YOUNG PEOPLE WITH OLD KNEES: POST-TRAUMATIC OSTEOARTHRITIS FOLLOWING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Brooke Patterson

Bachelor of Physiotherapy (Honours)

Submitted in total fulfilment of the requirements of the degree of Doctor of Philosophy

School of Allied Health, Human Services, and Sport

College of Science, Health and Engineering

La Trobe University, Victoria, Australia

December 2020

Table of Contents

List of Figures

List of Tables

List of Abbreviations

AAOS	American Academy of Orthopaedic Surgeons
ACL	Anterior cruciate ligament
ACL-QoL	Anterior Cruciate Ligament Quality of Life questionnaire
ACLR	Anterior cruciate ligament reconstruction
ACL-RSI	Anterior Cruciate Ligament Return-to-sport after Injury scale
ADL	Activities of daily living
AGREE	Appraisal of Guidelines for REsearch and Evaluation
AKPS	Anterior Knee Pain Scale
APTA	American Physical Therapy Association
β	Standardised regression coefficient
BLOKS	Boston Leeds Osteoarthritis Knee Score
BMI	Body mass index
BML	Bone marrow lesion
BPTB	Bone patella tendon bone
CERT	Consensus on Exercise Reporting Template
CI	Confidence interval
CL	Contralateral limb
cm	Centimetres
CONSORT	CONsolidated Standards Of Reporting Trials guidelines
CPG	Clinical practice guideline
CPM	Continuous passive motion
DOA	Dutch Orthopaedic Association
FOV	Field of view
GEE	Generalised estimating equations
GROC	Global rating of change
HEC	Human Ethics Committee
MREC	Medical Research Ethics Committee
ICC	Intra-class correlation coefficient
IKDC	International Knee Documentation Committee
IQR	Interquartile range
KANON	Knee Anterior Cruciate Ligament Nonsurgical Versus Surgical trial
Kg	Kilograms

KNALL	The Knee Osteoarthritis Anterior Cruciate Ligament Lesion study
KNGF	Royal Dutch Society for Physical Therapy
KOALA	Knee Osteoarthritis Anterior Cruciate Ligament Longitudinal Assessment study
KOOS	Knee injury and Osteoarthritis Outcome Score
KOSS	Knee Osteoarthritis Scoring System
KT-1000	Knee laxity Testing device
LSI	Limb symmetry index
m	Metre
MCID	Minimal clinically important difference
MDC	Minimal detectable change
mm	Millimetres
MOAKS	Magnetic resonance imaging OsteoArthritis Knee Score
MOON	Multicentre Orthopaedic Outcomes Network
MRI	Magnetic resonance imaging
msec	Milliseconds
n	Number
n.a	Not applicable
NHMRC	National Health and Medical Research Council
NZGG	New Zealand Guidelines Group
OA	Osteoarthritis
OARSI	OsteoArthritis Research Society International
OR	Odds ratio
p	Statistical significance level
PABAK	Prevalence-adjusted bias-adjusted kappa
PASS	Patient acceptable symptom state
PD	Proton density
PF	Patellofemoral
PrE-OA	The Alberta Youth PRevention of Early Osteoarthritis study
PROs	Patient-reported outcomes
QoL	Quality of life
RCT	Randomised controlled trial
ROM	Range of motion
RR	Risk ratio
RTS	Return-to-sport
SD	Standard deviation

SEM	Standard error of measurement
SRD	Smallest real difference
STIR	Short-tau inversion-recovery
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUPER-KNEE	SUpervised exercise therapy and Patient Education Rehabilitation study
TF	Tibiofemoral
TIDieR	Template for Intervention Description and Replication guidelines
TKR	Total knee replacement
TR	Repetition time
TE	Echo time
TSE	Turbo spin echo
USA	United States of America
VISTA	Volumetric isotropic turbo spin echo acquisition sequence
WB	Weight-bearing
WORMS	Whole-Organ Magnetic Resonance Imaging Score

Abstract

Anterior cruciate ligament (ACL) injury predominantly occurs in young people participating in jumping and pivoting sports. Despite surgical ACL reconstruction (ACLR), approximately 50% will develop post-traumatic knee osteoarthritis (OA) within 10 years. These 'young people with old knees' often live with persistent symptoms and poor quality of life (QoL). Magnetic resonance imaging (MRI) is sensitive to change in all joint features, providing a better alternative to assess early OA features and their changes over shorter follow-ups, than traditional radiographs. Evaluating changes in post-traumatic OA features on MRI and their association with patient-reported and functional outcomes will enhance understanding of post-traumatic OA. Testing potential solutions for those with persistent symptoms following ACLR will provide new opportunities for research and clinical practice.

This thesis aimed to evaluate:

(i) changes in OA features on MRI, patient-reported and functional outcomes, between one and five years post-ACLR and to identify factors associated with structural and symptomatic changes; and

(ii) the feasibility of a randomised controlled trial (RCT) evaluating a physiotherapist-guided intervention for individuals with persistent symptoms one-year post-ACLR.

A longitudinal prospective study, including four published papers, addressed the first aim and a pilot RCT addressed the second aim.

Worsening of OA features was mostly evident in the patellofemoral compartment and in those with a high body mass index. Half of the participants had persistent symptoms, and only one-in-five passed the functional performance test battery at the one-year assessment. Poor function at the one-year assessment was associated with higher risk of worsening patellofemoral OA features.

The physiotherapist-guided intervention was feasible, with an acceptable eligibility rate (47%) and physiotherapy attendance (>85%). Potential worthwhile effects for knee-related symptoms, function, and QoL were observed, and a fully-powered trial is now needed. These findings are an important step towards reducing the burden of post-traumatic OA in young adults following ACLR.

Keywords

knee, anterior cruciate ligament, reconstruction, osteoarthritis, magnetic resonance imaging, patient-reported outcomes, functional performance, rehabilitation, physiotherapy

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 110314, Orthopaedics, 40%

ANZSRC code: 110317, Physiotherapy, 40%

ANZSRC code: 110322, Rheumatology and Arthritis, 20%

Fields of Research (FoR) Classification

FoR code: 1103, Clinical Sciences 100

Statement of Authorship

I, Brooke Elise Patterson, declare that this thesis includes work by the author that has been published or accepted for publication as described in the text. Except where reference is made in the text of the thesis, this thesis contains no other material published elsewhere or extracted in whole or in part from a thesis accepted for the award of any other degree or diploma. No other person's work has been used without due acknowledgment in the main text of the thesis. This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

I am the primary author on all publications in this thesis (four published, one under review). Details of the extent and nature of my contribution, as well as that of co-authors and collaborators, is outlined in on pages xix-xxiii, with confirmation of authorship documentation presented in Appendix X. I am a co-author on additional publications obtained during the period of candidature, which are listed on pages xxvi-xxvii; these are not submitted as a component of this PhD.

All research procedures reported in this thesis were approved by the La Trobe University Human Ethics Committee. This PhD candidature was supported by a National Health and Medical Research Council (NHMRC) postgraduate scholarship (No. 1114296) and a La Trobe University Postgraduate Research top-up scholarship. Project costs were funded by a University of Melbourne Research Collaboration Grant (Crossley & Pandy, 2009), the Queensland Orthopaedic Physiotherapy Network (Culvenor, 2013), an Arthritis Australia National Research Program Grant (Culvenor, Crossley, & Vicenzino, 2015), a La Trobe University Sport, Exercise and Rehabilitation Research Focus Area Grant (Crossley, Culvenor, & Patterson, 2016), a Physiotherapy Research Foundation, Beryl Haines Memorial Grant (Patterson, Crossley, & Culvenor, 2016), and the La Trobe University Social Research Platform (Patterson & Barton, 2017).

Name: Brooke Patterson 4th December 2020

Acknowledgements

Thank you to my amazing supervisors Professor Kay Crossley, Dr Adam Culvenor, and Dr Christian Barton. I am incredibly thankful to have you as mentors; you are like a second family and you constantly inspire me in your own unique ways. Kay, I will be forever grateful for your generosity and patience, and the thousands of hours of meetings, phone calls, and reviewing work. Thank you for the opportunities to travel the world, to connect with and learn from your international colleagues and friends. I am constantly learning from you and being challenged; thank you for doing it in the most supportive and thoughtful way. Thank you for teaching me to celebrate the little wins, to be vulnerable, and to (sometimes) say no. I hope that one day I can return your incredible generosity and investment into my career. You are an absolute inspiration to me and everyone around you, and I cherish your mentorship and friendship more than I can describe. Adam, I cannot thank you enough for opening the door for me to embark on a PhD in what has been a life-changing and rewarding experience. I admire your enthusiasm, humble nature, and ability to explain complex concepts in a simple way without ever making me feel silly! Thank you for all the early morning online meetings and your patience with teaching me something new. Christian, I value your opinion so highly, whether it be related to work or life, and I can't wait to keep learning from you over the next few years. You inspire me with your passion to improve outcomes for patients, your commitment to developing your colleagues professionally, and bringing as many people in the team along for the ride.

A huge thank you to my LASEM family, you make coming to work something I look forward to every day. To the original KC Sunshine Band – Jade, Josh, Mark, and Matt, you have made the last four years so enjoyable and I will cherish your friendships forever. You have been so generous with your time in providing guidance and advice, whether it be research-related, general adulting assistance, or the latest injury. Jade, you are hands-down one of the most caring and thoughtful people I know. Thank you for all the coffees and commuting chats and for going above and beyond to offer assistance. Josh and Mark, thank you for being the voices of reason and for making us all laugh at the most appropriate and inappropriate times. Matt, I am very lucky to have someone who I know I can rely on to always have my back and to know, without even asking, when a pick-me-up is needed. Thank you to some inspiring LASEM women – Dr Joanne Kemp, Dr Andrea Mosler, Dr Andrea Bruder, Melissa Haberfield, and Maddi Hannington for your genuine mentorship, advice, and care. To Brukie, thank you for your mentorship, guidance, and support.

Todd, thank you for your unwavering support of all my pursuits in life and for encouraging me to take opportunities as they presented. Thank you for knowing when to tell me to take a break and when to push, and for organising all our date nights and holidays. Thank you mum and dad for the opportunities you have provided for me, for encouraging me to do what I love, and for being role models for what it means to work hard and be humble. Erin, thank you for listening to my long-winded explanations of the latest project or current state of my PhD. I cherish our relationship more than you know and I admire your work ethic, care for others, and ability to have fun while you are doing it. To Rod, Maree, and Lisa, thank you for your support and for always checking in, providing baked goods, and understanding our crazy and busy lifestyles over the last four years. To my teammates, coaches, and support staff at the Melbourne Football Club; embarking on a journey as a semi-professional football player while completing a PhD was never going to be an easy task, but your encouragement, understanding, and flexibility have made it one of the most rewarding experiences of my life. Thanks to my friends, for understanding the busy times and for keeping me balanced with social outings, adventures, and holidays.

Thank you to my panel members, Randall Cooper and Associate Professor Jodie McClelland; your guidance always provides perspective and balance, and is greatly appreciated. Thank you to Mr Hayden Morris, Mr Timothy Whitehead, Mr Dirk Van Bavel, Mr Justin Wong, Mr Ben Campbell, Mr Nigel Hartnett, and Mr Paul Einoder; without your support and facilitation of recruitment, these projects would not be possible. To Mark Ward and the administrative staff at Imaging @ Olympic Park, your patience, collaboration, and endorsement of this research is greatly appreciated. Thank you to the participants who gave up their time to be involved in each project.

Thanks must also go to the National Health and Medical Research Council for providing me with a post-graduate scholarship and La Trobe University for a top-up scholarship. This work was also supported by an Australian Government Research Training Program Scholarship. Thank you to Associate Professor Jacki Whittaker, Associate Professor Martin Hagglund, Professor Carolyn Emery, Dr Merete Moller, and Associate Professor Joshua Stefanik for hosting me at your institutions and homes. Those trips were invaluable to my learning and I have made long-lasting professional and personal friendships. Thank you to the family of Felice Rosemary-Lloyd for a travelling scholarship and to La Trobe University for helping make these international trips financially possible.

Never have I been so challenged in a mental, physical, and emotional sense, but it would not have been one of the most enjoyable periods of my life without all of you that have helped in some way along the journey. So, thank you, and this sense of achievement and pride would not exist without you all in my life.

Professional service acknowledgements:

- Reduced service fees were granted by Imaging @ Olympic Park for completion of participant MRI and radiographs.
- Reduced service fees were granted by Complete Sports Care and BodySystem Physiotherapy for the physiotherapy-guided intervention in Chapter 8.
- Olympic Park Sports Medicine Centre provided access to their facility for assessments in Part B, free of charge.
- Kirsty Balog (KBS Academic Proofreading; The Expert Editor) for editing and proofreading services for this thesis. These services were provided in accordance with the Guidelines for Editing Research Theses under the Australian Standards for Editing Practices

Contribution by others to thesis:

Substantial inputs were made by others to the research design, data collection, and analysis represented in this thesis. Prof Karim Khan, Prof Marcus Pandy, and Prof Bill Vencenzino assisted my supervisors Prof Kay Crossley and Dr Adam Culvenor in obtaining project funding for the longitudinal cohort in Part B. Dr Luke Perraton assisted Adam Culvenor to complete the data collection one year following ACLR for Part B.

Grants and Funding Awarded During PhD

Description	Organisation	Amount
Patterson BE, Culvenor AG. (2019). Are we listening? Patient perspective and experience on rehabilitation following anterior cruciate ligament reconstruction surgery.	La Trobe University Social Research Platform Grant	$2,000
Patterson BE, Crossley KM, Culvenor AG. (2016). Feasibility of an RCT for physiotherapy intervention in patients at high risk of early-onset knee osteoarthritis and symptomatic decline following ACLR.	Physiotherapy Research Foundation, Beryl Haines Memorial Research Grant	$9,600
Patterson BE. (2017).	Felice Rosemary Lloyd Scholarship (ID: 2000001482)	$6,500
Patterson BE, Barton CJ. (2017). Developing patient resources for an RCT for physiotherapy intervention in patients at high risk of early-onset knee osteoarthritis and symptomatic decline following ACLR.	La Trobe University Social Research Platform Grant	$2,700
Patterson BE. (2017). Higher degree support grant.	School of Allied Health, La Trobe University	$5,000
Patterson BE. (2016). Dora Lush Post Graduate Scholarship.	National Health and Medical Research Council (NHMRC) (ID: GNT1114296)	$99,954
Patterson BE. (2019). Post Graduate Top-up Scholarship.	School of Allied Health, La Trobe University	$33,318
Crossley KM, Culvenor AG, **Patterson BE** (nee Howells). (2016). Identification of individuals at risk of early knee osteoarthritis following ACLR: An exploratory study.	La Trobe University Sport, Exercise & Rehabilitation Research Focus Area Grant (ID: 1025950)	$25,000
Unrelated to PhD topic:		
Crossley KM, Mosler AB, Bruder AM, **Patterson BE**, Cowan, S. (2020). Implementing prep-to-play in women's community football.	Australian Football League Research Board Grant	$150,000
Crossley KM, Mosler AB, Bruder AM, **Patterson BE**, Donaldson A. (2018). Development of an injury risk reduction program for elite female Australian Rules footballers.	Australian Football League Research Board Grant	$53,000
King MG, **Patterson BE**. (2018). PhD symposium.	Research Education and Development, La Trobe University	$350
		$387,422

Publications, Presentations, and Awards Arising from this Thesis

Peer-reviewed publications

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2018). Worsening knee osteoarthritis features on magnetic resonance imaging 1 to 5 years after anterior cruciate ligament reconstruction. *American Journal of Sports Medicine, 46*(12), 2873-2883.

Incorporated as Chapter 3

Contributor	Statement of Contribution
Brooke E Patterson (Candidate)	Designed research question (30%), ethics application (60%), recruited participants (30%), performed data collection (50%), performed X-ray grading (40%), statistical analysis (40%), prepared tables and figures (70%), wrote manuscript (55%).
Adam G Culvenor	Designed research question (30%), obtained project funding (50%), ethics application (20%), recruited participants (50%), performed data collection (50%), performed X-ray grading (40%), statistical analysis (20%), prepared tables and figures (10%), edited manuscript (10%).
Christian J Barton	Designed research question (10%), statistical analysis (10%), prepared tables and figures (10%), edited manuscript (10%).
Ali Guermazi	Performed MRI grading (100%), edited manuscript (5%).
Joshua J Stefanik	Assisted in data analysis (10%), statistical analysis (20%), edited manuscript (5%).
Hayden G Morris	Performed surgery (50%), recruitment (10%), edited manuscript (5%).
Timothy S Whitehead	Performed surgery (50%), recruitment (10%), edited manuscript (5%).
Kay M Crossley	Designed research question (30%), obtained project funding (50%), ethics application (20%), performed X-ray grading (20%), statistical analysis (10%), prepared tables and figures (10%), edited manuscript (5%).

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., & Crossley, K.M. (2020). Patient-reported outcomes one to five years after anterior cruciate ligament reconstruction: the effect of combined injury and associations with osteoarthritis features defined on magnetic resonance imaging. *Arthritis Care & Research, 72*(3), 412-422.

Incorporated as Chapter 4

Contributor	Statement of Contribution
Brooke E Patterson (Candidate)	Designed research question (30%), wrote ethics application (60%), recruited participants (40%), performed data collection (50%), performed X-ray grading (40%), statistical analysis (40%), prepared tables and figures (70%), wrote manuscript (60%).
Adam G Culvenor	Designed research question (30%), obtained project funding (50%), edited ethics application (20%), recruited participants (60%), performed data collection (50%), performed X-ray grading (40%), statistical analysis (20%), prepared tables and figures (10%), edited manuscript (10%).
Christian J Barton	Designed research question (10%), statistical analysis (10%), prepared tables and figures (10%), edited manuscript (10%).
Ali Guermazi	Performed MRI grading (100%), edited manuscript (5%).
Joshua J Stefanik	Assisted in data analysis (10%), statistical analysis (20%), edited manuscript (5%).
Kay M Crossley	Designed research question (30%), obtained project funding (50%), edited ethics application (20%), performed X-ray grading (20%), statistical analysis (10%), prepared tables and figures (10%), edited manuscript (10%).

Patterson, B.E., Crossley, K.M., Perraton, L.G., Kumar, A.S., King, M.G., Heerey, J.J., Barton, C.J., & Culvenor, A.G. (2020). Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function. *Physical Therapy in Sport, 44*, 67-74.

Incorporated as Chapter 5

Contributor	Statement of Contribution
Brooke E Patterson (Candidate)	Designed research question (30%), wrote ethics application (60%), recruited participants (30%), performed data collection (30%), statistical analysis (40%), prepared tables and figures (50%), wrote manuscript (55%).
Kay M Crossley	Designed research question (30%), obtained project funding (50%), edited ethics application (20%), statistical analysis (20%), prepared tables and figures (10%), edited manuscript (5%).
Luke G Perraton	Recruited participants (20%), performed data collection (20%), edited manuscript (5%).
Avnish S Kumar	Prepared tables and figures (20%), edited manuscript (5%).
Matthew G King	Recruited participants (10%), performed data collection (10%), edited manuscript (5%).
Joshua J Heerey	Recruited participants (10%), performed data collection (10%), edited manuscript (5%).
Christian J Barton	Designed research question (10%), prepared tables and figures (10%), statistical analysis (20%), edited manuscript (10%).
Adam G Culvenor	Designed research question (30%), obtained project funding (50%), edited ethics application (20%), recruited participants (30%), performed data collection (30%), statistical analysis (20%), prepared tables and figures (10%), edited manuscript (10%).

Patterson, B.E, Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2020). Poor functional performance 1 year after ACL reconstruction increases the risk of early osteoarthritis progression. *British Journal of Sports Medicine, 54*(9), 546-553.

Incorporated as Chapter 6

Contributor	Statement of Contribution
Brooke E Patterson (Candidate)	Designed research question (30%), wrote ethics application (60%), recruited participants (30%), performed data collection (50%), performed X-ray grading (40%), statistical analysis (40%), prepared tables and figures (70%), wrote manuscript (55%).
Adam G Culvenor	Designed research question (30%), obtained project funding (50%), edited ethics application (20%), recruited participants (50%), performed data collection (50%), performed X-ray grading (40%), statistical analysis (20%), prepared tables and figures (10%), edited manuscript (10%).
Christian J Barton	Designed research question (10%), statistical analysis (10%), prepared tables and figures (10%), edited manuscript (10%).
Ali Guermazi	Performed MRI grading (100%), edited manuscript (5%).
Joshua J Stefanik	Assisted in data analysis (10%), statistical analysis (20%), edited manuscript (5%).
Hayden G Morris	Performed surgery (50%), assisted with recruitment (10%), edited manuscript (5%).
Timothy S Whitehead	Performed surgery (50%), assisted with recruitment (10%), edited manuscript (5%).
Kay M Crossley	Designed research question (30%), obtained project funding (50%), edited ethics application (20%), performed X-ray grading (20%), statistical analysis (10%), prepared tables and figures (10%), edited manuscript (5%).

Patterson BE, Culvenor AG, Cooper RL, Barton CJ, Crossley KM. Exercise therapy and education for individuals one year after anterior cruciate ligament reconstruction: A pilot randomised controlled trial. Under review at *BMC Musculoskeletal Disorders*.

Incorporated as Chapter 8

Contributor	Statement of Contribution
Brooke E Patterson (Candidate)	Designed research question (20%), wrote ethics application (60%), obtained project funding (30%), recruited participants (100%), designed intervention protocol (40%), performed data collection (100%), statistical analysis (60%), prepared tables and figures (60%), wrote manuscript (50%).
Adam G Culvenor	Designed research question (30%), obtained project funding (30%), edited ethics application (20%), designed intervention protocol (10%), statistical analysis (20%), prepared tables and figures (10%), edited manuscript (10%).
Randall L Cooper	Designed intervention protocol (20%), prepared tables and figures (10%), edited manuscript (10%).
Christian J Barton	Designed research question (20%), obtained project funding (10%), edited ethics application (10%), designed intervention protocol (20%), statistical analysis (10%), prepared tables and figures (10%), edited manuscript (20%).
Kay M Crossley	Designed research question (30%), obtained project funding (30%), edited ethics application (10%), designed intervention protocol (10%), statistical analysis (10%), prepared tables and figures (10%), edited manuscript (10%).

Conference presentations

1. **Patterson BE**, Crossley KM, Perraton L, Kumar A, Heerey J, King, M, Barton CJ, Culvenor AG. Limb symmetry on functional tests improves between 1 and 5 years after ACLR, primarily due to worsening contralateral limb function. *Abstract accepted for oral presentation at the International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) conference,* 2020, October 6-8, Melbourne, Australia - cancelled due to COVID-19.
2. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Worse functional performance 1-year after ACLR increases risk of worsening osteoarthritis features on MRI. *OsteoArthritis Research Society International (OARSI),* 2020, April 30-May 4, Vienna, Austria – cancelled due to COVID-19.
3. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Worse functional performance 1-year after ACLR increases risk of worsening osteoarthritis features on MRI. *St Vincents Hospital, Department of Orthopaedics, Annual Orthopaedic Showcase,* 2019, December 6, Melbourne, Australia.
   Winner: Best Student Presentation
4. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Exercise therapy and education for early-onset knee osteoarthritis following ACL reconstruction: A pilot randomised clinical trial, *Sports Medicine Australia Conference,* 2019, October 23-27, Twin Waters, Australia.
5. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Worse functional performance 1-year after ACLR increases risk of worsening osteoarthritis features on MRI. *World Congress of Science and Football,* 2019, June 4-6, Melbourne, Australia.
6. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Worse function 1-year after ACLR increases risk of worsening MRI osteoarthritis features. *XXVIII International Conference of Sport Rehabilitation and Traumatology Football Medicine Strategies,* 2019, April 28-30, London, UK.
7. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Patient-reported outcomes after anterior cruciate ligament reconstruction: Effect of combined injury and early osteoarthritis features. *Sports Medicine Australia Conference,* 2018, October 10-13, Perth, Australia.
8. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Changes in MRI osteoarthritis features damage between 1 and 5 years following anterior cruciate ligament reconstruction. *Canadian Bone and Joint Conference,* 2018, May 10-12, London, Ontario.
9. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Changes in cartilage damage between 1 and 5 years following anterior cruciate ligament reconstruction. *Australian Physiotherapy Association Conference,* 2017, October 19-21, Sydney, Australia.

10. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Shared decision making rarely occurs during return-to-sport following anterior cruciate ligament reconstruction. *Australian Physiotherapy Association Conference,* 2017, October 19-21, Sydney, Australia.
11. **Patterson BE**, Crossley KM, Culvenor AG, Barton CJ. Shared decision making rarely occurs during return-to-sport following anterior cruciate ligament reconstruction. *XXVI International Conference of Sport Rehabilitation and Traumatology Football Medicine Strategies*, 2016, May 9-11, Barcelona, Spain.

Awards

1. Winner: Best Student Presentation

   Patterson BE, Crossley KM, Culvenor AG, Barton CJ. Worse functional performance 1-year after ACLR increases risk of worsening osteoarthritis features on MRI. *St Vincents Hospital, Department of Orthopaedics, Annual Orthopaedic Showcase,* 2019.
2. Winner: Sports Physiotherapy Australia Best New Investigator

   Patterson BE, Crossley KM, Culvenor AG, Barton CJ. Shared decision making rarely occurs during return-to-sport following anterior cruciate ligament reconstruction. *Australian Physiotherapy Association Conference 2017, October 19-21, Sydney, Australia.*
3. Runner-up: School of Allied Health, Three-minute thesis

   Patterson BE. Young adults with old knees. *School of Allied Health, Three-minute thesis* 2019.

Additional Publications and Presentations During Candidature

Additional peer-reviewed publications obtained during candidature

1. Haberfield MJ, **Patterson BE**, Crossley KM, Bruder AM, Guermazi AG, Whitehead TS, Morris HG, & Culvenor AG. (2020). Should return to pivoting sport be avoided for the secondary prevention of osteoarthritis after anterior cruciate ligament reconstruction? A prospective cohort study with MRI, radiographic and symptomatic outcomes. *Osteoarthritis and Cartilage* (under review).
2. Crossley KM, **Patterson BE**, Culvenor AG, Bruder AM, Mosler AB, & Mentiplay BF. (2020). Making football safer for women: A systematic review and meta-analysis of injury prevention programmes in 11 773 female football (soccer) players. *British Journal of Sports Medicine, 54*(18), 1089-1098.
3. Bruder AM, Crossley KM, Mosler AB, **Patterson BE,** Haberfield M, & Donaldson A. (2020). Co-creation of a sport-specific anterior cruciate ligament injury risk reduction program for women: A concept mapping approach. *Journal of Science and Medicine in Sport*, *23*(4), 353-360.
4. Collins NJ, Tan JM, Menz HB, Russell, TG, Smith AJ, Vicenzino B, Munteanu SE, Hinman RS, Haines TP, Hart HF, **Patterson BE**, Cleary G, Donnar JW, Maclachlan LR, & Crossley KM. (2019). The FOOTPATH study: Protocol for a multicentre, participant- and assessor-blind, parallel group randomised clinical trial of foot orthoses for patellofemoral osteoarthritis. *British Medical Journal Open*, *9*(4), e025315.
5. Bourne MN, Mentiplay BF, Carey DL, **Patterson BE**, & Crossley KM. (2019). Eccentric knee flexor weakness in elite female footballers 1-10 years following anterior cruciate ligament reconstruction. *Physical Therapy in Sport, 37*, 144-149.
6. Barton CJ, de Oliveira Silva D, **Patterson BE**, Crossley KM, Pizzari T, & Nune GS. (2019). A proximal progressive resistance training program targeting strength and power is feasible in people with patellofemoral pain. *Physical Therapy in Sport, 38,* 59-65.
7. Macri EM, **Patterson BE**, Crossley KM, Stefanik, JJ, Guermazi A, Blomqwist E, Khan KM, Whitehead TS, Morris HG, & Culvenor, AG. (2019). Does patellar alignment or trochlear morphology predict worsening of patellofemoral disease within the first 5 years after anterior cruciate ligament reconstruction? *European Journal of Radiology, 113,* 32-38.

8. Skou ST, Pedersen BK, Abbott JH, **Patterson BE**, & Barton CJ. (2018). Physical activity and exercise therapy benefits more than just symptoms and impairments in people with hip and knee osteoarthritis. *Journal of Orthopaedic Sports Physical Therapy, 48*(6), 439-447.
9. Culvenor AG, **Patterson BE**, Guermazi A, Morris HG, Whitehead TS, Crossley KM. (2017). Accelerated return-to-sport after ACL reconstruction and early knee osteoarthritis features at 1 year: An exploratory study. *Physical Medicine and Rehabilitation, 4*(10), 349-356.

Presentations (invited speaker) during candidature

1. **Patterson BE**. Injury reduction strategies for educators and school sport*, Australian Independent Schools Heads of Sport Conference*, 2019, August 12-13, Hunter Valley, NSW, Australia.
2. **Patterson BE**. Two for one: Enhance performance and reduce injury, *Australian Strength and Conditioning Association Special Interest Group,* Melbourne Girls Grammar School, 2019, December 14.
3. **Patterson BE**. Co-creation of an injury reduction program for elite female football players, XXVIII *International Conference of Sport Rehabilitation and Traumatology Football Medicine Strategies*, 2019, April 28-30, London, UK.
4. **Patterson BE**. Primary prevention for serious knee injuries in Australian football, *La Trobe University Sports and Exercise Medicine Research Centre Symposium - Early Osteoarthritis in the Athlete*, 2019, April 12-13, Melbourne, Australia.
5. **Patterson BE**. Injury prevention for female football players, *AFL Grand Final Symposium*, 2019, September 27, Melbourne, Australia.
6. **Patterson BE**. Injury reduction strategies for coaches of females, *National Female Coaching Forum,* November 20, 2019, Melbourne, Australia
7. **Patterson BE**. Injury reduction strategies for coaches of females, *Queensland State Female Coaching Forum*, 2019, June 30, Brisbane, Australia.
8. **Patterson BE**. Injury reduction strategies for coaches of females, *National Female Coaching Forum*, 2018, November 29, Melbourne, Australia.

Part A: Introduction

1 Chapter One: Introduction

1.1 Anterior cruciate ligament

The anterior cruciate ligament (ACL) is one of four main ligaments that provide the knee with mechanical stability (Markatos et al., 2013). Primarly made up of collagen fibres, the ACL is an extrasynovial 3-4 cm long ligament that lies within the knee joint capsule (Welsh, 1980). The ACL is named for its wide distal attachment to the anterior aspect of the tibial intercondylar area, and it partly blends with the anterior portion of the lateral meniscus (Markatos et al., 2013). Proximally, the ACL attaches to the posteromedial aspect of the lateral femoral condyle, and as the ligament passes through the knee, it rotates, turning on itself before fanning into a broad femoral insertion (Markatos et al., 2013; Welsh, 1980). This rotation and the broad attachments result in variation in the length and orientation of the collagen fibres within the ACL, and have given rise to the idea that the ACL is made up of two separate fibre bundles (anteromedial and posterolateral, named according to their tibial insertion points) (Markatos et al., 2013; Welsh, 1980). The posterolateral bundle is shorter and has a more oblique orientation than the anteromedial bundle, which is longer and more vertically orientated. The unique structure of the two bundles provides the required tension in the ACL throughout the full range of knee motion. The primary function of the ACL is to provide 90% of the static resistance to anterior translation of the tibia (relative to the femur) (Markatos et al., 2013). In addition to providing the knee with mechanical stability, the ACL has an important proprioceptive role (Relph et al., 2014). Mechanoreceptors within the ACL provide information to the central nervous system regarding the position and movement of the knee, facilitating appropriate muscular action to optimise dynamic knee stability during functional tasks (Riemann & Lephart, 2002).

1.2 Anterior cruciate ligament injury

Despite its inherent strength, rupture of the ACL occurs in active adolescents and young adults often involved in cutting, jumping, and pivoting sports such as football, basketball, and handball (Prodromos et al., 2007; Renstrom et al., 2008). The three common mechanisms responsible for ACL injuries are: (i) contact (direct external contact to the knee), (ii) non-contact (no bodily contact with another person), and (iii) indirect contact (contact with a part of the body other than the injured knee) (Della Villa et al., 2020). Seventy per cent of all ACL injuries are non-contact or indirect contact in nature and usually occur during a deceleration or change of direction manoeuvre, typically involving landing on one leg from a jump or pivoting with a planted foot (Della Villa et al., 2020; Renstrom et al., 2008). The exact position and movements of the knee (e.g., hyperextension, tibial rotation), hip (e.g., adduction, internal rotation), trunk (e.g., rotation,

lateral flexion), and foot (e.g., rotated and planted away from the body) that lead to increased ACL strain and rupture are frequently debated (Quatman et al., 2010). Regardless, it appears that a multiplanar ACL injury mechanism exists, whereby ACL injury occurs due to a combination of motions and forces across multiple joints and planes of movement (Quatman et al., 2010).

Primary prevention programs can successfully reduce the incidence of ACL injuries (Crossley et al., 2020; Webster & Hewett, 2018), yet injury rates worldwide remain stable or continue to rise (Mall et al., 2014; Renstrom et al., 2008; Sutherland et al., 2019; Zbrojkiewicz et al., 2018). The global annual incidence of ACL injury is approximately 30 per 100,000 persons (Moses et al., 2012), although countries such as the United States of America (USA) (69 per 100,000 persons) (Sanders et al., 2016) and Norway (80 per 100,000 persons) (Granan et al., 2008) have much higher annual incidences. While Australian population-based ACL injury incidence data is unavailable, the rate of ACL reconstruction (ACLR) in Australia, the predominant treatment for ACL injury, is the highest in the world (Janssen et al., 2012; Moses et al., 2012; Zbrojkiewicz et al., 2018). The Australian ACLR rate increased by 43% between 2000 and 2015, from 54 to 77 per 100,000 persons (Zbrojkiewicz et al., 2018). This rate is substantially higher than North America (range 20 to 33 per 100,000 persons) (Csintalan et al., 2008; Lyman et al., 2009) and Scandinavia (range 32 to 38 per 100,000 persons) (Granan et al., 2009). The higher ACLR rates in Australia may reflect greater exposure to high-risk sports on a year-round basis or greater healthcare accessibility for diagnosis and surgical management (Moses et al., 2012). Adolescents and young adults are most at risk of ACL injury, with an incidence of 200 per 100,000 people aged 15 to 24 years (Sanders et al., 2016). When accounting for exposure, the risk of sustaining an ACL injury is two-to-four times higher for women than men (Montalvo et al., 2018; Smith et al., 2012).

1.3 Management options following ACL injury

Following ACL injury, the two main management options are: (i) ACLR followed by a period of rehabilitation or (ii) rehabilitation alone (with the option of a delayed ACLR). An ACLR is performed to improve the mechanical stability of the knee, facilitate a return to cutting and pivoting sports, and minimise secondary injuries to the joint (i.e., menisci and articular cartilage) (Lebel et al., 2008; Sanders et al., 2016; Swirtun et al., 2006). An ACLR is also thought to reduce the high risk of osteoarthritis (OA) following ACL injury (Chen et al., 2019; Cinque et al., 2018; Lie et al., 2019). However, ACLR does not prevent OA development when compared to rehabilitation alone (Lien-Iversen et al., 2020), in contrast to patient beliefs that ACLR will prevent OA (Bennell et al., 2016; Feucht et al., 2016). Several literature reviews conclude that there are few differences between ACLR and rehabilitation (with optional delayed ACLR) for sub-elite athletes with respect to symptoms, function, return-to-sport, and quality of life (QoL) (Chalmers et al., 2014; Filbay et al.,

2015; Filbay & Grindem, 2019; Lien-Iversen et al., 2020; Smith et al., 2014). However, most reviews do not include randomised controlled trials (RCTs), and have a high risk of bias due to retrospective matched comparisons. For most (90%) Australians, ACLR remains the treatment of choice (Moses et al., 2012; Rooney, 2016).

1.3.1 ACLR

An ACLR involves arthroscopic surgery to replace the ruptured ACL with a graft. While graft choices typically include autografts (normally harvested from tendons in the ACL-injured individual), allografts (harvested from a cadaver or tissue donor), or those fabricated from synthetic material (Middleton et al., 2014), the most common grafts are hamstring-tendon and bone-patella-tendon-bone autografts. Choice also exists in relation to tunnel placement (i.e., orientation or size) and graft fixation devices (i.e., types of screws or pins). Surgical technique does not appear to influence clinical outcomes (i.e., graft failure, symptoms, return-to-sport) (Ajrawat et al., 2019; Gabler et al., 2016; Li et al., 2012; Li et al., 2011b; Li et al., 2014; Mouarbes et al., 2019; Mulford et al., 2013; Riboh et al., 2013; Shaerf et al., 2014) or longer-term burden (i.e., risk of OA) (Holm et al., 2010; Holm et al., 2012), as reported in most systematic reviews and large prospective cohort studies.

A recent summary of systematic reviews on the topic of the ACL revealed that 97 of the 240 reviews (40%) were related to surgical technique or graft choice and 18% were related to patient-reported or clinical outcomes (Anderson et al., 2016). Only 7% and 2% were related to rehabilitation and longer-term burden (i.e., development of OA), respectively (Anderson et al., 2016), highlighting the lack of research in these areas. Improved outcomes following ACLR may be more strongly related to post-operative factors such physical performance than intraoperative factors such as surgical technique (Culvenor & Barton, 2017; Ericsson et al., 2013; Grindem et al., 2015b).

1.3.2 Outcomes following ACLR

Many individuals achieve an excellent outcome following ACLR and a period of rehabilitation, including being symptom-free and maintaining a high level of function and QoL (Spindler et al., 2018). Yet, approximately 50% will develop radiographic OA within a decade following injury (Chen et al., 2019; Lie et al., 2019; Luc et al., 2014). On average, following ACLR, individuals have worse knee-related symptoms and QoL compared to their uninjured peers (Filbay et al., 2014). Following ACLR, 55% return to competitive sports participation (Ardern et al., 2014b). Of those who return to strenuous sports, only 23% are estimated to meet recommended physical strength and functional criteria prior to return (Webster & Hewett, 2019). While physical deficits can increase

the risk of subsequent ACL injury (Ashigbi et al., 2020), their relationships with OA development, knee-related symptoms, and QoL are unclear (Losciale et al., 2019). There is an urgent need to further understand the trajectory of structural (e.g., OA features), patient-reported (e.g., symptoms, function, QoL), and physical outcomes (e.g., functional performance) following ACLR, and to identify factors associated with poor outcomes. The remainder of Chapter 1 will outline the current evidence for these three specific domains – structural outcomes, patient-reported outcomes (PROs), and physical outcomes following ACLR (**Figure 1.1**). The course of these outcomes and their associations with individual characteristics, as well as peri-operative and post-operative factors, will be summarised, highlighting the gaps within the literature. This will provide a rationale for this thesis.

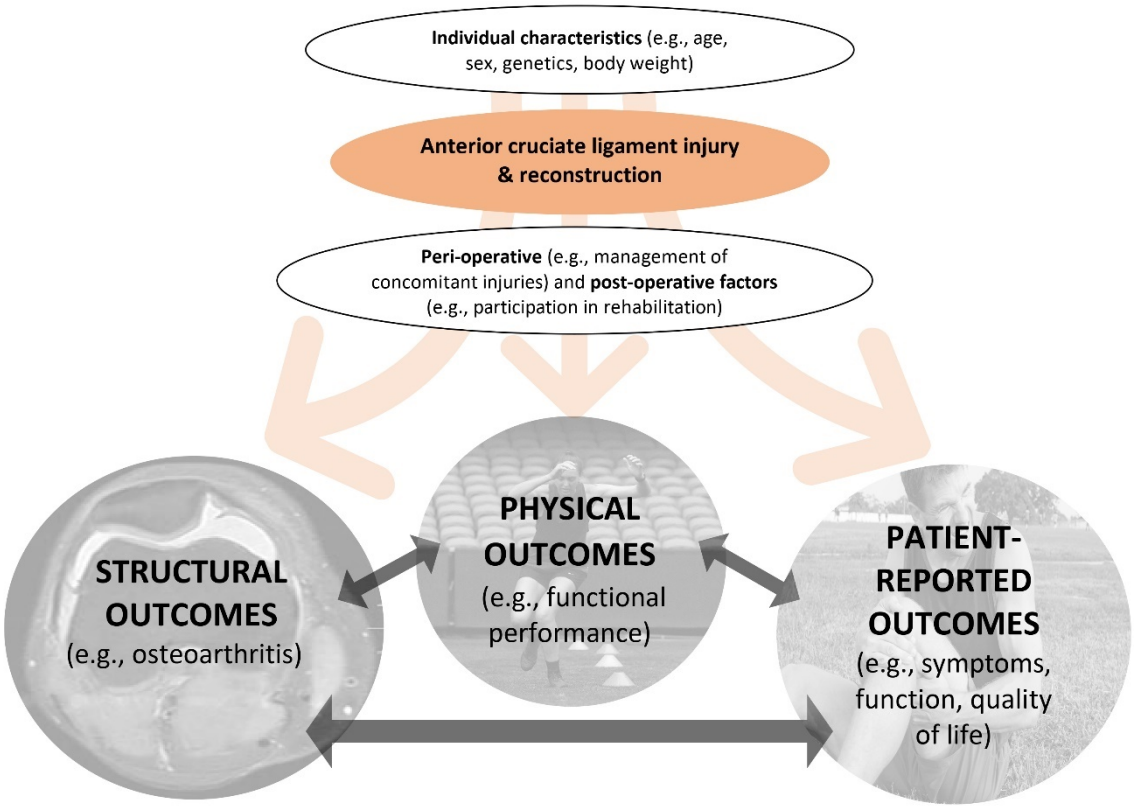


Figure 1.1 Outcomes following ACLR and associated factors outlined in the remainder of Chapter 1.

1.4 Structural outcomes following ACLR

An ACL injury rarely occurs in isolation, with concomitant damage to other joint structures, intra-articular bleeding, and inflammation common (Wang et al., 2020). This concomitant joint damage and inflammation, together with altered joint loading, may contribute to the development of OA following ACLR. Changes to the knee joint structure are typically assessed with X-ray or magnetic resonance imaging (MRI).

1.4.1 Pathogenesis of post-traumatic OA following ACLR

Osteoarthritis is a chronic disease of the whole joint involving structural and compositional changes to the articular cartilage, subchondral bone, menisci, synovium, ligaments, tendons, and periarticular muscles (Hunter & Bierma-Zeinstra, 2019). In contrast to non-traumatic (primary) OA in the general population, which occurs in older adults with no specific inciting event, post-traumatic OA typically occurs in younger adults following a joint injury (Thomas et al., 2017). To understand the pathogenesis of post-traumatic OA, the biomechanical and biochemical processes of the healthy knee joint should be considered.

Healthy articular cartilage in the knee facilitates low-friction movement. It consists of a highly organised extracellular matrix of collagen fibrils and proteoglycans giving cartilage the ability to resist tension, shear, and deform under load (Buckwalter et al., 2005; Pollard et al., 2008) (**Figure 1.2**). The matrix is controlled by chondrocytes, which synthesise new tissue and release cytokines – a normal inflammatory response in a healthy joint to remove damaged tissue. Healthy articular cartilage is avascular (no blood supply) and aneural (no sensory nerve fibres). Beneath cartilage, the highly vascularised, dense subchondral bone acts as an important structure to absorb forces placed upon the knee and consists of the bone plate (cortical bone) and the underlying trabecular bone and bone marrow (Madry et al., 2010). Osteoclast and osteoblast cells maintain an equilibrium of bone synthesis and breakdown (Goldring, 2008; Madry et al., 2010) (**Figure 1.2**). The lateral and medial menisci sit between the articular cartilage surfaces of the tibial plateau and femoral condyles, absorbing horizontal shear and compressive forces and providing lubrication and nutrition for articular cartilage (Makris et al., 2011). Unlike articular cartilage, the menisci have a vascularised and neural region in the outer edges (Makris et al., 2011).

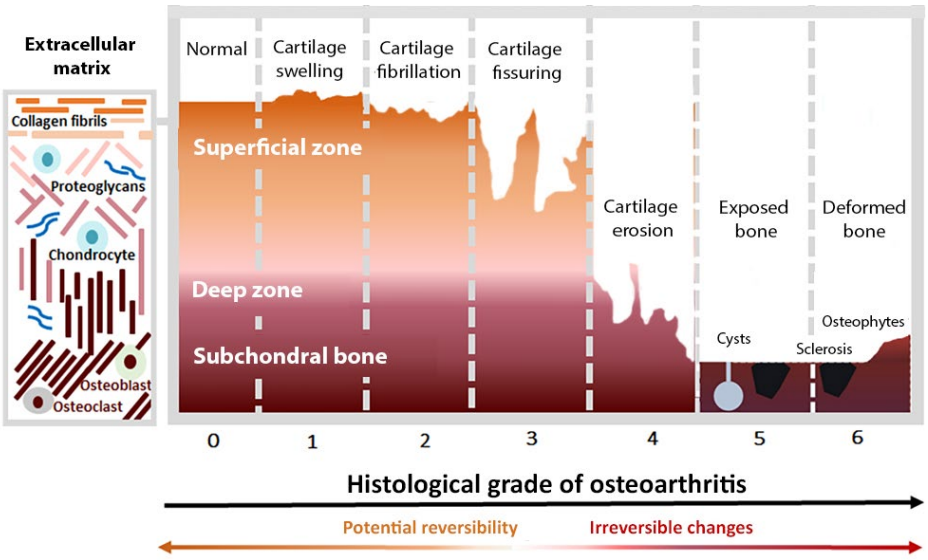


Figure 1.2 Normal joint structure and OA progression adapted from Pollard et al. (2008).

The pathogenic mechanisms that underpin the development and progression of post-traumatic OA following ACLR likely involve an interaction of mechanical, biological, and structural processes which lead to an imbalance between tissue synthesis and breakdown, and ultimately, structural degeneration (Andriacchi et al., 2020; Hunter & Bierma-Zeinstra, 2019; Punzi et al., 2016; Wang et al., 2020). At the time of ACL rupture, physical damage to the cartilage, bone, and/or menisci usually occurs, alongside considerable haemarthrosis (Hagino et al., 2015; Van Ginckel et al., 2013). Concomitant meniscal damage appears to be an important driver of post-traumatic OA development (Jones & Spindler, 2017; van Meer et al., 2015). The process of reconstructing the ACL creates additional physical damage (e.g., tunnel drilling) and bleeding, facilitating inflammatory processes which can inhibit cartilage synthesis (Wang et al., 2020). Synovial inflammation may persist for months post-operatively, and this altered biochemical environment can lead to structural damage to the cartilage, bone, and menisci, just as altered structural integrity of joint tissue can increase inflammation (Ding et al., 2010; Punzi et al., 2016). As the disease progresses, features associated with OA become evident; bone oedema, cartilage and menisci fissuring and erosion, joint space narrowing, osteophyte formation, bony sclerosis, and cysts (Punzi et al., 2016) (**Figure 1.2**). The temporal sequence of changes in OA features associated with the development of post-traumatic OA is uncertain, highlighting the importance of longitudinal studies to monitor the trajectory of OA feature development and progression over time (Andriacchi et al., 2020).

1.4.2 Diagnosis of radiographic knee OA following ACLR

Knee OA is traditionally evaluated with radiography (X-ray) and is based on the severity of bony changes (i.e., osteophyte formation) and joint space narrowing (Glyn-Jones et al., 2015). The most common classification systems for radiographic OA are the Kellgren-Lawrence (Kellgren & Lawrence, 1957) and OsteoArthritis Research Society International (OARSI) scales (Altman & Gold, 2007; Altman et al., 1995). The Kellgren-Lawrence system defines OA across five grades (from 0=none to 4=severe), with ≥grade 2 (i.e., definite osteophytes with or without the presence of joint space narrowing) indicating the presence of radiographic OA (Culvenor et al., 2015b; Kellgren & Lawrence, 1957). The more recently developed OARSI system provides an atlas to semi-quantitatively grade the severity of each OA feature (i.e., joint space narrowing, osteophytes) from 0 (normal) to 3 (severe), and defines radiographic knee OA as present if any of the following criteria are met: (i) joint space narrowing of ≥grade 2, (ii) sum of osteophytes $\geq$2, or (iii) grade 1 osteophytes in combination with grade 1 joint space narrowing (Altman & Gold, 2007; Altman et al., 1995).

1.4.3 Prevalence of radiographic knee OA following ACLR

The reported prevalence of radiographic OA following ACL injury and ACLR varies considerably across systematic reviews. **Figure 1.3** presents the mean post-traumatic radiographic OA prevalence up to 20 years following ACL injury or ACLR, as obtained from 11 systematic reviews (Ajuied et al., 2014; Belk et al., 2018; Chalmers et al., 2014; Chen et al., 2019; Cinque et al., 2018; Claes et al., 2013; Harris et al., 2017; Lie et al., 2019; Luc et al., 2014; Rothrauff et al., 2020; Spahn et al., 2016). A 2019 systematic review and meta-analysis reported a pooled mean prevalence of 52% in any compartment (range 8% to 79%, 16 studies), 62% (range 34% to 87%, 4 studies) in the tibiofemoral compartment, and 47% (range 28% to 80%, 4 studies) in the patellofemoral compartment, 10 to 23 years following ACLR (Chen et al., 2019). From the studies rated as high-quality in another 2019 review (Lie et al., 2019), the mean prevalence of radiographic OA was 25% in any compartment (5 studies), 30% in the tibiofemoral compartment (19 studies), and 20% in the patellofemoral compartment (8 studies), 10 to 24 years following ACL injury/ACLR. The different definitions of OA (e.g., OARSI, Kellgren-Lawrence) and confounding participant characteristics (e.g., surgical or non-surgical treatment, age, sex, concomitant injuries) in the studies included in each review likely contribute to the variability in the reported prevalence of radiographic OA (Chen et al., 2019; Lie et al., 2019). The Kellgren-Lawrence classification typically results in a lower prevalence than the OARSI classification (Culvenor et al., 2015b).

In comparison, the prevalence of non-traumatic radiographic knee OA in the general (uninjured) population is <15% in those aged under 45 years (Cross et al., 2014), 20-30% in middle-aged adults (45 to 65 years) (Jordan et al., 2007; Pereira et al., 2011; van Saase et al., 1989), and 30-60% in older adults (>65 years) (Collins et al., 2014; Dillon et al., 2006; Felson et al., 1987; Peat et al., 2006; Pereira et al., 2011; van Saase et al., 1989) (**Figure 1.3**). At 10 to 20 years following ACLR (i.e., individuals aged 30-40 years), the prevalence of OA is similar that of the general population aged >65 years (**Figure 1.3**), emphasising the concept of 'young people with old knees'.

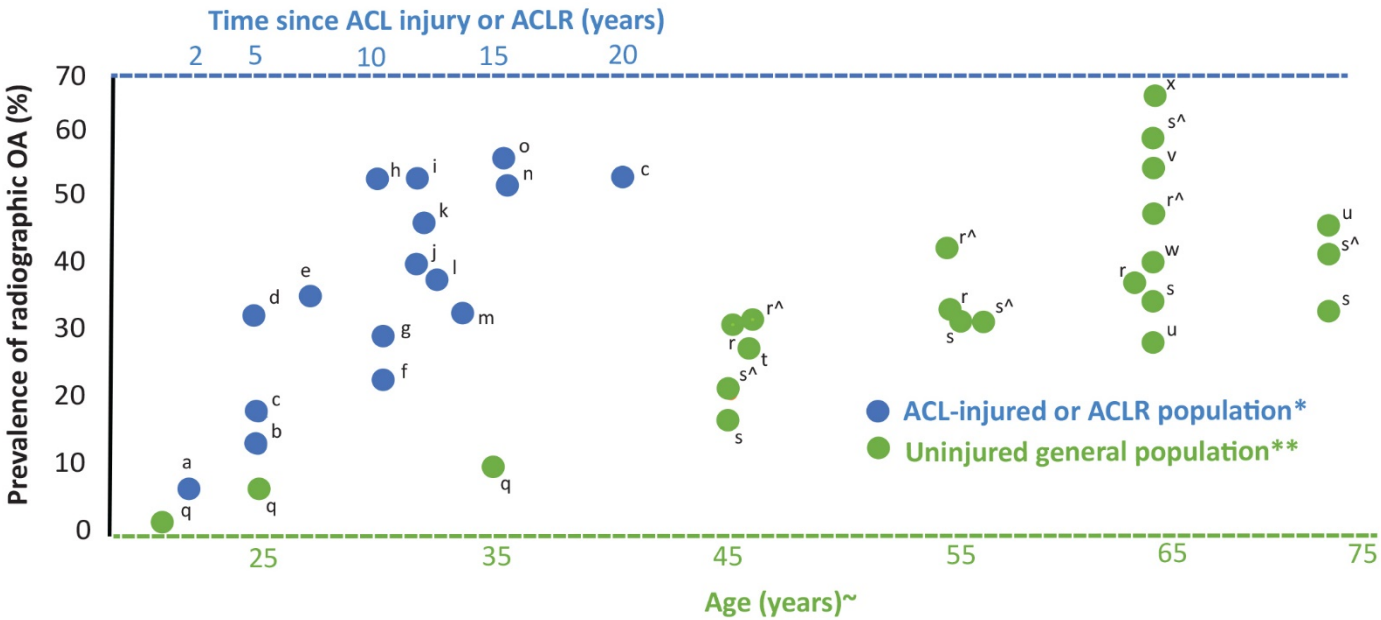


Figure 1.3 Prevalence of radiographic OA following ACLR from systematic reviews, compared to uninjured general population from cohort studies.

ACL=anterior cruciate ligament; ACLR=anterior cruciate ligament reconstruction; OA=osteoarthritis.
* Each dot represents the mean prevalence reported/calculated from systematic reviews of ACL-injured or ACLR cohorts. Details are provided below.
**Each dot represents the mean prevalence reported/calculated from uninjured population-based cohorts. Details are provided below.
~represents minimum age of participants in the study.
ACL population: [a] 7% from 4 studies (Spahn et al., 2016); [b] 11% from 38 studies (Cinque et al., 2018); [c] 15% from 8 studies (Belk et al., 2019); [d] 32% from 14 studies (Luc et al., 2014); [e] 36% from 14 studies (Luc et al., 2014); [f] 21% from 7 studies (Cinque et al., 2018); [g] 28% from 16 studies (Claes et al., 2013); [h] 52% from 6 studies (Ajuied et al., 2014); [i] 52% from 7 studies (Belk et al., 2018); [j] 37% from 4 studies (Harris et al., 2017); [k] 44% from 21 studies (Luc et al., 2014); [l] 35% from 27 studies (Chalmers et al., 2014); [m] 31% in tibiofemoral compartment from 19 studies rated as high quality (Lie et al., 2019); [n] 52% from 19 studies (Chen et al., 2019); [o] 51% from 38 studies (Cinque et al., 2018).
Uninjured population: [q] estimated <10% from global burden of disease study (Cross et al., 2014); [r] review of population-based cohorts, male participants: 30% (>45 years), 31% (>55 years), 34% (>65 years) (Pereira et al., 2011); [r^] review of population-based cohorts, female participants: 31% (>45 years), 41% (>55 years), 45% (>65 years) (Pereira et al., 2011); [s] Dutch cohort, male participants: 13% (>45 years), 29% (>55 years), 31% (>65 years) (van Saase et al., 1989); [s^] Dutch cohort, female participants: 19% (>45 years), 29% (>55 years), 56% (>65 years) (van Saase et al., 1989); [t] 28% from Johnston County OA project (Jordan et al., 2007); [u] 27% (>65-70 years) and 44% (>75-80 years) Framingham Ostseoarthritis Study (Felson et al., 1987); [v] 52% from Osteoarthritis Initiative Study (Collins et al., 2014); [w] 37% from United States population data (Dillon et al., 2006); [x] 68% from United kingdom population data (Peat et al., 2006).

1.4.4 A shift to evaluating early OA features on MRI following ACLR

Although radiography is the most common modality to assess OA, it cannot detect changes occurring in the early stages of OA disease or changes in all joint tissues (Pollard et al., 2008) (**Figure 1.4**). The use of MRI, which can visualise all joint tissues in multiple planes, provides a more sensitive measure to identify OA features early in the disease, when some features may be reversible (Chu et al., 2012; Quatman et al., 2011) (**Figure 1.4**). Early OA features on MRI can include: (i) changes in cartilage quality (e.g., volume, thickness, water or proteoglycan content), (ii) cartilage fibrillation and fissuring, (iii) bone marrow lesions (BMLs) (a marker of increased cellular activity, defined as areas of high signal), (iv) early osteophytes not visible on radiographs, (v) synovitis or effusion, or (vi) meniscal tears, maceration, or extrusion (Chu et al., 2012; Ding et al., 2010; Katsuragi et al., 2015). Early OA features that may be reversible include biochemical changes to cartilage, synovitis, effusion, cartilage fibrillation and fissuring, and BMLs (Pollard et al., 2008; Riordan et al., 2014).

Early features of OA on MRI are assessed with a variety of semi-quantitative and quantitative scoring methods (Chu et al., 2012; Quatman et al., 2011). Semi-quantitative methods evaluate morphological features of OA (e.g., cartilage lesions, BMLs, meniscal lesions, osteophytes), while more advanced quantitative techniques evaluate cartilage quality (e.g., proteoglycan content, cartilage volume/thickness) (Chu et al., 2012). Semi-quantitative grading systems include the Whole-Organ Magnetic Resonance imaging Score (WORMS) (Peterfy et al., 2004), the Knee Osteoarthritis Scoring System (KOSS) (Kornaat et al., 2005), and the Boston Leeds Osteoarthritis Knee Score (BLOKS) (Hunter et al., 2008). The MRI OsteoArthritis Knee Score (MOAKS) was developed due to the limitations of the WORMS, KOSS, and BLOKS. The MOAKS removed redundant features (e.g., cartilage signal), added relevant features (e.g., meniscal maceration) and subregions (e.g., anterior, central, and posterior tibial regions), and renamed features (e.g., Hoffa's synovitis) (Hunter et al., 2006a; Hunter et al., 2011a; Hunter et al., 2008). The improved inter-rater and intra-rater reliability of the MOAKS system compared to the WORMS, KOSS, and BLOKS is facilitated by the simplified and repeatable subregional scoring of all features and accompanying sample images (Hunter et al., 2011a).

Quantitative MRI assessment can evaluate structural and biochemical changes in cartilage (Chu et al., 2012; Conaghan, 2006; Oei et al., 2014) that may precede the morphological changes scored with semi-quantitative methods (**Figure 1.4**). Quantitative MRI mapping can assess cartilage volume and thickness as well as cartilage quality (e.g., proteoglycan content) (Chu et al., 2012; Conaghan, 2006; Oei et al., 2014). While quantitative imaging techniques might offer advantages

(i.e., earlier detection of cartilage changes), they often require administration of an intravenous contrast agent (dGEMRIC), additional MRI sequences, and complex imaging analyses, and further work is needed to determine their validity as measures of OA (Chu et al., 2012; Oei et al., 2014).

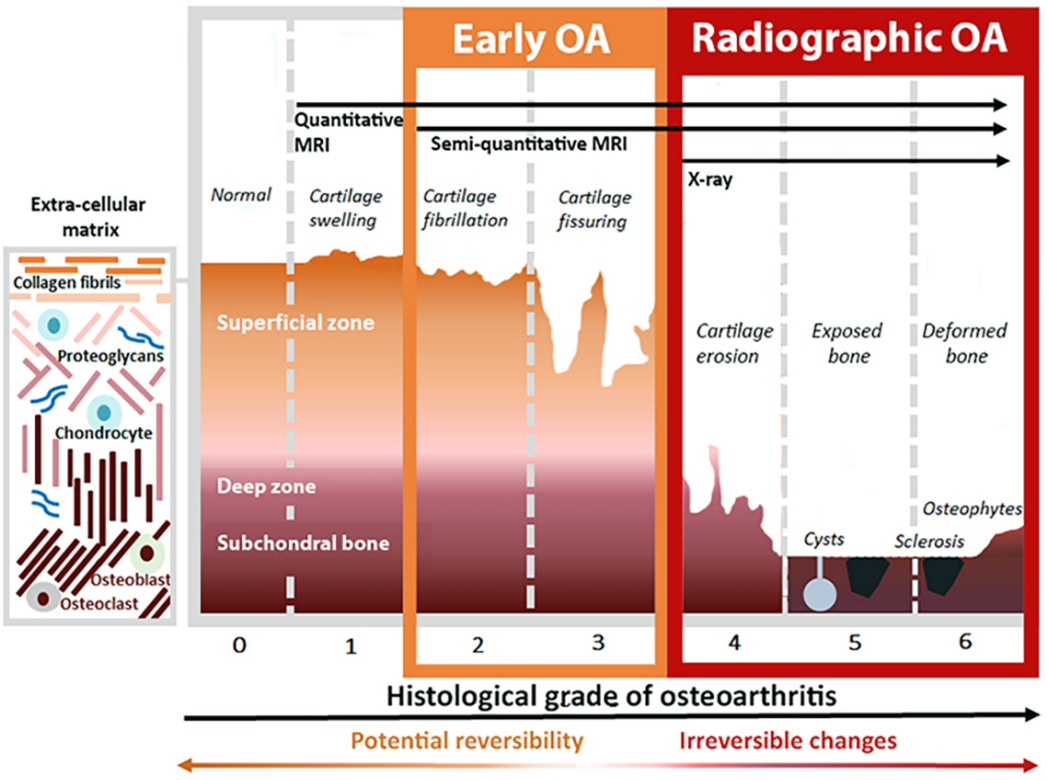


Figure 1.4 Sensitivity of MRI techniques and radiography for assessment of OA features, adapted from Pollard et al. (2008).

MRI=magnetic resonance imaging; OA=osteoarthritis.

Semi-quantitative assessment of MRI features is recommended by the OARSI guidelines as a sensitive measure of structural changes over shorter follow-ups (12 to 24 months), facilitating more feasible longitudinal studies of OA (Hunter et al., 2015). Early structural changes may identify individuals on a trajectory towards more severe radiographic post-traumatic OA. Changes to cartilage, bone, and menisci early in the disease process captured using semi-quantitative MRI are prognostic factors for incident radiographic OA in the general population (Katsuragi et al., 2015; Roemer et al., 2015; Sharma et al., 2016), can be strongly associated with pain (e.g., BMLs) (Stefanik et al., 2015; Wang et al., 2015; Yusuf et al., 2011), and increase the risk of persistent or incident symptoms (Javaid et al., 2010; Sharma et al., 2014; Sharma et al., 2016) and/or future total knee replacement (TKR) (Hunter et al., 2011b; Liu et al., 2017; Nagai et al., 2018) Characterising early OA on MRI following ACLR is vital to advancing understanding of post-traumatic OA disease (Chu et al., 2012; Watt et al., 2019).

Early changes in cartilage and bone marrow are potentially modifiable, providing opportunity for implementation of interventions aimed at slowing or preventing OA progression (Chu et al., 2012; Ding et al., 2010; Pollard et al., 2008). In the early stages of cartilage degeneration, the integrity of the cellular matrix may still be intact (i.e., minimal proteoglycan loss), allowing the chondrocytes to maintain homeostasis, slowing down degradation or synthesising new cartilage (Pollard et al., 2008). Early changes to cartilage and bone appear to be amenable to interventions such as exercise (Bricca et al., 2018; Roos & Dahlberg, 2005). Regular moderate-impact exercise in middle-aged individuals following meniscectomy (Roos & Dahlberg, 2005) is associated with increased cartilage proteoglycan content, which is important for maintaining cartilage structural integrity. Other MRI studies in middle-aged women with no or mild knee OA also report that regular exercise is associated with a reduced rate of cartilage volume loss (Koli et al., 2015; Wijayaratne et al., 2008), and high-impact exercise induces positive effects (increased bone density) on bone structure (Multanen et al., 2014).

1.4.5 Prevalence of OA features on MRI following ACLR

Features of early OA are frequently identified using MRI as early as 1-2 years post-operatively (Culvenor et al., 2015a; Frobell et al., 2009; Wang et al., 2017). A longitudinal cohort named the **K**nee **O**steoarthritis **A**nterior cruciate ligament **L**ongitudinal **A**ssessment (KOALA) study reported prevalent cartilage lesions (68%), BMLs (45%), osteophytes (66%), and meniscal lesions (59%) one year following ACLR (Culvenor et al., 2015a). The mean prevalence of OA features on MRI from the KOALA cohort and other cohorts with MRI data (Frobell, 2011; van Meer et al., 2016; Whittaker et al., 2018) are summarised in **Figure 1.5.** These data are mostly from the first two years post-ACL injury and reconstruction, from an RCT (**K**nee **A**nterior cruciate ligament **NON**surgical versus Surgical; KANON) (Frobell, 2011) and longitudinal prospective cohorts (the **KN**ee osteo**A**rthritis anterior cruciate **L**igament **L**esion (KNALL; van Meer et al., 2016) and The Alberta Youth **PR**evention of **E**arly **O**steoarthritis (PrE-OA) studies). The KANON study predominantly reported quantitative measurements of cartilage thickness and BML volume, but also described morphological changes at the time of injury (i.e., presence of cartilage or meniscal lesions, BMLs, or osteophytes) (Filbay et al., 2017b) and at two-year follow-up (i.e., presence of BMLs) (Frobell, 2011). The KNALL study reported morphological changes using the MOAKS from the time of ACL injury up to two years post-injury (65% treated with ACLR). The PrE-OA cohort reported the prevalence of cartilage lesions (59%), BMLs (26%), and meniscal lesions (48%) using the MOAKS in a cross-sectional evaluation 3 to 10 years following intra-articular knee injury (39 ACL injuries treated with ACLR) (Whittaker et al., 2018). Other semi-quantitative evaluations of all OA features on MRI beyond 2-3 years following ACLR are scarce. Wang et al. (2017) reported that the prevalence of cartilage lesions in any knee compartment was 69% 2.5 years post-ACLR and 10% in

age- and sex-matched healthy controls. The high rates of OA features on MRI following ACLR are in contrast to the general population rates without a history of knee injury, where the pooled prevalence of cartilage lesions (11%), BMLs (14%), osteophytes (8%), and meniscal lesions (4%) in young adults under 40 years of age is low (Culvenor et al., 2019b) (**Figure 1.5**).

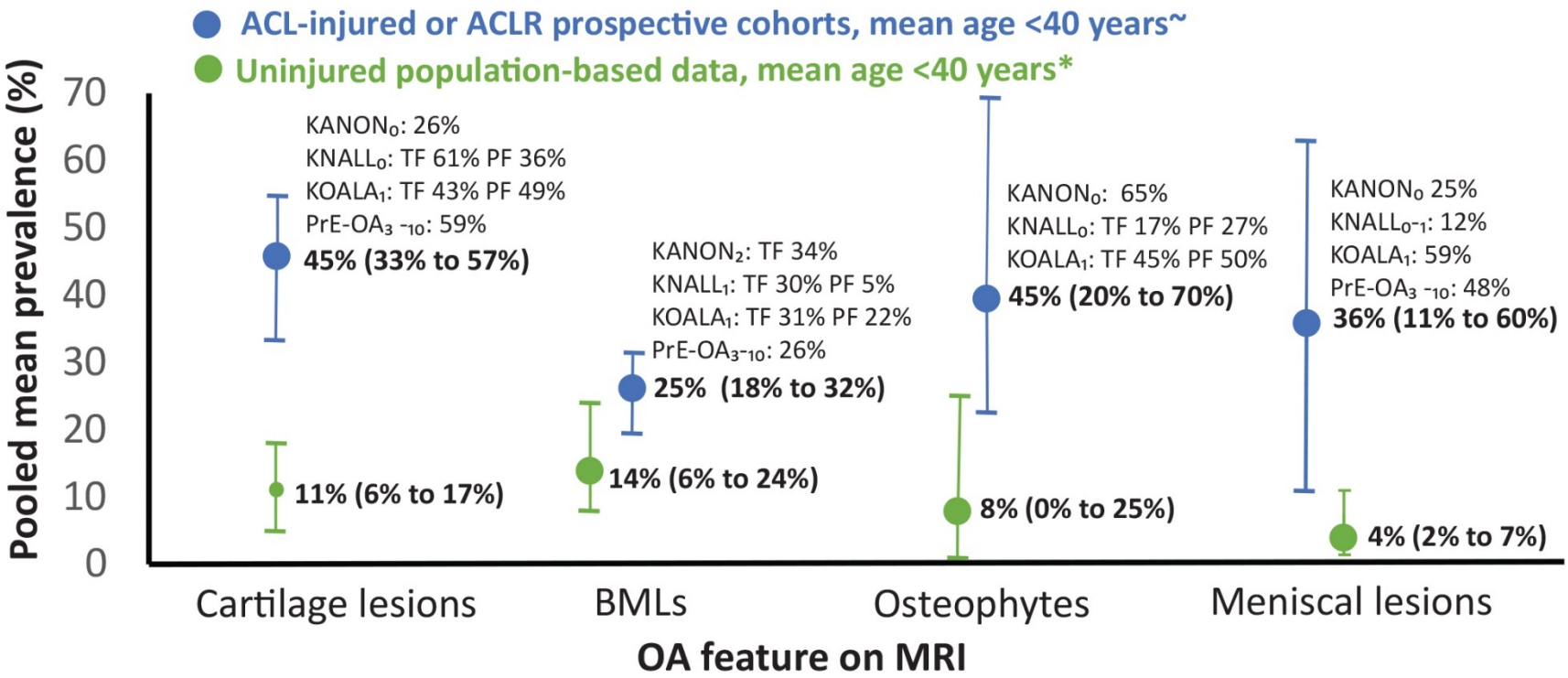


Figure 1.5 Pooled mean prevalence of OA features on MRI following ACL injury/ACLR compared with uninjured healthy individuals.

ACL=anterior cruciate ligament; ACLR=anterior cruciate ligament reconstruction; BMLs=bone marrow lesions; CI=confidence interval; PF=patellfemoral; TF=tibiofemoral.
KANON=Knee Anterior Cruciate Ligament Nonsurgical versus Surgical study – cartilage lesion, osteophytes, meniscal lesion data from time of injury (n=118) (Filbay et al., 2017b), BML from 2-years post-ACL injury (n=61) (Frobell, 2011).
KNALL=KNee osteoArthritis anterior cruciate Ligament Lesion study – cartilage lesion and osteophyte data from time of ACL injury (n=143), BML prevalence at 1-year post-ACL injury assessment, and meniscal lesion data any time up to 2 years post-ACL injury (n=143) (van Meer et al., 2016).
KOALA=Knee Osteoarthritis Anterior cruciate ligament Longitudinal Assessment study – prevalence of all features from the 1-year post-ACLR assessment of the longitudinal cohort in this thesis (n=111) (Culvenor et al., 2015a).
PrE-OA=The Alberta Youth Prevention of Early Osteoarthritis study – prevalence of all features from 3 to 10 years following sports-related knee injury (n=73, n=39 ACLR) (Whittaker et al., 2018).
~ Pooled mean (95% CI) prevalence weighted by participant numbers for each respective cohort. Subscript numbers represent years since ACL injury/ACLR.
* Pooled mean (95% CI) prevalence in any knee compartment in asymptomatic uninjured adults from a recent meta-analysis (Culvenor et al., 2019b).

1.4.6 Clinical relevance of OA features on MRI following ACLR

Given that degenerative joint features on MRI are prevalent in asymptomatic uninjured adults (Culvenor et al., 2019b; Zanetti et al., 2003) (**Figure 1.5**), careful consideration of the clinical relevance (i.e., relationship with symptoms) following ACLR is needed. The relationships between cartilage lesions, BMLs, osteophytes, and meniscal lesions on MRI and patient-reported symptoms have rarely been studied in ACLR populations. This is important given that meniscal and cartilage lesions are considered responsible for persistent or new symptoms following ACLR, resulting in secondary surgery to repair or resect the lesion (Rochcongar et al., 2015). For knee OA in the general population, BMLs are the MRI feature most commonly associated with knee pain (Yusuf et al., 2011), particularly in the patellofemoral compartment (Stefanik et al., 2015; Wang et al., 2015). Studies evaluating this relationship in post-traumatic OA populations have reported that tibiofemoral cartilage lesions and BMLs were not associated with knee symptoms cross-sectionally at 2 (Costa-Paz et al., 2001) and 12 years following ACLR (Hanypsiak et al., 2008). Evaluation of patellofemoral features on MRI is lacking following ACLR (i.e., only half of the studies in a review of cartilage changes following ACL injury evaluated patellofemoral cartilage on MRI) (Van Ginckel et al., 2013), despite radiographic patellofemoral disease being common and associated with greater symptom severity (Culvenor et al., 2013; Culvenor et al., 2014b).

1.4.7 Longitudinal changes in OA features on MRI following ACLR

Longitudinal changes in OA features may provide greater insight than cross-sectional prevalence studies and may help to identify individuals with degenerative changes on an accelerated trajectory towards post-traumatic OA. Structural changes may precede the onset of symptoms, and this can only be evaluated with a longitudinal study design. Assessing changes in individual OA features on MRI via a longitudinal study design overcomes many of the methodological challenges of cross-sectional investigations of OA features (Runhaar et al., 2014; Zhang et al., 2010). For example, recording new or progressive lesions (termed “worsening” in this thesis) between two time-points enables identification of those who demonstrate structural deterioration regardless of their baseline status. Using this definition, lesions on MRI at baseline that may have occurred prior to, or during the ACL injury/ACLR are taken into account.

