TITLE PAGE

PHYSICAL PROGNOSTIC FACTORS PREDICTING OUTCOME FOLLOWING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION: A SYSTEMATIC REVIEW AND NARRATIVE SYNTHESIS

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ABSTRACT

Background

Anterior cruciate ligament (ACL) injuries are common. Many patients undergo ACL reconstruction (ACLR), with rehabilitation key to successful outcome. Understanding physical prognostic factors is integral to clinical decision-making, but factors predicting outcome are inadequately defined. The objective was to establish physical prognostic factors predicting outcome following ACLR.

Methods

A systematic review following a published protocol (CRD42019127732) searched MEDLINE, CINAHL, EMBASE, key journals and grey literature to 28/11/2020. Prospective cohort studies, participants ≥16 years of age who had undergone ACLR were included, with multi-ligament and/or ACL repair surgery, and studies not published in English excluded. Two independent reviewers conducted searches, extracted data, assessed risk of bias (QUIPS) and overall quality of evidence (GRADE). Meta-analysis was not possible, therefore narrative synthesis was performed.

Results

13 studies (16 articles) were included (1 low, 12 high risk of bias). Low-level evidence supports postoperative degenerative changes and poor lower-limb strength predicting poorer outcome long term (KOOS). Very low-level evidence supports greater postoperative quadriceps strength predicting improved functional performance medium term; with lower body mass index predicting improvement of multiple outcome measures.

Conclusion

Limited evidence of low or very low-level indicates multiple prognostic factors predicting outcome following ACLR. A high-quality prognostic study is required.

INTRODUCTION

Anterior cruciate ligament (ACL) injuries are common amongst both the general and sporting population [1]. In the United States alone the incidence of ACL injuries is rising particularly in females and those younger than 20 or older than 40 years of age [2]. The ACL is integral to maintenance of normal knee function [3], with its main role to reduce and control anterior tibial translation [4]. ACL rupture is therefore a significant musculoskeletal injury [3] with many patients undergoing ACL reconstruction (ACLR) [5]. ACL injuries and subsequent ACLR can significantly impact an individual's personal life [6], as rehabilitation aiming to achieve goals such as a return to sport (RTS) or pre-injury activity levels is lengthy, and not guaranteed regardless of rehabilitation [7]. High quality pre and post ACLR rehabilitation are key to the likelihood of a successful outcome (patient defined positive change) [8].

A body of literature exists evaluating both physical and psychological prognostic factors for predicting outcome following ACLR [9-12], with multiple systematic reviews summarising physical and psychological prognostic factors [13-17]. However, unlike psychological prognostic factors, physical prognostic factors have not been evaluated in more recent and higher quality reviews [13, 14]. Prognostic research can contribute to clinical decision making [18] and therefore is a growing field [19]. It is valuable for the patient and their care team to have knowledge of physical prognostic factors (modifiable and non-modifiable), preoperatively and postoperatively to inform expectations, management and rehabilitation. In earlier studies, definitions of successful outcome are variable and quantified using patient-reported outcome measures (PROMs) or performance-based outcome measures (PBOMs), with

numerous factors highlighted as being associated with outcome [7, 12, 20]. This is highlighted further in three systematic reviews focused on physical prognostic factors, whereby a range of outcome measures are used for defining successful outcome [15-17]. Using A MeaSurement Tool to Assess systematic Reviews-2 (AMSTAR-2) [21], all three reviews are low quality, supporting low confidence in their findings (see Table 1 for details). Common key prognostic factors linked to outcome include age, smoking and gender. However, no review was fully encompassing with a range of outcomes evaluated. Furthermore, variability with respect to risk of bias tools, study design and reporting was observed [15-17].

Despite numerous systematic reviews investigating prognostic factors, no high-quality review has investigated prospective cohort studies – the gold standard for prognostic research, and utilised a validated risk of bias tool for prognostic research such as the Quality in Prognostic Studies (QUIPS) tool. Furthermore, no review has evaluated both PROMs and PBOMs.

Objective

To establish physical prognostic factors predictive of outcome in adults following ACLR. This will assist patients and clinicians to decide on the most appropriate management plan and tailor pre and postoperative rehabilitation to agreed goals e.g. RTS, physical activity, or greater perceived quality of life.

Table 1: Comparison of previous systematic reviews

Study	Key Findings	Outcome	Study Designs Included	Study Limitations
de Valk et al., (2013)	Male sex, <30 years of age at surgery, reconstruction <3 months post-injury and high baseline activity level were found to be predictive of better functional outcomes. Higher BMI, smoking, preoperative quadriceps strength deficits of >20% and range of movement deficits were found to be predictive of poorer functional outcomes.	Subjective & objective markers e.g. muscle strength, knee function & activity levels	Cohort studies (both prospective & retrospective) RCT and Non-randomised trials Case control studies	Includes all studies designs, which is not recommended for prognostic research. Risk of bias tool was not specific to prognostic research (Newcastle Ottawa Scale). Only preoperative factors investigated. Not reported in line with PRISMA.
Wiggins et al., (2016)	Younger age and return to higher level of activity was found to be predictive of a higher re-injury rate.	Re-Injury rate	Cohort studies (both retrospective and prospective including registry databases) Case control/case series studies	Includes all study designs, which is not recommended for prognostic research. Risk of bias tool was not specific to prognostic research (Pedro and modified Downs and Black).
Hamrin Senorski et al., (2019)	Younger age, male sex, non-smoker, hamstring autograft and absence of concomitant injuries were found to be predictive of a superior score in patient reported outcome measures.	PROMs:- KOOS, EQ-5D-5L & Tegner Activity Scale.	Cohort studies which were from registries	Only included studies from registry databases. Risk of bias tool not specific to prognostic research (Downs and Black). Only patient reported measures used for outcome.

BMI; body mass index, PROMs; patient reported outcome measures, RCT; randomised controlled trials

METHODS

Protocol and Registration

This systematic review followed a published protocol [22] and was prospectively registered on PROSPERO (CRD42019127732). An amendment to the planned data synthesis was made whereby long term studies were not divided into <5 years and >5 years as only one study was >5 years (6 years). The search date was extended until November 2020. This review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

Eligibility Criteria

Inclusion Criteria

Study design

Prospective cohort studies (gold standard for prognostic reviews), with a follow-up of any duration. Both preoperative and postoperative measured variables were included.

Population

Any adult aged ≥16 years with ACLR or revision were eligible. For studies including subjects aged both <16 years and ≥16 years, if data analysis provided opportunity to analyse the data for ≥16 years separately then the study was included.

Physical prognostic factors

Any study evaluating physical prognostic factors was included. Physical prognostic factors were pre-defined as any physical measure in nature and included modifiable (e.g. quadriceps strength, hop distance) or non-modifiable (e.g. age, gender) factors [22].

Outcomes

All outcome measures were included in this review as, due to wide variation in the literature; a focus on one measure was not possible.

Timing and Setting

No restrictions on setting, follow-up length or time points were applied to ensure all studies were included.

Exclusion Criteria

Studies which included multi-ligament or ACL repair surgeries were excluded. Any studies not published in English were excluded.

Information Sources

An updated comprehensive search from inception to 28th November 2020 was conducted using the following databases:

- MEDLINE, CINAHL, EMBASE, ZETOC.
- Hand searching of key journals (The American Journal of Sports Medicine, The British Journal of Sports Medicine and Knee Surgery, Sports Traumatology and Arthroscopy).
- Screening of reference lists of included studies.
- Grey literature search including British National Bibliography and Open Grey for dissertation abstracts.

Search Strategy

A pre-defined published search strategy was used [22] and was not deviated from. A validated methodological search filter was used in MEDLINE to identify prognostic studies [24], and then adapted for other databases. Searches were performed by two independent reviewers (AM, NM).

Study Selection

Title and abstract screening was completed by two independent reviewers (AM, NM). Full texts were obtained for any studies where eligibility could not be determined based on information in the abstract. Full text screening was completed by the same two independent reviewers (AM, NM). Any discrepancies between reviewers were resolved by discussion between the reviewers, and a third reviewer (AR) to resolve any disagreement. Authors were contacted via email if further information was required. A follow-up email was sent to authors two weeks after the initial email if no response was received.

Data collection process

Data extraction was completed by two independent reviewers (AM, NM) using a standardised form which was piloted prior to the review. Authors were contacted using the same process as above if further information was required.

Data Items

Data items extracted for this review included:

- General study information (title, authors, publication date).
- Study characteristics (Sample size, duration of follow-up, country).
- Patient characteristics (age, gender).
- ACL reconstruction (graft site, graft type).
- Physical prognostic factors (quadriceps strength, age).
- Outcome (e.g. Lysholm Score, functional tests).
- Results (main findings, statistical analysis).

Risk of bias in individual studies

The Quality in Prognostic Studies (QUIPS) tool was utilised to evaluate risk of bias for each included study. The QUIPS tool consists of six domains which include study participation,

study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting [25]. Overall risk of bias was classified as low risk of bias or high risk of bias (when ≥1 domain was rated as high risk of bias) [26]. Risk of bias was independently assessed by two reviewers (AM, NM), with a third reviewer (AR) to resolve any disagreement.

Summary Measures

Where possible, bivariate and univariate analysis and then multivariate analysis results are reported, which include odd ratios, regression coefficients, 95% confidence intervals and p-values. However, due to variation in reporting across studies this was not always possible.

Synthesis of Results

A meta-analysis was planned in the published protocol dependant on homogeneity of predictive factors and outcomes and overall risk of bias of individual studies. Due to the wide range of prognostic factors and high risk of bias of studies, this was not possible, and a qualitative best evidence synthesis of results was conducted [27]. The synthesis was centred around the risk of bias for individual studies and the strength of the association with the outcomes. Prognostic factors were synthesised per outcome measure and assessment point, specifically pre or postoperative and short (<3 months), medium (≥3 months, <12 months) and long term (≥12 months). Where appropriate, the specific assessment timepoint within short, medium, and long term will be stated in the summary of results.

A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) was utilised. GRADE has been adapted previously for prognostic research and includes five factors which decrease overall quality (phase of investigation, study limitation, inconsistency, indirectness, imprecision and publication bias) and two factors which can

increase overall quality (moderate/large effect size or exposure-response gradient) [28]. When using the adapted GRADE tool for prognostic research to score overall quality of evidence [28], the starting point for all studies was grade one explanatory or predictive modelling studies designed to generate a hypothesis, meaning that quality of evidence was moderate as a starting point.

RESULTS

Study selection

Initial searches yielded 6873 citations. After excluding duplicates, 4433 records were screened through title and abstract. This resulted in 332 articles being assessed for eligibility at the full text stage, where 16 articles fulfilled the eligibility criteria and were included. The number of articles at each stage are shown in Figure 1. There was full agreement at each stage of the selection process between reviewers. Of the 16 studies included, 4 studies presented data from the same cohort [29-32]. Given this, the data are presented as the same study to allow for appropriate presentation in the narrative synthesis. Therefore, 13 studies were included, representing 16 articles.

Fig. 1: PRISMA flow diagram [33]

Study characteristics

The key characteristics of included studies are presented in Table 2.

