longitudinal cohort study. The long-term follow-up of a prospective longitudinal cohort study was granted ethical approval by the Regional Ethical committee of Linkoping, Dnr: 2017/119-31. In 1980–1985, 251 patients aged 15–40 years presented to the emergency department of Linköping Hospital (Sweden) with an acute ACL rupture (within 14 days of injury). All patients underwent an arthroscopic knee examination under anaesthesia at a mean(SD) 5(4) days after injury, to diagnose ACL and concomitant injury severity. Minor concomitant meniscal injuries were treated non-operatively, whilst more severe meniscal injuries were managed with surgical repair or partial meniscectomy, irrespective of ACL management strategy. Complete ruptures of the collateral ligaments were managed with surgical repair.

Based on an odd or even birth year, patients were allocated to 'early surgical repair' (acute diagnostic arthroscopy plus augmented or non-augmented ACL repair (mean 5 $\pm$ 4 days post-injury) +/− meniscus surgery, 6 weeks post-operative immobilisation followed by physiotherapist-supervised rehabilitation) or 'rehabilitation-alone' (diagnostic arthroscopy with or without concomittant meniscal surgery, plus 4–6 months of physiotherapist-supervised rehabilitation). ACL repair was performed using an open technique, augmented using a 1.5 cm wide strip of the iliotibial band, or non-augmented ($n = 19$ in total), as described previously[17,18]. Following surgery, patients were non-weight bearing in a long-leg cast for 6 weeks in 30 degrees of knee flexion, before undertaking approximately 9 months of physiotherapist-supervised structured rehabilitation. Patients allocated to rehabilitation-alone who experienced limitations participating in desired activities due to knee instability, were managed with delayed ACL surgery. Delayed ACL surgery comprised an open technique ACL reconstruction (open technique performed in the 1980's), followed by 6 weeks post-operative immobilisation.

A follow-up assessment was performed a mean 4 $\pm$ 1 years after ACL injury. During this assessment a range of knee measures were collected, including isokinetic quadriceps and hamstrings strength, a single-leg-hop for distance test, knee flexion and extension range of motion, the Stryker Knee Laxity Test, Tegner Activity Scale (TAS) and Lysholm Scale.

In 2017, 234 patients (10 no contact details, 7 deceased) were invited to complete a follow-up assessment, 32–37 years after ACL injury. Potential study participants were sent a study information sheet, consent form and paper questionnaire by post. Up to three reminder letters were sent if no response was received. Study participation comprised three components; a questionnaire, knee radiographs and a clinical assessment. Individuals could consent to take part in one, two or all of these components. We have published a study investigating prognostic factors for 32–37 year patient reported outcomes in the subgroup of participants who completed the follow-up questionnaire[34].

To be eligible for the current analysis, participants were required to have completed all 4-year follow-up assessments, and the questionnaires and knee radiographs at 32–37 year follow-up. Additional exclusion criteria were a non-acute ACL injury (i.e., enrolled into the study >21 days after ACL injury), or a comorbidity with potential for pain, functional or cognitive disability (e.g., stroke, rheumatoid arthritis, widespread joint pain).

Prognostic factors

Potential prognostic factors were identified through clinical reasoning and a review of the literature. This resulted in the identification of the following potential prognostic factors for inclusion in this study: participant sex; baseline meniscal status (dummy variable: no meniscus injury (reference category) vs non-surgically treated meniscus injury vs surgical treated meniscus injury); ACL management at 4-year follow-up (dummy variable: early ACL repair (reference category) vs delayed ACL reconstruction vs rehabilitation alone); 4-year isokinetic quadriceps and hamstrings strength[19] (strength deficit = a limb symmetry index (LSI) < 90%); 4-year single-leg-hop for distance[19] (reduced performance = LSI <90%); 4-year knee extension ($\geq 5°$ extension deficit (i.e., $-5°$ from neutral)) and flexion (<135 degrees of knee flexion) deficit; 4-year anterior-posterior knee laxity assessed using The Stryker Knee Laxity Tester[20] (deficit = side-to-side difference (SSD) >3 mm); 4-year activity level assessed with the Tegner Activity Scale (TAS)[21] (scores range from 0 (disability pension due to knee) to 10 (competition in elite sport), 0–5 represents non-participation in recreational or competitive sports); and 4-year self-reported knee function assessed with the Lysholm Scale (scores range from 0 (extreme disability) to 100 (no symptoms or disability) and have been categorised as excellent (95–100), good (84–94), fair (65–83), and poor (≤64))[18,22,23]. The assessment procedures and psychometric properties for these measures, as well as a rationale for the categorisation of variables, are described in Supplementary Appendix 1.