Cartilage changes on MRI following ACLR

A 2013 systematic review evaluated longitudinal changes in cartilage on MRI (semi-quantitative or quantitative) from 12 prospective studies, 2 to 11 years following ACL injury or ACLR (Van Ginckel et al., 2013). From the two high-quality studies in the review that used semi-quantitative methods (Li et al., 2011c; Potter et al., 2012), one reported no change in cartilage lesion size

between injury and one year post-ACLR (Li et al., 2011c), while the other reported that average cartilage lesion size doubled in the first year post-ACLR (Potter et al., 2012). Only one high-quality study from the review evaluated semi-quantitative cartilage changes beyond two years post-ACLR; this study reported that the most rapid increase in cartilage lesion size was between five and seven years following injury (Potter et al., 2012). Further evaluation of cartilage changes beyond one to two years post-operative is important as this represents a window following the resolution of traumatic lesions, and is when neuromuscular recovery has likely taken place. This provides an opportunity to possibly identify those individuals who may be at highest risk of progressing towards radiographic OA.

The variation in grading systems, poor reporting of MRI grading reliability, and lack of adjustment for confounders combined with underpowered (<50 participants) and retrospectively recruited convenience samples poses considerable risks to the internal and external validity of the Van Ginckel et al. (2013) review. Since this 2013 systematic review, the KNALL cohort reported that 34% of participants had cartilage lesion worsening; this study used the updated MOAKS scoring system in 143 individuals from the time of injury to two years post-injury (van Meer et al., 2016). The KANON study reported that tibiofemoral cartilage thinning continues to occur between two and five years post-injury (Eckstein et al., 2015). While evaluations of early structural changes following ACL injury have centred on tibiofemoral cartilage loss and defect progression, changes to other joint tissues such as BMLs, osteophytes, and meniscal lesions may initiate the post-traumatic OA disease process.

BML changes on MRI following ACLR

Longitudinal data evaluating BMLs show that 80-90% of ACL-injured knees will have a BML associated with the initial trauma (typically in the posterolateral tibia or lateral femur) (Patel et al., 2014), with most of these resolving within the first 12 months (Li et al., 2011c; Su et al., 2013). However, new BMLs in other regions of the knee also frequently develop in the first two years following initial trauma, and these may be related to changes in biomechanics (e.g., contact forces) in adaptation to the initial bone bruise or other concomitant injuries (Li et al., 2011c; Su et al., 2013). Compared to traumatic BMLs, persistent or new BMLs are more likely to display degenerative characteristics (i.e., more circumscribed, located directly subchondral to the associated with cartilage damage) (Roemer et al., 2014). While semi-quantitative scoring systems (i.e., MOAKS) can differentiate degenerative BMLs (from acute traumatic lesions) based on the presence of associated subchondral cysts (Xu et al., 2012), the longitudinal evaluation of change in BMLs beyond two to three years post-ACLR is scarce. Potter et al. (2012) reported a notable increase in tibiofemoral and patellofemoral BML size in the lateral femoral condyle, patella, and

trochlea between three and five years following ACLR. Conversely, a study evaluating changes in tibiofemoral BMLs (using the MOAKS) between 2.5 and 4.5 years following ACLR reported minimal changes, except for improvement in the medial tibia (Wang et al., 2019). Greater understanding of the trajectory of BMLs in all regions of the knee is required, given that BMLs are the first markers of early change to bone structure (representing increased metabolic activity) and may progress to irreversible bony deformation (Madry et al., 2010; Nakamae et al., 2006). Following ACLR, acute BMLs are often associated with degenerative changes in other features such as cartilage (Costa-Paz et al., 2001; Roemer et al., 2009; Van Ginckel et al., 2013; van Meer et al., 2016). Similarly, worsening BMLs in older individuals increase the risk of future cartilage loss and radiographic OA (Hunter et al., 2006b; Sharma et al., 2016). While BMLs are a source of pain in general knee OA populations (Yusuf et al., 2011), particularly in the patellofemoral compartment (Stefanik et al., 2015; Wang et al., 2015), no studies have evaluated their relationship with pain and symptoms over time following ACLR.

Osteophytic changes on MRI following ACLR

In terms of osteophytes, few studies have evaluated longitudinal post-traumatic changes on MRI following ACLR. While osteophytes are often considered an end-stage bone adaptation in OA disease, osteophytes on MRI can exist without the presence of radiographic osteophytes or "earlier" features of OA (i.e., BMLs or cartilage lesions) (Markhardt et al., 2018). Early bony deformation may cause load on other soft tissue structures and increase the risk of cartilage and menisci worsening (Zhu et al., 2017). The KNALL study is the only longitudinal cohort to evaluate worsening osteophytes after ACL injury (van Meer et al., 2016), occurring in 9% and 8% of participants in the tibiofemoral and patellofemoral compartment, respectively (van Meer et al., 2016). Further studies with longer-term follow-ups will help to understand the trajectory and relevance of worsening osteophytes following ACLR.

Meniscal changes on MRI following ACLR

Meniscal lesions are frequently reported arthroscopically at the time of ACLR (50% to 80%) (Culvenor et al., 2015a; Hagino et al., 2015; Lee et al., 2013); however, no studies have reported changes on MRI in the proceeding years. Evaluation of worsening meniscal lesions on MRI over time via a longitudinal study design is needed to identify those with degenerative changes, regardless of whether they had a pre-existing meniscal lesion (i.e., prior to ACL injury or occurring at the time of injury). The strong link between meniscal pathology, secondary arthroscopic surgery, and radiographic OA indicates the importance of evaluating longitudinal meniscal health (Sharma et al., 2016; van Meer et al., 2015).

1.5 Patient-reported outcomes following ACLR

There is discordance between the severity of radiological pathology and symptoms following ACLR (Oiestad et al., 2013; Oiestad et al., 2010b; Salmon et al., 2006). Of those with radiographic OA 10 to 15 years following ACLR, approximately half have knee symptoms (Lie et al., 2019), consistent with the mismatch between symptoms and radiographic OA in non-traumatic knee OA populations (Bedson & Croft, 2008). Considering how individuals following ACLR perceive their knee symptoms, function, and QoL in relation to their other objective measures of health, such as imaging features and physical testing, is crucial to a well-rounded assessment after ACLR. Patient-reported outcome measures used in ACL and OA research and clinical practice assess self-reported symptoms, function, health-related and knee-related QoL, participation in physical activity and sport, and psychological and emotional well-being. This section will summarise the current evidence regarding the course of patient-reported *knee-related* symptoms, function, and QoL following ACLR, as these domains are the focus of the studies in this thesis.

1.5.1 Patient-reported *knee-related* symptoms, function, and QoL following ACLR

The ease with which PROs can be assessed (i.e., via online questionnaires) has facilitated population-based ACLR studies, including national registries in Scandinavia (Ahldén et al., 2012; Granan et al., 2009) and the USA (Spindler et al., 2018). These registries include up to 30,000 patients and evaluate PROs up to 10 years following ACLR. They consistently demonstrate that patient-reported symptoms, function, and QoL improve up to two years following ACLR and plateau beyond this point (Ahldén et al., 2012; Granan et al., 2009; Spindler et al., 2018). Importantly, PROs following ACLR appear to remain below the age-matched values of uninjured peers (Antosh et al., 2018; Cameron et al., 2013; Paradowski et al., 2006) (**Figure 1.6**). While many instruments are used to capture patient-reported symptoms, function, and QoL, the most commonly used questionnaire is the Knee injury and Osteoarthritis Outcome Score (KOOS). The KOOS, established in 1998 (Roos et al., 1998), consists of five subscales separately assessing knee-related symptoms (KOOS-Symptoms), pain (KOOS-Pain), activities of daily living (ADL; KOOS-ADL), function in sport/recreation (KOOS-Sport), and QoL (KOOS-QoL). The best available summary of KOOS data up to 20 years following ACLR stems from combining data from the Scandinavian (Ahldén et al., 2012; Filbay et al., 2018b; Granan et al., 2009; Grindem et al., 2015a; Lind et al., 2009) and USA registries (Spindler et al., 2018) with established high-quality longitudinal cohorts (Barenius et al., 2014; Moller et al., 2009; Oiestad et al., 2011; Risberg et al., 2016b) (**Figure 1.6**). These large datasets generally show consistent mean group patient-reported scores at different time-points following ACLR. **Figure 1.6** presents the average KOOS-Symptoms, KOOS-Sport, and KOOS-QoL subscale scores at each post-operative time-period (up to 1 year, 1 to 2 years, 2 to 10 years, 10 to 20 years, >20 years), compared to previously published normative values from

uninjured adults (Antosh et al., 2018; Cameron et al., 2013; Paradowski et al., 2006). These three subscales are typically the most impaired following ACLR compared to normative data (Filbay et al., 2014; Frobell et al., 2015). At 10 to 20 years after ACLR (i.e., individuals in their 30s and 40s), KOOS-Symptoms, KOOS-Sport, and KOOS-QoL scores are below the respective subscale scores from those aged 55 to 75 years in the general population (**Figure 1.6**), reiterating the concept of 'young people with old knees'.

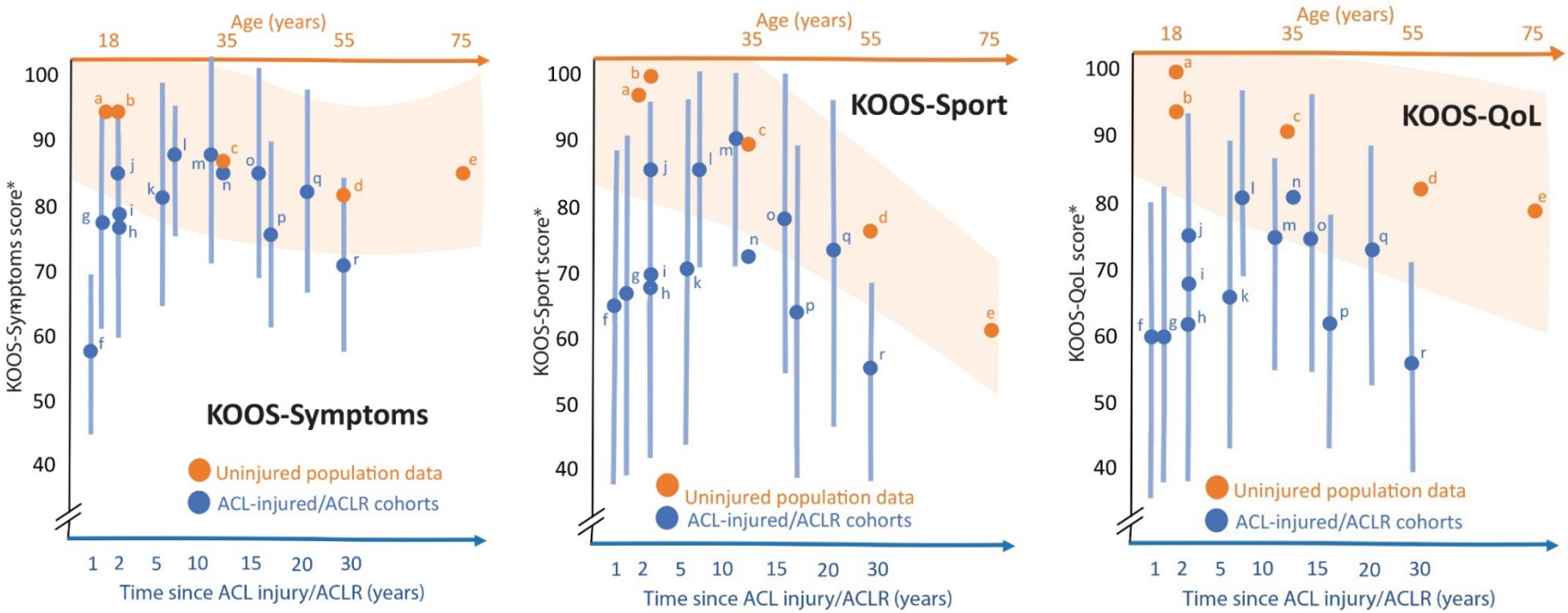


Figure 1.6. KOOS-Symptoms, KOOS-Sport, and KOOS-QoL scores after ACLR compared with uninjured (no history of knee problems) normative data.

ACLR=anterior cruciate ligament reconstruction; KOOS=Knee injury and Osteoarthritis Outcome Score; QoL=quality of life.
[*]Each dot and error bar/orange shading represents the reported (or calculated from available data) mean±standard deviation from each study.
[a-b] Uninjured healthy athletic population (no history of knee problems) aged 18 to 25 years (Antosh et al., 2018; Cameron et al., 2013).
[c] Uninjured population-based sample (with or without history of knee problems) aged 18 to 35 years (Paradowski et al., 2006).
[d] Uninjured population-based sample (with or without history of knee problems) aged 55 to 74 years (Paradowski et al., 2006).
[e] Uninjured population-based sample (with or without history of knee problems) aged 75 to 84 years (Paradowski et al., 2006).
[f-g] 1 year post-ACLR from Swedish (Ahldén et al., 2012) and Danish (Lind et al., 2009) national registries.
[h – j] 2 years post-ACLR from Swedish (Ahldén et al., 2012), Norwegian (Granan et al., 2008), and USA national registries (Spindler et al., 2018).
[k] 5 years post-ACLR from Swedish national registry (Ahldén et al., 2012).
[l] 6 years post-ACLR from USA national registry (Spindler et al., 2018).
[m] 10 years post-ACLR from USA registry (Spindler et al., 2018).
[n] 11.5 years post-ACLR from Swedish surgical cohort (Moller et al., 2009).
[o] 20 years post-ACLR from Norwegian surgical cohort (Oiestad et al., 2011).
[p] 14 years post-ACLR from Swedish surgical cohort (Barenius et al., 2014).
[q] 20 years post-ACLR from Norwegian surgical cohort (Risberg et al., 2016b).
[r] 32 to 37 years post-ACLR from Swedish registry (Filbay et al., 2018b).

1.5.2 Consideration of individual variation in PROs following ACLR

Some individuals have an excellent outcome (i.e., return to normative values) while others have persistent (knee-related) symptoms, functional limitations, and QoL impairments. This variation is evidenced by the large standard deviations (SD) in the mean group-level scores for the KOOS-Symptoms, KOOS-Sport, and KOOS-QoL subscales up to 30-years following ACLR in the Scandinavian and USA registries (Ahldén et al., 2012; Grindem et al., 2015a; Spindler et al., 2018) (**Figure 1.6**). Most studies report group-level data (i.e., group mean) and indicate variability using SD. Other concepts such as the patient-acceptable symptom state (PASS) calculate a reference or "PASS" value for each of the KOOS subscales at which the ACLR patients consider their current knee function as satisfactory (Tubach et al., 2005). In the Norwegian Knee Ligament Registry, approximately half of patients at six months post-ACLR, and two-thirds at 1-2 years post-ACLR report satisfactory knee function (Ingelsrud et al., 2015). Fifty per cent of participants in the Swedish National Knee Ligament Registry report satisfactory outcomes in four of the five KOOS subscales one year following ACLR (Hamrin Senorski et al., 2018). In contrast, a USA-based cohort calculated lower PASS cut-off values, and consequently reported a much higher (89%) rate of knee function satisfaction at a mean of 3.4 years following ACLR (Muller et al., 2016). However, the response rate of 51% in Muller et al. (2016) poses a high risk of selection bias, as those who declined to participate were on average five years younger and mostly male (Muller et al., 2016). Taken together, these results highlight that individual recovery may differ due to varied patient characteristics and expectations, healthcare access, and evidence-based rehabilitation participation (Grindem et al., 2018).

As there is no ACL registry in Australia, observational cohort studies can provide information on trajectories of symptoms, function, and QoL. Assessment of PROs after the initial recovery and rehabilitation period (>one year post-ACLR) and over the proceeding years might identify individuals who have not yet reached an acceptable state, or are experiencing symptomatic decline. Early identification of individuals with unacceptable PROs may provide opportunity for the implementation of interventions to a targeted group who need them the most, before impairments become persistent and irreversible. Persistent symptoms may lead to undesirable lifestyle changes with negative health consequences, such as reduced physical activity (Bell et al., 2017; Kuenze et al., 2019) and weight gain (Toomey et al., 2017; Whittaker et al., 2015). As these impairments begin to impact daily function and QoL, patients are more likely to pursue costly pharmacological and surgical treatments, with potentially harmful side-effects (Skou et al., 2018).

1.6 Physical assessment of knee function following ACLR

Following ACLR, the measures of physical function in clinical and research settings commonly include muscle strength and/or power or functional performance (e.g., hop testing). Biomechanical assessment is more common in the research setting following ACLR, where joint movements and forces are quantified during functional tasks.

1.6.1 Muscle strength assessment

Knee extensor (i.e., quadriceps) and knee flexor (i.e., hamstrings) muscle strength are often assessed using isokinetic dynamometers (Undheim et al., 2015). The ACLR limb often displays deficits of greater than 10% in quadriceps and hamstring strength compared to the contralateral limb, and to healthy uninjured controls, and these deficits can persist for up to 12 to 24 months (Lisee et al., 2019a; Turpeinen et al., 2020). The limb symmetry index (LSI) is used to describe the performance of the ACLR limb compared to the contralateral limb, and is expressed as a percentage (score of ACLR knee divided by contralateral knee, multiplied by 100). An LSI >90% is frequently used to define functional recovery and clearance for return-to-sport (Abrams et al., 2014; Undheim et al., 2015; Wellsandt et al., 2017), as 10% asymmetry is considered "normal" (Ageberg et al., 2001a; Lisee et al., 2019b).

1.6.2 Biomechanical assessment following ACLR

Altered biomechanics, such as lower external knee flexion joint moments (compared to the contralateral or uninjured healthy controls) during walking (Capin et al., 2018; Capin et al., 2019; Hart et al., 2016; Slater et al., 2017), running (Hart et al., 2010; Pairot-de-Fontenay et al., 2019), and landing tasks (Baumgart et al., 2017; Johnston et al., 2018; Gokeler et al., 2010; Perraton et al., 2019) are evident up to two years following ACLR. Biomechanical outcomes are an important consideration for the development and/or progression of post-traumatic OA following ACLR. As discussed in Section 1.4, altered kinematics and kinematics may underload or overload the knee joint structures (Wang et al., 2020). However, assessment of biomechanics requires expensive equipment, specialised training, and time-consuming assessment and data processing, and thus, was not performed in this thesis.

1.6.3 Functional performance outcomes following ACLR

Hop tests can evaluate lower-limb function and are less expensive than isokinetic muscle testing, are quick and easy to administer, and require minimal equipment or training. Compared with isokinetic testing, which assesses strength in an open-chain movement, hop tests evaluate all lower-limb muscle groups functioning together in a predominantly closed-chain movement. A hop-test battery can assess multiple aspects of lower-limb function (e.g., strength, endurance,

power, balance, coordination) in multiple planes of movement (Grip et al., 2015; Noyes et al., 1991; Reid et al., 2007), and is moderately associated with isokinetic muscle strength (Birchmeier et al., 2019a; Hamilton et al., 2008).

The most commonly utilised functional performance tests are the single-hop and triple-hop for distance (Abrams et al., 2014; Lepley, 2015). Other hop tests include a triple-crossover hop for distance, 6-metre timed hop, or a side-hop (number of repetitions hopped over two lines 40 cm apart in 30 seconds). Two systematic reviews reported single-hop, triple-hop, and triple-crossover hop limb symmetry averages >90% at the group level at 6, 9, 12, and 24 months post-ACLR (Abrams et al., 2014; Lepley, 2015). Cross-sectional evaluations of hop performance (predominantly single-hop) beyond two years following ACLR report that >90% limb symmetry is achieved by the majority (>80%) of individuals at three (Ageberg et al., 2008; Laxdal et al., 2005; Reinke et al., 2011), five (Heijne et al., 2015; Jonsson et al., 2004), and seven years (Salmon et al., 2006). Longitudinal evaluations of single-hop and triple-hop tests suggest that minimal changes occur up to 10 years following ACLR, with most (>80%) achieving >90% LSI (Oiestad et al., 2010a; Pinczewski et al., 2007). It appears that on average, individuals achieve an "acceptable" (>90%) LSI in most functional performance measures in the first year following ACLR (Abrams et al., 2014; Lepley, 2015), providing objective clearance for return-to-sport and discharge from supervised rehabilitation.

Despite the apparent recovery of function, subsequent ACL injuries continue to occur at unacceptably high rates in the ipsilateral (i.e., graft rupture) (7%) (Wiggins et al., 2016) and contralateral knee (8%) (Wiggins et al., 2016) in the first two years following ACLR. Part of this puzzle may be that the LSI is not the most accurate representation of ACLR limb function (Wellsandt et al., 2017). The LSI relies on the uninjured contralateral limb as the benchmark for performance, when there are known bilateral muscle activation and strength deficits following ACLR (Benjaminse et al., 2018; Gokeler et al., 2017; Lisee et al., 2019b). Longitudinal assessments should evaluate change in performance (i.e., cm hopped) in the ACLR and contralateral limbs, and consider their impact on the LSI. Most longitudinal cohorts only report symmetry (Lepley, 2015) at the group level, and a recent review called for better reporting standards for hop testing procedures, scoring, and interpretation in the ACL field (Read et al., 2020). Functional performance assessment is often focussed on non-fatigued tests in a linear direction, such as the single- or triple-hop for distance tests (Lepley, 2015). The few studies evaluating the side-hop or fatigued single-hop show greater functional performance deficits (i.e., <90% LSI) compared with the standard single-hop or triple-hop regime (Abrams et al., 2014). Evaluation of endurance or

multidirectional capacity may highlight deficits in aspects of lower-limb function important for the risk of structural or symptomatic decline.

The implications of persistent functional performance deficits after ACLR are uncertain and require further investigation. The relationships between functional performance and patient-reported and structural outcomes are less clear (Losciale et al., 2019). Evaluating functional performance alongside structural outcomes and PROs will provide a better appreciation of the relationships between function, symptoms, and post-traumatic OA.

1.7 Factors associated with structural and patient-reported outcomes following ACLR

This chapter highlighted the greater risk of developing radiographic post-traumatic OA, and the poorer knee-related symptoms and QoL in individuals following ACLR, compared to their uninjured peers. Early identification of factors associated with an increased risk of development or progression of OA and symptoms is required to direct potential interventions. Post-traumatic OA is a complex whole-person disease with many potential modifiable and non-modifiable *risk factors* (associated with disease onset) and *prognostic factors* (associated with disease progression) (Andriacchi et al., 2020). These factors may be pre-existing, occur at the time of injury or ACLR, occur post-operatively, and/or persist or change over time (Andriacchi et al., 2020; Punzi et al., 2016). This section will explore the influence of non-modifiable (e.g., age, sex, concomitant injuries) and modifiable (e.g., body mass index (BMI), muscle strength, functional performance, activity level) factors on the development and/or progression of OA and symptoms, with occurrence (and assessment) of these factors both at the time of, and following, ACLR.

Table 1.1 summarises the non-modifiable and modifiable factors associated with OA development (Jones & Spindler, 2017; van Meer et al., 2015) or worse PROs (An et al., 2017; Galea-O'Neill et al., 2019; Hamrin Senorski et al., 2018; Spindler et al., 2018) up to 10 years following ACL injury/ACLR. Data from registries in the USA (Jones & Spindler, 2017; Spindler et al., 2018) and Scandinavia (Hamrin Senorski et al., 2018), and systematic reviews (An et al., 2017; Galea-O'Neill et al., 2019; van Meer et al., 2015) conducted in the last decade with the primary aim of identifying factors associated with OA outcomes or patient-reported symptoms, function, and QoL are included.

Table 1.1 Factors associated with structural and patient-reported outcomes following ACLR

	Osteoarthritis		Worse patient-reported symptoms/function/QoL**			
Review or registry	*MOON (nested)*	*Systematic review*	*MOON registry*	*Scandinavian registries*	*Systematic review*	*Systematic review*
Primary author	*Jones (2017)*	*van Meer (2015)**	*Spindler (2018)*	*Hamrin Senorski (2019)*	*An (2017)*	*Galea O'Neill (2019)*
No. of studies in review	n.a	64	n.a	35	26	12
High risk of bias, no. (%)	n.a	62 (97%)[a]	n.a	14 (40%)[b]	14 (54%)[c]	11 (92%)[d]
Study design, no. (%)^						
Level 1 (prospective)	n.a	22 (34%)	n.a	0 (0%)	4 (15%)	2 (17%)
Level 2 (retrospective)	n.a	40 (63%)	n.a	35 (100%)	7 (27%)	7 (58%)
Level 3+ (case series)	n.a	2 (3%)	n.a	0 (0%)	15 (58%)	3 (25%)
Patient characteristics						
Older age	Y	?	Y	Y	Y	-
Female sex	-	N	Y	Y	Y	-
Smoker	-	-	?	Y	Y	Y
Less educated	-	-	?	-	?	-
Lower pre-injury activity level	N	?	?	-	-	-
Medial meniscal lesion~	Y	Y	?	Y	Y	-
Lateral meniscal lesions~	-	N	?	Y	Y	-
Full-thickness cartilage lesion~	?	?	y	Y	Y	-
Peri-operative modifiable						
Time from injury to ACLR	-	N	-	?	?	?
Prehabilitation	-	-	-	?	-	?
Graft type	N	?	N	Y	?	-
Lower PROs at ACLR	-	-	Y	Y	?	-
Surgical technique	-	?	-	N	?	-
Medial meniscal procedure~	Y	Y	Y	Y	?	-
Lateral meniscal procedure~	-	N	Y	Y	?	-
Higher body mass index~	N	?	Y	-	?	?
Post-operative modifiable						
Rehab supervision/duration	-	-	-	?	-	-
Muscle weakness	-	-	-	-	-	-
Poor functional performance	-	?	-	-	-	-
Activity level	-	-	?	-	-	-
Increased knee laxity	-	N	-	-	-	-
Higher body mass index	-	-	-	-	-	-
Revision ACLR	-	-	Y	Y	-	-

Y	Moderate evidence supports relationship	N	Moderate evidence supports no relationship
?	Limited, conflicting, or weak evidence	-	Not assessed

ACL=anterior cruciate ligament; ACL=anterior cruciate ligament reconstruction; PROs=patient-reported outcomes; MOON=Multicenter Orthopaedic Outcomes Network; n.a=not applicable; QoL=quality of life.
* 62 studies reported radiographic OA as the outcome, 2 studies reported cartilage lesions on MRI.
** PROs not related to re-injury or factors associated with revision ACLR.
^ Level of evidence according to Orthopaedic Journal guidelines (Wright et al., 2003).
[a] according to ratings reported in the van Meer et al. (2015) review using a customised checklist.
[b] considered low quality if Downs and Black score lower than median (16 points).
[c] according to ratings reported in the An et al. (2017) review (Downs and Black score <median 20 points).
[d] considered low quality if risk of bias evident for internal validity item.
~ at the time of ACLR.

The evidence for non-modifiable and modifiable prognostic factors in **Table 1.1** should be interpreted with caution. All reviews (An et al., 2017; Galea-O'Neill et al., 2019; Hamrin Senorski et al., 2018; van Meer et al., 2015) had many studies (>40%) with high risk of bias and included mostly (>60%) retrospective or case-series analyses (**Table 1.1**). Common threats to internal validity in these studies are related to attrition bias (consideration of participants lost to follow-up), lack of statistical power, or appropriate multivariate modelling (An et al., 2017; Hamrin Senorski et al., 2018; van Meer et al., 2015). Only 21% and 42% of studies in the van Meer et al. (2015) and An et al. (2017) reviews, respectively, adjusted for the influence of confounders. External validity is compromised as the reviews mostly consisted of Scandinavian and USA registry data (Hamrin Senorski et al., 2018; Jones & Spindler, 2017; Spindler et al., 2018) or examined specific ACLR techniques (An et al., 2017). Use of the same patient data from registries increases the risk of multiple significance, providing further justification for more prospective cohort studies (An et al., 2017). Most studies in the van Meer et al. (2015) review evaluated factors associated with the development of tibiofemoral (radiographic) OA. Less than 20% evaluated patellofemoral radiographic OA, while only two studies evaluated prognostic factors for early OA features on MRI (van Meer et al., 2015). In summary, although some factors may increase the risk of post-traumatic radiographic OA or worse PROs, the limitations of the primary studies these reviews are based upon highlights the need for further prospective studies to identify factors associated with poor prognosis following ACLR.

1.7.1 Non-modifiable factors

The only non-modifiable factor with moderate and consistent evidence for an increased risk of radiographic OA development (tibiofemoral or unspecified) or worse symptoms following primary ACLR is a concomitant meniscal injury or meniscal procedure (i.e., meniscectomy or meniscal repair) (An et al., 2017; Filbay et al., 2014; Hamrin Senorski et al., 2018; Jones & Spindler, 2017; Spindler et al., 2018; van Meer et al., 2015), particularly in the medial compartment (**Table 1.1**). Full-thickness cartilage lesions noted arthroscopically at the time of ACLR are also associated with worse PROs in the Scandinavian (Hamrin Senorski et al., 2018) and USA registries (Spindler et al., 2018) (**Table 1.1**). Older age, female sex, and history of smoking have weak and conflicting associations with radiographic OA development following ACLR (Jones & Spindler, 2017; van Meer et al., 2015), but moderate and more consistent associations with worse PROs (An et al., 2017; Galea-O'Neill et al., 2019; Hamrin Senorski et al., 2019; Spindler et al., 2018) (**Table 1.1**). Concomitant meniscal and cartilage lesions, larger pre-operative BML size, persistent BMLs at one year, and male sex appear to increase the risk of progression of tibiofemoral cartilage lesions on MRI in the first two years following ACLR (Van Ginckel et al., 2013; van Meer et al., 2016). Few

studies have investigated the factors associated with development and/or progression of other early OA features on MRI (e.g., BMLs, meniscal lesions, osteophytes).

1.7.2 Modifiable factors

While non-modifiable factors help to build the risk profile for post-traumatic OA, evaluation of modifiable peri-operative or post-operative factors related to outcomes following ACLR provides opportunity for implementation of interventions targeting these factors. Peri-operative factors such as time from injury to ACLR, graft type, knee laxity, and surgical technique are frequently evaluated, but appear to have weak or no influence on patient-reported or structural outcomes following ACLR (**Table 1.1**). Re-injury to the ACL graft and revision ACLR appear to be associated with greater risk of OA and worse PROs (Hamrin Senorski et al., 2018; Spindler et al., 2018; Wright et al., 2012).

BMI

Obesity (BMI >30kg/m^2) is associated with the development of symptomatic radiographic knee OA in the general population (Felson et al., 1997; Roos & Arden, 2016), yet the effect of higher peri-operative BMI on the risk of worsening knee structure or symptoms in post-traumatic populations is uncertain (**Table 1.1**). No relationship has been observed between peri-operative BMI and the rate of worsening OA features on MRI up to five years following ACLR (Eckstein et al., 2015; van Meer et al., 2016), but further investigation is warranted as these studies typically consisted of participants with normal BMIs (Eckstein et al., 2015; van Meer et al., 2016). Post-operative BMI should also be considered given that weight gain is common following ACL injury (Whittaker et al., 2019).

Physical activity

Physical activity and surgical success following ACLR are mostly assessed by participation in pre-injury sports. While those who return to their pre-injury level of sport often report better PROs (Filbay et al., 2017a; Spindler et al., 2018), the relationship between participation in sports placing high demands on the knee and the development or progression of post-traumatic OA following ACLR is uncertain and rarely investigated (Ajuied et al., 2014; Hamrin Senorski et al., 2019; van Meer et al., 2015) (**Table 1.1**). At 15-years after ACLR, those who had returned to pivoting sports had 60% and 72% reduced odds of developing radiographic OA and symptomatic radiographic OA, respectively (Oiestad et al., 2018). However, this retrospective analysis relied on participant recall and the authors were unable to account for the type, duration, or frequency of sport exposure over the 15 year period (Oiestad et al., 2018). Evaluation of the impact of return-to-sport on structural outcomes following ACLR is challenging and is limited to retrospective cohorts or case

series with lack of adjustment for confounding factors (Ajuied et al., 2014). In the KOALA cohort, an accelerated return-to-sport (i.e., less than 10 months following ACLR) combined with poor function (<90% LSI on the side-hop test) was associated with an increased risk of BMLs on MRI at one year following ACLR (Culvenor et al., 2017a).

Physical function

Level I evidence demonstrates that quadriceps muscle weakness is associated with the development of symptomatic radiographic knee OA in the general population (Culvenor et al., 2017b; Oiestad et al., 2015; Segal & Glass, 2011; Thorstensson et al., 2004). Yet, few high-quality studies have evaluated this relationship in post-traumatic OA populations following ACLR (**Table 1.1**). In cross-sectional evaluations following ACLR, quadriceps weakness is associated with worse KOOS scores at the time of return-to-sport (Lentz et al., 2009; Lepley & Palmieri-Smith, 2015; Norte et al., 2018; Zwolski et al., 2015), but the association is attenuated in the longer-term (Norte et al., 2018). The effect of quadriceps weakness on risk of incident or progressive post-traumatic OA, or symptomatic decline, is uncertain (Oiestad et al., 2010b; Wellsandt et al., 2018). Functional performance (hop testing) has a fair association with PROs in the first two to three years following ACLR, but the relationship is weaker in the longer-term, while the relationship between hop testing and tibiofemoral radiographic OA development is uncertain (Losciale et al., 2019; Pinczewski et al., 2007). Further studies are needed to examine the relationships between objective knee function and early joint degeneration on MRI, as specific imaging features may be more sensitive to altered neuromuscular function and may be more modifiable with interventions such as exercise.

1.8 Secondary prevention interventions following ACLR

Secondary prevention interventions aim to prevent or slow the onset of post-traumatic OA or knee-related symptoms by targeting modifiable factors associated with disease onset and/or progression. While there is high-level evidence for interventions aimed at preventing the initial ACL injury (primary prevention) (Crossley et al., 2020; Webster & Hewett, 2018) or managing symptoms and functional limitations in end-stage OA (tertiary prevention) (Allen et al., 2016; Fransen et al., 2015; Skou et al., 2018), there is a lack of evidence supporting interventions to delay or prevent the onset of symptomatic post-traumatic OA following ACLR (secondary prevention) (Whittaker & Roos, 2019) (**Figure 1.7**). Poor knowledge of modifiable factors associated with structural and symptomatic changes following ACLR has limited the ability to develop and test recommendations for secondary prevention strategies (Whittaker & Roos, 2019).

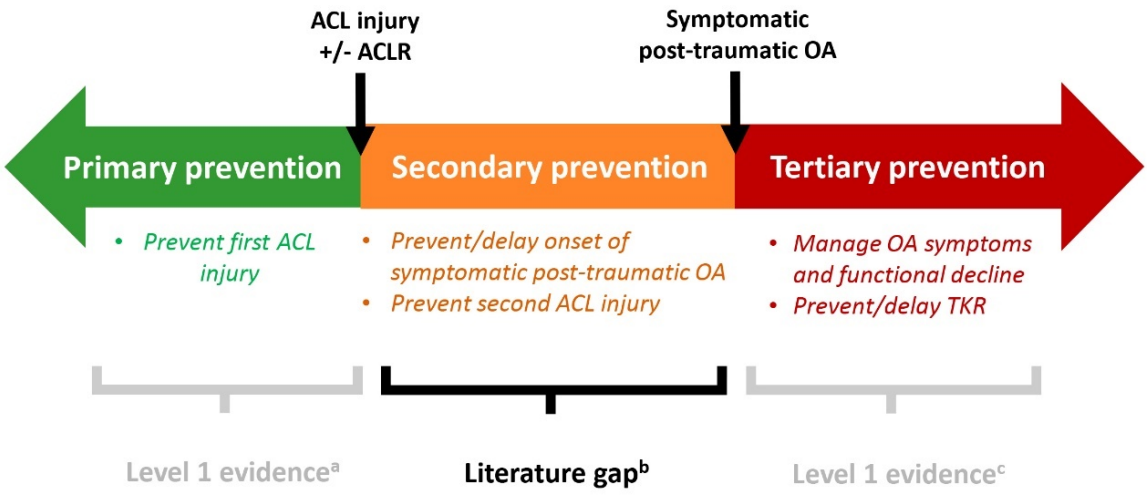


Figure 1.7 Primary, secondary, and tertiary prevention of post-traumatic osteoarthritis.

ACL=anterior cruciate ligament; ACLR=anterior cruciate ligament reconstruction; OA=osteoarthritis; QoL=quality of life; RCTs= randomised controlled trials; TKR=total knee replacement.
[a] Multiple RCTs report that ACL injuries in sporting populations can be reduced with injury prevention training programs (Webster & Hewett, 2018).
[b] Minimal high-quality RCTs to guide prevention of post-traumatic OA (Watt et al., 2019; Whittaker & Roos, 2019).
[c] Multiple RCTs report that knee-related symptoms, function, and QoL can be improved with exercise and education in individuals with knee OA (Allen et al., 2016; Fransen et al., 2015; Skou et al., 2018).

Once modifiable factors are identified, interventions that target specific impairments can be developed, and their effectiveness at improving structural, patient-reported, and/or physical outcomes can be evaluated. The utilisation of evidence-based rehabilitation in the first post-operative year is the most effective way to immediately address these impairments and optimise short-term outcomes (Risberg et al., 2016a). Recommendations from six clinical practice guidelines (CPGs) suggest that rehabilitation should continue for 9 to 12 months, or until achievement of a series of impairment, functional, and psychological criteria (van Melick et al., 2016). More information on evidence-based rehabilitation following ACLR is provided in Chapter 7.

Despite the CPGs recommendations, it appears that most (>80%) individuals do not participate in evidence-based rehabilitation for longer than six to nine months following ACLR (Ebert et al., 2018; Greenberg et al., 2018; Grindem et al., 2018; Rosso et al., 2018). This is concerning given that many (>80%) individuals require longer than nine months to achieve adequate functional performance (Herbst et al., 2015; van Melick et al., 2016). Therefore, many will continue with unsupervised exercise and independently decide (i.e., self-directed without professional consultation) if and when they will return-to-sport (Ebert et al., 2018; Greenberg et al., 2018). Individuals with persistent symptoms and functional impairments at the time of return-to-sport may be at an

increased risk of structural or symptomatic decline and are likely to benefit most from ongoing interventions. However, further prospective cohort studies are required to confirm these relationships, and RCTs are required to evaluate the influence of secondary prevention interventions on immediate and longer-term structural and symptomatic outcomes.

1.9 Summary of Chapter 1

The evidence outlined in Chapter 1 regarding the course of structural, patient-reported, and functional performance outcomes following ACLR provides a framework and rationale for the objectives of this thesis. **Figure 1.8** highlights specific gaps in the literature which exist in the period following ACLR recovery and rehabilitation (i.e., >one year post-ACLR) but prior to the onset of radiographic OA (i.e., <10 years post-ACLR). Given the urgent need to prevent or slow the progression of OA, the use of MRI to quantify early OA disease progression is necessary. Previous evaluations of the development of tibiofemoral radiographic OA (Lie et al., 2019) or tibiofemoral cartilage changes on MRI (Van Ginckel et al., 2013) have omitted the patellofemoral compartment and other joint features such as BMLs, despite them being potential sources of symptoms (Culvenor & Crossley, 2016; Culvenor et al., 2014b; Stefanik et al., 2015; Wang et al., 2015). No studies have performed semi-quantitative evaluations of OA features on MRI beyond two years post-ACLR.

Patient-reported symptoms, function, and QoL continue to improve up until one to two years following ACLR, with minimal change beyond this point (Ahldén et al., 2012; Granan et al., 2009; Oiestad et al., 2011; Risberg et al., 2016b; Spindler et al., 2018). While most achieve good outcomes, a proportion may have unacceptable PROs compared to their uninjured peers (Antosh et al., 2018; Cameron et al., 2013; Filbay et al., 2014; Ingelsrud et al., 2015; Paradowski et al., 2006) and identifying individuals with unacceptable outcomes may better direct secondary prevention interventions to those most in need. Evaluating PROs alongside structural and physical outcomes will provide insight into these relationships.

Functional performance recovery appears acceptable following ACLR (i.e., >90% LSI on hop tests), but cross-sectional study designs and reliance on the LSI limits the validity of prior studies. Prior studies have also focused on non-fatigued testing in a linear direction (i.e., single-hop), typically less than two years post-operatively (Abrams et al., 2014; Lepley, 2015) (**Figure 1.8**). Assessment of multiplanar movement, requiring repeated power generation, endurance, and coordination beyond the typical rehabilitation period should be considered, as these young adults continue to participate in multidirectional sports which place high demands on the knee. The LSI should not be the sole measure of functional performance due the potential for the contralateral limb to

experience functional decline (Engelen-Van Melick et al., 2013). Longitudinal evaluation of the ACLR and contralateral limb performance, and comparison to uninjured peers, is required to provide insight for clinical decision-making.

The only consistent factor identified to be associated with an increased risk of post-traumatic OA development, or worse symptoms and QoL following ACLR, is a concomitant meniscal lesion or meniscectomy, which is non-modifiable (**Figure 1.8**). Secondary prevention of OA relies on the identification of prognostic factors amenable to intervention (Whittaker & Roos, 2019). Yet, there is limited and conflicting evidence from multiple reviews regarding the influence of modifiable factors such as BMI, physical activity, strength, and functional performance on structural or patient-reported outcomes. A greater understanding of how early OA features develop and progress, and factors associated with worsening disease, is critical to inform management approaches to optimise outcomes in young adults following ACLR.

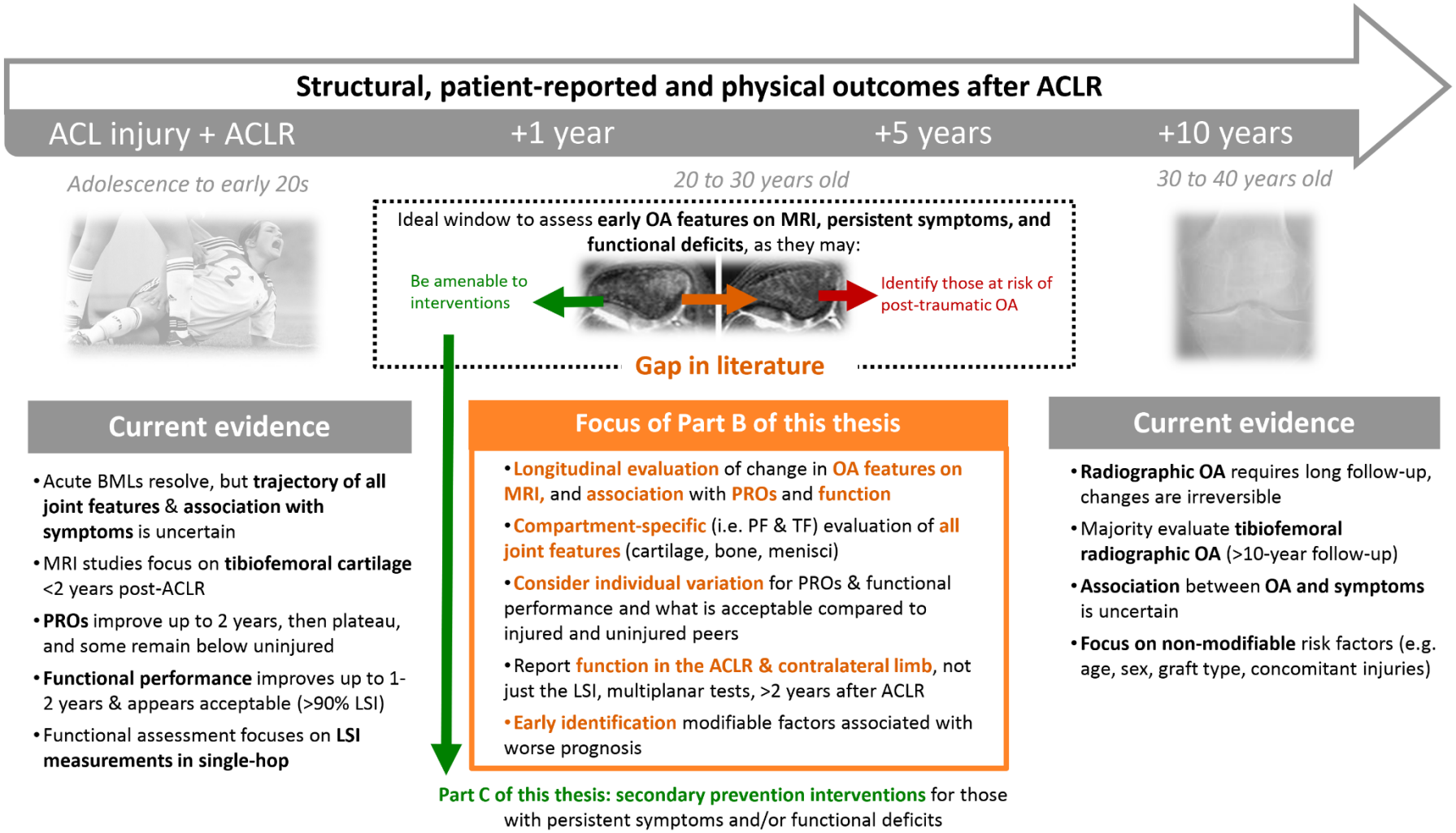


Figure 1.8 Summary of Chapter 1: Structural, patient-reported, and functional outcomes following ACLR.

ACL=anterior cruciate ligament; ACLR=anterior cruciate ligament reconstruction; BMLs=bone marrow lesions; OA=osteoarthritis; LSI=limb symmetry index; MRI=magnetic resonance imaging; PROs=patient-reported outcomes; QoL=quality of life.

1.10 Aims of this thesis

The overall aims of this thesis were to:

(i) evaluate changes in OA features on MRI, patient-reported outcomes, and functional performance between one and five years following ACLR (Part B);

(ii) identify factors associated with worsening OA features and change in PROs (Part B);

(iii) determine the feasibility of a physiotherapist-guided intervention targeting individuals with persistent symptoms one year following ACLR in a pilot RCT (Part C).

An overview of this thesis, the studies conducted to achieve these aims, and the associated chapters are provided in **Figure 1.9**. The remainder of this thesis consists of two parts (Part B and C), followed by a discussion and conclusion (Part D).

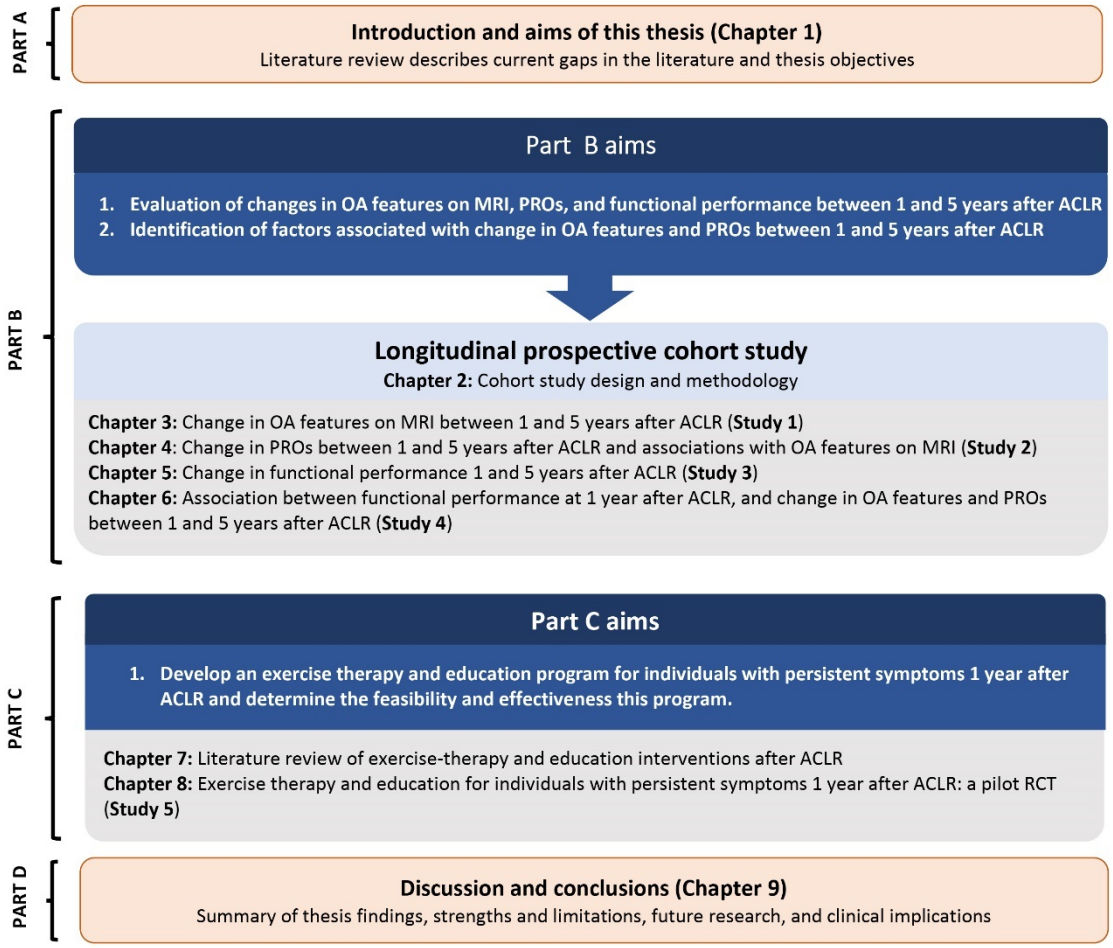


Figure 1.9 Visual summary of thesis.

ACLR=anterior cruciate ligament reconstruction; OA=osteoarthritis; RCT=randomised controlled trial; PROs=patient-reported outcomes; MRI=magnetic resonance imaging.

Part B: Changes in structural, patient-reported, and functional performance outcomes between one and five years following ACLR: A longitudinal prospective study

2 Chapter Two: Prospective longitudinal cohort study design, eligibility, recruitment, procedures, and outcome measures

The following chapter contains a detailed description of the methods used in the prospective longitudinal cohort study. From this cohort, there are four studies that make up Part B of this thesis. Specifically, these studies are:

CHAPTER 3 (STUDY 1)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2018). Worsening knee osteoarthritis features on magnetic resonance imaging 1 to 5 years after anterior cruciate ligament reconstruction. *American Journal of Sports Medicine, 46*(12), 2873-2883.

CHAPTER 4 (STUDY 2)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., & Crossley, K.M. (2020). Patient-reported outcomes one to five years after anterior cruciate ligament reconstruction: the effect of combined injury and associations with osteoarthritis features defined on magnetic resonance imaging. *Arthritis Care & Research, 72*(3), 412-422.

CHAPTER 5 (STUDY 3)

Patterson, B.E., Crossley, K.M., Perraton, L.G., Kumar, A.S., King, M.G., Heerey, J.J., Barton, C.J., & Culvenor, A.G. (2020). Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function. *Physical Therapy in Sport, 44*, 67-74.

CHAPTER 6 (STUDY 4)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2020). Poor functional performance 1 year after ACL reconstruction increases the risk of early osteoarthritis progression. *British Journal of Sports Medicine*, *54*(9), 546-553.

2.1 Introduction

This chapter outlines the methods used for the longitudinal prospective **K**nee **O**steoarthritis **A**nterior cruciate ligament **L**ongitudinal **A**ssessment (KOALA) study which evaluated the change in OA features on MRI, PROs, and functional performance between one and four years following ACLR. The one-year post-ACLR assessments were completed as part of a previous PhD (Dr Adam Culvenor, co-supervisor of this thesis) and the five-year assessments were completed specifically for this PhD thesis. Although the methods used for each of the studies (Study 1 to 4) arising from the KOALA cohort are summarised in the relevant chapters, additional and more detailed justifications and descriptions of the study design, participant eligibility, recruitment, procedures, and outcome measures are provided in this chapter. All studies related to this study are reported in accordance with the **ST**rengthening the **R**eporting of **OB**servational studies in **E**pidemiology (STROBE) guidelines for reporting observational studies (Elm et al., 2007).

2.2 Funding and ethical approval

The KOALA study was funded by a University of Melbourne Research Collaboration Grant (Crossley & Pandy, 2009), the Queensland Orthopaedic Physiotherapy Network (Culvenor, 2013), an Arthritis Australia National Research Program Grant (Culvenor et al., 2015), and a La Trobe University Sport, Exercise, and Rehabilitation Research Focus Area Grant (Crossley et al., 2016). The majority of the funds were used to acquire and score the MRI scans and radiographs, and for incidentals and consumables related to data collection at the one- and five-year post-ACLR assessments.

Ethical approval for the one-year post-ACLR assessment was granted by the University of Melbourne (HEC number 0931086) and the University of Queensland Research Ethics Committee (MREC number 2012000567). Ethical approval for the five-year post-ACLR assessment, and for use of the previously collected one-year data, was obtained by the PhD candidate from the La Trobe University Human Ethics Committee (HEC 15-100) (**Appendix A**). All participants were provided with a written patient information statement **(Appendix B)** and completed written informed consent **(Appendix C)** at each assessment time-point.

2.3 Participants

All 112 participants who previously underwent assessment one year following ACLR were invited to participate in the five-year assessment.

2.3.1 Participant recruitment and eligibility at one year following ACLR

Participants were consecutively recruited between July 2010 and August 2011 in Melbourne, Australia, from two high-volume orthopaedic surgeons, Hayden Morris (HM) and Timothy Whitehead (TS), who had over 25 and 15 years' experience performing ACLRs, respectively. Each participant was invited via a letter from their respective orthopaedic surgeon at their 12-month post-ACLR milestone. Individuals were eligible for inclusion if they were approximately 12 months (eligible range 11-14 months) following a primary single-bundle four-strand hamstring tendon autograft ACLR, and were aged between 18 and 50 years at the time of ACLR. The lower age limit ensured that the surgical technique was kept consistent across all participants, as a variety of techniques are used for those aged <18 years to reduce growth plate complications. The upper age limit minimised the influence of any pre-existing knee OA prior to ACLR. The exclusion criteria at one year post-ACLR were: (i) previous injury/symptoms to the ACL-injured knee; (ii) subsequent injury/surgery to the ACLR knee; (iii) inability to speak/read English; (iv) >five years between ACL injury and ACLR (to limit any potential effects of ACL deficiency on structural, patient-reported, and functional outcomes); (v) contraindications for X-ray (e.g., pregnancy or breastfeeding); (vi) contraindications for MRI (e.g., implanted metal such as a pacemaker); or (vii) another musculoskeletal, neurological, or cardiovascular condition affecting their daily function.

2.3.2 Participant recruitment and eligibility at five years following ACLR

All participants in the one-year assessment were contacted when they were five years post-ACLR (between July 2015 and December 2016) via a letter addressed from the research team (**Appendix D**). If the participant did not contact the research team, they were contacted by telephone and invited to participate**.** Details of participant recruitment and retention from one to five years following ACLR are provided in **Figure 2.1**. The inclusion and exclusion criteria at five years are outlined in **Table 2.1**. Participants were eligible if they had sustained an ACL graft rupture or contralateral ACL rupture between the one- and five-year assessments, as this is a common occurrence and representative of the wider ACLR population. Those with a subsequent injury to either knee were excluded from Study 3 in Chapter 5 (**Figure 2.1**), due to the nature of the research question.

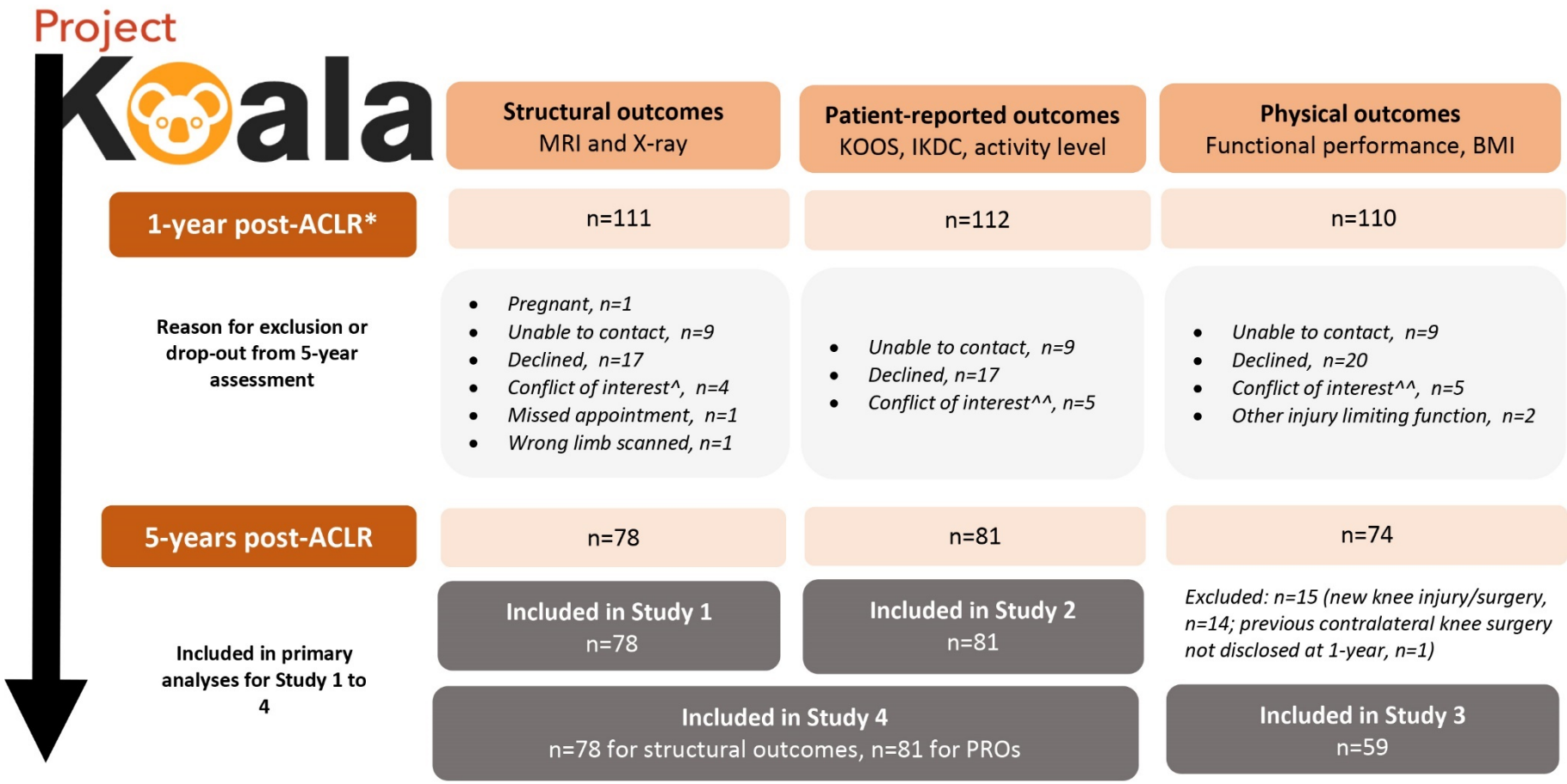


Figure 2.1 KOALA cohort participant recruitment and retention.

ACLR=anterior cruciate ligament reconstruction; BMI=body mass index; IKDC=International Knee Documentation Committee knee evaluation; KOALA=Knee Osteoarthritis Anterior cruciate ligament Longitudinal Assessment cohort study; KOOS=Knee injury and Osteoarthritis Outcome Score; MRI=magnetic resonance imaging; n=number of participants; PROs=patient-reported outcomes.
* The PhD candidate was not involved in the recruitment or testing of participants at one-year post-ACLR; this was completed by Dr Adam Culvenor.
^ n=4 due to participation in another study.
^^ n=4 due to participation in another study and n=1 had since become a member of the research team at 5 years.

Table 2.1 Inclusion and exclusion criteria for the five-year assessment

Inclusion criteria at 5 years following ACLR
• Participated in the 1-year assessment. • 5 years after ACLR (eligible range 4.5 to 5.5 years), regardless of subsequent ipsilateral or contralateral knee injury or surgery. • Able to complete at least one aspect of the assessment (imaging, PROs, or functional performance).
Exclusion criteria at 5 years following ACLR for imaging assessment
• Contraindications for MRI (e.g., implanted metal, pacemaker, cochlear implant, previous surgery for cerebral aneurysm) or X-ray (e.g., pregnancy or breastfeeding).
Exclusion criteria at 5 years following ACLR for self-reported or functional performance assessment
• Another musculoskeletal*, cardiovascular, or neurological condition affecting their lower-limb function (e.g., low back pain).

ACLR=anterior cruciate ligament reconstruction; MRI=magnetic resonance imaging; PROs=patient-reported outcomes.
*All individuals with an ACL graft rupture or contralateral ACL rupture between 1 and 5 years after ACLR were able to complete the functional performance assessment, as it was >12 months since their ACLR.

2.4 Procedures

2.4.1 ACLR

All ACLRs were performed arthroscopically and involved quadrupled hamstring-tendon grafts using semitendinous and gracilis tendons. A partial meniscectomy was performed if the meniscal lesion was unstable or deemed unrepairable. If the meniscal lesion was considered repairable, a repair procedure was performed. Significant cartilage lesions were managed with debridement, as deemed appropriate by the surgeon.

2.4.2 Rehabilitation

As this was a cohort study with first assessment at one year following ACLR, post-operative rehabilitation was not standardised. However, all participants were encouraged to undertake a typical rehabilitation protocol that encouraged early weight-bearing and range of motion, strength training, neuromuscular exercises, and graded return to activity. No braces or splints were used, and in general, most participants were full weight-bearing by three weeks and running by three to four months. Sport-specific drills could be introduced from four months, and return-to-sport could occur from six months, as advised by the surgeon.

2.4.3 Participant assessment

All PROs and clinical outcome assessments at one year following ACLR were performed by one researcher (AC) at The University of Melbourne. All PROs and clinical assessments at five years following ACLR were performed by the PhD candidate at Olympic Park Sports Medicine Centre.

Imaging assessments (unilateral MRI of index knee and bilateral knee radiographs) at one and five years following ACLR were conducted at a private radiology clinic in Melbourne (Imaging @ Olympic Park). At one year, imaging was completed within two weeks of the PROs and clinical assessment session, and at five years, they were completed on the same day.

2.5 Outcome measures

An overview of all outcome measures (primary outcomes, primary prognostic factors, and confounding variables) at one and five years following ACLR used in Part B of this thesis is provided in **Table 2.2**. Data obtained from the one-year assessment were used as the baseline for Study 1 to 4 (Chapter 3 to 6). Prior to commencing data collection, the PhD candidate (BP) was trained in all testing protocols for consistency with the one-year data collection for each outcome measure.

2.6 Participant characteristics

Age, sex, injury history (i.e., injury date, time from injury to surgery), duration of formal physiotherapy, and pre-injury sports participation were recorded one year following ACLR.

2.7 Structural outcomes

For the purpose of this thesis, structural outcomes include the following: (i) concomitant injuries (meniscal and chondral lesions) noted arthroscopically at the time of ACLR; (ii) subsequent intra-articular injuries or surgeries between one and five years following ACLR; (iii) cartilage lesions, BMLs, meniscal lesions, and osteophytes on MRI assessed at one and five years; and (iv) the presence of radiographic OA on X-ray at one and five years.

2.7.1 Concomitant injuries

Concomitant injuries were noted arthroscopically by the orthopaedic surgeon at the time of ACLR and this information was extracted from the surgical record. Cartilage lesions were graded using the Outerbridge classification system (grade 1=softening and swelling of the cartilage, grade 2=fragmenting and fissuring of the cartilage in an area <15 mm, grade 3=fragmenting and fissuring of the cartilage in an area >15 mm, grade 4=erosion of the cartilage to the subchondral bone) (Outerbridge, 1961). A significant cartilage lesion was defined as being present if the grade was ≥2, a cut-off which has been used previously (Li et al., 2011a). Meniscal tears (horizontal, vertical, or complex) were recorded as absent or present in the medial and lateral tibiofemoral compartments, and the procedure performed (nil/partial meniscectomy/repair) was recorded. No total meniscectomies were performed. For this thesis, a participant with a significant cartilage lesion or meniscal injury requiring meniscectomy at the time of ACLR was classified as having a

combined ACL injury at one and five years following ACLR. All other participants were classified as having an isolated ACL injury.

Table 2.2 Cohort outcome measures for Part B of this thesis

	Primary dependent variables	Primary prognostic variables	Confounding variables*
Chapter 3			
	Structural outcomes • MRI: worsening OA features between 1 and 5 years • Xray: radiographic OA	**Participant characteristics** • Age, sex, surgical delay **Structural features** • Concomitant injury **Physical performance** • BMI at 1 year, knee laxity	Each factor with a p value <0.20 in univariate analyses was entered into a multivariate logistic regression
Chapter 4			
	Patient-reported outcomes • KOOS and IKDC at 1 year, change between 1 and 5 years, and at 5 years	**Structural features** • MRI: OA features at 1 and 5 years • Concomitant injuries	**Participant characteristics** • Age, sex, surgical delay **Physical performance** • BMI at 1 year and 5 years **Patient-reported measures** • 1-year KOOS/IKDC scores
Chapter 5			
	Physical outcomes: • Functional performance (3 hop tests and the 1-leg rise test) at 1 and 5 years	Not a prognostic study	
Chapter 6			
	Structural outcomes • MRI: worsening OA features between 1 and 5 years **Patient-reported outcomes** • Change in KOOS and IKDC between 1 and 5 years	**Physical performance:** • Functional performance at 1 year; 3 hop tests and a 1-leg rise test	**Participant characteristics** • Age, sex **Structural features** • Concomitant injury **Physical performance** • Height, weight **Patient-reported measures** • 1-year KOOS/IKDC scores

ACLR=anterior cruciate ligament reconstruction; BMI=body mass index; IKDC=International Knee Documentation Committee subjective knee evaluation; KOOS=Knee injury and Osteoarthritis Outcome Score; LSI=limb symmetry index; MRI=magentic resonance imaging; OA=osteoarthritis.
*adjusted for in primary regression analyses. Refer to respective chapters for specific details on statistical methods.

2.7.2 Subsequent injuries and surgeries

Subsequent intra-articular knee injuries or surgeries (e.g., ACL re-rupture, ACLR revision, meniscectomy, or collateral ligament injury) to the index (n=11) and/or contralateral limb (n=6) were reported by the 81 participants completing PROs at the five-year assessment. All secondary arthroscopic procedures were performed by the same surgeons as the primary ACLR (HM or TW), as reported by participants at five years. Subsequent injuries were not used as a primary outcome or independent prognostic factor in Part B. However, participants with a subsequent intra-articular injury or surgery to the index knee between one and five years were added to the combined injury subgroup at five years. Those with a subsequent injury to the index knee were also excluded for sensitivity analyses in Study 1 and 2.

2.7.3 OA features on MRI

MRI acquisition

A unilateral MRI of the index knee was acquired on a single 3.0T system (Philips Achieva, The Netherlands). Participants were supine with the knee flexed 20–30° with thigh support. Axial, sagittal, and coronal sequences were obtained using a standardised protocol with a 16-channel phased-array knee coil (Invivo, Gainesville, Florida, USA). Images at one and five years following ACLR were acquired at the same location, on the same MRI scanner with identical image sequences. This was with the exception of three participants who had MRIs on a different scanner five years following ACLR, as they had relocated interstate for work or family reasons.

The two main MRI sequences used were:

1. A three-dimensional (3D) proton density (PD) weighted Volumetric Isotropic Turbo spin echo Acquisition (VISTA) sequence acquired at 0.35 millimetres (mm) isotropically (repetition time/echo time (TR/TE), 300 msec/27 msec, field of view (FOV) 150 mm^2, and echo train length 64 milliseconds (msec)).
2. A PD weighted turbo spin echo (TSE) sequence obtained in the axial plane due to its high accuracy, sensitivity, and specific sequences for assessing cartilage lesions (Mohr et al., 2003; Roemer et al., 2011; Sonin et al., 2002), osteophytes (Hunter et al., 2011a), and meniscal lesions (Escobedo et al., 1996; Fox, 2007; Jung et al., 2009). The parameters were TR/TE 3,850 msec/34 msec, slice thickness 2.5 mm, slice gap 2.0 mm, corresponding voxel size 0.5 x 0.55 x 2.5 mm, and FOV 140 mm^2.

The VISTA and TSE sequences were used to grade cartilage lesions, BMLs, osteophytes, and meniscal lesions. A third additional image was taken to assess BMLs (Hunter et al., 2011a), which

included a fluid sensitive short-tau inversion-recovery (STIR) sequence in the sagittal plane acquired at 2.5 mm thickness and 1.2 mm slice gap. An inversion time of 180 msec was applied with TR/TE 3,850 msec/30 msec, FOV 160 mm^2, and voxel size 0.45 x 0.50 x 2.5 mm. The STIR sequence is used to suppress the effects of the metallic hardware present in the knee (used for fixation in ACLR), which can cause image distortion.

MRI interpretation

The MRI scans at one and five years following ACLR were graded by a musculoskeletal radiologist, Ali Guermazi (AG), who has over 20 years' experience and established reliability in musculoskeletal MRI evaluation (Hunter et al., 2011a). The MOAKS scoring system was used to score each knee, with AG blinded to surgical, clinical, and radiographic information. Inter-rater reliability using the MOAKS is very good (ICC=0.61 to 0.80), and intra-rater reliability reaches near-perfect agreement (ICC =0.81 to 1.0) (Hunter et al., 2011a). At five years following ACLR, the MRI was read paired with participant's one-year MRI (i.e., side-by-side, unblinded to the time-points); this method has proven reliability (Runhaar et al., 2014).

The MOAKS divides the knee into 14 articular subregions to score cartilage lesions and BMLs (with the addition of a subspinous region for BML scoring) (**Figure 2.2**). Ten subregions form the tibiofemoral compartment (medial and lateral: femur central and posterior, tibia anterior, central, and posterior). Four subregions form the patellofemoral compartment (medial and lateral patella, medial and lateral trochlea). Osteophytes were scored in six tibiofemoral subregions (medial and lateral: tibia, central femur, posterior femur) and four patellofemoral subregions (medial patella trochlea, lateral patella and trochlea). Meniscal lesions were defined as medial or lateral, and divided into anterior, posterior, and central subregions.

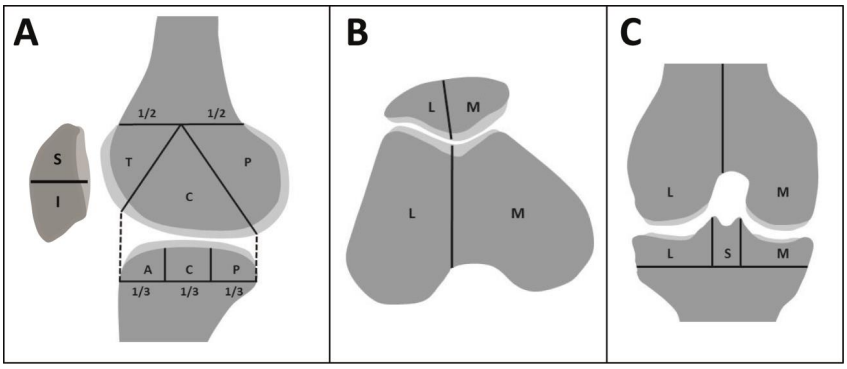


Figure 2.2 Regional subdivision of the knee using the MOAKS.

A. Sagittal plane subdivided into the trochlear femur (T), anterior tibia (A), central femur and tibia (C), posterior femur and tibia (P), and superior (S) and inferior (I) patella. **B.** Axial plane used to score the posterior femur and trochlea in lateral (L) and medial (M) subregions, and the lateral (L) and medial (M)

patella. **C.** Coronal plane subdivided into the lateral femur and tibia (L), medial femur and tibia (M), and subspinous region (S, scored as a separate region since it is not covered by cartilage).

The MOAKS was used to score the size and severity of cartilage lesions, BMLs, osteophytes, and meniscal lesions at one and five years. Cartilage lesions were graded from 0 to 3 based on size (percentage of surface area relative to each subregion) where 0=none, 1=<33%, 2=33–66%, and 3=>66%. Cartilage lesions were also graded based on depth (percentage of lesion that is full thickness), where 0=no full-thickness loss, 1=<10%, 2=10-75%, and 3=>75%. BMLs were scored based on size only (percentage of surface area relative to each subregion) where 0=none, 1=<33%, 2=33–66%, and 3=>66%. Osteophytes were graded according to size based on how far the lesion extended from the joint (0=none, 1=small, 2=medium, 3=large). Meniscal lesions (tear, maceration, or extrusion) were described as absent or present. A meniscal tear (vertical, horizontal, or complex) was defined as present if an area of abnormal signal extended to both meniscal articular surfaces. Meniscal maceration was defined as present if there was partial or complete loss of the morphologic substance of the meniscus. Meniscal extrusion was defined as subluxation from the edge of the tibial plateau, and was graded by size where 0=<2 mm, 1=2–2.9 mm, 2=3–4.9 mm, and 3=>5 mm. Meniscal extrusion was defined as present if the size was ≥grade 1.

Subregions were combined to create 'compartments' which will be referred to throughout Part B of this thesis; patellofemoral, medial tibiofemoral, lateral tibiofemoral, any tibiofemoral, and any knee compartment (**Figure 2.3**). When combining subregions to report the presence of an OA feature in a particular compartment (e.g., patellofemoral), only the largest size of each OA feature (e.g., cartilage lesions) from all the corresponding subregions (i.e., medial patella and trochlea, lateral patella and trochlea) was considered. For each OA feature, the size (and corresponding severity for cartilage lesions) at one and five years following ACLR was recorded and was then used to determine the "change" (i.e., new, progressive, or improving lesions) between one and five years.