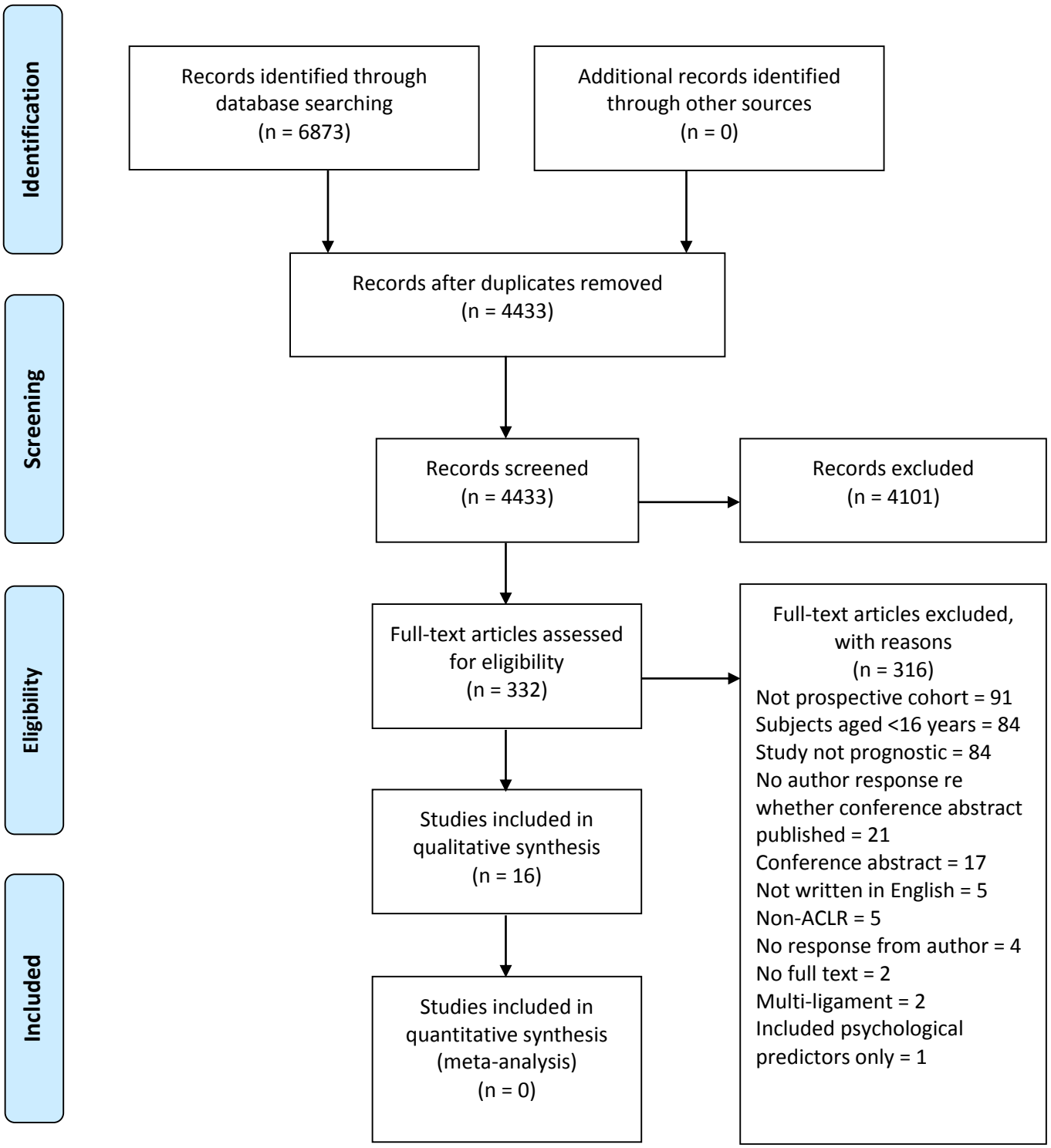
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 6873)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 4433)
Records screened (n = 4433)
Records excluded (n = 4101)
Full-text articles assessed for eligibility (n = 332)
Full-text articles excluded, with reasons (n = 316)
Not prospective cohort = 91
Subjects aged <16 years = 84
Study not prognostic = 84
No author response re whether conference abstract published = 21
Conference abstract = 17
Not written in English = 5
Non-ACLR = 5
No response from author = 4
No full text = 2
Multi-ligament = 2
Included psychological predictors only = 1
Studies included in qualitative synthesis (n = 16)
Studies included in quantitative synthesis (meta-analysis) (n = 0)

Table 2: Study Characteristics

Study	Country	Characteristics of Participants	Physical Prognostic Factors	Baseline Measurement Timepoint	Outcome Measures	Outcome Assessment Point
Avadhani et al., (2010)	India	n = 41 Age: mean 27, range 16-43. Gender: not stated.	- age at surgery - associated injuries - tunnel position	Pre ACLR - age at surgery - associated injuries Post ACLR (10 days) - tunnel position	- IKDC - Lysholm Score	**Long term outcome** 2 years n = 41 [100%]
Culvenor et al., (2016)	Australia	n = 111 Age: mean 29, range 18-50*. Gender: 56 males [60%], 37 females [40%]*.	- associated injuries - degenerative changes - hop distance - 1-leg rise	Post ACLR (1 year) - all prognostic factors	- KOOS	**Long term outcome** 3 years n = 93 [84%]
Grapar Zargi et al., (2017)	Slovenia	n = 29 Age: mean 33.5, SD 8.6, range 18-45*. Gender: 22 males [76%], 7 females [24%].	- quadriceps volume loss - quadriceps isometric endurance - knee joint effusion - knee range of motion - quadriceps strength (torque)	Pre ACLR - quadriceps volume loss - quadriceps isometric endurance - quadriceps strength (torque) Post ACLR (timepoint unclear) - knee joint effusion - knee range of motion	- quadriceps strength	**Short term outcome** 4 weeks **Medium term outcome** 3 months n = 25 [86%]
Heijne et al., (2009)	Sweden	n = 68 Age: mean 30.1, SD 7.8*, range 16-50. Gender: 36 males [53%], 32 females [47%].	- quadriceps strength (torque) - knee range of motion - associated injuries - gender - BMI - time from injury to ACLR - knee laxity - anterior knee pain score - graft site - age at surgery - pivot shift sign	Pre ACLR - all prognostic factors	- functional tests - KOOS - Tegner Activity Scale	**Long term outcome** 1 year n = 64 [94%]
Jurkonis et al., (2018)	Lithuania	n = 214 Age: mean 33.21, SD 9.78*, range 18-55.	- gender - BMI - age at surgery	Pre ACLR - all prognostic factors	- Tegner Activity Scale	**Long term outcome** 1 year n = 214 [100%]

		Gender: 159 males [74%], 55 females [26%]*.				
Keays et al., (2010)	Australia	n = 62 Age: Mean 27, range 18-38. Gender: 44 males [71%], 18 females [29%].	- age at surgery - time from injury to ACLR - associated injuries - graft site - quadriceps strength - hamstrings strength - knee laxity	<u>Pre ACLR</u> - all prognostic factors	- radiological assessment	**Long term outcome** 6 years n = 56 [90%]
Laboute et al., (2018)	France	n = 2424 Age: Mean 26.3, SD 7.3*, range 16-59. Gender: 1754 males [72%], 670 females [28%].	- age at surgery - gender - graft site - level and type of post ACLR sport	<u>Pre ACLR</u> - age at surgery - gender - graft site <u>Post ACLR (2 years)</u> - level and type of post ACLR sport	- graft failure	**Long term outcome** 2 years n = 955 [39%]
Macri et al., (2019)	Australia	n = 111 Age: Mean 29, SD 9*, range 18-50. Gender: 44 males [60%], 29 females [40%}*.	- trochlear morphology and patella alignment	<u>Post ACLR (1 year)</u> - all prognostic factors	- KOOS - radiological assessment	**Long term outcome** 5 years n = 73 [66%]
McHugh et al., (2002)	USA	n = 37 Age: Mean 31, SD 9^. Gender: 25 males [68%], 12 females [32%].	- quadriceps strength (torque) - knee range of motion - EMG	<u>Pre ACLR</u> - all prognostic factors <u>Post ACLR (5 weeks)</u> - all prognostic factors	- functional tests - quadriceps strength.	**Short term outcome** 5 weeks **Medium term outcome** 6 months. n = 37 [100%]
Patterson et al., (2020a)	Australia	Sample size: n = 111 Age: median 27, range 19-51. Gender: 71 males [64%], 40 females [36%].	- functional performance - triple crossover hop for distance - hop distance - side hop - 1-leg rise	<u>Post ACLR (1 year)</u> - all prognostic factors	- radiological assessment - KOOS - IKDC	**Long term outcome** 5 years Complete 1&5 year MRI data n = 78 [70%] Complete 1&5 year PROM data n = 81 [73%]
Patterson et al., (2020b)	Australia	Sample size: n = 111 Age: median 27, range 18-51 Gender: 50 males [63%], 30 females [37%]*.	- degenerative changes	<u>Post ACLR (1 year)</u> - all prognostic factors	- KOOS - IKDC	**Long term outcome** 5 years Complete 1&5 year MRI data n = 78 [70%]

						Complete 1&5 year PROM data n = 81 [73%]
Pua et al., (2017a)	Singapore	n = 106 Age: Mean 26, SD 8^. Gender: 83 males [78%], 23 females [22%].	- quadriceps strength (torque) - hamstrings strength (torque)	Post ACLR (3 months) - all prognostic factors	- functional tests - Lysholm score - Tegner Activity Scale	**Medium term outcome** 6 months n = 106 [100%]
Pua et al., (2017b)	Singapore	n = 70 Age: Mean 25.4, SD 5.9^. Gender: 60 males [86%], 10 females [14%].	- quadriceps strength (torque) - quadriceps rate of torque development	Post ACLR (6 weeks) - all prognostic factors	- functional tests - kinetic measures	**Medium term outcome** 6 months n = 70 [100%]
Radwan et al., (2014)	Egypt	n = 42 Age: Group I (no osteoarthritic changes) Mean 44.5, SD 3.95; Group II (osteoarthritic changes present) Mean 46.4, SD 4.68. Gender: 42 males [100%].	- age at surgery - associated injuries - BMI - time from injury to ACLR - degenerative changes	Pre ACLR - all prognostic factors	- IKDC - Lysholm score	**Long term outcome** 1 year n = 42 [100%]
Robb et al., (2015)	United Kingdom	n = 124 Age: median 27, range 16-65. Gender: 94 males [76%], 30 females [24%].	- age at surgery - gender - BMI - time from injury to ACLR - surgical techniques - associated injuries	Pre ACLR - all prognostic factors	- graft failure.	**Long term outcome** 2 years n = 92 [74%]
Wang et al., (2019)	Australia	n = 100 Age: range 18-40. ACLR isolated (n = 32) mean 30.7, SD 6.4; ACLR combined (n = 25) mean 30.6, SD 7.1*. Gender: 37 males [65%], 20 females [35%]*.	- associated injuries	Post ACLR (~2.5 years) - all prognostic factors	- radiological assessment	**Long term outcome** 2 years after baseline (4+ years post ACLR) n = 57 [57%]

IKDC; International Knee Documentation Committee, KOOS; Knee Injury & Osteoarthritis Outcome Score, BMI; body mass index, EMG; electromyography; PROM; patient reported outcome measure, ACLR; anterior cruciate ligament reconstruction.

* Study only reports details of subjects included in the final analysis.

^ Age range unavailable, but following communication with authors it was confirmed all participants were >18 years old.

Methods

The included studies were published between 2002-2020 and were undertaken in 10 countries. The outcome assessment point of the studies was from 4 weeks to 6 years.

Participants

The total number of participants across the 13 included studies was 3428, with sample sizes ranging from 29-2424. Age of participants ranged from 16-65 years. Three studies did not report the age range of participants [34-36], however following communication with the authors it was confirmed that all participants were aged ≥16 years, allowing inclusion of the studies

Physical prognostic factors

A total of 29 prognostic factors were evaluated across the 13 studies. The most frequently investigated physical prognostic factors were age at surgery (n = 7); [37-43] and associated injuries (n = 7); [29, 37, 38, 40, 42-44], followed by quadriceps strength (n = 6); [34-36, 38, 40, 45].

Outcome measures

Nine different outcome measures were utilised within included studies. PROMs included the International Knee Documentation Committee (IKDC), Lysholm Score and Knee Injury and Osteoarthritis Score (KOOS), whilst PBOMs included functional tests, radiological assessment and graft failure.

Risk of Bias within studies

Of the 13 included studies, 12 were assessed as high risk of bias (Table 3). There was full agreement between the 2 authors regarding assessment of risk of bias.