Radiographic and symptomatic osteoarthritis

A radiologist blinded to treatment allocation, graded plain weight-bearing radiographs using the Kellgren and Lawrence Scale[24]. Initial evaluation of the Kellgren and Lawrence Scale found good inter-rater and intra-rater reliability (correlation coefficients $r = 0.83$)[24]. A Kellgren and Lawrence Scale grade ≥2 of the TFJ or PFJ was classified as TFJ or PFJ ROA. Symptoms plus ROA (i.e., SOA) was defined as ROA plus knee pain and/or symptoms (defined as a ≥1-step decrease from the best response to ≥50% of items within the Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain and/or Symptoms subscales).

Statistical analysis

The distribution of continuous variables was assessed for normality using visual inspection (histograms, Q–Q plots) and statistical tests of normality (Kolmogorov–Smirnov and Shapiro–Wilk). Logistic regression assessed potential prognostic factors for TFJ and PFJ ROA and SOA. Odds ratio (OR) and 95% CIs are reported for crude and adjusted (including all other prognostic factors and age at injury) models, created for each potential prognostic factor. . Underlying assumptions for logistic regression were met, including linearity between independent and dependent variables, multivariate normality, multicollinearity, autocorrelation and homoscedasticity of residuals. Since participation in knee radiographs and 4-year follow-up formed the eligibility criteria for inclusion in this study, and there was no incomplete data for all potential prognostic factors, regression analysis was performed using a complete case analysis. One participant was excluded from the PFJ analysis as they were missing a PFJ radiograph. People who had TKA ($n = 9$) were classified as having both TFJ ROA and SOA and were excluded from the PFJ analyses. All analyses were performed using IBM SPSS Statistics 27 software.

Results

Participant characteristics

Of 234 potentially eligible patients, 190 (81%) completed the KOOS at 32–37 year follow-up. Of these, 153 (81%) had knee radiographs or a TKA on the index knee ($n = 9$), 127 (83%) of whom had completed 4-year follow-up and were included in the analyses (Fig. 1). Participants were aged a mean(SD) 58(6) years, with a BMI of 27(4) kg/m^2, and 28% were female. At 4-year follow-up, 59 (47%) had undergone early ACL repair, 60 (47%) had not had ACL surgery and 8 (6%) had a delayed ACL reconstruction prior to completing 4-year follow-up. The eight patients who had a delayed ACL reconstruction prior to 4-year follow-up had the surgery between 6 and 28 months (mean 15 months) after ACL injury (≥34 months prior to 4-year follow-up). Detailed participant characteristics are reported in Table I and outcomes from 4-year and 32–37 year follow-up are reported in Table II, stratified by knee OA status. Seventy participants (59%) had TFJ ROA, of whom 61 (87%) had TFJ SOA. Of the 41 (36%) participants with PFJ ROA, 31 (76%) had PFJ SOA. Twenty-nine (24%) individuals had both TFJ and PFJ ROA, and 24 (83%) of these individuals had knee symptoms (Fig. 2). Nine individuals had a TKA on their index knee, of whom four had also had TKA on their contralateral knee. Figure 2 depicts radiographic and symptomatic knee status at 32–37 year follow-up.

Of the 44 patients who declined participation or did not respond to the study invitation (Fig. 1), 39% were female compared to 28% of study participants. Compared to the study sample ($n = 127$), the 44 excluded patients had a similar age at injury (mean 23 vs 24 years), a similar proportion had baseline meniscal injury (50% vs 59%), meniscal surgery (55% vs 55%), pre-injury activity levels were similar (mean Tegner score 8 vs 8) and a similar proportion were managed with early ACL repair (48% vs 47%). The characteristics of the 66 patients that were excluded due to electing not to undergo a knee radiograph, not participating in 4-year follow-up, or meeting pre-specified exclusion criteria (Fig. 1) were also compared with the characteristics of study participants. The 66 excluded patients were similar in sex (29% vs 28% female), age at injury (mean 25 vs 24 years), baseline meniscal injury (60% vs 59%), meniscal surgery (55% vs 55%), and pre-injury activity level (Tegner mean score 8 vs 8). At 32–37 year follow-up excluded patients had a similar BMI (mean 26.6 vs 27.2 kg/m2), age (59 vs 58 years), history of contralateral injury (11% vs 12%), KOOS Symptoms score (mean 74 vs 69), KOOS Pain score (mean 81 vs 79), KOOS Sport/Rec score (mean 55 vs 51), KOOS QOL score (mean 55 vs 54), and ACL-QOL score (mean 70 vs 68). The only difference observed between groups was a smaller proportion undergoing early ACL repair amongst excluded patients (33% vs 47%).

Prognostic factors for TJF ROA

In the crude analyses, baseline meniscal injury was associated with greater odds of TFJ ROA (OR: 3.2 (95% CI: 1.3 to 8.3)), compared to no meniscal injury. However, the uncertainty of this effect increased in the adjusted model (Table III). Baseline meniscal surgery was related to a higher odds of TFJ ROA in the crude (3.2 (1.3, 7.7)) and adjusted (3.0 (1.2, 7.8)) analyses, compared to no meniscal injury or surgery (Table III).