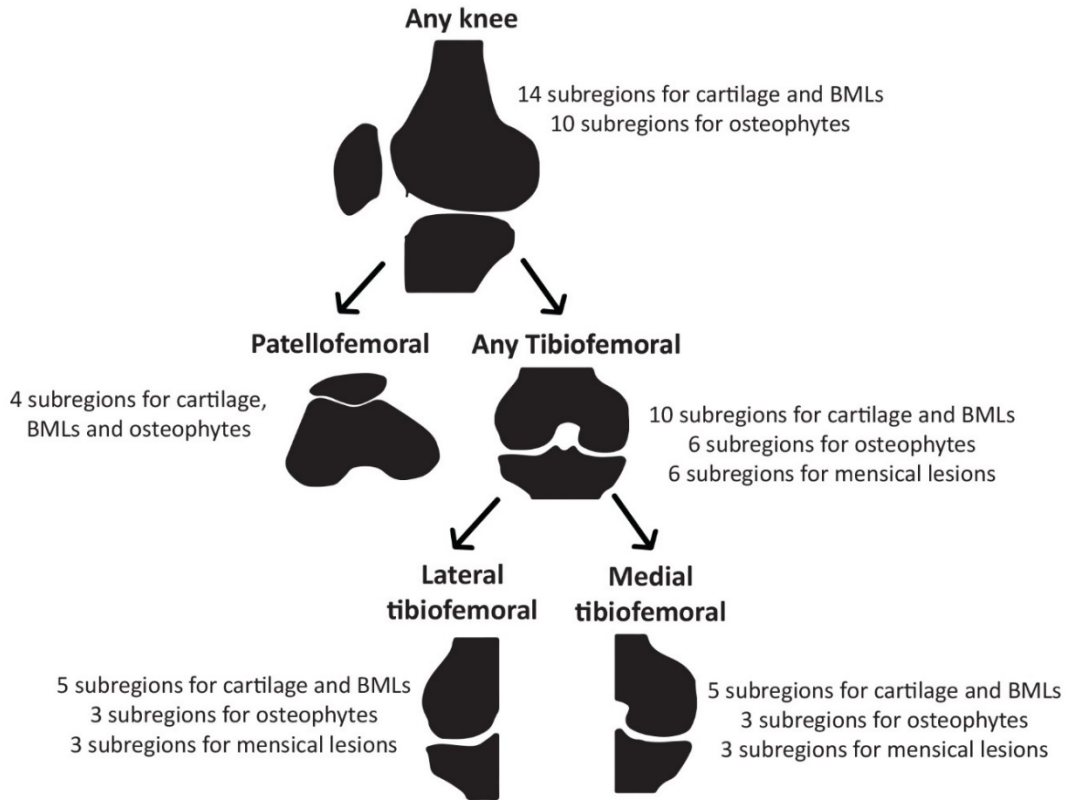


Figure 2.3 Knee compartments and respective number of subregions.

BMLS=bone marrow lesions.

Definitions of change in OA features on MRI

Scoring methods for change (worsening, improving, or stable) in MOAKS features have been defined (Runhaar et al., 2014) and utilised following ACLR (van Meer et al., 2016). The Runhaar et al. (2014) definition of "progression" of OA features using the MOAKS includes both incident (i.e., new lesions) and progressive lesions (i.e., increase in lesion size/severity). Therefore, the term "worsening" instead of "progression" was used to define degenerative changes in OA features in this thesis. Either progression of an OA feature (i.e., increase in lesion severity) or a new OA feature (i.e., from no lesion to present lesion) between one and five years following ACLR was classified as worsening. Increase in lesion severity was defined as an increase of at least 1 point on the MOAKS in terms of size (i.e., size=1 to size=2) or depth (i.e., partial- to full-thickness cartilage lesion). New lesions were defined as those with size=0 at one year and size $\geq$1 at five years. Osteophytes needed to be $\geq$2 at five years as the definition of a definite osteophyte has not been delineated (Hunter et al., 2011a). For each OA feature (i.e., cartilage, BMLs, osteophytes, and meniscal lesions), worsening was defined as present in each of the aforementioned compartments (e.g., patellofemoral) if any of the corresponding subregions (i.e., medial patella and trochlea, lateral patella and trochlea) for that compartment demonstrated worsening (**Figure 2.3**). Conversely, improvement (i.e., resolution of BMLs) between one and five years following ACLR

was defined as a decrease in size or severity, or complete resolution (i.e., lesion present at one year, to no lesion present at five years). Stable lesions were those demonstrating neither improvement nor worsening between one and five years. The classifications of improving and stable lesions were adopted from the Runharr et al. (2014) definition. The intra-rater and inter-rater reliability of changes in MOAKS features were determined by prevalence-adjusted bias-adjusted kappa (PABAK) statistics and percentage agreement between readers, respectively. The average PABAK values for cartilage, BMLs, osteophytes, and meniscal lesions were >0.85, while agreement was >85% for all features (Runhaar et al., 2014).

2.7.4 Radiograph acquisition and interpretation

At one and five years, all participants eligible for radiographic assessment underwent bilateral posterior-anterior and lateral weight-bearing (**Figure 2.4**) X-rays of both knees. A SynaFlexor frame (Synarc) was used to hold the knees in 30° flexion with the feet externally rotated 10°. A non-weighting skyline view was taken with the participant supine, knee flexed 30°, to assess the patellofemoral compartment (**Figure 2.4**). The radiographs were assessed for the presence of osteophytes and joint space narrowing in the medial and lateral tibiofemoral and the patellofemoral compartments. To grade the presence and severity of osteophytes and joint space narrowing, the OARSI atlas was used (Altman & Gold, 2007; Altman et al., 1995), grading both features on a scale of 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe). To maximise the identification of osteophytes and joint space narrowing, multiple views were used. Radiographic OA was deemed present in the tibiofemoral or patellofemoral compartment if any of the following criteria were met: (i) joint space narrowing of ≥grade 2, (ii) sum of osteophytes ≥2, or (iii) grade 1 osteophytes in combination with grade 1 joint space narrowing.

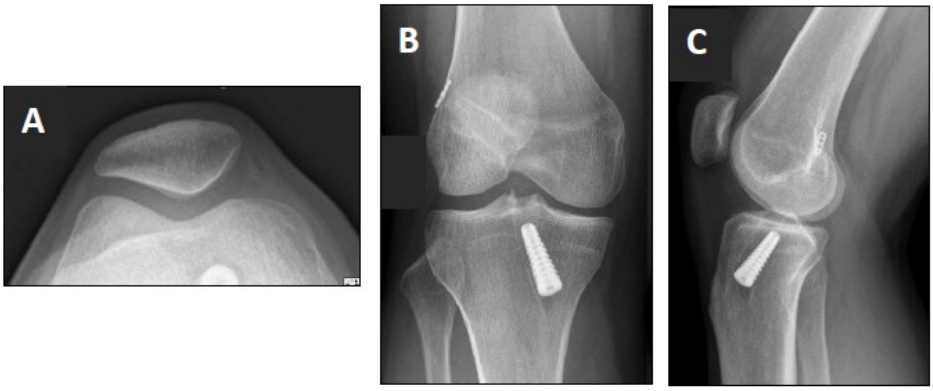


Figure 2.4 Radiographic assessment of the tibiofemoral and patellofemoral compartments**.**

A: posterior-anterior view; **B**: lateral view; **C:** skyline view.

All radiographs one year following ACLR were assessed independently by researcher AC and Kay Crossley (KC) (primary supervisor of this thesis). Researcher AC has seven years of radiographic grading experience, while KC has over 10 years' experience. Radiographs at five years were assessed independently by two trained researchers (AC and BP), and a consensus meeting with researcher KC was held to resolve any discrepancies. All raters were blinded to the clinical outcomes and MRI findings at one and five years following ACLR. The radiographs at five years were read paired with the one-year radiographs (i.e., side by side, unblinded to the time-points).

2.8 Patient-reported outcomes

At one and five years following ACLR, participants completed the KOOS (**Appendix E**) and International Knee Documentation Committee (IKDC) subjective knee evaluation (**Appendix F**), rating their knee condition during the previous week. Participants completed the questionnaires via pen and paper or via an online platform (MySQL, Oracle Corporation, California, USA and Promptus, DS-PRIMA, Melbourne, Australia), with matching instructions to the original version. The KOOS (ICC=0.96) (Gudbergsen et al., 2011) and IKDC (ICC=0.79) (Nguyen et al., 2017) exhibited excellent test-retest reliability between paper and electronic formats. The KOOS and IKDC are the most commonly used instruments in ACL-injured cohorts (Gagnier et al., 2018).

The KOOS is freely available and has 42 items across five subscales related to pain (KOOS-Pain, nine items), symptoms (KOOS-Symptoms, seven items), activities of daily living (KOOS-ADL, 17 items), function in sport and recreational activities (KOOS-Sport, five items), and knee-related QoL (KOOS-QoL, four items). All items are self-rated on a five-point Likert scale from 0=no problems to 4=extreme problems, and a total score for each of the five sections was summed and transformed to a 0 to 100 scale, where 100 represents the best result/no knee problems. The KOOS was designed for use in young and middle-aged adults with knee injuries that may lead to post-traumatic knee OA or in elderly adults with knee OA (Roos & Lohmander, 2003). Therefore, it is useful for use in a longitudinal prospective cohort study to evaluate the short- (<2 years), medium- (2 to 10 years), and long-term (>10 years) consequences of ACLR, as the risk of OA and associated symptoms increases (van Meer et al., 2013). A recent systematic review and meta-analysis reported excellent internal consistency (pooled Cronbach's alpha from 24 studies: >0.76), test-retest reliability (pooled ICC from 11 studies: >0.86), and responsiveness (effect sizes >0.5) to surgical (i.e., ACLR) and non-surgical (i.e., physiotherapy) interventions in young populations with knee injuries (Collins et al., 2016). The minimal clinically important difference (MCID) for the KOOS has not been calculated in any population. However, 8 to 10 points is the recommended minimal detectable change (MDC) - the amount of change required to exceed random error, based on

changes observed in all KOOS subscales in the first post-operative year following ACLR (Roos & Lohmander, 2003).

The IKDC was designed to evaluate symptoms, function, and sports activity in a variety of knee conditions, including ACL injuries (Irrgang et al., 1998). The IKDC is freely available and has 18 items which are summed and then converted to a 0 to 100 scale, where 100 represents the best score/no symptoms or limitations with daily/sporting activities. The IKDC was chosen for concurrent use with the KOOS as it evaluates constructs specific to shorter-term recovery which are not covered in the KOOS (e.g., instability and the ability to participate in different activities relevant to sport, work, or household duties) (van Meer et al., 2013). The IKDC has excellent internal consistency (Cronbach's alpha: 0.77 to 0.91), test-retest reliability (ICC: 0.90 to 0.95), and is responsive to change in individuals with a variety of knee conditions, with the MDC reported to be 12.8 points (Irrgang et al., 2006).

At one and five years following ACLR, participants were asked what sports and physical activities they participated in using a customised questionnaire (**Appendix G**). The highest level of regular (at least once per week in the previous month) activity for each participant was recorded at one and five years. Participants were classified according to the Sports Activity Level Classification system (Grindem et al., 2014); where level 1=pivoting/jumping/hard cutting sports (e.g., football, basketball), level 2=pivoting/jumping sports but less intense cutting (e.g., tennis, skiing), level 3=straight line activities (e.g. running, weight-lifting), and level 4=sedentary.

2.9 Physical outcomes

One year following ACLR, the physical assessments were performed by researcher AC at The University of Melbourne. At five years, the physical assessments were performed by the PhD candidate at Olympic Park Sports Medicine Centre.

2.9.1 Anteroposterior laxity, height, and weight

A KT-1000 arthrometer (MEDmetric Corp., California, USA) was used to assess anteroposterior laxity of both the hamstring-tendon autograft and the ACL on the contralateral limb by researcher AC one year post-ACLR. Participants were positioned in the supine position with the knee flexed at approximately 30° over a support placed underneath the thigh. Anterior tibial displacement at 30 pounds of force was recorded in millimetres, as previously described (Daniel et al., 1985). The average of three measures was obtained and used for analysis, and the between-limb difference reported in millimetres. At one year following ACLR, there was a (median) 1.6 mm difference in anteroposterior laxity between ACLR and contralateral limbs. This is within the normal between-

limb differences from uninjured control data (≤3 mm) (Collette et al., 2012). Most (>75%) participants had a between-limb difference of ≤3 mm. Laxity assessed at one year was used as a confounder in analyses in Study 1 of this thesis. Laxity was not assessed at five years. At one and five years following ACLR, participant height and weight were assessed with a standardised tape measure and scales, and BMI was calculated (kg/m^2).

2.9.2 Functional performance

The battery of functional performance tests, including the single-hop, triple-crossover hop, side-hop and one-leg rise were assessed at one and five years. These tests were chosen as they incorporate varying aspects of physical performance (i.e., strength, power, endurance, coordination, balance) in multiple planes of movement (Gustavsson et al., 2006; Reid et al., 2007). The single-hop for distance is the most commonly used hop test (Abrams et al., 2014) evaluating linear power, while the triple-crossover hop requires repeated linear and lateral power generation and absorption as well as multidirectional control and balance (Birchmeier et al., 2019a). The side-hop requires endurance, repeated power generation in the mediolateral direction, and rotational stability (Grip et al., 2015). The one-leg rise test is a global measure of lower-limb strength and endurance (Thorstensson et al., 2004). Functional performance tests are clinically feasible (Schelin et al., 2017) and require no associated licensing or software costs. They also require minimal time, equipment, space, and training to perform.

After a standardised warm-up (30 seconds of high knee running on the spot, 10 star jumps, and 10 burpees), the functional tests were performed in the following order: single-hop, triple-crossover hop, side-hop, and one-leg rise. Three minutes rest was given between each hop test, and five minutes rest between each limb for the one-leg rise. Participants wore their own athletic shoes, and both the ACLR and contralateral limb were tested. The assessor was blind to the ACLR limb by Tubigrip placed over both knees by the participant; hence, the left limb always tested first. The raw score (i.e., number of repetitions or distance in cm) in both the ACLR and contralateral limb for each test was recorded. The LSI, used to describe the function of the ACLR limb compared to the contralateral limb, was calculated by dividing the score of the contralateral limb by the score of the ACLR limb, and is expressed as a percentage.

2.9.3 Single-hop for distance

The single-hop test evaluates the distance that the participant can hop from a stationary position, hands held behind the back, taking off and landing on the same foot with a balanced landing (≥2 seconds without placing the other foot to the floor) (Gustavsson et al., 2006) (**Figure 2.5**). If participants made subsequent smaller hops or did not remain balanced, the hop was not recorded.

The distance hopped (cm) was recorded from the toe at take-off to the heel at landing. There was no set number of trials; additional hops were performed until no increase in distance was seen, and the best recorded distance was used for analysis. This method was used to account for learning effects that exist with this test (Munro & Herrington, 2011). The test was scored 0 if the participant was unable to achieve a successful trial (i.e., due to lack of strength/confidence/balance or pain). The single-hop test has excellent test-retest (Gustavsson et al., 2006; Kockum & Heijne, 2015) and inter-rater reliability (Haitz et al., 2014) (**Table 2.3**).

Figure 2.5 Single-hop test.

2.9.4 Triple-crossover hop for distance

The triple-crossover hop assesses the maximum distance that the participant can achieve by hopping three times, hands held behind the back, crossing over the outside of two strips of tape placed 15 cm apart each time (Reid et al., 2007) (**Figure 2.6**). A trial was deemed unsuccessful and not recorded if the participant: (i) let go of their hands held behind their back; (ii) made subsequent smaller hops on any of the three hop landings; (iv) touched their contralateral foot on the floor on any of the three hops; or (iii) did not remain balanced (≥2 seconds without placing the other foot to the floor) on the final hop. The distance hopped (cm) was recorded from the toe at take-off to the heel at the third landing. There was no set number of trials; additional hops were performed until no increase in distance was observed, to account for known learning effects with this test (Munro & Herrington, 2011). The best recorded distance was used for analysis. The test was scored 0 if the participant was unable to score any successful trials (i.e., due to lack of strength/confidence/balance or pain). The triple-crossover hop test has excellent test-retest (Gustavsson et al., 2006; Kockum & Heijne, 2015; Reid et al., 2007) and inter-rater reliability (Haitz et al., 2014) (**Table 2.3**).

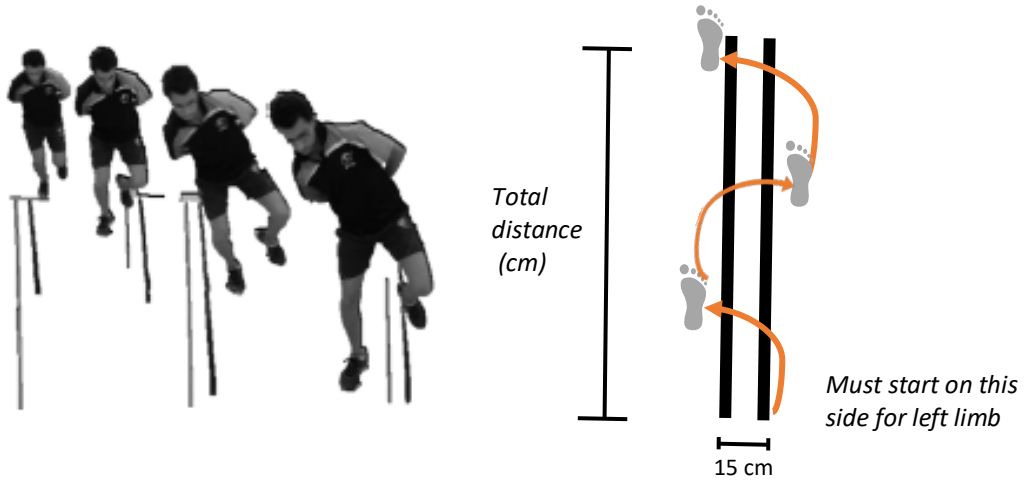


Figure 2.6 Triple-crossover hop test.

2.9.5 Side-hop

The side-hop test evaluates the number of hops the participant can achieve in 30 seconds, hopping side-to-side outside two parallel strips of tape placed 40 cm apart on the floor (Gustavsson et al., 2006; Kockum & Heijne, 2015) (**Figure 2.7**). The participant held their hands behind their back, and the number of successful hops (i.e., without foot touching the tape, landing on two feet, or falling off balance) was recorded. If ≥25% of total hops were not successful, the test was scored 0, and the participant was given two additional attempts. The side-hop test has excellent test-retest reliability (Gustavsson et al., 2006; Kockum & Heijne, 2015) (**Table 2.3**).

Figure 2.7 Side-hop test.

2.9.6 One-leg rise

For this test, participants sat on the edge of a height-adjustable plinth with the heel of the test leg positioned on a line marked on the floor 10 cm in front of the edge of the plinth (**Figure 2.8**). The plinth height was adjusted so that the angle of the test knee in sitting was 90°. Holding their arms folded across their chest and non-test leg straight out in front, participants were instructed to rise

from the sitting position to an upright standing position, achieving full hip and knee extension, and return to sitting in a controlled manner. Rises were performed to a metronome to maintain a consistent cadence of 45 beats per minute. The maximum numbers of rises achieved at the predetermined cadence was recorded. The one-leg rise test has excellent test-retest reliability (Bremander et al., 2007) (**Table 2.3**).

Figure 2.8 One-leg rise test.

2.9.7 Functional performance psychometric properties

Hop tests are sensitive to change over time in observational ACLR cohorts (Abrams et al., 2014; Heijne et al., 2015; Thomee et al., 2012). If known, the test-retest and inter-rater reliability, responsiveness, and normative scores from uninjured healthy adults, for each individual test, are summarised in **Table 2.3.** As no MCID is available for any of the four functional performance tests, the MDC was used to approximate the amount of change required to exceed random error. The MDC in the listed studies (**Table 2.3**) (Haitz et al., 2014; Kockum & Heijne, 2015; Reid et al., 2007) was calculated by multiplying the standard error of measurement (SEM) by the square root of 2 and the *z* value for 90% confidence (1.64) (Reid et al., 2007) (or 95% confidence, 1.96 pending on the study) (Haitz et al., 2014; Kockum & Heijne, 2015). The MDC is used interchangeably with the smallest real difference (SRD), but each is calculated using the same method.

Table 2.3 Reliability, responsiveness, and normative scores for the functional performance tests

Test	Reliability ICC 95% CI	Minimal detectable change	Normative scores
Single-hop			
	Test-retest 0.89-0.99 (Kockum & Heijne, 2015) ***Inter-rater*** ICC: 1.00 (Haitz et al., 2014)	14 cm* (Kockum & Heijne, 2015) LSI: 8% (Reid et al., 2007)	***18 to 50 years general population*** (Kemp et al., 2013): 153±26 cm (men), 111±31 cm (women) ***20 to 25 years healthy active adults (mixed sex)*** (Kockum & Heijne, 2015): 145±26 cm (right limb), 147±28 cm (left limb) ***20 to 35 years healthy general population (all men)*** (Baltaci et al., 2012): 177±12 cm (dominant), 170±22 cm (non-dominant) ***15 to 44 years healthy active adults*** *(*Ageberg et al., 2001a): 203±21 cm (men), 163±21 cm (women)
Triple-crossover hop			
	Test-retest ICC: 0.74-0.93 (Reid et al., 2007) ***Inter-rater*** ICC: 0.99-1.00 (Haitz et al., 2014)	73 cm (Haitz et al., 2014) LSI: 12% (Reid et al., 2007)	***20 to 35 years healthy general population (mixed sex)*** (Baltaci et al., 2012): 430±54 cm (dominant), 431±58 cm (non-dominant) ***18 to 24 years college athletes*** (Myers et al., 2014): 570±75 cm (men), 406±54 cm (women)
Side-hop			
	Test-retest ICC: 0.84-0.96 (Kockum & Heijne, 2015) ***Inter-rater:*** n.a	11 reps* (Kockum & Heijne, 2015) LSI: 10%** (Reid et al., 2007)	***20 to 25 years healthy active adults (mixed sex)*** (Kockum & Heijne, 2015): 50±14 repetitions (right limb), 47±13 repetitions (left limb)
One-leg rise			
	Test-retest ICC: 0.86-0.96 (Bremander et al., 2007) ***Inter-rater*** n.a	*n.a*	*n.a*

cm=centimetres; CI=confidence interval; ICC=intraclass correlation coefficient; MDC=minimal detectable change; n.a=not available.
* average of left and right limbs from Kockum et al. (2015).
** the MDC for the side-hop LSI is not known; therefore, the MDC was estimated as 10%, as an average of 8% and 12% for the single-hop and triple-crossover hop from Reid et al. (2007).

2.10 Data management and statistical analyses

Data collected were manually entered into an electronic spreadsheet (Microsoft Office, Excel 2016). The five-year post-ACLR data were combined with the one-year post-ACLR data in a master spreadsheet. Analyses were performed using Stata (Stata-Corp) version 14.2. More detail regarding specific statistical methods and analyses is provided in the respective chapters.

3 Chapter Three: Worsening knee osteoarthritis features on magnetic resonance imaging one to five years following anterior cruciate ligament reconstruction

Chapter 3 contains the following publication in its entirety (**Appendix H**), with the addition of **Figure 3.1** to depict participant recruitment into the study consistent with the other chapters.

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2018). Worsening knee osteoarthritis features on magnetic resonance imaging 1 to 5 years after anterior cruciate ligament reconstruction. *American Journal of Sports Medicine, 46*(12), 2873-2883.

3.1 Introduction

ACLR is often performed with the intention to improve the stability of a mechanically unstable ACL-deficient knee, facilitate a return to competitive sport and reduce the risk of subsequent meniscal or cartilage damage (Church & Keating, 2005; Lebel et al., 2008; Swirtun et al., 2006). While typically restoring mechanical stability, ACLR does not protect against the long-term development of knee OA (Lohmander et al., 2007). Radiographic knee OA is evident in as many as 50-90% of individuals 10 to 15 years following ACL injury, regardless of treatment, and often with an onset during early adulthood (Frobell et al., 2015; Lohmander et al., 2007).

With rates of ACL injuries continuing to rise (Zbrojkiewicz et al., 2018), secondary prevention strategies to delay or halt OA onset following injury are vital (Roos & Arden, 2016). Unlike established radiographic OA, the trajectory of early pre-radiographic stages of disease, such as post-traumatic changes to cartilage and bone marrow, have the capacity to be modified (Pollard et al., 2008; Roos & Dahlberg, 2005). This is particularly pertinent for post-traumatic OA, which is often evident 15 years earlier than non-traumatic OA (Lohmander et al., 2007), resulting in substantial and prolonged effects on QoL (Filbay et al., 2014) and risk of early knee arthroplasty (Blagojevic et al., 2010).

Magnetic resonance imaging can identify and monitor early structural changes to all joint tissues. Whilst radiography can detect osteophytes, joint space narrowing, bony sclerosis, and cysts, MRI is more sensitive to changes in early OA features such as cartilage, particularly during shorter follow-up periods (Amin et al., 2005; Hunter et al., 2006a; Hunter et al., 2011c). Studies of longitudinal changes in OA features on MRI have focussed on cartilage degeneration within the acute recovery phase (i.e., 1-2 years post-ACLR) (Van Ginckel et al., 2013; van Meer et al., 2016), and have mostly assessed and observed the tibiofemoral compartment. In the patellofemoral joint, the trochlea is at greatest risk of early degeneration within the first two years post-ACL injury (Culvenor et al., 2015a; Frobell, 2011), which may contribute to high rates of longer-term radiographic patellofemoral OA (Culvenor et al., 2013). Identifying individuals with progressive early OA features following natural biological graft healing and functional rehabilitation (>two years post-injury), but prior to established joint disease, may present opportunities to target secondary prevention strategies.

Therefore, the primary aims of this study were to: (i) describe the changes to early OA features on MRI between one and five years following ACLR, and (ii) determine the associations between participant characteristics (age, sex, BMI, time from injury to surgery, presence of a combined ACL

injury, anteroposterior knee laxity, re-injury) and changes in OA features on MRI. Changes in radiographic OA between one and five years post-ACLR, in both knees, were also evaluated.

3.2 Methods

All 111 consecutively recruited patients (median age at time of ACLR, 26 years (range 18-50 years)) who participated in our previously reported MRI evaluation at one year following ACLR (Culvenor et al., 2015a) were eligible for the current study. The inclusion and exclusion criteria at one year following ACLR, the ACLR technique, and post-operative rehabilitation are described in Chapter 2. Briefly, the inclusion criteria at one year following ACLR included primary single-bundle hamstring-tendon autograft ACLR by one of two orthopaedic surgeons in Melbourne, Australia. The exclusion criteria at one year following ACLR included: (i) any injury, symptoms, or surgery to the ACLR knee prior to ACL injury; (ii) greater than five years between ACL injury and reconstruction; and (iii) any secondary injury or surgery to the ACLR knee (between ACLR and one-year assessment). Secondary injury was defined as a new index or contralateral knee injury (ACL, meniscus, collateral ligament), surgery, or intra-articular knee injection. Participants with a secondary injury between one and five years were invited to participate at the five year assessment, as this is a common occurrence and representative of the wider ACLR population. Of the 111 participants with an MRI at one year, 78 (70%) (48 men; median age 32 years (range 23-56 years)) completed MRI assessment at five years (median 5.2 years after ACLR (range 4.7-6.3 years)) (**Figure 3.1**). Ethical approval was granted by La Trobe University Human Ethics Committee (HEC 15-100) and informed consent was obtained from all individual participants included in the study.

3.2.1 Demographic, injury, and surgical factors

Participant age, sex, ACL injury history (date of ACL injury, time from injury to surgery), and previous activity level were obtained at one year after ACLR. Activity level was defined as level 1 (pivoting/jumping sports) to level 4 (sedentary) (Grindem et al., 2014). Each participant's BMI was calculated at one and five years following ACLR. If a participant had a significant cartilage lesion or meniscal injury requiring meniscectomy at the time of ACLR, they were classified as having a "combined" ACL injury. Arthroscopically identified cartilage lesions were defined as significant when the Outerbridge grade was ≥2 (Outerbridge, 1961). Anteroposterior laxity at one year was assessed using a KT-1000 arthrometer (MEDmetric Corp., California, USA) at 30° flexion with a 30 lb load (Daniel et al., 1985). Participants were questioned about new injuries or surgery between one and five years following ACLR. Tibiofemoral and patellofemoral radiographic OA in the ACLR and contralateral knee were determined at one and five years following ACLR using previously published protocols (Culvenor et al., 2015a) and OARSI definitions (Altman et al., 1995), as described in Chapter 2. Radiographic OA was defined as present if any of the following criteria

were met: (i) joint space narrowing of ≥grade 2, (ii) sum of osteophytes >2, or (iii) grade 1 osteophyte in combination with grade 1 joint space narrowing (Altman et al., 1995).

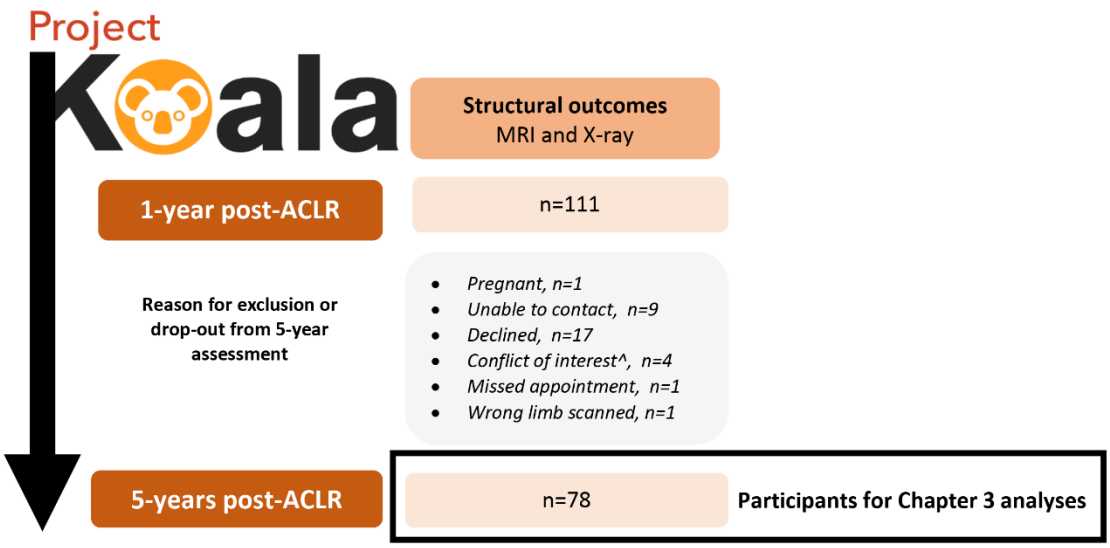


Figure 3.1 KOALA cohort participant recruitment and retention for Chapter 3.

ACLR=anterior cruciate ligament reconstruction; KOALA=Knee Osteoarthritis Anterior cruciate ligament Longitudinal Assessment cohort study; MRI=magnetic resonance imaging; n=number of participants.
^ n=4 due to participation in another study.

3.2.2 MRI acquisition and interpretation

All participants had unilateral knee MRI scans acquired at one year following ACLR using a single 3.0T system (Philips Achieva, The Netherlands), as described in Chapter 2. The same MRI scanner was used to acquire the five-years post-ACLR scans of the ACLR knee, with identical sequences to those obtained at one year. Briefly, the sequences consisted of a 3D PD weighted VISTA acquired at 0.35 mm isotropically, an STIR sequence, and an axial proton-density TSE sequence. All MRI scans were evaluated using the MOAKS by a single musculoskeletal radiologist (AG) with over 20 years' experience and established inter- and intra-rater reliability (kappa 0.61-0.80) in semi-quantitative MRI assessment (Hunter et al., 2011a). The radiologist evaluated the one- and five-year images paired (not blinded to time-points of the MRI), but blind to the clinical and radiographic information. The MOAKS divides the knee into 14 articular subregions to score cartilage lesions (assessed using VISTA sequence) and BMLs (assessed using STIR and fluid sensitive TSE sequences), and six tibiofemoral and six patellofemoral subregions to score osteophytes (Hunter et al., 2011a). Meniscal lesions were scored separately for the medial meniscus and lateral meniscus, and divided into anterior, posterior, and central subregions for each meniscus. Cartilage lesions were graded from 0 to 3 based on size (percentage of surface area relative to each subregion) and depth (percentage of lesion that is full thickness). Size was graded as: 0=none,

1=<33%, 2=33–66%, 3=>66%. Depth was graded as: 0=no full-thickness loss, 1=<10%, 2=10-75%, 3=>75%. BMLs were based on size only (percentage of surface area affected, relative to each subregion), where 0=none, 1=<33%, 2=33–66%, and 3=>66%. Osteophytes were graded according to size based on how far they extended from the joint (0=none, 1=small, 2=medium, 3=large). Given that the definition of a definite osteophyte has not been delineated (Hunter et al., 2011a), an osteophyte was considered present when it was scored ≥2. Meniscal tears (vertical, horizontal, or complex) and maceration (partial, complete, or progressive) were described as absent or present. Meniscal extrusion was graded by size, where 0=<2 mm, 1=2–2.9 mm, 2=3–4.9 mm, and 3=>5 mm, and defined "present" if the size was ≥grade 1. Hoffa's fat pad synovitis was graded as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). More information on the MRI sequences used and MOAKs scoring system appears in Chapter 2.

3.2.3 Definition of worsening OA features

The subregions were combined to define three compartments: patellofemoral (medial patella and trochlea, lateral patella and trochlea), medial tibiofemoral (medial femur central and posterior, medial tibia anterior, central and posterior), and lateral tibiofemoral (lateral femur central and posterior, lateral tibia anterior, central and posterior). Worsening of OA features in each compartment was defined as any increase in score (in any corresponding subregion for that compartment). Therefore, either progression of an OA feature (i.e., increase in lesion severity) or a new OA feature (i.e., from no defect to present defect) between one and five years was classified as worsening. Increase in lesion severity was defined as an increase of at least 1 point on the MOAKS in terms of size (i.e., size=1 to size=2) or depth (i.e., partial- to full-thickness cartilage lesion). New lesions were defined as those with size=0 at one year post-ACLR and size ≥1 at five years post-ACLR (osteophytes needed to be ≥2 at five years post-ACLR as the definition of a definite osteophyte has not been delineated) (Hunter et al., 2011a). This definition is reliable and sensitive to changes in ACL-injured individuals and other populations at high risk of OA (Runhaar et al., 2014; van Meer et al., 2016).

3.2.4 Statistical analyses

Descriptive statistics were used to define worsening of OA features on MRI and radiographic OA for each compartment. Both the medial and lateral patella and trochlea subregions were included in the analyses of the patellofemoral compartment outcomes (four observations per knee). The medial and lateral tibiofemoral compartments had six observations per knee (femur central and posterior, tibia anterior, central and posterior). Logistic regression models with generalised estimating equations (GEE) (to account for correlations between subregions within the same compartment) were used to determine if participant characteristics (age, sex, BMI at one year

post-ACLR, time from injury to surgery, presence of a combined injury, re-injury, and anteroposterior laxity) were associated with worsening OA features. Age and time from injury to ACLR were dichotomised at their median values, while BMI was dichotomised based on the established overweight cut-off of 25 kg/m^2 (median at one year post-ACLR: 25.3kg/m^2), so that odds ratios (ORs) and 95% confidence intervals (CIs) could be estimated and descriptively compared with the nominal variable of concomitant injuries. Univariate regression analyses were performed initially; participant characteristics with a p value <0.20 were entered into a multivariate logistic regression GEE model to calculate ORs and 95% CIs. The McNemar test was used to determine any significant change in repeated-measure nominal data (i.e., worsening radiographic OA between one and five years following ACLR). Stata V.14.2 (StataCorp LLC, Texas, USA) was used for statistical analyses. P values <0.05 were considered statistically significant.

3.3 Results

3.3.1 Participants

The demographic characteristics of the 78 participants included in the current study are presented in **Table 3.1.** Apart from medial meniscal lesions, which were more prevalent in the participating group at one year following ACLR, there were no demographic, surgical, or MRI related differences between those who did and did not participate in the assessment at five years (p>0.05) (**Tables 3.1 and 3.2**). Thirty-eight of the 78 participants (49%) had a combined injury and 12 (15%) participants reported a new index knee injury/surgery between one and five years following ACLR (ACLR revision n=3, partial meniscectomy n=6, intra-articular injection n=1, collateral ligament injury n=2). Six participants had a new contralateral knee injury (ACLR n=3, meniscectomy n=1, collateral ligament injury n=1, investigative arthroscopy n=1).

3.3.2 Cartilage lesions

Worsening of cartilage lesions in any compartment occurred in 40 (51%) participants, with worsening most commonly occurring in the patellofemoral compartment (n=34 (44%)) (**Figure 3.2**). Medial and lateral tibiofemoral cartilage worsening occurred in 8 (10%) and 10 (13%) participants, respectively (**Figure 3.2**). Twenty-five (63%) of those with cartilage worsening had isolated patellofemoral worsening, compared with six (15%) who had isolated tibiofemoral cartilage worsening. The prevalence of patellofemoral full-thickness cartilage defect more than doubled between one and five years following ACLR (n=15 (19%) to n=32 (41%)) (**Figure 3.3**). The prevalence of full-thickness cartilage lesions also increased from one to five years in the medial (n=2 (3%) to n=5 (6%)) and lateral tibiofemoral (n=12 (15%) to n=14 (18%)) compartments (**Figure 3.2)**

Table 3.1. Participant characteristics at the one- and five-years post-ACLR assessments

	Not participating in 5-year assessment (n=33)£	**Participating in 1- and 5-year assessments (n=78)**	
	1-year post-ACLR	*1-year post-ACLR*	*5-years post-ACLR*
Age, median±IQR (range)	27±13 (20 to 50)	28±15 (19 to 52)	32±15 (23 to 56)
Male sex, no. (%)	23 (70%)	48 (62%)	48 (62%)
Activity level pre-injury, no. (%)*			
Level 1. Jumping, pivoting sports	26 (79%)	54 (69%)	54 (69%)
Level 2. Lateral movement sports	5 (15%)	18 (23%)	18 (23%)
Level 3. Straight-line activities	2 (6%)	6 (8%)	6 (8%)
Level 4. Sedentary	0 (0%)	0 (0%)	0 (0%)
Activity level at time of MRI, no. (%)*			
Level 1. Jumping, pivoting sports	9 (27%)	19 (24%)	25 (32%)
Level 2. Lateral movement sports	4 (12%)	10 (13%)	11 (14%)
Level 3. Straight-line activities	8 (24%)	19 (24%)	32 (41%)
Level 4. Sedentary	12 (37%)	30 (39%)	10 (13%)
Time between injury and ACLR, median±IQR (range), weeks	12±13 (2.5 to 241)	14±20 (1 to 231)	14±20 (1 to 231)
BMI^, median±IQR (range) kg/m^2	26±7 (20 to 37)	25±5 (20 to 37)	26±5 (20 to 35)
Concomitant injuries, no. (%)*			
Medial meniscectomy¥ | repair¥	7 (21%) | 3 (9%)	16 (21%) | 9 (12%)	16 (21%) | 9 (12%)
Lateral meniscectomy¥ | repair¥	5 (15%) | 2 (6%)	18 (23%) |1 (1%)	18 (23%) |1 (1%)
Patellofemoral cartilage defect¤	5 (15%)	7 (9%)	7 (9%)
Medial tibiofemoral cartilage defect¤	3 (9%)	7 (9%)	7 (9%)
Lateral tibiofemoral cartilage defect¤	3 (9%)	4 (5%)	4 (5%)
Anteroposterior laxity between-limb difference^, median±IQR (range), mm	1.3±2.3 (-3.8 to 7.2)	1.6±2.9 (-1.9 to 3.5)	n.a
IKDC score, median±IQR (range)	84±14 (53 to 98)	87±16 (54 to 100)	91±15 (53 to 100)

ACLR=anterior cruciate ligament reconstruction; BMI=body mass index; IQR=interquartile range; MRI=magnetic resonance imaging; IKDC=International Knee Documentation Committee subjective knee evaluation; n.a=not assessed at 5 years; mm=millimetres.
* Sports Activity Classification (Grindem et al., 2014).
^ n=72 at 5-year assessment (i.e., those with 5-year clinical testing).
¥ Performed at the time of ACLR.
¤ Outerbridge grade ≥2 assessed arthroscopically at time of ACLR.
£ Reasons for exclusion and drop-out are presented in detail in Chapter 2, **Figure 2.1**.

Table 3.2 Imaging results at one and five years following ACLR

	Not participating in 5-year assessment (n=33) £	Participating in 5-year assessment (n=78)	
	1 year	*1 year*	*5 years^*
OA features on MRI, no. (%)*			
Cartilage defect (≥grade 1)			
Patellofemoral	13 (39%)	37 (48%)	47 (60%)
Medial tibiofemoral	9 (27%)	23 (29%)	28 (36%)
Lateral tibiofemoral	11 (33%)	18 (23%)	26 (33%)
Bone marrow lesion (≥grade 1)			
Patellofemoral	6 (18%)	20 (26%)	18 (23%)
Medial tibiofemoral	4 (12%)	14 (18%)	13 (17%)
Lateral tibiofemoral	8 (24%)	14 (18%)	16 (21%)
Osteophyte (≥grade 2)			
Patellofemoral	0 (0%)	3 (4%)	7 (9%)
Medial tibiofemoral	0 (0%)	1 (1%)	10 (12%)
Lateral tibiofemoral	2 (6%)	6 (8%)	9 (12%)
Meniscal lesion (≥grade 1)§			
Medial tibiofemoral	18 (55%)#	52 (67%)	53 (68%)
Lateral tibiofemoral	20 (60%)	38 (49%)	40 (52%)
Hoffa's synovitis (≥ grade 1)	20 (60%)	47 (60%)	69 (88%)
Radiographic OA, no. (%)			
Patellofemoral (ACLR limb | CL limb)	1 (3%) | 2 (6%)	4 (5%) | 2 (3%)	14 (18%) | 4 (5%)
Medial tibiofemoral (ACLR limb | CL limb)	1 (3%) | 1 (3%)	2 (3%) | 2 (3%)	4 (5%) | 2 (3%)
Lateral tibiofemoral (ACLR limb | CL limb)	2 (6%) | 0 (0%)	1 (1%) | 1 (1%)	4 (5%) | 1 (1%)

ACLR=anterior cruciate ligament reconstruction; IQR=interquartile range; MRI=magnetic resonance imaging; OA=osteoarthritis; CL=contralateral limb.
£ Reasons for exclusion and drop-out are presented in detail in Chapter 2, **Figure 2.1**.
Characteristic statistically significant (p<0.05) compared with participating group.
^ Three participants had an MRI on a different scanner at 5 years post-ACLR due to being interstate.
§ Includes tearing (vertical/horizontal/complex), maceration (partial/degenerative), or extrusion.

3.3.3 Bone marrow lesions

Although the prevalence of any BMLs was the same (47%) at one and five years (**Table 3.2**), worsening of BMLs in any compartment occurred in 23 (29%) participants (**Figure 3.2**). This was due to new or progressive lesions in one compartment, with concurrent improvement in BMLs in another compartment. Patellofemoral, medial, and lateral tibiofemoral BML worsening occurred in 14 (18%), 5 (6%), and 10 (13%) participants, respectively (**Figure 3.2**). Improvement in BMLs in any compartment occurred in 31 (40%) participants between one and five years following ACLR. Patellofemoral, medial tibiofemoral, and lateral tibiofemoral BML improvement occurred in 16 (21%), 11 (14%), and 14 (18%) participants, respectively (**Figure 3.2).**

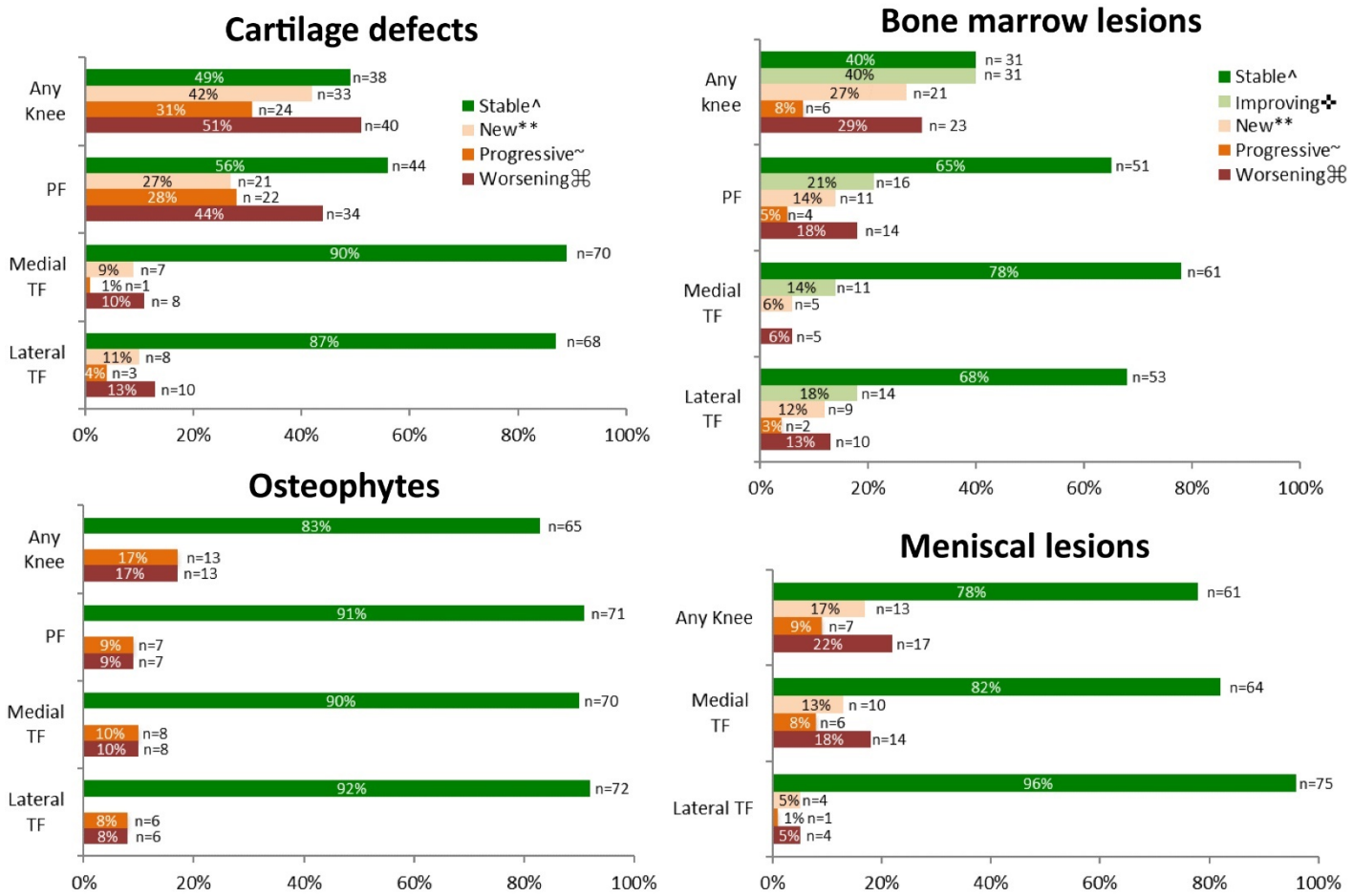


Figure 3.2 Worsening OA features on MRI between one and five years following ACLR.

PF=patellofemoral compartment; TF=tibiofemoral compartment; n=number of participants.
^Stable lesions=participants with no worsening (i.e., no new or progressive features or improvement).
*New=no lesion at 1 year (i.e., MOAKS size=0) and a size score of ≥1 at 5 years for cartilage lesions, BMLs, and meniscal lesions (≥2 for osteophytes).
~Progressive=lesion at 1-year post-ACLR (i.e., MOAKS size ≥1), with an increase in the severity of lesion at 5-years post-ACLR (i.e., ≥1-point increase in size or depth).
⌘Worsening=participants with either progressive or new features.

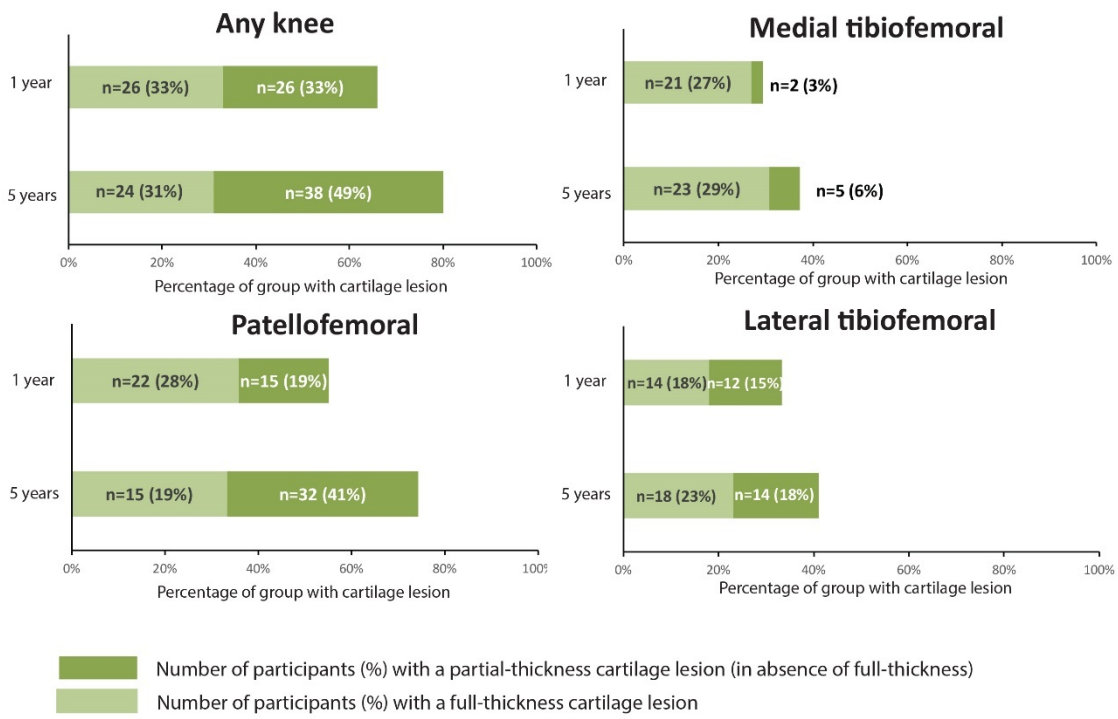


Figure 3.3 Prevalence of cartilage lesions at one and five years following ACLR.

3.3.4 Osteophytes

Worsening of osteophytes in any compartment occurred in 13 (17%) participants (**Figure 3.2**). Patellofemoral, medial tibiofemoral, and lateral tibiofemoral osteophyte worsening occurred in 7 (9%), 8 (10%), and 6 (8%) participants, respectively. All worsening was due to progressive lesions (i.e., increase in size), with no new osteophytes (≥grade 2) at five years post-ACLR (**Figure 3.2**).

3.3.5 Meniscal lesions

The prevalence of medial and lateral meniscal pathology only increased by 1% and 3%, respectively, from one to five years post-ACLR (**Table 3.2**). However, worsening of meniscal lesions (i.e., increase in size) occurred in the medial or lateral compartment in 17 (22%) participants, with 14 (18%) and 4 (5%) occurring in the medial and lateral compartments, respectively (**Figure 3.2**).

3.3.6 Radiographic OA

The prevalence of radiographic OA increased significantly from one to five years post-ACLR in the patellofemoral compartment in the ACLR knee (n=4 (5%) to n=14 (18%); $p<0.05$), but not in the contralateral knee (n=2 (3%) to n=4 (5%); $p>0.05$). Smaller and non-significant increases were seen in the ACLR and contralateral medial and lateral tibiofemoral compartments (**Table 3.2**).

3.3.7 Factors associated with worsening OA features on MRI

In the multivariate analyses, participants with a BMI >25 kg/m^2 at one year post-ACLR consistently displayed 2 to 5 times greater odds of worsening of all OA features (except for patellofemoral BMLs) (**Tables 3.3** and **Table 3.4**). All participants with a BMI >25 kg/m^2 at one year had worsening patellofemoral osteophytes. Older age (>26 years) at the time of ACLR was related to greater odds of worsening patellofemoral cartilage lesions (OR 4.19; 95% CI: 1.78 to 9.86). Although an ACLR performed greater than three months following injury was associated with greater odds of worsening tibiofemoral osteophytes (OR 3.91; 95% CI: 1.04 to 14.66) and meniscal lesions (OR 6.35; 95% CI: 1.38 to 29.29) (**Table 3.3**), it was associated with lower odds of patellofemoral cartilage defect worsening (OR 0.44; 95% CI: 0.21 to 0.94) (**Table 3.4**). Anteroposterior knee laxity (≥3 mm between-limb difference) was associated with 4 times greater odds of worsening meniscal lesions (OR 4.51; 95% CI: 1.35 to 15.10).

The effect of re-injury was unable to be assessed due to the small number of reinjuries in the index knee (n=12); thus, a sensitivity analysis excluding participants with re-injury was performed. This sensitivity analysis resulted in similar effect sizes (but wider CIs), suggesting that the effect of re-injury on worsening OA features on MRI in this study was minimal. Meniscectomy or significant cartilage defect noted at the time of ACLR was not significantly associated with increased odds of worsening OA features on MRI in the regression analysis (**Table 3.3** and **Table 3.4**). However, the relatively small number of individuals with worsening of some OA features detrimentally affected the stability of this regression analysis. Therefore, a sensitivity analysis was performed, comparing the rate of worsening OA features between those with a combined injury (meniscectomy or a significant cartilage defect at the time of ACLR) (n=38) and those with an isolated injury (n=40). The rates of any OA feature worsening were significantly greater in those with a combined injury (combined: 31 out of 38 (82%); isolated: 22 out of 40 (55%); chi^2 p=0.012). In addition, to determine the effect of pre-existing OA, a sensitivity analysis was performed by excluding individuals with radiographic OA (as described in **Table 3.1**) at one year post-ACLR (n=5). Additional analyses comparing the worsening rates in the individuals with (n=5) and without radiographic OA (n=73) at one year revealed similar (and non-significantly different) rates of worsening OA features, except for tibiofemoral osteophytes (no radiographic OA at one year: 7 out of 73 (10%) had worsening; radiographic OA at one year; 2 out of 5 (40%) had worsening; chi^2 p=0.112).

Table 3.3 Demographic and surgical factors associated with worsening tibiofemoral OA features on MRI

	Cartilage lesion[a]		**Bone marrow lesion[b]**		**Osteophyte[c]**		**Meniscal lesion[d]**	
	Univariate	*Multivariate*	*Univariate*	*Multivariate*	*Univariate*	*Multivariate*	*Univariate*	*Multivariate*
Prevalence of worsening, n/N(%)	16/78 (21%)		12/78 (15%)		9/78 (12%)		17/78 (22%)	
Age	**3.17**	**3.27**	0.94		1.82		0.50	0.39
(ref <26 years)[a]	**(1.04, 9.66)**	**(0.92, 11.60)**	(0.27, 3.33)		(0.26, 12.49)		(0.18, 1.43)	(0.12, 1.24)
Sex	0.86		0.39	0.59	1.03		1.07	
(ref female)	(0.29, 2.57)		(0.12, 1.28)	(0.20, 1.79)	(0.22, 4.90)		(0.38, 3.05)	
Body mass index	2.77	2.96	**5.29**	**4.58**	2.67		**3.79**	**4.62**
(ref <25 kg/m^2)[g]	(0.86, 8.96)	(0.81, 10.79)	**(1.45, 19.34)**	**(1.36, 15.49)**	(0.49, 14.43)		**(1.02, 14.03)**	**(1.57, 13.55)**
Time from injury to ACLR	2.77	2.47	1.11		**4.56**	**3.91**	**3.79**	**6.35**
(ref <3 months)[f]	(0.97, 7.88)	(0.83, 7.40)	(0.31, 3.96)		**(1.20, 17.37)**	**(1.04, 14.66)**	**(1.02, 14.03)**	**(1.38, 29.29)**
Meniscectomy	1.99	0.90	1.62		1.50		0.86	
(at time of ACLR)	(0.70, 5.64)	(0.27, 3.03)	(0.48, 5.51)		(0.31, 7.17)		(0.30, 2.41)	
Cartilage defect	1.73		1.21		1.97		0.75	
(at time of ACLR)	(0.50, 5.92)		(0.36, 4.03)		(0.30, 12.76)		(0.18, 3.04)	
Anteroposterior knee laxity (ref ≤3 mm between-limb difference)	1.03 (0.37, 2.85)		0.34 (0.04, 2.61)		0.13 (0.02, 1.09)	0.17 (0.02, 14.67)	2.15 (0.73, 6.26)	4.51 (1.35, 15.10)

ACLR=anterior cruciate ligament reconstruction; MRI=magnetic resonance imaging; n=number of participants with the feature; N=total number of participants in the group; mm=millimetres.

Values are odds ratios (95% confidence interval). Univariate regression analysis was performed initially; participant characteristics with a p value <0.20 were entered into a multivariate logistic regression GEE model to calculate ORs and 95% CIs. An odds ratio >1 represents greater odds of the OA feature worsening in the presence of the participant factor. **Bold** values indicate a significant association (p<0.05).

[a] Ten subregions per participant.

[b] Ten subregions per participant.

[c] Six subregions per participant.

[d] Six subregions per participant. Includes worsening tear, maceration, or extrusion.

[e] Dichotomised based on the median value.

[f] Dichotomised based on the overweight cut-off, which was similar to the median value at 1-year post-ACLR of 25.3 kg/m^2.

Table 3.4 Demographic and surgical factors associated with worsening patellofemoral OA features on MRI

	Cartilage defect[b]		**Bone marrow lesion[c]**		**Osteophyte[d]**	
	Univariate	*Multivariate*	*Univariate*	*Multivariate*	*Univariate*	*Multivariate*
Prevalence of worsening, n/N (%)	34/78 (44%)		14/78 (18%)		4/78 (5%)	
Age	**3.67**	**4.19**	1.11		0.51	
(ref ≤26 years)[e]	**(1.66, 8.13)**	**(1.78, 9.86)**	(0.37, 3.29)		(0.09, 2.75)	
Sex	1.12		**3.13**	2.55	0.17	0.14
(ref female)	(0.54, 2.34)		**(1.02, 9.62)**	(0.85, 7.67)	(0.19, 1.55)	(0.01, 1.72)
Body mass index	2.03	**2.51**	1.02		**n.a****	
(ref <25 kg/m^2)[f]	(0.96, 4.32)	**(1.19, 5.27)**	(0.34, 3.02)			
Time from injury to ACLR	0.56	**0.44**	0.36	0.37	8.39	6.28
(ref <3 months)[e]	(0.27, 1.18)	**(0.21, 0.94)**	(0.11, 1.19)	(0.11, 1.23)	(0.94, 75.14)	(0.76, 52.84)
Meniscectomy	1.02		1.45		1.07	
(at time of ACLR)	(0.47, 2.24)		(0.49, 4.31)		(0.20, 5.74)	
Cartilage defect	1.68	1.85	0.62		7.37	6.06
(at time of ACLR)	(0.85, 3.31)	(0.60, 5.76)	(0.09, 4.47)		(0.85, 64.19)	(0.70, 52.49)
Anteroposterior knee laxity (ref ≤3 mm between-limb difference)	0.66 (0.30, 1.47)		0.95 (0.25, 3.59)		**n.a ****	

MRI=magnetic resonance imaging; ACLR=anterior cruciate ligament reconstruction; n=number of participants with the feature; N=total number of participants in the group; mm=millimetres; n.a.=unable to perform analysis as all participants with a worsening patellofemoral osteophyte had a high BMI.
Values are odds ratios (95% confidence interval). Univariate regression analysis was performed initially; participant characteristics with a p value <0.20 were entered into a multivariate logistic regression GEE model to calculate ORs and 95% CIs. An odds ratio >1 represents greater odds of the OA feature worsening in the presence of the participant factor. **Bold** values indicate a significant association (p<0.05).
[b] Four subregions per participant.
[c] Four subregions per participant.
[d] Six subregions per participant.
[e] Dichotomised based on the median value.
[f] Dichotomised based on the overweight cut-off, which was similar to the median value at 1-year of 25.3 kg/m.

3.4 Discussion

Worsening early OA features on MRI were evident in more than two-thirds of young individuals over a four year period, between one and five years following ACLR. Despite cartilage lesions being most prevalent in the patellofemoral compartment one year following ACLR, the patellofemoral compartment displayed the most frequent cartilage deterioration (evident in half of the cohort). The results of this study suggest that joint features are not stable, even following surgical restoration of mechanical stability and a 12-month recovery period. Being overweight (BMI >25 kg/m^2) was a particularly strong determinant of deteriorating knee joint status. These worsening early OA features on MRI may reflect a progressive disease pathway that identifies those likely to suffer future radiographic OA and symptoms.

Accelerated nature of post-traumatic OA

The considerable progression of existing cartilage lesions (n=21 (27%)) and development of new lesions (n=22 (28%)) up to five years post-operatively extends previously reported worsening of cartilage damage on semi-quantitative scoring during the first two years post-ACL injury (van Meer et al., 2016). Although 80% of participants in the current study had a cartilage defect one year post-ACLR, worsening cartilage damage occurred in half of the participants over the proceeding four years, reflecting the rapid nature of post-traumatic OA. The rate of cartilage progression observed post-ACLR (i.e., approximately 13% per annum in the current study) is similar to individuals with or at risk of established (i.e., radiographic) OA (9-17%) (Amin et al., 2005; Runhaar et al., 2014) and far exceeds rates observed in uninjured older healthy knees (2% per annum) (Hanna et al., 2009; Pan et al., 2011). These results highlight a potential post-traumatic early OA phenotype, demonstrating accelerated progression of joint features in young adults compared with non-traumatic OA (Driban et al., 2014). Since early cartilage changes offer a promising window to disrupt the disease trajectory (Pollard et al., 2008), these individuals should be identified and development of potential disease-modifying therapies, such as those that have shown initial promise (Anderson et al., 2014; Roos & Dahlberg, 2005), prioritised.

High rates of worsening in the patellofemoral compartment

The patellofemoral joint was the knee compartment where worsening OA features were most commonly observed. Although the patellofemoral joint is rarely investigated following ACLR (Culvenor et al., 2013), our findings add to the growing body of evidence pointing to high rates of patellofemoral degeneration. The patellofemoral compartment may be at particular risk of worsening cartilage and BMLs in an altered chemical environment post-ACLR (Harkey et al., 2015) due to pre-existing or altered patellofemoral biomechanics (Culvenor et al., 2014c; Macri et al.,

2017; Van de Velde et al., 2008; Yoo et al., 2005) and/or quadriceps muscle dysfunction (Wunschel et al., 2011). Our MRI data are consistent with quantitative MRI measures (Frobell, 2011) and second-look arthroscopic studies (Wang et al., 2011) which have demonstrated rapid patellofemoral cartilage loss during the first two years post-ACLR. Greater development of radiographic patellofemoral OA than tibiofemoral OA during the four-year observation period was observed, and more so in the ACLR knee than the contralateral knee. However, another prospective study (van Meer et al., 2016) did not report higher rates of early degeneration in the patellofemoral compared to the tibiofemoral compartment. Semi-quantitative MRI patellofemoral cartilage worsening was reported in only 3% of knees (compared to 34% with tibiofemoral cartilage worsening) over the first two years post-ACL injury, with this lower rate potentially reflecting lower BMIs and less patellofemoral pathology at baseline (van Meer et al., 2016). Nevertheless, our findings suggest that consideration and management of patellofemoral joint health following ACLR are critical.

Worsening of BMLs and osteophytes

Worsening of BMLs occurred in 29% of participants, providing insight into longer-term (>two years) post-traumatic BML behaviour not previously reported (Papalia et al., 2015). As our baseline was one year following ACLR, the majority of acute trauma-related BMLs should have resolved. Therefore, the BMLs observed may be more degenerative in nature, which was confirmed by the characteristics of the BMLs in the current study (more circumscribed, located directly subchondral, and with associated cartilage lesions) (Roemer et al., 2014). Conversely, many BMLs in our cohort were stable (40%) or improved (40%), indicating that not all BMLs persisting at one year post-ACLR are degenerative in nature, and that resolution may require more than one year. In contrast to BMLs, osteophytes are more permanent and typically represent later stages of disease. This is reflected in the lower rates of worsening observed compared to other features, which is consistent with previous reports of osteophytes within the first five years post-ACLR (8% patellofemoral and 9% tibiofemoral worsening within two years post-ACL injury) (van Meer et al., 2016). Importantly, only incident osteophytes ≥grade 2 were counted, which likely contributed to our observation of no new osteophytes over the four years. While small osteophyte development may reflect pathological bone shape changes and increased risk of incident radiographic OA (Neogi et al., 2013), the clinical significance of small osteophyte development requires further evaluation.

Worsening meniscal lesions

Apart from worsening meniscal lesions, which were more common in the medial (18%) than the lateral (5%) tibiofemoral compartment, worsening OA features were observed similarly in the

medial and lateral tibiofemoral joint. These observations are consistent with post-traumatic radiographic OA having a similar medial and lateral tibiofemoral distribution, and contrast with non-traumatic OA, which is typically a disease of the medial tibiofemoral joint (Sward et al., 2010). This is the first study, to our knowledge, to investigate longitudinal semi-quantitative menisci changes following ACLR. Despite the notion that surgical reconstruction can protect worsening meniscal pathology (Anstey et al., 2012; Lebel et al., 2008), one in five participants demonstrated meniscal lesion worsening in the current study. Although the presence of meniscal pathology is common in non-injured asymptomatic populations aged over 50 years (Ding et al., 2010), this ACLR cohort demonstrates a much higher prevalence (80%) than age-matched individuals (6-40%) (Jerosch et al., 1996; LaPrade et al., 1994). The observed rate (5% per annum) of meniscal lesion worsening is higher in these young adults than previous reports in non-injured older individuals (1-3% per annum) at risk of OA (>50 years old, BMI >25 kg/m^2) (Runhaar et al., 2014; Sharma et al., 2016). Whilst surgical delay ≥three months and knee anteroposterior laxity (≥3 mm between-limb difference) was associated with 3-6 times greater odds of worsening meniscal lesions (**Table 3.3**), the clinical significance of MRI-detected meniscal lesions is uncertain.

Factors associated with worsening OA features on MRI

Evaluation of demographic and surgical factors at one year post-ACLR revealed that being overweight (BMI >25 kg/m^2) was a particularly strong determinant of deteriorating knee joint status. An elevated BMI was associated with 2- to 5-fold greater odds of most OA features, irrespective of knee compartment. However, the odds ratios had relatively wide CIs, and further studies are required to validate the association between BMI and worsening OA features after ACLR. Our findings are consistent with the impact of BMI on radiographic changes in the general population (Blagojevic et al., 2010). The longer follow-up compared to previous studies evaluating BMI in relation to MRI structural changes post-ACLR may have allowed more time for BMI, in combination with probable changes in physical function and activity participation, to have an effect on joint structure. Young adults are at risk of increased BMI 3 to 10 years following acute knee injury (Whittaker et al., 2015). Our results support this, with a significant increase in BMI from one (25.7 kg/m^2) to five years (26.3 kg/m^2) ($p<0.05$). These results reinforce and strengthen the need for early OA secondary prevention interventions to address weight control through education about diet and physical activity. Each pound of lost weight leads to a 4-fold reduction in knee joint load upon every step (Messier et al., 2005). Older age is also a risk factor for worsening of patellofemoral cartilage damage, reflecting the fact that degenerative changes are more prevalent in older adults (Blagojevic et al., 2010). However, the changes cannot be explained entirely by age, evident from the higher rates of radiographic degeneration in the index knee (3.5% per annum) compared to the contralateral knee (0.25% per annum). This is supported by greater

worsening of OA features on MRI in the current study, as compared to normal age-related changes published previously (Davies-Tuck et al., 2009; Ding et al., 2010; Ding et al., 2007; Hanna et al., 2009; Pan et al., 2011; Panzer et al., 2012). Considering the high rate of new and progressive lesions following ACLR, future studies should explore other factors (i.e., strength, function, alignment, and participation) that may be related to worsening of early OA features, especially given the modifiable nature of many of these factors.

Limitations

A limitation of this prospective study was the loss of 33 participants, resulting in a follow-up rate of 70%. Participant drop-out was mostly due to an inability to contact participants and relocation, reflecting a particularly young mobile population in Australia. Medial meniscal lesions were more prevalent at the one-year assessment in those who participated in the five-year assessment, compared to those that did not. While this may have introduced some selection bias and influenced the prognosis of the current sample, there were no differences in any other participant or surgical characteristics at one year post-ACLR between those who did and did not attend the five-year assessment. In addition, the current cohort appears generalisable to other large ACLR cohorts, with similar IKDC scores (Cox et al., 2014) and return-to-sport rates (Ardern et al., 2014b) at comparable follow-ups. Second, the one- and five-year MRI scans were read paired, unblinded to time-point. While this approach could cause over-estimation of worsening, paired reading overcomes the limitations of the inherently crude grading system of the MOAKS (Runhaar et al., 2014). Future research should, however, examine the clinical implications (i.e., association with symptoms) of post-traumatic OA features on MRI. Third, the limited number of individuals with worsening of some OA features influenced the statistical stability of the regression models. Although the GEEs increased the statistical power of the analyses, the CIs were relatively wide for some OA features, and these findings need to be interpreted with caution.

Finally, individuals with re-injury and combined injuries were included to represent a typical ACLR cohort. While it is acknowledged that OA features on MRI may have been pre-existing, sensitivity analysis (excluding those with radiographic OA at one year post-ACLR) revealed similar rates of worsening of all OA features on MRI (except tibiofemoral osteophytes). Although combined injuries are associated with increased risk of radiographic OA 10 to 15 years following ACL injury (Risberg et al., 2016b; van Meer et al., 2015), meniscectomy or a cartilage lesion at the time of surgery did not significantly increase the risk of worsening of individual OA features on MRI between one and five years following ACLR. It is possible that the impact of meniscal pathology on the joint structure may take many years to eventuate, or that many more ACLR individuals would be needed to demonstrate an effect. A sensitivity analysis revealed that any worsening OA

feature on MRI was significantly greater in those with a combined injury. These results highlight that combined injuries play a role in the worsening of OA features on MRI; however, our regression analysis adjusting for other demographic factors (i.e., BMI) highlights the multifactorial nature of post-traumatic early OA post-ACLR. Regardless, the rates of worsening OA features on MRI (i.e., estimated per annum; cartilage 13%, meniscus 6%, BMLs 7.5%) were higher than those observed in knees of older individuals with/at risk of OA (i.e., estimated per annum; cartilage 2-8%, meniscus 1-3%, BMLs 3-8%) (Davies-Tuck et al., 2009; Ding et al., 2007; Hanna et al., 2009; Pan et al., 2011; Runhaar et al., 2014; Stefanik et al., 2010), highlighting that the ACL injury/reconstruction is likely driving the considerable degeneration in these otherwise healthy young adults.

Clinical implications

Our findings demonstrate that young adults following ACLR are at risk of worsening early OA features on MRI. This is important, as it is likely that worsening cartilage, bone marrow, and meniscal lesions in young individuals are not benign and may be associated with future knee OA, symptoms, or functional decline (Javaid et al., 2010; Sharma et al., 2016; White et al., 2010). Importantly, these findings are contrary to the prominent belief among patients that ACLR will prevent OA (Bennell et al., 2016; Feucht et al., 2016). Considering the rapid progression of post-traumatic OA, patients should be provided with information and educated about early OA secondary prevention interventions. In particular, the potential reversibility or prevention of deterioration in structural pathology, symptoms, and function (Pollard et al., 2008; Wang et al., 2006). Education should refer to the consequences of increased BMI, such as the increased risk of early degenerative changes that may lead to future established joint disease and symptoms (Javaid et al., 2010; Sharma et al., 2016).

3.5 Conclusion

In conclusion, high rates of OA-related degenerative changes were observed on MRI in young adults between one and five years following ACLR, with two-thirds demonstrating some joint deterioration. Patellofemoral cartilage appears to be at particularly high risk of early accelerated degeneration, especially in older and overweight individuals. The concerning joint deterioration within the first five years following ACLR may help to identify those at greatest risk of more severe (radiographic) OA, in whom secondary prevention strategies may need to be targeted.

4 Chapter Four: Patient-reported outcomes one to five years after ACL reconstruction: Effect of combined injury, and associations with osteoarthritis features defined on MRI

Preface

Chapter 1 highlighted that the recovery of patient-reported symptoms, function, and QoL varies considerably following ACLR. Identifying those individuals with unacceptable PROs may provide opportunity for targeted interventions, before impairments become irreversible and difficult to manage. Chapter 3 reported that two-thirds of the KOALA cohort had worsening OA features on MRI between one and five years following ACLR, particularly in the patellofemoral joint cartilage. Chapter 1 highlighted the potential discordance between non-traumatic radiographic knee OA and symptoms in older adults; however, it is unknown if OA features on MRI are associated with knee-related symptoms in a younger population with accelerated structural deterioration. Chapter 1 also highlighted that concomitant meniscal and cartilage lesions noted at the time of ACLR are associated with worse PROs. Therefore, concomitant meniscal and cartilage lesions noted at the time of ACLR (combined injury) and OA features on MRI were considered the primary exposure variables for this analysis.

Chapter 4 contains the following publication in its entirely (**Appendix I**), with the following minor amendments: (i) **Figure 4.1** is a replacement flow chart from the original publication, to provide consistent formatting with the flow charts of participant recruitment and retention provided throughout this thesis; (ii) the addition of **Figure 4.2**, which was included as a supplementary file in the original publication.

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., & Crossley, K.M. (2020). Patient-reported outcomes one to five years after anterior cruciate ligament reconstruction: the effect of combined injury and associations with osteoarthritis features defined on magnetic resonance imaging. *Arthritis Care & Research, 72*(3), 412-422.