Table 3: Risk of Bias assessment according to the six domains of potential biases (QUIPS) [25]

Study [n = 13]	Study Participation	Study Attrition [follow-up]	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis & Reporting	Overall Risk of Bias
Avadhani et al. (2010)	High	Low	Moderate	Low	High	Moderate	High
Culvenor et al. (2016)*	Low	Low	Low	Low	Low	Low	Low
Grapar Zargi et al (2017)	High	Low	Moderate	Moderate	High	Moderate	High
Heijne et al. (2009)	High	Moderate	High	Low	High	Moderate	High
Jurkonis et al. (2018)	Moderate	High	High	High	High	High	High
Keays et al. (2010)	High	High	Moderate	Moderate	High	High	High
Laboute et al. (2018)	Moderate	High	Moderate	Moderate	High	Low	High
McHugh et al. (2002)	High	Moderate	Moderate	Moderate	High	Moderate	High
Pua et al. (2017a)	High	Moderate	Low	Low	Moderate	Moderate	High
Pua et al. (2017b)	High	High	Moderate	Low	Low	Low	High
Radwan et al. (2014)	High	Low	Low	Low	Moderate	Low	High
Robb et al. (2015)	High	High	Moderate	Low	Moderate	High	High
Wang et al. (2019)	High	Low	Low	Low	Low	Low	High

* Risk of bias assessment for Culvenor et al. (2016) and associated papers is accumulative across papers as the papers reported different information.
A study was considered low risk of bias if all domains were rated as low-moderate risk of bias.
A study was considered high risk of bias if ≥1 domain[s] were rated as high risk of bias.

Results per outcome measure

Nine outcome measures were investigated. A summary assessment of GRADE for each outcome measure and prognostic factor is provided in the Supplementary Material Tables S1 and S2.

Functional tests

Four studies [34-36, 38] evaluated 14 prognostic factors for medium or long term functional test outcome (Table 4). In the medium term (6 months), greater preoperative EMG (quadriceps contraction and endurance; 1 study [34]), and postoperative quadriceps strength (6 weeks and 3 months; 2 studies [35, 36]), quadriceps rate of torque development (6 weeks, 1 study [36]), and hamstrings strength (3 months, 1 study [35]) were associated with greater function; while preoperative quadriceps strength (1 study [34]) and postoperative EMG (5 weeks, 1 study [34]) were not associated with function. In the long term (12 months), preoperative associated injuries (1 study [38]) were not associated with function. Using GRADE, very low-level evidence supports: preoperative EMG, postoperative quadriceps strength, quadriceps rate of torque development and hamstring strength associated; with preoperative quadriceps strength and postoperative EMG not associated with greater function medium term, with preoperative associated injuries not associated with function long term.

Table 4: Summary of prognostic factors for performance-based outcome measures.

PHYSICAL PROGNOSTIC FACTORS	STUDY & RISK OF BIAS	RESULTS	FINDINGS (BASED ON MULTIVARIATE ANALYSES WHERE SIGNIFICANT DIRECTION OF EFFECT IS REPORTED)	GRADE	SUMMARY OF FINDINGS ACROSS STUDIES
Functional Tests					
Quadriceps strength (torque)	**McHugh et al. (2002)** HIGH ROB Outcome: medium term Baseline: pre ACLR	**Bivariate or univariate analyses** - Patients with greater preoperative quadriceps strength were more likely to report improvement in hop test in the medium term (6 months) ($r = 0.38$, $p < 0.05$). **Multivariate analyses** - Preoperative quadriceps strength was not a significant predictor of hop test performance in the medium term (6 months) (p value not reported).	Quadriceps strength (torque) **was not** a significant predictor of functional test performance medium term.	+ Very low	Using GRADE, there is very low-level evidence (1 study) that preoperative quadriceps strength is not associated with performance on functional tests medium term.
	McHugh et al. (2002) HIGH ROB Outcome: medium term Baseline: post ACLR **Pua et al. (2017b)** HIGH ROB Outcome: medium term Baseline: post ACLR **Pua et al. (2017a)**	**Bivariate or univariate analyses** - None of the 5 week postoperative quadriceps deficits correlated with hop test deficiency in the medium term (6 months (p value not reported). **Multivariate analyses** - None reported. **Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with greater quadriceps strength at 6 weeks post ACLR were more likely to have a greater hop distance in the medium term (6 months) ($p < 0.001$). - Patients with greater quadriceps strength at 6 weeks post ACLR were more likely to have a greater vertical jump height in the medium term (6 months) ($p < 0.03$). **Bivariate or univariate analyses**	No relevant findings. Quadriceps strength **was** a significant predictor of functional test performance medium term.	+ Very low	Using GRADE, there is very low-level evidence (2 studies) that postoperative quadriceps strength is associated with performance on functional tests medium term.

	HIGH ROB Outcome: medium term Baseline: post ACLR	- None reported. **Multivariate analyses** - Patients with a greater limb symmetry index % for both isokinetic (p = 0.01 OR 2.10, [95% CI 1.18-3.73]) and isotonic (p <0.01 OR 3.02, [95% CI 1.59-5.74]) quadriceps strength at 3 months post ACLR were more likely to report a greater single leg hop distance in the medium term (6 months).	Quadriceps strength (isokinetic and isotonic) **was** a significant predictor of functional test performance medium term.		
	Heijne et al. (2009) HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Muscle strength showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Knee range of motion	**McHugh et al. (2002)** HIGH ROB Outcome: medium term Baseline: pre ACLR	- Unclear.	-	-	No summary possible.
	Heijne et al. (2009) HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Reduced knee flexion showed no correlation with one-leg hop test in the long term (12 months). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
EMG	**McHugh et al. (2002)** HIGH ROB Outcome: medium term Baseline: pre ACLR	**Bivariate or univariate analyses** - Patients with greater preoperative quadriceps contraction intensity (measured by integrated EMG) were more likely to report improvement in hop test in the medium term (6 months) (r = 0.56, p <0.001). - Patients with greater endurance (measured by median frequency) were more likely to report improvement in hop test in the medium term (6 months) (r = 0.35, p <0.05). **Multivariate analyses** - The best predictor of hop test deficit in the medium term (6 months) was the combination of preoperative deficits in integrated EMG analysis and median frequency (r^2 = 0.4, p <0.001).	Preoperative EMG **was** a significant predictor of functional test performance medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative EMG is associated with performance on functional tests medium term.
	McHugh et al (2002) HIGH ROB	**Bivariate or univariate analyses** - None of the 5 week postoperative integrated EMG or median frequency measurements correlated with hop test deficiency in the medium term (6 months) (p value not reported).	Postoperative EMG **was not** a significant predictor of functional test	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative

	Outcome: medium term Baseline: post ACLR	**Multivariate analyses** - Postoperative quadriceps contraction intensity (measured by integrated EMG) and endurance (fatigue - measured by median frequency) at 5 weeks were not significant predictors of hop test performance in the medium term (6 months) (p value not reported).	performance medium term.		EMG is not associated with performance on functional tests medium term.
Hamstrings strength (torque)	**Pua et al. (2017a)** HIGH ROB Outcome: medium term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with a greater limb symmetry index % for isotonic hamstring strength (p = 0.01 OR 2.08, [95% CI 1.18, 3.64]) at 3 months post ACLR are more likely to report a greater single leg hop distance in the medium term (6 months). - Limb symmetry index % for isokinetic hamstring strength (p = 0.08 OR 1.71, [95% CI 0.95, 3.11]) at 3 months post ACLR was not associated with greater single leg hop distance in the medium term (6 months).	Isotonic hamstrings strength **was** a significant prognostic factor for single leg hop test distance medium term.	+ Very low	Using GRADE, there is very low-level evidence (1 study) that hamstring strength at 3 months is associated with performance on functional tests medium term.
Quadriceps rate of torque development	**Pua et al. (2017b)** HIGH ROB Outcome: medium term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with greater quadriceps rate of torque development at 6 weeks post ACLR were more likely to have a greater hop distance in the medium term (6 months) (p <0.01). - Patients with greater quadriceps rate of torque development at 6 weeks post ACLR were more likely to have a greater vertical jump height in the medium term (6 months) (p <0.01).	Quadriceps rate of torque development **was** a significant predictor of functional test performance medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative quadriceps rate of torque development is associated with performance on functional tests medium term.
Associated injuries	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Preoperative cartilage damage was correlated with one-leg hop test distance in the long term (12 months) (r -0.28, p = 0.03). - Preoperative meniscus injury and medial collateral ligament injury were not correlated with one-leg hop test distance in the long term (12 months) (p value not reported). **Multivariate analyses** - Preoperative cartilage damage was not a significant predictor of hop test distance in the long term (12 months) (r^2 0.06, p = 0.056).	Associated injury **was not** a significant predictor of functional test performance long term.	+ Very low	Using GRADE, there is very low-level evidence (1 study) that associated injury is not associated with performance on functional tests long term.
Gender	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Gender showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.

BMI	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - BMI showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Time from injury to ACLR	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Time from injury to ACLR showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Knee laxity	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Greater knee laxity showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Anterior knee pain Score	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - The anterior knee pain score showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Graft site	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Graft site of ACLR showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Age at surgery	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Age at surgery showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Pivot shift sign	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - A positive pivot shift sign showed no correlation with one-leg hop test in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
<u>Radiological Assessment</u>					
Age at surgery	**Keays et al. (2010)** HIGH ROB Outcome: long term	**Bivariate or univariate analyses** - Older age at surgery was correlated with patellofemoral osteoarthritis in the long term (6 years) (r = 0.65). **Multivariate analyses**	No relevant findings.	-	No summary possible.

	Baseline: pre ACLR	- None reported.			
Time from injury to ACLR	**Keays et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Time from injury to ACLR showed no correlation with patellofemoral and tibiofemoral osteoarthritis in the long term (6 years) (p values not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Associated injuries	**Keays et al. (2010)** HIGH ROB Outcome: long term Baseline: Pre ACLR	**Bivariate or univariate analyses** - Chondral bone damage was correlated with patellofemoral (r = 0.75) and tibiofemoral (r = 0.41) osteoarthritis in the long term (6 years). - Reconstruction with meniscectomy was correlated with patellofemoral (r = 0.45) and tibiofemoral (r = 0.72) osteoarthritis in the long term (6 years). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
	Wang et. al. (2019) HIGH ROB Outcome: long term Baseline: Post ACLR	**Bivariate or univariate analyses** - Tibial cartilage lesions at 2.5 years post ACLR were associated with an increase in cartilage volume in the medial (0.039 95% CI 0.006, 0.071 p = 0.02) and lateral (0.015 95% CI 0.003, 0.026 p = 0.01) tibia. - Bone marrow lesions at 2.5 years post ACLR were associated with a decrease in cartilage volume in the medial tibia (-0.015 95% CI -0.025, -0.005 p = 0.005) but not lateral tibia (p = 0.31). **Multivariate analyses** - Lateral tibial cartilage lesions at 2.5 years post ACLR were predictive of lateral tibial cartilage volume increase (0.02 95% CI 0.008, 0.032 p = 0.002) in the long term (4.5 years). - Bone marrow lesions at 2.5 years post ACLR were predictive of medial tibial volume increase (-0.017 95% CI -0.027, -0.007 p = 0.001) in the long term (4.5 years).	Cartilage and bone marrow lesions **were** significant predictors of cartilage volume changes in the long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that cartilage and bone marrow lesions are associated with radiological changes long term.
Graft site	**Keays et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Use of a patella tendon graft was correlated with tibiofemoral osteoarthritis in the long term (6 years) (r = 0.37). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Quadriceps strength	**Keays et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Lower quadriceps to hamstrings strength ratio was correlated with tibiofemoral osteoarthritis in the long term (6 years) (r = 0.6). - Lower quadriceps strength was correlated with tibiofemoral osteoarthritis in the long term (6 years) (r = 0.39). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.

Hamstrings strength	**Keays et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Hamstrings strength showed no correlation with patellofemoral and tibiofemoral osteoarthritis in the long term (6 years) (p values not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Knee laxity	**Keays et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate analyses** - Knee laxity showed no correlation with patellofemoral and tibiofemoral osteoarthritis in the long term (6 years) (p values not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Functional performance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Poor functional performance at 12 months (<90% limb symmetry index on all tests - single hop, triple crossover hop, side hop and 1 leg rise) (p <0.05 RR 3.66, 95% CI 1.12, 12.01) was predictive of worsening bone marrow lesions in the patellofemoral joint in the long term (5 years).	Poor functional performance (combination of 4 tests) **was** a significant predictor of radiological changes long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that poor functional performance is associated with radiological changes long term.
Triple crossover hop for distance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index on the triple crossover hop for distance at 12 months (p <0.05 RR 2.09 95% CI 1.15, 3.81) was predictive of worsening cartilage lesions in the patellofemoral joint in the long term (5 years).	Poor triple crossover hop performance **was** a significant predictor of radiological changes long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that poor triple crossover hop performance is associated with radiological changes long term.
Hop distance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index on the single hop for distance at 12 months (p <0.05 RR 4.17 95% CI 1.37, 12.72) was predictive of worsening bone marrow lesions in the patellofemoral joint in the long term (5 years).	Poor single hop performance **was** a significant predictor of radiological changes long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that poor single hop performance is associated with radiological changes long term.