Prognostic factors for TFJ SOA

The crude analysis found that a single-leg-hop LSI <90% was associated with a 3.0 (1.1–8.3) times higher odds of TFJ SOA, compared to a single-leg-hop LSI ≥90%. No prognostic factors for TFJ SOA remained in the adjusted analysis (Table III).

Prognostic factors for PFJ ROA

A single-leg-hop LSI <90% was associated with a 3.5 (1.2–9.9) times higher odds of PFJ ROA compared to a single-leg-hop LSI ≥90%, in the crude analysis (Table IV). The size of this effect increased in the adjusted model (5.1 (1.4–18.7)). An extension deficit was also associated with a higher odds of PFJ ROA in the crude analyses (3.0 (1.1–8.3)). However, the uncertainty of this effect increased in the adjusted model (3.6 (1.0, 13.5)).

Prognostic factors for PFJ SOA

Management with rehabilitation-alone at 4 year follow-up was associated with *reduced* odds of PFJ SOA in the crude (0.4 (0.2–0.9)) and adjusted (0.2 (0.1–0.7)) analyses, compared to undergoing

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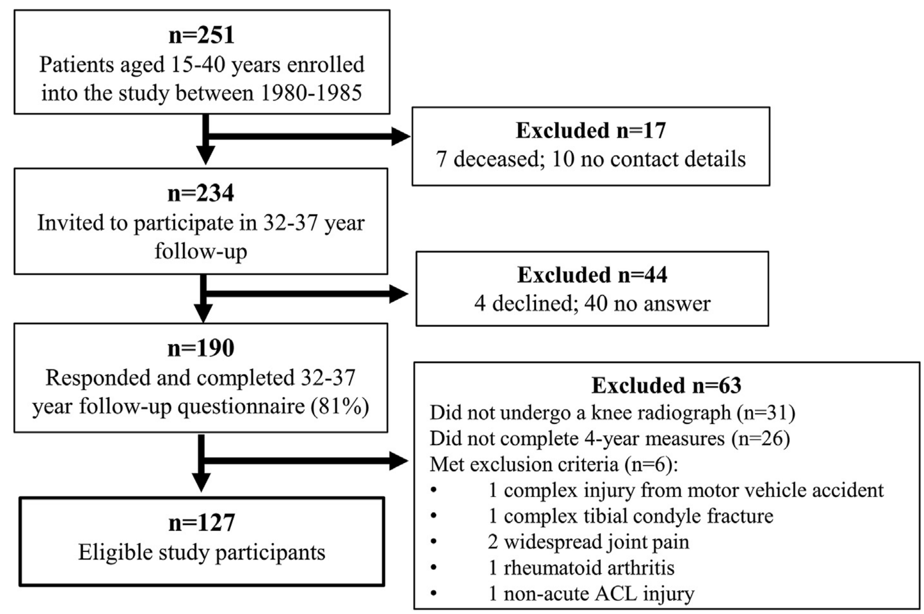

Fig. 1 OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Participant recruitment.

early ACL repair. A hamstring strength LSI <90% was associated with an increased odds of PFJ SOA in the crude (4.0 (1.4–11.0)) and adjusted (5.0 (1.3, 19.3)) analyses. A single-leg-hop LSI <90% was also a prognostic factor for PFJ SOA in the crude (3.4 (1.2–9.6)) and adjusted (4.9 (1.2, 19.7)) analyses.

Discussion

There is a need for an improved understanding of risk factors for osteoarthritis following ACL injury, to inform early interventions. In this exploratory analysis, a surgically treated meniscal injury at baseline (compared to no meniscal injury) was a prognostic factor for TFJ ROA. In comparison, no prognostic factors were identified for TFJ SOA in the adjusted analysis. Worse 4-year single-leg-hop distance was a prognostic factor for PFJ ROA and PFJ SOA. Management with rehabilitation-alone was associated with an 80% reduction in the odds of PFJ SOA, compared with undergoing early ACL repair. Reduced hamstrings strength was also a prognostic factor for PFJ SOA. These results are hypothesis generating and highlight the need for further research to determine whether targeting these prognostic factors has an impact on osteoarthritis incidence in ACL-injured individuals.

In the adjusted analysis, only meniscal surgery remained as a prognostic factor for TFJ ROA. This aligns with previous research that identified meniscal injury and surgery as prognostic factors for TFJ ROA in ACL injured individuals[25]. This may reflect meniscal injuries of a greater severity being treated with surgical management rather than the surgical management itself as a precursor to TFJ ROA. Importantly, meniscal injury or surgery were not prognostic factors for TFJ SOA, so the clinical relevance of this finding is unclear. It is possible that the relationship between meniscal status and TFJ SOA becomes less apparent with greater follow-up periods due to the confounding of other lifestyle and age-related prognostic factors for OA development. A recent study found that individuals were at greater risk of TKA if they had ACL reconstruction compared to the general population at ages 30–59 years, however, the risk was not elevated in those aged 60 years and above[26]. Thus, patients in our study with concomitant meniscal injury/surgery may have developed TFJ SOA at a younger age than those without, although this was not explored in our study.