4.1 Introduction

Anterior cruciate ligament reconstruction is commonly performed following ACL injury for individuals seeking a return to pre-injury sports participation. Patient-reported symptoms, function, and QoL typically improve during the first 6 to 12 months following ACLR, but appear to plateau beyond this point (Ahldén et al., 2012; Cox et al., 2014; Frobell et al., 2010; Spindler et al., 2011). While 65% of young people return to pre-injury sports participation following ACLR (Ardern et al., 2014b), as many as 34% report unacceptable symptoms up to two years following surgery (Ingelsrud et al., 2015). Persistent symptoms could induce negative lifestyle modifications (i.e., reduced physical activity, weight gain) (Filbay et al., 2016), increasing the burden on health-care systems in the longer term. Successfully identifying people with persistent symptoms early following ACLR may allow for development of targeted interventions.

A combined injury (i.e., ACL injury *and* meniscectomy and/or significant cartilage lesion assessed at time of ACLR) might increase the risk of worse symptoms and QoL in the short- to medium- (one to six years) (Ahldén et al., 2012; Cox et al., 2014) and long-term (15 to 20 years) (Risberg et al., 2016b). However, some studies report no or minimal association between combined injuries and PROs in the medium- to long-term (Barenius et al., 2013; Oiestad et al., 2010a; Rotterud et al., 2013). Previous studies (Ahldén et al., 2012; Risberg et al., 2016b; Rotterud et al., 2013; Spindler et al., 2011) have utilised group-level data (i.e., in order to determine if a significant group mean effect exists between isolated and combined ACLR groups). This may not be relevant to patients and clinicians who are most interested in their own individual effect in relation to the treatment they have undergone. The group-level approach does not describe the number of individuals who present with unacceptable outcomes, who may require and benefit from additional interventions. Identifying individuals with poor outcomes, and enhanced clinical interpretability of PROs, may be achieved by comparing scores from each ACLR individual (as opposed to group means) to scores from other ACLR individuals who report “acceptable” knee function, or to normative scores from uninjured individuals.

Persistent symptoms following ACLR may be related to early deterioration of joint structure. Radiographic OA occurs in 50 to 90% of knees 10 to 15 years following ACLR, but the relationship with PROs is unclear (Lohmander et al., 2004; Oiestad et al., 2011). In older populations with established knee OA, more specific imaging markers of disease observed on MRI, such as BMLs, inflammation, and cartilage lesions, are associated with knee pain and symptoms (Felson et al., 2001; Felson et al., 2007; Hunter et al., 2011b; Zhang et al., 2011). While early structural pathology identified on MRI may be pre-existing or occur with the injury, OA features continue to deteriorate

at an accelerated rate compared to non-traumatic OA between one and five years following ACLR (Patterson et al., 2018). Yet, there is limited research on how these early OA features on MRI affect PROs. Tibiofemoral cartilage lesions and BMLs have little association with knee symptoms cross-sectionally at two (Costa-Paz et al., 2001) and 12 years post-ACLR (Hanypsiak et al., 2008). An important omission in previous research is the patellofemoral joint, which is a potential contributor to knee symptoms following ACLR (Culvenor et al., 2014b). Recently, patellofemoral cartilage lesions at one year post-ACLR were found to be associated with worse PROs at three years (Culvenor et al., 2016c). Further cross-sectional and longitudinal evaluation of the relationships between OA features on MRI and PROs beyond three years is important in order to determine if imaging features of OA affect patient-reported pain, function, or QoL.

The aims of the current study were to determine: (i) the influence of combined injuries on PROs between one and five years following ACLR, and compare these to known normative PRO scores (in uninjured and ACLR individuals); and (ii) the associations between patellofemoral and tibiofemoral cartilage lesions, BMLs, meniscal lesions, and PROs, at one and five years post-ACLR.

4.2 Methods

4.2.1 Study design and participants

All 112 consecutively recruited individuals who had completed PROs at one year post-ACLR as part of our previous evaluation (Culvenor et al., 2015a) (median age at surgery, 27 years (range 18-51 years)) were eligible for the five-year assessment. The eligibility criteria at one year are reported in Chapter 2, while changes in cartilage, bone marrow, and meniscus between one and five years are reported in Chapter 3. Briefly, all individuals were operated on by one of two Melbourne-based orthopaedic surgeons; all surgeries were single-bundle hamstring-autograft ACLR. The exclusion criteria at entry into the study one year post-ACLR included knee injury/symptoms prior to ACL injury, greater than five years between ACL injury and reconstruction, and any secondary injury/surgery (between surgery and one year post-ACLR). Secondary injury was defined as a new index or contralateral knee injury (ACL, meniscus, collateral ligament) or surgery. All participants were invited to participate in the five-years post-ACLR assessment, including 10 participants who sustained a secondary injury between one and five years, as this is a common occurrence and represents the wider ACLR population. Eighty-one (72%) participants completed the same PROs at the five-years post-ACLR evaluation (**Figure 4.1**). Ethical approval was granted by La Trobe University Human Ethics Committee (HEC 15-100) and all participants signed informed consent.

4.2.2 Demographic, injury, and surgical factors

Participant age, sex, injury history, BMI, previous and current activity level (defined as level 1=pivoting/jumping sports up to level 4 sedentary) (Grindem et al., 2014) were obtained at one and five years. The combined injury group at one year consisted of individuals with ACL injury and concomitant meniscectomy or significant cartilage defect (i.e., Outerbridge grade ≥2) (Outerbridge, 1961) noted at the time of ACLR (i.e., extracted from surgical notes). Those reporting to investigators a secondary injury/surgery to the index knee between one and five years were added to the combined injury group at five years. Defining a combined injury as the presence of a concomitant injury at the time of ACLR and/or a secondary injury over time is consistent with previous longitudinal cohort studies (Oiestad et al., 2010a; Risberg et al., 2016b). Individuals without a combined injury were defined as having an "isolated" injury.

4.2.3 Patient-reported outcome measures

At one and five years, participants completed the KOOS and IKDC subjective knee evaluation, as described in Chapter 2, in relation to their index knee condition during the previous week. Briefly, the KOOS-Pain, KOOS-Symptoms, KOOS-Sport, and KOOS-QoL subscales were used (Roos & Lohmander, 2003). The KOOS-ADL subscale was excluded due to the ceiling effects observed in young active populations (Frobell et al., 2015). The KOOS and IKDC were completed either in person (pen and paper) or via an online portal (Promptus, DS PRIMA, Melbourne, Australia) with matching instructions to the original paper version. The KOOS (ICC>0.96) (Gudbergsen et al., 2011) and IKDC (ICC=0.79) (Nguyen et al., 2017) have demonstrated test-retest reliability between paper and electronic formats.

4.2.4 Cartilage lesions, BMLs, and meniscal lesions on MRI

Of the 112 participants completing PROs at the one-year assessment, 111 completed the MRI assessment at one year and 80 (71%) at five years (**Figure 4.1**) using an identical MRI scanner and sequences as described in Chapter 2. Briefly, the 3T system (Philips Achieva, The Netherlands) sequences consisted of a 3D proton-density weighted VISTA acquired at 0.35 mm isotropically, a short-tau inversion-recovery sequence, and an axial proton-density turbo spin-echo sequence. Cartilage lesions, BMLs, and meniscal lesions were scored using the MOAKS by a musculoskeletal radiologist (AG) with over 20 years' experience and established inter- and intra-rater reliability in semi-quantitative MRI assessment (kappa 0.61-0.80) (Hunter et al., 2011a). The one- and five-year images were read paired (not blinded to time-points), but blind to clinical information. The MOAKS divides the knee into 14 articular subregions to score cartilage lesions and BMLs. For the tibiofemoral compartment, cartilage lesions and BMLs were graded in each of the 10 subregions: central and posterior femur (medial and lateral) and anterior, central, and posterior tibia (medial

and lateral). Four subregions were used to grade cartilage lesions and BMLs in the patellofemoral compartment - the patella (medial and lateral) and trochlea (medial and lateral). Meniscal lesions were defined as medial or lateral, and divided into anterior, posterior, and central subregions. Cartilage lesions and BMLs were graded as present or absent in the tibiofemoral and patellofemoral compartments if any corresponding subregions for that compartment had a lesion ≥grade 1 in size. Meniscal lesions were graded as present if in either tibiofemoral compartment subregion there was (i) a vertical, horizontal, or complex tear, observed as an area of abnormal signal that extended to the meniscal articular surface; (ii) partial or complete maceration (loss of the morphologic substance of the meniscus); or (iii) ≥grade 1 extrusion (i.e., >2 mm) (Hunter et al., 2011a). Further detail on the MRI sequences and MOAKS is provided in Chapter 2.

4.2.5 Statistical analyses

Combined and isolated injury group medians and interquartile ranges (IQRs) for the KOOS and IKDC were calculated at one and five years post-ACLR due to non-normally distributed data (assessed with Shapiro-Wilk tests). For the KOOS and IKDC, visual comparisons were performed to determine whether the ACLR group median scores were at least an MDC (i.e., 10 points for KOOS, 13 points for IKDC) (Irrgang et al., 2006; Roos & Lohmander, 2003) below the normative (uninjured) median scores (Anderson et al., 2006; Cameron et al., 2013; Paradowski et al., 2006). Non-parametric analyses were used to account for the non-normal distribution of the KOOS and IKDC scores at the one- and five-year assessments. Mann-Whitney U tests were used to cross-sectionally compare PROs between the isolated and combined groups at the one- and five-year assessments. The absolute change in PROs between one and five years was normally distributed and reported as mean±standard deviation (SD), and parametric analyses (paired t-tests and independent samples t-tests) were used to examine within- and between-group changes from one to five years post-ACLR.

In addition, each individual was classified as having an “acceptable” KOOS or IKDC score if it was greater than a pre-determined cut-off (Ingelsrud et al., 2015; Muller et al., 2016). The KOOS cut-offs were determined from the Norwegian Knee Ligament Registry (n=1197), using the lower 95% CI score for each subscale (Pain: 88/100, Symptoms: 83/100, Sport: 73/100, QoL: 73/100) of individuals who perceived their knee function as acceptable 24 months post-ACLR (Ingelsrud et al., 2015). The IKDC cut-off (75/100) was determined using the mean IKDC score (85/100) minus the SD (10 points) of individuals who perceived their knee function as acceptable 3.5 years post-ACLR (Muller et al., 2016). Fisher's exact test was used to compare the proportions of participants in the isolated and combined groups defined as “acceptable”.

Multivariable linear regression was used to determine the cross-sectional relationships between PROs (continuous KOOS and IKDC scores) and the presence of cartilage lesions, BMLs, and meniscal lesions (dichotomous independent variables) in the patellofemoral and tibiofemoral compartment at one and five years post-ACLR. Regression analyses were adjusted for sex, age, presence of a combined injury, and BMI at one year due to their potential influences on PROs (Supplementary File A - in **Appendix J**, reports the univariate associations). The relationships between cartilage lesions, BMLs, and meniscal lesions at one year and PROs at five years were also evaluated, with adjustment for one-year PROs (in addition to age, sex, BMI, and combined injury). Stata for Windows V.14.2 was used for statistical analyses (StataCorp LLC, Texas, USA). P values <0.05 were considered statistically significant.

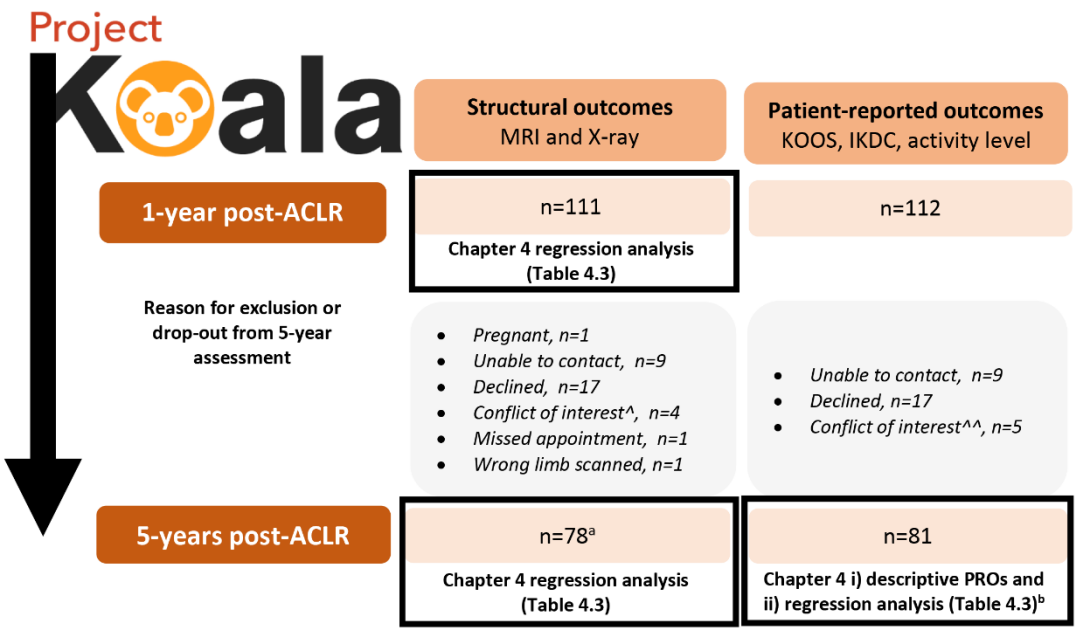


Figure 4.1. KOALA cohort participant recruitment and retention for Chapter 4.

ACLR=anterior cruciate ligament reconstruction; BMI=body mass index; IKDC=International Knee Documentation Committee knee evaluation; KOALA=Knee Osteoarthritis Anterior cruciate ligament Longitudinal Assessment cohort study; KOOS=Knee injury and Osteoarthritis Outcome Score; MRI=magnetic resonance imaging; n=number of participants; PROs=patient-reported outcomes.
^ n=4 due to participation in another study.
^^ n=4 due to participation in another study and n=1 became a member of the research team at 5 years.
[a] n=5 without BMI at 5-year assessment; therefore, not included in the analysis evaluating the associations between 5-year OA features on MRI and 5-year PROs, as BMI was a covariate.
[b] n=1 without 1-year MRI assessment not included in the analysis evaluating the associations between 1-year OA features on MRI and 5-year PROs.

4.3 Results

4.3.1 Participant characteristics

The demographic characteristics of the 81 participants included in the PROs analysis at one and five years following ACLR are presented in **Table 4.1.** There were no demographic, surgical, or MRI-related differences at one year post-ACLR between those who did (n=81) and did not participate (n=31) in the five-year assessment (p≥0.05) (Supplementary File B - in **Appendix K**). An exception was medial meniscal lesions, which were more prevalent in the participating group at one year post-ACLR. Forty (49%) and 46 (57%) of the 81 participants were classified as having a combined injury at one and five-years following ACLR, respectively (i.e., six were added to the combined injury group at five years due to a secondary injury between the one- and five-year assessments). Between one year and five years post-ACLR, 10 participants had a secondary injury to the index knee (**Table 4.1**); however, four of these were already classified as a combined injury at one year.

Table 4.1 Participant characteristics of combined and isolated injury groups one and five years following ACLR

	1 year (n=81)		**5 years (n=81)**	
	Combined (n=40)~	*Isolated (n=41)~*	*Combined (n=46)~*	*Isolated (n=35)~*
Age, median±IQR, years	31±12*	25±12	35±14*	29±13
Sex, no. (% male)	26 (65)	24 (59)	31 (67)	19 (54)
Body mass index^, median±IQR, kg/m^2	26.9±5.4*	24.8±3.0	27.5±5.1*	24.7±4.2
Pre-injury activity level 1 sport◊, no. (%)	28 (70)	28 (68)	34 (74)	22 (63)
Anteroposterior laxity between-limb difference∂, median±IQR, millimetres	1.1±2.7	1.9±2.1	n.a	n.a
Time injury to surgery, median±IQR, weeks	19±32*	12±9	17±26*	12±9
Meniscectomy at time of ACLR, no. (%)	32 (80)	0 (0)	32 (40)	0 (0)
Cartilage defect at time of ACLR¤, no. (%)	16 (40)	0 (0)	16 (35)	0 (0)
New knee Injuries (either limb), no. (%)	0 (0)	0 (0)	13 (28)	3 (9)
ACLR limb✪	0 (0)	0 (0)	10 (22)	0 (0)
Contralateral limb★	0 (0)	0 (0)	3 (7)	3 (9)
Returned to cutting/pivoting sport, no. (%)	9 (23)	11 (27)	11 (24)	9 (26)

ACLR=anterior cruciate ligament reconstruction; IQR=interquartile range; n.a.=not assessed.
~Participants classified as combined injury at 1- and 5-years if they had a meniscal lesion requiring surgical intervention or a significant cartilage defect at the time of ACLR. At 5-years, individuals were added to the combined injury group if they had a new injury/surgery to the ACLR knee.
^ n=75 participating in BMI assessment at 5-years follow-up.
∂ Assessed using a KT-1000 arthrometer at 30° flexion with 30 lb load (Daniel et al., 1985).
¤ Assessed arthroscopically, defined as Outerbridge grade ≥2 (Outerbridge, 1961).
✪ 5-year assessment new ACLR limb knee injuries/surgery n=10 (n= 3 ACLR revision, n=6 meniscectomy, n=1 lateral collateral ligament sprain).
★ 5-year asessment new contralateral limb knee injuries/surgery n=6 (combined: n=2 ACLR, n=1 meniscectomy, isolated: n=1 ACLR, n=1 meniscectomy, n=1 lateral collateral sprain).
* Statistically significant (p<0.05) difference between combined and isolated injury groups.

4.3.2 Patient-reported outcome measures

The entire cohort (n=81) demonstrated significant improvement (i.e., less knee symptoms, better function and QoL) between one and five years for all KOOS subscales (except KOOS-Symptoms) and IKDC. (**Figure 4.2**) The mean (95% CI) change for each subscale was: Pain: 2.8 (0.8, 4.8), Symptoms: 0.5 (-3.0, 4.1), Sport: 6.0 (2.0, 10.0), QoL: 10.0 (5.8, 14.2), IKDC 4.7 (2.3, 7.1). At one year post-ACLR, individuals in the combined injury group had significantly worse KOOS-Sport and IKDC scores (median difference±IQR: 15±4.6 and 5.0±3.5, respectively) ($p<0.05$). At five years, all PROs (except KOOS-Sport) were significantly worse in the combined injury group. The median ±IQR differences were as follows: KOOS±Pain 5.0±2.5, KOOS-Symptoms 11.0±4.2, KOOS-QoL 13.0±4.6, IKDC 4.0±3.2. KOOS and IKDC scores at one and five years for both groups are presented in **Figure 4.3**. Improvement between one and five years following ACLR did not differ between the combined and isolated groups ($p\geq0.05$). At five years, the combined injury group median scores for the KOOS-Symptoms and KOOS-QoL subscales were 14 and 25 points, respectively, below age-matched normative values from non-injured young adults (Anderson et al., 2006), which is greater than the recommended MDC (i.e., 8 to 10 points) for individuals with an ACL injury (Roos & Lohmander, 2003).

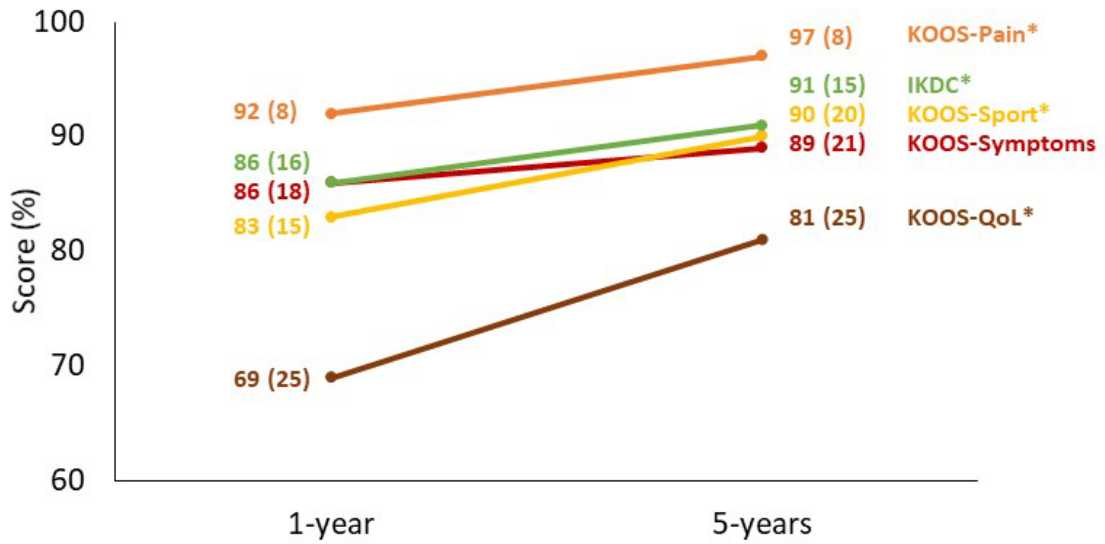


Figure 4.2 KOOS and IKDC scores at one and five years post-ACLR (n=81).

ACLR=anterior cruciate ligament reconstruction; KOOS=Knee Osteoarthritis Outcome Score; IKDC=International Knee Documentation Committee subjective knee evaluation; QoL=quality of life.
*Group median value increased significantly ($p<0.05$ Wilcoxon signed rank test) between 1 and 5 years. Supplementary File C (in Appendix L) presents the PROs for all groups at the 1- and 5-years following ACLR assessments and the crude p-values for the between-group analyses.

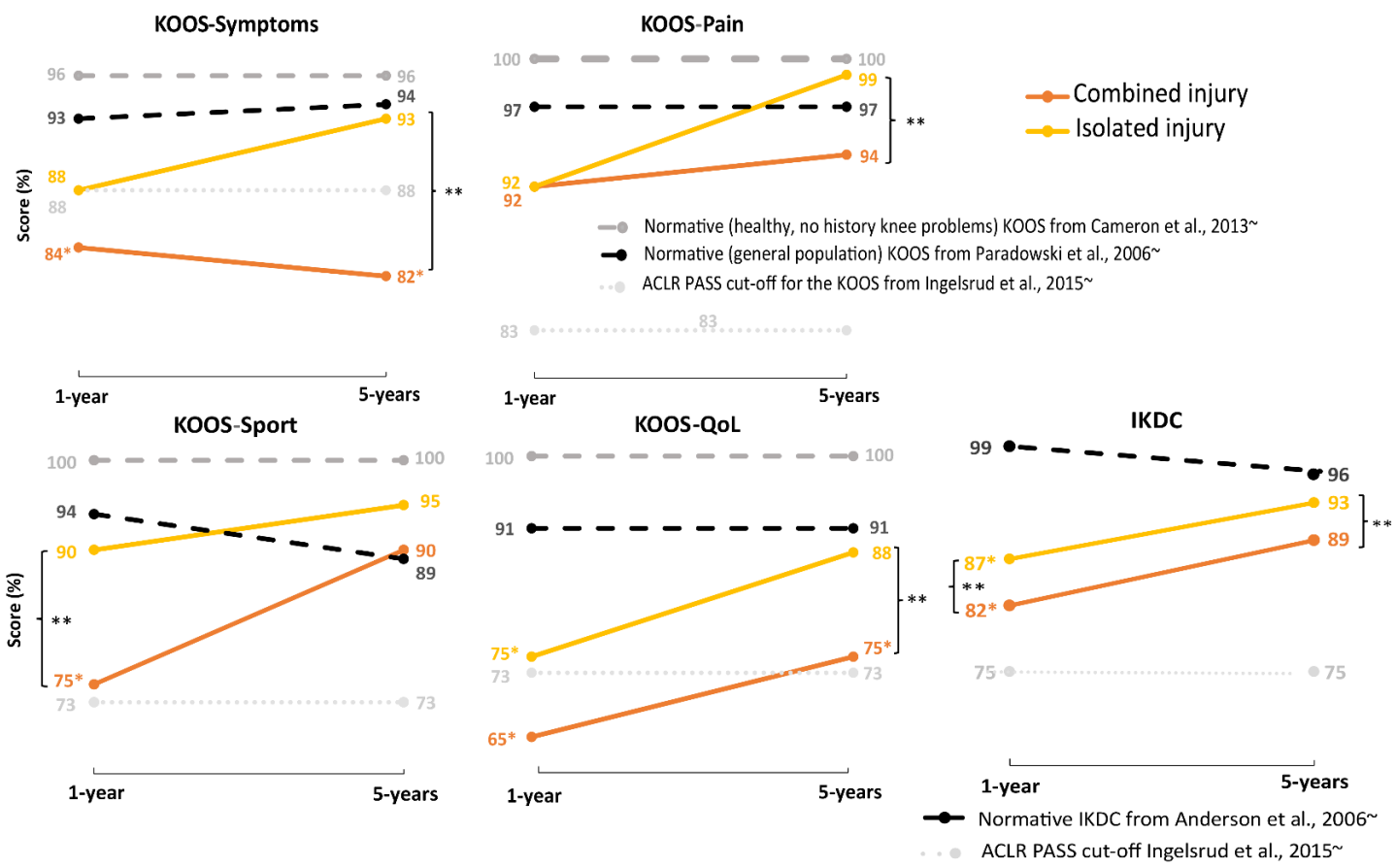


Figure 4.3 Comparison of isolated and combined ACLR groups, normative data, and acceptable cut-offs for ACLR individuals for the KOOS and IKDC^.

ACLR=anterior cruciate ligament reconstruction; KOOS=Knee Osteoarthritis Outcome Score; IKDC=International Knee Documentation Committee subjective knee evaluation; PASS=patient acceptable symptom state; QoL=quality of life.
^All values are presented as medians at 1-year and 5-years**.**
*Indicates that the median value at 1-year or 5-years is ≥MDC (Collins et al. 2011; Collins et al. 2016) below the general population normative median for the KOOS (Cameron et al. 2013) and IKDC (Anderson et al. 2006).
**Represents statistically significant difference ($p<0.05$) between combined and isolated injury groups.
~ Weighted average median values for the KOOS and IKDC were calculated using respective healthy uninjured (no history of knee problems) data (Cameron et al. 2013), general population (may have history of knee problems) age- and sex-matched data (Anderson et al. 2006; Paradowski et al. 2006), and "acceptable" cut-off scores in individuals following ACLR (Ingelsrud et al. 2015; Muller et al. 2016).

The number of individuals above the "acceptable" cut-off for the KOOS subscales and the IKDC are presented in **Table 4.2**. A significantly lower percentage of combined injury individuals reported acceptable IKDC scores at one year, and KOOS-Symptoms, KOOS-Pain, KOOS-QoL, and IKDC scores at five years. These significant relationships persisted in the sensitivity analyses, which excluded the 10 participants with re-injury between one and five years following ACLR (Supplementary File D, Table 1 - in **Appendix M**).

Table 4.2 Number of participants with "acceptable" KOOS and IKDC scores

		Number (%) acceptable~		**Between-group differences^**	
Outcome measure (acceptable cut-off score)	**Group***	***1-year***	***5-years***	***1-year***	***5-years***
KOOS-Pain (88)	*Whole group*	63 (78)	66 (81)		
	Isolated	33 (80)	33 (94)	0.601	**0.010**
	Combined	30 (75)	33 (72)		
KOOS-Symptoms (83)	*Whole group*	47 (58)	47 (58)		
	Isolated	27 (66)	25 (71)	0.180	**0.042**
	Combined	20 (50)	22 (48)		
KOOS-Sport (73)	*Whole group*	60 (75)	69 (85)		
	Isolated	32 (78)	33 (94)	0.455	0.060
	Combined	28 (70)	36 (78)		
KOOS-QoL (73)	*Whole group*	38 (47)	55 (68)		
	Isolated	22 (54)	30 (86)	0.268	**0.004**
	Combined	16 (40)	25 (54)		
IKDC (75)	*Whole group*	62 (77)	71 (88)		
	Isolated	37 (90)	35 (100)	**0.004**	**0.004**
	Combined	25 (63)	36 (78)		

KOOS=Knee injury and Osteoarthritis Outcome Score; IKDC=International Knee Documentation Committee knee evaluation.
~Reported as the number of participants (%) with a score above the "acceptable" cut-off from previously published data in ACLR individuals for the KOOS (Ingelsrud et al., 2015) and IKDC (Muller et al., 2016).
*Whole group at 1- and 5-years, n=81. Participants classified as combined injury at 1- and 5-years if they had a meniscal lesion requiring surgical intervention or a significant cartilage defect at the time of ACLR. At 5-years, individuals were added to the combined injury group if they had a new injury/surgery to the ACLR knee. At 1-year; n=40 combined, n=41 isolated. At 5-years; n=46 combined, n=35 isolated.
^ Fisher's exact test was used to compare the proportions of the isolated and combined groups above the acceptable cut-off value. Values in **bold** represent p<0.05.

4.3.3 Associations between cartilage lesions, BMLs, and meniscal lesions on MRI and PROs

There were no significant cross-sectional associations between cartilage lesions, BMLs, or meniscal lesions and KOOS or IKDC scores at one year post-ACLR. The presence of a patellofemoral cartilage lesion at the one-year assessment was significantly associated with worse KOOS-Symptoms (β: -9.79; 95%CI:-16.67 to -2.91; p=0.006), KOOS-Sport (β: -7.94; 95%CI:-15.27 to -0.61;

p=0.034), KOOS-QoL (β: -8.29; 95%CI:-15.28 to -1.29; p=0.021), and IKDC (β: -4.79; 95%CI:-9.34 to -0.24; p=0.039) scores at the five-year assessment (**Table 4.3**). The presence of a meniscal lesion at one year was significantly associated with worse KOOS-Symptoms at five years (β: -8.47; 95%CI:-16.54 to -0.42; p=0.039). Similarly, at five years, the presence of a patellofemoral cartilage lesion or meniscal tear was associated with worse PROs, and tibiofemoral BMLs were associated with better PROs (**Table 4.3**). Regression analysis was also performed without adjustment for sex, age, presence of a combined injury, and BMI at one year post-ACLR. The unadjusted analysis resulted in larger effect sizes and an increased number of significant relationships (Supplementary File E - in **Appendix N**), suggesting that these factors modulate the influence of combined injury on PROs following ACLR. Sensitivity analysis excluding 10 participants with re-injury between one and five years resulted in similar effect sizes (but wider CIs), suggesting that the effect of re-injury on the relationship between lesions on MRI and PROs in this study was minimal (Supplementary File D, Table 2 – in **Appendix M**).

Table 4.3 Associations between OA features on MRI and PROs~

1-year OA features^ (% with feature)#	1-year PROs*				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport*	*KOOS-QoL*	IKDC
PF Any Cartilage (45)	-0.87 (-6.35, 4.62)	-0.37 (-4.18, 3.43)	2.69 (-3.77, 9.14)	5.34 (-2.20, 12.89)	-0.03 (-4.47, 4.52)
PF Any BML (23)	-1.73 (-7.78, 4.31)	-1.87 (-6.04, 2.30)	-6.39 (-13.39, 0.61)	-3.01 (-11.26, 5.24)	-1.02 (-5.96, 3.92)
TF Any Cartilage (48)	2.81 (-2.33, 7.94)	1.25 (-2.32, 4.83)	-0.93 (-7.02, 5.16)	2.69 (-4.45, 9.85)	2.52 (-1.68, 6.74)
TF Any BML (31)	0.86 (-4.71, 6.44)	1.03 (-2.81, 4.90)	-0.26 (-6.81, 6.29)	-0.17 (-7.79, 7.45)	1.03 (-3.52, 5.58)
Meniscal lesion (72)	-1.61 (-5.96, 9.17)	-1.06 (-6.66, 4.54)	-2.92 (-12.61, 6.77)	1.42 (-9.74, 12.58)	-3.29 (-10.07, 3.48)
1-year OA features^ (% with feature)#	**5-years PROs****				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport*	*KOOS-QoL*	*IKDC*
PF Any Cartilage (46)	**-9.79 (-16.67, -2.91)**	-2.88 (-6.62, 0.86)	**-7.94 (-15.27, -0.61)**	**-8.29 (-15.28, -1.29)**	**-4.79 (-9.34, -0.24)**
PF Any BML (26)	-4.60 (-12.02, 2.81)	-1.28 (-6.44, 2.36)	-2.49 (-10.32, 5.34)	1.82 (-5.63, 9.27)	-1.62 (-6.39, 3.15)
TF Any Cartilage (47)	-5.32 (-11.84, 1.20)	-1.26 (-4.73, 2.19)	0.47 (-6.39, 7.34)	1.95 (-4.67, 8.58)	0.24 (-4.09, 4.58)
TF Any BML (30)	0.12 (-6.89, 7.13)	1.97 (-1.67, 5.62)	3.46 (-3.79, 10.73)	-0.94 (-7.97, 6.09)	1.06 (-3.48, 5.61)
Meniscal Lesion (79)	**-8.47 (-16.54, -0.42)**	-0.99 (-5.33, 3.34)	-0.44 (-8.21, 9.10)	-5.19 (-13.41, 3.04)	-3.74 (-9.07, 1.58)
5-years OA features^ (% with feature)#	**5-years PROs***				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport*	*KOOS-QoL*	*IKDC*
PF Any Cartilage (58)	**-6.86 (-13.49, -0.24)**	-2.49 (-6.78, 1.79)	-3.99 (-11.06, 3.07)	**-11.71 (-19.08, -4.33)**	-3.86 (-9.08, 1.36)
PF Any BML (22)	-1.19 (-8.77, 6.40)	-0.74 (-5.96, 4.46)	2.12 (-10.03, 5.79)	-0.99 (-9.78, 7.80)	-4.36 (-10.16, 1.44)
TF Any Cartilage (56)	-3.23 (-9.93, 3.45)	-0.16 (-4.10, 4.42)	1.53 (-5.48, 8.56)	6.83 (-0.78, 14.45)	4.23 (-0.89, 9.36)
TF Any BML (27)	3.26 (-4.23, 10.76)	4.19 (-0.47, 8.85)	**9.32 (1.79, 16.86)**	**11.84 (3.60, 20.07)**	**6.89 (1.28, 12.49)**
Meniscal Lesion (81)	**-9.12 (-17.41, -0.82)**	-1.81 (-7.23, 3.61)	-1.66 (-10.62, 7.29)	-3.74 (-13.64, 6.16)	-4.10 (-10.69, 2.49)

BML=bone marrow lesion; KOOS=Knee injury and OA Outcome Score; IKDC= International Knee Documentation Committee knee evaluation; MRI=magnetic resonance imaging; OA=osteoarthritis; PROs=patient-reported outcomes; PF= patellofemoral; QoL=quality of life; TF=tibiofemoral.
~Values represent coefficient and 95% confidence interval. Values in **bold** represent p<0.05.
#1-year MRI associations with 1-year PROs, n=111; 1-year MRI associations with 5-year PROs, n=80 (n=1 no MRI assessment at 1-year); 5-year MRI associations with 5-year PROs, n=73 (n=2 no MRI at 5-years; n=5 no BMI (covariate) assessment at 5-years). Refer to **Figure 4.1** for participant recruitment into current study.
^Cartilage, BMLs, and meniscal lesions ≥grade 1 size as per the MOAKS. Meniscal lesions include any type of tear, maceration, or extrusion ≥grade 1 in the medial or lateral tibiofemoral compartment.
*Adjusted for age, sex, BMI, presence of a combined injury. Unadjusted results appear in Supplementary File E (**in Appendix N**).
Adjusted for age, sex, BMI, presence of a combined injury, and 1-year KOOS and IKDC values. Unadjusted results appear in Supplementary File E **(in Appendix N).

4.4 Discussion

Despite improvements in KOOS and IKDC scores between one and five years following ACLR, individuals with a combined injury (i.e., concomitant meniscectomy and/or arthroscopic chondral defect at the time of ACLR and/or secondary injury/surgery to ACL knee) had worse PROs at five years, compared to those with an isolated injury. At five years, a lower proportion of individuals with a combined injury met previously reported "acceptable" PRO scores for individuals following ACLR (Ingelsrud et al., 2015), and presented with worse PRO scores compared to healthy uninjured populations. In the second part of our analysis, OA features on MRI had minimal associations with PROs at one and five years, except for patellofemoral cartilage lesions at one year, which was associated with worse KOOS-Symptoms, KOOS-Sport, KOOS-QoL, and IKDC scores at five years. Patellofemoral cartilage lesions on MRI at one and five years were generally associated with worse KOOS and IKDC scores at five years. The only other OA features on MRI to be associated with PROs were meniscal lesions at one and five years (worse KOOS-Symptoms at five years) and tibiofemoral BMLs at five years (better KOOS-Sport, KOOS-QOL, and IKDC at five years).

Interpret group-level PRO scores with caution

At an entire group level, all PROs, except KOOS-Symptoms, improved from one to five years post-ACLR. Although improvements did not exceed known clinically meaningful change scores for the KOOS (Roos & Lohmander, 2003) or IKDC (Irrgang et al., 2001), all KOOS subscales and IKDC entire group median scores at five years were near normative values (within MDC score (Collins et al., 2011; Collins et al., 2016)) when compared to the general population (Anderson et al., 2006; Paradowski et al., 2006). Whilst group-level scores for most KOOS subscales and IKDC in the combined and isolated injury groups at five years exceeded patient acceptable symptom state (PASS) cut-off values for ACLR populations (Ingelsrud et al., 2015; Muller et al., 2016) (**Figure 4.2**), our novel analysis (**Table 4.2**) identified that many individuals within the group did not achieve PASS values. Up to 42% (range: 0-42%; average: 22%) of all participants had not recovered to KOOS or IKDC PASS values at five years. Deficits were most evident for the KOOS-Symptom and KOOS-QoL subscales, in which 42% and 32% of participants (whole group), respectively, had not recovered to PASS values at five years. Entire group PRO scores in ACLR cohorts should be interpreted with caution, as they may depict successful outcomes but may not necessarily represent the widespread disparity and considerably poor outcomes observed in some individuals.

Individuals with a combined injury have worse PROs

Individuals with a combined injury demonstrated worse PROs at one year and a greater deficit at five years, compared to those with an isolated ACLR and non-injured peers. KOOS-Symptoms and

KOOS-QoL subscales were particularly impaired in those with a combined injury at five years, being 14 and 25 points, respectively, below normative values (Cameron et al., 2013). The proportions of people with acceptable scores on all of the KOOS subscales and IKDC improved from one to five years in the combined (one-year: 40-75%, average: 60%; five-years: 48-78%, average 66%) and isolated groups (one-year: 54-90%, average 73%; five-years: 71-100%, average 89%). This is consistent with previous reports indicating that one-third of individuals have unacceptable symptoms two years post-ACLR (Barenius et al., 2013; Ingelsrud et al., 2015). The combined injury group had a higher proportion of people not achieving PASS values for KOOS-Pain, -Symptoms, -QoL, and IKDC scores at five years. Specifically, the KOOS-Symptoms and KOOS-QoL subscales in the combined injury group had the greatest proportions (52% and 46%, respectively) of individuals who had not recovered to PASS values. These results may assist in the clinical interpretation of PROs following ACLR. Clinicians can identify individuals with an acceptable outcome based on PASS scores (Ingelsrud et al., 2015) and can provide education on realistic expectations of recovery for different patient groups. Clinicians should be cognisant that approximately half of patients with a combined injury may not achieve an acceptable outcome for symptoms or QoL five years following ACLR. Further research is needed to determine if targeted secondary prevention interventions can address current and potential future symptoms, and functional and participation restrictions.

Our findings extend previous research reporting worse PROs in the presence of a combined injury in the short- (injury to one year) (Ahldén et al., 2012; Cox et al., 2014) and long-term (15+ years) (Risberg et al., 2016b), confirming this relationship in the medium-term. Interventions targeting symptoms and QoL should be a high priority for individuals with a combined ACL injury. This may include additional pre-operative education and potentially ongoing intervention beyond one year post-ACLR to enable achievement of similar outcomes to those with isolated injuries. The combined injury group was significantly older and had a higher average BMI at one year; therefore, addressing potential negative lifestyle modifications, including physical inactivity (Daniel et al., 1994) and weight gain (Whittaker et al., 2015), which could be associated with poorer QoL following ACLR (Culvenor et al., 2016c; Filbay et al., 2016), may be important. Such interventions are beneficial in older adults with established knee OA (Fransen et al., 2015; Skou et al., 2018), but further high-quality trials are required to determine the efficacy in younger individuals with post-traumatic knee OA following ACLR.

Associations between OA features on MRI and PROs

Overall, minimal cross-sectional associations were observed between tibiofemoral or patellofemoral cartilage lesions, BMLs, meniscal lesions, and PROs between one and five years following ACLR. These findings extend previous reports of no associations between tibiofemoral

radiographic OA and PROs in the longer-term (Lohmander et al., 2004; Oiestad et al., 2011). However, consistent with three-year post-ACLR PRO data from the KOALA cohort (Culvenor et al., 2016c), patellofemoral cartilage lesions at one year were associated with worse KOOS-Symptoms, KOOS-Sport, KOOS-QoL, and IKDC scores at five years post-ACLR. Additionally, patellofemoral cartilage lesions at five years were cross-sectionally associated with worse KOOS-Symptoms and KOOS-QoL. Whilst clinicians should consider the patellofemoral compartment as a potential source of symptoms and a driver of poorer function following hamstring-autograft ACLR (Culvenor & Crossley, 2016; Culvenor et al., 2014b), patient education should express that MRI findings are often unrelated to symptoms. Further, the regression models evaluating the association between patellofemoral cartilage lesions and PROs had relatively wide CIs, and the large number of tests increases the likelihood that findings may be due to chance. Further studies are required to validate the association between OA features on MRI and PROs after ACLR.

In Chapter 3, it was reported that one-third of individuals will have worsening BMLs between one and five years following ACLR (Patterson et al., 2018). An interesting finding of this current analysis in the same cohort is that the presence of tibiofemoral BMLs was associated with better KOOS-Sport, KOOS-QoL, and IKDC at five years. This could indicate that BMLs reflect increased joint loading due to participation in sport, particularly in the presence of poor function (Culvenor et al., 2017a). The future symptomatic consequences of BMLs following ACLR are unknown, but in individuals at risk of OA (i.e., older, higher BMI), worsening BMLs are reported to predict subsequent knee symptoms, progression of OA features on MRI, and radiographic OA four to seven years later (Felson et al., 2007; Sharma et al., 2016). Further research is required to understand the long-term implications of BMLs on MRI in an ACLR population and to measure the responses of individual joint features and PROs to potential interventions.

Limitations

Our follow-up rate at five years of the original one-year cohort was 72%, which may introduce some selection bias. However, there were no significant differences in participant or surgical characteristics at the one-year post-ACLR assessment between those participating and those lost to follow-up (Supplementary File B – in **Appendix K**), and the current cohort had similar IKDC scores (Cox et al., 2014) and return-to-sport rates (Ardern et al., 2014b) as other larger ACLR cohorts at comparable follow-up time-points. The combined injury group included 10 individuals who sustained a secondary injury between one and five years, which could influence the results. However, sensitivity analyses excluding these 10 participants showed that the association between combined injury and PROs at five years, and the relationships between cartilage, bone marrow, and meniscal lesions and PROs at five years, were generally similar to the results from

the whole cohort (Supplementary File D - in **Appendix M**). Slightly smaller effect sizes with wider CIs were typically observed in these sensitivity analyses, likely due to the lower sample size and the fact that participants with a secondary injury reported more symptoms at five years. Finally, the regression findings should be interpreted cautiously; the wide CIs observed in the regression analyses were likely driven by the wide range in scores and the multiple factors that may influence PROs.

4.5 Conclusion

In conclusion, individuals with a combined injury following ACLR may be an important subgroup requiring additional interventions, given their likely worse outcomes compared to those of their peers with an isolated ACLR. Individuals with patellofemoral cartilage lesions may also require more targeted interventions due to the associations with worse symptoms, function, and QoL at five years post-ACLR. Despite tibiofemoral BMLs being associated with fewer knee function and QoL impairments at five years, there seem to be minimal relationships between other compartment-specific cartilage lesions, BMLs, and meniscal lesions identified on MRI and patient-reported symptoms, function, and QoL.

5 Chapter Five: Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function

Preface

Chapter 4 reported that up to 50% of young adults have unacceptable symptoms and QoL at one year post-ACLR, and these deficits persist in one-third of people at five years post-ACLR. While structural pathology (combined injury or patellofemoral cartilage lesions) may explain worse symptoms in some individuals, an important piece to the "symptoms and OA" puzzle following ACLR is objective function. Chapter 1 highlighted that functional performance deficits are associated with an increased re-injury risk, which can have important implications for the progression of post-traumatic OA. Chapter 1 also highlighted that functional performance is mostly assessed in the first one to two years following ACLR, and reporting of procedures and scoring methodology is poor. To date, studies have focused on reporting the LSI, typically on a single-hop test, and omit the quantitative performance of the ACLR and contralateral limb. The primary aim of the study in Chapter 5 was to evaluate changes in functional performance in the ACLR and contralateral limbs in order to determine their influence on the LSI, between one and five years following ACLR in the KOALA cohort.

Chapter 5 contains the following publication in its entirety (**Appendix O**) with the addition of **Figure 3.1** to depict participant recruitment into the study, consistent with the other chapters.

Patterson, B.E., Crossley, K.M., Perraton, L.G., Kumar, A.S., King, M.G., Heerey, J.J., Barton, C.J., & Culvenor, A.G. (2020). Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function. *Physical Therapy in Sport, 44*, 67-74.

5.1 Introduction

Following ACLR, functional performance testing is advocated to determine readiness for return-to-sport and mitigate risk of re-injury (Grindem et al., 2018; Kyritsis et al., 2016; van Melick et al., 2016). The LSI is frequently used to describe the function of the ACLR limb compared to the contralateral limb, and is expressed as a percentage (score of ACLR knee divided by contralateral knee, multiplied by 100). An LSI >90% on a functional test battery (e.g., hop tests, muscle strength) frequently defines functional recovery and return-to-sport clearance (Abrams et al., 2014).

Symmetry (>90%) on hop testing is associated with reduced re-injury risk (Grindem et al., 2016; Kyritsis et al., 2016), better patient-reported symptoms and QoL (Ericsson et al., 2013), and reduced risk of OA (Culvenor et al., 2017a; Patterson et al., 2020a; Pinczewski et al., 2007). However, the LSI assumes that the contralateral limb is the acceptable standard, equivalent to pre-injury status and immune to decline (Benjaminse et al., 2018; Wellsandt et al., 2017). In reality, bilateral neuromuscular deficits (e.g., muscle strength, activation or size, biomechanics, balance and functional performance) exist following unilateral ACLR (Benjaminse et al., 2018; Culvenor et al., 2016a; Gokeler et al., 2017; Lisee et al., 2019b); hence, the LSI may overestimate post-operative knee function (Wellsandt et al., 2017), which is an important consideration given the high risk of second ACL injury (Wiggins et al., 2016). To determine whether the LSI overestimates knee function, it is important to compare raw scores from the ACLR and contralateral limb to healthy uninjured controls, providing the benchmark for functional performance.

While functional improvements in hop testing LSI are well documented within the first year following ACLR (Abrams et al., 2014; Nagelli & Hewett, 2017; Thomee et al., 2012), functional changes beyond the period of active rehabilitation (i.e., >one to two years post-ACLR) are less often reported (Oiestad et al., 2010a). Specifically, it is not known whether functional LSI changes beyond the initial one to two years post-ACLR are driven by changes in the ACLR or contralateral limb. Evaluating the magnitude of functional performance (e.g., hop distance) in the ACLR and contralateral limb, together with the LSI over time compared to uninjured controls, is important to understand the longer-term functional burden of ACLR.

The primary aim of the current study was to evaluate changes in functional performance in the ACLR and contralateral limbs from one to five years post-ACLR to determine their influence on the LSI. It was hypothesised that change in functional performance would differ between the ACLR and contralateral limb, primarily due to worsening contralateral limb function. Our secondary aim was to compare functional performance at one and five years following ACLR with uninjured

healthy controls. It was hypothesised that functional performance following ACLR at both time-points would be significantly lower than uninjured healthy controls.

5.2 Methods

5.2.1 Participants

Adults (aged 18-50 years) who had undergone primary hamstring-autograft ACLR by one of two orthopaedic surgeons were consecutively recruited into this prospective cohort study at their routine 12-month surgical review (Culvenor et al., 2016d). The exclusion criteria at baseline were: (i) injury/surgery to the ACLR knee prior to ACL rupture, (ii) post-operative injury or follow-up surgery to the ACLR knee, (iii) history of contralateral knee injury or surgery, (iv) other conditions influencing function (e.g., neurological conditions, current low back pain), (v) pregnant/breastfeeding. Participants attended baseline and follow-up assessments at one and five years following ACLR, respectively. Those reporting new injuries to either knee between the one- and five-year assessments were excluded.

Two healthy control groups were utilised to provide reference data for the functional performance tests. Asymptomatic uninjured recreational athletes recruited from sporting clubs provided control data for the three hop tests at a single time-point (Perraton et al., 2017). A second asymptomatic uninjured control group of recreational football players provided reference data at a single time-point for the one-leg rise test, as this was not part of our earlier healthy control study. Ethical approval for the ACLR and control cohorts was granted by the La Trobe University Human Ethics Committee (HEC15-100 and HEC16-045, respectively) and the University of Melbourne (1136167), and participants provided informed consent.

5.2.2 Procedures

Four lower-limb functional performance tests were completed at both baseline and follow-up (one and five years following ACLR, respectively) for the ACLR group, and at one time-point for the healthy controls. Identical methods were used for all participants and for both limbs, with assessors blind to the ACLR limb (elastic bandage over both knees covering scars). Details of the test battery are provided in Chapter 2; testing was performed based on previously reported methods for the single-hop (Gustavsson et al., 2006), triple-crossover hop (Reid et al., 2007), side-hop (Gustavsson et al., 2006), and one-leg rise (Thorstensson et al., 2004). Briefly, the single-hop assessed the maximum distance (cm) achieved from a stationary position with a balanced landing (Gustavsson et al., 2006). The triple-crossover hop assessed the cumulative distance (cm) achieved with three consecutive hops, with each hop crossing over two parallel lines 15 cm apart (Reid et

al., 2007). The side-hop assessed the number of hops over two parallel lines 40 cm apart in 30 seconds (Gustavsson et al., 2006). The one-leg rise (Thorstensson et al., 2004), a global measure of lower-limb strength and endurance, was performed from a seated position and standardised height (90° knee flexion). Participants were instructed to rise on one leg as many times as possible (up to 50 repetitions) at a controlled speed (45 beats per minute using a metronome). In addition to functional performance testing, participant age, sex, BMI, injury history, and activity level (defined as level 1 pivoting/jumping sports, level 2 lateral movement sports (i.e., tennis), level 3 straight line activities (i.e., running, weight-lifting, cycling), and level 4 sedentary) (Grindem et al., 2014), were obtained at the one- and five-year assessments.

5.2.3 Statistical analyses

Data were examined for normality and homogeneity of variance. Baseline, follow-up, and one- to five-year (absolute) changes (mean±SD) in ACLR and contralateral limb performance (cm or repetitions) and LSI (%) were calculated. Within the ACLR group, within-limb and LSI changes between one and five years were evaluated using a paired t-test. A linear mixed-effects model incorporating random effects (accounting for the between-limb correlation) assessed the difference in change in function (mean difference, 95% CI) between the ACLR and contralateral limb. The proportion of participants classified as having stable, improving, or worsening function between one and five years relative to previously published MDC thresholds (Haitz et al., 2014; Kockum & Heijne, 2015; Reid et al., 2007) are reported descriptively (except for the one-leg rise, as there is no known MDC). To determine the healthy control group scores, data from both limbs at the single time-point were averaged on a per-participant basis, and an overall group average was calculated (mean±SD). Linear regression models assessed the differences in functional performance between the ACLR group (separate model for each limb and LSI) and the healthy control group at one and five years following ACLR. The model was adjusted for age and BMI, as the ACLR group was significantly older and had a higher average BMI ($p<0.05$). Analyses were performed using Stata V.14.2 with an α level of 0.05.

5.3 Results

5.3.1 Participants

Of the 110 participants who were included in our cross-sectional study of function at one year post-ACLR (Culvenor et al., 2016d), 74 (67%) were re-tested five years post-operatively (5.2±0.2 years). The reasons for dropout (n=36) included (i) unable to contact (n=9), (ii) unable to attend in person (n=9), (iii) declined participation due to time (n=11), (iv) conflict with participation in another study (n=5), and (v) other conditions limiting participation (n=2) (**Figure 5.1**). A further 14

participants were excluded due to new knee injury/surgery between one and five years. One additional participant was excluded due to a previous contralateral knee arthroscope reported at the five-year assessment which was not reported at the one-year assessment (**Figure 5.1**). The 59 ACLR participants (37% women) were (median±IQR) aged 29±16 years at the one-year assessment and 33±16 years at the five-year assessment, with a (mean±SD) BMI of 24.9±3.3 kg/m^2 at one year and 25.6±3.6kg/m^2 at five years post-ACLR. Prior to ACL injury, 88% (n=52) participated in Level 1 or 2 sports, 12% (n=7) in Level 3 activities and no participants were classified as sedentary (Level 4). At the one-year post-ACLR assessment, 34% (n=20) of ACLR participants played Level 1 or 2 sports, 24% (n=14) participated in Level 3 activities, and 42% (n=25) were classified as (Level 4) sedentary. At the five-year assessment, activity level increased to 41% (n=24) for Level 1 or 2 sports, 47% (n=28) for Level 3 activities, and fewer participants (n=7, 12%) were classified as sedentary. The 41 healthy controls providing hopping reference data were similar in sex distribution (39% female) and BMI (mean±SD: 24.0±2.6 kg/m^2), but were five years younger (median±interquartile range: 24±3 years) (Perraton et al., 2017). The 31 healthy controls providing one-leg rise test reference data (34% female) were three years younger (median±interquartile range: 26±10 years) with a similar average BMI (mean±SD: 24.6±3.1 kg/m^2). At the time of assessment, 74% of the healthy controls were participating in Level 1 or 2 sports.

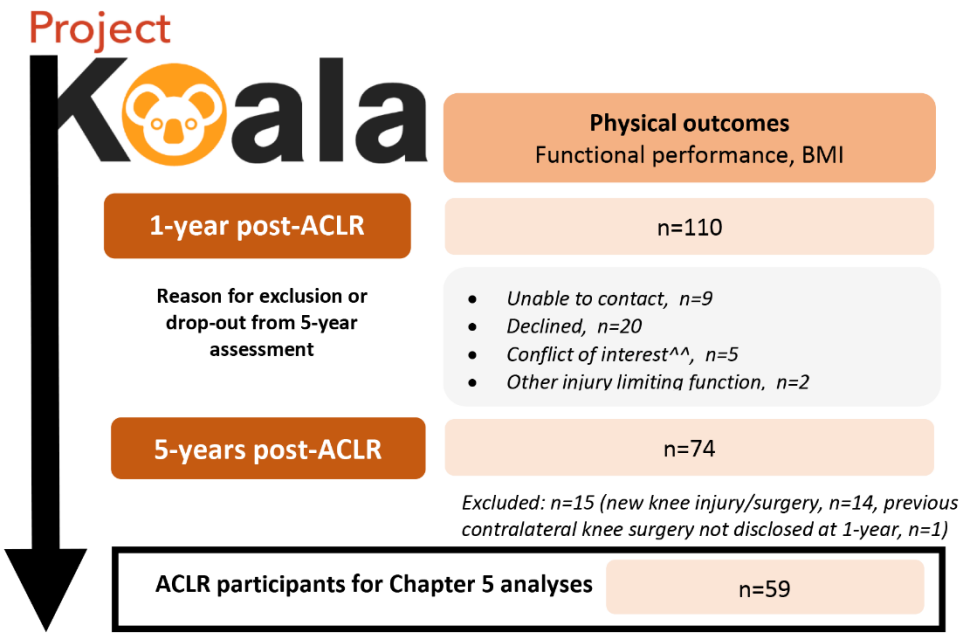


Figure 5.1. KOALA cohort participant recruitment and retention for Chapter 5.

ACLR=anterior cruciate ligament reconstruction; BMI=body mass index; KOALA=Knee Osteoarthritis Anterior cruciate ligament Longitudinal Assessment cohort study; n=number of participants.
^^ n=4 due to participation in another study and n=1 became a member of the research team at 5 years.

5.3.2 ACLR group changes

Functional performance in the ACLR limb did not significantly change between one and five years, except for the single-hop distance, which increased significantly (p=0.017) (**Table 5.1**, **Figure 5.2**). In contrast, contralateral limb performance decreased between one and five years, and this was significant for the triple-crossover (p=0.004), side-hop (p=0.019), and one-leg rise tests (p=0.001) (**Figure 5.2, Table 5.1**). Between one and five years, the contralateral limb had a significantly greater decrease in function compared to the ACLR limb for all functional tests (**Table 5.1**). This resulted in the LSI increasing significantly over time for the single-hop (p=0.003), side-hop (p<0.001), and one-leg rise (p=0.069) (**Table 5.1**, **Figure 5.2**).

Table 5.1. Functional performance from one to five years post-ACLR^

	1 year	5 years	Change 1 to 5 years	Mean (95% CI) difference in change
Single-hop (cm)				
ACLR	103.2 (29.7)	109.8 (27.5)	6.5 (20.5)[i]	**-8.3 (-13.4, -3.3)**
Contralateral	118.3 (21.9)	116.5 (26.7)	-1.8 (12.9)	**p=*0.001***
LSI (%)	86.5 (17.4)	95.4 (18.0)	8.9 (22.4)[i]	-
Triple-crossover hop (cm)				
ACLR	327.7 (100.0)	321.6 (98.9)	-6.1 (59.2)	**-16.4 (-30.0, -2.8)**
Contralateral	363.5 (85.5)	341.0 (90.2)	-22.5 (46.0)[d]	**p=*0.018***
LSI (%)	89.4 (17.0)	93.2 (16.9)	3.8 (18.5)	-
Side-hop (reps)				
ACLR	24.9 (14.0)	24.0 (14.0)	-0.9 (7.9)	**-3.7 (-5.6, -1.9)**
Contralateral	30.8 (14.0)	26.2 (13.7)	-4.7 (7.9)[d]	**p=*0.000***
LSI (%)	77.2 (31.2)	85.7 (32.5)	10.4 (26.1)[i]	-
One-leg rise (reps)				
ACLR	28.1 (18.9)	25.2 (18.4)	-2.8 (14.4)	-1.9 (-4.0, 0.25)
Contralateral	31.9 (17.1)	27.1 (17.7)	-4.8 (13.5)[d]	p=*0.083*
LSI (%)	75.6 (38.9)	85.4 (40.3)	11.1 (37.7)[i]	-

ACLR=anterior cruciate ligament reconstructed limb; CI=confidence interval; cm=centimetre; LSI=limb symmetry index.
^Values are mean (±standard deviation) unless otherwise indicated. **Bold values** indicate a statistically significant (p<0.05) difference in the change score between the ACLR and contralateral limb.
[i] Statistically significant (p<0.05) increase in average group score between 1 and 5 years.
[d] Statistically significant (p<0.05) decrease in average group score between 1 and 5 years.

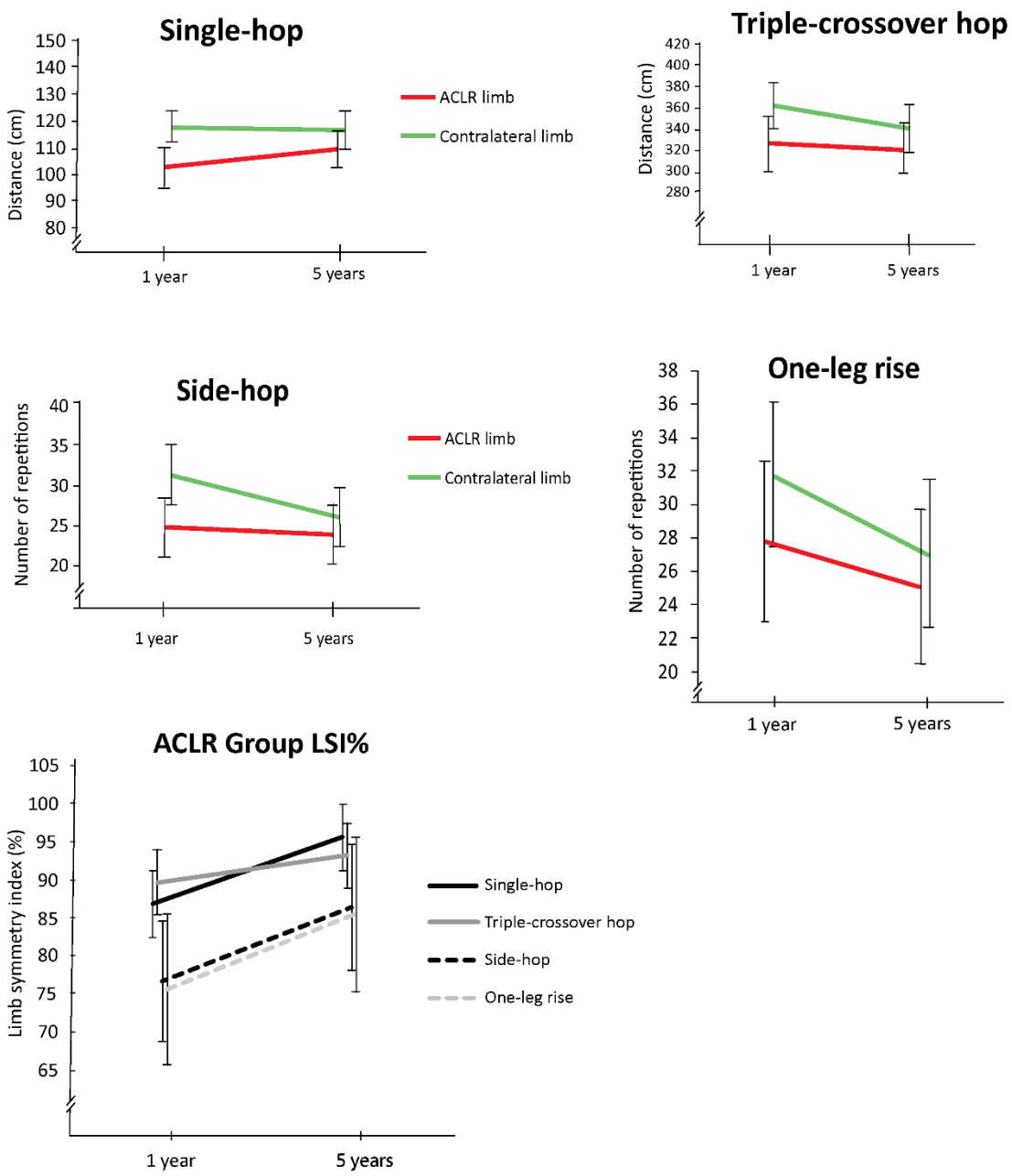


Figure 5.2 Functional performance at one and five years following ACLR~.

ACLR=anterior cruciate ligament reconstruction; LSI=limb symmetry index.
~Values are mean±standard deviation.

5.3.3 Were the ACLR group changes meaningful?

When evaluating each participant's functional change between one and five years following ACLR in each limb (e.g., distance hopped) according to MDC thresholds, most participants (63-85%) had stable function (i.e., increase/decrease <MDC) (**Figure 5.3**). Worsening function (decrease >MDC) was more common across all three hop tests in the contralateral limb (12-19%) than the ACLR limb (8-10%). Improvement (increase >MDC) was more common across all three hop tests in the ACLR limb (7-27%) than the contralateral limb (0-8%). The LSI improved (increase >MDC) in

approximately one-third of participants in the three hop tests (single-hop: 41%, triple-crossover hop: 25%, side-hop: 44%) (**Figure 5.3**).

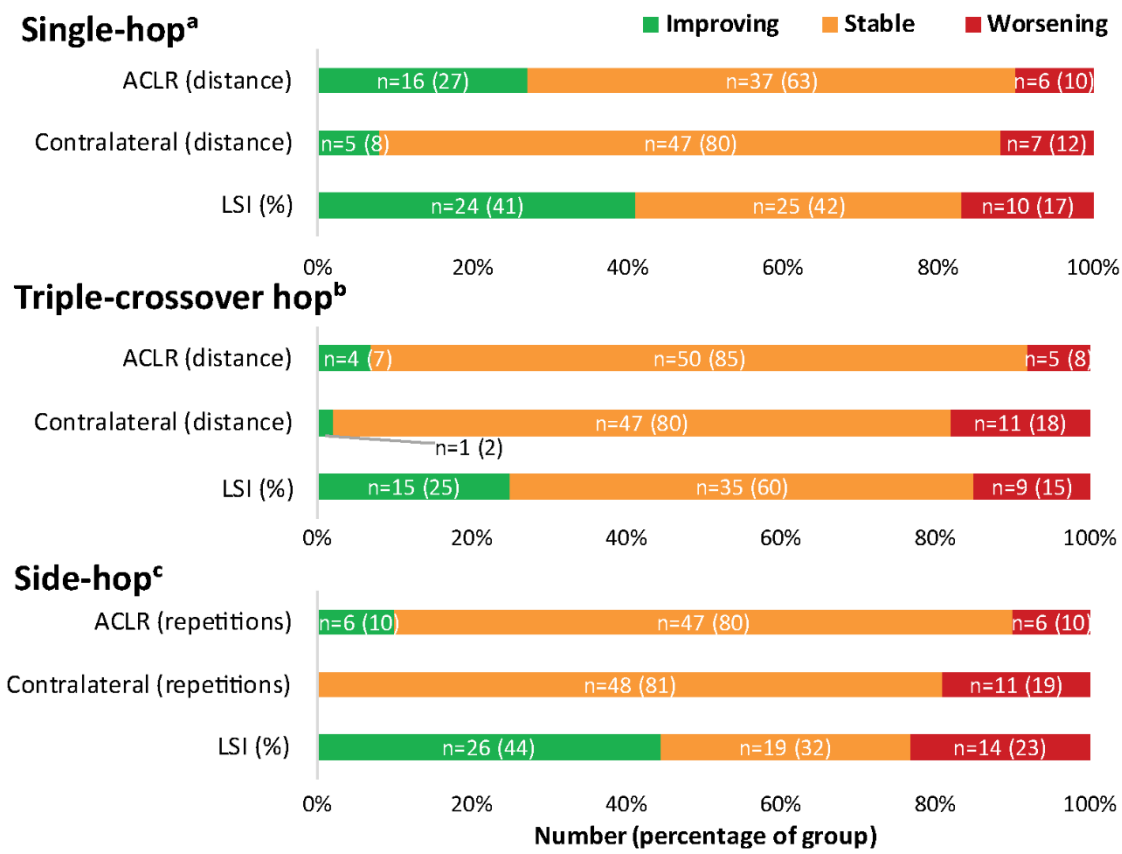


Figure 5.3. Number of participants with stable, improving, or worsening functional performance between one and five years post-ACLR, according to the MDC.

ACLR=anterior cruciate ligament reconstruction; LSI=limb symmetry index; MDC=minimal detectable change; n=number of participants.
[a] MDC for the single-hop distance (14 cm) and LSI (8%) is informed by Kockum et al. (2015) and Reid et al. (2007), respectively.
[b] MDC for the triple-crossover distance (73 cm) and LSI (12%) is informed by Haitz et al. (2014) and Reid et al. (2007), respectively.
[c] MDC for side-hop repetitions (n=11 repetitions) and LSI (10%) is informed by Kockum et al. (2015) and Reid et al. (2007), respectively. The MDC for the side-hop LSI is not specifically reported; therefore, a 10% MDC was estimated (as an average of the 8% and 12% from the single- and triple-crossover hop tests).

5.3.4 Comparison to healthy control data

At one year post-ACLR, the single-hop results for the ACLR ($p<0.001$) and contralateral limb ($p=0.012$) were significantly lower than healthy controls, with adjustment for age and BMI. No differences were observed between the ACLR or contralateral limb and the healthy control group for the triple-crossover, side-hop, and one-leg rise. At the one-year post-ACLR assessment, the LSIs for the single-hop ($p<0.001$), triple-crossover hop ($p=0.003$), side-hop ($p<0.001$), and one-leg rise ($p=0.003$) were significantly lower than healthy controls. At five years post-ACLR, the side-hop LSI was the only test that was significantly lower ($p=0.016$) than healthy controls. There were no

differences between the ACLR and control limbs, and the healthy controls, at five years. Healthy control data from the single time-point is presented in **Table 5.2**.

Table 5.2. Functional performance of the healthy controls~

	Raw score	Limb symmetry index (%)
Single-hop (cm)^	135.0 (27.3)	101.8 (5.6)
Triple-crossover hop (cm)^	392.5 (102.2)	101.4 (6.0)
Side-hop (repetitions)^	33.9 (14.5)	108.2 (14.5)
One-leg rise (repetitions)^^	31.7 (15.7)	109.0 (36.4)

cm=centimetres
~Values are mean (standard deviation) unless otherwise indicated.
^n=41 for the three hop tests.
^^n=31 for one-leg rise.

5.4 Discussion

Functional performance changes differ between the index and contralateral limb during the first five years post-ACLR. Although function in the ACLR limb remained relatively stable from one to five years post-ACLR, with the average changes not exceeding the MDC thresholds, worsening function in the contralateral limb resulted in statistically significant LSI improvements for the single-hop, side-hop, and one-leg rise tests. This highlights the limitations of using the LSI in isolation to evaluate functional change, as it may overstate improvements in the ACLR limb.

LSI overestimates function

In the current study, improved LSI between one and five years following ACLR was primarily driven by worsening function in the contralateral limb, rather than improved function in the ACLR limb. These findings extend previous cross-sectional data at six months post-ACLR (Wellsandt et al., 2017), which showed that the LSI using the post-operative status of the contralateral limb as a reference overestimates function (i.e., 57% of individuals achieve >90% LSI) compared to using pre-operative contralateral limb function as the reference (i.e., 29% achieve >90% LSI). Combined, it appears that caution must be used when interpreting the LSI at a single time-point and over time when determining treatment success and readiness to progress milestones (including clearance for return-to-sport).

Why does the contralateral limb worsen, and why more so than the ACLR limb?

The contralateral limb exhibited a significantly greater decrease in function on the three hop tests compared to the ACLR limb. Different responses in the functional capacity of the ACLR and contralateral limb over time are supported by one of the few studies reporting raw changes in hop

test performance in both limbs (i.e., distance hopped) following ACLR (Thomee et al., 2012). In that report, the ACLR limb improved by 11 cm (single-hop) and 6 repetitions (side-hop) from 6 to 12 months post-operatively, with minimal change between 12 and 24 months, while the contralateral limb was stable or declined in both tests (Thomee et al., 2012). Concurrent strength testing demonstrated a deterioration in quadriceps and hamstring strength from 12 to 24 months in the contralateral limb and stable/improving in the ACLR limb (Thomee et al., 2012). Functional recovery is reported to occur up to two years post-ACLR (Abrams et al., 2014; Nagelli & Hewett, 2017), but is often limited to reports of LSI, which concurs with the improving LSI in the current study.

Worsening function in the contralateral limb might reflect a combination of age-related changes, deconditioning following rehabilitation cessation, bilateral movement adaptations (e.g., reduced knee flexion moments) (Hart et al., 2016; Pairot-de-Fontenay et al., 2019), or fear of movement (Hart et al., 2020). However, worsening in the contralateral limb between one and five years cannot entirely be explained by age-related deterioration in muscle function (Doherty, 2001; Faulkner et al., 2007), since muscle mass and strength appear to be maintained until age 40 or 50, especially when regular sporting activity is continued (Culvenor et al., 2016b; Doherty, 2001; Faulkner et al., 2007). In the current study, the proportion of individuals participating in jumping/pivoting sports increased between one year (34%) and five years (41%) post-ACLR. The proportion of individuals participating in Level 3 activities increased from 24% to 47%, while those classified as sedentary (Level 4) decreased from 42% to 12% between one and five years following ACLR. Overall, 39% (n=24) increased their activity level according to the classification used (Grindem et al., 2014) between one and five years. Greater worsening of knee function observed in one limb (i.e., the contralateral leg) might be considered surprising since most dynamic activities are performed using both limbs. Patients and therapists may also prioritise rehabilitation of the ACLR limb, neglecting the contralateral limb, despite the known bilateral neuromuscular deficits (Benjaminse et al., 2018; Gokeler et al., 2017; Lisee et al., 2019b) and the decline in function due to changing demands from high-level sport to only walking/activities of daily living for 6-12 months.

Should the LSI be used in clinical practice?

These findings have important implications for current return-to-sport criteria, given that the current criteria are highly dependent on achieving >90% LSI on a battery of hop tests (Barber-Westin & Noyes, 2011; van Melick et al., 2016). The overestimation of functional ability with the LSI might contribute to the high re-rupture rates (7%) (Wiggins et al., 2016) or high rates of contralateral ACL injury (8%) (Wiggins et al., 2016) if the acceptable LSI results from low

contralateral limb function (Webster & Hewett, 2019). In addition to LSI, return-to-sport criteria should also incorporate individual limb performance scores (e.g., distance hopped or peak muscle power) benchmarked to the individual's body composition (e.g., height) as well as to age-, sex-, and activity-level matched non-injured populations obtained from context-specific databases or peer-reviewed reports (Bennell et al., 1998). In addition to our healthy reference data, other functional reference data are available for the single-hop (Baltaci et al., 2012; Kemp et al., 2013), triple-crossover hop (Baltaci et al., 2012; Kockum & Heijne, 2015), and side-hop (Kockum & Heijne, 2015). In an ideal (but often unrealistic or uncommon) scenario, pre-injury index limb testing data or pre-operative functional testing of the non-injured limb (i.e., prior to deterioration) may be used as the benchmark. Pre-operative function in the non-injured limb as the reference standard for LSI calculations is more sensitive in predicting second ACL injury, compared to using post-operative performance of the non-injured limb at the time of ACLR limb assessment (Wellsandt et al., 2017). Further research is required to determine the best type and combination of assessments and interventions, and their relationships with future injury risk and patient-reported symptoms, function, and QoL.