	Baseline: post ACLR				
Side hop	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index on the side hop at 12 months (p <0.05 RR 3.77 95% CI 1.15, 12.43) was predictive of worsening bone marrow lesions in the patellofemoral joint in the long term (5 years). - Fewer side hop repetitions at 12 months (p <0.05 RR 1.08 95% CI 1.01, 1.15) was predictive of worsening bone marrow lesions in the patellofemoral joint in the long term (5 years).	Poor side hop performance **was** a significant predictor of radiological changes long term. Fewer side hop repetitions **was** a significant predictor of radiological changes long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that poor side hop performance is associated with radiological changes long term.
1-leg rise	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index on the 1-leg rise at 12 months (p <0.05 RR 2.92 95% CI 1.19, 7.18) was predictive of worsening bone marrow lesions in the patellofemoral joint in the long term (5 years). - Fewer 1-leg rises at 12 months (p <0.05 RR 0.96 95% CI 0.94, 0.99) was predictive of reduced deterioration of cartilage lesions in the tibiofemoral joint in the long term (5 years).	Poor 1-leg rise performance **was** a significant predictor of radiological changes long term Fewer 1-leg rises **was** a significant predictor of reduced radiological changes long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that 1-leg rise is associated with radiological changes long term.

Trochlear morphology and patella alignment	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - A greater bisect offset (lateral displacement of the patella) (p <0.05 RR 1.09, 95% CI 1.01, 1.16), higher lateral tilt (p <0.05 RR 0.91, 95% CI 0.83, 0.99) and lower trochlear angle (p <0.05 RR 0.88, 95% CI 0.77, 1.00) at 12 months were predictive of cartilage worsening in the lateral patellofemoral compartment in the long term (5 years). - A higher medial trochlear inclination (p <0.05 RR 1.07, 95% CI 1.00, 1.15) and a lower trochlear angle (p <0.05 RR 0.85, 95% CI 0.73, 0.99) at 12 months were predictive of bone marrow lesions in the patellofemoral joint in the long term (5 years). - A lower trochlear angle (p <0.05 RR 0.80, 95% CI 0.67, 0.96) at 12 months was predictive of bone marrow lesions in the lateral patellofemoral compartment in the long term (5 years).	Trochlear morphology and patella alignment **were** significant predictors of radiological changes long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that trochlear morphology and patella alignment are associated with radiological changes long term.
<u>Quadriceps Strength</u>					
Quadriceps volume loss	**Grapar Zargi et al. (2017)** HIGH ROB Outcome: short term. Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - When comparing to the non-injured leg, preoperative quadriceps volume loss was not predictive of quadriceps atrophy in the short term (4 weeks) (p = 0.517, ß-0.127).	Preoperative quadriceps volume loss on the injured leg **was not** a significant predictor of quadriceps atrophy short term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative quadriceps volume loss (injured leg) is not associated with quadriceps atrophy short term.
	Grapar Zargi et al. (2017) HIGH ROB Outcome: medium term. Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - When comparing to the non-injured leg, preoperative quadriceps volume loss was not predictive of quadriceps atrophy in the medium term (3 months) (p = 0.100, ß-0.398).	Preoperative quadriceps volume loss on the injured leg **was not** a significant predictor of quadriceps atrophy medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative quadriceps volume loss (injured leg) is not associated with quadriceps atrophy medium term.

Quadriceps isometric endurance	**Grapar Zargi et al. (2017)** HIGH ROB Outcome: short term. Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Lower quadriceps isometric endurance was predictive of quadriceps atrophy in the short term (4 weeks) (p = 0.016, ß-0.470).	Preoperative isometric endurance **was** a significant predictor of quadriceps atrophy short term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative quadriceps isometric endurance is associated with quadriceps atrophy short term.
	Grapar Zargi et al. (2017) HIGH ROB Outcome: medium term. Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Lower quadriceps isometric endurance was not predictive of quadriceps atrophy in the medium term (3 months) (p = 0.457, ß-0.176).	Preoperative isometric endurance **was not** a significant predictor of quadriceps atrophy medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative quadriceps isometric endurance is not associated with quadriceps atrophy medium term.
Knee joint effusion	**Grapar Zargi et al. (2017)** HIGH ROB Outcome: short term. Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Postoperative knee joint effusion (timepoint unclear) was not predictive of quadriceps atrophy in the short term (4 weeks) (p = 0.492, ß-0.135).	Postoperative knee joint effusion **was not** a significant predictor of quadriceps atrophy short term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative knee joint effusion is not associated with quadriceps atrophy short term.
	Grapar Zargi et al. (2017) HIGH ROB Outcome: medium term. Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Postoperative knee joint effusion (timepoint unclear) was not predictive of quadriceps atrophy in the medium term (3 months) (p = 0.155, ß0.334).	Postoperative knee joint effusion **was not** a significant predictor of quadriceps atrophy medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative knee joint effusion is not associated with quadriceps atrophy medium term.
Knee range of motion	**Grapar Zargi et al. (2017)** HIGH ROB Outcome: short term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Greater postoperative knee extension deficit (timepoint unclear) was predictive of quadriceps atrophy at 4 weeks post ACLR (p = 0.005, ß0.578).	Postoperative knee extension deficit **was** a significant predictor of quadriceps atrophy short term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative knee extension deficit is associated with

					quadriceps atrophy short term.
	McHugh et al. (2002) HIGH ROB Outcome: medium term Baseline: pre ACLR	- Unclear.	No relevant findings.	-	No summary possible.
	Grapar Zargi et al. (2017) HIGH ROB Outcome: medium term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Greater postoperative knee extension deficit (timepoint unclear) was not predictive of quadriceps atrophy in the medium term (3 months) post ACLR (p = 0.361, ß-0.213).	Postoperative knee extension deficit **was not** a significant predictor of quadriceps atrophy medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative knee extension deficit is not associated with quadriceps atrophy medium term.
Quadriceps strength (torque)	**Grapar Zargi et al. (2017)** HIGH ROB Outcome: short term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Preoperative quadriceps strength was not predictive of quadriceps atrophy in the short term (4 weeks) (p = 0.128, ß0.376).	Preoperative quadriceps strength **was not** a significant predictor of quadriceps atrophy short term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative quadriceps strength is not associated with quadriceps atrophy short term.
	Grapar Zargi et al. (2017) HIGH ROB Outcome: medium term Baseline: pre ACLR **McHugh et al. (2002)** HIGH ROB Outcome: medium term Baseline: pre ACLR	**Bivariate or univariate analyses** - The difference between pre and postoperative quadriceps strength was correlated (p <0.05, r^2 = 0.457) with quadriceps volume change in the medium term (3 months). **Multivariate analyses** - Preoperative quadriceps strength was not predictive of quadriceps atrophy in the medium term (3 months) (p = 0.777, ß-0.080). **Bivariate or univariate analyses** - Patients with greater preoperative quadriceps strength were more likely to report greater quadriceps strength in the medium term (6 months) (r = 0.4, p <0.01). **Multivariate analyses** - Preoperative quadriceps strength was not a significant predictor of quadriceps strength in the medium term (6 months) (p value not reported).	Preoperative quadriceps strength **was not** a significant predictor of quadriceps atrophy or strength medium term.	+ Very Low	Using GRADE, there is very low-level evidence (2 studies) that preoperative quadriceps strength is not associated with quadriceps atrophy or strength medium term.

	McHugh et al. (2002) HIGH ROB Outcome: medium term Baseline: post ACLR	**Bivariate or univariate analyses** - Patients with greater postoperative quadriceps strength at 5 weeks were more likely to report greater quadriceps strength in the medium term (6 months) (r = 0.54, p <0.01). **Multivariate analyses** - Postoperative quadriceps strength deficit at 5 weeks was a significant predictor of quadriceps strength deficit in the medium term (6 months) when entered into the multivariate analysis grouped with one other variable (p <0.001, r^2 = 0.45).	Postoperative quadriceps strength **was** a significant predictor of quadriceps strength deficit medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative quadricep strength is associated with quadriceps strength medium term.
EMG	**McHugh et al. (2002)** HIGH ROB Outcome: medium term Baseline: pre ACLR	**Bivariate or univariate analyses** - Patients with greater preoperative quadriceps contraction intensity (measured by integrated EMG) were more likely to report greater quadriceps strength in the medium term (6 months) (p <0.05, r = 0.34). - Patients with greater endurance (measured by median frequency) were more likely to report greater quadriceps strength in the medium term (6 months) (p <0.001, r = 0.54). **Multivariate analyses** - Preoperative endurance (fatigue - measured by median frequency) was a significant predictor of quadriceps strength deficit in the medium term (6 months) when entered into the multivariate analysis grouped with one other variable (p <0.001, r^2 = 0.45).	Preoperative EMG **was not** a significant predictor of quadriceps strength deficit medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative EMG is not associated with quadriceps strength medium term.
	McHugh et al. (2002) HIGH ROB Outcome: medium term. Baseline: post ACLR	**Bivariate or univariate analyses** - Patients with greater postoperative quadriceps contraction intensity (measured by integrated EMG) at 5 weeks were more likely to report greater quadriceps strength in the medium term (6 months) (p <0.05, r = 0.36). - Patients with greater endurance (fatigue - measured by postoperative median frequency) at 5 weeks were more likely to report greater quadriceps strength in the medium term (6 months) (p <0.05, r. = 0.35). **Multivariate analyses** - Postoperative quadriceps contraction intensity (measured by integrated EMG) and endurance (fatigue - measured by median frequency) at 5 weeks were not significant predictors of quadriceps strength in the medium term (6 months) (p value not reported).	Postoperative EMG **was not** a significant predictor of quadriceps strength deficit medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative EMG is not associated with quadriceps strength medium term.
<u>Graft Failure</u>					
Age at surgery	**Robb et al. (2015)** HIGH ROB Outcome: long term	**Bivariate or univariate analyses** - Age at surgery was not a significant predictor of graft failure in the long term (2 years) (p value not reported, HR 0.97 [95% CI 0.9, 1.0]). **Multivariate analyses**	Age at surgery **was not** a significant predictor of graft failure long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that age at surgery is

	Baseline: pre ACLR **Laboute et al (2018)** HIGH ROB Outcome: long term Baseline: pre ACLR	- Age at surgery was not a significant predictor of graft failure in the long term (2 years) (p value not reported, HR 0.95 [95% CI 0.9, 1.0]). **Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Age <25 years at surgery was a significant risk factor for graft failure (p <0.001, OR 3.894, [95% CI 1.887, 8.719]) and time to graft failure (p <0.001, HR 3.741 [95% CI 1.867, 8.359]) in the long term (2nd year post ACLR).	Age at surgery **was** a significant predictor graft failure long term.		associated with graft failure in the long term.
Gender	**Robb et al. (2015)** HIGH ROB Outcome: long term Baseline: pre ACLR **Laboute et al (2018)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Male gender was not a significant predictor of graft failure in the long term (2 years) (p value not reported, HR 3 [95% CI 0.7, 13.1]). Female gender not reported. **Multivariate analyses** - Male gender was not a significant predictor of graft failure in the long term (2 years) (p value not reported, HR 2.7 [95% CI 0.6, 11.9]). Female gender not reported. **Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Gender was not a significant risk factor for graft failure (p = 0.249, OR 0.651, [95% CI 0.299, 1.304]) and time to graft failure (p = 0.198, HR 0.632 [95% CI 0.3, 1.226]) in the long term (2nd year post ACLR).	Male gender **was not** a significant predictor of graft failure long term. Gender **was not** a significant predictor of graft failure long term.	+ Very Low	Using GRADE, there is very low-level evidence (2 studies) gender is not associated with graft failure in the long term.
Graft site	**Laboute et al (2018)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Hamstrings graft was a significant risk factor for graft failure (p = 0.007, OR 3.637 [95% CI 1.552, 10.662]) and time to graft failure (p =. 0.008, HR 3.500 [95% CI 1.529, 10.107]) compared to patella tendon graft in the long term (2nd year post ACLR).	Hamstring graft **was** a significant predictor graft failure long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that use of hamstring graft is associated with graft failure in the long term.
Level and type of post ACLR sport	**Laboute et al (2018)** HIGH ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Level of post ACLR sport was not a significant risk factor for graft failure (p = 0.066) and time to graft failure (p = 0.067) in the long term (2nd year post ACLR).	Level and type of post ACLR sport **were not** significant predictors of graft failure long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that level and type of post ACLR sport are not associated with graft failure in the long term.