We found that undergoing non-surgical management of ACL injury was associated with reduced odds of PFJ SOA compared with undergoing early ACL repair. Analysis of the KANON Trial found that people randomized to early ACL reconstruction had a greater loss of patella cartilage thickness at 2 and 5 year follow-up, compared to people randomized to rehabilitation and optional delayed ACL reconstruction[14]. Atypical for a young, active population, individuals treated with early ACL surgery experienced an annual loss of PFJ cartilage similar to individuals with established OA[14,15]. Notably, the proportion of people with patella cartilage loss after ACL surgery who subsequently develop PFJ SOA is unknown. However, loss of patella cartilage one-year after ACL injury has been identified as a prognostic factor for worse patient-reported function and symptoms three years after ACL injury[27], suggesting a potential association with PFJ SOA.

Another analysis of KANON Trial data found that people randomised to early ACL surgery had a greater concentration of inflammatory cytokines at 4-month, 8-month and 5-year follow-up, compared to those randomised to rehabilitation and optional delayed ACL surgery[16]. Inflammatory cytokines have been implicated in the process of OA development[28], and provide one potential explanation for the higher odds PFJ SOA in patients who underwent early ACL surgery. Other potential explanations include the prolonged period of minimal and altered weight-bearing that follows ACL surgery and the reduction in muscular strength observed in the postoperative period. In our study, post-operative

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	Total cohort $n = 127$	OA status at 32–37 year follow-up							
		TFJ ROA		TFJ SOA		PFJ ROA*		PFJ SOA*	
		Yes ($n = 79$)	No ($n = 48$)	Yes ($n = 61$)	No ($n = 66$)	Yes ($n = 41$)	No ($n = 74$)	Yes ($n = 31$)	No ($n = 84$)
Female sex	36 (28)	22 (28)	14 (29)	20 (33)	16 (24)	15 (37)	18 (24)	12 (39)	21 (25)
Age at injury (years)	23 (19, 28)	24 (20, 29)	22 (18, 28)	23 (20, 30)	22 (18, 28)	22 (19, 26)	23 (19, 28)	23 (19, 26)	22 (19, 28)
Baseline meniscus injury	75 (59)	55 (70)	20 (42)	39 (64)	36 (55)	24 (59)	44 (60)	18 (58)	50 (60)
Baseline meniscus surgery	41 (32)	30 (38)	11 (23)	20 (33)	21 (32)	13 (32)	25 (34)	9 (29)	29 (35)
Pre-injury activity level (TAS)	9 (7, 9)	9 (7, 9)	9 (7, 9)	8 (7, 9)	9 (7, 9)	9 (7, 9)	9 (7, 9)	9 (7, 9)	9 (7, 9)
History of regular tobacco use†	67 (53)	44 (56)	23 (48)	35 (57)	32 (49)	21 (51)	37 (50)	17 (55)	41 (49)
Age at 32–37 year FU (years)	57 (54, 62)	58 (55, 62)	56 (53, 61)	58 (55, 64)	57 (53, 61)	55 (53, 60)	57 (54, 62)	57 (53, 61)	57 (54, 62)
BMI at 32–37 year FU (kg/m^2)	27 (24, 29)	28 (25, 30)	26 (23, 28)	27 (25, 30)	26 (23, 28)	28 (24, 30)	27 (24, 28)	28 (25, 30)	27 (24, 28)
Contralateral ACL injury	15 (12)	9 (11)	6 (13)	6 (10)	9 (14)	6 (15)	8 (11)	5 (16)	9 (11)
ACL treatment at 4 year FU									
Early ACL repair	59 (47)	32 (41)	27 (56)	28 (46)	31 (47)	23 (56)	29 (39)	20 (65)	32 (38)
Delayed ACL reconstruction	8 (6)	6 (8)	2 (4)	4 (7)	4 (6)	3 (7)	5 (7)	1 (3)	7 (8)
Rehabilitation-alone	60 (47)	41 (52)	19 (40)	29 (48)	31 (47)	15 (37)	40 (54)	10 (32)	45 (54)

Descriptive statistics are reported as median (IQR) or count (%).
* Data from the $n = 9$ who had undergone knee arthroplasty were excluded.
† Assessed with the item: 'have you ever smoked/used snuff regularly, for at least 6 months (yes/no)'; OA = osteoarthritis; TFJ = tibiofemoral joint osteoarthritis; ROA = radiographic osteoarthritis; SOA = knee symptoms plus ROA; PFJ = patellofemoral joint; FU = follow-up; TAS = Tegner Activity Scale; BMI = body mass index; ACL = anterior cruciate ligament.