The benefits of functional performance symmetry (>90%) at one and five years post-ACLR, even after return-to-sport, should not be discounted. However, symmetry should not come at the expense of inadequate or deteriorating performance in the contralateral limb. Given the known associations between reduced strength and function and increased risk of re-injury and OA (Oiestad et al., 2015; Patterson et al., 2020a; Segal & Glass, 2011), restoring or maintaining symmetry and performance should remain an ongoing priority for both limbs, regardless of sports participation. Regardless of return-to-sport and ongoing sports participation, asymmetries on hop testing are relevant to everyday activities such as walking, as less than 90% LSI on hop tests is associated with lower knee loading on the ACLR limb (Gardinier et al., 2014; Sritharan et al., 2020), which has been recently linked to OA risk (Wellsandt et al., 2016).

Clinical implications for functional performance assessment

Hop testing provides a highly accessible, low-cost alternative to isokinetic and biomechanical testing, and has moderate associations with quadriceps peak torque and rate of torque development (Birchmeier et al., 2019a), force control (Perraton et al., 2017), and kinetics and kinematics (Perraton et al., 2019; Perraton et al., 2018). However, due to persistent morphological changes (i.e., quadriceps volume) post-ACLR (Birchmeier et al., 2019b), clinicians should endeavour to evaluate isolated quadriceps and hamstring muscle function (e.g., isokinetic testing). Assessment of muscle function and movement quality is important, as some individuals can use

compensatory mechanisms and sub-optimal kinematics and kinetics to achieve adequate performance in hop tests (Kotsifaki et al., 2020).

Changes in functional performance following ACLR may differ between tasks. The single-hop (ACLR limb) was the only test that demonstrated statistically and clinically important improvement in performance (one-third of participants had performance increase >MDC). The majority of participants did not demonstrate clinically meaningful changes in the ACLR or contralateral limb for the triple-crossover hop and side-hop (**Figure 5.3**). Improvement in the ACLR limb single-hop may reflect a return to sagittal plane activities such as running following ACLR. No change or decrease in function in more dynamic tasks, such as the triple-crossover and side-hop, may reflect lack of progression to multidirectional rehabilitation tasks or sport. These findings are supported by our activity level data, whereby only 41% were participating in Level 1 or 2 sports at five years and a larger proportion (47%) were participating in Level 3 (running, cycling, weight-training) activities at five years. Test batteries should include different aspects of function (i.e., multiplanar strength, power, and endurance), as a single-hop alone may overstate functional improvement, particularly if the patient is returning to multi-directional cutting and pivoting sports (Dingenen & Gokeler, 2017).

Should healthy control data be used as a reference group?

The LSIs on all four tests at the one-year post-ACLR assessment were significantly lower than healthy controls but did not generally differ between groups at five years. At the one-year post-ACLR assessment, performance on the ACLR and contralateral limb were also lower than healthy controls for all tests, with significant deficits being observed on the single-hop test. The ACLR and contralateral limb performance on all tests were also lower than previously published normative values for those aged 18-50 years (Baltaci et al., 2012; Kemp et al., 2013; Kockum & Heijne, 2015). Together, these findings concur with previous research indicating that functional deficits can persist up to 1-2 years post-ACLR (Nagelli & Hewett, 2017; Thomee et al., 2012). Despite this, most supervised rehabilitation ceases before six months, with little evidence of ongoing plyometric or lower-limb resistance training (Ebert et al., 2018; Greenberg et al., 2018). Evidence-based interventions (van Melick et al., 2016) targeting both limbs following ACLR may need to be implemented beyond the typical 6-12-month rehabilitation period in order to restore function and reduce the risk of re-injury (Kyritsis et al., 2016; Wiggins et al., 2016). Beyond the immediate recovery following ACLR, maintenance of lower-limb exercises will also likely benefit function over the lifespan. This is particularly relevant following a joint injury where an elevated risk of early-onset post-traumatic OA exists (Culvenor et al., 2015a; Culvenor et al., 2014b; Patterson et al.,

2018). It is encouraging that functional performance in those with an ACLR at five years did not generally differ to healthy controls. However, it is likely that a sub-group of individuals with inadequate function exists. For example, at five years, 54% (n=32) and 44% (n=26) of those with an ACLR could not perform >22 one-leg rises on their ACLR and contralateral limb, respectively, placing them at even greater risk of longer-term symptomatic and radiographic OA (Culvenor et al., 2016c; Thorstensson et al., 2004).

Limitations

The findings of this study should be considered in the context of its limitations. Selection bias may be evident, as those included in the current analysis (n=59) were older than our original 110 participants (Culvenor et al., 2016d). As a result, our ACLR group was an average of two years older at baseline than the healthy control group recruited at the time. This was primarily a result of younger participants being excluded due to a second injury or being lost to follow-up at five years due to relocation and time commitments (e.g., work, family, study). Conversely, those motivated to attend follow-up may have had knee problems and functional deficits. Importantly, the between-group analyses for differences were adjusted for age (and BMI). Moreover, all participants underwent a hamstring-tendon autograft ACLR. While this limits generalisability to other graft types, there are no known differences in hop test performance or self-reported knee function between graft types (Holm et al., 2010; Li et al., 2012). Despite this, our cohort is representative of the wider ACLR population, given that the majority (88%) were participating in cutting/pivoting sports pre-injury with return-to-sport rates similar to large ACL cohorts at comparable follow-ups (Ardern et al., 2014b).

A longitudinal follow-up of the healthy control group to demonstrate potential age-related change was not included in this study. However, our comparison of functional performance between the ACLR and healthy control groups included a regression model with adjustment for age and BMI. Additionally, the scores in our healthy controls (single-hop: 135 cm, triple-crossover-hop: 393 cm, side-hop: 34 repetitions) are comparable to hop test scores for recreational athletes aged 18-50 years (Baltaci et al., 2012; Gustavsson et al., 2006; Kockum & Heijne, 2015). Further, this was a *post-hoc* analysis of a prospective cohort study and no a-priori sample size calculations were performed. While our sample size was sufficiently powered to detect a statistically significant difference in change over time between the ACLR and contralateral limb for all hop tests, we may have been underpowered to detect differences between the ACLR and contralateral limb for the one-leg rise test. While the one-leg rise between-limb difference approached statistical significance, the mean difference of 1.9 repetitions is not likely to be clinically significant.

Additionally, the one-leg rise on both limbs exhibited floor effects (scored 0) at one year (ACLR: n=8, contralateral: n=5) and five years (ACLR: n=6, contralateral: n=5) and ceiling effects (scored 50) at one year (ACLR: n=21, contralateral: n=23) and five years (ACLR: n=16, contralateral: n=17), which may have influenced our statistical analyses of change in functional performance.

5.5 Conclusion

In conclusion, the contralateral limb exhibited a significantly greater decrease in functional performance compared to the ACLR limb for the three hop tests between one and five years following ACLR. Worsening function in the contralateral limb combined with a relatively stable ACLR limb resulted in significant improvements in the LSI. Clinicians should be aware the LSI may overstate improvement in functional performance over time. Interventions should target dynamic tasks in both the ACLR and contralateral limbs, considering the deficits at one year post-ACLR compared to healthy controls (adjusted for age and BMI) and the minimal improvement observed over the proceeding four years. Exercise-based interventions may need to continue beyond the typical rehabilitation period of 6-12 months in order to restore or maintain function in both limbs, given the known influence of lower-limb function on future knee symptoms, OA development, and QoL.

6 Chapter Six: Poor functional performance one year after ACLR increases the risk of early OA progression

6.1 Preface

Chapter 1 highlighted the paucity of research investigating modifiable prognostic factors for early structural and symptomatic deterioration following ACLR. Functional performance deficits are one such modifiable factor, and Chapter 5 reported deficits in hop testing one year post-ACLR. Chapter 5 recommended that raw performance (i.e., cm hopped) should be considered when evaluating and reporting functional performance following ACLR, as the LSI may overestimate functional performance recovery. Despite the limitations of the LSI, Chapter 1 highlighted that restoring limb symmetry (>90%) on a test battery is important, as it may reduce re-injury risk. Therefore, in Chapter 6, raw ACLR limb performance and the LSI were utilised as explanatory variables to determine the influence of poor functional performance at one year post-ACLR on worsening OA features on MRI and change in PROs.

Chapter 6 contains the following publication in its entirety **(Appendix P)** with the exception of **Figure 4.1,** which is a replacement flow chart from the original publication. This is to provide consistent formatting with the flow charts of participant recruitment and retention provided throughout Part B of this thesis.

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2020). Poor functional performance 1 year after ACL reconstruction increases the risk of early osteoarthritis progression. *British Journal of Sports Medicine*, *54*(9), 546-553.

6.2 Introduction

Rupture and subsequent reconstruction of the ACL substantially increases the risk of knee OA development and poor QoL (Lohmander et al., 2004; Poulsen et al., 2019). Yet, not everyone develops OA following ACLR; radiographic OA is evident in approximately one in two (Lie et al., 2019; Oiestad et al., 2010b), and one in three will have symptomatic radiographic OA within 10-15 years of injury (Lie et al., 2019; Oiestad et al., 2010b). Magnetic resonance imaging can detect OA features within five years of ACLR (Culvenor et al., 2015a; Patterson et al., 2018; van Meer et al., 2016), and can be used to identify individuals who may be on an accelerated trajectory towards radiographic symptomatic OA (Sharma et al., 2016). Understanding modifiable factors associated with early structural changes following ACLR is a priority for informing secondary OA prevention strategies.

Impaired functional performance, often measured through hop tests, is common following ACLR (Abrams et al., 2014) and may influence the development of early knee OA and symptoms. Quadriceps weakness is a risk factor for the development of radiographic and/or symptomatic OA, based on the theory of impaired shock absorption, consequent excessive load to joint structures, and subsequent initiation of the degenerative process (Oiestad et al., 2015). Hop test batteries provide a clinically-feasible method to assess multiple aspects of lower-limb muscle function (including quadriceps strength and sensorimotor control), and may indicate a reduced ability to control mechanical loading in the knee (Gardinier et al., 2014; Palmieri-Smith & Lepley, 2015; Roos & Arden, 2016), thus influencing joint degeneration and/or potential symptoms. Functional performance impairments may also represent a lack of confidence in the limb (Hart et al., 2020) and may be reflected in reduced physical activity and worse PROs.

Following ACLR, the link between functional performance and worsening symptomatic and early structural OA outcomes is unclear. While single-hop test performance at one year post-ACLR was associated with the presence of tibiofemoral radiographic OA at 10 years in one study (Pinczewski et al., 2007), other studies have reported minimal associations between post-operative functional performance and future radiographic OA 5-15 years post-ACLR (Losciale et al., 2019; Oiestad et al., 2010b; Wellsandt et al., 2018). Prior studies have focused on radiographic tibiofemoral OA, and have not evaluated early structural *change* (i.e., worsening) in individual joint features. Despite the patellofemoral joint being burdensome post-ACLR (Culvenor et al., 2016d; Culvenor et al., 2014b), few studies consider the patellofemoral joint structure. Further, radiographic measures lack the sensitivity to detect early structural changes which are identifiable on MRI over shorter follow-up periods (Hunter et al., 2011c; Pollard et al., 2008). No studies have reported the

relationships between functional performance and early (<five years) structural changes on MRI in an ACLR population.

Evaluation of risk factors for early OA following ACLR should also include concurrent assessment of change in PROs, given the discordance between knee imaging findings and symptoms (Patterson et al., 2020c; Yusuf et al., 2011). Functional performance may exhibit differing relationships with change in individual early OA features and PROs. Functional performance deficits at the time of return-to-sport are often associated with worse PROs 2-3 years post-ACLR (Bodkin et al., 2017; Culvenor et al., 2016c; Grindem et al., 2011; Logerstedt et al., 2012; Losciale et al., 2019; Menzer et al., 2017), with few studies evaluating changes in PROs beyond three years due to cross-sectional study designs. It is this change in patient-reported and structural outcomes that equates to the problematic accelerated trajectory of symptomatic OA in young adults post-ACLR.

If early functional impairments are related to worsening structural or symptomatic OA, functional deficits can be targeted through exercise therapy to halt or slow the trajectory towards radiographic symptomatic OA. The aim of the current study was to determine if functional performance one year post-ACLR is associated with risk of worsening patellofemoral and tibiofemoral OA features on MRI and change in PROs between one and five years.

6.3 Methods

6.3.1 Study design and participants

A longitudinal prospective cohort study assessed the trajectory of PROs, functional performance, and early OA features one to five years post-ACLR. Individuals assessed one year post-ACLR (n=111; 64% male, median age 27 years (range 19-51 years)) (Culvenor et al., 2015a) were eligible for the five-year assessment. Descriptions of eligibility criteria at one year post-ACLR, ACLR technique, and post-operative rehabilitation are provided in Chapter 2. Briefly, all participants underwent primary single-bundle hamstring-tendon autograft ACLR. The exclusion criteria were: knee injury/symptoms prior to ACL injury, >five years between ACL injury and reconstruction, and any secondary injury/surgery to the ACLR knee (between ACLR and one year post-ACLR). Participants with a secondary injury between one and five years were invited to participate in the five-year assessment, as this is a common occurrence and represents the wider ACLR population. Of the 112 participants who completed PROs at one year post-ACLR, 81 (72%) completed PROs at five years. Of the 111 who underwent MRI evaluation at one year post-ACLR, 78 (70%) were re-

imaged at five years (**Figure 6.1**). Ethical approval was granted (La Trobe University Human Ethics Committee HEC15-100) and all participants signed informed consent.

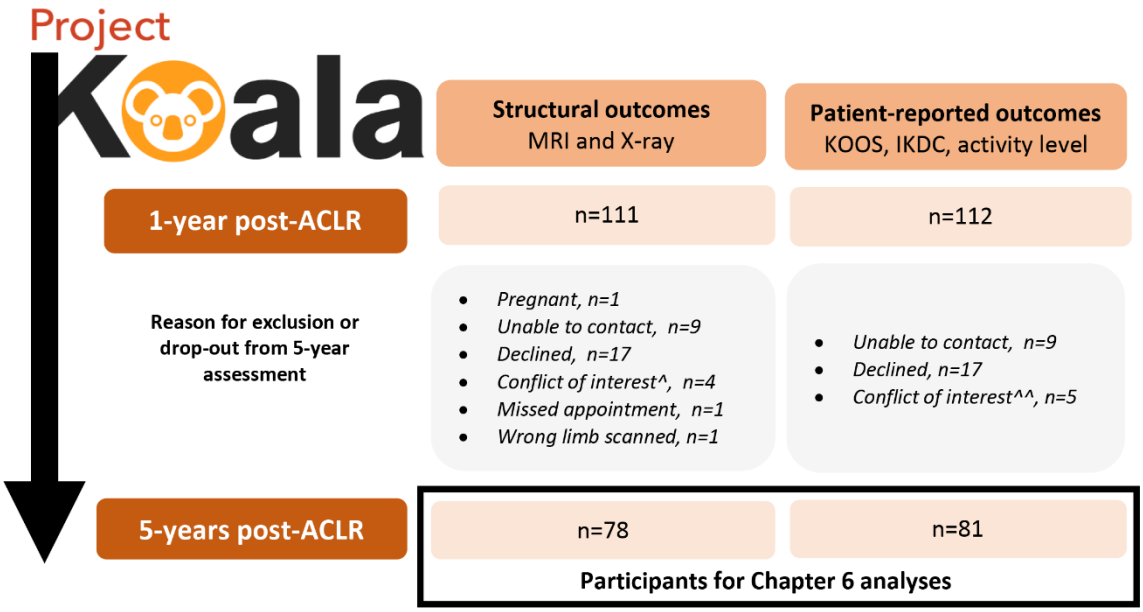


Figure 6.1 KOALA cohort participant recruitment and retention for Chapter 6.

ACLR=anterior cruciate ligament reconstruction; KOALA=Knee Osteoarthritis Anterior cruciate ligament Longitudinal Assessment cohort study; KOOS=Knee injury and Osteoarthritis Outcome Score; IKDC=International Knee Documentation Committee knee evaluation; MRI=magnetic resonance imaging; n=number of participants.
^ n=4 due to participation in another study.
^^ n=4 due to participation in another study and n=1 became a member of the research team at 5 years.

6.3.2 Demographic, injury, and surgical factors

Participant age, sex, height, weight, injury history, and activity level (defined as level 1 pivoting/jumping sports to level 4 sedentary (Grindem et al., 2014)) were obtained at the one- and five-year assessments. Participants were classified as having a "combined injury" if they had (at the time of ACLR): (i) significant cartilage defect identified arthroscopically (Outerbridge grade ≥2) (Marx et al., 2005) or (ii) surgical resection or repair of the meniscus. To determine the presence of tibiofemoral and patellofemoral OA in the ACLR limb, posteroanterior and lateral weight-bearing and non-weight-bearing skyline views were taken, and were graded according to the OARSI atlas definitions (Altman et al., 1995). Radiographic OA was defined as joint space narrowing of grade ≥2, sum of osteophytes ≥2, or grade 1 osteophyte in combination with grade 1 joint space narrowing (Altman et al., 1995).

6.3.3 Functional performance

At one and five years following ACLR, participants completed a battery of functional tests in the following order: single-hop, triple-crossover hop, side-hop, and one-leg rise. The left leg was always tested first after two to three practice trials. The single-hop assessed the maximum distance (cm) achieved from a stationary position with a balanced landing (≥2 seconds without placing the other foot to the floor) (Gustavsson et al., 2006). The triple-crossover hop assessed the cumulative distance (cm) achieved with three consecutive hops with a balanced landing, with each hop crossing over two parallel lines 15 cm apart (Reid et al., 2007). Hops were repeated for the single-hop and triple-crossover until three successful trials were recorded and until no increase in distance was seen, due to the known learning effects (Munro & Herrington, 2011). The side-hop assessed the number of hops over two parallel lines 40 cm apart in 30 seconds (Gustavsson et al., 2006). The one-leg rise assessed the maximum number of times (up to 50) the participant was able to rise on one leg from 90° knee flexion, at a consistent speed of 45 beats per minute (using a metronome) (Thorstensson et al., 2004). The hop tests and one-leg rise test were scored 0 if the participant was unable (due to lack of strength/balance/confidence) to perform one successful trial. The test was stopped if the participant received three warnings for deviating from speed or touching the ground with the opposite foot. The one-leg rise was added to the traditional battery of hops as it also assesses endurance and has been associated with the development of radiographic OA in those with chronic knee pain (Thorstensson et al., 2004).

The raw score (i.e., distance hopped) and LSI (% score of ACLR knee ÷ contralateral knee) were recorded for each test. Poor functional performance on an individual test was defined as <90% LSI, a common benchmark used to define return-to-sport readiness (Abrams et al., 2014; Burgi et al., 2019), and is associated with risk of re-injury (Grindem et al., 2016; Kyritsis et al., 2016). Poor function on the battery was defined as <90% LSI on all four tests, to specifically capture individuals with poor function.

6.3.4 OA features on MRI

At one and five years following ACLR, participants had unilateral (index) knee MRI scans acquired using a single 3T system (Philips Achieva, The Netherlands), as described in Chapter 2. The 3D proton-density weighted VISTA sequence was acquired at 0.35 mm isotropically (TR/TE 1,300 msec/27 msec, FOV 150 mm^2, and echo train length 64 msec) and reconstructed in the coronal and axial planes. The sagittal short-tau inversion-recovery sequence was at 2.5 mm thickness; 1.2 mm slice gap and an inversion time of 180 msec were applied with TR/TE 3,850 msec/30 msec, FOV 160 mm^2, and voxel size 0.45 x 0.50 x 2.5 mm. The axial proton-density turbo spin-echo sequence was obtained with the imaging parameters of TR/TE 3,850 msec/34 msec, slice thickness

2.5 mm, slice gap 2.0 mm, corresponding voxel size 0.5 x 0.55 x 2.5 mm, and FOV 140 mm^2. All MRI scans were evaluated using the MOAKS by a musculoskeletal radiologist (AG) with 19 years' experience in semi-quantitative MRI analysis of knee OA and established inter- and intra-rater reliability (kappa 0.61-0.80) (Hunter et al., 2011a). The one- and five-year images were read paired (not blinded to time-points), but blind to clinical information. The MOAKS divides the knee into subregions to score specific OA features. For the current study, cartilage lesions, BMLs, and meniscal lesions were semi-quantitatively graded.

Four subregions defined the patellofemoral joint (medial and lateral patella, medial and lateral trochlea) and 10 subregions defined the tibiofemoral joint (medial and lateral: femur central and posterior, tibia anterior, central and posterior). For grading of meniscal lesions, six subregions (medial and lateral: anterior, posterior and central) were combined. Cartilage lesions and BMLs were graded from 0 to 3 based on size (percentage of surface area relative to each subregion; where 0=none, 1=<33%, 2=33–66%, 3=>66%). Cartilage lesions were also scored on severity based on the depth of the lesion (percentage of lesion that is full thickness; 0=no full-thickness loss, 1=<10%, 2=10-75%, 3=>75%). A meniscal tear was defined as an area of abnormal signal that extended to both meniscal articular surfaces, and meniscal macerations were defined as loss of morphologic substance of the meniscus. Meniscal lesions were described as absent or present, and by type (a tear was either vertical, horizontal, or complex; maceration was partial, progressive, or complete). These abnormalities were scored according to the MOAKS scoring system. Meniscal extrusion was graded by size (0 (<2 mm), 1 (2–2.9 mm), 2 (3–4.9 mm), or 3 (>5 mm)) in each of the subregions. Meniscal extrusion, while based on the amount of extrusion in mm, was also scored using the MOAKS.

Worsening OA features in each subregion was defined as any increase in the size or severity of the feature. Therefore, either progression of an OA feature (i.e., increase in severity) or a new OA feature (i.e., from absent to present) from one year to five years was classified as worsening. New OA features were defined as those with size=0 at one year and size $\geq$1 at five years. Increase in severity was defined as an increase in the size or depth of an existing OA feature at one year by ≥1 point on the MOAKS. Worsening OA features in the patellofemoral and tibiofemoral compartment were defined as worsening in any corresponding subregion for that compartment, as described in Chapter 2. This definition of worsening is reliable and sensitive to change in ACL-injured individuals (Patterson et al., 2018; van Meer et al., 2016).

6.3.5 Patient-reported-outcomes

Participants completed the KOOS and the IKDC subjective knee form one and five years following ACLR, with respect to their knee condition during the previous week. The KOOS and IKDC have established reliability and validity in people with ACL injuries (Collins et al., 2011). Four of the five subscales of the KOOS were assessed (activities of daily living subscale excluded due to ceiling effects in ACL populations). The scales were completed by pen and paper or via an online portal (MySQL, Oracle Corporation, California, USA and Promptus, DS PRIMA, Melbourne, Australia) with matching instructions to the original paper version, as described in Chapter 2. The KOOS and IKDC raw scores were recorded and converted to a percentile score, with 100 being the best possible score (i.e., no knee problems). The absolute change (five-year score minus one-year score) was calculated for each subscale (a negative value indicating worsening knee problems).

6.3.6 Statistical analyses

Generalised linear models with Poisson regression and GEE (accounting for correlations between subregions within the same participant) assessed whether functional performance at the one-year post-ACLR assessment (both as a dichotomous [poor function=<90%LSI] and a continuous [ACLR limb raw score in cm/repetitions] variable) was associated with risk of worsening OA features on MRI. Risk ratios (RR) and 95% CIs were calculated. A RR >1.0 represents an increased risk of worsening OA features in the presence of poor functional performance (<90% LSI) or a lower functional performance score (i.e., fewer repetitions). The GEE regression was adjusted for presence of a combined injury (noted at the time of ACLR, or secondary injury to the index knee), and one-year age, sex, height, and weight, due to their potential influences on function and OA features on MRI (Ackerman et al., 2018). Linear regression (β, 95% CI) determined the relationship between one-year functional performance and change in KOOS/IKDC scores between one and five years (adjusted for combined injury (noted at time of ACLR, or secondary injury to the index or contralateral knee), one-year age, sex, height, and weight, and one-year KOOS/IKDC score, due to their potential to influence function and PROs (Patterson et al., 2020c)). Analyses were performed using Stata V.14.2 with α=0.05.

6.4 Results

The characteristics of the 81 participants who completed PROs at one and five years are provided in **Table 6.1**. Of the 81 participants, 10 (12%) had poor functional performance (<90% LSI) on all four tests, while only 14 (18%) would have passed the test battery (>90% on all four tests) at one year post-ACLR. The proportion of participants with <90% LSI on individual tests and the functional performance outcomes are presented in **Table 6.2**. Of the 78 participants with radiographs at the five-year assessment, the prevalence of any radiographic OA increased from 6% to 19% between

one and five years (**Table 6.1**). In those with poor function on the battery at the one-year assessment (n=9/78), 33% (n=3) had patellofemoral or tibiofemoral radiographic OA at the five-year assessment.

Table 6.1. Participant characteristics at one and five years following ACLR

	Participants at 1 year post-ACLR (n=81)	**Participants at 5 years post-ACLR (n=81)**
Age, median±IQR years	28±14	32±14
Male Sex, no. (%)	50 (62)	50 (62)
Body Mass Index, median±IQR kg/m^2	25.7±4.2	26.4±5.0
Pre-Injury activity level 1 sport◊, no. (%)	56 (69)	56 (69)
Time injury to surgery, median±IQR weeks	14±20	14±20
Combined injuryϑ**,** no. (%)	40 (49)	46 (57)
New knee injuries, no. (%)	0 (0)*	16 (20)
ACLR limb✪	0 (0)*	10 (11)
Contralateral limb★	0 (0)*	6 (7)
Returned to Level 1 sports◊, no. (%)	20 (25)	26 (32)
Radiographic OA, no. (%)**	5 (6)	15 (19)
Patellofemoral	4 (5)	14 (18)
Tibiofemoral	2 (3)	6 (8)

ACLR=anterior cruciate ligament reconstruction; IQR=interquartile range; OA=osteoarthritis.
◊ Level 1 sport=jumping/cutting/pivoting as per Grindem et al. (2012) classification.
ϑ Participants were defined as a combined injury at 1 and 5 years if they had a significant cartilage defect and/or meniscectomy assessed/performed at the time of ACLR. Those who had a secondary injury to the index knee between 1 and 5 years were added to the combined injury group at 5 years.
✪5-year new ACLR limb knee injuries/surgery n=10 (n=3 ACLR revision, n=6 meniscectomy, n=1 lateral collateral ligament sprain).
★5-year new contralateral limb knee injuries/surgery n=6 (combined: n=2 ACLR, n=1 meniscectomy, isolated: n=1 ACLR, n=1 meniscectomy, n=1 lateral collateral sprain).
* No new knee injuries were reported at 1 year as this was an exclusion criterion at the 1-year post-ACLR assessment.
**n=78 completed imaging assessment; the characteristics of these participants are reported in Chapter 4.

Table 6.2. Functional performance one year post-ACLR~

	Raw score	LSI %
Single-hop, median±IQR (range) cm	108±40 (3 to 169)	92±15 (4 to 109)
≥90% LSI (n=50/81)	119±27 (71 to 169)	96±6 (90 to 109)
<90% LSI (n= 31/81)	85±34 (3 to 142)	79±17 (4 to 88)
Triple-crossover hop, median±IQR (range) cm	337±130 (0 to 569)*	95±11 (0 to 129)
≥90% LSI (n=55/81)	383±119 (146 to 569)	98±5 (90 to 129)
<90% LSI (n= 26/81)	262±83 (0 to 403)	79±11 (0 to 89)
Side-hop, median±IQR (range) repetitions	25±17 (0 to 63)*	83±28 (0 to 156)
≥90% LSI (n=29/81)	29±13 (14 to 63)	100±11 (90 to 155)
<90% LSI (n=52/81)	23±18 (0 to 51)	70±20 (0 to 89)
One-leg rise, median±IQR (range) repetitions	26±39 (0 to 50)*	96±40 (0 to 167)
≥90% LSI (n=40/76)	50±8 (5 to 50)	100±0 (92 to 325)
<90% LSI (n= 36/76)	12±15 (0 to 43)	59±36 (0 to 89)

cm=centimetres; IQR=interquartile range; LSI=limb symmetry index.
~n=81 completed functional performance assessment at 1 year and PROs at 1 and 5 years. n=76 for the one-leg rise as 5 participants were excluded as they could not perform a valid test on either limb.
*some participants had a score of 0 for the ACLR limb for the triple-crossover hop (n=1), side-hop (n=5), and one-leg rise (n=8).

6.4.1 Imaging outcomes

Worsening compartment-specific OA features on MRI and radiographic OA prevalence are reported in detail in Chapter 4 (Patterson et al., 2018). Briefly, patellofemoral and tibiofemoral cartilage worsening (34 (44%) and 16 (21%) participants, respectively) was more common than BML worsening (14 (18%) and 12 (15%) participants, respectively). Seventeen (22%) participants displayed worsening meniscal lesions. Five (6%) participants displayed worsening of all three features, while 20 (26%), 4 (5%), and 7 (9%) had isolated cartilage, BML, and meniscal worsening, respectively. Worsening osteophytes were not included in the current study due to low numbers in the patellofemoral (n=7) and tibiofemoral (n=9) compartments (Patterson et al., 2018).

6.4.2 Functional performance and risk of worsening early OA features

Poor functional performance on the test battery (<90% on all four tests) resulted in an increased risk of worsening patellofemoral BMLs (RR 3.66; 95%CI: 1.12, 12.01) (**Table 6.3**). The majority (86%) of those with a worsening patellofemoral BML had <90% LSI on the side-hop (**Figure 6.2**). Individuals with <90% LSI on the triple-crossover hop-for-distance had an increased risk of worsening patellofemoral cartilage lesions (RR 2.09; 95%CI 1.15, 3.81). Individuals with <90% LSI on the single-hop, side-hop, and one-leg-rise had an increased risk of worsening patellofemoral BMLs (RR 4.17; 95%CI: 1.37, 12.72; RR: 3.77; 95%CI 1.15, 12.43; and RR: 2.92; 95%CI 1.19, 7.18, respectively). Fewer side-hop repetitions was associated with an increased risk of worsening patellofemoral BMLs (RR 1.08; 95% CI: 1.15, 12.43). In contrast, fewer one-leg rises was associated

with a small reduction in risk of worsening tibiofemoral cartilage lesions (RR 0.96; 95% CI: 0.94, 0.99) (**Table 6.3**).

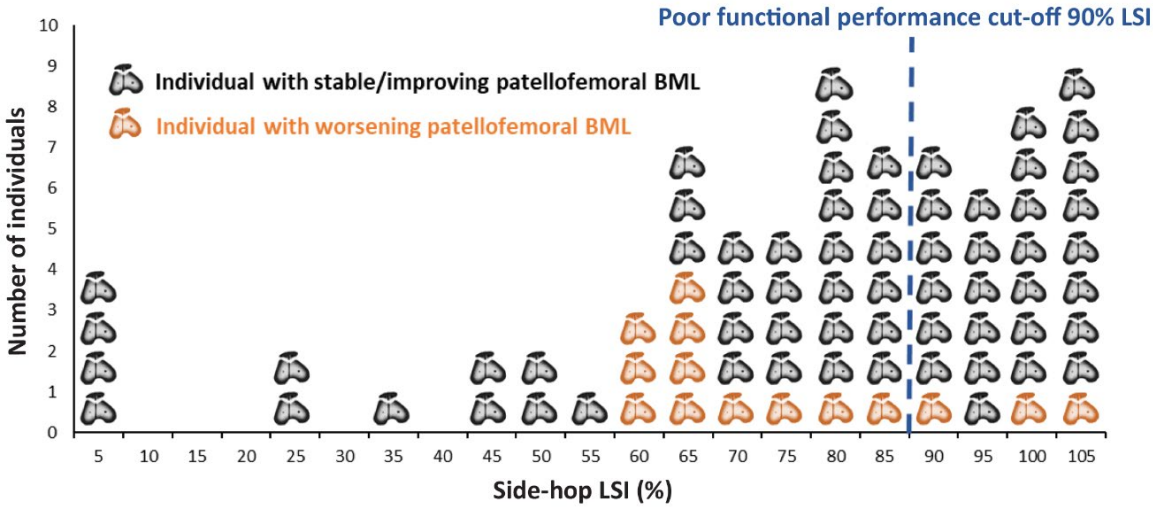


Figure 6.2 Individuals with and without change in patellofemoral BMLs and respective side-hop LSI*.

BMLs=bone marrow lesions; LSI=limb symmetry index.
*LSI scores are presented in categories of 0-5%, 5-10%, etc. in increasing increments of 5% for the purpose of visualisation.

6.4.3 Functional performance relationship with KOOS and IKDC.

The one- and five-years KOOS and IKDC scores (n=81) have been reported in detail previously (Patterson et al., 2020c). Significant ($p<0.05$) improvement (i.e., less knee symptoms, better function and QoL) was observed for all KOOS subscales (except KOOS-Symptoms) and IKDC between one and five years (Patterson et al., 2020c). The mean±standard deviation changes were: Pain: 2.8±9; Symptoms: 0.5±16.1; Sport: 6.0±18.2; QoL: 10.0±18.9; IKDC 4.7±10.9. Generally, functional performance one year post-ACLR was not associated with change in KOOS or IKDC scores between one and five years (**Table 6.4**). Participants with <90% LSI for the side-hop test had a mean KOOS-QoL change value 8 points higher (β: 8.08; 95%CI: 1.56, 14.61), as compared to those with >90% LSI for the side-hop test.

Table 6.3. Functional performance at one year post-ACLR: Associations with risk of worsening early OA features on MRI between one and five years~

		Worsening early OA features on MRI				
		PF Cartilage *n=34/78(44%)*	**PF BML** *n=14/78 (18%)*	**TF Cartilage** *n=16/78 (21%)*	**TF BML** *n=12/78 (15%)*	**TF Meniscal** *n=17/78 (22%)*
Single-hop	*No. (%)*					
Raw score (cm)^		1.00 (0.99, 1.01)	1.01 (0.98, 1.03)	0.98 (0.96, 1.01)	1.00 (0.97, 1.03)	0.98 (0.96, 1.02)
Poor function (ref ≥90% LSI)^^	*31(38%)*	1.26 (0.66, 2.41)	**4.17 (1.37, 12.72)**	0.69 (0.21, 2.35)	0.68 (0.20, 2.31)	1.65 (0.62, 4.44)
Triple-crossover hop						
Raw score (cm)^		1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)
Poor function (ref ≥90% LSI)^^	*25(32%)*	**2.09 (1.15, 3.81)**	2.60 (0.79, 8.62)	1.02 (0.31, 3.38)	1.02 (0.29, 3.57)	1.76 (0.52, 6.01)
Side-hop						
Raw score (repetitions)^		1.01 (0.98, 1.05)	**1.08 (1.01, 1.15)**	0.96 (0.91, 1.02)	1.00 (0.95, 1.06)	0.97 (0.92, 1.02)
Poor function (ref ≥90% LSI)^^	*49(63%)*	1.02 (0.51, 2.03)	**3.77 (1.15, 12.43)**	1.10 (0.47, 2.60)	1.69 (0.34, 8.45)	0.89 (0.35, 2.28)
One-leg-rise						
Raw score (repetitions)^		1.01 (0.99, 1.02)	1.02 (0.99, 1.05)	**0.96 (0.94, 0.99)**	0.99 (0.94, 1.04)	0.98 (0.95, 1.02)
Poor function (ref ≥90% LSI)^^	*35(48%)*	1.32 (0.72, 2.41)	**2.92 (1.19, 7.18)**	0.30 (0.08, 1.05)	0.58 (0.19, 1.78)	0.98 (0.33, 2.93)
Functional battery^^						
Poor function all 4 tests* (ref ≥90% LSI ≥ any 1 test)	*9(12%)*	1.99 (0.92, 4.30)	**3.66 (1.12, 12.01)**	n.a[#]	1.32 (0.30, 5.78)	1.25 (0.32, 4.88)

BML=bone marrow lesion; cm=centimetres; LSI=limb symmetry index; MRI=magnetic resonance imaging; n=number of participants with worsening; PF=patellofemoral; TF=tibiofemoral.

~Bold values indicate a statistically significant association (p<0.05). Values are risk ratios (RR) (95% confidence intervals). Analysis performed in n=78 who completed functional assessment at 1 year and MRI and X-ray evaluations at 1 and 5 years. n=73 for the one-leg rise and battery LSI% as 5 participants were not included because they could not perform a valid one-leg rise on both the ACLR and contralateral limb.

^For continuous exposure variables (raw score in cm or repetitions in ACLR limb), a RR >1 represents greater risk of worsening OA feature in the presence of lower functional performance (i.e., less distance or fewer repetitions). For example, a one-repetition decrease on the side-hop test could be interpreted as having a 7% increased risk of worsening patellofemoral BMLs.

^^For dichotomous exposure variables (poor function defined as <90% LSI), a RR >1 represents a greater risk of worsening OA feature in the presence of poor function. For example, individuals with <90% LSI on the one-leg-rise were 2.92 times more likely to have worsening patellofemoral BMLs than those with >90% LSI.

[#]Unable to perform analysis as all participants with <90% on the functional performance battery had TF cartilage defect worsening.

Table 6.4. Functional performance at one year post-ACLR: Associations with change in KOOS and IKDC between one and five years~

		Change in KOOS and IKDC between 1- and 5-years				
		KOOS-Symptoms	**KOOS-Pain**	**KOOS-Sport**	**KOOS-QoL**	**IKDC**
Single-hop	*No. (%)*					
Raw score (cm)^		0.05 (-0.09, 0.19)	-0.06 (-0.13, 0.01)	-0.11 (-0.27, 0.05)	-0.03 (-0.18, 0.12)	-0.02 (-0.12, 0.08)
Poor function (ref >90% LSI)^^	*31(38%)*	1.35(-5.70, 8.41)	-2.57 (-6.08, 0.94)	-1.68 (-9.04, 5.67)	-1.81 (-9.01, 5.41)	-1.27 (-6.07, 3.52)
Triple-crossover hop						
Raw score (cm) ^		0.02 (-0.02, 0.07)	-0.02 (-0.05, 0.00)	-0.03 (-0.08, 0.02)	-0.01 (-0.05, 0.04)	0.00 (-0.03, 0.03)
Poor function (ref >90% LSI)^^	*26(32%)*	2.56 (-4.30, 9.42)	-3.14 (-6.65, 0.37)	-3.14 (-6.65, 0.37)	-3.40 (-10.27, 3.46)	0.38 (-4.17, 4.94)
Side-hop						
Raw score (repetitions)^		0.22 (-0.08, 0.52)	0.06 (-0.22, 0.10)	-0.07 (-0.40, 0.27)	0.08 (-0.24, 0.40)	0.07 (-0.15, 0.28)
Poor function (ref >90% LSI)^^	*52(64%)*	5.50 (-1.23, 12.24)	2.97 (-0.43, 6.37)	2.96 (-0.44, 6.37)	**8.08 (1.56, 14.61)**	1.27 (-3.08, 5.63)
One-leg-rise						
Raw score (repetitions)^		-0.08 (-0.11, 0.26)	0.00 (-0.10, 0.10)	-0.04 (-0.25, 0.18)	0.09 (-0.10, 0.29)	0.09 (-0.04, 0.22)
Poor function (ref >90% LSI)^^	*36(47%)*	2.92 (-3.72, 9.58)	0.45 (-3.07, 3.97)	0.45 (-3.08, 3.97)	6.19 (-0.75, 13.15)	3.79 (-0.62, 8.21)
Functional battery^^						
Poor function all 4 tests* **(ref ≥90% LSI ≥ any 1 test)**	10 (13%)	-2.78 (-12.44, 6.88)	-3.00 (-7.80, 1.79)	0.30 (-11.23, 11.83)	0.47(-9.66, 10.61)	-0.05 (-6.64, 6.54)

cm=centimetres; IKDC=International Knee Documentation Committee subjective knee evaluation; KOOS=Knee injury and Osteoarthritis Outcome Score; LSI=limb symmetry index; QoL=quality of life.

~ **Bold** values indicate a statistically significant association (p<0.05). Values are beta co-efficient (95% confidence intervals). Analysis performed in n=81 who completed functional assessment at 1 year and both KOOS and IKDC at 1 and 5 years. n=76 for the one-leg rise and battery LSI% as 5 participants were not included because they could not perform a valid one-leg rise on both ACLR and contralateral limb.

^ The beta coefficient represents the adjusted difference in KOOS or IKDC change score per unit decrease in the continuous exposure variables. (i.e., cm or number of side-hop repetitions, ACLR limb).

^^ The beta coefficient represents the adjusted difference in KOOS or IKDC in the presence of the dichotomous exposure variable (i.e., poor function defined as <90% LSI). For example, those with <90% LSI had an average of 8.08 points greater improvement on the KOOS-QoL than those with >90%.

6.5 Discussion

Only one in five participants met common functional performance criteria (≥90% LSI on all hopping and one-leg rise tests) one year following ACLR – a time when function is typically expected to be restored. In this first evaluation of the implications of not meeting functional performance criteria on early OA outcomes following ACLR, poor function (<90% LSI) was consistently associated with 2-4 times increased risk of worsening patellofemoral BMLs. Performance on the triple-crossover hop was associated with worsening patellofemoral cartilage over the subsequent four years. However, the regression models had wide CIs, and there were weak/no associations were generally observed between poor function and tibiofemoral cartilage, bone marrow, and meniscal lesions as well as changes in PROs. Further studies are required to validate an association between worse functional performance and degenerative joint changes after ACLR.

Poor function and risk of worsening patellofemoral OA features

Poor functional performance was associated with an increased risk of worsening patellofemoral OA features, particularly BMLs. An LSI <90% on all four tests in the battery was associated with 3.66 times greater risk of worsening patellofemoral BMLs. When considered as a continuous variable (i.e., number of repetitions), the side-hop test was associated with worsening patellofemoral BMLs – each one repetition decrease on the side-hop test was associated with an 8% increased risk of worsening patellofemoral BMLs (RR: 1.08). Given the associations between BMLs and incident symptoms, future damage to adjacent features (i.e., cartilage), and incident radiographic OA (Hunter et al., 2006b; Lo et al., 2009; Sharma et al., 2016), these findings may help identify individuals on an accelerated trajectory towards radiographic OA (Sharma et al., 2016). There is a need to validate the findings of this study in larger cohorts due to the wide CIs for the worsening patellofemoral OA features risk estimates.

Future studies must determine which factors influence functional recovery if worse function is prognostic for early degenerative changes. Previous cross-sectional evaluations of this cohort at one year post-ACLR found that worse hop test performance at one year post-ACLR was associated with patellofemoral pain, kinesiophobia, lower psychological readiness for return-to-sport, and worse knee confidence (Culvenor et al., 2016d; Hart et al., 2020). Other factors that have been linked to functional recovery following ACLR, such as motivation, stress, and self-efficacy (Everhart et al., 2015), may also be important to target during supervised rehabilitation (Ebert et al., 2018)

in order to optimise function. Future interventional studies should determine if improving functional performance can positively impact longer-term patellofemoral joint health.

Do tibiofemoral and patellofemoral post-traumatic OA have different risk profiles?

Functional performance one year post-ACLR had little association with worsening tibiofemoral OA features in the following four years, concurring with other studies reporting minimal associations between greater post-operative function or muscle strength and tibiofemoral radiographic OA 5-15 years later (Oiestad et al., 2010b; Wellsandt et al., 2018). Factors associated with the development and/or progression of OA may differ between the tibiofemoral and patellofemoral compartments. Our results extend those from older non-traumatic OA populations, where lower-limb function (i.e., quadriceps muscle strength) was more strongly associated with risk of patellofemoral disease progression than tibiofemoral (Amin et al., 2009; Culvenor et al., 2019c). In contrast to patellofemoral disease worsening, our results indicate that poorer function (fewer one-leg-rises) reduced the risk of tibiofemoral disease worsening. The mechanism underpinning this inverse (and unexpected) relationship is uncertain but is consistent with results in military recruits (aged 18), where lower quadriceps strength reduced the incidence of tibiofemoral OA 20 years later (Turkiewicz et al., 2017). Taken together with the demographic and surgical-related factors, which display compartment-specific relationships with post-traumatic OA progression (Patterson et al., 2020c; Patterson et al., 2018; van Meer et al., 2015), future studies should evaluate the patellofemoral and tibiofemoral compartments independently to determine distinct risk profiles - particularly as they may have differing impacts on disease burden (Culvenor et al., 2014b). For example, patellar alignment (lateral patellar displacement) was weakly associated with worsening patellofemoral cartilage in this cohort (Macri et al., 2019) – although, when added as a covariate to the current statistical models, the relationships between function and worsening patellofemoral bone marrow and cartilage lesions did not change (data not shown). There is emerging appreciation of the greater risk of early (Culvenor et al., 2015a; Patterson et al., 2018) and longer-term radiographic patellofemoral OA (Culvenor et al., 2013), and potential contribution to symptoms (Culvenor et al., 2014b), compared to tibiofemoral OA.

Challenges in predicting PROs

Functional performance one year post-ACLR was mostly not associated with change in PROs between one and five years. The only significant finding was that individuals with poor function (<90% LSI) on the side-hop test had an 8 point greater improvement in KOOS-QoL compared with those with good function (>90% LSI). Due to a low proportion (12%) of participants scoring <90%

LSI on all four tests, a sensitivity analysis was performed to calculate the RRs for poor function (<90% LSI) on *any* 1, 2, or 3 tests, or *at least* 1, 2, or 3 tests (i.e., at least 2=all participants with 2, 3, or 4 tests <90% LSI) (Supplementary File A **– in Appendix Q**). Similarly, poor function at one year on *any* or *at least* 2 tests was associated with 8-12 points greater improvement in KOOS scores. While 8-12 points approaches a clinically meaningful difference for the KOOS (≥8-10 points) (Collins et al., 2011), these results should be interpreted with caution. Individuals with poor function one year post-ACLR have greater potential for future improvement in physical and self-reported function, compared to those who have already restored good function. Only 7 (9%) participants had a KOOS-QoL >90 at the one-year assessment, demonstrating that the majority of the cohort had not reached a ceiling point, and may continue to improve between one and five years.

The only other study to evaluate the relationship between function at the time of return-to-sport and PROs beyond two years reported conflicting findings (Ericsson et al., 2013). Greater between limb asymmetry on the one-leg rise 6-15 months post-ACL injury was associated with worse KOOS scores at five years (Ericsson et al., 2013). Due to the multifactorial fluctuating nature of life for a young active adult, it is likely that many other subjective factors influence change in KOOS and IKDC scores; hence, predicting PROs post-ACLR is challenging (An et al., 2017; Losciale et al., 2019). Further research should consider the potential psychosocial and contextual influences on PROs, such as fear avoidance, confidence, coping, and healthcare utilisation (Ardern et al., 2016; Ardern et al., 2014a; Feucht et al., 2016; Grindem et al., 2018; Hart et al., 2015).

Limitations

This prospective study lost 31 (28%) participants between one and five years. However, there were no significant differences in pre-injury activity level, age, sex, BMI at the one-year assessment, or combined injury presence at the time of ACLR, between those who did and did not participate in the five-year assessment (Patterson et al., 2018). The current study included 6 (8%) participants who did not participate in jumping or cutting sports pre-injury (i.e. Level 3 or 4) (Grindem et al., 2014), which may have influenced the raw hop test scores at one year. The current study may also have been underpowered to detect potential relationships with functional performance for some outcome variables (i.e., tibiofemoral worsening), affecting the statistical stability of some regression models. Future approaches should combine large sets of individual-level data from multiple sites to provide sufficient power to detect risk factors and develop a risk profile for early OA development and progression in this young active population. Mechanical (e.g., movement

patterns (Culvenor et al., 2016e), physical activity (Culvenor et al., 2017a; Oiestad et al., 2018; Whittaker & Roos, 2019), time from injury to ACLR (Patterson et al., 2018)) and systemic factors (e.g., adiposity) (Toomey et al., 2017) may also influence the development of post-traumatic OA (Whittaker & Roos, 2019) and warrant consideration in future risk profiles.

The LSI has inherent limitations and may overestimate knee function due to the bilateral neuromuscular deficits observed post-ACLR (Wellsandt et al., 2017). Also, the use of a discrete cut-off (i.e., >90% LSI) as an independent risk factor may result in overestimation of risk estimates (Carey et al., 2018). Therefore, both the magnitude of performance as a continuous outcome (repetitions or distance) as well as symmetry (LSI%) were included, with generally a closer association observed between worsening OA features and dichotomised outcomes (<90%LSI). A floor effect for the functional performance tests should be noted as some participants scored 0 on their ACLR limb (**Table 6.2**), with reasons (anecdotally reported) such as lack of physical capability (strength/power/control) or confidence to attempt the task. Future studies should explore reasons for poor functional performance in order to better direct intervention strategies.

Clinical considerations

Despite the limitations of the LSI, better limb symmetry in hop tests has been associated with greater likelihood of return-to-sport and reduced re-injury risk (Ardern et al., 2015; Kyritsis et al., 2016). Our results show that restoring limb symmetry is also an attractive intervention target, given that only 18% "passed" the test battery (>90% LSI all four tests), and poor function was associated with increased risk of worsening patellofemoral bone marrow and cartilage lesions. Our sensitivity analyses (Supplementary File A, Table 1 - in **Appendix Q**) demonstrated that the highest RRs for worsening patellofemoral cartilage, patellofemoral BMLs, and tibiofemoral meniscal lesions were observed when *any* 3 tests, or *at least* 2 or 3 tests, were failed (<90% LSI). A battery of tests assessing multiple functional domains (i.e., strength, endurance, balance) may better categorise individuals with poor functional performance, and may be more predictive of clinical outcomes (Kyritsis et al., 2016). Multi-faceted neuromuscular deficits may affect joint loading (Gardinier et al., 2014), and consequently, joint health. Regardless of return-to-sport aspirations, continuing rehabilitation to achieve "functional criteria" on a test battery may optimise future joint health. Future studies should continue to investigate the relationships between symptomatic and structural changes in a post-traumatic OA population following ACLR. Underlying early stages of OA without the presence of symptoms may not be "incidental" in those at risk of OA, and may lead to future symptomatic radiographic OA (Sharma et al., 2016).

6.6 Conclusion

Only one in five participants met common functional performance criteria (≥90% LSI all four tests) one year post-ACLR. Poor function was consistently associated with 2-4 times increased risk of worsening patellofemoral (but not tibiofemoral) BMLs. These results highlight the importance of optimising function beyond the short-term re-injury risk, as functional performance may help identify individuals on an accelerated trajectory towards (patellofemoral) radiographic OA.

Part C: Rehabilitation interventions following ACLR, with consideration for those with persistent symptoms

7 Chapter Seven: Rehabilitation interventions following ACLR

7.1 Preface

Chapters 1 to 6 provide important insight into individuals with a worse prognosis, who are most likely to benefit from secondary OA prevention interventions. Part B highlighted that at least one-third of individuals will have unacceptable symptoms and QoL at one and five years following ACLR. Only one in five passed the functional performance test battery at one year following ACLR, and poor functional performance was associated with an increased risk of worsening patellofemoral OA features on MRI over the proceeding four years. The next step is to determine if rehabilitation targeting persistent impairments (e.g., functional performance) associated with worse prognosis can improve knee-related symptoms and QoL following ACLR. Chapter 7 provides an overview of the evidence base for different aspects of rehabilitation for all individuals following ACLR, irrespective of time since surgery or risk profile (e.g., age, BMI). This information will inform the content of the intervention to be evaluated in a pilot RCT in Chapter 8 (Study 5).

7.2 Evidence-based rehabilitation following ACLR

Irrespective of a patient's risk profile, rehabilitation following ACLR, focused on progressive exercise therapy and education, is critical to reduce symptoms, restore knee range of motion, restore muscular strength and function, and aid in returning to pre-injury activity levels (Andrade et al., 2019). Restoration of strength and functional performance may be an important first step in preventing the development or progression of post-traumatic OA and symptomatic decline following ACLR. Based on the best available evidence, it is recommended that rehabilitation following ACLR consist of three distinct phases:

i) early post-operative care to minimise pain and swelling and restore range of motion and normal walking gait.
ii) resistance, neuromuscular, and sport-specific exercises.
iii) graded return-to-sport.

For the purpose of this thesis, resistance training is an "umbrella" term for exercises prescribed to address muscular strength and power deficits (i.e., includes plyometrics/hopping). Muscular strength is the ability to produce force against given resistance, while muscular power is the ability to produce force at a high speed (American College of Sports Medicine, 2009). Neuromuscular training refers to exercises which aim to improve movement control, balance, coordination, muscle activation patterns, and dynamic stability (Ageberg, 2002; Ageberg & Roos, 2015). Sport-specific exercises include activities such as jogging, sprinting, agility, or kicking a ball. Exercise

therapy is the overarching term used to describe all forms of resistance, neuromuscular, and sport-specific training. Education interventions include provision of information, advice, or behavioural modification techniques that may influence patient knowledge, beliefs, and/or health behaviour. Rehabilitation aims to address impairments, and can include physical (e.g., exercise, cryotherapy) and non-physical (e.g., education) interventions.

Clinical practice guidelines (CPGs) are a systematically developed set of evidence-based recommendations to guide clinical assessment and treatment of a condition. Six peer-reviewed CPGs (formulated with a systematic review and a team of multidisciplinary experts) were published in the last 20 years, providing recommendations for post-operative rehabilitation following ACLR in adults (Andrade et al., 2019; Arroll et al., 2003; Logerstedt et al., 2017; Meuffels et al., 2012; Shea et al., 2015; van Melick et al., 2016; Wright et al., 2008). The quality and consistency of the ACLR rehabilitation recommendations from the six CPGs were evaluated with the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument (Andrade et al., 2019). The AGREE II is a 23-item tool that assesses six domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence (Agree Collaboration, 2003). The median AGREE II percentile score of the six CPGs was 63% (IQR: 48-83%), with scores under 50% indicating lower quality (Andrade et al., 2019). **Table 7.1** is adapted from Andrade et al. (2019) and summarises the recommendations for interventions following ACLR.

Consistent recommendations among CPGs include immediate range of motion exercises, resistance and neuromuscular training, and the use of patient-reported and physical outcome measures to monitor progress (Andrade et al., 2019) (**Table 7.1**). Progressive resistance and neuromuscular training from six weeks after ACLR should continue until physical and patient-reported criteria are met (Andrade et al., 2019). All other recommendations were conflicting, highlighting the need for more high-quality original research via RCTs to evaluate interventions following ACLR.

Table 7.1. Recommendations related to rehabilitation following ACLR: Based on a review of six CPGs~

	Clinical Practice Guideline						
	NZGG	**DOA**	**MOON**	**AAOS**	**KNGF**	**APTA**	**Consistency**
Year of publication	*2003*	*2012*	*2008*	*2015*	*2016*	*2017*	
Phase 1: Early post-operative*							
Immediate CPM							×
Immediate knee ROM exercises							✓
Immediate full WB as tolerated							×
Immediate post-operative bracing							×
Immediate cryotherapy							×
Neuromuscular electrostimulation							×
Phase 2: Resistance, neuromuscular, and sport-specific exercises							
Strength/neuromuscular exercises							✓
OKC restricted ROM ≥4 weeks							×
OKC full ROM ≥12 weeks							✓
Phase 3: Return-to-sport							
Criteria-based clearance using objective measures							×
Delivery methods							
Supervised rehabilitation							×
Rehabilitation can be home-based							✓
Outcome measures to monitor exercise progression							
Self-reported symptoms							✓
Self-reported function							✓
Self-reported psychological							✓
Self-reported quality of life							✓
Objective physical function							✓
Lachman/pivot shift test							✓
Activity level							✓

No recommendations
Should be used (strong recommendation to use)
May be used (according to individual circumstances)
Uncertain recommendation (recommendation was not clear to authors)
Should not be used (strong recommendation not to use)

AAOS=American Academy of Orthopaedic Surgeons (Shea et al., 2015); ACL=anterior cruciate ligament; APTA=American Physical Therapy Association (Logerstedt et al., 2017); DOA=Dutch Orthopaedic Association (Meuffels et al., 2012); KNGF=Royal Dutch Society for Physical Therapy (van Melick et al., 2016); MOON=Multicenter Orthopaedic Outcomes Network (Wright, 2008); NZGG=New Zealand Guidelines Group (Arroll et al., 2003); OKC=open kinetic chain quadriceps or hamstring strengthening exercises; ROM=range of movement; WB=weight bearing.
~ Table adapted from Andrade et al. (2019) systematic review of 6 CPGs.
*Immediate=within 1 week following ACLR.
✓Agreement amongst CPGs.
×Lack of agreement amongst CPGs.

The CPGs fail to provide clear recommendations for end-stage rehabilitation, particularly beyond 12 months following ACLR. Yet, a high proportion of individuals present with persistent symptoms (~50%), poor knee-related QoL (~50%), and functional performance deficits (~80% failed the test battery) at one year following ACLR (Part B of this thesis), consistent with other reports (Hamrin Senorski et al., 2018; Ingelsrud et al., 2015; Wellsandt et al., 2017). Those failing to fully recover in the first year may require additional rehabilitation focusing on exercise therapy and education, tailored to their individual needs. However, the benefit of ongoing resistance, neuromuscular, and sport-specific exercises beyond 12 months is unclear (Andrade et al., 2019). The CPGs provide no clear recommendations for formal education throughout rehabilitation programs following ACLR (Andrade et al., 2019), but due to the potential to positively influence outcomes (Coronado et al., 2018; Truong et al., 2020), education should be considered in future intervention trials.

To develop an evidence-based exercise therapy and education intervention for the pilot RCT in this thesis (Chapter 8), the recommendations from the CPGs and wider literature were considered, together with interventions tailored to address specific impairments.

7.3 Rehabilitation following ACLR

7.3.1 Resistance, neuromuscular, and sport-specific training

Resistance training

Resistance training for knee extensor (quadriceps) and knee flexor (hamstrings) muscles should be included (Andrade et al., 2019) to target strength and power deficits (Lisee et al., 2019a; Petersen et al., 2014; Thomas et al., 2013; Turpeinen et al., 2020) (**Table 7.2**). Quadriceps and hamstring resistance training may include open kinetic chain and/or closed kinetic chain, concentric and/or eccentric exercises (Andrade et al., 2019; Kruse et al., 2012; van Melick et al., 2016). Although the use of open kinetic chain quadriceps and hamstring strengthening exercises (particularly during the early post-operative phase) are widely debated, four of the six CPGs suggest that they may be introduced early (from four weeks) in the range of 45° to 90°, and from 12 weeks through full range (Meuffels et al., 2012; Shea et al., 2015; van Melick et al., 2016; Wright et al., 2008) (**Table 7.1**). The early and/or late introduction of open kinetic chain exercises throughout ACLR rehabilitation is safe, and does not increase anteroposterior knee laxity (Perriman et al., 2018).

Table 7.2 Rehabilitation recommendations based on evidence-based impairments and CPG recommendations

Type of intervention	INTERVENTION											
	Resistance training						Neuromuscular training			Sport-specific training		Education
Intervention target	Muscle strength and/or power[a]						Neuromuscular function			Sport-specific function		Psychosocial contextual
	Knee extensors	*Knee flexors*	*Hip**	*Calf*	*Trunk*	*Combined (e.g., hop)*	*Postural control[b]*	*Movement patterns[c]*	*Muscle activation[d]*	*E.g., fitness, speed,agility[e]*	*E.g., skill, performance[f]*	*E.g., knowledge, fear,beliefs[g]*
Deficits exist following ACLR												
Deficits up to 12 months	✓	✓	✓	?	?	✓	✓	✓	✓	?	✓	✓
Deficits >12 months	✓	✓	✓	?	?	✓	✓	✓	✓	?	✓[f]	?
Interventions to address deficits are reccommended by CPGs												
Recommended by CPGs up to 12 months	✓	✓	?	?	?	✓	✓	✓	✓	?	?	?
Recommended by CPGs >12 months	?	?	?	?	?	?	?	?	?	?	?	?

ACLR=anterior cruciate ligament reconstruction; CPGs=clinical practice guidelines; RCT=randomised controlled trial.
✓evidence exists to suggest deficits exist**;** intervention is recommended by CPG.
?evidence is limited to provide definite recommendation that deficits exist, or that interventions should be included following ACLR.
×not included in the control (trunk-focussed) intervention in Chapter 8.
*evidence to support hip extensor deficits, but not hip abductors, adductors, internal and external rotators.
[a] References: isokinetic muscle strength (Lisee et al. 2019a; Petersen et al. 2014; Thomas et al. 2013) and power (rate of force development) (Turpeinen et al. 2020), hop/jump performance (Abrams et al. 2014; Almangoush & Herrington, 2014; Thomee et al. 2012) deficits compared to the uninjured limb or healthy controls.
[b] References: single-leg stance increased postural sway and reaction time to perturbation (Abrams et al. 2014; Ageberg, 2002; Culvenor et al. 2016a; Negahban et al. 2014) compared to uninjured limb or healthy controls.
[c] References: reduced knee flexion moment and/or lower knee power absorption in walking (Hart et al. 2016; Hart et al. 2010; Kaur et al. 2016; Slater et al. 2017), running (Hart et al. 2010; Pairot-de-Fontenay et al. 2019), or single-leg landing (Johnston et al. 2018; Kotsifaki et al. 2020).
[d] References (Ageberg, 2002; He et al. 2020; Lisee et al. 2019a).
[e] References: shuttle run, carioca test, or agility tests insufficient evidence to suggest deficits exist compared to healthy populations (Abrams et al. 2014).
[f] Reference from elite population data only regarding sport-specific statistics (e.g., shooting percentage) (Mohtadi & Chan, 2018).
[g] References: psychosocial factors (e.g., confidence, social support, athletic identity, motivation, stress, fear of re-injury) (Everhart et al. 2015; Truong et al. 2020; Walker et al. 2020) and contextual factors (e.g., knowledge, beliefs, expectations) (Bennell et al. 2016; Feucht et al. 2016) are evident and associated with worse outcomes.

Resistance training for specific hip (e.g., extensors, abductors), ankle (e.g., calf), and/or trunk (e.g., core) muscle groups following ACLR is not mentioned in the CPGs (**Table 7.2**) (Andrade et al., 2019). However, recent systematic reviews reveal deficits up to 24 months following ACL injury in hip extensor strength (Petersen et al., 2014; Thomas et al., 2013) and functional performance testing (e.g., hop tests) involving muscle power and strength in all lower-limb muscle groups (Abrams et al., 2014; Almangoush & Herrington, 2014; Noyes et al., 1991; Reid et al., 2007; Thomee et al., 2012) (**Table 7.2**). Calf, hip, and trunk muscles can dissipate ground reaction forces throughout the whole kinetic chain, and provide dynamic stability at the knee (e.g., resisting knee valgus) (Ageberg, 2002; Besier et al., 2003). Considering the wider literature, quadriceps, hamstring, calf, hip, and trunk muscle groups appear to be important inclusions for resistance training programs following ACLR.

Exercises targeting strength and power should be prescribed and progressed according to age-appropriate resistance training principles (American College of Sports Medicine, 2009; Behm et al., 2008). To improve strength, resistance or load sufficient to create fatigue after 8-12 repetitions (i.e., unable to physically complete two more repetitions), and repeated for three to five sets, is recommended (American College of Sports Medicine, 2009). Unilateral, bilateral, single (e.g., leg extension) and multiple joint (e.g., squat) strength exercises should be considered. Exercises to improve muscular power (American College of Sports Medicine, 2009) are required, to enable safe return to sporting activities, and considering the power deficits evident up to three years following ACLR (Ageberg et al., 2009; Neeter et al., 2006; Thomee et al., 2012; Turpeinen et al., 2020). Compared to strengthening exercise prescription, heavier loads (i.e., fatigue is reached after 3-6 repetitions), or lighter loads performed at a faster contraction velocity, with a focus on multiple joint and whole-body movement (e.g., plyometric exercises such as box jumps) may be used to improve muscle power following ACLR (American College of Sports Medicine, 2009; Bieler et al., 2014).

Neuromuscular training

Neuromuscular exercises are typically performed in functional weight-bearing positions, with a focus on targeting postural control and balance, movement, and muscle activation patterns (Ageberg & Roos, 2015) (**Table 7.2**). Neuromuscular exercises following ACLR can: (i) change movement patterns during walking (e.g., increase knee flexion during stance) (Chmielewski et al., 2005; Risberg et al., 2009), (ii) increase quadriceps activation (i.e., number and frequency of motor unit recruitment) (Sonnery-Cottet et al., 2019), (iii) increase quadriceps strength (i.e., maximal isometric or isokinetic force output) (Cooper et al., 2005b), (iv) reduce co-contraction of the

quadriceps, hamstrings, and gastrocnemius during walking (Chmielewski et al., 2005), and (v) improve lower-limb functional performance in hop tests (Ageberg et al., 2001b) following ACLR.

Neuromuscular exercises typically progress from standing on one leg, to squatting on one leg to jumping, landing, and cutting with perturbations, with a focus on dynamic alignment of the lower-limb and trunk. Balance exercises may include internal perturbations (e.g., balancing on one leg while moving the upper limb) or external perturbations (e.g., landing on one leg while being pushed) (Ageberg & Roos, 2015). Some neuromuscular exercises (e.g., jumping and landing, unilateral squatting) may have crossover with strength and power-based exercises. Maximising force output (e.g., jump height or external load) and optimising movement quality (e.g., alignment of the lower-limb during take-off and landing) should be encouraged during these exercises. Neuromuscular training should be combined with resistance training following ACLR to optimise outcomes (Andrade et al., 2019) (**Table 7.1**). Most RCTs comparing neuromuscular and resistance training programs report large, but similar improvements in physical outcomes (e.g., strength, functional performance on hop tests) and PROs up to one year following ACLR (Arundale et al., 2018; Cooper et al., 2005a; Hartigan et al., 2009; Liu-Ambrose et al., 2003).

Sport-specific exercises

Sport-specific exercises individualised to the patient's goals may be incorporated as appropriate strength and neuromuscular control is gained. Programs to develop aerobic capacity, speed, deceleration, agility, and sports-related skills (e.g., kicking a ball) are advocated to progress towards return-to-sport (Burgi et al., 2019; Davies et al., 2017; Yabroudi & Irrgang, 2013).

Exercise progression

The use of physical strength and functional performance measures, patient-reported symptoms, QoL, function (i.e., KOOS or IKDC), activity level, or psychological readiness (ACL Return-to-sport after Injury scale (ACL-RSI)) to monitor exercise progression was agreed upon by four of the six CPGs (Logerstedt et al., 2017; Meuffels et al., 2012; Shea et al., 2015; van Melick et al., 2016) (**Table 7.1**). Exercise progression can based on: (i) resistance training principles (American College of Sports Medicine, 2009), (ii) ability to perform the activity with optimal movement quality and neuromuscular control, (iii) minimal pain and swelling response, and (iv) patient-specific psychosocial and contextual factors (e.g., goals, confidence, expectations, adherence, and motivation) (Davies et al., 2017).

7.3.2 Graded return-to-sport

Resistance, neuromuscular, and sport-specific exercises should be progressed until the achievement of physical "return-to-sport" criteria (**Table 7.1**). Passing an extensive battery of strength and hop tests assessing quantity and quality of movement is encouraged, yet the exact cut-off scores or predictive ability of physical tests are uncertain. The most common physical criterion reported in the CPGs was achieving >90% LSI on a battery of strength (i.e., quadriceps and hamstrings) and hop tests (Logerstedt et al., 2017; van Melick et al., 2016). Given many patients (~50%) do not return-to-sport 12 months after ACLR (Ardern et al., 2014b) and few (~20%) meet recommended physical criteria prior to return (Webster & Hewett, 2019), the return-to-sport phase may continue beyond 12 months following ACLR.

Passing a battery of physical and patient-reported measures of function, and completion of sport-specific rehabilitation, might reduce re-injury risk (Ashigbi et al., 2020; Grindem et al., 2016; Kyritsis et al., 2016). Kyritsis et al. (2016) reported that those completing sport-specific graded on-field rehabilitation and agility testing, combined with meeting >90% strength and functional criteria, had a four-fold reduction in re-injury risk. Not everyone wants to return-to-sport following ACLR, but achieving physical and patient-reported criteria should be encouraged, due to the potential implications for future joint health (Chapter 6), and to facilitate return to other types of physical activities such as running (Rambaud et al., 2018).

7.4 Education

Education in the form of information and advice, or behaviour modification techniques (e.g., motivational interviewing), might enhance rehabilitation outcomes (De Oliveira Silva et al., 2020; O'Halloran et al., 2014). Understanding the rationale for the exercise program and criteria-based progression, combined with advice on goal setting and pain management, may be important following ACLR. Education can address knowledge gaps and unrealistic expectations regarding recovery, the risk of OA, and the potential benefits of exercise and joint loading (Bennell et al., 2016; Feucht et al., 2016; Truong et al., 2020). Education and support strategies can change behaviour, facilitate lifestyle modifications (e.g., improve diet, optimise physical activity participation), and manage the psychosocial and contextual factors that may be implicated in poor outcomes after ACLR (Truong et al., 2020; Walker et al., 2020). Interventions targeting factors such as fear, anxiety, or confidence are effective in other musculoskeletal conditions (Ehde et al., 2014), and show promise following ACLR (Coronado et al., 2018). Identifying patient-specific social and contextual barriers (e.g., lack of gym access), and working through solutions (e.g., home-based alternatives) may enhance adherence.

7.5 Level of supervision and duration of rehabilitation following ACLR

Exercise therapy is the cornerstone of ACLR rehabilitation. Yet, it is unclear whether exercises should be regularly supervised or progressed by a qualified health professional (e.g., physiotherapist) (Arroll et al., 2003; Logerstedt et al., 2017; van Melick et al., 2016; Walker et al., 2020; Wright et al., 2008) (**Table 7.1**). Supervised exercise therapy may be valuable for some, or all patients, but there is little evidence in patients following ACLR, particularly for end-stage rehabilitation (Walker et al., 2020). The more recent publications from the Walker et al. (2020) review (i.e., those published since 2016) suggest that more frequent supervision (≥two appointments per month compared to less than once per month) and a longer duration (≥six months following ACLR) of supervised physiotherapy are associated with better PROs and physical outcomes (Walker et al., 2020). While supervised rehabilitation may be important, it appears that few patients (<20%) continue supervised or guided exercise beyond six to nine months (Ebert et al., 2018; Greenberg et al., 2018; Rosso et al., 2018). The value of ongoing supervised rehabilitation for those with persistent symptoms is yet to be determined.

An intervention for those with persistent symptoms one year following ACLR might consider physiotherapist-guided exercise therapy, combining elements of supervised and unsupervised exercise. The sub-group of individuals with persistent symptoms and functional impairments following ACLR might represent a group of individuals who require additional supervision to facilitate them to complete home exercises. Supervised one-to-one sessions may increase motivation, reduce fear of exercise, and progress exercises based on individual needs, response, and quality of technique. They may require additional education about future symptoms and OA risk, and the importance of exercise and weight management. Independent exercise is also important for this young population following ACLR in order to increase the feasibility of the intervention due to the known barriers for physiotherapy attendance and exercise adherence (e.g., financial costs; lack of time due to work, study, or family-related commitments (Truong et al., 2020; Walker et al., 2020).

8 Chapter Eight: Exercise therapy and education for individuals with persistent symptoms one year following ACLR: A pilot RCT

8.1 Preface

Chapter 7 highlighted that progressive exercise therapy and education should continue for 9 to 12 months following ACLR, or until achievement of physical and patient-reported criteria. The work from this thesis indicates that many individuals will achieve these criteria within the first year following ACLR, but a subgroup of individuals will have persistent symptoms and functional impairments. This subgroup may have a higher risk of structural and symptomatic decline, and may benefit from ongoing and more individualised interventions targeting modifiable factors associated with poor prognosis. Yet, there is a lack of Level 1 evidence from RCTs to support the effectiveness of exercise and education interventions, beyond typical rehabilitation periods, for those who have not achieved an acceptable outcome one year following ACLR. Combining the evidence in Chapter 7 with clinical expertise, a physiotherapist-guided, lower-limb-focussed exercise therapy and education intervention was designed for individuals with persistent symptoms one year following ACLR. The pilot RCT in Chapter 8 evaluated the feasibility of this lower-limb-focussed exercise therapy and education intervention compared to a (control) trunk-focussed intervention.

8.2 Introduction

Following ACLR, CPGs recommend that post-operative rehabilitation continues for at least 9 to 12 months, or until achievement of sport-specific strength, functional, and psychological criteria (van Melick et al., 2016). Yet, many patients have symptoms, muscle weakness, and functional deficits that persist beyond one year post-ACLR (Culvenor et al., 2016a; Patterson et al., 2020b; Xergia et al., 2013), which may increase the risk of re-injury, post-traumatic OA, and worse knee-related QoL (Culvenor et al., 2019a; Culvenor et al., 2017a; Culvenor et al., 2017b; Ericsson et al., 2013; Grindem et al., 2016; Patterson et al., 2020a). Yet, no clinical trials have evaluated exercise and education beyond the typical rehabilitation period for those who have not achieved an acceptable outcome within the first post-operative year.