		- Type of post ACLR sport was not a significant risk factor for graft failure (p = 0.877) and time to graft failure (p = 0.903) in the long term (2nd year post ACLR).			
BMI	**Robb et al. (2015)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - BMI was not a significant predictor of graft failure in the long term (2 years) (p value not reported, HR 0.98 [95% CI 0.9, 1.2]). **Multivariate analyses** - BMI was not a significant predictor of graft failure in the long term (2 years) (p value not reported, HR 1.03 [95% CI 0.9, 1.2]).	BMI **was not** a significant predictor of graft failure long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that BMI is not associated with graft failure in the long term.
Time from injury to ACLR	**Robb et al. (2015)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Time from injury to ACLR was not a significant predictor of graft failure in the long term (2 years) (p value not reported, HR 1.0 [95% CI 1.0, 1.0]). **Multivariate analyses** - Time from injury to ACLR was not a significant predictor of graft failure in the long term (2 years) (p value not reported, HR 1.0 [95% CI 1.0, 1.0]).	Time from injury to ACLR **was not** a significant predictor of graft failure long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that time from injury to ACLR is not associated with graft failure in the long term.
Surgical techniques	**Robb et al. (2015)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Surgical techniques were not a significant predictor of graft failure in the long term (2 years) (p values not reported). - Hamstring stand number (HR 0.5 [95% CI 0.1, 1.6]). - Hamstring tripling (HR 0.4 [95% CI 0.1, 1.7]). - Hamstring size (HR 0.83 [95% CI 0.4, 2.1]). - Hamstring graft <8mm (HR 1.4 [95% CI 0.56, 3.6]). **Multivariate analyses** - Surgical techniques were not a significant predictor of graft failure in the long term (2 years) (p values not reported). - Hamstring stand number (HR 0.47 [95% CI 0.1, 1.8]). - Hamstring tripling (HR 0.42 [95% CI 0.1, 1.8]). - Hamstring size (HR 0.96 [95% CI 0.4, 2.6]). Hamstring graft <8mm (HR 1.4 [95% CI 0.5, 3.5]).	Surgical techniques **were not** a significant predictor of graft failure long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that surgical techniques are not associated with graft failure in the long term.
Associated injuries	**Robb et al. (2015)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Meniscal repair was not a significant predictor of graft failure in the long term (2 years) (p values not reported). - Medial meniscus repair (HR 1.28 [95% CI 0.3, 5.6]). - Lateral meniscus repair (HR 1.1 [95% CI 0.26, 4.8]). - Medial meniscal deficiency (resection) was a significant predictor of graft failure in the long term (2 years) p = 0.008 (HR 3.4 [95% CI 1.4, 8.4]).	Meniscal repair **was not** a significant predictor of graft failure long term. Meniscal deficiency (resection) **was** a significant predictor	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that associated injuries (meniscal deficiency) are associated with graft failure in the long term.

		- Lateral meniscus deficiency (resection) was not a significant predictor of graft failure in the long term (2 years), p value not reported (HR 2.4 [95% CI 0.94, 6.1]). **Multivariate analyses** - Meniscal repair was not a significant predictor of graft failure in the long term (2 years) (p values not reported). - Medial meniscus repair (HR 1.6 [95% CI 0.4, 7.2]). - Lateral meniscus repair (HR 1.4 [95% CI 0.3, 6.3]). - Medial meniscal deficiency (resection) was a significant predictor of graft failure in the long term (2 years) p = 0.0017 (HR 4.5 [95% CI 1.8, 11.5]). - Lateral meniscus deficiency (resection) was a significant predictor of graft failure in the long term (2 years), p = 0.011 (HR 3.5 [95% CI 1.3, 9.3]).	graft failure long term.		
<u>Kinetic Measures</u>					
Quadriceps strength (torque)	**Pua et al. (2017b)** HIGH ROB Outcome: medium term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with lower quadriceps strength at 6 weeks post ACLR were more likely to have a greater vertical ground reaction force (p = 0.01, OR 3.10, [95% CI 1.29, 7.42]) in the medium term (6 months). - Patients with lower quadriceps strength at 6 weeks post ACLR were more likely to have a greater loading rate (p = 0.04, OR 2.22, [95% CI 1.02, 4.82]) in the medium term (6 months).	Quadriceps strength **was** a significant predictor of kinetic performance medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative quadriceps strength is associated with kinetic performance medium term.
Quadriceps rate of torque development	**Pua et al. (2017b)** HIGH ROB Outcome: medium term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with lower quadriceps rate of torque development at 6 weeks post ACLR were more likely to have a greater vertical ground reaction force (p <0.001, OR 4.64, [95% CI 2.04, 10.56]) in the medium term (6 months). - Patients with lower quadriceps rate of torque development at 6 weeks post ACLR were more likely to have a greater loading rate (p = 0.02, OR 2.46, [95% CI 1.18, 5.09]) in the medium term (6 months).	Quadriceps rate of torque development **was** a significant predictor of kinetic performance medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative quadriceps rate of torque development measured is associated with kinetic performance medium term.

ROB; risk of bias, ACLR; anterior cruciate ligament reconstruction, GRADE; Gradings of Recommendations Assessment Development and Evaluation, OR; odds ratio, CI; confidence intervals, EMG; electromyography, RR; risk ratio, HR; hazard ratio; BMI; body mass index.

Radiological assessment

Three studies (6 articles) [29-32, 40, 44] evaluated 13 prognostic factors for long term radiological assessment outcome (Table 4). In the long term (4.5 & 5 years), postoperative associated injuries (cartilage and bone marrow lesions; 2.5 years, 1 study [44]), decreased postoperative functional performance, triple crossover hop for distance, hop distance, side hop, poor 1 leg-rise performance and trochlear morphology and patella alignment (12 months; 1 study [29-32]) were associated with worsening radiological changes. Using GRADE, low-level evidence supports: decreased functional performance, triple crossover hop for distance, hop distance, side hop, poor 1-leg rise performance and trochlear morphology and patella alignment associated with worsening radiological changes long term. Very low-level evidence supports: associated injuries associated with worsening radiological changes long term.

Quadriceps strength

Two studies [34, 45] evaluated 6 prognostic factors for short or medium term quadriceps strength outcome (Table 4). In the short term (4 weeks), preoperative reduced quadriceps isometric endurance (1 study [45]), postoperative knee extension deficit (postoperative time point unclear, 1 study [45]) were associated with quadriceps atrophy; while preoperative quadriceps volume loss (1 study [45]), quadriceps strength (1 study [45]), and postoperative knee joint effusion (1 study [45]) were not associated with quadriceps atrophy. In the medium term (3 & 6 months), postoperative quadriceps strength deficiency (5 weeks, 1 study [34]) was associated with quadriceps strength; while preoperative quadriceps volume (1 study [45]), quadriceps isometric endurance (1 study [45]), quadriceps strength (2 studies [34, 45]), EMG (1 study [34]), and postoperative EMG (5 weeks, 1 study [34]), knee joint effusion (postoperative time point unclear, 1 study [45]), knee extension deficit (postoperative time point unclear, 1 study [45]), quadriceps strength (5 weeks, 1 study [34]) were not associated

with quadriceps strength deficit or atrophy. Using GRADE, very low-level evidence supports: all prognostic factors associated or not associated with quadriceps strength atrophy or quadriceps strength deficits short or medium term.

Graft failure

Two studies [41, 43] evaluated 8 prognostic factors for long term outcome (Table 4). In the long term (2 years), graft site (hamstring graft; 1 study [41]), preoperative associated injuries (meniscal deficiency; 1 study [43]) were associated with graft failure; while there are inconsistencies between age at surgery and graft failure (2 studies [41, 43]). Gender (preoperative, 2 studies [41, 43]), preoperative BMI (1 study [43]), time from injury to ACLR (1 study [43]), surgical techniques (1 study [43]), preoperative associated injuries (meniscal repair; 1 study [43]) and postoperative level and type of ACLR sport (1 study [41]) were not associated with graft failure. Using GRADE, very low-level evidence supports: all prognostic factors associated or not associated with graft failure long term.

Kinetic measures

One study [36] evaluated 2 prognostic factors for medium term outcome (Table 4).

In the medium term (6 months), postoperative quadriceps strength (6 weeks, 1 study [36]), and quadriceps rate of torque development (6 weeks, 1 study [36]) were associated with greater kinetic performance (vertical ground reaction force and higher loading rate). Using GRADE, very low-level evidence supports: all prognostic factors associated with greater kinetic performance long term.

KOOS

Two studies (5 articles) [29-32, 38] evaluated 18 prognostic factors for long term outcome (Table 5). In the long term (12 months, 3 and 5 years), preoperative BMI, knee range of

motion (lower flexion deficit) and quadriceps strength (eccentric) were associated with greater KOOS-QOL subscale (1 study [38]); with preoperative anterior knee pain score associated with greater KOOS-QOL and KOOS-SR subscales (1 study [38]). Postoperative degenerative changes, and inability to perform ≥22 1-leg rises (12 months, 1 study [29-32]) were associated with poorer KOOS scores on all subscales; with postoperative side hop performance (12 months, 1 study [29-32]) associated with poorer KOOS-QOL scores; and postoperative trochlear morphology and patella alignment (12 months, 1 study [29-32]) associated with poorer KOOS-SR and KOOS-QOL subscales. Associated injuries and gender (preoperative) were not associated with KOOS-SR (1 study [38]); with preoperative reduced knee laxity (1 study [38]) not associated with KOOS-QOL subscale. Postoperative functional performance, hop distance and triple crossover hop for distance were not associated with any KOOS subscales (1 study [29-32]). Using GRADE, low-level evidence supports: postoperative degenerative changes, 1-leg rise, side hop and trochlear morphology and patella alignment associated; and postoperative functional performance, hop distance and triple crossover hop for distance not associated with KOOS scores long term. Very low-level evidence supports: BMI, preoperative knee range of motion, anterior knee pain score and quadriceps strength associated; and associated injuries, gender and preoperative reduced knee laxity not associated with KOOS scores long term.

Table 5: Summary of prognostic factors for patient-reported outcome measures

PHYSICAL PROGNOSTIC FACTORS	STUDY & RISK OF BIAS	RESULTS	FINDINGS (BASED ON MULTIVARIATE ANALYSES WHERE SIGNIFICANT DIRECTION OF EFFECT IS REPORTED)	GRADE	SUMMARY OF FINDINGS ACROSS STUDIES
KOOS					
Associated injuries	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Preoperative cartilage damage was correlated with the KOOS-SR subscale in the long term (12 months) ($p = 0.07$, $r = -0.23$), but was not correlated with KOOS-QOL subscale (p value not reported). - Preoperative meniscus injury and medial collateral ligament injury were not correlated with the KOOS-SR or KOOS-QOL in the long term (12 months) (p value not reported). **Multivariate analyses** - KOOS-SR: Preoperative cartilage damage was a significant predictor of greater KOOS-SR score in the long term (12 months) when entered into the multivariate analysis grouped with other variables ($p = 0.0002$, $r^2 = 0.37$). However, it was not selected for forwards stepwise regression analysis as an independent predictor.	Associated injuries **were not** a significant independent predictor of KOOS-SR long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that associated injuries are not associated with KOOS-SR long term.
Gender	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Gender showed a significant correlation with KOOS-SR in the long term (12 months) ($p = 0.06$, $r = 0.23$). - Gender showed no correlation with KOOS-QOL in the long term (12 months) (p value not reported). **Multivariate analyses** - KOOS-SR: Gender was a significant predictor of higher KOOS-SR score in the long term (12 months) when entered into the multivariate analysis grouped with other variables ($p = 0.0002$, $r^2 = 0.37$). However, it was not selected for forwards stepwise regression analysis as an independent predictor.	Gender **was not** a significant independent predictor of KOOS-SR long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that gender is not associated with KOOS-SR long term.
BMI	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - BMI showed no correlation with KOOS-SR in the long term (12 months) (p value not reported). - BMI showed a significant correlation with KOOS-QOL in the long term (12 months) ($p = 0.02$, $r = -0.29$).	BMI **was** a significant independent predictor of KOOS-QOL long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that BMI is associated with KOOS-QOL long term.