Table I OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Participant characteristics

	Total cohort $n = 127$	OA status at 32–37 year follow-up							
		TFJ ROA		TFJ SOA		PFJ ROA*		PFJ SOA*	
		Yes ($n = 79$)	No ($n = 48$)	Yes ($n = 61$)	No ($n = 66$)	Yes ($n = 41$)	No ($n = 74$)	Yes ($n = 31$)	No ($n = 84$)
4-year outcomes									
Quadriceps strength <90% LSI	36 (28)	14 (29)	22 (28)	16 (26)	20 (30)	11 (27)	22 (30)	7 (23)	26 (31)
Hamstrings strength <90% LSI	19 (15)	12 (15)	7 (15)	8 (13)	11 (17)	10 (24)	9 (12)	10 (32)	9 (11)
Single-leg-hop <90% LSI	20 (16)	14 (18)	6 (13)	14 (23)	6 (9)	11 (27)	7 (10)	9 (29)	9 (11)
Knee extension deficit (≥5deg‡)	25 (20)	16 (20)	9 (19)	14 (23)	11 (17)	11 (27)	8 (11)	8 (26)	11 (13)
Knee flexion deficit (<135deg‡)	39 (31)	27 (34)	12 (25)	21 (34)	18 (27)	12 (29)	22 (30)	8 (26)	26 (31)
Knee laxity (>3 mm SSD)	49 (39)	30 (38)	19 (40)	24 (39)	25 (38)	18 (44)	28 (38)	12 (39)	34 (41)
Lower activity level (TAS 0–5)	45 (35)	29 (37)	16 (33)	25 (41)	20 (30)	14 (34)	26 (35)	13 (42)	27 (32)
Fair/poor Lysholm score†	27 (21)	19 (24)	8 (17)	16 (26)	11 (17)	9 (22)	14 (19)	8 (26)	15 (18)
32–37 year outcomes									
KOOS Pain	86 (67, 97)	79 (66, 94)	92 (67, 100)	76 (58, 83)	94 (82, 100)	75 (58, 92)	89 (78, 97)	64 (50, 78)	92 (78, 97)
KOOS Symptoms	75 (54, 86)	66 (46, 82)	82 (61, 93)	56 (43, 75)	82 (69, 93)	61 (41, 75)	79 (57, 91)	46 (36, 64)	79 (61, 93)
KOOS Sport-Rec	55 (30, 75)	44 (25, 69)	65 (35, 90)	35 (20, 60)	65 (43, 86)	35 (23, 69)	65 (35, 75)	30 (15, 44)	65 (35, 76)
KOOS QOL	56 (44, 65)	56 (38, 63)	63 (50, 69)	44 (38, 56)	63 (56, 69)	50 (38, 63)	63 (44, 69)	44 (38, 56)	63 (44, 69)
ACL-QOL	69 (51, 87)	67 (48, 82)	81 (51, 94)	60 (42, 74)	82 (60, 95)	63 (41, 84)	75 (56, 90)	53 (37, 69)	78 (60, 91)

Descriptive statistics are reported as median (IQR) or count (%).
* Data from the $n = 9$ who had undergone knee arthroplasty were excluded.
† Reference category = excellent/good Lysholm Score.
‡ Maximal passive knee extension was converted to a binary variable, whereby an extension deficit was defined as ≥ 5° knee extension deficit, maximal passive knee flexion was converted to a binary variable; no flexion deficit (≥135 degrees of knee flexion) vs a flexion deficit (<135 degrees of knee flexion); OA = osteoarthritis; TFJ = tibiofemoral joint osteoarthritis; ROA = radiographic osteoarthritis; SOA = knee symptoms plus ROA; PFJ = patellofemoral joint; KOOS=Knee Injury and Osteoarthritis Outcome Score; LSI = limb symmetry index; SSD = side-to-side difference; KOOS=Knee Injury and Osteoarthritis Outcome Score.

Table II OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Outcomes at 4 and 32–37 years, stratified by OA status at 32–37 years

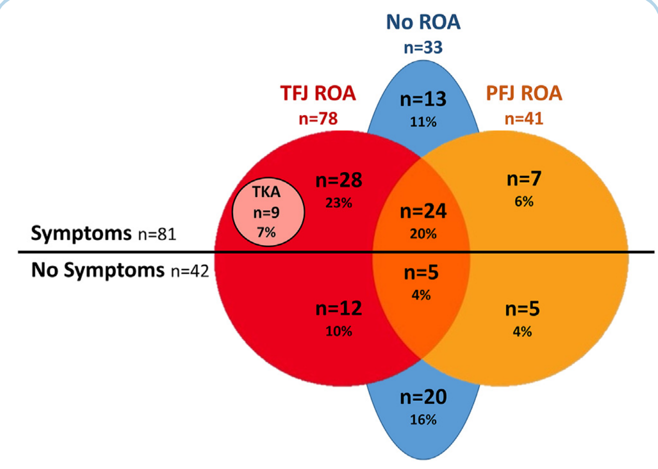

Fig. 2 Osteoarthritis and Cartilage

OSTEOARTHRITIS PREVENTION

A Venn diagram depicting osteoarthritis and symptom status at 32–37 years following acute ACL injury. Numbers represent count (%); Numbers above the black horizontal line depict a 'symptomatic' knee status, and below the line depict a 'non-symptomatic' status; Symptom status was assessed using criteria applied to the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and symptoms subscales; Radiographic Osteoarthritis (ROA) was defined as a Kellgren and Lawrence Grade 2 or above; TFJ = tibiofemoral joint; PFJ = patellofemoral joint; TKA = total knee arthroplasty; $n = 4$ were excluded from this diagram due to missing PFJ radiographs ($n = 3$) or missing KOOS Pain and Symptoms subscale data ($n = 1$).