Approximately 50% of individuals report unacceptable knee symptoms and QoL one to two years after ACLR (Ingelsrud et al., 2015; Patterson et al., 2020c). Minimal improvement occurs beyond one to two years (Patterson et al., 2020c; Spindler et al., 2018), and symptoms and QoL remain worse than uninjured peers in the longer-term (>five years) (Filbay et al., 2015; Patterson et al., 2020c). Persistent symptoms at one year post-ACLR often co-exist with impairments in functional performance and loss of knee confidence (Culvenor et al., 2016d; Hart et al., 2020). Functional performance impairments are typically defined as 10% lower performance in the ACLR compared to the contralateral limb on hop testing. Persistent symptoms and functional deficits at one year post-ACLR increase the risk of developing short-term (<five years) and longer-term (5 to 10 years) symptoms, impaired knee-related QoL, and OA on radiographs or MRI (Culvenor et al., 2016c; Ericsson et al., 2013; Filbay et al., 2018a; Patterson et al., 2020a). Therefore, the one-year post-operative milestone provides an ideal window to identify “at-risk individuals” with persistent symptoms who have ceased supervised rehabilitation, and to implement interventions for these individuals. Physiotherapist-guided exercise therapy and education to address persistent physical impairments and symptoms may be important for the secondary prevention of re-injury, post-traumatic OA, and poor QoL in young adults post-ACLR (Culvenor & Barton, 2017; Whittaker & Roos, 2019).

The primary aim of this pilot study was to determine the feasibility of an RCT evaluating a physiotherapist-guided exercise therapy intervention for individuals with persistent symptoms one year post-ACLR. The secondary aim was to determine if a worthwhile treatment effect could be observed for the lower-limb-focussed intervention (compared to the trunk-focussed intervention), for improvement in knee-related QoL, symptoms, and function.

8.3 Methods

8.3.1 Study design

This double-blind (assessor and participant), parallel-arm, pilot feasibility RCT was conducted in accordance with the National Health and Medical Research Council ethical guidelines (National Health Medical Research Council, 2007), and reporting adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement for pilot and feasibility studies (Eldridge et al., 2016) (**Appendix R**). Ethical approval was gained from the La Trobe University Human Ethics Committee (HEC 16-077) and all participants were provided with a written participant information statement and completed written informed consent prior to participating. The trial was prospectively registered through the Australia and New Zealand Clinical Trials Registry (ACTRN12616000564459).

8.3.2 Setting

All assessments and treatments were conducted at two private physiotherapy clinics in Australia, located in Hobart and Melbourne, respectively.

8.3.3 Participant recruitment and eligibility

Individuals 12-15 months following a hamstring-tendon autograft ACLR were recruited from five orthopaedic surgeons, advertisements at La Trobe University, and via social media (December 2016 to August 2017). Individuals aged 18 to 50 years were considered eligible if they scored <87.5/100 on KOOS-QoL (threshold below which has been defined as a symptomatic knee (Englund et al., 2003)) and met one of the following criteria: a) <22 repetitions on the one-leg rise test, b) single-hop <90% LSI, or c) <87/100 on the Anterior Knee Pain Scale (AKPS) (Kujala et al., 1993). These functional performance thresholds are associated with worse symptoms and poorer knee-related QoL (Culvenor et al., 2016c; Ericsson et al., 2013; Reinke et al., 2011), and the AKPS threshold is associated with worse functional performance at one year post-ACLR (Culvenor et al., 2016d). The exclusion criteria were: i) >five years between injury and ACLR, ii) subsequent injury (for which medical treatment was sought) or follow-up surgery to the ACLR knee, iii) another condition influencing daily function, iv) unable to speak or read English, and v) unable to attend eight supervised sessions.

8.3.4 Deviations from initial trial protocol

Participants were initially deemed ineligible if they had sustained a previous ACL or knee injury to either limb prior to their recent ACLR. After commencing recruitment, it was evident that a previous knee injury was common in those with persistent symptoms, and these individuals are at

increased risk of symptomatic post-traumatic OA (Wright et al., 2012). The inclusion criteria were adjusted at the start of recruitment to include those with a previous ACL or knee injury. Hypothesis testing in a regression model was not performed as initially planned, due to the limitations of significance testing in clinical research (Herbert, 2019), and was not considered appropriate for a feasibility trial. Instead, the between-group differences and 95% CIs were used to verify that a worthwhile effect was contained within the CI. We defined a worthwhile effect as greater than the MDC score for the respective outcome measure, where available. While the primary purpose of feasibility was implied throughout the trial registration and included as such in the trial title, we did not list feasibility as a separate outcome in the trial registration. We have maintained our focus on feasibility by including it as the primary aim of this pilot study. Several other exploratory PROs were outlined in the trial registration but were beyond the scope of this evaluation due to the primary aim of feasibility.

8.3.5 Procedures

Eligible participants underwent a baseline assessment with a blinded assessor (BP) and randomisation into one of two intervention groups. The same blinded assessor completed all follow-up assessments, unaware of group allocation. Participant age, sex, BMI, injury history, ACLR surgical details (i.e., meniscal procedures), and previous activity level were obtained at baseline. All PROs were completed via an online portal (Promptus, DS PRIMA, Melbourne, Australia).

Randomisation and blinding

Non-stratified, permuted block randomisation (random blocks of three or six) occurred at a 2:1 (lower-limb-focussed: trunk-focussed) ratio. The randomisation sequence was computer-generated using Excel. The administrative staff at the participating physiotherapy clinic revealed the allocation using sequentially numbered, sealed opaque envelopes. Administrative staff were blind to block size. They entered the group allocation into the participant's clinical record for the treating physiotherapist. Participants were blind to group allocation to ensure allocation did not influence adherence, other treatment use, or drop-out. The physiotherapists could not be blinded to the allocation but were encouraged to deliver both interventions with equal enthusiasm and assertion of exercise value.

Treating physiotherapists and treatment fidelity

Treating physiotherapists were experienced (≥five years treating musculoskeletal conditions) in ACLR rehabilitation, and completed a four-hour training session (led by BP) related to delivering both interventions. A manual outlining the exercise prescription and progressions, manual treatment algorithm, education material, and trial procedures (attendance sheet, clinical notes,

adherence monitoring) was provided to each physiotherapist (Appendix S). Prescribed exercises were entered via the Physitrack© smartphone application for participants to access via the participant-facing application PhysiApp© (Physitrack Ltd, London, UK).

8.4 Interventions

Participants were randomised to a lower-limb-focussed or trunk-focussed exercise therapy intervention, which were both delivered in eight face-to-face 30-minute physiotherapy sessions over 16 weeks. Both interventions were reported according to the Template for Intervention Description and Replication (TIDieR) guidelines (Hoffmann et al., 2014) and the Consensus on Exercise Reporting Template (CERT) (Slade et al., 2016) (**Table 8.1**). The program included elements of supervised and unsupervised exercise, due to the potential benefits of one-on-one sessions in this group of individuals with a poor outcome, combined with the known barriers to attending supervised therapy and adherence to exercise following ACLR (Walker et al., 2020).

Table 8.1. Summary of intervention delivery and components for both groups

WHAT	LOWER-LIMB-FOCUSSED INTERVENTION	TRUNK-FOCUSSED INTERVENTION
WHO	Physiotherapists who have all undergone study-specific training	
HOW	1-to-1 face-to-face sessions to assess and progress unsupervised exercise therapy program	
WHERE	*Physiotherapy sessions:* Private clinics in Hobart and Melbourne *Unsupervised exercise therapy program:* Clinic/public gym or home	
WHEN & HOW MUCH	*Physiotherapy 1-to-1 sessions:* 30 minutes duration, weekly for 4 weeks then every 2 to 3 weeks for 12 weeks *Unsupervised exercise therapy program:* instructions provided via PhysiApp©, 30 to 45 minutes duration, minimum 3 sessions per week, unsupervised	
TAILORING	• Standardised lower-limb exercises (i.e., strength, power, balance), functional retraining (e.g., plyometric, agility), and cardiovascular program • Choice of priority exercises* (from the standard set) individualised • Exercise progression individualised • Individualised education (e.g., exercise rationale, goal setting) • Passive therapy treatment algorithm if appropriate (e.g., taping)	• Standardised, non-specific trunk strengthening exercises • Progression of exercises individualised • Optional stretching • Standardised education (e.g., rationale for trunk exercises)
	Both groups: exercises progressed based on assessment of pre-defined criteria at each session (i.e., pain, swelling, technique) and resistance training principles	

HOW WELL	Attendance at physiotherapy recorded by physiotherapists Unsupervised exercise program adherence recorded by participants in PhysiApp© smartphone app or paper diaries, and monitored by physiotherapists via Physitrack©

*Physiotherapists could choose 3 to 4 priority exercises (out of a possible 8), based on the participant's needs and goals. If necessary, all 8 exercise types were included, but it was not compulsory for all 8 to be incorporated.

8.4.1 Lower-limb-focussed exercise therapy intervention

The lower-limb-focussed intervention included standardised (with individualised progression) lower-limb, functional, and cardiovascular exercises, and individualised, ACL-specific education (Appendix S). The protocol was informed by current evidence-based recommendations (Andrade et al., 2019) outlined in Chapter 7 (**Table 7.1**), and developed by the research team, two of whom regularly (weekly) treated patients after ACLR (CB and RC). The lower-limb-focussed exercise therapy program targeted typical strength, neuromuscular and functional impairments, and movement patterns during sport-specific tasks related to ACL injury mechanisms (i.e., landing and cutting) outlined in Chapter 7 (**Table 7.2**). The eight types of exercises in the program were: 1) movement retraining (e.g., landing); 2) lower-limb strength (e.g., squats); 3) balance (e.g., perturbation exercises); 4) hip-abductor strength; 5) calf strength; 6) trunk strength; 7) hip extensor and knee flexor strength; and 8) cardiovascular exercise (e.g., cycling, running, graded sport-specific activities). Each of the eight exercises had three or more phases of difficulty for individualised progression (Appendix S). Physiotherapists were provided with a summary of the participant's injury history, goals, three to four priority exercises, and suggested starting phases based on baseline assessment of each area. Physiotherapists could add target exercises based on participant need, but it was not compulsory for all eight exercises to be incorporated. Exercise progression was based on: i) good technique; ii) minimal irritability (i.e., <2/10 pain during/after and no increase in swelling); iii) resistance training principles related to muscular strength and power(Garber et al., 2011); and iv) participant-specific goals and feedback. Strength exercises were prescribed in 3 sets of 12 repetitions (each repetition performed as 2 seconds concentric, 1 second isometric, 2 seconds eccentric), and could be progressed to a power dosage prescribed in 3 to 5 sets of 5 to 10 repetitions (<1 second concentric, 0 isometric, 2 seconds eccentric) (Garber et al., 2011). Treating physiotherapists were encouraged to use the face-to-face sessions to check exercise technique and adjust loads so that participants were reaching fatigue (i.e., they could not physically perform >two more repetitions) after their prescribed dosage (American College of Sports Medicine, 2009). Thirty minutes was considered an appropriate appointment duration to supervise at least one set of their prescribed exercises (where the other two sets could be completed unsupervised in the clinic gym) and provide education.

8.4.2 Trunk-focussed exercise therapy (control) intervention

An active control intervention was chosen to ensure that both treatment groups received equal exposure to physiotherapy (Higgins & Green, 2011). The trunk-focussed intervention was considered the active control and included standardised (with individualised progression) trunk strengthening exercises, stretching, and education. Physiotherapists could choose a minimum of three trunk strengthening exercises (from a maximum of five options), and each exercise had three or more phases of difficulty (Appendix S). Exercises were prescribed according to resistance training principles; they were typically prescribed in 3 sets of 60 seconds (isometric), and progressed to achieve adequate fatigue (i.e., could not physically perform >five more seconds) (Garber et al., 2011). Lower-limb and trunk stretching appropriate to the participant could be prescribed (Appendix S). The trunk exercises were predominantly isometric, non-weight-bearing, and had minimal lower-limb involvement; thus, they were not expected to impact knee-related QoL, symptoms, or function. This was chosen as the control intervention as trunk muscle strength deficits have not been reported following ACLR, nor has addressing trunk strength been found to impact knee-related outcomes following ACLR. Trunk exercises were considered to provide a credible intervention to enhance control participants' blinding to group allocation and minimise drop-outs.

8.4.3 Unsupervised exercise therapy program (both groups)

Participants in both groups were prescribed an unsupervised exercise therapy program relevant to their allocation, to be completed three times per week, at home or in a gym, to enhance likelihood of muscular strength and power improvements (Garber et al., 2011). Physiotherapists entered the participant's exercises via the Physitrack© app, and the participant used the PhysiApp© to guide their exercises and record adherence on their own smartphone, tablet, or computer. Paper diaries of the exercise therapy programs were used as required. PhysiApp© included video examples (created specifically for the trial) of correct (and incorrect) technique for each exercise (Appendix T) and exercise dosage (e.g., number of sets/repetitions, time under tension, external load, rest time), according to resistance training and muscle adaptation guidelines (Garber et al., 2011; Toigo & Boutellier, 2006). Co-interventions were discouraged. If participants chose to receive other treatments, they recorded them on an "other treatments calendar". The trunk-focussed unsupervised program could be completed at home with minimal equipment. When gym equipment was required for the lower-limb-focussed unsupervised program, gym access was provided at no cost to participants.

8.4.4 Education component (both groups)

Both groups received education, including face-to-face discussion and/or provision of handouts (Appendix S). Handouts for the lower-limb-focussed group consisted of the following topics: i) surgical information and post-operative expectations; ii) goal setting and return-to-sport criteria; iii) injury prevention; iv) psychosocial influences on recovery; and v) post-traumatic OA risk. The purpose of the education for the lower-limb-focussed group was to provide informational support regarding ACL-specific topics, address common knowledge gaps regarding evidence-based rehabilitation (Bennell et al., 2016) and provide psychosocial support for kinesiophobia, fear of re-injury, confidence, or negative lifestyle modifications due to their known relationships with functional recovery (Truong et al., 2020). For the trunk-focussed group, physiotherapists were asked to deliver standardised education on the rationale for trunk strengthening (e.g., theoretical influence of lumbo-pelvic stability on lower-limb biomechanics) and/or provide handouts/face-to-face discussion on the topics "surgical information and post-operative expectations", "psychosocial influences on recovery", and "post-traumatic OA risk" (Appendix S).

8.5 Feasibility outcomes

Feasibility was assessed according to previously published recommendations (Lancaster et al., 2004). Proceeding to a full-scale RCT was deemed feasible if all criteria were met or if reasonable amendments could be made to achieve these criteria in future trials (Avery et al., 2017).

Recruitment, adherence, and retention were evaluated by: i) recruitment rate (criteria: four participants per month); ii) proportion of eligible participants who were willing to enrol (criteria: >80%); iii) physiotherapy attendance rate (criteria: >80%); iv) adherence to unsupervised exercise therapy program (criteria: >80%); and v) proportion of drop-outs (criteria: <20%).

Acceptability of the study protocol was assessed via the appropriateness of the inclusion criteria (criteria: at least one in three eligible) and acceptability of the intervention content, delivery, adherence monitoring, and barriers or facilitators to adherence. Acceptability was determined via informal interviews conducted with the participants and physiotherapists (Appendix U).

Adverse events (i.e., any injury or illness requiring medical attention as a result of participating in the trial) were noted by the physiotherapist on a standardised recording sheet (criteria: <10% of all participants). Pain level (on a visual analogue scale; 0=no pain, 10=worst possible pain) during the unsupervised exercise therapy program was entered on PhysiApp© by participants (criteria: each participant mean <2/10 across all sessions).

Randomisation integrity was determined by contamination between groups (reported by participant or physiotherapist) (criteria: 0% contamination) or knowledge of group allocation by the participants or assessor (criteria: <10% unblinded).

Acceptability of the outcome measures was determined by the time needed to collect the data and the completeness of the outcome measures at baseline and follow-up (criteria: >90%).

8.6 Patient-reported outcomes

Knee-related QoL was assessed via the KOOS-QoL and ACL-QoL. The KOOS-QoL is one of the five KOOS subscales and evaluates knee-related QoL (Roos & Lohmander, 2003). The KOOS-QoL has the highest content validity of all subscales and the greatest responsiveness in young adults following knee injury (Collins et al., 2016). The ACL-QoL was designed to assess additional domains (e.g., work-related, social and emotional) of knee-related QoL specific to a young, active ACL-injured population (Mohtadi, 1998). The KOOS-QoL and ACL-QoL are converted to a total score out of 100 (0=extreme problems; 100=no problems). The KOOS-QoL and ACL-QoL have established content validity (Cronbach's alpha >0.76), test-retest reliability (ICC>0.86), and responsiveness (effect sizes >0.5) (Collins et al., 2016; Lafave et al., 2017). The MDC is 8-10 points for KOOS-QoL (Roos & Lohmander, 2003) and 12 points for ACL-QoL (Lafave et al., 2017).

The KOOS pain, symptoms, and sport subscales were assessed and all combined with the KOOS-QoL to calculate an overall $KOOS_4$ score. The KOOS is a valid, reliable, and responsive instrument for use following ACL injury (Collins et al., 2016). Psychological readiness for return-to-sport (a common goal of ACLR) and fear of re-injury were measured by the ACL-RSI (Webster et al., 2008). The ACL-RSI has established test-retest reliability (ICC=0.89), responsiveness (MDC=19 points) (Kvist et al., 2013), and validity, with higher scores associated with better return-to-sport rates, self-reported symptoms, and function (Kvist et al., 2013; Webster et al., 2018). The global rating of change (GROC), measured on a seven-point Likert scale ("much worse" to "much better"), was measured separately for knee pain and knee function. The change in proportion of patients answering "yes" to the PASS question (Ingelsrud et al., 2015) was evaluated. The GROC has good face validity (Pearson's r=0.72 to 0.90), test-retest reliability (ICC>0.90), responsiveness following knee injury (0.5 to 2.7 points on seven-point scale), and construct validity (e.g., correlated with changes in hop tests) (Kamper et al., 2009). The PASS assists in the interpretation of improvement in PROs by evaluating the concept of "feeling good" as opposed to "feeling better" (Tubach et al., 2006) and answering yes to "PASS" corresponds with better KOOS scores after ACL injury (Ingelsrud et al., 2015).

8.7 Functional performance outcomes

Functional performance outcomes were measured at baseline and follow-up, including the single-hop (maximum distance on one hop forward) (Gustavsson et al., 2006), side-hop (maximum

number of hops over two parallel lines 40 cm apart in 30 seconds) (Gustavsson et al., 2006), and one-leg rise test (maximum number of repetitions from a standardised height) (Thorstensson et al., 2004). We recorded the raw score (e.g., cm hopped, repetitions) on the ACLR and contralateral limb, and calculated the LSI (score of ACLR knee divided by contralateral knee, multiplied by 100, expressed a percentage). The hop tests and one-leg rise have high intra-rater reliability (ICC>0.80) and responsiveness after knee injury (Bremander et al., 2007; Gustavsson et al., 2006; Reid et al., 2007).

8.8 Data analysis

The sample size of 27 was not formally determined; it was based on previous pilot RCTs evaluating health-professional-guided interventions for musculoskeletal conditions (Kemp et al., 2018b; Stanton et al., 2020), and was deemed sufficient to assess the feasibility criteria. Participants who completed baseline and follow-up evaluations were included in the analysis, as recommended in the CONSORT guidelines (Moher et al., 2012). Feasibility outcomes were reported descriptively. Most (>50%) baseline and follow-up scores, and the change scores for the patient-reported and functional performance outcomes, were normally distributed (assessed with the Shapiro-Wilk's test). Therefore, within-group and between-group differences were reported as mean±SD and mean and 95% CI, respectively (Lafave et al., 2017; Roos & Lohmander, 2003). The treatment effects for the respective outcome measures were considered potentially worthwhile if the MDC (**Table 8.4**) was contained within the 95% CI of the mean between-group difference. The GROC and PASS outcomes were reported descriptively. Decision criteria for progression to a full-scale RCT were based on: i) all feasibility criteria being met or recommendations to achieve criteria in future trials; and ii) presence of worthwhile treatment effects for knee-related QoL, symptoms, and function.

8.9 Results

8.9.1 Feasibility

All feasibility criteria were met, or reasonable recommendations could be made to achieve the criteria in future trials (**Table 8.2**). Eighty people expressed interest in participation via response to letters from their surgeon (n=55) or advertisements on social media and at La Trobe University (n=25) over a nine month period. In total, 72% (n=57) agreed to be screened, with 47% of those screened (n=27) deemed eligible (**Figure 8.1**). The results of each aspect of feasibility are summarised in **Table 8.2**, with the detailed feedback provided by participants at follow-up provided in **Appendix T**.

Table 8.2. Feasibility outcomes

	Criteria	Lower-limb group (n=17)	Trunk group (n=10)	Proceed	Proceed with amendments
Recruitment, retention, adherence					
Recruitment rate	>4 per month	3 participants per month		No	Strategies to increase recruitment rate
Enrolment rate	>90%	100% completed baseline assessment, were enrolled, and randomised		Yes	
Drop-out rate	<20%	n=2 (12%)*	n=2 (20%)**	Yes	
Physiotherapy attendance	>80%	Mean=89% of intended 8 sessions	Mean=86% of intended 8 sessions	Yes	
Exercise adherence	>80%	52% of sessions completed	48% of sessions completed	No	Strategies to increase adherence
Study protocol acceptability					
Eligibility rate	1 in 3	47% of interested participants were eligible		Yes	
Acceptability of intervention to physiotherapists	Descriptive	• Training and supportive material sufficient • Reflected clinical practice, but time allocation insufficient		No	Appointments >30 minutes or provide additional more frequent appointments
Acceptability of intervention to participants	Descriptive	• Appointment duration/frequency and facilities appropriate • Interventions were credible and acceptable		Yes	
Barriers to adherence	Descriptive	Work, study, and family commitments; lack of motivation; boredom with exercises		No	Strategies to address common barriers
Adverse events					
Injury or illness	<20%	n=4 (24%) unrelated to exercise program^	Nil	Yes	
Pain during/after exercise	<2/10	Mean pain <2/10 for each participant (across all sessions)		Yes	
Randomisation integrity					
Integrity of blinding	90%	Assessor unblinded for n=1	1 participant (medical professional) unblinded	Yes	
Group contamination	0%	Nil	Physiotherapists discussed patient-specific topics	No	Control education difficult to standardise
Acceptability of outcomes					
Time to collect data	<90 minutes	Baseline and follow-up assessments were completed in 60-90 minutes		Yes	
Completeness of PROs	>90%	All 23 participants who finished the trial completed the PROs, with no missing data		Yes	
Completeness of functional performance outcomes	>90%	16% (n=4) did not complete follow-up^^	10% (n=1) did not complete follow-up (overseas)	No	Consider PROs as primary outcome for complete data
Adherence monitoring	Descriptive	• 23 used PhysiApp© and 2 used paper diaries • Enjoyed the accountability PhysiApp© provided, and the exercise videos • Inconsistently used PhysiApp© to record adherence (e.g. technical issues, forgot)		No	Strategies to increase adherence (e.g., incentives, interactive features such as benchmarking, education)

*n=1 severe increase in knee pain; n=1 unable to commit to requirements.
**n=2 decided they could not commit to the trial before commencing intervention.
^n=1 severe increase in knee pain (group fitness class); n=2 hamstring strains (sprint training, sprint in basketball match); n=1 ankle sprain (football training).
^^ n=2 could not complete hop test (recovering from ankle sprain and hamstring strain); n=2 could not attend (located internationally, work commitments).

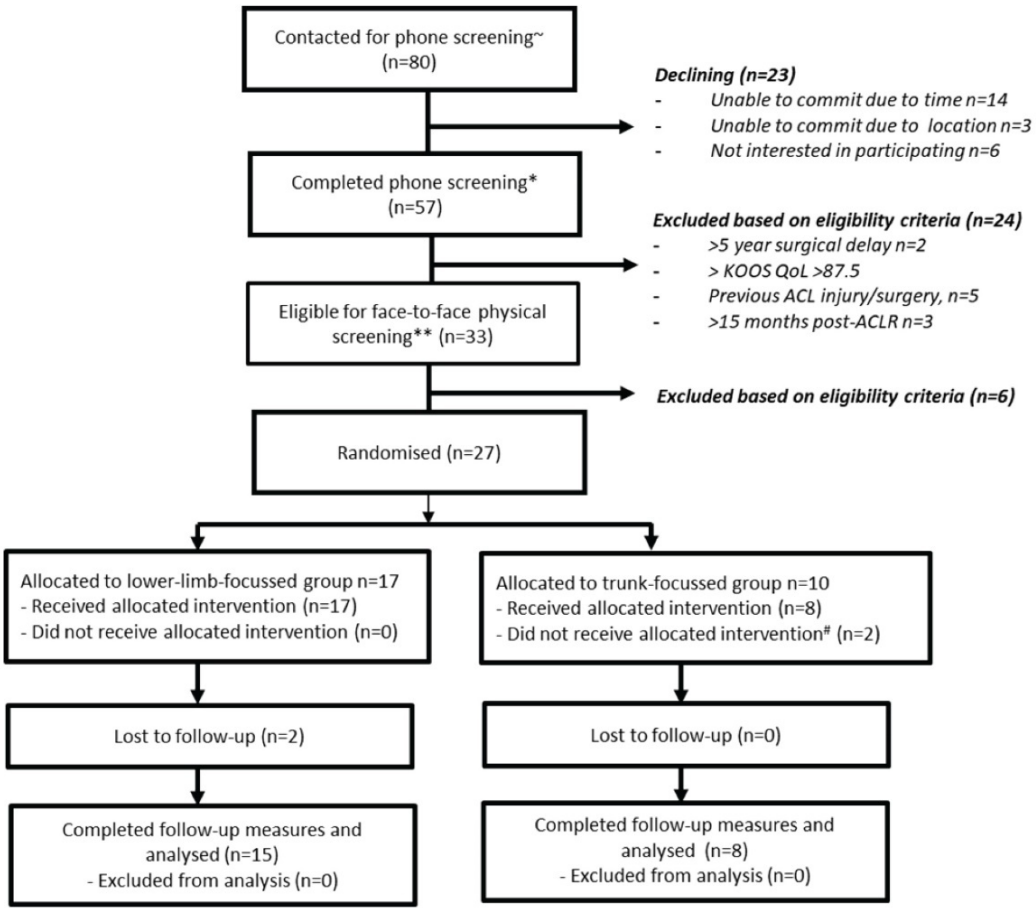


Figure 8.1 Flow of participants through the study.

ACL=anterior cruciate ligament; ACLR=anterior cruciate ligament reconstruction; KOOS-QoL=Knee injury and Osteoarthritis Outcome Score Quality of Life subscale.
#n=2 unable to find appointments to suit work/study commitments.
*n=1 severe increase in knee pain; n=1 unable to commit to requirements.

8.9.2 Participant characteristics

The trunk-focussed group had a higher proportion of men, a higher proportion of individuals participating in Level 1 or 2 sports pre-injury, and a higher proportion of concomitant meniscal surgery at the time of ACLR (**Table 8.3**).

Table 8.3. Participant characteristics at baseline

	Lower-limb-focussed group (n=17)	Trunk-focussed group (n=10)
Age, mean±SD years	34±12	33±12
Male sex, no. (%)	6 (35%)	7 (70%)
Body mass index, mean±SD kg/m^2	24.7±2.8	25.4±3.8
Pre-injury activity level*, no. (%)		
Level 1 or 2 (e.g., jumping/pivoting sports)	19 (53%)	10 (100%)
Level 3 (e.g., straight-line activities)	6 (35%)	0 (0%)
Level 4 (sedentary)	2 (12%)	0 (0%)
Concomitant meniscal procedure~, no. (%)	9 (50%)	3 (30%)

SD=standard deviation.
*Grindem classification system (Grindem et al., 2014).
~at the time of ACLR, reported by participants at baseline assessment.

8.9.3 Patient-reported outcomes

The desired treatment effect for KOOS-QoL (improvement >8-10 points) and ACL-QoL (improvement >12 points) was contained within the 95% CI. Appendix V reports the individual treatment responses for KOOS-QoL and ACL-QoL, and the proportion of participants with improvements greater than the MDC. The MDC was contained within the 95% CI for KOOS-Pain, KOOS-Sport, and $KOOS_4$ (**Table 8.4**). The GROC and PASS indicated that both groups improved, potentially to a greater extent in the lower-limb-focussed group. The majority (87%) were at least "better" in terms of knee function and knee pain in the lower-limb-focussed group, compared to 50% and 75%, respectively, in the trunk-focussed group. Satisfaction (PASS question) with current knee function improved in the lower-limb-focussed group from 27% to 67%, but remained the same in the trunk-focussed group (63%).

8.9.4 Functional performance outcomes

The MDC (where available) was contained within the 95% CI for all functional performance tests, except for the side-hop ACLR limb performance (**Table 8.4**). Appendix V reports the individual treatment responses for the functional performance tests, and the proportion of participants with improvements greater than the MDC.

Table 8.4. Secondary outcomes at baseline and follow-up

	Lower-limb-focussed intervention (n=15)			Trunk-focussed intervention (n=8)			Lower-limb vs trunk	Previously published MDC values
	Baseline mean±SD	Follow-up^ mean±SD	Change mean±SD	Baseline mean±SD	Follow-up^ mean±SD	Change mean±SD	Mean difference in change* (95%CI)	
ACL-QoL	45±20	64±20	20±17	56±9	78±16	22±13	-2.5 (-18.2 to 13.2)	12 points (Lafave et al., 2017)
KOOS-QoL	39±20	62±23	23±25	52±14	67±19	16±12	7.1 (-12.3 to 26.4)	8 to 10 points (Roos & Lohmander, 2003)
KOOS-Symptoms	68±23	74±19	7±17	81±9	90±9	9±7	-2.0 (-15.7 to 11.6)	8 to 10 points (Roos & Lohmander, 2003)
KOOS-Pain	77±15	86±12	9±14	90±7	92±8	2±7	6.7 (-4.0 to 17.9)	8 to 10 points (Roos & Lohmander, 2003)
KOOS-Sport	57±24	77±22	20±25	76±1	83±22	8±13	12.1 (-7.9 to 32.0)	8 to 10 points (Roos & Lohmander, 2003)
$KOOS_4$	60±17	75±17	15±18	75±9	83±14	9±7	5.9 (-7.9 to 19.8)	8 to 10 points (Roos & Lohmander, 2003)
ACL-RSI	36±18	53±22	17±18	41±18	67±24	26±22	-9.2 (-27.2 to 8.7)	19 points (Kvist et al., 2013)
Single-hop								
ACLR (cm)	65±42	97±33	33±34	108±39	115±42	8±9	24.1 (-5.9 to 54.1)	14 cm (Kockum et al., 2015; Reid et al., 2007)
CL (cm)	93±30	106±32	14±18	116±25	120±34	4±15	9.6 (-8.9 to 28.2)	14 cm (Kockum et al., 2015; Reid et al., 2007)
LSI (%)	59±38	88±11	29±37	90±21	94±12	4±10	15.5 (-27.7 to 58.7)	8% (Kockum et al., 2015; Reid et al., 2007)
Side-hop								
ACLR (reps)	8±8	16±12	9±9	20±13	29±19	9±8	-0.6 (-9.4 to 8.7)	11 reps (Kockum et al., 2015; Reid et al., 2007)
CL (reps)	9±9	17±12	8±10	23±16	31±21	9±15	-0.5 (-13.4 to 12.2)	11 reps (Kockum et al., 2015; Reid et al., 2007)
LSI (%)[a]	71±42	82±29	11±28	73±13	94±14	21±18	-10.4 (-43.1 to 22.2)	~10% (Kockum et al., 2015; Reid et al., 2007)
One-leg rise								
ACLR (reps)	17±16	33±15	17±14	27±19	34±20	7±11	9.9 (-4.1 to 23.9)	Not available
CL (reps)	25±19	35±15	10±14	31±15	34±15	4±7	6.4 (-6.5 to 19.3)	Not available
LSI (%)[b]	67±57	98±9	31±54	68±32	83±47	16±32	15.7 (-40 to 71.5)	Not available

ACLR=anterior cruciate ligament reconstructed limb; ACL-RSI=ACL Return-to-sport Index; ACL-QoL=Anterior Cruciate Ligament Quality of Life questionnaire; CI=confidence interval; CL=contralateral limb; KOOS=Knee injury and Osteoarthritis Outcome Score; LSI=limb symmetry index; MDC=minimal detectable change; SD=standard deviation; QoL=quality of life.

*Positive value indicates between-group differences are in favour of the lower-limb-focussed group.

^n=3 participants did not complete functional performance follow-up (could not attend due to being overseas or work commitments). An additional 2 participants did not complete the single-hop and side-hop tests as they were recovering from adverse events (n=1 hamstring strain and n=1 ankle sprain).

[a] n=3 not included in LSI calculation at baseline (3 in lower-limb-focussed) and n=3 not included at follow-up (2 in lower-limb-focussed, 1 in trunk-focussed) as unable to perform a valid score on either limb.

[b] n=5 not included in LSI calculation at baseline (n=3 in lower-limb-focussed group and n=2 in trunk-focussed group) and n=1 (in trunk-focussed group) not included at follow-up as unable to perform a valid score on either limb.

8.10 Discussion

The results of this study suggest that it is worthwhile proceeding to a large-scale RCT evaluating the effectiveness of a physiotherapist-guided lower-limb-focussed exercise therapy and education intervention for young adults who have persistent symptoms one year post-ACLR. All feasibility criteria were either met or reasonable recommendations could be made to achieve the criteria in future trials. Additionally, worthwhile treatment effects were observed in participants receiving the lower-limb-focussed intervention for knee-related symptoms, function, and QoL.

Feasibility: Recruitment, retention, adherence, study protocol acceptability

Of those screened, almost half (47%) were eligible, and we achieved a modest recruitment rate (three per month). For a large-scale RCT, the number of participating surgeons (and study advertising) would need to be increased, which is possible due to the large number of ACLRs performed worldwide (Moses et al., 2012). Although all eligible participants were willing to enrol, two participants did not commence the intervention and two others dropped out during the intervention, resulting in an overall drop-out rate of 16%, which is considered acceptable (Furlan et al., 2009). Physiotherapy attendance was high (>85%), similar to previous physiotherapist-guided exercise therapy RCTs (>80%) for lower-limb musculoskeletal conditions in young adults (Arundale et al., 2018; Kemp et al., 2018b). Suggestions and feedback provided by the five participants who dropped out or attended less than 80% of study appointments align with previous reported strategies to maintain attendance – i.e., increasing appointment availability after hours and exercise variety, and implementing strategies to increase motivation (Pizzari et al., 2002; Walker et al., 2020). These strategies, in addition to consideration of telehealth appointments and multiple clinic locations, might reduce drop-outs and improve attendance in future trials. Physiotherapist feedback indicated that longer appointment duration or more frequent appointments may be required in future trials to provide physiotherapists with sufficient time to review exercise programs and provide education. Those with persistent symptoms may also require additional informational and emotional support, given that their knee-related QoL, symptoms, and function is much lower than most patients one year post-ACLR (Granan et al., 2009; Patterson et al., 2020c; Spindler et al., 2018).

Feasibility: Adherence to the unsupervised exercise therapy program

According to Physitrack© adherence data, only half of the prescribed unsupervised exercise therapy program sessions were completed. However, these data may under-estimate true exercise adherence in this trial as participants reported inconsistently entering their adherence

data in Physiapp© due to technical difficulties, and rarely using the app once familiar with their exercises. Regardless of true adherence rates, participants did report typical barriers to exercise adherence (Pizzari et al., 2002; Truong et al., 2020), including other commitments (work, study, and family) and reduced motivation. Exercise adherence rates were lower than previously reported for rehabilitation during the first six months following ACLR (75-80%) (Brewer et al., 2000; Pizzari et al., 2005). This may reflect the burden of exercise therapy on participants who have already attempted unsuccessful rehabilitation with the physical, mental, and time commitment it entails. Strategies to increase adherence to the unsupervised exercise therapy program may include goal setting (Wilson & Brookfield, 2009), motivational interviewing (O'Halloran et al., 2014), supervised group classes, or alternate exercise options (e.g., non-gym-based) (Goddard et al., 2020). Personalised adherence monitoring data collection methods, including paper diaries and email or text message reminders, and strategies to maintain engagement with apps (e.g., incentivisation, positive reinforcement, benchmarking) should be considered (Nussbaum et al., 2019; Reynoldson et al., 2014).

Feasibility: Adverse events, integrity of group allocation, acceptability of outcomes

Two participants sustained hamstring strains in their ACLR limb and one sustained an ankle sprain as they returned to sporting activities. Graded return to high-speed running protocols should be emphasised in future trials to reduce soft tissue injury risk, especially given that ACL injury is a well-recognised risk factor for hamstring strain (Green et al., 2020). Future trials should include strategies to maintain participant blinding (e.g., control interventions that are acceptable) and sufficient study personnel to maintain blinding of assessors. Completion of follow-up PROs (100%) and functional performance measures (81%) suggests that PROs may be the most appropriate outcome tool to maximise data completion in future trials.

Future trial recommendations: Treatment effects for knee-related QoL

A worthwhile within-group effect (>MDC) was observed in the lower-limb- and trunk-focussed interventions for the ACL-QoL and KOOS-QoL. Our results concur with other trials comparing two types of physiotherapy-guided exercise interventions (Arundale et al., 2018; Kruse et al., 2012). The trunk-focussed intervention was hypothesised to produce a minimal effect on knee-related QOL, but greater trunk strength and endurance may have improved perceived performance in sport and work-related activities, resulting in better QoL. Improvements in knee-related QoL might be strongly influenced by education (provided in both groups). In both groups, physiotherapists were able to educate participants and address psychological factors (e.g., kinesiophobia, fear, confidence), which are known determinants of adherence, recovery, and self-reported outcomes

after sports-related knee injury (Goddard et al., 2020; Truong et al., 2020). The physiotherapists reported discussing patient- and ACL-specific topics with the trunk-focussed participants, although directed not to do so in the study protocol, which may have had a direct or indirect effect on knee-related QoL. Future trial designs might consider comparing exercise therapy and education with a comparator that better reflects usual care (e.g., self-directed exercise). Given that health-professional-delivered education alone may be effective in young people with persistent knee pain (De Oliveira Silva et al., 2020), future RCTs might compare: (i) exercise therapy versus education alone and/or (ii) exercise therapy with and without education, to guide interventions for those at risk of post-traumatic OA after ACLR.

Future trial recommendations: Treatment effects for knee-related function

While the study was not powered to detect between-group differences, the lower-limb-focussed group exhibited improvements in KOOS-Sport, single-hop, and one-leg rise that are likely to be clinically meaningful in a larger trial. However, these findings should be interpreted with caution due to the wide CIs and differences in baseline scores between groups. The LSI improvements for the single-hop (29%) were larger than those in the ACL-SPORTS trial (10%) with a similar lower-limb-focussed intervention (Arundale et al., 2018). This larger improvement we observed may be due to the lower baseline function of our participants (particularly in the lower-limb-focussed group) compared to the ACL-SPORTS trial where all participants had already achieved ≥80% LSI, had begun running, and had no pain (Arundale et al., 2018). Future studies should also consider that LSI improvement can reflect worsening contralateral limb function, rather than improved ACLR limb function (Patterson et al., 2020b). Therefore, it is important to note that in the current interventional study, LSI improvements occurred alongside clinically meaningful improvements in both limbs, indicating that the increase in LSI was due to greater improvement in the ACLR limb. Given that poor function on hop tests at one year post-ACLR may be associated with an increased risk of future OA (Patterson et al., 2020a; Pinczewski et al., 2007) and re-injury (Grindem et al., 2016), addressing persistent functional deficits may be an important step forward in secondary prevention of post-traumatic knee OA. Considering the influence of the lower-limb-focussed intervention in this study on OA risk factors, future larger-scale trials should consider longer-term follow-up including imaging outcomes, physical activity monitoring, healthcare utilisation, and cost-effectiveness evaluation.

Recommendations for future trials: Intervention content and format

Despite improvements, knee-related function and QoL remained lower than uninjured normative values (Baltaci et al., 2012; Kockum & Heijne, 2015; Paradowski et al., 2006) and satisfaction with

knee function was less than 70% in the lower-limb-focussed group at follow-up, indicating that the lower-limb-focussed intervention could be improved for future trials. The participants were low functioning and may not have had sufficient time to progress exercises and improve function to an acceptable level. Future trials may consider a longer intervention with more frequent supervised sessions (either one-on-one or group exercise classes) to provide further opportunity for education and exercise progression in order to address persistent functional and QoL impairments. Some lower-functioning patients with persistent symptoms at one year post-ACLR may not wish to return-to-sport, and therefore, have reduced motivation to adhere to plyometric and agility exercises. Future trials should consider a pragmatic individualised approach to exercise prescription, similar to the current study, allowing the physiotherapist to choose from a set of exercises according to the participant's needs and goals. Isolated quadriceps exercises (e.g., leg extension) may be important to include in future interventions for those with persistent symptoms, due to the known association between quadriceps weakness and development of symptomatic OA in the general population (Culvenor et al., 2017b).

Limitations and recommendations for full-scale RCT

Given that this was a pilot feasibility study, it did not have adequate power to establish superiority of one intervention over the other. Further, the lower-limb-focussed group started with worse knee-related QoL and functional performance, allowing greater room for improvement compared to the trunk-focussed group (**Table 8.4**). A larger sample size would reduce the likelihood of baseline between-group heterogeneity. Future RCTs should consider factors that may affect baseline status or treatment response (e.g., sex) (Culvenor et al., 2019c). Many participants (>50%) had a routine surgical review during the trial and were given "clearance for return-to-sport", which may have improved PROs or physical activity in both groups. Future trials should regularly (weekly or monthly) monitor all types of physical activity completed during the intervention period. Consistent with other ACLR cohorts (Risberg et al., 2016b) and RCTs (Arundale et al., 2018), there was large individual variation in baseline scores (i.e., SDs) in both groups and large changes between baseline and follow-up for all outcomes (**Appendix V**). We did not assess lower-limb or trunk strength so we cannot determine if the improvements in functional performance or PROs were mediated by strength increases. Future trials should consider including muscle capacity (strength, power) testing to also ensure that adequate loading and progression has occurred to stimulate muscle capacity improvements (Culvenor et al., 2016b). Moreover, participating surgeons and clinic locations were limited to metropolitan Melbourne and Hobart. Future trials should be aware that recruitment, eligibility, attendance, and adherence rates may differ in other settings.

8.11 Conclusion

A large-scale trial to evaluate the effectiveness of a physiotherapist-guided exercise therapy and education program for individuals with persistent symptoms at one year post-ACLR is feasible. All feasibility criteria were met, or reasonable recommendations could be made to achieve the criteria in future trials. Strategies to increase recruitment rate, adherence to exercise, and data completion are required. Potential worthwhile treatment effects for knee-related QoL, symptoms, and function were observed, indicating that a fully-powered RCT may detect a clinically meaningful difference.

Part D: Discussion and conclusions

9 Chapter Nine: Discussion and conclusions

9.1 Summary of thesis findings

The overarching aims of this thesis were to evaluate changes in OA features on MRI, PROs, and functional performance between one and five years following ACLR (Part B), to identify factors associated with worse prognosis (Part B), and to evaluate an intervention targeting individuals with persistent symptoms one year following ACLR (Part C). To address these aims, five studies were completed. Key outputs for each study are summarised below and in **Figure 9.1.** This final chapter will summarise the clinical and research implications of this thesis and the strengths and limitations of the research designs.

The findings of Chapter 3 revealed high rates (up to 44%) of worsening OA features on MRI and incident radiographic OA between one and five years following ACLR, particularly in the patellofemoral compartment. The estimated rates of worsening were substantially higher than young uninjured adults (Ding et al., 2005; Pan et al., 2011) and similar to older adults with established knee OA (Cooper et al., 2000; Ding et al., 2010; Runhaar et al., 2014). Factors that increased the odds of worsening OA features on MRI included an elevated BMI and older age. Surgical delay increased the risk of worsening tibiofemoral osteophytes and meniscal lesions, but decreased the risk of patellofemoral cartilage worsening.

In Chapter 4, longitudinal evaluation of knee symptoms revealed improvement in KOOS and IKDC scores between one and five years following ACLR; however, some individuals failed to return to levels reported by their uninjured peers. Notably, those with a combined injury tended to report significantly worse symptoms and QoL than those with an isolated ACL injury. Participant-level analyses revealed unacceptable symptoms and QoL for half of the participants at one year and two-thirds at five years, regardless of (isolated or combined) injury type. Patellofemoral cartilage lesions on MRI at one and five years were associated with worse KOOS and IKDC scores at five years post-ACLR, indicating that the patellofemoral joint may be a potential source of symptoms after ACLR (Culvenor & Crossley, 2016; Culvenor et al., 2014b).

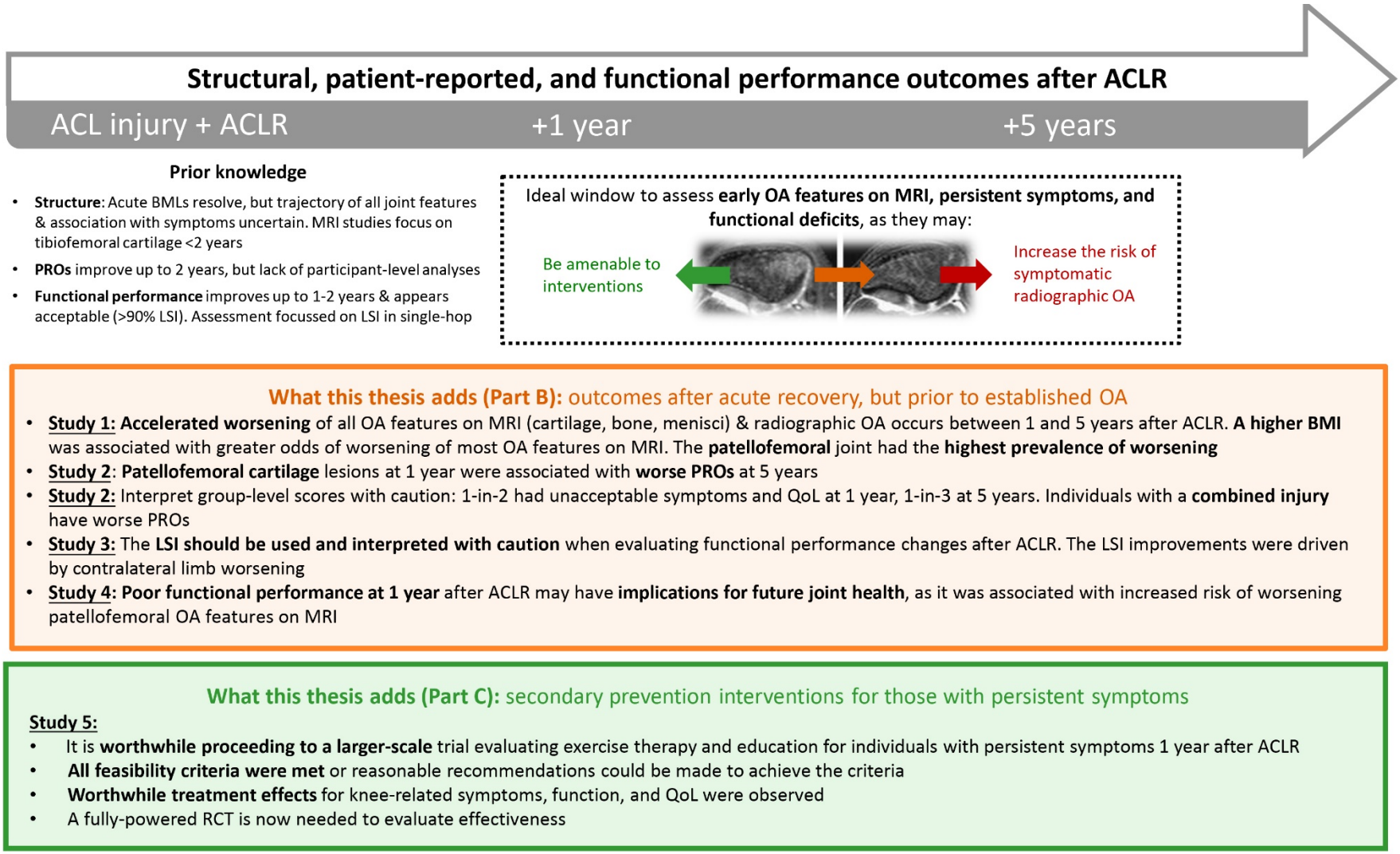


Figure 9.1 Summary of thesis findings and key additions to the literature.

ACL=anterior cruciate ligament; ACLR=anterior cruciate ligament reconstruction; BMLS=bone marrow lesions; OA=osteoarthritis; PROs=patient-reported outcomes; LSI=limb symmetry index; QoL=quality of life; MRI=magnetic resonance imaging.

Chapter 5 demonstrated improvements in functional performance up to five years following ACLR using the common LSI approach, but these improvements were largely driven by worsening contralateral limb function. Therefore, the LSI may overestimate functional recovery following ACLR, emphasising that caution is needed when relying on the LSI alone to assess changes in functional performance. Other reference standards, such as pre-operative or early post-operative contralateral limb function or uninjured controls, migth be more valid (Engelen-Van Melick et al., 2013; Gokeler et al., 2017; Wellsandt et al., 2017). Functional performance on the ACLR limb for the single-hop at one year was lower than healthy controls, with LSIs for all four tests being lower than healthy controls at one and five years following ACLR.

In Chapter 6, the influence of impaired function at one year post-ACLR (Chapter 5) on worsening MRI OA features at five years was evaluated, taking into account both the LSI and raw performance score (e.g., repetitions). Fewer repetitions on the side-hop test and poor functional performance (defined as <90% LSI) on the test battery were associated with an increased risk of worsening patellofemoral OA features on MRI. These findings extend cross-sectional data linking poor function and patellofemoral OA (Culvenor & Crossley, 2016; Culvenor et al., 2014b) and highlight the potential importance of optimising function in the context of secondary prevention of post-traumatic OA.

Findings from Part B of the thesis, together with CPGs, informed the development of a lower-limb-focussed intervention for those with persistent symptoms one year following ACLR, which was assessed for feasibility in Chapter 8. The results from the pilot RCT indicated that a larger-scale trial is feasible, with all feasibility criteria met or the ability to implement reasonable trial alterations to achieve the criteria identified. Strategies to increase recruitment rate, adherence to prescribed exercise, and data completion are required. Worthwhile treatment effects for knee-related symptoms, function, and QoL were observed, indicating that a fully-powered RCT may detect a clinically meaningful difference.

9.2 Clinical implications

9.2.1 Accelerated nature of post-traumatic OA following ACLR

Clinicians may be aware that patients are at increased risk of developing knee OA within 10 to 15 years following ACLR. However, this thesis found that post-traumatic OA was evident within the initial years following ACL injury, and structural joint degeneration was accelerated compared to non-traumatic knee OA. While most other imaging findings on MRI were not associated with symptoms, worsening OA features on MRI might precede symptom development and may

represent an individual on an accelerated trajectory towards more severe and symptomatic radiographic post-traumatic OA. For example, early changes to cartilage, bone, and menisci captured on MRI are associated with more severe future radiographic OA in the general population (Katsuragi et al., 2015; Liebl et al., 2015; Roemer et al., 2015; Sharma et al., 2016), persistent or incident symptoms (Javaid et al., 2010; Sharma et al., 2014; Sharma et al., 2016), and/or future TKR (Hunter et al., 2011b; Liu et al., 2017; Nagai et al., 2018). Further research is needed before MRI could be used to guide clinical management for patients following ACLR.

9.2.2 Patellofemoral joint considerations

Higher rates of worsening, and greater associations with symptoms and objective function, were observed in the patellofemoral compartment in studies forming this thesis. Therefore, clinicians need to evaluate and address factors that may be associated with patellofemoral joint health following ACLR. The high rates of patellofemoral worsening may be surprising to clinicians; the ACL is not structurally or functionally related to the patellofemoral joint, acute trauma related to ACL rupture is typically observed in the tibiofemoral joint, and all participants had an ACLR using a hamstring-tendon autograft. The results of this thesis highlight that clinicians should be mindful that a hamstring-tendon autograft ACLR does not protect against accelerated development and progression of patellofemoral OA. The rates of patellofemoral radiographic OA (Chapter 3) are similar to those reported up to five years following bone-patella-tendon-bone autograft (Belk et al., 2018). While patellofemoral joint damage could occur at the time of injury, this is unlikely given only 9% of KOALA cohort participants had a patellofemoral cartilage lesion assessed arthroscopically at the time of ACLR.

Improving functional performance and quadriceps strength may benefit patients, due to the associations between poor function and worsening patellofemoral OA features (Chapter 6) and between quadriceps weakness and development of (patellofemoral) OA in the general population (Amin et al., 2009; Culvenor et al., 2017b; Culvenor et al., 2019c). Clinicians may also consider assessing and treating biomechanical factors such as patellofemoral malalignment, increased tibial rotation, and increased knee valgus (Andriacchi et al., 2006; Culvenor et al., 2014c; Macri et al., 2019; Paterno et al., 2010; Scanlan et al., 2010; Webster & Feller, 2011), due to their potential influence on patellofemoral joint loading (Lee et al., 2003; Powers, 2003) and structural deterioration. In the KOALA cohort, greater lateral displacement and lateral tilt of the patella, and greater medial trochlea inclination, increased the risk of worsening lateral patellofemoral cartilage and patellofemoral BMLs, respectively (Macri et al., 2019). Movement retraining during functional tasks may be needed to optimise patellofemoral loads. In the KOALA cohort, smaller knee flexion moments (e.g., possibly due to landing on a more extended knee, having less knee flexion

excursion, or altered trunk lean) during a hop-landing task were associated with an increased risk of patellofemoral OA features on MRI (Culvenor et al., 2016e). Clinicians should be mindful that the mechanisms by which strength, function, and/or biomechanics influence patellofemoral joint health are largely theoretical and may be due to a combination of mechanical underloading or overloading in the setting of a vulnerable biochemical joint environment.

The patellofemoral joint should be considered a potential source of symptoms following ACLR (Culvenor & Crossley, 2016). Patellofemoral cartilage lesions were associated with worse PROs five years following ACLR (Chapter 4), and patellofemoral radiographic OA has been associated with worse function and symptoms compared to tibiofemoral OA in the longer-term (Culvenor et al., 2013; Culvenor et al., 2014b). Anterior knee pain was common (~30% scored ≤87 on the AKPS) one year following ACLR in previous reports from the KOALA cohort, and was associated with worse functional performance on hop testing (Culvenor et al., 2014a). Clinicians should aim to improve patellofemoral-related pain following ACLR, as it might enhance quadriceps activation, improve strength and/or functional performance (Lepley et al., 2018). However, clinicians should be mindful that post-operative imaging findings on MRI may not be the source of patient nociception or symptoms following ACLR, especially since most other OA features on MRI were not associated with PROs in Chapter 4. The relationship between patellofemoral cartilage damage and knee-related symptoms is likely to be indirect, and may be mediated by physical impairments or nociception from other joint structures, especially given cartilage is considered aneural and avascular (Miller et al., 2015). Patellofemoral cartilage lesions can co-exist with persistent inflammation or irritation of the infra-patellar fat pad and surrounding ligaments, tendons, and muscles, which may drive nociception (Miller et al., 2015).

Specific evidence for treating patellofemoral pain or OA following ACLR is limited, but CPGs for patellofemoral pain and OA recommend incorporating exercise therapy (e.g., knee and hip muscle strengthening, neuromuscular exercises) and education (e.g., pain coping skills) (Collins et al., 2018; van Middelkoop et al., 2018; Willy et al., 2019), similar to the CPG recommendations for post-ACLR rehabilitation. How the quadriceps are strengthened should be considered, as high patellofemoral joint forces can occur during some exercises (e.g., leg extension in the range of 45° to 0° flexion) (Escamilla et al., 1998). Some patellofemoral specific treatment options might also include other physical interventions (e.g., taping, bracing, orthoses, gait retraining) (Collins et al., 2018; van Middelkoop et al., 2018; Willy et al., 2019).

9.2.3 Clinical assessment of PROs and objective function

This thesis highlights the importance of assessing both self-reported and objective function following ACLR in clinical practice. While only 18% passed the functional performance test battery (>90% in all four tests) one year following ACLR (Chapter 6), more than 75% reported acceptable function in sport and recreation (KOOS-Sport and IKDC) at one year (Chapter 4). Furthermore, poor objective functional performance was not associated with worsening KOOS or IKDC scores over the proceeding four years in Chapter 6. The mismatch between objective function and self-reported symptoms and function is not uncommon (Losciale et al., 2019), highlighting the need to assess multiple constructs throughout rehabilitation and prior to discharge. While the patient's own perception of their function is important, physical deficits could have future implications unbeknown to them, such as structural deterioration (Chapter 6) (Pinczewski et al., 2007) or future symptoms (Losciale et al., 2019).

The results of this thesis suggest that clinicians should use a battery of functional tasks assessing different aspects of function (e.g., strength, power, endurance, balance, coordination). Traditional linear and non-fatigued tests such as the single- and triple-crossover hop tests could be complemented with the side-hop and one-leg rise tests. Deficits were most evident in the side-hop and one-leg rise tests, which assess other aspects of lower-limb function (i.e., mediolateral power and coordination, endurance). This is important as poor performance on the side-hop and the test battery was associated with the greatest risk of worsening patellofemoral BMLs (Chapter 6). Expanding the hop test battery will also increase the chance of identifying those at higher risk of re-injury (Grindem et al., 2016; Kyritsis et al., 2016) or future symptoms and QoL impairments (Bodkin et al., 2017; Culvenor et al., 2016c; Ericsson et al., 2013; Losciale et al., 2019). Even for those who do not wish to return-to-sport, restoring and maintaining full function via ongoing exercise therapy has future joint health and general health benefits (Skou et al., 2018). Regular re-assessment and performance benchmarks on a range of tests patient-specific tests may enhance motivation and exercise adherence (Grindem et al., 2015b; Walker et al., 2020).

The LSI should be interpreted with caution, as this thesis found it may overestimate improvement when the contralateral limb function is used as the reference standard. The potential overestimation of functional ability calls into question the wide use of the LSI following ACLR for return-to-sport clearance in clinical settings (Almangoush & Herrington, 2014; Burgi et al., 2019; Engelen-Van Melick et al., 2013) or as an outcome measure in research. Over-reliance on the LSI as part of return-to-sport clearance might contribute to the high rates of subsequent ACL injury (Wiggins et al., 2016). Clinicians might consider using pre-operative or early post-operative

assessment of contralateral limb hop test performance (once acute pain and swelling have resolved) as the performance benchmark (Wellsandt et al., 2017), or comparing performance to normative data from age-, sex-, and activity-matched healthy individuals (Ageberg et al., 2001a; Baltaci et al., 2012; Engelen-Van Melick et al., 2013; Kemp et al., 2013; Kockum & Heijne, 2015; Myers et al., 2014). Pre-operative or early post-operative assessment of contralateral limb function also has inherent limitations, as pre-injury physical performance may be poor and set the bar too low. Rehabilitation should aim to improve functional performance to a level appropriate for the patient's age, sex and desired activity level. Published normative data may not be generalisable, as it is often determined from college athletes (Myers et al., 2014) or small sample sizes (Baltaci et al., 2012; Kemp et al., 2013; Kockum & Heijne, 2015;). College athlete performance values may be unrealistic for amateur athletes to achieve. Clinicians should use a combination of pre-operative, early and late post-operative assessment of contralateral limb performance to calculate the LSI, and compare both limbs to normative data.

9.2.4 Secondary prevention strategies

Secondary prevention interventions aim to prevent or slow post-traumatic OA or knee-related symptoms by targeting modifiable factors associated with disease onset and/or progression. This thesis identified individuals at one year who were at risk of a worse structural or symptomatic prognosis five years following ACLR and in greatest need of early secondary prevention interventions. Individuals most at risk of worsening OA features were those with: (i) a high BMI >25 kg/m^2 (Chapter 3) and (ii) poor functional performance (Chapter 6) one year post-operatively. Individuals with worse PROs at five years had: (i) a combined injury (and were older and heavier) (Chapter 4) and (ii) lower KOOS/IKDC scores one year post-operatively. While there is little evidence supporting interventions to slow or prevent symptomatic post-traumatic OA following ACLR, current best practice for clinicians should address modifiable prognostic factors (Whittaker & Roos, 2019). The intervention in Chapter 8 was based on current recommendations for post-operative rehabilitation and secondary prevention strategies.

Clinicians may consider applying dietary and/or exercise-based interventions to optimise body weight in the post-traumatic OA population. Weight gain is common following ACLR (Toomey et al., 2017; Whittaker et al., 2019), and in this thesis BMI increased (by 4%) between one and five years post-ACLR, and the cohort was classified as overweight at both time-points. Importantly, a higher BMI at one year was associated with an increased risk of worsening of most OA features on MRI. Weight gain can cause mechanical overload on joint tissues and/or, via fat mass have a biological pro-inflammatory effect on the joint environment (Malfait, 2016). Therefore, achieving and maintaining a healthy body weight may prevent or slow OA progression, particularly as obesity

is one of the strongest risk factors for incident non-traumatic OA (Blagojevic et al., 2010). Further, weight loss can reduce compressive joint load, inflammatory markers, and meniscal worsening (Loeser et al., 2017; Messier et al., 2020; Messier et al., 2011; Munugoda et al., 2020), and improve OA symptoms (Chu et al., 2018) in the general population. The intervention evaluated in Chapter 8 was not specifically designed to address weight gain or body composition; however, the education component included topics such as the importance of weight management.

Addressing patient-specific lower-limb impairments with exercise therapy might assist with secondary prevention of post-traumatic OA, given the association between poor functional performance and worsening (patellofemoral) OA features identified n Chapter 6. Persistent lower-limb strength and functional deficits may contribute to joint *overload*, impairing the ability to dissipate forces (Bennell et al., 2013; Palmieri-Smith & Thomas, 2009; Segal & Glass, 2011). Alternatively, strength and functional deficits may *underload* joint tissues, as they are often associated with lower peak knee moments during functional tasks (Gardinier et al., 2014; Schmitt et al., 2015). Underloading might cause cartilage thinning and weakness, contributing to post-traumatic OA development (Chaudhari et al., 2008; Clark et al., 2006; Herzog et al., 1993; Shiomi et al., 2010). Quadriceps weakness can increase the risk of symptomatic radiographic non-traumatic knee OA development in the general population (Culvenor et al., 2019c; Oiestad et al., 2015; Segal & Glass, 2011), but this relationship is not clear in those with post-traumatic OA (Oiestad et al., 2010b; Wellsandt et al., 2018). Chapter 8 indicates that exercise therapy and education have potential to improve functional performance one year following ACLR, but a fully-powered RCT is required to determine if the improvements are clinically meaningful and if improved strength and/or function can prevent or slow the progression of structural features of OA.

In this thesis, the presence of a combined injury at the time of ACLR as well as worse PROs at one year after ACLR were the biggest predictors of worse PROs at five years. Clinicians should consider ongoing education and exercise therapy for individuals with persistent symptoms and impaired QoL at one year. Having “failed” their first attempt at recovery, it is likely that individuals with persistent symptoms may present with unique challenges (e.g., misguided beliefs, decreased motivation, negative experiences with rehabilitation). In Chapter 8, exercise adherence was low; therefore, developing strong rapport and providing education regarding criteria-based progression and the rationale for ongoing rehabilitation may be particularly important for this group of individuals in order to increase motivation (Truong et al., 2020; Walker et al., 2020). Individuals who are willing to accept changes to their lifestyle or activity preferences may have better longer-term QoL (Filbay et al., 2016). Despite low adherence, Chapter 8 indicated that

exercise therapy and education have the potential to provide worthwhile effects on knee-related symptoms and QoL in a full-scale RCT. Health professional delivered education and exercise therapy can improve knee-related QoL, lower use of medications, and delay the need for TKR in those with non-traumatic knee OA (Skou et al., 2018; Thorlund et al., 2020), supporting their use for those with or at risk of post-traumatic OA following ACLR until further research is conducted.

9.3 Future perspectives and research implications

9.3.1 Future directions for observational cohort studies

This thesis has highlighted important considerations for future observational cohort studies investigating the early stages of post-traumatic OA following ACLR.

Confirming patellofemoral and tibiofemoral OA trajectory following ACLR

The patellofemoral and tibiofemoral compartments should be evaluated separately, due to their apparent differences in OA progression (Chapter 3), associations with symptoms (Chapter 4), and prognostic factors (Chapter 6). Compared to the tibiofemoral joint, the patellofemoral joint is under-researched following ACLR. The sequelae of OA development is of interest, as patellofemoral OA may precede tibiofemoral OA, whereby joint disease is initially isolated to the patellofemoral compartment (i.e., without tibiofemoral involvement), proceeded by whole knee joint degeneration (Stefanik et al., 2016; Stefanik et al., 2013). The higher rates of patellofemoral worsening in this thesis require confirmation in future longitudinal MRI evaluations due to conflicting results in other cohorts (van Meer et al., 2016; Whittaker et al., 2018). The lower rates of patellofemoral OA on MRI in the KNALL (van Meer et al., 2016) and PrE-OA study (Whittaker et al., 2017) may be due to their different MRI acquisition methods (i.e., lower magnetic field strength), or their younger, more active populations, with a lower BMI and fewer concomitant patellofemoral chondral lesions. Further investigation of the factors and mechanisms underpinning structural degeneration in each compartment is needed, ideally in studies with larger samples and consistent MRI evaluation methods. In this thesis, worse functional performance was associated with increased risk of worsening patellofemoral OA features, but not tibiofemoral OA. This appears consistent with prior work in the general population where quadriceps strength is more strongly associated with risk of patellofemoral than tibiofemoral OA (Amin et al., 2009; Culvenor et al., 2019c). Future studies should investigate the influence of other modifiable factors with potential to influence post-traumatic patellofemoral structural degeneration in the KOALA cohort, such as patellofemoral alignment (Macri et al., 2019) and biomechanics during functional tasks (Culvenor et al., 2014c; Culvenor et al., 2016e; Sritharan et al., 2020).

Determine a core set of outcome measures for longitudinal cohort studies

Future studies should aim to utilise a core set of structural (OA features on MRI), patient-reported (e.g., KOOS, IKDC), and physical measures (e.g., functional performance, BMI) that are responsive to change and/or have prognostic capabilities following ACLR. The worsening OA features on MRI over four years supports the feasibility and sensitivity of the MOAKS for monitoring structural changes over short periods of time, and informing future effect sizes for natural changes. The relationship between early OA features on MRI with future symptomatic radiographic post-traumatic OA requires further investigation. Future longer-term cohorts should include concurrent radiographic examinations, healthcare system (e.g. TKR rates, risk of other chronic diseases) and societal costs (e.g., absenteeism, early retirement) (Ackerman et al., 2017). Chapter 4 and 5 highlighted the importance of considering individual patient data as well as mean group-level scores in longitudinal cohorts evaluating patient-reported and functional performance outcomes following ACLR. Future studies should consider reporting the proportion of individuals who improve, remain stable, or worsen.

The KOOS is widely used and is valid for ACLR populations and older individuals with knee OA, but ceiling effects were observed in a substantial proportion of KOALA participants for the KOOS-Symptoms (9%), KOOS-Pain (17%), and KOOS-Sport (21%) subscales. Future cohort studies may consider valid, ACL-specific measures such as the ACL-QoL, which have minimal ceiling effects and evaluate different aspects of knee-related QoL (e.g., emotional and social impact) not evaluated by the KOOS (Lafave et al., 2017). For functional performance, the hop tests and one-leg rise test can identify individuals who are at risk of structural degeneration. Importantly, these tests were responsive to change following a 16-week exercise therapy and education intervention in Chapter 8. However, less challenging tests may be required across the OA disease continuum for lower-functioning individuals. In the KOALA cohort, 6% at one and five years, and 30% in the pilot RCT at one year, were unable to complete a successful side-hop on their ACLR limb. The one-leg rise may be suitable for individuals unable to hop, but easier tests (e.g., a sit to stand test) should be considered to monitor functional changes across the lifespan (Emery et al., 2019), as the one-leg rise also had floor effects (score of 0) in 10% of the KOALA cohort participants at one and five years, and 17% in the pilot RCT.

To advance understanding of the relationships between functional performance, structure, and symptoms observed in this thesis, replication in multiple independent studies and a meta-analysis of individual participant data may be required (Nielsen et al., 2020; Riley et al., 2013). Therefore, researchers should decide on a standardised set of structural, patient-reported, and functional

performance measures and their reporting methods, to facilitate evidence synthesis and data sharing initiatives (Emery et al., 2019). Additional outcomes might include - physical outcomes (return-to-sport, muscle strength, biomechanics, body composition) and psychosocial and contextual factors, to provide insight into the mechanisms underpinning symptomatic decline and post-traumatic OA progression.

Determine the role of other physical outcomes in post-traumatic OA

The role of physical activity and sports participation on development and/or progression of post-traumatic OA and symptoms should be investigated. The relationship between poor function at one year post-ACLR and increased risk of worsening (patellofemoral) OA features (Chapter 6) might be moderated by return-to-sport. Returning to sport is not associated with an increased risk of worsening OA features on MRI at 5-years (Haberfield et al., 2020), and might protect against longer-term radiographic or symptomatic OA at 15 years (Oiestad et al., 2018). However, larger prospective cohort studies with sufficient power to detect the longer-term risks or benefits of return-to-sport are required, and if the effect is moderated by the type of sport, timing of return, physical impairments at time of return, or participant characteristics (e.g., sex). Longitudinal assessment of structural outcomes, muscle strength, body composition (e.g., BMI, fat mass), and biomechanics during sport-specific tasks, at the (expected) time of return-to-sport with a short- to medium-term follow-up (two to five years), combined with regular (i.e., monthly) activity monitoring, may provide insight into the potential loading mechanisms underpinning post-traumatic OA. Given that surgical success is often judged on a return to pre-injury sport, and some patients have misguided beliefs that repetitive joint loading (e.g., running) will increase their risk of OA (Bennell et al., 2016), prospective cohorts designed to evaluate the impact of return-to-sport on structural and patient-reported outcomes are required.

Determine the role of psychosocial and contextual factors

In this thesis, functional deficits and persistent symptoms were noted in many individuals at one and five years following ACLR, but psychosocial and contextual factors contributing to inadequate recovery were not explored and warrant investigation. Psychosocial factors such as self-motivation, optimism, and athletic identity can influence patient-reported and physical recovery (Everhart et al., 2015; Truong et al., 2020; Walker et al., 2020). Greater fear of re-injury is common following ACLR (Flanigan et al., 2013), and greater fear is associated with knee load avoidance during single-leg landing tasks (Trigsted et al., 2018). Underloading may increase the risk of post-traumatic OA development (Wellsandt et al., 2018; Wellsandt et al., 2016); hence, future studies should evaluate the relative contribution of psychological factors to joint loading or avoidance of physical activity, and their effect on structure over time. Importantly, factors such as confidence,

fear, and emotional impacts are potentially modifiable as evidenced by the improvements in the ACL-RSI and ACL-QoL in Chapter 8. Contextual factors such as participation in rehabilitation may also impact functional recovery (Walker et al., 2020). Retrospective participant recall from the KOALA cohort at one year suggests that there is underutilisation of rehabilitation, with approximately 70% ceasing prior to six months post-ACLR (Patterson et al., 2016). However, future prospective studies designed to assess rehabilitation participation, via regular independent assessment methods (e.g., clinical notes) to avoid recall and reporting bias, will provide insight into current practice and can inform strategies to increase uptake of evidence-based care.

Include surgical and non-surgically treated ACL-injured patients

The KOALA cohort only included individuals who underwent ACLR, as this is the treatment of choice in Australia (Moses et al., 2012; Rooney, 2016). Emerging evidence suggests that on average, there are few differences between those who undergo ACLR compared to those with non-surgical management with respect to symptoms, function, return-to-sport, QoL, and prevalence of radiographic OA (Chalmers et al., 2014; Filbay et al., 2015; Filbay & Grindem, 2019; Lien-Iversen et al., 2020; Smith et al., 2014). The KOOS scores and prevalence of tibiofemoral radiographic OA in the KOALA cohort at 5 years were similar to those treated non-surgically in the KANON trial at 5 years post-injury, while patellofemoral radiographic OA was higher in the KOALA cohort (Frobell et al., 2013). Most other surgical and non-surgical management comparisons have focussed on long-term (>5 years) radiographic OA and QoL outcomes (Chalmers et al., 2014; Filbay et al., 2015 Lien-Iversen et al., 2020). Given the equally high risk of post-traumatic OA and poor QoL, future prospective cohorts should evaluate if early prognostic factors differ between surgical and non-surgical management. Evaluation shorter-term structural (MRI), patient-reported (confidence, physical activity) and physical performance (e.g., muscle strength, hop tests) prognostic factors in both ACL-deficient and ACLR populations may help inform treatment choice and rehabilitation after ACL injury.

9.3.2 Future directions for secondary prevention trials

The findings of this thesis can inform larger secondary prevention trials to evaluate the effectiveness of interventions aiming to slow or prevent structural or symptomatic deterioration (poor prognosis) following ACLR. A physiotherapy-guided intervention is feasible, and the target population at higher risk of poor prognosis appears to be those with either a higher BMI, combined injury, poor functional performance, and/or worse PROs one year following ACLR.

Eligibility criteria

Future clinical trials should select individuals who are at greatest risk of a worse prognosis. While individuals with a combined injury have worse outcomes (Hamrin Senorski et al., 2019; van Meer et al., 2015), not everyone with a combined injury had persistent symptoms or worsening OA features (Chapter 3 and 4 and 8). Eligibility for secondary prevention clinical trials should be focused on the presence of symptoms and functional or QoL impairments. The large individual variation in PROs at one year following ACLR in this thesis indicates that trial design might need to take factors affecting baseline status or treatment response (e.g., age, sex, pre-injury activity level) into consideration. Future trials could include patients from public and private healthcare settings as well as rural and lower socioeconomic areas, who may have more limited access to evidence-based rehabilitation to enhance external validity. Clinical trials in ACL-deficient populations are also required, due to their equally high risk of post-traumatic OA development (Lien-Iversen et al., 2020).