		Multivariate analyses - KOOS-QOL: Lower BMI was a significant predictor of greater KOOS-QOL score in the long term (12 months) when entered into the multivariate analysis grouped with other variables (p = 0.000015, r^2 = 0.44). - Lower BMI was selected as a predictor for the stepwise regression analysis (adjusted $r^{2.}$ = 0.34, ß-0.36).			
Knee range of motion	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Preoperative knee flexion deficit was correlated with both the KOOS-SR (p = 0.02, r = -0.29) and KOOS-QOL (p = 0.001, r = -0.38) subscales in the long term (12 months). - Preoperative knee extension deficit showed no correlation with KOOS-SR or KOOS-QOL subscales in the long term (12 months) (p values not reported). **Multivariate analyses** - KOOS-SR: Lower preoperative knee flexion deficit was a significant predictor of greater KOOS-SR score in the long term (12 months) when entered into the multivariate analysis grouped with other variables (p = 0.0002, r^2 = 0.37). However, it was not selected for forwards stepwise regression analysis as an independent predictor. - KOOS-QOL: Lower preoperative knee flexion deficit was a significant predictor of higher KOOS-QOL score in the long term (12 months) when entered into the multivariate analysis grouped with other variables (p = 0.000015, r^2 = 0.44). Lower knee flexion deficit was selected as a predictor for the stepwise regression analysis (adjusted r^2 = 0.26, ß-0.36).	Lower knee flexion deficit **was** a significant independent predictor of KOOS-QOL long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that lower preoperative knee flexion deficit is associated with KOOS-QOL long term.
Knee laxity	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Preoperative knee laxity showed no correlation with KOOS-SR in the long term (12 months) (p value not reported). - Knee laxity showed a significant correlation with KOOS-QOL in the long term (12 months) (p = 0.08, r = 0.22). **Multivariate analyses** - KOOS-QOL: Reduced preoperative knee laxity was a significant predictor of higher KOOS-QOL score in the long term (12 months) when entered into the multivariate analysis grouped with other variables (p = 0.0002, r^2 = 0.37). However, it was not selected for forwards stepwise regression analysis as an independent predictor.	Reduced preoperative knee laxity **was not** a significant independent predictor of KOOS-SR long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative laxity is not associated with KOOS-QOL long term.
Anterior knee pain score	**Heijne et al. (2009)** HIGH ROB Outcome: long term	**Bivariate or univariate analyses** - Preoperative anterior knee pain score was correlated with both the KOOS-SR (p = 0.002, r = 0.38) and KOOS-QOL (p = 0.004, r = 0.36) subscales in the long term (12 months).	Lower preoperative anterior knee pain score **was** a significant	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that lower preoperative

	Baseline: pre ACLR	**Multivariate analyses** - KOOS-SR: Lower preoperative anterior knee pain score was a significant predictor of greater KOOS-SR score in the long term (12 months) when entered into the multivariate analysis grouped with other variables (p = 0.0002, r^2 = 0.37). Lower preoperative anterior knee pain score was selected as a predictor for the stepwise regression analysis (adjusted r^2 = 0.21, ß-0.37). - KOOS-QOL: Lower preoperative anterior knee pain score was a significant predictor of greater KOOS-QOL score in the long term (12 months) when entered into the multivariate analysis grouped with other variables (p = 0.000015, r^2 = 0.44). Lower preoperative anterior knee pain score was selected as a predictor for the stepwise regression analysis (adjusted r^2 = 0.14, ß-0.35).	independent predictor of both KOOS-SR and KOOS-QOL long term.		anterior knee pain score is associated with both KOOS-SR and KOOS-QOL long term.
Quadriceps strength (torque)	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Preoperative concentric quadriceps strength showed no correlation with KOOS-SR or KOOS-QOL subscales in the long term (12 months) (p values not reported). - Preoperative eccentric quadriceps strength was correlated with the KOOS-QOL (p = 0.08, r = -0.22) but not with KOOS-SR (p value not reported) subscales in the long term (12 months). **Multivariate analyses** - KOOS-QOL: Preoperative eccentric quadriceps strength was a significant predictor of greater KOOS-QOL score in the long term (12 months) when entered into the multivariate analysis grouped with other variables (p =0.000015, r^2 = 0.44). - Preoperative eccentric quadriceps strength was selected as a predictor for the stepwise regression analysis (adjusted r^2 = 0.38, ß-0.25).	Preoperative quadriceps strength (eccentric) **was** a significant independent predictor of KOOS-QOL long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative eccentric quadriceps strength is associated with KOOS-QOL long term.
Time from injury to ACLR	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Time from injury to ACLR showed no correlation with both KOOS-SR and KOOS-QOL subscales in the long term (12 months) (p values not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Graft site	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Graft site showed no correlation with both KOOS-SR and KOOS-QOL subscales in the long term (12 months) (p values not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.

Age at surgery	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Age at surgery showed no correlation with both KOOS-SR and KOOS-QOL subscales in the long term (12 months) (p values not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Pivot shift sign	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Pivot shift sign showed no correlation with both KOOS-SR and KOOS-QOL subscales in the long term (12 months) (p values not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Degenerative changes	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Postoperative cartilage damage in the patellofemoral compartment at 12 months was a significant predictor of a poorer score on all KOOS subscales in the long term (3 years): - KOOS-symptoms: ß-0.3, 95% CI -9.1, -1.2, p = 0.01. - KOOS-pain: ß-0.2, 95% CI -6.7, -1.4, p <0.01. - KOOS-SR: ß-0.3, 95% CI -11.0, -2.4, p <0.01. - KOOS-QOL: ß-0.3, 95% CI -15.1, -2.1, p = 0.01. - Postoperative bone marrow lesions and osteophytes in the patellofemoral compartment at 12 months were not significant predictors of any KOOS subscale in the long term (3 years) (p >0.05). - Postoperative cartilage damage, bone marrow lesions and osteophytes in the tibiofemoral compartment at 12 months were not significant predictors of any KOOS subscale in the long term (3 years) (p >0.05). - Postoperative patellofemoral cartilage lesions at 12 months were a significant predictor of a poorer score on KOOS-symptoms (ß-9.79 95% CI -16.67, -2.91), KOOS-SR (ß-7.94 95% CI -15.27, -0.61) & KOOS-QOL (ß-8.29 95% CI -15.28, -1.29) subscales, but not for KOOS-pain (p value not reported) in the long term (5 years). - Postoperative meniscal lesions at 12 months were a significant predictor of a poorer score on KOOS-symptoms subscale only (ß-8.47 95% CI-16.54, -0.42) in the long term (5 years). - Postoperative patellofemoral and tibiofemoral bone marrow lesions or tibiofemoral cartilage lesions at 12 months were not significant predictors of any KOOS subscale in the long term (5 years) (p value not reported).	Degenerative changes **were** a significant predictor of KOOS long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that degenerative changes are associated with KOOS long term.

Functional performance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Poor functional performance (<90% limb symmetry index on all tests – single hop, triple crossover hop, side hop and 1-leg rise) at 12 months was not predictive of change in any KOOS subscales long term (5 years) (p value not reported).	Functional performance **was not** a significant predictor of KOOS long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that functional performance is not associated with the KOOS long term.
Hop distance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Postoperative hop distance at 12 months was not a significant predictor of any KOOS subscales (p >0.05) in the long term (3 years). - <90% limb symmetry index and hop distance at 12 months were not predictive of change in any KOOS subscales long term (5 years) (p value not reported).	Hop distance **was not** a significant predictor of KOOS long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that hop distance is not associated with KOOS long term.
1-leg rise	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - The inability to perform ≥22 1-leg rises at 12 months post ACLR was a significant predictor of poorer outcome, as defined by the KOOS-QOL subscale (ß-0.2, 95% CI -12.4, -0.5, p = 0.03) in the long term (3 years). - The remaining three KOOS subscales (KOOS-symptoms, KOOS-pain, KOOS-SR) were not significant predictors in the long term (3 years). - <90% limb symmetry index and 1-leg rise repetitions at 12 months were not predictive of change in any KOOS subscales long term (5 years) (p value not reported).	1-leg rise performance **was** a significant predictor of KOOS-QOL long term. 1-leg rises **were not** a significant predictor of KOOS long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that the inability to perform ≥ 22 1-leg rises is associated with KOOS-QOL long term.
Triple crossover hop for distance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)**	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index and triple crossover hop distance at 12 months were not predictive of change in any KOOS subscales long term (5 years) (p value not reported).	Triple crossover hop **was not** a significant predictor of KOOS long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that triple crossover hop is not associated with KOOS long term.

	LOW ROB Outcome: long term Baseline: post ACLR				
Side hop	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index on the side hop at 12 months (p <0.05 ß8.08 95% CI 1.56, 14.61) was predictive of higher change in KOOS-QOL score in the long term (5 years). - The number of side hop repetitions at 12 months was not predictive of any KOOS subscale in the long term (p value not reported).	Side hop **was** a significant predictor of KOOS-QOL long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that side hop is associated with the KOOS-QOL long term.
Trochlear morphology and patella alignment	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - A bisect offset (lateral displacement of the patella) of >61.6% at 12 months was a significant predictor of lower KOOS-SR (p <0.05, ß-11.02, 95% CI -1.16, -20.88) and KOOS-QOL (p <0.05, ß-10.52, 95% CI -0.65, -20.40) scores in the long term (5 years).	Trochlear morphology and patella alignment **were** significant predictors of KOOS-SR and KOOS-QOL long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that greater bisect offset is associated with KOOS-SR and KOOS-QOL long term.
<u>IKDC</u>					
Age at surgery	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR **Avadhani et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Age at surgery was not a significant predictor of successful outcome in the long term (12 months), defined as an IKDC ranking of A and B (p value not reported). **Bivariate or univariate analyses** - Age at surgery did not influence outcome in the long term (12 months), based on reported IKDC Score (p = 0.32). **Multivariate analyses** - None reported.	Age at surgery **was not** a significant predictor of overall function (IKDC Score) long term. No relevant findings.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that age at surgery is not associated with overall function (IKDC Score) long term.

Associated injuries	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR **Avadhani et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Presence of meniscal injury was not a significant predictor of successful outcome in the long term (12 months), defined as an IKDC ranking of A and B (p value not reported). **Bivariate or univariate analyses** - Presence of meniscal injury did not influence outcome in the long term (12 months), based on reported IKDC Score (p = 0.48). **Multivariate analyses** - None reported.	Associated injuries **were not** significant predictors of overall function (IKDC Score) long term. No relevant findings.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that associated injuries are not associated with overall function (IKDC Score) long term.
BMI	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with lower BMI at time of surgery were more likely to have successful outcome in the long term (12 months), defined as an IKDC ranking of A and B (p = 0.042, OR 1.21, [95% CI 1.01, 1.46]).	BMI **was** a significant predictor of overall function (IKDC Score) long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that BMI is associated with overall function (IKDC Score) long term.
Time from injury to ACLR	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with shorter time between ACL injury and ACLR (<2 years) were more likely to have a successful outcome in the long term (12 months), defined as an IKDC ranking of A and B (p = 0.004, OR 0.15, [95% CI 0.04, 0.55]).	Time from injury to ACLR **was** a significant predictor of overall function (IKDC Score) long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that time from injury to ACLR is associated with overall function (IKDC Score) long term.
Degenerative changes	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Preoperative degenerative changes were not a significant predictor of successful outcome in the long term (12 months), defined as an IKDC ranking of A and B (p value not reported).	Preoperative degenerative changes **were not** a significant predictor of overall function (IKDC Score) long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative degenerative changes are not associated with overall function (IKDC Score) long term.

	Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b) LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patellofemoral cartilage lesions (ß-4.79 95% CI -9.34, -0.24) at 12 months were predictive of worse IKDC score in the long term (5 years). - Patellofemoral and tibiofemoral bone marrow lesions and tibiofemoral cartilage lesions at 12 months were not predictive of IKDC scores in the long term (5 years) (p values not reported). - Meniscal lesions at 12 months were not predictive of IKDC scores in the long term (5 years) (p values not reported).	Degenerative changes (patellofemoral cartilage lesions) **were** significant predictors of overall function (IKDC score) long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that degenerative changes (patellofemoral cartilage lesions) are associated with overall function (IKDC) long term.
Functional performance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Poor functional performance (<90% limb symmetry index on all tests – single hop, triple crossover hop, side hop and 1-leg rise) at 12 months was not predictive of change in IKDC scores long term (5 years). (p value not reported).	Functional performance **was not** a significant predictor of overall function (IKDC score) long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that functional performance is not associated with overall function (IKDC) long term.
Triple crossover hop for distance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index and triple crossover hop distance at 12 months were not predictive of change in IKDC scores long term (5 years). (p value not reported).	Triple crossover hop for distance **was not** a significant predictor of overall function (IKDC score) long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that triple cross over hop for distance is not associated with overall function (IKDC) long term.
Side hop	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index and side hop repetitions at 12 months were not predictive of change in IKDC scores long term (5 years) (p value not reported).	Side hops **were not** a significant predictor of overall function (IKDC score) long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that side hop repetitions is not associated with overall function (IKDC) long term.

1-leg rise	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index and 1 leg rise repetitions at 12 months were not predictive of change in IKDC scores long term (5 years). (p value not reported).	1-leg rises **were not** a significant predictor of overall function (IKDC score) long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that 1-leg rise repetitions is not associated with overall function (IKDC) long term.
Hop distance	**Culvenor et al. (2016), Macri et al. (2019), Patterson et al. (2020a), & Patterson et al. (2020b)** LOW ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - <90% limb symmetry index and hop distance at 12 months were not predictive of change in IKDC scores long term (5 years) (p value not reported).	Hop distance **was not** a significant predictor of overall function (IKDC score) long term.	++ Low	Using GRADE, there is low-level evidence (1 study) that functional hop test is not associated with overall function (IKDC Score) long term.
Tunnel position	**Avadhani et al. (2010)** HIGH ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - Tibial tunnel position in the sagittal plane at 10 days post ACLR did influence outcome in the long term (12 months), based on reported IKDC Score (p <0.01). - Tibial tunnel (p = 0.12) and femoral tunnel (p = 0.25) positions at 10 days post ACLR in the coronal plane and femoral tunnel position in the sagittal plane (p = 0.28) did not influence outcome in the long term (12 months), based on reported IKDC Score. **Multivariate analyses** - Tibial tunnel position in the sagittal plane at 10 days post ACLR was a significant predictor of successful outcome in the long term (12 months), based on reported IKDC Score (p = 0.031).	Tibial tunnel position in the sagittal plane **was** a significant predictor of overall function (IKDC Score) long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that tibial tunnel position in the sagittal plane is associated with overall function (IKDC Score) long term.
<u>Tegner Activity Scale</u>					
Quadriceps strength (torque)	**Pua et al. (2017a)** HIGH ROB Outcome: medium term. Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with a higher limb symmetry index % for both isokinetic (p = 0.02 OR 1.68, [95% CI 1.10, 2.56]) and isotonic (p <0.01 OR 1.96, [95% CI 1.18, 3.25]) quadriceps strength at 3 months post ACLR are	Quadriceps strength (isokinetic and isotonic) **was** a significant predictor of Tegner Activity Scale medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that quadriceps strength is associated with activity levels medium term.

		more likely to report higher activity levels, defined by Tegner Activity Scale, in the medium term (6 months).			
	Heijne et al. (2009) HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Concentric quadriceps strength showed a significant correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p = 0.004, r = -0.36). - Eccentric quadriceps strength showed no correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p value not reported). **Multivariate analyses** - Concentric quadriceps strength was a significant predictor of higher activity levels, defined by Tegner Activity Scale in the long term (12 months), when entered in to the multivariate analysis grouped with other variables (p = 0.02, r^2 = 0.18). However, it was not selected for forwards stepwise regression analysis as an independent predictor.	Quadriceps strength (concentric) **was not** a significant independent predictor of Tegner Activity Scale long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that quadriceps strength is not associated with activity levels long term.
Hamstrings strength (torque)	**Pua et al. (2017a)** HIGH ROB Outcome: medium term. Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Limb symmetry index % for both isokinetic (p = 0.66 OR 1.12, [95% CI 0.67, 1.87]) and isotonic (p = 0.17 OR 1.41, [95% CI 0.86, 2.32]) hamstring strength at 3 months was not associated with higher activity levels, defined by Tegner Activity Scale in the medium term (6 months).	Hamstrings strength (isokinetic and isotonic) **was not** a significant predictor of Tegner Activity Scale medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that hamstrings strength is not associated with activity levels medium term.
Gender	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR **Jurkonis et al. (2018)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Gender showed no correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported. **Bivariate analyses** - None reported. **Multivariate analyses** - Gender was eliminated as a non-significant predictor, (p value not reported).	No relevant findings.	-	No summary possible.
BMI	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR **Jurkonis et al. (2018)**	**Bivariate or univariate analyses** - BMI showed no correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported. **Bivariate or univariate analyses**	BMI **was** a significant predictor of Tegner Activity Scale long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that BMI is associated with activity levels long term.

	HIGH ROB Outcome: long term Baseline: pre ACLR	- BMI showed a significant correlation with activity, defined by Tegner Activity Scale in the long term (12 months) ($p < 0.001$, $r = -0.33$). **Multivariate analyses** - BMI was a significant predictor of activity levels, defined by Tegner Activity Scale in the long term (12 months) ($b = -0.042$, $p = 0.008$).			
Age at surgery	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR **Jurkonis et al. (2018)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Age at surgery showed no correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported. **Bivariate or univariate analyses** - Age at surgery showed a significant correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) ($p < 0.001$, $r = -0.43$). **Multivariate analyses** - Age at surgery was a significant predictor of activity levels, defined by Tegner Activity Scale in the long term (12 months) ($b = -0.015$, $p = 0.028$).	Age at surgery **was** a significant predictor of Tegner Activity Scale long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that age at surgery is associated with activity levels long term.
Graft site	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Graft site choice showed a significant correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) ($p = 0.006$, $r = -0.34$). **Multivariate analyses** - Graft site choice was a significant predictor of greater activity levels, defined by Tegner Activity Scale in the long term (12 months) when entered into the multivariate analysis grouped with other variables ($p = 0.02$, $r^2 = 0.18$). - Graft site was the only predictor selected for the stepwise regression analysis (adjusted $r^2 = 0.08$, ß-0.23), with a patella tendon graft found to be the strongest predictor compared to a hamstring graft.	Patella tendon graft **was** a significant predictor of Tegner Activity Scale long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that patella graft is associated with activity levels long term.
Knee laxity	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Knee laxity showed a significant correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) ($p = 0.1$, $r = 0.21$). **Multivariate analyses** - Knee laxity was a significant predictor of higher activity levels, defined by Tegner Activity Scale in the long term (12 months) when entered into the multivariate analysis grouped with other variables (p	Knee laxity **was not** a significant independent predictor of Tegner Activity Scale long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that knee laxity is not associated with activity levels long term.

		= 0.02, r^2 = 0.18). However, it was not selected for forwards stepwise regression analysis as an independent predictor.			
Time from injury to ACLR	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Time from injury to ACLR showed a significant correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p = 0.02, r = -0.29). **Multivariate analyses** - Time from injury to ACLR was a significant predictor of higher activity levels, defined by Tegner Activity Scale in the long term (12 months) when entered in to the multivariate analysis grouped with other variables (p = 0.02, r^2 = 0.18). However, it was not selected for forwards stepwise regression analysis as an independent predictor.	Time from injury to ACLR **was not** a significant independent predictor of Tegner Activity Scale long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that time from injury to ACLR is not associated with activity levels long term.
Knee range of motion	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Knee range of motion showed no correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Anterior knee pain score	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Anterior knee pain score showed no correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Associated injuries	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Preoperative cartilage damage, meniscus injury and medial collateral ligament injury were not correlated with one-leg hop test distance in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
Pivot shift sign	**Heijne et al. (2009)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - Pivot shift sign showed no correlation with activity levels, defined by Tegner Activity Scale in the long term (12 months) (p value not reported). **Multivariate analyses** - None reported.	No relevant findings.	-	No summary possible.
<u>Lysholm Score</u>					

Quadriceps strength (torque)	**Pua et al. (2017a)** HIGH ROB Outcome: medium term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with a greater limb symmetry index % for both isokinetic (p = 0.02 OR 1.57, [95% CI 1.07, 2.29]) and isotonic (p = 0.03 OR 1.69, [95% CI 1.06, 2.72]) quadriceps strength at 3 months post ACLR are more likely to report a greater Lysholm Score in the medium term (6 months).	Postoperative quadriceps strength (isokinetic and isotonic) **was** a significant predictor of greater Lysholm Score medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative quadriceps strength is associated with greater Lysholm Score medium term.
Hamstrings strength (torque)	**Pua et al. (2017a)** HIGH ROB Outcome: medium term Baseline: post ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with a greater limb symmetry index % for both isokinetic (p = 0.03 OR 1.94, [95% CI 1.14, 3.31]) and isotonic (p = 0.03 OR 1.77, [95% CI 1.06, 2.94]) hamstrings strength at 3 months post ACLR are more likely to report a greater Lysholm Score in the medium term (6 months).	Postoperative hamstrings strength (isokinetic and isotonic) **was** a significant predictor of greater Lysholm Score medium term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that postoperative hamstrings strength is associated with greater Lysholm Score medium term.
Age at surgery	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR **Avadhani et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Age at surgery was not a significant predictor of successful outcome in the long term (12 months), defined as a Lysholm Score of >76 points (p value not reported). **Bivariate or univariate analyses** - Age at surgery did not influence outcome in the long term (12 months), based on reported Lysholm Score (p = 0.59). **Multivariate analyses** - None reported.	Age at surgery **was not** a significant predictor of greater Lysholm Score long term. No relevant findings.	+ Very low.	Using GRADE, there is very low-level evidence (1 study) that age at surgery is not associated with greater Lysholm Score long term.

Associated injuries	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR **Avadhani et al. (2010)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Presence of a meniscal injury was not a significant predictor of successful outcome in the long term (12 months), defined as a Lysholm Score of >76 points (p value not reported). - Preoperative cartilage defect was not a significant predictor of successful outcome in the long term (12 months), defined as a Lysholm Score of >76 points (p value not reported). **Bivariate or univariate analyses** - Presence of a meniscal injury did not to influence outcome in the long term (12 months), based on reported Lysholm Score (p = 0.43). **Multivariate analyses** - None reported.	Associated injuries **were not** significant predictors of greater Lysholm Score long term. No relevant findings.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that associated injuries are not associated with greater Lysholm Score long term.
BMI	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with lower BMI at time of surgery were more likely to have greater outcome in the long term (12 months), defined as a Lysholm Score of >76 points (p = 0.042, OR 1.21, [95% CI 1.01, 1.46]).	Preoperative BMI **was** a significant predictor of greater Lysholm Score long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative BMI is associated with greater Lysholm Score long term.
Time from injury to ACLR	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Patients with greater time from ACL injury to ACLR (>2 years) reported poorer outcome in the long term (12 months), defined as a Lysholm Score of <76 points (p = 0.004, OR 0.15, [95% CI 0.04, 0.55]).	Time from injury to ACLR **was** a significant predictor of lower Lysholm Score long term.	+ Very Low.	Using GRADE, there is very low-level evidence (1 study) that greater time from injury to ACLR is associated with lower Lysholm Score long term.