protocols required surgical patients to be non-weight bearing in a long-leg cast for 6 weeks in 30 degrees of knee flexion. These factors can alter PFJ loading and kinematics and may contribute to patella cartilage loss and subsequent OA development[29,30]. It is also possible that the surgical procedure itself contributed to the higher risk of PFJ SOA after ACL surgery. Notably, most participants in our cohort received ACL repair augmented with a 1.5 cm wide strip of the iliotibial band. The iliotibial band attaches via the lateral retinaculum to the patella, and although the central portion of the ITB was used for graft harvesting, this could have implications for patella kinematics and PFJ loading.

Macri *et al.*, 2019, found that lateral displacement and tilt of the patella one-year following ACL reconstruction, predicted worsening of PFJ ROA features at five-year follow-up and worse patient-reported outcomes[31]. Patella displacement can be altered through rehabilitation comprising neuromuscular exercise and strengthening the knee and hip musculature, which has been shown to reduce patellofemoral pain and improve single-leg-hop performance[32]. Considering reduced hamstrings strength and single-leg-hop performance were prognostic factors for PFJ SOA, it is possible that these patients also had altered patella kinematics, although this was not assessed in our study. Further prospective studies are needed to determine whether targeted interventions to increase hamstrings strength and improve single-leg-hop performance have potential to reduce the rate of PFJ SOA following ACL injury.

Approximately three out of every four people in our study with TFJ or PFJ ROA experienced knee symptoms. This proportion is higher compared to other ACL injury studies with shorter follow-up. For example, 10–15 years after ACL injury only half of participants with TFJ or PFJ ROA reported knee pain[9]. At 20 years after ACL reconstruction, Risberg *et al.*, 2016 found that only 41% of people with TFJ ROA and 31% with PFJ ROA, reported knee pain[33]. Furthermore, in people with a symptomatic knee state 5–20 years after ACL injury, only 62% had TFJ and/or PFJ ROA[8]. In comparison we found that 84% of patients with a symptomatic knee had TFJ and/or PFJ ROA 32–37 years after ACL injury, using the same ROA criteria. Collectively, comparison with other studies with shorter follow-up periods suggests that a greater proportion of ACL injured individuals with OA on radiograph experience knee symptoms with longer follow-up periods. Further research is needed to determine whether altering prognostic factors for SOA after ACL injury (e.g., increasing hamstring strength and single-leg-hop performance) in those with ROA could prevent or delay progression to a symptomatic state.

Limitations

A key strength of this prospective longitudinal cohort study is the high response rate, 32–37 years following enrolment into the study. However, 66 patients were excluded from the analysis due to electing not to undergo a knee radiograph, not participating in 4-year follow-up, or meeting pre-specified exclusion criteria. Although the baseline characteristics and 32–37 year patient-reported outcomes were similar amongst excluded patients and study participants, a higher proportion of study participants underwent early ACL repair (47% vs 33%) suggesting potential selection bias. Since this was an exploratory analysis, results may be biased and should not be interpreted for a generalised population or used to inform clinical decision making without further research. This exploratory study involved multiple comparisons, resulting in a threat of type-1 error and spurious findings. Thus, it is possible that a number of findings were found to be of statistical significance, due to chance alone. This highlights the need for a subsequent study with adequate power and a pre-defined hypothesis, to replicate these findings before they are considered trustworthy enough to inform clinical decision making.

Additionally, we assumed that TFJ SOA was an indication for undergoing TKA in our participants, and excluded them from the PFJ analyses. However, it is possible that a number of these patients with knee symptoms also had PFJ ROA prior to TKA, thus we may have underestimated the rate of PFJ SOA. There is also no established method for classifying TFJ and PFJ symptomatic OA using a combination of patient-reported outcomes and radiographs. We adapted previously used KOOS criteria, however since an arbitrary cut-off was used, it is possible that some patients with less severe pain and symptoms were misclassified as being asymptomatic. Furthermore, information on subsequent and contralateral ACL injury after 4-year follow-up was based on self-report, and subject to recall bias. Experiencing a subsequent or contralateral ACL injury before 4-year follow-up has potential to confound the relationship between prognostic factor and outcome. Since only six patients had a contralateral ACL injury before 4-year follow-up (at least 3 years before 4-year follow-up) we did not adjust for this in the analysis, and instead performed a post-hoc sensitivity analysis with these patients removed. This did not alter our study findings (crude and adjusted effects were similar).