Study design: Comparator group

The comparator group for future RCTs evaluating exercise and education interventions requires careful consideration. A wait-list or no/minimal-intervention control group might better represent standard care 6 to 12 months following ACLR than the trunk-focussed intervention provided in Chapter 8. However, a minimal intervention control group poses problems with uneven contact with clinicians between groups due to the non-specific effects of therapeutic alliance and placebo (Chen et al., 2020). Minimal intervention control groups would require reliable monitoring of participation in co-therapies, exercise, physical activity, and sport.

Intervention content: Weight management

Given that a higher BMI increased the risk of worsening OA features on MRI, interventions targeting weight loss in those who are overweight or obese may prove powerful in improving symptoms and structural progression after ACLR, based on results in older adults with knee OA (Chu et al., 2018; Loeser et al., 2017; Messier et al., 2020; Munugoda et al., 2020). Future trials may consider including more advanced assessments of body composition (e.g., dual-energy X-ray absorptiometry) and evaluating the effect of multidisciplinary diet and/or exercise-based interventions.

Intervention content: Education and psychological interventions

The effects of education and/or psychological interventions should be determined in future studies. Education alone may as effective as exercise therapy (De Oliveira Silva et al., 2020), and future trials could evaluate the effect of formalised education by assessing changes in participant knowledge, beliefs, and psychosocial factors in addition to changes in symptoms. Future

evaluation of psychological interventions (e.g., motor imagery, role modelling, or motivational interviewing) that target known psychological impairments following ACLR (e.g., fear, confidence, self-efficacy) might be effective for those with persistent symptoms one year following ACLR in order to increase exercise adherence (Everhart et al., 2015; Truong et al., 2020; Walker et al., 2020).

Intervention format: Duration, frequency, and individualisation

Further research is required to determine the optimal dose and duration of supervised rehabilitation following ACLR, particularly for those with persistent symptoms and previous burden (e.g., time, financial, inconvenience, emotional) of rehabilitation over an extended period (Walker et al., 2020). The influence of a longer, more intense, and individualised intervention could be evaluated in future trials, given that the 16-week intervention (Chapter 8) may have been insufficient to achieve optimal patient-reported and functional performance outcomes. Future trials might consider a pragmatic approach, whereby those who are progressing independently attend less frequently, and those not improving have increased supervision. Exercises should be prescribed according to individual needs and preferences (e.g., duration, gym- or non-gym, individual or group) to maximise adherence (Aboagye, 2017). In Chapter 8, participants reported that there were too many exercises to complete in addition to their sports-related activities (e.g., running, team-based training). Future trials may consider three to four priority exercises combined with optional additional exercises to enhance adherence (Chapter 8). Supervised group classes provide opportunity for peer support, and are equally effective as one-to-one physiotherapy at improving pain and function in musculoskeletal conditions, with lower healthcare costs (O'Keeffe et al., 2017). Group-based exercise can improve symptoms, function, and QoL in individuals with knee OA (Skou & Roos, 2017), but evaluation of its effectiveness in a younger post-traumatic OA population is required.

Strategies to increase unsupervised exercise adherence

To increase effectiveness of future interventions, strategies to increase exercise adherence (<52% in Chapter 8) are required. Adherence monitoring following ACLR is prone to attrition bias and lacks consistent definition of parameters (e.g., frequency, duration, intensity) and reliable measurement tools (Walker et al., 2020). The use of mobile apps (such as Physiapp© in Chapter 8) can increase adherence to data entry initially, but may be less useful once patients are familiar with their program. Increasing the interactivity (e.g., progress reports, informational or peer support) or incentivising use (e.g., gamification) of apps to promote adherence and data completion may be required (Nussbaum et al., 2019; Reynoldson et al., 2014). Regular goal setting and re-assessment may facilitate adherence (Walker et al., 2020), concurring with participant

feedback in Chapter 8. Social support (i.e., from family) can allow patients to prioritise time to complete their rehabilitation (Brewer et al., 2003).

Future perspectives: Determining treatment effects and mechanisms

While this thesis highlights that exercise therapy and education have the potential to improve knee-related QoL, symptoms and function in those at higher risk of post-traumatic OA, the mechanisms underpinning their concurrent improvement are likely to be multifactorial and require further investigation. Improved physical function may increase activity level, confidence, and QoL, or reduce nociception by optimising joint load (Bennell et al., 2013; Palmieri-Smith et al., 2013). Conversely, improvement in symptoms or confidence via co-therapies (education) or the placebo effect may moderate improvements in physical outcomes. Future trials might evaluate individual treatment responses across multiple constructs (e.g., do improvements in physical function correlate with improved confidence?) to understand these mechanisms. Future trials are needed to determine if improved function can slow the progression of OA or symptoms, and if interventions are cost-effective. Future RCTs may include structural measures in the short- (e.g., quantitative MRI), medium- (e.g., semi-quantitative MRI), and longer-term (e.g., X-ray). Short follow-ups (<2-years) utilising MRI may be appropriate given the sensitivity to change noted in Chapter 3. Intervention costs evaluated against potential benefits at a societal (work productivity), healthcare system (e.g., surgery), and individual level (e.g., symptoms, function, health-related QoL, co-morbidities) should be assessed in the short- and long-term. Findings from the pilot RCT have provided guidance for a large-scale RCT commencing in 2021, titled "**SU**pervised exercise therapy and **P**atient **E**ducation **R**ehabilitation after knee injury" (**SUPER** knee trial). The trial will evaluate quantitative cartilage changes on MRI following a 12-month physiotherapist-guided exercise and education program for individuals with poor knee-related QoL following ACLR, and will include health economic evaluation.

9.4 Strengths of the research design

The KOALA cohort, from which Study 1 to 4 is based, is one of the few longitudinal prospective cohort studies evaluating structural outcomes alongside symptomatic and functional outcomes beyond the first post-operative year. The natural course and relationships between structural, patient-reported, and functional performance outcomes are highlighted in an under-investigated time-period after acute recovery, but prior to end-stage disease. Utilising the sensitivity of MRI and semi-quantitative scoring systems, this cohort has built upon other large ACL-injured and ACLR cohorts by evaluating worsening of focal OA features (i.e., cartilage, bone, and menisci) in both the tibiofemoral and patellofemoral compartments and modifiable prognostic factors. While

imaging evaluation following ACL injury cannot determine if the pathology was pre-existing, using a worsening definition of OA features incorporates baseline lesions which may have pre-existed.

Most characteristics of the KOALA cohort are similar to previous reviews and registry data, increasing the generalisability of the findings of this thesis. The proportion of female participants (Ahldén et al., 2012; Sarraj et al., 2019; Spindler et al., 2018), the prevalence of concomitant injuries (Granan et al., 2009; Sarraj et al., 2019; Spindler et al., 2018), re-injuries (Wright et al., 2011), radiographic OA (Belk et al., 2019; Cinque et al., 2018), and the KOOS (Ahldén et al., 2012; Spindler et al., 2018) and IKDC (Sarraj et al., 2019) scores at one and five years were similar to previous reviews and registry data. While participants from the KOALA cohort were slightly older at the time of ACLR compared to registry data (Ahldén et al., 2012; Spindler et al., 2018), age was adjusted for in all regression models, and did not strongly influence patient-reported or structural outcomes. At five years, the follow-up rate of 70% minimises the risk of attrition bias. There were no differences between those who did and did not participate at five years regarding participant characteristics and structural, patient-reported, and functional performance outcomes at the one-year assessment. This was except for medial meniscal lesions on MRI at one year, which were more prevalent in those who participated in the five-year assessment.

The research design in Part B and Part C minimised potential systematic biases by using recommended study designs, outcome measures (Emery et al., 2019), and reporting methods (Elm et al., 2007). All ACLRs used consistent surgical techniques, by one of two high-volume orthopaedic surgeons. All MRIs were evaluated by an experienced musculoskeletal radiologist with established inter- and intra-rater reliability (Hunter et al., 2011a), who was blind to clinical and radiographic information. The reliability of the KOOS, IKDC, ACL-QoL, and ACL-RSI is well-established (Chapter 2). All objective functional performance measures were collected by a researcher blind to the side of surgery. Procedures for the functional performance tests (Chapter 2,) were completed with standardised procedures (e.g., testing order, landing requirements, hand placement) according to reporting standards (e.g., best or mean score) for hop testing (Read et al., 2020). Reporting in Part B adhered to the STROBE guidelines (Elm et al., 2007) for observational cohort studies, while the pilot RCT in Part C was prospectively registered, and reporting complied with the CONSORT guidelines for pilot feasibility RCTs (Eldridge et al., 2016). The exercise intervention in Chapter 8 adhered to resistance training principles (American College of Sports Medicine, 2009) and was reported according to the TiDier (Hoffmann et al., 2014) and CERT templates (Slade, 2016). Detailed descriptions of the exercise therapy program and education materials used in Chapter 8 are available online. Clinicians could replicate the intervention, increasing the potential real-world

impact of the research in this thesis and meeting the call for better reporting of exercise dosage (Goff et al., 2018).

The studies in Part B adopted statistical methods recommended for prognostic and sports injury research (Riley et al., 2013;Nielsen et al., 2020). The analysis of longitudinal data poses many challenges, such as handling dependencies due to repeated measures on each individual, the complexity of OA disease over time, and multiple confounding variables (Nielsen et al., 2020). Study 1 and 4 accounted for correlated data (e.g., worsening OA features between subregions within the same participant) by using an appropriate statistical approach (GEE). This approach also increased the statistical power of the analysis, as each participant contributed multiple data points for each worsening model, according to the number of subregions (e.g., 10 subregions for tibiofemoral cartilage worsening). Age, sex, BMI, and presence of a combined injury were adjusted for in regression analyses, given the potential influence of these factors and the previous underutilisation of multivariate analyses (An et al., 2017; van Meer et al., 2015). The one-year KOOS and IKDC scores were adjusted for in Study 2 and 4 (when five-year KOOS/IKDC scores were the outcome variable), due to the known associations between baseline PROs and future outcomes (Spindler et al., 2018).

9.5 Limitations of the research design

Specific limitations of each study are reported in their respective chapters. Generally, there was potential for selection bias at entry into the KOALA cohort study at one year. All consecutive eligible patients with an ACLR from the two privately operating orthopaedic surgeons were invited to participate at one year, but only two-thirds accepted the invitation and enrolled. However, there were no differences between those who did and did not participate in the one-year assessment with respect to age, sex, pre-injury level of sports activity, time from injury to ACLR, and prevalence of concomitant injuries (Culvenor et al., 2015a). The ACL-injured individuals accessing the private healthcare system in metropolitan Melbourne for ACLR may differ to other ACL-deficient and ACLR individuals in the public healthcare system or in rural areas, decreasing the generalisability of the findings in the KOALA cohort. Lack of private healthcare access or geographic location may limit the ability to have an ACLR for a ruptured ACL, and may reflect different socioeconomic status, cultural beliefs (e.g., about pain), access to evidence-based rehabilitation, motivation to return to full function, and lifestyle (e.g., diet). Hence, the results of this thesis may not accurately reflect the burden of post-traumatic OA following ACLR. The KOALA cohort had lower return-to-sport rates and inferior function compared to several other cohorts (Abrams et al., 2014; Ardern et al., 2014b; Lepley, 2015), potentially reflecting the slightly older

age of the KOALA cohort or the lack of standardised rehabilitation in the first post-operative year, which was not part of this thesis.

The small sample size resulted in low numbers of participants with worsening of some OA features (e.g., osteophytes, BMLs), which may have affected the statistical stability of the regression models in Chapter 3 to 6. The risk estimates for prognostic factors identified in this thesis (BMI, patellofemoral cartilage lesions, functional performance) had wide CIs and may be due to chance. Clinical interpretation of the findings was difficult as the CIs ranged from clinically unimportant (e.g. those with a patellofemoral cartilage lesion had on average 3-points lower KOOS-Symptom score compared to those without a patellofemoral cartilage lesion) to clinically important (e.g. 17 points lower). Further adequately powered cohort studies, and individual participant data meta-analyses amongst other ACLR cohorts are required to validate these prognostic factors. A larger sample size might facilitate adequately powered sub-group analyses (e.g. sex, subsequent injuries) in future studies. Osteophytes and radiographic OA were excluded from prognostic evaluations in Chapter 3, 4, and 6, due to the low numbers of osteophytes ≥grade 2 reported at one and five years. As many patients as possible were recruited into the KOALA cohort at study inception over a 12 month period; due to the feasibility of the original PhD project, an a-priori power calculation was not completed.

9.6 Conclusions

This thesis aimed to evaluate changes in OA features on MRI, PROs, and functional performance between one and five years following ACLR (Part B), identify factors associated with worsening OA features and change in PROs (Part B), and determine the feasibility and effectiveness of a physiotherapist-guided intervention for individuals with persistent symptoms at one year following ACLR (Part C).

Worsening of OA features was most frequent in the patellofemoral compartment, particularly cartilage lesions (44%), which were associated with worse symptoms and QoL at five years. Approximately half of the KOALA cohort had unacceptable symptoms and QoL one year following ACLR, which persisted in one-third at five years. Individuals with a combined injury were older and heavier, and had worse patient-reported symptoms, function, and QoL than their peers with an isolated injury. Only one in five passed the functional performance test battery at one year, a time when most patients expect to be fully recovered and participating in high-demand sports. This thesis builds upon previous cohorts and registry data by identifying modifiable factors (poor functional performance, high BMI) associated with OA development and/or progression, much earlier in the disease process than previously described due to utilisation of MRI. Together these

findings indicate that interventions should aim to reduce body weight, improve patient-reported symptoms and QoL, and improve functional performance, particularly in older individuals with a combined injury, in order to improve prognosis for young adults following ACLR.

The physiotherapist-guided lower-limb-focussed exercise therapy and education intervention appears feasible to test in a larger-scale clinical trial. It also demonstrated potential to provide worthwhile treatment effects for knee-related symptoms, function, and QoL, even beyond the typical rehabilitation period. Future trials will assist in evaluating the effect of improved function and strength via exercise therapy and education on structural outcomes, longer-term knee-related QoL, and cost-effectiveness in those at risk of post-traumatic OA following ACLR.

In summary, this thesis combines three important steps integral to prognostic research and secondary prevention of post-traumatic OA following ACLR: (i) an improved understanding of the natural trajectory of structural, patient-reported, and functional performance outcomes in a critical time-period after acute recovery, but prior to established OA; (ii) early identification of modifiable factors associated with worse prognosis; and (iii) development of a feasible and potentially effective intervention for individuals with a worse prognosis, that can now be tested in a larger RCT. The findings of this thesis provide an important step forward in reducing the burden of post-traumatic OA on young adults following ACLR.

Appendices

The following section contains all appendices associated with Chapters 1 to 9, including:

- Publications and supplementary files associated with this thesis
- Copyright permissions and restrictions
- Confirmation of authorship

Appendix A: Ethical approval letter for studies in Part B

University Human Ethics Committee

RESEARCH OFFICE

MEMORANDUM

To: **Professor Kay Crossley, School of Allied Health, College of SHE**
Brooke Howells, School of Allied Health, College of SHE

From: **Senior Human Ethics Officer, La Trobe University Human Ethics Committee**

Subject: **Review of Human Ethics Committee Application No. 15-100**

Title: **Prevalence of early-onset knee osteoarthritis following anterior cruciate ligament reconstruction and exploration of clinical risk factors**

Date: **16 December 2015**

Thank you for your recent correspondence in relation to the research project referred to above. The project has been assessed as complying with the *National Statement on Ethical Conduct in Human Research*. I am pleased to advise that your project has been granted ethics approval and you may commence the study now.

The project has been approved from the date of this letter until 1 December 2021.

Please note that your application has been reviewed by a sub-committee of the University Human Ethics Committee (UHEC) to facilitate a decision before the next Committee meeting. This decision will require ratification by the UHEC and it reserves the right to alter conditions of approval or withdraw approval at that time. You will be notified if the approval status of your project changes. The UHEC is a fully constituted ethics committee in accordance with the National Statement under Section 5.1.29.

The following standard conditions apply to your project:

- **Limit of Approval.** Approval is limited strictly to the research proposal as submitted in your application while taking into account any additional conditions advised by the UHEC.

- **Variation to Project.** Any subsequent variations or modifications you wish to make to your project must be formally notified to the UHEC for approval in advance of these modifications being introduced into the project. This can be done using the appropriate

form: *Modification to Project – Human Ethics* which is available on the Human Ethics website at http://www.latrobe.edu.au/researchers/ethics/human-ethics If the UHEC considers that the proposed changes are significant, you may be required to submit a new application form for approval of the revised project.

- **Adverse Events.** If any unforeseen or adverse events occur, including adverse effects on participants, during the course of the project which may affect the ethical acceptability of the project, the Chief Investigator must immediately notify the Senior Human Ethics Officer. An *Adverse Event Form – Human Ethics* is available at the Research Office website (see above address). Any complaints about the project received by the researchers must also be referred immediately to the Senior Human Ethics Officer.

- **Withdrawal of Project.** If you decide to discontinue your research before its planned completion, you must advise the UHEC and clarify the circumstances.

- **Monitoring.** All projects are subject to monitoring at any time by the University Human Ethics Committee.

- **Annual Progress Reports.** If your project continues for more than 12 months, you are required to submit a Progress Report annually, **on or just prior to 12 February**. The form is available on the Research Office website (see above address). Failure to submit a Progress Report will mean approval for this project will lapse.

- **Auditing**. An audit of the project may be conducted by members of the UHEC.

- **Final Report.** A Final Report (see above address) is required within six months of the completion of the project or by **1 June 2021.**

If you have any queries on the information above or require further clarification please email: **humanethics@latrobe.edu.au** or contact me by phone.

On behalf of the University Human Ethics Committee, best wishes with your research!

Kind regards,

Ms Sara Paradowski
Senior Human Ethics Officer
Executive Officer – University Human Ethics Committee
Ethics and Integrity / Research Office
La Trobe University Bundoora, Victoria 3086
P: (03) 9479 – 1443 / F: (03) 9479 - 1464
http://www.latrobe.edu.au/researchers/ethics/human-ethics

Appendix B: Participant information statement for studies in Part B

Knee Joint Changes after Anterior Cruciate Ligament Reconstruction Research Project

School of Allied Health; Department of Physiotherapy

LA TROBE UNIVERSITY

Patient Information Sheet

Thank you for participating in our anterior cruciate ligament reconstruction (ACLR) research project in 2011/2012. Our magnetic resonance imaging (MRI) results showed that 31% participants had signs of early-stage knee osteoarthritis (OA) at one year following ACLR. Because of this, it is important to continue to study the changes in the longer-term following ACLR, to identify factors that may place you more at risk of developing knee OA. We may then be able to develop specific treatments to reduce the risk of OA developing. Therefore, we would like to invite you to participate in our follow-up study, now that you are approximately 5 years following your ACLR.

We will also be performing follow up assessments, at eight and ten years following your ACLR (with your consent, we will contact you prior to these assessments, to enquire about your willingness to participate in further testing)

What does this project involve?

Part A

You will be asked to attend the private radiology clinic where you will have a standard knee x-ray. Also, at this location you will also be asked to have an MRI scan of your reconstructed knee – exactly the same as you underwent in the initial study in 2011/2012. For the MRI scan you will be asked to lie on a narrow table that can slide inside a large tunnel-like tube with a scanner. The scanner creates a magnetic field around you, then pulses radio waves at the knee. This does not contain any radiation. The MRI will be reviewed by a radiologist and if any abnormalities (apart from your knee injury) are detected, you will be informed by one of the researchers and advised to contact your medical practitioner. All imaging will be provided at **no cost** to you (funding provided by Arthritis Australia), and will take approximately 45mins to complete.

You may be asked to attend a physical assessment session at the same time as your appointment at the radiology clinic. At the testing session you should allow approximately 30 minutes of your time. You will undergo a physical examination in which you will be asked to wear shorts (provided) and a small piece of stocking over both of your knees so that the examiner is unable to tell which knee is your operated one. The tests conducted in the physical examination will include measures of knee joint motion and flexibility, functional tasks such as squatting and hopping, and measures of your leg posture/alignment. We will also record your height and weight.

We will video your performance during a clinical test (single-leg squat). These videos will not include your face, so you cannot be identified from the footage. If any part of your face or head is inadvertently videoed, this will be masked (by electronically blurring the area) prior to data analysis.

A series of questionnaires will be sent to you, which will ask questions about your pain, physical function levels, confidence with physical movements and physical activity, as well as details about you (gender, body size, limb dominance) and details of your knee pain (e.g. location of pain; history of knee pain) and quality of life. You may choose the preferred option of completing an online survey, printing the questionnaires and bring these completed to the testing session or completing the questionnaires at the testing session with provided copies, which will take 15 – 20 minutes.

Part B (Optional)

You may be contacted and invited to participate in another section of our research, which involves a telephone interview. This would involve questions about factors not addressed in the questionnaires, such as the psychological impact of sports restriction, impact on social and family life and knowledge and beliefs about knee OA. The telephone interviews will be recorded to be coded into different research themes. Your name or personal information will not be used during the recording so that you cannot be identified from the recording.

Part C (Optional)

For the third part of this study, some time after Part A, you may be asked to attend a testing session at the La Trobe University Movement Laboratory. This session will evaluate the

biomechanics and function at your hip, knee and ankle during functional tasks such as walking, running and hopping. Both legs will be tested. You should allow approximately 2 hours for the evaluation. For the measurements, you will be required to change into shorts. You may either bring your own shorts or we can provide you with some. Reflective skin markers and electrodes will be attached to your skin at various sites such as the ankle, knee, hip and trunk as well as over the muscles of your leg. You will be filmed as you walk, run, jump and/or hop. Following this assessment you will be given a short (10 minute) physiotherapy "movement retraining intervention." This involves video feedback of your performance, cueing and practice of improved technique for the tasks assessed previously, followed by reassessment of the tasks.

Who can participate in this study?
You can participate in this study if you participated in our initial study in 2011/2012 when you were one year after your ACLR. You are still able to participate if you have endured subsequent injury or follow-up surgery to the ACLR or opposite knee.
You are **not** eligible to participate in the imaging part of this study if you have become contraindicated since 2011/2012 for x-ray or MRI (see details below).

Because you will be asked to have an x-ray, if you are pregnant or maybe pregnant, or if you are breastfeeding you will not be eligible. Also, if you have a pacemaker, a history of metallic foreign body in the eye, previous surgery for cerebral aneurysm, or other implanted metal material (for example a cochlear implant or surgical screws/plate) there is potential for harm and you should not participate in this part of the project. Your metal implants inserted as part of your ACL reconstruction are NOT cause for concern and do not preclude you from participating in the study. If you are not eligible to have an MRI, you will still be able to take part in the rest of the project.

You may not want to undergo an MRI if you get claustrophobia as you will be required to lie still in an enclosed chamber for the duration of the MRI scan.

If you are not eligible to have an MRI or X-ray you are still able to take part in the rest of the project (i.e. physical testing, Part B: telephone interview, Part C: biomechanics).

Conversely, if you have another injury/condition affecting daily function and the ability to perform clinical testing you will be excluded from this but still able to participate in Part A (MRI and X-ray).

Are there any potential side effects?
X-ray
This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 0.030 mSv. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. The risk is believed to be minimal.

Magnetic Resonance Imaging
There is a side effect related to the use of MRI in individuals with some metal in their body. Thus, it is imperative that you inform the investigator of your full medical history and of previous surgical procedures and any metal implants. You will be given a safety screening form to complete to ensure that it is safe for you to be scanned by the MRI machine. If the practitioner who is assessing your MRI scan believes that you have an abnormal finding that is potentially significant, you will be notified and referred to an appropriate practitioner for further management and investigation.

It is important to be aware that with any imaging investigation there is a small chance of a previously unknown medical condition being detected. In the unlikely event that this occurs, we will contact you directly and inform you of the findings. Should you require further medical review, we will also organise a referral to your chosen GP. It must be emphasized that the purpose of this study is to investigate the lower limb biomechanics and not to identify other potential medical conditions. While we will ensure that you are made aware of any incidental findings reported on by the consulting radiologist, neither the radiologist, nor the Universities involved, will be held accountable if a medical condition exists that is not detected during the process.

Physical testing

The physical tests represent usual examination by a physiotherapist. You may experience a small amount of discomfort in the joints or muscles during the physical examination. Please report to the researcher any undue discomfort or pain experienced during the testing. If the pain or discomfort is deemed to be excessive by yourself or the investigators, then testing will cease. There is a very slight risk of falling during the balance and the hopping tasks.

What if I have any concerns during the study?

If at any stage you have any concerns during the study you can contact chief investigator Professor Kay Crossley (03 9479 2169). Alternatively, investigator Brooke Howells (0418527768), will be available throughout the study if you have any questions. The other investigators will be available if required. La Trobe University Human Ethics Committee has approved this project. If you have concerns about the way the study is being conducted you should contact the Human Ethics Co-ordinator, La Trobe University, ph: (03) 9479 1443

Can I withdraw from the study if I wish?

Your participation in this study is voluntary. If you do not wish to take part you are under no obligation to do so. Also, if you decide to take part but later change your mind, you are free to withdraw from the project at any stage. You may also withdraw any unprocessed data previously supplied by you.

If you are a patient of any of the investigators, your decision whether to take part or not to take part, or to withdraw, will **not** affect your management or influence your clinical care in any way.

If you are a staff member at the University, or of any of the investigators, your decision whether to take part or not to take part, or to withdraw, will **not** affect your future employment in any way.

If you are a student at the University, your decision whether to take part or not to take part, or to withdraw, will **not** affect your future grades or assessment in any way.

Will my details be kept confidential?

The anonymity of your participation is assured by our procedure, in which a code number and not your name will identify you. Video recordings may be taken of your physical performance, and may be used by the researchers to illustrate findings in conference presentations. However, if this is the case, you will be de-identified via editing techniques (blurring/box over face etc). No findings that could identify you will be published and access to individual results is restricted to the investigators. Coded data will be stored for at least 10 years. This data may be accessed at a later time point for evaluation and you may be recontacted for follow-up testing. All data and results will be handled in a strictly confidential manner, under guidelines set out by the National Health and Medical Research Council.

How do I get more information?

You should ask for any information you want. If you would like more information about the study, or if there is any matter about it that concerns you, either now or in the future, do not hesitate to ask one of the researchers. Before deciding whether or not to take part you may wish to discuss the matter with a relative or friend or with your local doctor. You should feel free to do this.

About the researchers:

Chief Investigator: Professor Kay Crossley is a physiotherapist and Professor in the School of Allied Health at La Trobe University.
Associate investigator: Dr Adam Culvenor is a physiotherapist, post-doctoral research fellow at Paracelsus Medical University, Salzburg, Austria, and an honorary research fellow at La Trobe University.
Postgraduate student: Brooke Howells is a physiotherapist and a PhD Candidate at La Trobe University, Department of Physiotherapy.

To contact any of the researchers, please telephone 94792169

Appendix C: Participant consent form for studies in Part B

LA TROBE UNIVERSITY
School of Allied Health, Department of Physiotherapy
Ph: (03) 9479 5815

Consent form for persons participating in research projects

Name of participant: _____

Project title: Knee Joint Changes after Anterior Cruciate Ligament Reconstruction Research Project

Investigator(s): Miss Brooke Howells, Professor Kay Crossley, Dr Adam Culvenor

1) I consent to participate in the above project, the particulars of which - including details of tests or procedures - have been explained to me to my satisfaction; including (Please tick)
   - ☐ X-ray of both knees
   - ☐ MRI of reconstructed knee
   - ☐ Performance physical tests
   - ☐ Video of single leg squat and single leg drop jump performance
   - ☐ Collection of personal information (pain, function, quality of life)

2) I authorize the investigator or his or her assistant to use with me the tests, which includes procedures referred to under (1) above

3) I acknowledge that:
   (a) The possible effects of the tests or procedures have been explained to me to my satisfaction;
   (b) My participation is voluntary and I have been informed that I am free to withdraw from the project at any time and to withdraw any unprocessed data previously supplied;
   (c) The project is for the purpose of research and not for treatment;
   (d) I have been informed that the confidentiality of the information I provide will be safeguarded subject to any legal requirements (including consent to contact my GP in the case of any incidental findings on MRI/X-ray)
   (e) Once signed this consent form will be retained by the researchers.
   (f) The results of this study may appear in conference presentations and journal publications (including de-identified video recording of physical performance)
   (g) I am happy to be contacted for future research projects including the following;
   - ☐ A telephone interview evaluating; impact of early-onset knee osteoarthritis post ACL reconstruction on quality of life
   - ☐ A physical assessment evaluating gait and movement patterns

   (Please tick)

I _____ (the participant) have read (or where appropriate have had read to me) and understood the participant information statement and consent form, and any questions I have asked have been answered to my satisfaction. I agree to participate in the project, realising that I may withdraw at any time. I agree that research data provided by me or with my permission during the project may be included in a thesis, presented at conferences and published in journals on the condition that neither my name nor nay other identifying information is used.

I, _____ consent to participate in the above project.

Signature (participant) Date

Name of Chief Investigator Signature: Date

Name of Student Supervisor Signature: Date

Appendix D: Participant recruitment letter at five years following ACLR

December 30, 2015

Dear XXXXXX:

Thank you for participating in our anterior cruciate ligament reconstruction (ACLR) research project in 2011/2012 with Adam Culvenor.

Our magnetic resonance imaging (MRI) results showed that 31% participants had signs of early-stage knee osteoarthritis (OA) at one year following ACLR. Because of this, it is important to continue to study the changes in the longer-term following ACLR to identify factors that may place you more at risk of developing knee OA. We may then be able to develop specific treatments to reduce the risk of OA developing.

Therefore, we would like to invite you to participate in our follow-up study, now you are approximately 5 years following your ACLR. Please see attached an information sheet, which outlines the details of the project.

Please note you do not have to participate in all parts of the project. Part A can be completed on the same day in 1.5-2 hours at Olympic Park Sports Medicine (includes an MRI, X-ray and physical testing. I can also provide a medical certificate for your employer (as the time is for a medical condition). Part B and C are optional and will occur at a later stage, but if you are interested in participating and happy to be contacted for these projects please tick the box on the consent form.

What to do now;

- Please contact me (0418527768 or B.Howells@latrobe.edu.au) if you have any questions or would like to arrange a time for testing. I will follow up with a phone call
- Even if you cannot attend the testing session, we would appreciate if you could answer some short questionnaires via the online link below

To answer online questionnaires:

1. Click/copy the link: http://koala-latrobe.promptus.com.au/
2. Enter your "First Name" and "Email" (please use email in which we contacted you via)
3. Enter access code (emailed to you)
4. Fill out consent form (will pop up initially). This will also have a link to an information sheet, which you can read more detail about the project and privacy information.
5. Click on questionnaires on dashboard to complete.
6. Please complete all questionnaires to the best of your ability. If you are not sure about any questions you have an option to click "I need help" and this will alert me and we can discuss.

Thank you for your help with our study so far.

Brooke Howells	Adam Culvenor	Kay Crossley
PhD Student,	Co-investigator	Chief Investigator

Appendix E: KOOS questionnaire

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

Appendix F: IKDC questionnaire

2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

Name: _____ _____ **Date:** _____
First Last

Physician: _____ **Date of Injury:** _____

SYMPTOMS*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1.What is the highest level of activity that you can perform without significant knee pain?

- ◯ Very strenuous activities like jumping or pivoting as in basketball or soccer
- ◯ Strenuous activities like heavy physical work, skiing or tennis
- ◯ Moderate activities like moderate physical work, running or jogging
- ◯ Light activities like walking, housework or yard work
- ◯ Unable to perform any of the above activities due to knee pain

2.During the past 4 weeks, or since your injury, how often have you had pain?

	0	1	2	3	4	5	6	7	8	9	10	
Never	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	Constant

3.If you have pain, how severe is it?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	Worst pain imaginable

4.During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

- ◯ Not at all
- ◯ Mildly
- ◯ Moderately
- ◯ Very
- ◯ Extremely

5.What is the highest level of activity you can perform without significant swelling in your knee?

- ◯ Very strenuous activities like jumping or pivoting as in basketball or soccer
- ◯ Strenuous activities like heavy physical work, skiing or tennis
- ◯ Moderate activities like moderate physical work, running or jogging
- ◯ Light activities like walking, housework or yard work
- ◯ Unable to perform any of the above activities due to knee swelling

6.During the past 4 weeks, or since your injury, did your knee lock or catch?

◯ Yes ◯ No

7.What is the highest level of activity you can perform without significant giving way in your knee?

- ◯ Very strenuous activities like jumping or pivoting as in basketball or soccer
- ◯ Strenuous activities like heavy physical work, skiing or tennis
- ◯ Moderate activities like moderate physical work, running or jogging
- ◯ Light activities like walking, housework or yard work
- ◯ Unable to perform any of the above activities due to giving way of the knee

SPORTS ACTIVITIES:

8.What is the highest level of activity you can participate in on a regular basis?

- ◯ Very strenuous activities like jumping or pivoting as in basketball or soccer
- ◯ Strenuous activities like heavy physical work, skiing or tennis
- ◯ Moderate activities like moderate physical work, running or jogging
- ◯ Light activities like walking, housework or yard work
- ◯ Unable to perform any of the above activities due to knee

9.How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	◯	◯	◯	◯	◯
b.	Go down stairs	◯	◯	◯	◯	◯
c.	Kneel on the front of your knee	◯	◯	◯	◯	◯
d.	Squat	◯	◯	◯	◯	◯
e.	Sit with your knee bent	◯	◯	◯	◯	◯
f.	Rise from a chair	◯	◯	◯	◯	◯
g.	Run straight ahead	◯	◯	◯	◯	◯
h.	Jump and land on your involved leg	◯	◯	◯	◯	◯
i.	Stop and start quickly	◯	◯	◯	◯	◯

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

	0	1	2	3	4	5	6	7	8	9	10	
Couldn't perform daily activities	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	No limitation in daily activities

CURRENT FUNCTION OF YOUR KNEE:

	0	1	2	3	4	5	6	7	8	9	10	
Cannot perform daily activities	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	No limitation in daily activities

[ ] IKDC Score

Print Form

Submit

Appendix G: Customised activity level questionnaire

Subject Code:
Date:

	Type of activity/Sport	Level (social, amateur, semi professional, professional)	Frequency per week
Example *You may list more than one activity if this is applicable*	*Basketball*	*Semi Professional*	*2*
	Swimming	*Social*	*3*
	Gym	*Social*	*3*
1-2 years post ACL surgery I.e. Aug 2011 – Aug 2012			
2-3 years post ACL surgery I.e. Aug 2012 – Aug 2013			
3-4 years post ACL surgery I.e. Aug 2013– Aug 2014			
4-5 years post ACL surgery I.e. Aug 2014 – Aug 2015			
Current (5 -6 years post ACL surgery) I.e. Aug 2015 – Aug 2016			

Appendix H: Chapter 3 original publication: American Journal of Sports Medicine

Worsening Knee Osteoarthritis Features on Magnetic Resonance Imaging 1 to 5 Years After Anterior Cruciate Ligament Reconstruction

Brooke E. Patterson,* PT, Adam G. Culvenor,*† PT, PhD, Christian J. Barton,* PT, PhD, Ali Guermazi,‡ MD, PhD, Joshua J. Stefanik,§ PT, Hayden G. Morris,‖ MD, Timothy S. Whitehead,¶ MD, PhD, and Kay M. Crossley,*# PT, PhD
Investigation performed at La Trobe Sport and Exercise Medicine Research Centre, School of Allied Health, La Trobe University, Melbourne, Victoria, Australia

Background: An anterior cruciate ligament (ACL) injury is a well-established risk factor for the long-term development of radiographic osteoarthritis (OA). However, little is known about the early degenerative changes (ie, <5 years after injury) of individual joint features (ie, cartilage, bone marrow), which may be reversible and responsive to interventions.

Purpose: To describe early degenerative changes between 1 and 5 years after ACL reconstruction (ACLR) on magnetic resonance imaging (MRI) and explore participant characteristics associated with these changes.

Study Design: Case-control study; Level of evidence, 3.

Methods: Seventy-eight participants (48 men; median age, 32 years; median body mass index [BMI], 26 kg/m^2) underwent 3.0-T MRI at 1 and 5 years after primary hamstring autograft ACLR. Early tibiofemoral and patellofemoral OA features were assessed with the MRI Osteoarthritis Knee Score. The primary outcome was worsening (ie, incident or progressive) cartilage defects, bone marrow lesions (BMLs), osteophytes, and meniscal lesions. Logistic regression with generalized estimating equations evaluated participant characteristics associated with worsening features.

Results: Worsening of cartilage defects in any compartment occurred in 40 (51%) participants. Specifically, worsening in the patellofemoral and medial and lateral tibiofemoral compartments was present in 34 (44%), 8 (10%), and 10 (13%) participants, respectively. Worsening patellofemoral and medial and lateral tibiofemoral BMLs (14 [18%], 5 [6%], and 10 [13%], respectively) and osteophytes (7 [9%], 8 [10%], and 6 [8%], respectively) were less prevalent, while 17 (22%) displayed deteriorating meniscal lesions. Worsening of at least 1 MRI-detected OA feature, in either the patellofemoral or tibiofemoral compartment, occurred in 53 (68%) participants. Radiographic OA in any compartment was evident in 5 (6%) and 16 (21%) participants at 1 and 5 years, respectively. A high BMI (>25 kg/m^2) was consistently associated with elevated odds (between 2- and 5-fold) of worsening patellofemoral and tibiofemoral OA features.

Conclusion: High rates of degenerative changes occur in the first 5 years after ACLR, particularly the development and progression of patellofemoral cartilage defects. Older patients with a higher BMI may be at particular risk and should be educated about this risk.

Keywords: knee; anterior cruciate ligament; osteoarthritis; cartilage

Anterior cruciate ligament (ACL) reconstruction (ACLR) is often performed with the intention to improve the stability of a mechanically unstable ACL-deficient knee, facilitate a return to competitive sports, and reduce the risk of subsequent meniscal or cartilage damage.[8,31,50] While typically restoring mechanical stability, ACLR does not protect against the long-term development of knee osteoarthritis (OA).[21,32] Radiographic knee OA is evident in as many as 50% to 90% of patients 10 to 15 years after an ACL injury, regardless of treatment, and often with an onset during early adulthood.[32]

With rates of ACL injuries continuing to rise,[47] secondary prevention strategies to delay or halt OA onset after an injury are vital.[43] Unlike established radiographic OA, the trajectory of early pre radiographic stages of disease, such as posttraumatic changes to cartilage and bone marrow, has the capacity to be modified.[40,44] This is particularly pertinent for posttraumatic OA, which is often evident 15

The American Journal of Sports Medicine
2018;46(12):2873–2883
DOI: 10.1177/0363546518789685

years earlier than primary OA,[32] resulting in substantial and prolonged effects on quality of life[19] and the risk of early knee arthroplasty.[7]

Magnetic resonance imaging (MRI) can be used to identify and monitor early structural changes to all joint tissues. While radiography can detect osteophytes, joint space narrowing, subchondral sclerosis, and cysts, MRI is more sensitive to changes in early OA features such as cartilage, particularly during shorter follow-up periods.[2,25,27] Longitudinal changes to MRI-detected OA features have focused on cartilage degeneration within the acute recovery phase after ACLR (ie, first 1-2 years),[52,54] mostly assessed and observed in the tibiofemoral compartment. In the patellofemoral joint, the trochlea is at greatest risk of early degeneration within the first 2 years after an ACL injury,[10,20] which may contribute to high rates of longer-term radiographic patellofemoral OA.[11] Identifying patients with progressive early OA features after natural biological graft healing and functional rehabilitation (>2 years after injury), but before established joint disease, may present opportunities to develop secondary prevention strategies.

Therefore, the primary aims of this study were to (1) describe longitudinal changes to early OA features on MRI from 1 to 5 years after ACLR and (2) determine the association between participant characteristics (age, sex, body mass index [BMI], time from injury to surgery, meniscectomy/cartilage defects at the time of ACLR, anteroposterior knee laxity) and changes in MRI findings. Second, we evaluated longitudinal changes in radiographic OA between 1 and 5 years in both knees.

METHODS

Participants

All 111 consecutively recruited patients (median age at the time of surgery, 26 years [range, 18-50 years]) who participated in our previously reported MRI evaluation at 1 year after ACLR[10] (ie, baseline for the current study) were eligible for the current study. Baseline inclusion and exclusion criteria, ACLR technique, and postoperative rehabilitation are described in a previous publication.[10] Briefly, baseline inclusion criteria included primary single-bundle hamstring autograft ACLR by 1 of 2 orthopaedic surgeons (T.W., H.M.) in Melbourne, Australia. Baseline exclusion criteria included knee injuries/symptoms/surgery before the ACL injury, >5 years between the ACL injury and ACLR, and any secondary injury/surgery to the ACLR knee (between surgery and 1-year assessment). A secondary injury was defined as a new index or contralateral knee injury (ACL, meniscus, collateral ligament), surgery, or intra-articular knee injection. Patients with a secondary injury between 1 and 5 years were invited to participate at 5 years after ACLR follow-up, as this is a common occurrence and representative of the wider ACLR population. Of the 111 participants with baseline MRI data, 78 (70%) (48 men; median age, 32 years [range, 23-56 years]) completed an MRI assessment at follow-up (median, 5.2 years after ACLR [range, 4.7-6.3 years]). Ethical approval was granted by La Trobe University's Human Ethics Committee (HEC 15-100), and informed consent was obtained from all individual participants included in the study.

Demographic, Injury, and Surgical Factors

Participant age, sex, ACL injury history (date of ACL injury, time from injury to surgery), and previous activity level were obtained at the baseline assessment. Activity level was defined as level 1 (pivoting/jumping sports) to level 4 (sedentary).[22] Participant BMI was calculated at baseline and follow-up. Information on meniscectomy and significant cartilage defects assessed at the time of surgery were obtained from surgical records at baseline, and these were termed "combined injuries." Arthroscopically identified cartilage defects were defined as significant when the Outerbridge grade was ≥2 (ie, at least partial-thickness defect).[36] Anteroposterior laxity at baseline was assessed using the KT-1000 arthrometer (MEDmetric) at 30° of flexion with a 30-lb load.[13] Participants were questioned about new injuries or surgery between baseline and follow-up. Participants with new index or contralateral knee injuries/surgery were included, as this is a common occurrence and representative of the wider ACLR population. Tibiofemoral and patellofemoral radiographic OA in the ACLR and contralateral knees was determined at baseline and follow-up using previously published protocols[10] and Osteoarthritis Research Society International atlas definitions[1] (see the Appendix, available in the online version of this article). Bilateral posteroanterior and lateral weightbearing and nonweightbearing skyline views were taken. Radiographic OA was defined as (1) joint

[#]Address correspondence to Kay M. Crossley, PT, PhD, La Trobe Sport and Exercise Medicine Research Centre, School of Allied Health, La Trobe University, Bundoora, VIC, 3086, Australia (email: K.Crossley@latrobe.edu.au).

[*]La Trobe Sport and Exercise Medicine Research Centre, School of Allied Health, La Trobe University, Melbourne, Victoria, Australia.

[†]Institute of Anatomy, Paracelsus Medical University, Salzburg, Austria.

[‡]Department of Radiology, Boston University School of Medicine, Boston, Massachusetts, USA.

[§]Department of Physical Therapy, University of Delaware, Newark, Delaware, USA.

[||]Park Clinic Orthopaedics, St Vincent's Private Hospital, Melbourne, Victoria, Australia.

[¶]OrthoSport Victoria, Epworth Richmond, Melbourne, Victoria, Australia.

One or more of the authors has declared the following potential conflict of interest or source of funding: Support for this study was provided by Arthritis Australia (Grant in Aid), La Trobe University's Sport, Exercise and Rehabilitation Research Focus Area (Project Grant), the Queensland Orthopaedic Physiotherapy Network (Project Grant), the University of Melbourne (Research Collaboration Grant), and the University of British Columbia's Centre for Hip Health and Mobility (Society for Mobility and Health). B.E.P. is a recipient of a National Health and Medical Research Council (NHMRC) postgraduate scholarship (GNT 1114296). A.G.C.'s work was supported by an NHMRC Early Career Fellowship (Neil Hamilton Fairley Clinical Fellowship; GNT 1121173). The sponsors were not involved in the design and conduct of this study; in the analysis and interpretation of the data; and in the preparation, review, or approval of the article. A.G. is the president of Boston Imaging Core Lab and a consultant to Merck Serono, AstraZeneca, Pfizer, GE Healthcare, OrthoTrophix, Sanofi, and TissueGene.

space narrowing of grade ≥2, (2) sum of osteophytes ≥2, or (3) grade 1 osteophyte in combination with grade 1 joint space narrowing.[1]

MRI Acquisition and Interpretation

All participants underwent unilateral knee MRI at baseline using a single 3.0-T system (Achieva; Philips), as previously described.[10] The same MRI scanner was used to acquire follow-up scans of the ACLR knee, with identical sequences to those obtained at baseline. The sequences consisted of 3-dimensional proton density–weighted volume isotropic turbo spin echo acquisition (VISTA) at 0.35 mm, short tau inversion recovery (STIR), and axial proton density–weighted turbo spin echo. All MRI scans were evaluated using the MRI Osteoarthritis Knee Score (MOAKS) by a single musculoskeletal radiologist (A.G.) with 14 years of experience and established interrater and intrarater reliability (kappa, 0.61-0.80) by a semiquantitative MRI assessment.[26] The radiologist evaluated the baseline and follow-up scans paired (not blinded to the time points of MRI) but blind to clinical/radiographic information. The MOAKS divides the knee into 14 articular subregions to score cartilage defects (assessed using the VISTA sequence) and bone marrow lesions (BMLs) (assessed using STIR and fluid-sensitive turbo spin echo sequences) and 6 tibiofemoral and 6 patellofemoral subregions to score osteophytes.[26] Meniscal lesions were scored separately for the medial meniscus and lateral meniscus and divided into anterior, posterior, and central subregions for each meniscus. Cartilage defects were graded from 0 to 3 based on size (percentage of the surface area relative to each subregion) and depth (percentage of the lesion that is full thickness). Size was graded as the following: 0 = none; 1 = <33%; 2 = 33%-66%; and 3 = >66%. Depth was graded as the following: 0 = no full-thickness loss; 1 = <10%; 2 = 10%-75%; and 3 = >75%. BMLs were based on size only (percentage of the surface area affected relative to each subregion): 0 = none; 1 = <33%; 2 = 33%-66%; and 3 = >66%. Osteophytes were graded according to size based on how far they extended from the joint: 0 = none; 1 = small; 2 = medium; and 3 = large. Given that the definition of a definite osteophyte has not been delineated,[26] we considered an osteophyte present if it was scored ≥2. Meniscal tears were described as absent or present and by type (vertical, horizontal, or complex). Meniscal maceration was described as absent or present and by type (partial, complete, or progressive). Meniscal extrusion was described by size: 0 = <2 mm; 1 = 2-2.9 mm; 2 = 3-4.9 mm; and 3 = ≥5 mm. Hoffa fat pad synovitis was graded as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). More information on the MRI sequences used and the MOAKS scoring system appears in the Appendix.

Definition of Worsening OA Features

Subregions were combined to define 3 compartments: patellofemoral (patella and trochlea), medial tibiofemoral (medial femur: central and posterior; medial tibia: anterior, central, and posterior), and lateral tibiofemoral (lateral femur: central and posterior; lateral tibia: anterior, central, and posterior). Worsening of OA features in each compartment was defined as any increase in the score (in any corresponding subregions for that compartment). Therefore, either progression of an OA feature (ie, increase in defect severity) or a new OA feature (ie, from no defect to present defect) from baseline to follow-up was classified as worsening. This definition is reliable and sensitive to changes in ACL-injured patients and other populations at high risk for OA.[45,54] Increase in defect severity was defined as an increase in the size or depth of the lesion of at least 1 point on the MOAKS. New lesions were defined as those with size 0 at baseline and size ≥1 at follow-up (osteophytes needed to be ≥2 at follow-up, as the definition of an osteophyte has not been delineated).[26]

Statistical Analyses

Descriptive statistics were used to define worsening of MRI-detected OA features for each compartment and radiographic OA. Both the medial and lateral patellar and trochlear subregions were included in analyses for patellofemoral compartment outcomes (4 observations per knee). The medial and lateral tibiofemoral compartments had 5 observations per knee (femur: central and posterior; tibia: anterior, central, and posterior). Logistic regression models with generalized estimating equations (GEEs) (to account for correlations between subregions within the same compartment) were used to determine if participant characteristics (age, sex, BMI at baseline, time from injury to surgery, meniscectomy and cartilage defects at the time of ACLR, reinjury, and anteroposterior knee laxity) were associated with worsening OA features. Age and time from injury to ACLR were dichotomized at their median values, while BMI was dichotomized based on the established overweight cutoff of 25 kg/m^2 (median at baseline, 25.3 kg/m^2), so that odds ratios (ORs) and 95% CIs could be estimated and descriptively compared with the nominal variable of concomitant injuries. Univariate regression analysis was performed initially; participant characteristics with a P value <.20 were entered into a multivariate logistic regression GEE model to calculate ORs and 95% CIs. The McNemar test was used to determine any significant change in repeated-measures nominal data (ie, worsening radiographic OA from baseline to follow-up). Stata v 14.2 (StataCorp) was used for statistical analyses. P values <.05 were considered statistically significant.

RESULTS

Participants

Characteristics of the 78 participants included in the current study are presented in Table 1. Apart from medial meniscal lesions, which were more prevalent in the participating group at baseline, there were no demographic, surgical, or baseline MRI–related differences between those who did and did not participate in the follow-up assessment at 5 years (P > .05) (Tables 1 and 2). Thirty-eight

TABLE 1
Participant Characteristics at 1 and 5 Years After ACLR[a]

	No Follow-up[b] (n = 33)	Follow-up (n = 78)	
	1 y	1 y	5 y
Age, y	27 (13) [20 to 50]	28 (15) [19 to 52]	32 (15) [23 to 56]
Male sex, n (%)	23 (70)	48 (62)	48 (62)
Activity level before injury,[c] n (%)			
Level 1	26 (79)	54 (69)	54 (69)
Level 2	5 (15)	18 (23)	18 (23)
Level 3	2 (6)	6 (8)	6 (8)
Level 4	0 (0)	0 (0)	0 (0)
Activity level at time of MRI,[c] n (%)			
Level 1	9 (27)	19 (24)	25 (32)
Level 2	4 (12)	10 (13)	11 (14)
Level 3	8 (24)	19 (24)	32 (41)
Level 4	12 (37)	30 (39)	10 (13)
Time to surgery, wk	12 (13) [3 to 241]	14 (20) [1 to 231]	14 (20) [1 to 231]
Body mass index,[d] kg/m^2	26 (7) [20 to 37]	25 (5) [20 to 37]	26 (5) [20 to 35]
Concomitant injuries/procedures at time of ACLR, n (%)			
Medial meniscectomy/repair	7 (21)/3 (9)	16 (21)/9 (12)	16 (21)/9 (12)
Lateral meniscectomy/repair	5 (15)/2 (6)	18 (23)/1 (1)	18 (23)/1 (1)
Patellofemoral cartilage defect[e]	5 (15)	7 (9)	7 (9)
Medial tibiofemoral cartilage defect[e]	3 (9)	7 (9)	7 (9)
Lateral tibiofemoral cartilage defect[e]	3 (9)	4 (5)	4 (5)
Anteroposterior laxity (between-limb difference),[f] mm	1.3 (2.3) [–3.8 to 7.2]	1.6 (2.9) [–1.9 to 3.5]	NA
IKDC score	84 (14) [53 to 98]	87 (16) [54 to 100]	91 (15) [53 to 100]

[a]Values are shown as median (interquartile range) [range] unless otherwise specified. ACLR, anterior cruciate ligament reconstruction; IKDC, International Knee Documentation Committee; MRI, magnetic resonance imaging; NA, not available.

[b]Reasons for exclusion: pregnant (n = 1), unable to contact (n = 10), unable to attend because of distance/time (n = 17; interstate: n = 5, overseas: n = 4), ruled out by participating surgeon because of conflict with participation in other study (n = 4), and incorrect limb scanned (n = 1).

[c]Classification based on Grindem et al[22]: level 1, jumping, cutting, and pivoting sports; level 2, lateral movement sports; level 3, straight line activities; and level 4, sedentary.

[d]n = 72 at follow-up (ie, those who participated in follow-up clinical testing).

[e]Outerbridge grade ≥2 assessed arthroscopically.

[f]Assessed using the KT-1000 arthrometer. Not included in 5-year clinical testing measures.

of the 78 participants (49%) had a combined injury (arthroscopic meniscectomy/cartilage defect at the time of index surgery), and 12 (15%) participants reported a new index knee injury/surgery between baseline and follow-up (revision ACLR: n = 3; partial meniscectomy: n = 6; intra-articular injection: n = 1; collateral ligament injury: n = 2). Six participants had a new contralateral knee injury (ACLR: n = 3; meniscectomy: n = 1; collateral ligament injury: n = 1; investigative arthroscopic surgery: n = 1).

Cartilage Defects

Worsening of cartilage defects in any compartment occurred in 40 (51%) participants, with worsening most commonly occurring in the patellofemoral compartment (n = 34 [44%]) (Figure 1). Medial and lateral tibiofemoral cartilage worsening occurred in 8 (10%) and 10 (13%) participants, respectively (Figure 1). Twenty-five (63%) of those with cartilage worsening had isolated patellofemoral cartilage worsening compared with 6 (15%) who had isolated tibiofemoral cartilage worsening. The prevalence of participants with a patellofemoral full-thickness cartilage defect more than doubled from baseline to follow-up (n = 15 [19%] to n = 32 [41%]) (Figure 2). The prevalence of those with full-thickness cartilage defects also increased from baseline to follow-up in the medial (n = 2 [3%] to n = 5 [6%]) and lateral tibiofemoral (n = 12 [15%] to n = 14 [18%]) compartments (Figure 2).

Bone Marrow Lesions

Although the frequency of any BMLs remained the same (47%) from baseline to follow-up (Table 2), worsening of BMLs in any compartment occurred in 23 (29%) participants (Figure 1). This was caused by new or progressive lesions in one compartment, with concurrent improvement in BMLs in another compartment. Patellofemoral and medial and lateral tibiofemoral BML worsening occurred in 14 (18%), 5 (6%), and 10 (13%) participants, respectively (Figure 1). Improvement of BMLs in any compartment occurred in 31 (40%) participants from baseline to follow-up. Patellofemoral, medial tibiofemoral, and lateral tibiofemoral BML improvement occurred in 16 (21%), 11 (14%), and 14 (18%) participants, respectively (Figure 1).

TABLE 2
Imaging Results at 1 and 5 Years After ACLR[a]

	No Follow-up (n = 33)	Follow-up (n = 78)	
	1 y	1 y	5 y[b]
MRI-detected OA features[c]			
Cartilage defect (grade ≥1, full- or partial-thickness)			
Patellofemoral	13 (39)	37 (48)	47 (60)
Medial tibiofemoral	9 (27)	23 (29)	28 (36)
Lateral tibiofemoral	11 (33)	18 (23)	26 (33)
Bone marrow lesion (grade ≥1)			
Patellofemoral	6 (18)	20 (26)	18 (23)
Medial tibiofemoral	4 (12)	14 (18)	13 (17)
Lateral tibiofemoral	8 (24)	14 (18)	16 (21)
Osteophyte (grade ≥2)[d]			
Patellofemoral	0 (0)	3 (4)	7 (9)
Medial tibiofemoral	0 (0)	1 (1)	10 (12)
Lateral tibiofemoral	2 (6)	6 (8)	9 (12)
Meniscal lesion (grade ≥1)[e]			
Medial tibiofemoral	18 (55)[f]	52 (67)	53 (68)
Lateral tibiofemoral	20 (60)	38 (49)	40 (52)
Hoffa fat pad synovitis (grade ≥1)	20 (60)	47 (60)	69 (88)
Radiographic OA[g]			
Patellofemoral (ACLR/contralateral limb)	1 (3)/2 (6)	4 (5)/2 (3)	14 (18)/4 (5)
Medial tibiofemoral (ACLR/contralateral limb)	1 (3)/1 (3)	2 (3)/2 (3)	4 (5)/2 (3)
Lateral tibiofemoral (ACLR/contralateral limb)	2 (6)/0 (0)	1 (1)/1 (1)	4 (5)/1 (1)

[a]Values are shown as n (%). ACLR, anterior cruciate ligament reconstruction; MRI, magnetic resonance imaging; OA, osteoarthritis.
[b]Three participants underwent MRI on a different scanner at follow-up because of being interstate.
[c]The MRI OA Knee Score (MOAKS) was used to grade each feature.[26]
[d]Given that the definition of a definite osteophyte has not been delineated, we considered an osteophyte to be present if it was graded ≥2.
[e]Includes tearing (vertical/horizontal/complex), maceration (partial/degenerative), or extrusion.
[f]Statistically significant ($P < .05$) compared with the follow-up group.
[g]Radiographic OA was defined as (1) joint space narrowing of grade ≥2, (2) sum of osteophytes ≥2, or (3) grade 1 osteophyte in combination with grade 1 joint space narrowing.[1]

Osteophytes

Worsening of osteophytes in any compartment occurred in 13 (17%) participants (Figure 1). Patellofemoral, medial tibiofemoral, and lateral tibiofemoral osteophyte worsening occurred in 7 (9%), 8 (10%), and 6 (8%) participants, respectively. All worsening was caused by progressive lesions (increase in size), with no new osteophytes (grade ≥2) at follow-up (Figure 1).

Meniscal Lesions

The prevalence of medial and lateral meniscal lesions only increased by 1% and 3%, respectively, from baseline to follow-up (Table 2). However, worsening of meniscal lesions (increase in size) occurred in the medial or lateral compartment in 17 (22%) participants, with 14 (18%) and 4 (5%) occurring in the medial and lateral compartments, respectively (Figure 1).

Radiographic OA

The prevalence of radiographic OA increased significantly from baseline to follow-up in the patellofemoral compartment in the ACLR knee (n = 4 [5%] to n = 14 [18%]; $P < .05$) but not in the contralateral knee (n = 2 [3%] to n = 4 [5%]; $P > .05$). Smaller and nonsignificant increases were seen in the ACLR and contralateral medial and lateral tibiofemoral compartments (Table 2).

Factors Associated With Worsening MRI-Detected OA Features

In multivariate analyses, participants with a baseline BMI >25 kg/m^2 consistently displayed 2 to 5 times greater odds of worsening of all MRI-detected OA features (except for patellofemoral BMLs) (Tables 3 and 4). All participants with a baseline BMI >25 kg/m^2 had worsening patellofemoral osteophytes. Older age (>26 years) at the time of surgery was related to greater odds of worsening patellofemoral cartilage defects (OR, 4.19 [95% CI, 1.78-9.86]). Although ACLR performed >3 months after the injury had greater odds of worsening tibiofemoral osteophytes (OR, 3.91 [95% CI, 1.04-14.66]) and meniscal lesions (OR, 6.35 [95% CI, 1.38-29.29]) (Table 3), it had lower odds of patellofemoral cartilage defect worsening (OR, 0.44 [95% CI, 0.21-0.94]) (Table 4). Anteroposterior knee laxity (>3-mm between-limb difference) was related to 4 times greater odds of worsening meniscal lesions (OR, 4.51 [95% CI, 1.35-15.10]). As we were unable to assess the effect of reinjuries because of

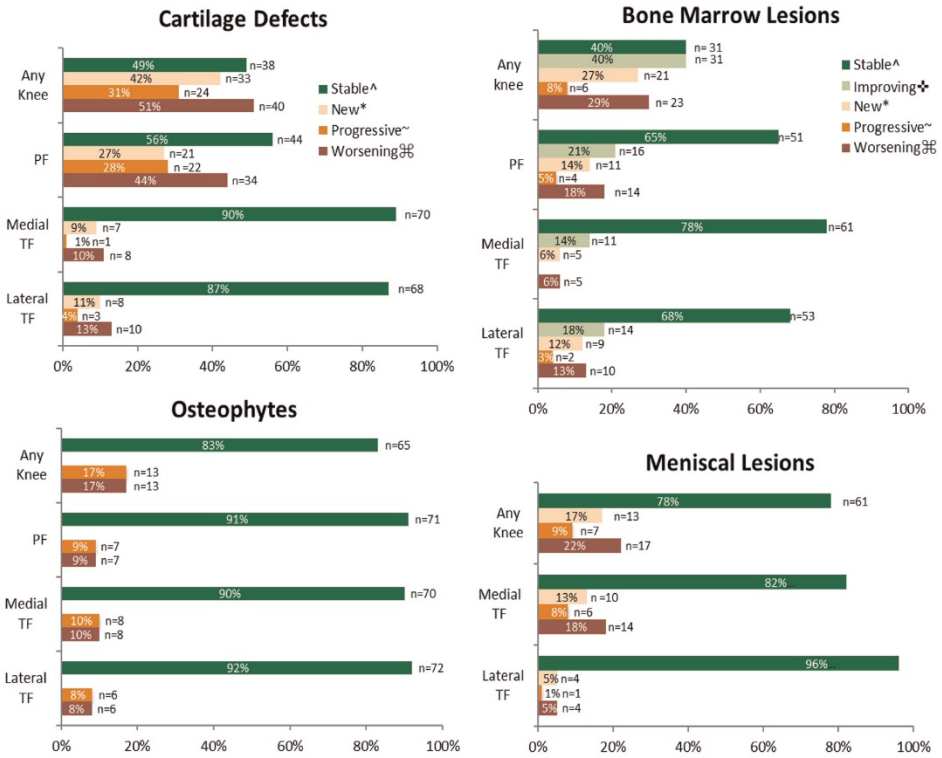


Figure 1. Worsening of magnetic resonance imaging (MRI)-detected osteoarthritis features from baseline (1 year after anterior cruciate ligament reconstruction [ACLR]) to follow-up (5 years after ACLR). Worsening meniscal lesions include worsening tear, maceration, and extrusion. PF, patellofemoral compartment; TF, tibiofemoral compartment.
^Stable lesions = participants with no worsening (i.e., no new or progressive features, or BML improvement)
*New = participants with no lesion at baseline (ie, MRI Osteoarthritis Knee Score [MOAKS] size score = 0), with score of ≥1 at follow-up for cartilage defects, bone marrow lesions (BMLs) and meniscal lesions (≥2 for osteophytes).
~Progressive = participants with a lesion at baseline (ie, MOAKS size score ≥1), with an increase in severity of lesion (ie, at least a 1-point increase in size or depth of lesion).
⌘ Worsening = participants with either progressive or new feature.
✣ Improving = participants with a BML at baseline (ie, MOAKS score ≥1), with a decrease in severity of BML (ie, at least a 1-point decrease in size of BML).

the small number of reinjuries in the index knee (n = 12), a sensitivity analysis excluding participants with a reinjury was performed. This sensitivity analysis resulted in similar effect sizes (but wider 95% CIs), suggesting that the effect of reinjuries on worsening MRI features in this study was minimal. A combined injury (meniscectomy/cartilage defect at the time of ACLR) was not significantly associated with increased odds of worsening MRI-detected OA features in the regression analysis (Tables 3 and 4). However, the relatively small number of patients with worsening of some OA features detrimentally affected the stability of the regression analysis. Therefore, we performed a second sensitivity analysis, comparing the rate of worsening MRI-detected OA features between those with a combined injury (n = 38) and isolated injury (n = 40). The rates of any MRI-detected OA feature worsening were significantly greater in those with a combined injury than in those with an isolated injury (31/38 vs 22/40, respectively; chi-square, $P = .012$). In addition, to determine the effect of pre-existing OA, we performed a third sensitivity analysis by excluding patients with radiographic OA (as described in Table 1) at 1 year after ACLR (n = 5). Additional analyses comparing the worsening rates in the patients with (n = 5) and without radiographic OA (n = 73) at 1 year revealed similar (and nonsignificantly different) rates of MRI-detected OA feature worsening, except for tibiofemoral osteophytes (2/5 vs 7/73, respectively; chi-square, $P = .112$).

DISCUSSION

Worsening early OA features were evident in more than two-thirds of young patients over a 4-year period: 1 to 5

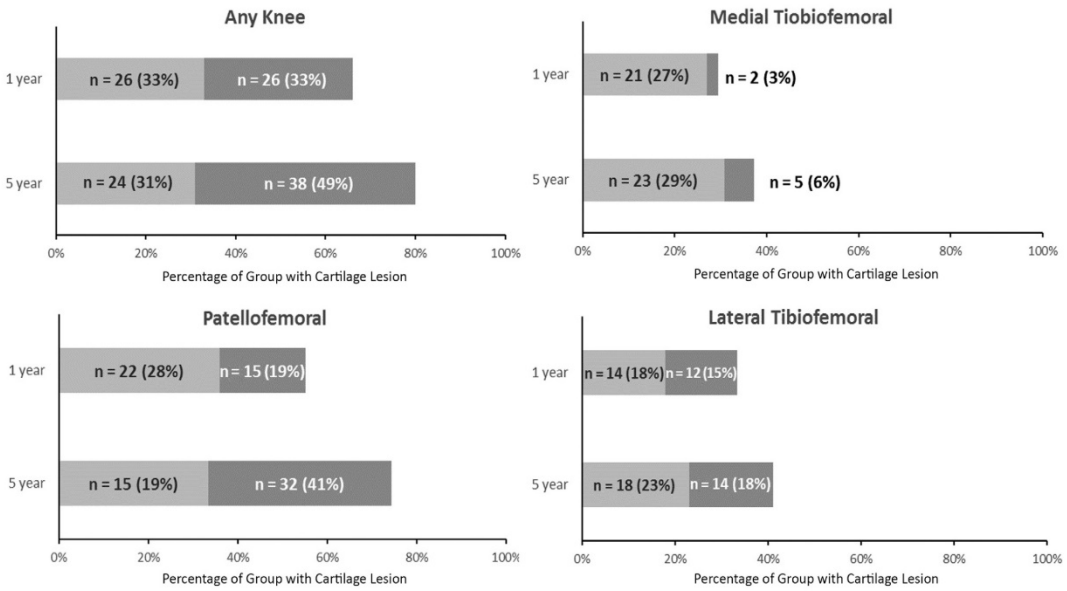


Figure 2. Cartilage worsening (increase in the number and severity of defects) in the patellofemoral and tibiofemoral joints at baseline and follow-up. Light grey shading indicates the number of participants with a partial-thickness defect (in absence of a full-thickness defect). Dark grey shading indicates the number of participants with a full-thickness cartilage defect.

years after ACLR. Despite cartilage defects being most prevalent in the patellofemoral compartment 1 year after ACLR, the patellofemoral compartment displayed the most frequent cartilage deterioration (evident in half of the cohort). The results of this study suggest that joint features are not stable, even after surgical restoration of mechanical stability and a 12-month recovery period. Being overweight (BMI >25 kg/m^2) was a particularly strong determinant of deteriorating knee joint status. These worsening early OA features on MRI may reflect a progressive disease pathway that identifies those likely to suffer future radiographic OA and symptoms.

The considerable progression of existing cartilage defects (n = 24 [31%]) and the development of new defects (n = 33 [42%]), up to 5 years postoperatively, extends previous reports of worsening cartilage damage on semiquantitative scoring during the first 2 years after an ACL injury.[54] Although 80% of participants in the current study had a cartilage defect 1 year after ACLR, worsening cartilage damage occurred in half of the participants over the proceeding 4 years, reflecting the rapid nature of posttraumatic OA. The rate of cartilage degeneration observed after ACLR (ie, approximately 13% per annum in the current study) is similar to patients with or at risk of established (ie, radiographic) OA (9%-17%)[2,45] and far exceeds rates observed in uninjured older healthy knees (2% per annum).[23,37] These results highlight a potential posttraumatic early OA phenotype, demonstrating the accelerated progression of pathologic joint features in young adults, compared with primary OA.[17] Because early cartilage changes offer a promising window to disrupt the disease trajectory,[40] these patients should be identified and the development of potential disease-modifying therapies, such as those that have shown initial promise,[3,44] prioritized.

The patellofemoral joint was the knee compartment in which worsening OA features were most frequent. Although the patellofemoral joint is rarely investigated after ACLR,[11] our findings add to the growing body of evidence pointing to high rates of patellofemoral degeneration. The patellofemoral compartment may be at particular risk for worsening cartilage defects and BMLs in an altered chemical environment after ACLR[24] because of pre-existing or altered patellofemoral biomechanics[12,33,51,60] and/or quadriceps muscle dysfunction.[59] Our MRI data are consistent with quantitative MRI measures[20] and second-look arthroscopic studies,[55] which demonstrate rapid patellofemoral cartilage loss during the first 2 years after ACLR. We also observed greater development of radiographic patellofemoral OA than tibiofemoral OA during the 4-year observation period, more so in the ACLR knee than the contralateral knee. However, one other prospective study[54] did not report higher rates of early degeneration in the patellofemoral compartment compared with the tibiofemoral compartment. Semiquantitative MRI–identified patellofemoral cartilage worsening was reported in only 3% of knees (compared with 34% tibiofemoral cartilage worsening) over the first 2 years after an ACL injury, with this lower rate potentially reflecting a lower BMI and fewer patellofemoral abnormalities at baseline.[54] Nevertheless, our findings suggest that considering and managing patellofemoral joint health after ACLR are critical.

Worsening of BMLs occurred in 29% of participants, providing insight into longer-term (>2 years) posttraumatic

TABLE 3
Demographic and Surgical Factors Associated With Worsening Tibiofemoral MRI-Detected OA Features[a]

	Cartilage Defect[b]		Bone Marrow Lesion[c]		Osteophyte[d]		Meniscal Lesion[e]	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Prevalence of worsening, n (%)	16/78 (21)		12/78 (15)		9/78 (12)		17/78 (22)	
Age at time of surgery[f] (reference: ≤26 y)	**3.17 (1.04-9.66)**	3.27 (0.92-11.60)	0.94 (0.27-3.33)		1.82 (0.26-12.49)		0.50 (0.18-1.43)	0.39 (0.12-1.24)
Sex (reference: female)	0.86 (0.29-2.57)		0.39 (0.12-1.28)	0.59 (0.20-1.79)	1.03 (0.22-4.90)		1.07 (0.38-3.05)	
Body mass index[g] (reference: ≤25 kg/m^2)	2.77 (0.86-8.96)	2.96 (0.81-10.79)	**5.29 (1.45-19.34)**	**4.58 (1.36-15.49)**	2.67 (0.49-14.43)		**3.79 (1.02-14.03)**	**4.62 (1.57-13.55)**
Time from injury to ACLR[f] (reference: ≤3 mo)	2.77 (0.97-7.88)	2.47 (0.83-7.40)	1.11 (0.31-3.96)		**4.56 (1.20-17.37)**	**3.91 (1.04-14.66)**	**3.79 (1.02-14.03)**	**6.35 (1.38-29.29)**
Meniscectomy[h]	1.99 (0.70-5.64)	0.90 (0.27-3.03)	1.62 (0.48-5.51)		1.50 (0.31-7.17)		0.86 (0.30-2.41)	
Cartilage defect[i]	1.73 (0.50-5.92)		1.21 (0.36-4.03)		1.97 (0.30-12.76)		0.75 (0.18-3.04)	
Anteroposterior laxity[j] (reference: ≤3-mm between-limb difference)	1.03 (0.37-2.85)		0.34 (0.04-2.61)		0.13 (0.02-1.09)	0.17 (0.02-14.67)	2.15 (0.73-6.26)	**4.51 (1.35-15.10)**

[a]Values are shown as odds ratios (95% CI) unless otherwise specified. Univariate regression analysis was performed initially; participant characteristics with a P value <.20 were entered into a multivariate logistic regression generalized estimating equation model to calculate odds ratios and 95% CIs. An odds ratio >1 represents greater odds of the MRI-detected OA feature in the presence of the demographic/surgical factor. Bold values indicate a significant association (P < .05). ACLR, anterior cruciate ligament reconstruction; MRI, magnetic resonance imaging; OA, osteoarthritis.
[b]Ten subregions per participant.
[c]Ten subregions per participant.
[d]Six subregions per participant.
[e]Six subregions per participant. Includes worsening tearing, maceration, or extrusion.
[f]Dichotomized based on the median value.
[g]Dichotomized based on the overweight cutoff, which was similar to the median value at 1 year of 25.3 kg/m^2.
[h]Performed at the time of ACLR.
[i]Assessed arthroscopically at the time of ACLR.
[j]Assessed using the KT-1000 arthrometer.