Degenerative changes	**Radwan et al. (2014)** HIGH ROB Outcome: long term Baseline: pre ACLR	**Bivariate or univariate analyses** - None reported. **Multivariate analyses** - Preoperative osteoarthritic change was not a significant predictor of successful outcome in the long term (12 months), defined as a Lysholm Score of >76 points (p value not reported).	Preoperative osteoarthritic change **was not** a significant predictor of greater Lysholm Score long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that preoperative osteoarthritic change is not associated with greater Lysholm Score long term.
Tunnel position	**Avadhani et al. (2010)** HIGH ROB Outcome: long term Baseline: post ACLR	**Bivariate or univariate analyses** - Tibial tunnel position in the sagittal plane at 10 days post ACLR did influence outcome in the long term (12 months), based on reported Lysholm Score (p <0.01). - Tibial tunnel (p = 0.31) and femoral tunnel (p = 0.19) positions at 10 days post ACLR in the coronal plane and femoral tunnel position in the sagittal plane (p = 0.39) did not influence outcome in the long term (12 months), based on reported Lysholm Score. **Multivariate analyses** - Tibial tunnel position in the sagittal plane was predictive of successful outcome in the long term (12 months), based on reported Lysholm Score (p = 0.031).	Tibial tunnel position in the sagittal plane **was** a significant predictor of greater Lysholm Score long term.	+ Very Low	Using GRADE, there is very low-level evidence (1 study) that tibial tunnel position in the sagittal plane is associated with greater Lysholm Score long term.

ROB; risk of bias, ACLR; anterior cruciate ligament reconstruction, KOOS; Knee injury and Osteoarthritis Outcome Score, KOOS-QOL; Knee injury and Osteoarthritis Outcome Score-Quality of Life, KOOS-SR; Knee injury and Osteoarthritis Outcome Score-Sport/Recreation, GRADE; Gradings of Recommendations Assessment Development and Evaluation, BMI; body mass index, CI; confidence intervals, IKDC; International Knee Documentation Committee, OR; odds ratio.

IKDC

Three studies (6 articles) [29-32, 37, 42] evaluated 11 prognostic factors for long term IKDC outcome (Table 5). In the long term (12 months & 5 years) preoperative BMI, time from injury to ACLR (1 study [42]) and postoperative tunnel position (10 days, 1 study [37]) were associated with greater overall function (IKDC score); whereas postoperative degenerative changes (patellofemoral cartilage lesions; 12 months, 1 study [29-32]) was associated with poorer overall function (IKDC score). Age at surgery, preoperative associated injuries, degenerative changes (1 study [42]), postoperative functional performance, triple crossover hop for distance, side hop, 1-leg rise and hop distance (12 months, 1 study [29-32]) were not associated with IKDC scores. Using GRADE, low-level evidence supports: postoperative degenerative changes associated; and postoperative functional performance, triple crossover hop for distance, side hop 1-leg rise and hop distance not associated with IKDC scores long term. Very low-level evidence supports: preoperative BMI, time from injury to ACLR and postoperative tunnel position associated; and age at surgery, preoperative associated injuries, degenerative changes were not associated with IKDC scores long term.

Tegner Activity Scale

Three studies [35, 38, 39] evaluated 12 prognostic factors for medium and long term outcome Tegner Activity Scale outcome (Table 5). In the medium term (6 months), postoperative greater quadriceps strength (3 months, 1 study [35]) was associated with greater Tegner Activity Scale score; while postoperative hamstring strength (3 months, 1 study [35]) was not associated with Tegner Activity Scale. In the long term (12 months), preoperative BMI, age at surgery (1 study [39]) and graft site (patella tendon; 1 study [38]) were associated with greater Tegner Activity Scale score; while preoperative quadriceps strength, knee laxity and time from injury to ACLR were not associated (1 study [38]) with the Tegner Activity Scale. Using GRADE, very low-level evidence supports: all prognostic

factors associated or not associated with greater Tegner Activity Scale scores for medium and long term outcome.

Lysholm Score

Three studies [35, 37, 42] evaluated 8 prognostic factors for medium or long term Lysholm Score outcome (Table 5). In the medium term (6 months), postoperative greater quadriceps and hamstring strength (3 months, 1 study [35]) was associated with greater Lysholm scores. In the long term (12 months), postoperative tunnel position (10 days, 1 study [37]) and lower preoperative BMI (1 study [42]) were associated with greater Lysholm scores; with time from injury to ACLR (>2 years; 1 study [42]) associated with poorer Lysholm scores; while age at surgery, associated injuries and degenerative changes (preoperatively; 1 study [42]) were not associated with Lysholm scores. Using GRADE, very low-level evidence supports: all prognostic factors associated or not associated with Lysholm scores for medium and long term.

DISCUSSION

This is the first low risk of bias systematic review focusing on physical prognostic factors predicting outcome following ACLR. The review included 13 prospectively designed studies (16 articles), with only 1 study at low risk of bias. Given this, confidence in the quality of current literature relating to physical prognostic factors is limited.

Based on GRADE, the key finding is there was low-level evidence demonstrating that postoperative degenerative changes and poorer lower-limb strength (and resultant poorer functional performance) were associated with poorer long term patient outcome. Specifically, postoperative cartilage damage in the patellofemoral joint may predict poorer

scores on all KOOS subscales at 3 years, whilst the inability to perform ≥22 1-leg rises (single leg sit-to-stand) at 12 months post-ACLR may predict poorer outcome at 3 years. Furthermore, <90% limb symmetry index on side hop at 12 months post-ACLR may predict poorer outcome at 5 years. As both modifiable prognostic factors and highly generic sporting movements, 1-leg rise and side hop may therefore be of particular clinical significance as measurable factors and used throughout rehabilitation to monitor overall lower-limb strength, performance and readiness for RTS.

Numerous physical prognostic factors and outcomes were investigated across included studies and overall many demonstrated very low-level evidence. Pre and postoperative prognostic factors were evident and were most commonly assessed for medium and long term outcome. A large proportion of the short and medium term outcomes (predominantly performance-based) demonstrated potential importance of both pre and postoperative knee range of motion (knee extension deficit) and muscle strength (quadriceps and hamstrings). However, it is noted these findings largely centre around two high risk of bias medium term outcome studies [35, 36]. When considering long term outcome, there was a preference to PROMs (e.g. KOOS), again with very low-level evidence for potential prognostic factors including knee range of motion, associated injuries and time from injury to ACLR.

Quadriceps strength featured heavily as a predictor of outcome (6 outcomes), and is consistent with previous reviews [15-17], and more recent guidelines [46]. However, other findings regarding graft site selection differ from the recent literature [16] with 2 studies providing very low-level evidence that long term failure was more likely with a hamstrings graft.

Importantly a number of modifiable prognostic factors were identified including 1-leg rise and side hop performance, which had overall low-level evidence for poorer outcome following ACLR. Notwithstanding a very low-level of evidence, low BMI was associated with an improvement in multiple measures (e.g. Tegner Activity Scale, KOOS and IKDC). Findings highlighted that multiple factors, (e.g. quadriceps strength), can predict outcome post- as well as preoperatively. This establishes the importance of measuring and reviewing quadriceps strength and functional performance throughout rehabilitation and not only at end-stage rehabilitation. Optimal quadriceps and lower-limb strength are essential in most sporting activities for greater performance and reducing risk of re-injury. Regular monitoring of quadriceps strength may be a useful tool/adjunct to support timely introduction of functional and sport specific movements and techniques in the rehabilitation process, rather than progression based solely on time since ACLR. However, although quadriceps strength has been identified as a potential prognostic factor to poorer outcome and an important marker to monitor throughout rehabilitation, clinically if quadriceps strength is not improving, further evaluation may be warranted by the therapist to establish potential reasons for this and to enable progression with rehabilitation and for an improved outcome long term. For example, increased pain, potential anxiety or lack of engagement with rehabilitation. This can be applicable not only for quadriceps strength but for any modifiable prognostic factor identified.

Interestingly when considering function (e.g. hop tests), quadriceps strength was identified as a physical prognostic factor – the only factor with synthesis across >1 study, whilst other factors such as age at surgery and BMI were not predictive. In contrast, when considering the Tegner Activity Scale (PROM), factors of age at surgery and BMI were predictive of outcome, but quadriceps strength was not. This represents a difference in physical prognostic factors, depending on approach to evaluation (PBOM or PROM). It could be

questioned whether general activity levels decrease with increasing age and BMI, meaning use of the Tegner Activity Scale is appropriate to acquire this data. Whereas younger people with lower BMI may arguably exhibit higher activity levels which demonstrate a ceiling effect in the sensitivity of the Tegner Activity Scale. Such thought is important clinically when considering patient-orientated goals and use of relevant monitoring outcome measures, which may vary dependent on the specific population. Given this, if RTS is a patient goal it is interesting to note that most PBOMs were evaluated over the medium term (≥3 months, <12 months) with muscle strength of particular significance. In contrast, long term outcome primarily focused on PROMs, which may have implications for end stage rehabilitation and RTS.

Many of the findings of this review are informed by single studies at high risk of bias and constituting very low-level evidence. Given that this body of literature and evidence is very low, discrimination between predictive factors is limited. Furthermore, the strongest findings of this review suggest greater postoperative quadriceps strength as a significant predictor of outcome following ACLR. Logic would therefore suggest that greater preoperative strength could contribute to greater postoperative strength. Clinically, these findings may inform preoperative management and rehabilitation and may assist in reducing the observed postoperative degenerative changes. However, it is acknowledged that although prognostic factors such as quadriceps strength have been identified to predict outcome, additional factors can contribute to why someone may have reduced quadriceps strength and these need to be taken into consideration when planning and progressing rehabilitation. A low risk of bias prospective observational cohort study with adequate follow-up, investigating the importance and optimal level of preoperative quadriceps strength to facilitate successful outcome following ACLR is therefore needed.

Strengths and limitations

A commonly encountered problem related to participant age, which was often poorly reported with some studies failing to report age range, making screening of eligible studies challenging. Furthermore, many studies included participants <16 years old, without the ability to separate results based on age, leading to numerous studies being excluded. However, given possible complications arising from involvement of the epiphyseal plate it can be argued that providing guidance and rehabilitation recommendations for wider populations based on skeletally immature participants would not be 'best practice' [47].

This study was conducted in line with PRISMA guidelines and synthesised evidence regarding physical prognostic factors that predict outcome following ACLR. The QUIPS tool was adopted to assess for risk of bias and overall quality of evidence was evaluated using a modified GRADE tool. However, the review is limited by high risk of bias across most included studies and this, alongside heterogeneity of prognostic factors contributed to meta-analyses not being possible. Studies not written in English were excluded (n = 5), and may result in missing important data.

CONCLUSIONS

Findings indicate a low-level evidence that postoperative lower-limb strength (1-leg rise and side hop) and degenerative changes are predictors of outcome long term. Furthermore, very low-level evidence showed associations between greater quadriceps strength and lower preoperative BMI with better outcome following ACLR. On a practical level, these are all modifiable factors and give insight into key factors which can be monitored by clinicians and

evaluated at an earlier stage to optimise rehabilitation. This is therefore highly relevant to clinical practice.

A wide body of literature exists within this field, but design and quality of many studies remains questionable. This review has identified multiple physical prognostic factors. However, these findings are from low or very-low quality evidence overall, bringing into question how confident we can be translating this evidence into clinical practice. Prognostic research is crucial for clinical decision making, with this review highlighting the potential importance of lower-limb strength in predicting outcome. However, further low risk of bias prognostic studies are now required to identify further potential prognostic factors. Future studies should consider both pre and postoperative physical factors and ensure appropriate outcome measures are used at consistent timepoints in order for comparisons and conclusions to be made.

DECLARATIONS

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Conflicts of Interest
None declared

Ethical Approval
Ethical approval was not required for this systematic review.

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Conflicts of Interest

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Ethical Approval

None declared

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Ethical Statement

No participants/informed consent was required due to the nature of the study being a systematic review. Therefore, ethical approval/informed consent was not required.