Allocation to treatment based on birth year was common practice in 1980–1985. A perceived advantage of this method at the time, was the ability to determine whether participants had been allocated the incorrect treatment, enabling an estimation of

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	TFJ ROA				TFJ SOA			
	Crude		Adjusted[‖]		Crude		Adjusted[‖]	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Female sex	0.9 (0.4, 2.1)	0.87	1.3 (0.5, 3.4)	0.55	1.5 (0.7, 3.3)	0.29	2.1 (0.8, 5.2)	0.11
Delayed ACL reconstruction[*]	2.5 (0.5, 13.6)	0.28	4.1 (0.6, 27.0)	0.14	1.1 (0.3, 4.9)	0.89	1.2 (0.2, 6.1)	0.81
Rehabilitation alone[*]	1.8 (0.9, 3.8)	0.12	2.0 (0.8, 5.0)	0.17	1.0 (0.5, 2.1)	0.92	1.0 (0.4, 2.4)	0.93
Meniscus injury, no surgery[†]	**3.2 (1.3, 8.3)**	**0.01**	2.7 (1.0, 7.6)	0.056	1.7 (0.7, 4.1)	0.22	1.5 (0.6, 4.1)	0.40
Meniscus injury and surgery[†]	**3.2 (1.3, 7.7)**	**0.01**	**3.0 (1.2, 7.8)**	**0.02**	1.3 (0.6, 3.0)	0.53	1.0 (0.4, 2.6)	0.97
Quadriceps strength LSI <90%	0.9 (0.4, 2.1)	0.87	0.7 (0.3, 1.8)	0.43	0.8 (0.4, 1.8)	0.61	0.6 (0.2, 1.6)	0.30
Hamstrings strength LSI <90%	1.0 (0.4, 2.9)	0.93	1.2 (0.4, 3.7)	0.76	0.8 (0.3, 2.0)	0.58	0.6 (0.2, 1.8)	0.35
Single-leg-hop LSI <90%	1.5 (0.5, 4.2)	0.44	1.0 (0.3, 3.2)	0.97	**3.0 (1.1, 8.3)**	**0.04**	2.6 (0.8, 8.4)	0.11
Extension deficit (≥5° deficit)	1.1 (0.4, 2.7)	0.84	1.3 (0.4, 4.1)	0.69	1.5 (0.6, 3.6)	0.38	1.4 (0.4, 4.1)	0.60
Flexion deficit (<135° flexion)	1.6 (0.7, 3.5)	0.28	1.8 (0.7, 4.6)	0.26	1.4 (0.7, 3.0)	0.38	1.8 (0.7, 4.5)	0.23
Knee laxity (SSD >3 mm)	0.9 (0.4, 1.9)	0.86	1.0 (0.4, 2.4)	0.99	1.1 (0.5, 2.2)	0.87	1.2 (0.5, 2.8)	0.68
Lower activity level[‡]	1.2 (0.5, 2.5)	0.70	0.8 (0.3, 2.0)	0.65	1.6 (0.8, 3.3)	0.21	1.2 (0.5, 2.8)	0.70
Poor/fair knee function[§]	1.8 (0.8, 4.2)	0.19	1.6 (0.6, 4.6)	0.40	1.8 (0.8, 4.2)	0.19	1.5 (0.6, 3.8)	0.45

TFJ = tibiofemoral joint; ROA = radiographic osteoarthritis; SOA = knee symptoms plus ROA; ACL = anterior cruciate ligament; BL = baseline; LSI = limb symmetry index; SSD = side-to-side difference. Bold text = $p < 0.05$.

[*] (Dummy variable) Reference category: Treated with early ACL repair.
[†] (Dummy variable) Reference category: No meniscus injury.
[‡] Defined as a Tegner Activity Scale score of 0–5 (reference category: 6–10).
[§] Defined as a Lysholm Scale score 0–83 (reference category: 84–100, good/excellent knee function).
[‖] Adjusted model includes all potential prognostic factors and age at injury.

Table III OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Logistic regression assessing potential prognostic factors for tibiofemoral osteoarthritis (***n*** = 127)

	PFJ ROA				PFJ SOA			
	Crude		Adjusted[‖]		Crude		Adjusted[‖]	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR	*p*
Female sex	1.8 (0.8, 4.1)	0.17	1.8 (0.6, 4.8)	0.28	1.9 (0.8, 4.5)	0.15	2.2 (0.7, 6.6)	0.18
Delayed ACL reconstruction[*]	0.8 (0.2, 3.5)	0.72	1.1 (0.2, 6.8)	0.89	0.2 (0.0, 2.0)	0.18	0.4 (0.0, 3.7)	0.38
Rehabilitation-alone[*]	0.5 (0.2, 1.1)	0.07	0.4 (0.2, 1.3)	0.12	**0.4 (0.2, 0.9)**	**0.02**	**0.2 (0.1, 0.7)**	**0.01**
Meniscus injury, no surgery[†]	1.0 (0.4, 2.6)	0.96	1.0 (0.3, 3.1)	0.97	1.1 (0.4, 3.1)	0.82	1.3 (0.4, 4.5)	0.71
Meniscus injury and surgery[†]	0.9 (0.4, 2.2)	0.85	1.2 (0.4, 3.6)	0.70	0.8 (0.3, 2.2)	0.68	1.0 (0.3, 3.3)	0.95
Quadriceps strength LSI <90%	0.9 (0.4, 2.0)	0.74	0.4 (0.1, 1.2)	0.09	0.7 (0.2, 1.7)	0.38	0.3 (0.1, 1.3)	0.11
Hamstrings strength LSI <90%	2.3 (0.9, 6.3)	0.10	2.6 (0.8, 8.8)	0.12	**4.0 (1.4, 11.0)**	**0.01**	**5.0 (1.3, 19.3)**	**0.02**
Single-leg-hop LSI <90%	**3.5 (1.2, 9.9)**	**0.02**	**5.1 (1.4, 18.7)**	**0.02**	**3.4 (1.2, 9.6)**	**0.02**	**4.9 (1.2, 19.7)**	**0.03**
Extension deficit (≥5° deficit)	**3.0 (1.1, 8.3)**	**0.03**	3.6 (1.0, 13.5)	0.06	2.3 (0.8, 6.4)	0.11	1.4 (0.3, 5.8)	0.68
Flexion deficit (<135° flexion)	1.0 (0.4, 2.3)	0.96	1.0 (0.4, 2.9)	0.99	0.8 (0.3, 2.0)	0.59	0.7 (0.2, 2.3)	0.54
Knee laxity (SSD >3 mm)	1.3 (0.6, 2.8)	0.53	1.7 (0.6, 4.4)	0.30	0.9 (0.4, 2.2)	0.86	0.8 (0.3, 2.6)	0.76
Lower activity level[‡]	1.0 (0.4, 2.1)	0.92	0.5 (0.2, 1.4)	0.19	1.5 (0.7, 3.6)	0.33	1.1 (0.4, 3.4)	0.86
Poor/fair knee function[§]	1.2 (0.5, 3.1)	0.70	1.5 (0.5, 4.6)	0.46	1.6 (0.6, 4.3)	0.35	2.0 (0.6, 6.6)	0.26

The difference in sample size between TFJ and PFJ analyses is due to exclusion due to total knee arthroplasty ($n = 9$) or missing PFJ X-ray data ($n = 3$).
PFJ: patellofemoral joint; ROA: radiographic osteoarthritis; SOA = knee symptoms plus ROA; ACL: anterior cruciate ligament; BL: baseline; LSI: limb symmetry index; SSD side-to-side difference. Bold text = $p < 0.05$.

[*] (Dummy variable) Reference category: Treated with early ACL repair.
[†] (Dummy variable) Reference category: No meniscus injury.
[‡] Defined as a Tegner Activity Scale score of 0–5 (reference category: 6–10).
[§] Defined as a Lysholm Scale score 0–83 (reference category: 84–100, good/excellent knee function).
[‖] Adjusted model includes all potential prognostic factors and age at injury.

Table IV OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Logistic regression assessing potential prognostic factors for patellofemoral osteoarthritis (***n*** = 115) selection bias. However, this method of treatment allocation has potential to result in systematic differences between characteristics of participants in different intervention groups. Additionally, all patients underwent a diagnostic arthroscopy. Whilst this allows for accurate diagnosis of ACL and concomitant injuries, it means people managed with rehabilitation alone were exposed to knee surgery. It is possible that diagnostic arthroscopy could affect subsequent osteoarthritis development. Therefore, these results may not be generalisable to patients managed with rehabilitation alone who are not exposed to knee surgery. Similarly, ACL repair and 6 weeks of postoperative immobilisation does not align with current practice, and these results should not be generalised to patients undergoing ACL reconstruction and early postoperative mobilisation. In the 1980's, Linköping Hospital was a world-leading center for orthopaedic science, led by Professor Jan Gillquist, one of the pioneers of knee arthroscopy[1,2]. The surgical techniques used in this study were more advanced than the typical surgical techniques used in the early 1980's. In Sweden, healthcare is provided to all citizens irrespective of their socioeconomic status. Therefore, this sample is generalisable to the Swedish population at that time but may not be generalisable to populations in other countries comprising privately funded patients with ACL injury. Further, we cannot determine whether self-reported knee pain and symptoms were attributable to ROA, nor whether the TFJ or PFJ were symptomatic in patients with ROA in both compartments. Despite these limitations, we identified different prognostic factors for ROA and SOA, of the TFJ and PFJ. Finally, although efforts were taken to minimise error in measurement of prognostic factors and outcomes, results could have been subject to measurement bias.

Contributions

All authors were involved in study conception and design, acquisition of data, critical revision of the article, and approved the final version of the manuscript. Dr Filbay and Joanna Kvist interpreted the data and Dr Filbay drafted the manuscript.

Conflict of interest

The authors have no competing interests.

Role of the funding source

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Supplementary data

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