TABLE 4
Demographic and Surgical Factors Associated With Worsening Patellofemoral MRI-Detected OA Features[a]

	Cartilage Defect[b]		Bone Marrow Lesion[c]		Osteophyte[d]	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Prevalence of worsening, n (%)	34/78 (44)		14/78 (18)		4/78 (5)	
Age at time of surgery[e] (reference: ≤26 y)	**3.67 (1.66-8.13)**	**4.19 (1.78-9.86)**	1.11 (0.37-3.29)		0.51 (0.09-2.75)	
Sex (reference: female)	1.12 (0.54-2.34)		**3.13 (1.02-9.62)**	2.55 (0.85-7.67)	0.17 (0.19-1.55)	0.14 (0.01-1.72)
Body mass index[f] (reference: ≤25 kg/m^2)	2.03 (0.96-4.32)	**2.51 (1.19-5.27)**	1.02 (0.34-3.02)		**NA**	
Time from injury to ACLR[e] (reference: ≤3 mo)	0.56 (0.27-1.18)	**0.44 (0.21-0.94)**	0.36 (0.11-1.19)	0.37 (0.11-1.23)	8.39 (0.94-75.14)	6.28 (0.76-52.84)
Meniscectomy[g]	1.02 (0.47-2.24)		1.45 (0.49-4.31)		1.07 (0.20-5.74)	
Cartilage defect[h]	1.68 (0.85-3.31)	1.85 (0.60-5.76)	0.62 (0.09-4.47)		7.37 (0.85-64.19)	6.06 (0.70-52.49)
Anteroposterior laxity[i] (reference: ≤3-mm between-limb difference)	0.66 (0.30-1.47)		0.95 (0.25-3.59)		**NA**	

[a]Values are shown as odds ratios (95% CI). Univariate regression analysis was performed initially; participant characteristics with a P value <.20 were entered into a multivariate logistic regression generalized estimating equation model to calculate odds ratios and 95% CIs. An odds ratio >1 represents greater odds of the MRI-detected OA feature in the presence of the demographic/surgical factor. Bold values indicate a significant association (P < .05). ACLR, anterior cruciate ligament reconstruction; MRI, magnetic resonance imaging; NA, not available (ie, unable to perform analysis as all participants with a worsening patellofemoral osteophyte had a high body mass index); OA, osteoarthritis.
[b]Four subregions per participant.
[c]Four subregions per participant.
[d]Six subregions per participant.
[e]Dichotomized based on the median value.
[f]Dichotomized based on the overweight cutoff, which was similar to the median value at 1 year of 25.3 kg/m^2.
[g]Performed at the time of ACLR.
[h]Assessed arthroscopically at the time of ACLR.
[i]Assessed using the KT-1000 arthrometer.

BML behavior not previously reported.[39] As our baseline was 1 year after ACLR, the majority of acute trauma–related BMLs should have resolved. Therefore, the BMLs observed may be more degenerative in nature, which was confirmed by the characteristics of the BMLs in the current study (more circumscribed, located directly subchondral, and with associated cartilage defects).[42] Conversely, many BMLs in our cohort were stable (40%) or improved (40%), indicating that not all BMLs persisting at 1 year after ACLR are degenerative in nature and that resolution may require more than 1 year. In contrast to BMLs, osteophytes are more permanent and typically represent later stages of disease. This is reflected in the lower rates of worsening observed compared with other features, which is consistent with previous reports of osteophytes within the first 5 years after ACLR (8% patellofemoral and 9% tibiofemoral worsening within the immediate 2 years after the ACL injury).[54] Importantly, we only considered incident osteophytes as those grade ≥2, which likely contributed to our observation of no new osteophytes over 4 years. While small osteophyte development may reflect pathological bone shape changes, and increase the risk of incident radiographic OA,[35] the clinical significance of small osteophyte development requires further evaluation.

Apart from worsening meniscal lesions, which were more common in the medial (18%) than the lateral (5%) tibiofemoral compartment, worsening OA features were observed similarly in the medial and lateral tibiofemoral joint. These observations are consistent with posttraumatic radiographic OA having similar medial and lateral tibiofemoral distribution and contrast primary OA, which is typically a disease of the medial tibiofemoral joint.[49] This is the first study, to our knowledge, to investigate longitudinal semiquantitative meniscal changes after ACLR. Despite the notion that surgical reconstruction can protect worsening meniscal abnormalities,[4,31] 1 in 5 demonstrated meniscal lesion worsening in the current study. Although the presence of meniscal lesions is common in noninjured asymptomatic populations aged over 50 years,[15] this ACLR cohort demonstrates a much higher prevalence (80%) than age-matched patients (6%-40%).[29,30] The observed rate (5% per annum) of meniscal lesion worsening is higher in these young adults than previous reports in noninjured older patients (1%-3% per annum) at risk of OA (age >50 years and BMI >25 kg/m^2).[45,46] While surgical delay >3 months and anteroposterior knee laxity (>3-mm between-limb difference) were associated with 3 to 6 times greater odds of worsening meniscal lesions (Table 3), the clinical significance of MRI-detected meniscal lesions is uncertain.

The evaluation of baseline demographic and surgical factors revealed that being overweight (BMI >25 kg/m^2) was a particularly strong determinant of deteriorating knee joint status. An elevated BMI was associated with 2- to 5-fold greater odds of most OA features, irrespective of the knee compartment. This is consistent with the effect of BMI on radiographic changes.[7] The longer follow-up compared with previous studies evaluating BMI in relation to MRI structural changes after ACLR may have allowed more time for BMI, in combination with probable changes in physical function and activity participation, to have an effect on joint structure. Young adults are at risk of having an increased BMI 3 to 10 years after an acute knee injury.[58] Our results support this, with a significant increase in BMI from 1 (25.7 kg/m^2) to 5 years (26.3 kg/m^2) ($P < .05$). These results reinforce and strengthen the need for early OA secondary prevention interventions to address weight control through education about diet and physical activity. Each pound of lost weight leads to a 4-fold reduction in knee joint loading upon every step.[34] Older age was a risk factor for worsening patellofemoral cartilage damage, reflecting degenerative changes being more prevalent in older adults.[7] However, the changes that we observed were not explained entirely by age, which is evident from the higher rates of radiographic degeneration in the index knee (3.5% per annum) compared with the contralateral knee (0.25% per annum). This is supported by greater worsening of MRI-detected OA features in the current study than the normal age-related changes published previously.[14-16,23,37,38] Considering the high rate of new and progressive lesions after ACLR, future studies should explore other factors (ie, strength, function, alignment, and participation), which may be related to worsening of early OA features, especially given the modifiable nature of many of these factors.

A limitation of this prospective study was the loss of 33 baseline participants, resulting in a follow-up rate of 70%. Dropout was mostly caused by an inability to contact participants and relocation, reflecting a particularly young mobile population in Australia. Medial meniscal lesions were more prevalent at 1 year in those who participated in follow-up compared with those who did not. While this may have introduced some selection bias and influenced the prognosis of the current sample, there were no differences in any other baseline participant or surgical characteristics between those who did and did not attend the follow-up assessment. In addition, the current cohort appears generalizable to other large ACLR cohorts, with similar International Knee Documention Committee scores[9] and return-to-sport rates[5] at comparable follow-ups. Second, baseline and follow-up MRI scans were read paired and unblinded to the time point. While this approach could cause the overestimation of worsening, paired reading overcomes the limitations of the inherently crude grading system of the MOAKS.[45] Future research should, however, examine the clinical implications (ie, association with symptoms) of posttraumatic MRI-detected OA features. Third, the limited number of patients with worsening of some OA features influenced the statistical stability of the regression models. Although we included worsening of all subregions and accounted for their correlation within knees with GEEs to increase statistical power, 95% CIs were relatively wide for some OA features. These need to be interpreted with caution.

Finally, we included patients with reinjuries and combined injuries to represent a typical ACLR cohort. While we acknowledge that MRI-detected OA features may have been pre-existing, a sensitivity analysis (excluding those with radiographic OA at 1 year) revealed similar rates of worsening of all MRI-detected OA features (except tibiofemoral osteophytes). Although combined injuries are associated with an increased risk of radiographic OA 10

to 15 years after an ACL injury,[41,53] meniscectomy or a cartilage defect at the time of surgery did not significantly increase the risk of worsening of individual MRI-detected OA features between 1 and 5 years after ACLR. It is possible that the effect of pre-existing meniscal lesions on the joint structure may take many years to eventuate or that many more patients who have undergone ACLR would be needed to demonstrate an effect. A sensitivity analysis revealed that any MRI-detected OA feature worsening was significantly greater in those with a combined injury. These results highlight that combined injuries play a role in the worsening of MRI-detected OA features; however, our regression analysis, adjusting for other demographic factors (ie, BMI), highlights the multifactorial nature of posttraumatic early OA after ACLR. Regardless, the rate of MRI-detected OA feature worsening that we observed (ie, estimated per annum; cartilage defect, 13%; meniscal lesion, 6%; BML, 7.5%) is higher than those observed in knees of older patients with or at risk of OA (ie, estimated per annum; cartilage defect, 2%-8%; meniscal lesion, 1%-3%; BML, 3%-8%),[14,16,23,37,45,48] highlighting that the ACL injury or ACLR is likely driving the considerable degeneration in these otherwise healthy young adults.

Our findings demonstrate that young adults after ACLR are at risk of worsening early MRI-detected OA features. This is important, as it is likely that worsening cartilage defects, BMLs, and meniscal lesions in young patients are not benign and may be associated with future knee OA, symptoms, or functional decline.[28,46,57] Importantly, these findings are contrary to persistent beliefs among patients that ACLR will prevent OA.[6,18] Considering the rapid progression of posttraumatic OA, patients should be provided with information and educated about early OA secondary prevention interventions, in particular, the potential reversibility or prevention of deterioration in structural abnormalities, symptoms, and function.[40,56] Education should refer to the consequences of increased BMI, such as the increased risk of early degenerative changes that may lead to future established joint disease and symptoms.[28,46]

In conclusion, we observed high rates of OA-related degenerative changes on MRI in young adults between 1 and 5 years after ACLR, with two-thirds demonstrating some joint deterioration. Patellofemoral cartilage appears to be at a particularly high risk of early accelerated degeneration, especially in older and overweight patients. The concerning joint deterioration within the first 5 years after ACLR may help to identify those at greatest risk of more severe (radiographic) OA in whom secondary prevention strategies may need to be targeted.

REFERENCES

1. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage*. 1995;(3)(suppl A):3-70.
2. Amin S, LaValley MP, Guermazi A, et al. The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. *Arthritis Rheum*. 2005;52(10):3152-3159.
3. Anderson JA, Little D, Toth AP, et al. Stem cell therapies for knee cartilage repair: the current status of preclinical and clinical studies. *Am J Sports Med*. 2014;42(9):2253-2261.
4. Anstey DE, Heyworth BE, Price MD, Gill TJ. Effect of timing of ACL reconstruction in surgery and development of meniscal and chondral lesions. *Phys Sportsmed*. 2012;40(1):36-40.
5. Ardern CL, Taylor NF, Feller JA, Webster KE. Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. *Br J Sports Med*. 2014;48(21):1543-1552.
6. Bennell KL, van Ginckel A, Kean CO, et al. Patient knowledge and beliefs about knee osteoarthritis after anterior cruciate ligament injury and reconstruction. *Arthritis Care Res (Hoboken)*. 2016;68(8):1180-1185.
7. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2010;18(1):24-33.
8. Church S, Keating JF. Reconstruction of the anterior cruciate ligament: timing of surgery and the incidence of meniscal tears and degenerative change. *J Bone Joint Surg Br*. 2005;87(12):1639-1642.
9. Cox CL, Huston LJ, Dunn WR, et al. Are articular cartilage lesions and meniscus tears predictive of IKDC, KOOS, and Marx activity level outcomes after anterior cruciate ligament reconstruction? A 6-year multicenter cohort study. *Am J Sports Med*. 2014;42(5):1058-1067.
10. Culvenor AG, Collins NJ, Guermazi A, et al. Early knee osteoarthritis is evident one year following anterior cruciate ligament reconstruction: a magnetic resonance imaging evaluation. *Arthritis Rheumatol*. 2015;67(4):946-955.
11. Culvenor AG, Cook JL, Collins NJ, Crossley KM. Is patellofemoral joint osteoarthritis an under-recognised outcome of anterior cruciate ligament reconstruction? A narrative literature review. *Br J Sports Med*. 2013;47(2):66-70.
12. Culvenor AG, Schache AG, Vicenzino B, et al. Are knee biomechanics different in those with and without patellofemoral osteoarthritis after anterior cruciate ligament reconstruction? *Arthritis Care Res (Hoboken)*. 2014;66(10):1566-1570.
13. Daniel DM, Malcom LL, Losse G, et al. Instrumented measurement of anterior laxity of the knee. *J Bone Joint Surg Am*. 1985;67(5):720-726.
14. Davies-Tuck ML, Wluka AE, Wang Y, et al. The natural history of bone marrow lesions in community-based adults with no clinical knee osteoarthritis. *Ann Rheum Dis*. 2009;68(6):904-908.
15. Ding C, Jones G, Wluka AE, Cicuttini F. What can we learn about osteoarthritis by studying a healthy person against a person with early onset of disease? *Curr Opin Rheumatol*. 2010;22(5):520-527.
16. Ding C, Martel-Pelletier J, Pelletier JP, et al. Knee meniscal extrusion in a largely non-osteoarthritic cohort: association with greater loss of cartilage volume. *Arthritis Res Ther*. 2007;9(2):R21.
17. Driban JB, Eaton CB, Lo GH, et al. Association of knee injuries with accelerated knee osteoarthritis progression: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. 2014;66(11):1673-1679.
18. Feucht MJ, Cotic M, Saier T, et al. Patient expectations of primary and revision anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(1):201-207.
19. Filbay SR, Ackerman IN, Russell TG, et al. Health-related quality of life after anterior cruciate ligament reconstruction: a systematic review. *Am J Sports Med*. 2014;42(5):1247-1255.
20. Frobell RB. Change in cartilage thickness, posttraumatic bone marrow lesions, and joint fluid volumes after acute ACL disruption: a two-year prospective MRI study of sixty-one subjects. *J Bone Joint Surg Am*. 2011;93(12):1096-1103.
21. Frobell RB, Roos HP, Roos EM, et al. Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. *BMJ*. 2013;346:F232.
22. Grindem H, Eitzen I, Snyder-Mackler L, Risberg MA. Online registration of monthly sports participation after anterior cruciate ligament injury: a reliability and validity study. *Br J Sports Med*. 2014;48(9):748-753.
23. Hanna FS, Teichtahl AJ, Wluka AE, et al. Women have increased rates of cartilage loss and progression of cartilage defects at the

knee than men: a gender study of adults without clinical knee osteoarthritis. *Menopause*. 2009;16(4):666-670.
24. Harkey MS, Luc BA, Golightly YM, et al. Osteoarthritis-related biomarkers following anterior cruciate ligament injury and reconstruction: a systematic review. *Osteoarthritis Cartilage*. 2015;23(1):1-12.
25. Hunter DJ, Conaghan PG, Peterfy CG, et al. Responsiveness, effect size, and smallest detectable difference of magnetic resonance imaging in knee osteoarthritis. *Osteoarthritis Cartilage*. 2006;14(suppl 1):112-115.
26. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthritis Cartilage*. 2011;19(8):990-1002.
27. Hunter DJ, Zhang W, Conaghan PG, et al. Responsiveness and reliability of MRI in knee osteoarthritis: a meta-analysis of published evidence. *Osteoarthritis Cartilage*. 2011;19(5):589-605.
28. Javaid MK, Lynch JA, Tolshtykh I, et al. Pre-radiographic MRI findings are associated with onset of knee symptoms: the most study. *Osteoarthritis Cartilage*. 2010;18(3):323-328.
29. Jerosch J, Castro WH, Assheuer J. Age-related magnetic resonance imaging morphology of the menisci in asymptomatic individuals. *Arch Orthop Trauma Surg*. 1996;115(3-4):199-202.
30. LaPrade RF, Burnett QM 2nd, Veenstra MA, Hodgman CG. The prevalence of abnormal magnetic resonance imaging findings in asymptomatic knees: with correlation of magnetic resonance imaging to arthroscopic findings in symptomatic knees. *Am J Sports Med*. 1994;22(6):739-745.
31. Lebel B, Hulet C, Galaud B, et al. Arthroscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone autograft: a minimum 10-year follow-up. *Am J Sports Med*. 2008;36(7):1275-1282.
32. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of ACL and meniscus injuries: osteoarthritis. *Am J Sports Med*. 2007;35(10):1756-1769.
33. Macri EM, Felson DT, Zhang Y, et al. Patellofemoral morphology and alignment: reference values and dose-response patterns for the relation to MRI features of patellofemoral osteoarthritis. *Osteoarthritis Cartilage*. 2017;25(10):1690-1697.
34. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum*. 2005;52(7):2026-2032.
35. Neogi T, Bowes MA, Niu J, et al. Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the Osteoarthritis Initiative. *Arthritis Rheum*. 2013;65(8):2048-2058.
36. Outerbridge RE. The etiology of chondromalacia patellae. *J Bone Joint Surg Br*. 1961;43:752-757.
37. Pan J, Pialat JB, Joseph T, et al. Knee cartilage T2 characteristics and evolution in relation to morphologic abnormalities detected at 3-T MR imaging: a longitudinal study of the normal control cohort from the Osteoarthritis Initiative. *Radiology*. 2011;261(2):507-515.
38. Panzer S, Augat P, Atzwanger J, Hergan K. 3-T MRI assessment of osteophyte formation in patients with unilateral anterior cruciate ligament injury and reconstruction. *Skeletal Radiol*. 2012;41(12):1597-1604.
39. Papalia R, Torre G, Vasta S, et al. Bone bruises in anterior cruciate ligament injured knee and long-term outcomes: a review of the evidence. *Open Access J Sports Med*. 2015;6:37-48.
40. Pollard TC, Gwilym SE, Carr AJ. The assessment of early osteoarthritis. *J Bone Joint Surg Br*. 2008;90(4):411-421.
41. Risberg MA, Oiestad BE, Gunderson T, et al. Changes in knee osteoarthritis, symptoms, and function after anterior cruciate ligament reconstruction: a 20-year prospective follow-up study. *Am J Sports Med*. 2016;44(5):1215-1224.
42. Roemer FW, Frobell R, Lohmander LS, et al. Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS): longitudinal MRI-based whole joint assessment of anterior cruciate ligament injury. *Osteoarthritis Cartilage*. 2014;22(5):668-682.
43. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. *Nat Rev Rheumatol*. 2016;12(2):92-101.
44. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis Rheum*. 2005;52(11):3507-3514.
45. Runhaar J, Schiphof D, van Meer B, et al. How to define subregional osteoarthritis progression using semi-quantitative MRI Osteoarthritis Knee Score (MOAKS). *Osteoarthritis Cartilage*. 2014;22(10):1533-1536.
46. Sharma L, Nevitt M, Hochberg M, et al. Clinical significance of worsening versus stable preradiographic MRI lesions in a cohort study of persons at higher risk for knee osteoarthritis. *Ann Rheum Dis*. 2016;75(9):1630-1636.
47. Shaw L, Finch CF. Trends in pediatric and adolescent anterior cruciate ligament injuries in Victoria, Australia 2005-2015. *Int J Environ Res Public Health*. 2017;14(6):e599.
48. Stefanik JJ, Zhu Y, Zumwalt AC, et al. Association between patella alta and the prevalence and worsening of structural features of patellofemoral joint osteoarthritis: the multicenter osteoarthritis study. *Arthritis Care Res (Hoboken)*. 2010;62(9):1258-1265.
49. Sward P, Kostogiannis I, Neuman P, et al. Differences in the radiological characteristics between post-traumatic and non-traumatic knee osteoarthritis. *Scand J Med Sci Sports*. 2010;20(5):731-739.
50. Swirtun LR, Eriksson K, Renstrom P. Who chooses anterior cruciate ligament reconstruction and why? A 2-year prospective study. *Scand J Med Sci Sports*. 2006;16(6):441-446.
51. Van de Velde SK, Gill TJ, DeFrate LE, et al. The effect of anterior cruciate ligament deficiency and reconstruction on the patellofemoral joint. *Am J Sports Med*. 2008;36(6):1150-1159.
52. Van Ginckel A, Verdonk P, Witvrouw E. Cartilage adaptation after anterior cruciate ligament injury and reconstruction: implications for clinical management and research? A systematic review of longitudinal MRI studies. *Osteoarthritis Cartilage*. 2013;21(8):1009-1024.
53. van Meer BL, Meuffels DE, van Eijsden WA, et al. Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. *Br J Sports Med*. 2015;49(15):975-983.
54. van Meer BL, Oei EH, Meuffels DE, et al. Degenerative changes in the knee 2 years after anterior cruciate ligament rupture and related risk factors: a prospective observational follow-up study. *Am J Sports Med*. 2016;44(6):1524-1533.
55. Wang HJ, Ao YF, Chen LX, et al. Second-look arthroscopic evaluation of the articular cartilage after primary single-bundle and double-bundle anterior cruciate ligament reconstructions. *Chin Med J (Engl)*. 2011;124(21):3551-3555.
56. Wang Y, Ding C, Wluka AE, et al. Factors affecting progression of knee cartilage defects in normal subjects over 2 years. *Rheumatology (Oxford)*. 2006;45(1):79-84.
57. White DK, Zhang Y, Niu J, et al. Do worsening knee radiographs mean greater chances of severe functional limitation? *Arthritis Care Res (Hoboken)*. 2010;62(10):1433-1439.
58. Whittaker JL, Woodhouse LJ, Nettel-Aguierre A, Emery CA. Outcomes associated with early post-traumatic osteoarthritis and other negative health consequences 3-10 years following knee joint injury in youth sport. *Osteoarthritis Cartilage*. 2015;23(7):1122-1129.
59. Wunschel M, Leichtle Y, Obloh C, et al. The effect of different quadriceps loading patterns on tibiofemoral joint kinematics and patellofemoral contact pressure during simulated partial weight-bearing knee flexion. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(7):1099-1106.
60. Yoo JD, Papannagari R, Park SE, et al. The effect of anterior cruciate ligament reconstruction on knee joint kinematics under simulated muscle loads. *Am J Sports Med*. 2005;33(2):240-246.

Appendix I: Chapter 4 original publication: Arthritis Care and Research

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 72, No. 3, March 2020, pp 412–422
DOI 10.1002/acr.23854

Patient-Reported Outcomes One to Five Years After Anterior Cruciate Ligament Reconstruction: The Effect of Combined Injury and Associations With Osteoarthritis Features Defined on Magnetic Resonance Imaging

Brooke E. Patterson,[1] Adam G. Culvenor,[2] Christian J. Barton,[1] Ali Guermazi,[3] Joshua J. Stefanik,[4] and Kay M. Crossley[1]

Objective. Persistent symptoms and poor quality of life (QoL) are common following anterior cruciate ligament reconstruction (ACLR). We aimed to determine the influence of a combined ACL injury (i.e., concomitant meniscectomy and/or arthroscopic chondral defect at the time of ACLR and/or secondary injury/surgery to ACLR knee) and cartilage defects defined on magnetic resonance imaging (MRI), bone marrow lesions (BMLs), and meniscal lesions on patient-reported outcomes 1 to 5 years after ACLR.

Methods. A total of 80 participants (50 men; mean ± SD age 32 ± 14 years) completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the International Knee Documentation Committee (IKDC) questionnaires as well as a 3T MRI assessment at 1 and 5 years after ACLR. Median patient-reported outcome scores were compared between isolated and combined ACL injuries and with published normative values. Using multivariate regression, we evaluated the association between compartment-specific MRI cartilage, BMLs, and meniscal lesions and patient-reported outcomes at 1 and 5 years.

Results. Individuals with a combined injury had significantly worse scores in the KOOS subscale of function in sport and recreation (KOOS sport/rec) and in the IKDC questionnaire at 1 year, and worse scores in the KOOS subscales of pain (KOOS pain), symptoms (KOOS symptoms), and QoL (KOOS QoL) and in the IKDC questionnaire at 5 years compared to those with an isolated injury. Although no feature on MRI was associated with patient-reported outcomes cross-sectionally at 1 year, patellofemoral cartilage defects at 1 year were significantly associated with worse 5-year KOOS symptoms (β = −9.79, 95% confidence interval [95% CI] −16.67, −2.91), KOOS sport/rec (β = −7.94, 95% CI −15.27, −0.61), KOOS QoL (β = −8.29, 95% CI −15.28, −1.29), and IKDC (β = −4.79, 95% CI −9.34, −0.24) scores. Patellofemoral cartilage defects at 5 years were also significantly associated with worse 5-year KOOS symptoms (β = −6.86, 95% CI −13.49, −0.24) and KOOS QoL (β = −11.71, 95% CI −19.08, −4.33) scores.

Conclusion. Combined injury and patellofemoral cartilage defects shown on MRI are associated with poorer long-term outcomes. Clinicians should be vigilant and aware of individuals with these injuries, as such individuals may benefit from targeted interventions to improve QoL and optimize symptoms.

INTRODUCTION

Anterior cruciate ligament reconstruction (ACLR) is commonly performed following ACL injury in individuals seeking a return to preinjury sports participation. Patient-reported symptoms, function, and quality of life (QoL) typically improve during the first 6–12 months following ACLR but appear to plateau beyond this point (1–4). Although 65% of young people return to preinjury sports participation following ACLR (5), as many as 34% report unacceptable symptoms up to 2 years following surgery (6).

Supported by Arthritis Australia, La Trobe University Sport, Exercise and Rehabilitation Research Focus Area (grant 1025950), the Queensland Orthopaedic Physiotherapy Network, the University of Melbourne (Research Collaboration grant), and the University of British Columbia Centre for Hip Health and Mobility (Society for Mobility and Health grant). Ms Patterson is recipient of a National Health and Medical Research Council postgraduate scholarship (award 1114296) and recipient of the Felice Rosemary-Lloyd Travel Scholarship. Dr. Culvenor's work was supported by a National Health and Medical Research Council of Australia Early Career Fellowship (Neil Hamilton Fairley Clinical Fellowship award 1121173). Mr. Stefanik's work was supported by the NIH (National Institute of General Medical Sciences grant U54-GM-104941).

[1]Brooke E. Patterson, PT, Christian J. Barton, PT, PhD, Kay M. Crossley, PT, PhD: La Trobe Sport and Exercise Medicine Research Centre, La Trobe University, Bundoora, Victoria, Australia; [2]Adam G. Culvenor, PT, PhD: La Trobe Sport and Exercise Medicine Research Centre, La Trobe University,

SIGNIFICANCE & INNOVATIONS

- Individuals with a combined injury or patellofemoral cartilage defect on magnetic resonance imaging (MRI) had worse 5-year patient-reported outcomes and may benefit from additional education and targeted interventions.
- This study assists clinical interpretability of patient-reported outcomes: approximately one-half of all patients with a combined injury at 5 years after anterior cruciate ligament reconstruction do not achieve acceptable symptoms or quality of life.
- Meniscal lesions were the only tibiofemoral feature on MRI associated with worse patient-reported outcomes. Tibiofemoral bone marrow lesions were associated with better patient-reported outcomes. The long-term significance of these should be explored further in populations with anterior cruciate ligament injuries.

Persistent symptoms could induce negative lifestyle modifications (i.e., reduced physical activity, weight gain) (7), increasing the burden on health care systems in the longer term. Successfully identifying patients with persistent symptoms early following ACLR may allow for the development of targeted interventions.

A combined injury (i.e., ACL injury and meniscectomy and/or cartilage lesion assessed at the time of ACLR) might increase the risk of worse symptoms and QoL in the short to medium term (1–6 years) (1,3) and long term (15–20 years) (8). However, some studies report no or minimal association between combined injuries and patient-reported outcomes in the medium to long term (9–11). Previous studies (2,3,8,9) have utilized group-level data (i.e., in order to determine if a significant group mean effect exists between isolated and combined ACLR groups). This may not be relevant to patients and clinicians, who are most interested in their own individual effect in relation to treatment. The group-level approach does not describe the number of individuals who present with unacceptable outcomes and who may require and benefit from additional interventions. Identifying individuals with poor outcomes and enhancing clinical interpretability of patient-reported outcomes may be improved by comparing scores from each ACLR patient (as opposed to group means) to scores from other ACLR patients who report acceptable knee function.

Persistent symptoms following ACLR may be related to early deterioration of joint structure. Radiographic osteoarthritis (OA) occurs in 50–90% of knees 10–15 years after ACLR, but the relationship with patient-reported outcomes is unclear (12,13). In older populations with established knee OA, more specific imaging markers of disease observed on magnetic resonance imaging (MRI), such as bone marrow lesions (BMLs), inflammation, and cartilage defects, are associated with clinical outcomes (i.e., pain) (14–17). While early structural pathology identified on MRI may be preexisting or occur with injury, features of OA continue to deteriorate at an accelerated rate compared to primary OA between 1 and 5 years after ACLR (18). Yet, there is limited research on how these early features of OA affect patient-reported outcomes. Tibiofemoral cartilage lesions and BMLs have little association with knee symptoms cross-sectionally at 2 (19) and 12 years after ACLR (20). An important omission in previous research is the patellofemoral joint, which is a potential contributor to knee symptoms after ACLR (21). We recently identified patellofemoral cartilage defects at 1 year after ACLR as being associated with worse patient-reported outcomes at 3 years (22). Further cross-sectional and longitudinal evaluation of the relationship between OA features seen on MRI and patient-reported outcomes beyond 3 years is important to determine if imaging features of OA affect patient reported pain, function, or QoL.

The aims of the current study were to determine the influence of a combined injury on patient-reported outcomes measures from 1 to 5 years after ACLR and to compare these outcomes to known normative patient-reported outcome scores (in uninjured and ACLR patients). We also aimed to determine the association between patellofemoral and tibiofemoral cartilage defects, BMLs, meniscal lesions, and patient-reported outcomes at 1 and 5 years after ACLR.

MATERIALS AND METHODS

Study design and participants. All 112 consecutively recruited individuals who had completed patient-reported outcomes at 1 year after ACLR as part of our previous evaluation (23) (median age at surgery 27 years [range 18–51 years]) were eligible for the current prospective 5-year follow-up study. Baseline (1 year after ACLR) eligibility criteria, ACLR technique, and changes in cartilage, bone marrow, and meniscus between 1 and 5 years have been reported previously (18,23). Briefly, all patients underwent ACLR performed by 1 of 2 Melbourne-based orthopedic surgeons using a single-bundle hamstring-autograft. Baseline exclusion criteria included knee injury/symptoms prior to ACL injury, >5 years between ACL injury and reconstruction, and any secondary injury/surgery (between surgery and 1 year after ACLR). Secondary injury was defined as a new index or contralateral knee injury (ACL, meniscus, collateral ligament) or surgery. All

Bundoora, Victoria, Australia, and Paracelsus Medical University, Salzburg, Austria; [3]Ali Guermazi, MD, PhD: Boston University School of Medicine, Boston, Massachusetts; [4]Joshua J. Stefanik, PT, PhD: University of Delaware, Newark.

Dr. Guermazi has received consulting fees from Galapagos, Roche, AstraZeneca, GE Healthcare (less than $10,000 each), Merck Serono, Pfizer, and TissueGene (more than $10,000 each) and is a shareholder of Boston Imaging Core Lab. No other disclosures relevant to this article were reported.

Address correspondence to Kay M. Crossley, PT, PhD, La Trobe Sport and Exercise Medicine Research Centre, School of Allied Health, La Trobe University, Bundoora 3086, Victoria, Australia. E-mail: K.Crossley@latrobe.edu.au.

Submitted for publication September 25, 2018; accepted in revised form February 12, 2019.

participants were invited to participate in the 5-year post-ACLR follow-up, including 10 participants who sustained a secondary injury between 1 and 5 years given that this is a common occurrence and represents the wider ACLR population. A total of 81 (72%) participants completed the same patient-reported outcomes measures at the 5-year post-ACLR evaluation (Figure 1). Ethics approval was granted by La Trobe University Human Ethics Committee (HEC 15–100), and all participants signed informed consent.

Demographic, injury, and surgical factors. Data on participant age, sex, injury history, body mass index (BMI), and previous and current activity level (level 1 = pivoting/jumping sports up to level 4 = sedentary) (24) were obtained at 1 and 5 years. The combined injury group at 1 year consisted of individuals with ACL injury and concomitant meniscectomy or a significant cartilage defect (i.e., Outerbridge grade ≥2 [25]) at the time of ACLR (i.e., extracted from surgical notes). Those reporting to investigators a secondary injury/surgery to the index knee between the 1- and 5-year follow-ups were added to the combined injury group at 5 years. Defining a combined injury by the presence of a concomitant injury at time of ACLR and/or a secondary injury over time via this method is consistent with previous longitudinal cohort studies (8,11). Individuals without a combined injury were defined as having an isolated injury.

Patient-reported outcome measures. At 1 and 5 years, participants completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire and the International Knee Documentation Committee (IKDC) subjective knee evaluation with respect to their index knee condition during the previous week. The KOOS and IKDC questionnaires are used extensively for patients with ACL injuries with established reliability and validity (26). The following 4 subscales of the KOOS were assessed: pain (KOOS pain), symptoms (KOOS symptoms), function in sport and recreation (KOOS sport/rec), and knee-related QoL (KOOS QoL). The KOOS activities of daily living subscale was excluded due to the ceiling effects observed in young active populations (27). Patient-reported outcomes measures were completed either in person (pen and paper) or via the online portal PROmptus–Medical (DS PRIMA) with instructions matching the original paper version. The KOOS (intraclass correlation coefficient [ICC] >0.96) (28) and IKDC (ICC 0.79) (29) questionnaires have demonstrated test–retest reliability between paper and electronic formats.

Cartilage defects, BMLs, and meniscal lesions. Of the 112 participants completing patient-reported outcomes at 1 year, 111 completed MRI assessment at 1 year, and 80 (71%) at 5 years (Figure 1) with an identical MRI scanner and sequences as described previously (23). Briefly, with an Achieva 3T MRI system (Philips), sequences consisted of a 3-dimensional proton density–weighted volume isotropic turbo spin-echo acquisition technique acquired at 0.35 mm isotropically, a short-tau inversion recovery sequence, and an axial proton-density turbo spin-echo sequence. Cartilage defects, BMLs, and meniscal lesions were scored using the MRI OA Knee Score (MOAKS) by a musculoskeletal radiologist (AG) with 19 years of experience who established interrater and

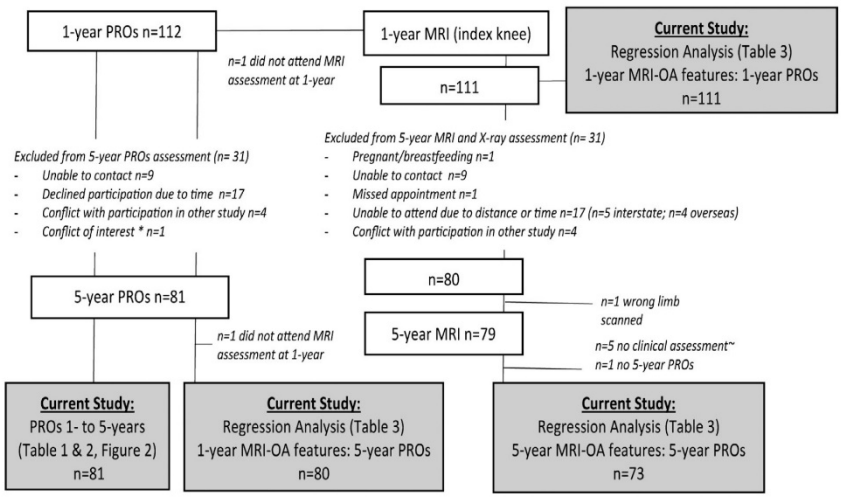


Figure 1. Flow chart of participant recruitment. Body mass index data from the clinical assessment were required for the regression analysis, which caused 6 patients to not be included in the analysis for the 5-year magnetic resonance imaging (MRI) assessment and the 5-year patient-reported outcomes (PROs) assessment. OA = osteoarthritis; * = the participant at 1 year was a member of the research team at 5 years; ~ = clinical assessment was also performed on a subset of the cohort at 1 and 5 years.

intrarater reliability in semiquantitative MRI assessment (κ = 0.61–0.80) (30). The 1- and 5-year images were read paired (i.e., using 1- and 5-year MRI scans side-by-side, the radiologist was not blinded to time points) and were blinded to clinical information. The MOAKS divides the knee into 14 articular subregions to score cartilage defects and BMLs. For the tibiofemoral compartment, cartilage defects and BMLs were graded in each of the following 10 subregions: central and posterior femur (medial and lateral) and anterior, central, and posterior tibia (medial and lateral). The following 4 subregions were used to grade cartilage defects and BMLs in the patellofemoral compartment: the patella (medial and lateral) and trochlea (medial and lateral). Meniscal lesions were defined as medial or lateral and divided into anterior, posterior, and central subregions. Cartilage defects and BMLs were graded as present or absent in the tibiofemoral and patellofemoral compartments if any corresponding subregions for that compartment had a lesion greater than or equal to grade 1 in size (i.e., any lesion >0% in size relative to each subregion surface area). Meniscal lesions were graded as present if in either tibiofemoral compartment subregion there was 1) a definite vertical, horizontal, or complex tear (definite = an area of abnormal signal that extends to the meniscal articular surface); 2) partial or progressive maceration (loss of morphologic substance of the meniscus); or 3) at least a grade-1 extrusion (i.e., >2 mm) (30). Details of the MRI sequences and MOAKS are presented in Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract.

Statistical analyses. Combined and isolated injury group medians and interquartile ranges (IQRs) for the KOOS and IKDC questionnaires were calculated at 1 and 5 years due to non-normally distributed data (assessed with Shapiro-Wilk's tests). For the KOOS and IKDC questionnaires, we visually compared and indicated if the ACLR median scores were at least a minimum detectable change (MDC) (i.e., ≥14 points) (26,31) below the normative median (32–34). Nonparametric analyses were used to account for the non-normal distribution of the KOOS and IKDC scores at 1 and 5 years. Mann-Whitney U tests compared patient-reported outcomes between the isolated and combined groups cross-sectionally at 1 and 5 years. The absolute change in patient-reported outcomes between 1 and 5 years was normally distributed and reported as mean ± SD, and parametric analyses (independent sample *t*-tests) compared the change in each group. In addition, each individual was classified as having an acceptable KOOS or IKDC score if it was greater than a predetermined cutoff (6,35). The KOOS cutoffs were determined from the Norwegian Knee Ligament Registry (n = 1,197) using the lower 95% confidence interval (95% CI) score for each subscale (KOOS pain 88 of 100; KOOS symptoms 83 of 100; KOOS sport/rec 73 of 100; KOOS QoL 73 of 100) for patients who perceived their knee function as acceptable 24 months after ACLR (6). The IKDC cutoff (75 of 100) was determined using the mean IKDC score (85 of 100) minus the SD (SD 10) for individuals who perceived their knee function as acceptable 3.5 years after ACLR (35). Fisher's exact test was used to compare the proportion of the isolated and combined groups defined as acceptable.

Multivariable linear regression was used to determine the cross-sectional relationship between the presence of cartilage lesions, BMLs, and meniscal lesions (dichotomous independent variables) in the patellofemoral and tibiofemoral compartments and patient-reported outcomes (continuous KOOS and IKDC scores) at 1 and 5 years. Regression was adjusted for age at the time of surgery, sex, BMI at 1 year, and combined injury due to their potential influence on patient-reported outcomes (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract). The relationship between cartilage lesions, BMLs, and meniscal lesions at 1 year with patient-reported outcomes at 5 years was also included, with additional adjustment for the baseline patient-reported outcome score. Stata, version 14.2 was used for statistical analyses. *P* values less than 0.05 were considered statistically significant.

RESULTS

Participant demographics. Demographic characteristics of the 81 participants included for patient-reported outcomes analysis at 1 and 5 years are presented in Table 1. There were no demographic, surgical, or baseline MRI-related differences between those who did (n = 81) and did not participate (n = 31) in the follow-up assessment at 5 years ($P \geq 0.05$) (see Supplementary Appendix C, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract). An exception was medial meniscal lesions, which were more prevalent in the participating group at baseline. Forty (49%) and 46 (57%) of the 81 participants were classified as having a combined injury at 1 and 5 years, respectively (i.e., 6 were added to the combined injury group at 5 years due to a secondary injury between 1 year and 5 years). Between 1 year and 5 years, 10 participants had experienced a secondary injury in the index knee (Table 1); however, 4 of these injuries were already classified as a combined injury at 1 year.

Patient-reported outcomes. At 1 year after ACLR, individuals in the combined injury group had significantly worse KOOS sport/rec and IKDC scores (median difference [IQR] 15 [4.6] and 5.0 [3.5], respectively; $P < 0.05$). At 5 years, all patient-reported outcomes (except KOOS sport/rec) were significantly worse in the combined injury group. The median differences (IQR) were as follows: KOOS pain 5.0 (2.5); KOOS symptoms 11.0 (4.2); KOOS QoL 13.0 (4.6); and IKDC 4.0 (3.2). KOOS and IKDC scores at

Table 1. Participant characteristics of combined and isolated injury groups at 1 and 5 years after ACLR*

	1 year (n = 81)		5 years (n = 81)	
	Combined (n = 40)	Isolated (n = 41)	Combined (n = 46)	Isolated (n = 35)
Age, median ± IQR years	31 ± 12†	25 ± 12	35 ± 14†	29 ± 13
Sex, male	26 (65)	24 (59)	31 (67)	19 (54)
BMI, median ± IQR kg/m^2‡	26.9 ± 5.4†	24.8 ± 3.0	27.5 ± 5.1†	24.7 ± 4.2
Preinjury activity level 1 sport§	28 (70)	28 (68)	34 (74)	22 (63)
Anteroposterior laxity between-knee difference, median ± IQR mm¶	1.1 ± 2.7	1.9 ± 2.1	NA	NA
Time of injury to surgery, median ± IQR weeks	19 ± 32†	12 ± 9	17 ± 26†	12 ± 9
Meniscectomy at time of ACLR#	32 (80)	0 (0)	32 (40)	0 (0)
Cartilage defect at time of ACLR**	16 (40)	0 (0)	16 (35)	0 (0)
New knee injuries (either knee)	0 (0)††	0 (0)††	13 (28)	3 (9)
ACLR knee‡‡	0 (0)††	0 (0)††	10 (22)	0 (0)
Contralateral knee§§	0 (0)††	0 (0)††	3 (7)	3 (9)
Returned to level 1 sport§	9 (23)	11 (27)	11 (24)	9 (26)

* Values are the number (%) unless indicated otherwise. Demographics for 111 participants from 1-year assessment were previously reported (23). Participants categorized as having a combined injury at 1 and 5 years if they had a significant cartilage defect/meniscectomy assessed at the time of anterior cruciate ligament reconstruction (ACLR). IQR = interquartile range; BMI = body mass index; NA = not assessed.
† Statistically significant ($P < 0.05$) difference between combined and isolated injury groups.
‡ N = 75 participating in BMI assessment at 5 years.
§ Level 1 sport = jumping, cutting, pivoting as per Sports Activity Classification based on Grindem et al (24).
¶ Assessed using the KT-1000 arthrometer (Mesmeric) at 30° of flexion with 30-pound load (45).
# Performed at the time of ACLR.
** Assessed arthroscopically at time of ACLR. Cartilage defect defined as in Outerbridge (25) grade ≥2 (i.e., at least a partial-thickness defect).
†† No new knee injuries were reported at 1 year because this was an exclusion criterion.
‡‡ 5-year new ACLR knee injuries/surgery: n = 10 (n = 3 ACLR revision, n = 6 meniscectomy, n = 1 lateral collateral ligament sprain).
§§ 5-year new contralateral knee injuries/surgery: n = 6 (combined injury group: n = 2 ACLR revision, n = 1 meniscectomy; isolated injury group: n = 1 ACLR, n = 1 meniscectomy, n = 1 lateral collateral ligament sprain).

1 and 5 years for both groups are presented in Figure 2. The entire cohort (n = 81) demonstrated significant ($P < 0.05$) improvement (i.e., fewer knee symptoms, better function, and QoL) between 1 and 5 years for all KOOS subscales (except KOOS symptoms) and the IKDC questionnaire. The mean ± SD changes for each of the subscales and the IKDC questionnaire were the following: KOOS pain 2.8 ± 9; KOOS symptoms 0.5 ± 16.1; KOOS sport/rec 6.0 ± 18.2; KOOS QoL 10.0 ± 18.9; and IKDC 4.7 ± 10.9. Improvement between 1 and 5 years did not differ between the combined and isolated groups ($P \geq 0.05$). At 5 years, the combined injury group median scores for the KOOS symptoms and KOOS QoL subscales were 14 and 25 points below age-matched normative values from uninjured young adults (34), which is greater than the recommended MDC (14–20 points) for individuals with an ACL injury (31) (see Supplementary Appendix D, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract, which presents patient-reported outcomes for all groups at 1 and 5 years and crude *P* values for between-group analyses).

The numbers of individuals above the acceptable cutoff for the KOOS subscales and the IKDC questionnaire are presented in Table 2. A significantly lower percentage of individuals with combined injury reported acceptable IKDC scores at 1 year and KOOS symptoms, KOOS pain, KOOS QoL, and IKDC scores at 5 years. These significant relationships persisted in the sensitivity analysis, which excluded the 10 participants with reinjury between 1 and 5 years (see Supplementary Appendix E, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract).

Association with OA features seen on MRI. There were no significant cross-sectional associations between cartilage defects, BMLs, or meniscal lesions and KOOS or IKDC scores at 1 year. The presence of a patellofemoral cartilage defect at 1 year was significantly associated with worse KOOS symptoms (β = –9.79, 95% CI –16.67, –2.91; $P = 0.006$), KOOS sport/rec (β = –7.94, 95% CI –15.27, –0.61; $P = 0.034$), KOOS QoL (β = –8.29, 95% CI –15.28, –1.29; $P = 0.021$), and IKDC (β = –4.79, 95% CI –9.34, –0.24; $P = 0.039$) scores at 5 years (Table 3). The presence of a meniscal lesion at 1 year was significantly associated with a worse KOOS symptoms score at 5 years (β = –8.47, 95% CI –16.54, –0.42; $P = 0.039$). Similarly, at 5 years, the presence of a patellofemoral cartilage defect or meniscal tear was associated with worse patient-reported outcomes, and tibiofemoral BMLs were associated with better patient-reported outcomes (Table 3). Regression analysis was also

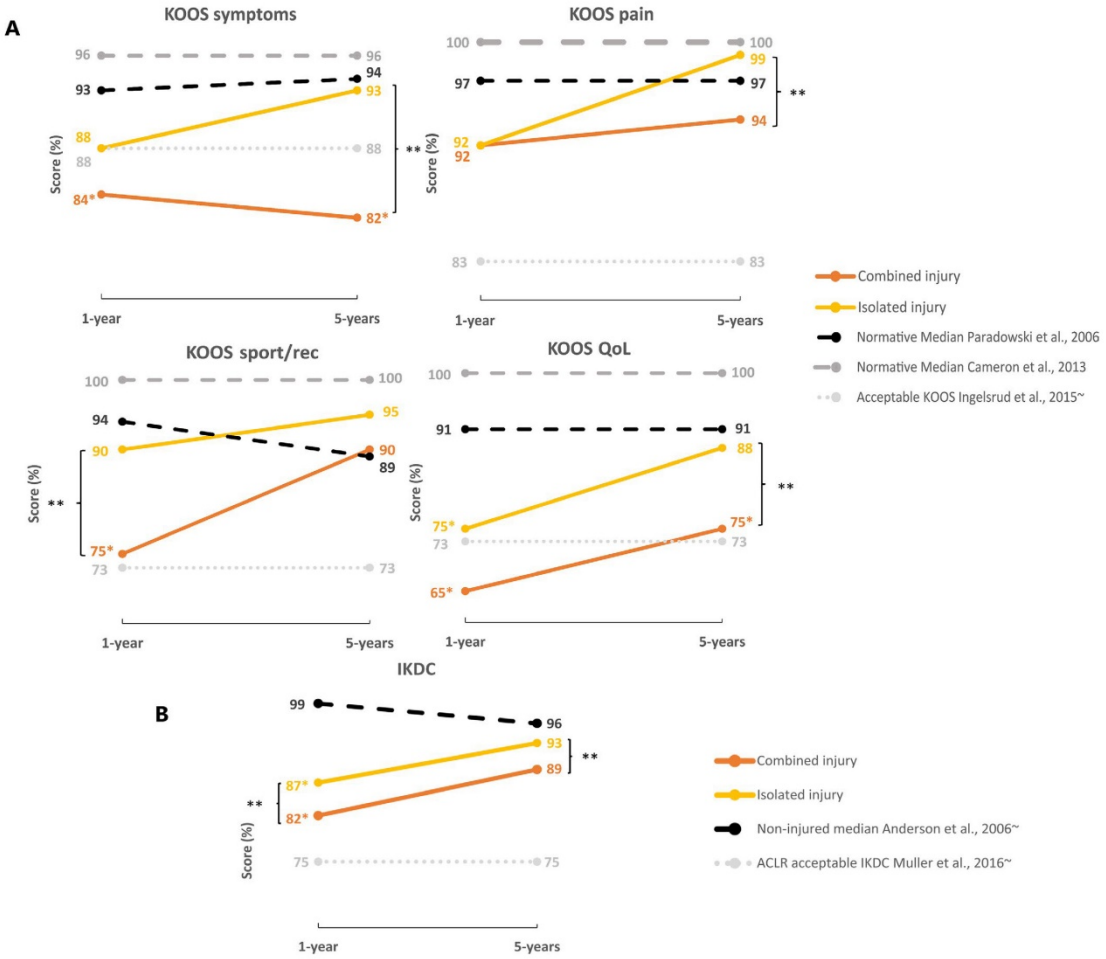


Figure 2. **A**, Comparison between isolated and combined anterior cruciate ligament reconstruction (ACLR) groups, uninjured and general population medians, and acceptable cutoff scores in ACLR patients for the Knee Osteoarthritis Outcome Score (KOOS) subscales. **B**, Comparison between isolated and combined ACLR groups, uninjured median values, and acceptable cutoff scores in ACLR patients for International Knee Documentation Committee (IKDC) scores. All values are presented as the median at 1 year and 5 years. Supplementary Appendix D (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract) presents interquartile range values and scores for the entire group (n = 81). At 1 year, n = 40 for the combined injury group and n = 41 for the isolated injury group. At 5 years, n = 46 for the combined injury group and n = 35 for the isolated injury group. QoL = quality of life; * = median value at 1 year or 5 years is greater than or equal to the minimal detectable change (26,31) below the general population (age-matched, uninjured) normative medians for the KOOS (32) and IKDC (34) questionnaires; ** = statistically significant difference ($P < 0.05$) between combined and isolated injury groups at 1 or 5 years; ~ = weighted average median values for KOOS and IKDC scores were calculated using respective data from healthy uninjured (no history of knee pain) participants (32), age- and sex-matched data in the general population (may have history of knee pain) (33,34), and acceptable cutoff scores in ACLR patients (6,35).

performed without adjustment for age at time of surgery, sex, BMI at 1 year, and presence of combined injury. The unadjusted analysis resulted in larger effect sizes and increased number of significant relationships (see Supplementary Appendix F, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract), suggesting that these factors somewhat influence patient-reported outcomes following ACLR. Sensitivity analyses excluding 10 participants with reinjury between 1 and 5 years resulted in similar effect sizes (but wider CIs), suggesting that the effect of reinjury on the relationship between

Table 2. Participants with acceptable KOOS and IKDC scores*

Outcome measure and group (acceptable cutoff score)†	1 year	5 years	Between-group difference, 1 year	Between-group difference, 5 years‡
KOOS pain (88)				
Whole group	63 (78)	66 (81)	0.601	0.010§
Isolated	33 (80)	33 (94)		
Combined	30 (75)	33 (72)		
KOOS symptoms (83)				
Whole group	47 (58)	47 (58)	0.180	0.042§
Isolated	27 (66)	25 (71)		
Combined	20 (50)	22 (48)		
KOOS sport/rec (73)				
Whole group	60 (75)	69 (85)	0.455	0.060
Isolated	32 (78)	33 (94)		
Combined	28 (70)	36 (78)		
KOOS QoL (73)				
Whole group	38 (47)	55 (68)	0.268	0.004§
Isolated	22 (54)	30 (86)		
Combined	16 (40)	25 (54)		
IKDC (75)				
Whole group	62 (77)	71 (88)	0.004§	0.004§
Isolated	37 (90)	35 (100)		
Combined	25 (63)	36 (78)		

* Values are the number (%) of participants in the group with a raw score above acceptable cutoffs using previously published data for anterior cruciate ligament reconstruction (ACLR) patients and the Knee Injury and Osteoarthritis Outcome Score (KOOS) (6) and International Knee Documentation Committee (IKDC) (35) questionnaires.
† N = 81 for whole group at 1 and 5 years. Participants were defined as having a combined injury at 1 and 5 years if they had a concomitant injury (significant cartilage defects/meniscectomy assessed at the time of surgery). At 5 years, individuals were added to the combined injury group if they had a new injury/surgery on the ACLR knee. All other participants were defined as having an isolated injury. At 1 year, n = 40 for the combined injury group and n = 41 for the isolated injury group. At 5 years, n = 46 for the combined injury group and n = 35 for the isolated injury group.
‡ Fisher's exact test was used to compare the proportions of the isolated and combined groups above the acceptable cutoff value.
§ Significant ($P < 0.05$).

lesions on MRI and patient-reported outcomes in this study was minimal (see Supplementary Appendix E, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract).

DISCUSSION

Despite improvement in KOOS and IKDC scores between 1 and 5 years following ACLR, individuals with a combined injury (i.e., concomitant meniscectomy and/or arthroscopic chondral defect at the time of ACLR and/or secondary injury/surgery to ACL knee) had worse patient-reported outcomes at 5 years after ACLR compared to those with an isolated injury. At 5 years, a lower proportion of individuals with combined injury met previously reported acceptable patient-reported outcome scores for ACLR patients (6) and presented with worse patient-reported outcome scores compared to healthy uninjured populations. In the second part of our analysis, MRI findings had minimal association with patient-reported outcomes at 1 and 5 years except for patellofemoral cartilage defects at 1 year, which were associated with worse KOOS symptoms, KOOS sport/rec, KOOS QoL, and IKDC scores at 5 years. Patellofemoral cartilage defects on MRI at 1 and 5 years were generally associated with worse KOOS and IKDC scores at 5 years. The only other MRI findings to be associated with patient-reported outcomes were meniscal lesions at 1 and 5 years (worse KOOS symptoms at 5 years) and tibiofemoral BMLs at 5 years (better KOOS sport/rec, KOOS QOL, and IKDC scores at 5 years).

At an entire group level, all patient-reported outcomes except KOOS symptoms improved from 1 to 5 years after ACLR. Although improvements did not exceed known clinically meaningful change scores for the KOOS (36) or IKDC (37) questionnaires, all KOOS subscales and IKDC entire group median scores at 5 years were near normative values (within MDC score) (26,31) when compared to the general population (33,34). While group-level scores for most KOOS subscales and IKDC questionnaire in the combined and isolated injury group at 5 years exceeded patient acceptable symptom state (PASS) cutoff values for ACLR populations (6,35) (Figure 2), our novel analysis (Table 3) identified many individuals within the group who did not achieve PASS values. Up to 42% (range 0–42%; average 22%) of all participants had not recovered to KOOS or IKDC PASS values at 5 years. Deficits were most evident for the KOOS symptoms and KOOS QoL subscales, in which 42% and 32% of participants (whole group) had not recovered to PASS values at 5 years, respectively. Entire group patient-reported

Table 3. Multivariable linear regression analysis of OA features shown on MRI (MRI-OA) associated with patient-reported outcomes at 1 and 5 years after ACLR*

MRI-OA features	With feature, %	KOOS symptoms	KOOS pain	KOOS sport/rec	KOOS QoL	IKDC
1-year/1-year PROs†						
PF any cartilage	45	−0.87 (−6.35, 4.62)	−0.37 (−4.18, 3.43)	2.69 (−3.77, 9.14)	5.34 (−2.20, 12.89)	−0.03 (−4.47, 4.52)
PF any BML	23	−1.73 (−7.78, 4.31)	−1.87 (−6.04, 2.30)	−6.39 (−13.39, 0.61)	−3.01 (−11.26, 5.24)	−1.02 (−5.96, 3.92)
TF any cartilage	48	2.81 (−2.33, 7.94)	1.25 (−2.32, 4.83)	−0.93 (−7.02, 5.16)	2.69 (−4.45, 9.85)	2.52 (−1.68, 6.74)
TF any BML	31	0.86 (−4.71, 6.44)	1.03 (−2.81, 4.90)	−0.26 (−6.81, 6.29)	−0.17 (−7.79, 7.45)	1.03 (−3.52, 5.58)
Meniscal lesion	72	−1.61 (−5.96, 9.17)	−1.06 (−6.66, 4.54)	−2.92 (−12.61 6.77)	1.42 (−9.74, 12.58)	−3.29 (−10.07, 3.48)
1-year/5-year PROs‡						
PF any cartilage	46	−9.79 (−16.67, −2.91)§	−2.88 (−6.62, 0.86)	−7.94 (−15.27, −0.61)§	−8.29 (−15.28, −1.29)§	−4.79 (−9.34, −0.24)§
PF any BML	26	−4.60 (−12.02, 2.81)	−1.28 (−6.44, 2.36)	−2.49 (−10.32, 5.34)	1.82 (−5.63, 9.27)	−1.62 (−6.39, 3.15)
TF any cartilage	47	−5.32 (−11.84, 1.20)	−1.26 (−4.73, 2.19)	0.47 (−6.39, 7.34)	1.95 (−4.67, 8.58)	0.24 (−4.09, 4.58)
TF any BML	30	0.12 (−6.89, 7.13)	1.97 (−1.67, 5.62)	3.46 (−3.79, 10.73)	−0.94 (−7.97, 6.09)	1.06 (−3.48, 5.61)
Meniscal lesion	79	−8.47 (−16.54, −0.42)§	−0.99 (−5.33, 3.34)	−0.44 (−8.21, 9.10)	−5.19 (−13.41, 3.04)	−3.74 (−9.07, 1.58)
5-year/5-year PROs†						
PF any cartilage	58	−6.86 (−13.49, −0.24)§	−2.49 (−6.78, 1.79)	−3.99 (−11.06, 3.07)	−11.71 (−19.08, −4.33)§	−3.86 (−9.08, 1.36)
PF any BML	22	−1.19 (−8.77, 6.40)	−0.74 (−5.96, 4.46)	2.12 (−10.03, 5.79)	−0.99 (−9.78, 7.80)	−4.36 (−10.16, 1.44)
TF any cartilage	56	−3.23 (−9.93, 3.45)	−0.16 (−4.10, 4.42)	1.53 (−5.48, 8.56)	6.83 (−0.78, 14.45)	4.23 (−0.89, 9.36)
TF any BML	27	3.26 (−4.23, 10.76)	4.19 (−0.47, 8.85)	9.32 (1.79, 16.86)§	11.84 (3.60, 20.07)§	6.89 (1.28, 12.49)§
Meniscal lesion	81	−9.12 (−17.41, −0.82)§	−1.81 (−7.23, 3.61)	−1.66 (−10.62, 7.29)	−3.74 (−13.64, 6.16)	−4.10 (−10.69, 2.49)

* Values are the beta coefficient (95% confidence interval). Cartilage, BMLs, and meniscal lesions were graded as present if greater than or equal to grade 1 in size as per the MRI-OA Knee Score. Meniscal lesions include any type of tear, maceration, or extrusion greater than or equal to grade 1 in either the medial or lateral tibiofemoral compartment. For 1-year MRI associations with 1-year patient-reported outcomes, n = 111; for 1-year MRI association with 5-year patient-reported outcomes, n = 80 (n = 1 patient with no MRI assessment at 1 year); for 5-year MRI associations with 5-year patient-reported outcomes, n = 73 (n = 2 patients with no MRI assessment at 5 years; n = 5 patients with no body mass index [covariate] assessment at 5 years). See Figure 1 for participant recruitment design. MRI = magnetic resonance imaging; OA = osteoarthritis; ACLR = anterior cruciate ligament reconstruction; KOOS = Knee Injury and Osteoarthritis Outcome Score; QoL = quality of life; IKDC = International Knee Documentation Committee; PROs = patient-reported outcomes; PF = patellofemoral; BML = bone marrow lesion; TF = tibiofemoral.
† Adjusted for age, sex, body mass index, and presence of a combined injury. Unadjusted results are reported in Supplementary Appendix F, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract.
‡ Adjusted for age, sex, body mass index, presence of a combined injury, and baseline KOOS and IKDC values. Unadjusted results are reported in Supplementary Appendix F.
§ Significant ($P < 0.05$).

outcome scores in ACLR cohorts should be interpreted with caution, as they may depict successful outcomes and do not necessarily represent the widespread disparity and considerably poor outcomes observed in some individuals.

Individuals with a combined injury demonstrate worse patient-reported outcomes at 1 year and a greater deficit at 5 years compared to those with an isolated ACLR and uninjured peers. KOOS symptoms and KOOS QoL subscales were particularly impaired in those with a combined injury at 5 years, being 14 and 25 points below normative values (32), respectively. The proportion of people with acceptable scores on all of the KOOS subscales and the IKDC questionnaire improved from 1 to 5 years in the combined injury group (1 year = 40–75% [average 60%], 5 years = 48–78% [average 66%]) and isolated injury group (1 year = 54–90% [average 73%], 5 years = 71–100% [average 89%]). This is consistent with previous reports that one-third of individuals have unacceptable symptoms 2 years after ACLR (6,10). The combined injury group had a higher proportion of people not achieving PASS values for KOOS pain, KOOS symptoms, KOOS QoL, and IKDC scores at 5 years. Specifically, the KOOS symptoms and KOOS QoL subscales in the combined injury group had the greatest proportion (52% and 46%, respectively) of individuals who had not recovered to PASS values. These results may assist clinical interpretation of patient-reported outcomes following ACLR. Clinicians can identify individuals with an acceptable outcome based on PASS scores (6) and provide education on realistic expectations of recovery for different patient groups. Clinicians should be cognizant that approximately one-half of patients with a combined injury may not achieve an acceptable outcome for symptoms or QoL 5 years after ACLR. Further research is needed to determine if targeted secondary prevention interventions can address current and potential future symptoms and functional and participation restrictions.

Our findings extend previous studies that describe worse patient-reported outcomes in the presence of a combined injury in the short term (injury to 1 year) (1,3) and long term (≥15 years) (8), confirming this relationship in the medium term. Interventions targeting symptoms and QoL should be a high priority for individuals with a combined ACL injury. This may include additional preoperative education and potentially ongoing intervention beyond 1 year after ACLR to enable the achievement of outcomes similar to those for patients with isolated injuries. The combined injury group

was significantly older and had a higher BMI at 1 year. Therefore, addressing potential negative lifestyle modifications, including physical inactivity (38) and weight gain (39), which could be associated with poorer QoL following ACLR (7,22), may be important. Such interventions are beneficial in older adults with established knee OA (40,41), but further high-quality trials are required to determine efficacy in younger individuals with posttraumatic knee OA following ACLR.

Overall, we found minimal cross-sectional associations between tibiofemoral or patellofemoral cartilage defects, BMLs, meniscal lesions, and patient-reported outcomes between 1 and 5 years after ACLR. These findings extend previous reports that there is no association between tibiofemoral radiographic OA and patient-reported outcomes in the longer term (12,13). However, consistent with our 3-year follow-up patient-reported outcome data (22), patellofemoral cartilage defects at 1 year were associated with worse KOOS symptoms, KOOS sport/rec, KOOS QoL, and IKDC scores at 5 years after ACLR. Additionally, patellofemoral cartilage defects at 5 years were cross-sectionally associated with worse KOOS symptoms and KOOS QoL scores. While clinicians should consider the patellofemoral compartment as a potential source of symptoms and driver of poorer function following hamstring-autograft ACLR (21,42), patient education should express that MRI findings are often unrelated to symptoms.

We recently reported that one-third of patients will have worsening BMLs between 1 and 5 years after ACLR (18). An interesting finding of the current analysis in the same cohort was that the presence of tibiofemoral BMLs was associated with better KOOS sport/rec, KOOS QoL, and IKDC scores at 5 years. This could indicate that BMLs reflect increased joint loading due to participation in sport, particularly in the presence of poor function (43). The future symptomatic consequences of BMLs following ACLR are unknown, but in individuals who were at risk of OA (i.e., older, higher BMI), worsening BMLs predicted subsequent knee symptoms, progression of OA features seen on MRI, and radiographic OA 4–7 years later (17,44). Further research is required to understand the long-term implications of BMLs on MRI in an ACLR population and measure the response of individual joint features and patient-reported outcomes to potential interventions.

Our follow-up rate of the original 1-year cohort was 72%, which may introduce some selection bias. However, there were no differences in baseline participant or surgical characteristics between those participating and those lost to follow-up (see Supplementary Appendix C, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract), and the current cohort had IKDC scores (1) and return-to-sport rates (5) that were similar to those of other larger ACLR cohorts at comparable follow-up time points. The combined injury group included 10 individuals who sustained a secondary injury between 1 and 5 years, which could influence results. Yet, sensitivity analyses excluding these 10 participants showed that the association between combined injury and patient-reported outcomes at 5 years and the relationship between cartilage, bone marrow, and meniscal lesions and patient-reported outcomes at 5 years were generally similar to the results from the whole cohort (see Supplementary Appendix E, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract). Slightly smaller effect sizes with wider CIs were typically observed in this sensitivity analysis, which was likely due to the lower sample size and participants with a secondary injury reporting more symptoms at 5 years. Finally, regression findings should be interpreted cautiously; wide CIs observed in the regression analysis were likely driven by a wide range in scores and the multiple factors that may influence patient-reported outcomes.

In conclusion, individuals with a combined injury following ACLR may be an important subgroup requiring additional interventions when considering the likely worse outcomes compared to those of their peers with an isolated ACLR. Individuals with patellofemoral cartilage defects may also require more targeted interventions due to the association with worse symptoms, function, and QoL at 5 years after ACLR. Despite tibiofemoral BMLs being associated with fewer knee function and QoL impairments at 5 years, there seems to be a minimal relationship between other compartment-specific cartilage lesions, BMLs, and meniscal lesions identified on MRI and patient-reported symptoms, function, and QoL.

ACKNOWLEDGMENTS

We thank Imaging @ Olympic Park for obtaining all MRIs and Mr. Hayden Morris and Mr. Timothy Whitehead (orthopedic surgeons) for assisting recruitment into the project. We also thank the participants and Olympic Park Sports Medicine Centre for use of their facility for data collection.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Crossley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Patterson, Culvenor, Crossley.

Acquisition of data. Patterson, Culvenor, Crossley.

Analysis and interpretation of data. Patterson, Culvenor, Barton, Guermazi, Stefanik, Crossley.

REFERENCES

1. Cox CL, Huston LJ, Dunn WR, Reinke EK, Nwosu SK, Parker RD, et al. Are articular cartilage lesions and meniscus tears predictive of IKDC, KOOS, and Marx activity level outcomes after anterior cruciate ligament reconstruction? A 6-year multicenter cohort study. Am J Sports Med 2014;42:1058–67.
2. Spindler KP, Huston LJ, Wright RW, Kaeding CC, Marx RG, Amendola A, et al. The prognosis and predictors of sports function and activity at minimum 6 years after anterior cruciate ligament reconstruction: a population cohort study. Am J Sports Med 2011;39:348–59.
3. Ahlden M, Samuelsson K, Sernert N, Forssblad M, Karlsson J, Kartus J. The Swedish National Anterior Cruciate Ligament Register: a report on baseline variables and outcomes of surgery for almost 18,000 patients. Am J Sports Med 2012;40:2230–5.

4. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. N Engl J Med 2010;363:331–42.
5. Ardern CL, Taylor NF, Feller JA, Webster KE. Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med 2014;48:1543–52.
6. Ingelsrud LH, Granan LP, Terwee CB, Engebretsen L, Roos EM. Proportion of patients reporting acceptable symptoms or treatment failure and their associated KOOS values at 6 to 24 months after anterior cruciate ligament reconstruction: a study from the Norwegian Knee Ligament Registry. Am J Sports Med 2015;43:1902–7.
7. Filbay SR, Crossley KM, Ackerman IN. Activity preferences, lifestyle modifications and re-injury fears influence longer-term quality of life in people with knee symptoms following anterior cruciate ligament reconstruction: a qualitative study. J Physiother 2016;62:103–10.
8. Risberg MA, Oiestad BE, Gunderson R, Aune AK, Engebretsen L, Culvenor A, et al. Changes in knee osteoarthritis, symptoms, and function after anterior cruciate ligament reconstruction: a 20-year prospective follow-up study. Am J Sports Med 2016;44:1215–24.
9. Rotterud JH, Sivertsen EA, Forssblad M, Engebretsen L, Aroen A. Effect of meniscal and focal cartilage lesions on patient-reported outcome after anterior cruciate ligament reconstruction: a nationwide cohort study from Norway and Sweden of 8476 patients with 2-year follow-up. Am J Sports Med 2013;41:535–43.
10. Barenius B, Forssblad M, Engstrom B, Eriksson K. Functional recovery after anterior cruciate ligament reconstruction, a study of health-related quality of life based on the Swedish National Knee Ligament Register. Knee Surg Sports Traumatol Arthrosc 2013;21:914–27.
11. Oiestad BE, Holm I, Aune AK, Gunderson R, Myklebust G, Engebretsen L, et al. Knee function and prevalence of knee OA after ACLR: a prospective study with 10–15 years follow-up. Am J Sports Med 2010;38:2201–10.
12. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum 2004;50:3145–52.
13. Oiestad BE, Holm I, Engebretsen L, Risberg MA. The association between radiographic knee OA and knee symptoms, function and quality of life 10–15 years after ACLR. Br J Sports Med 2011;45:583–8.
14. Hunter DJ, Zhang W, Conaghan PG, Hirko K, Menashe L, Li L, et al. Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. Osteoarthritis Cartilage 2011;19:557–88.
15. Zhang Y, Nevitt M, Niu J, Lewis C, Torner J, Guermazi A, et al. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. Arthritis Rheum 2011;63:691–9.
16. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001;134:541–9.
17. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum 2007;56:2986–92.
18. Patterson BE, Culvenor AG, Barton CJ, Guermazi A, Stefanik JJ, Morris HG, et al. Worsening knee osteoarthritis features on magnetic resonance imaging 1 to 5 years after anterior cruciate ligament reconstruction. Am J Sports Med 2018;363546518789685.
19. Costa-Paz M, Muscolo DL, Ayerza M, Makino A, Aponte-Tinao L. Magnetic resonance imaging follow-up study of bone bruises associated with anterior cruciate ligament ruptures. Arthroscopy 2001;17:445–9.
20. Hanypsiak BT, Spindler KP, Rothrock CR, Calabrese GJ, Richmond B, Herrenbruck TM, et al. Twelve-year follow-up on anterior cruciate ligament reconstruction: long-term outcomes of prospectively studied osseous and articular injuries. Am J Sports Med 2008;36:671–7.
21. Culvenor AG, Lai CC, Gabbe BJ, Makdissi M, Collins NJ, Vicenzino B, et al. Patellofemoral OA is prevalent and associated with worse symptoms and function after hamstring tendon autograft ACL reconstruction. Br J Sports Med 2014;48:435–9.
22. Culvenor AG, Collins NJ, Guermazi A, Cook JL, Vicenzino B, Whitehead TS, et al. Early patellofemoral osteoarthritis features one year after anterior cruciate ligament reconstruction: symptoms and quality of life at three years. Arthritis Care Res (Hoboken) 2016;68:784–92.
23. Culvenor AG, Collins NJ, Guermazi A, Cook JL, Vicenzino B, Khan KM, et al. Early knee osteoarthritis is evident one year following anterior cruciate ligament reconstruction: a magnetic resonance imaging evaluation. Arthritis Rheumatol 2015;67:946–55.
24. Grindem H, Eitzen I, Snyder-Mackler L, Risberg MA. Online registration of monthly sports participation after anterior cruciate ligament injury: a reliability and validity study. Br J Sports Med 2014;48:748–53.
25. Outerbridge RE. The etiology of chondromalacia patellae. J Bone Joint Surg Br 1961;43–B:752–7.
26. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S208–28.
27. Frobell RB, Roos HP, Roos EM, Roemer FW, Ranstam J, Lohmander LS. Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. Br J Sports Med 2015;49:700.
28. Gudbergsen H, Bartels EM, Krusager P, Waehrens EE, Christensen R, Danneskiold-Samsoe B, et al. Test-retest of computerized health status questionnaires frequently used in the monitoring of knee osteoarthritis: a randomized crossover trial. BMC Musculoskelet Disord 2011;12:190.
29. Nguyen J, Marx R, Hidaka C, Wilson S, Lyman S. Validation of electronic administration of knee surveys among ACL-injured patients. Knee Surg Sports Traumatol Arthrosc 2017;25:3116–22.
30. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage 2011;19:990–1002.
31. Collins NJ, Prinsen CA, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis Cartilage 2016;24:1317–29.
32. Cameron KL, Thompson BS, Peck KY, Owens BD, Marshall SW, Svoboda SJ. Normative values for the KOOS and WOMAC in a young athletic population: history of knee ligament injury is associated with lower scores. Am J Sports Med 2013;41:582–9.
33. Paradowski PT, Bergman S, Sunden-Lundius A, Lohmander LS, Roos EM. Knee complaints vary with age and gender in the adult population: population-based reference data for the Knee injury and Osteoarthritis Outcome Score (KOOS). BMC Musculoskelet Disord 2006;7:38.

34. Anderson AF, Irrgang JJ, Kocher MS, Mann BJ, Harrast JJ, International Knee Documentation Committee. The International Knee Documentation Committee Subjective Knee Evaluation Form: normative data. Am J Sports Med 2006;34:128–35.
35. Muller B, Yabroudi MA, Lynch A, Lai CL, van Dijk CN, Fu FH, et al. Defining thresholds for the patient acceptable symptom state for the IKDC Subjective Knee Form and KOOS for patients who underwent ACL reconstruction. Am J Sports Med 2016;44:2820–6.
36. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 2003;1:64.
37. Irrgang JJ, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P, et al. Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med 2001;29:600–13.
38. Daniel DM, Stone ML, Dobson BE, Fithian DC, Rossman DJ, Kaufman KR. Fate of the ACL-injured patient. A prospective outcome study. Am J Sports Med 1994;22:632–44.
39. Whittaker JL, Woodhouse LJ, Nettel-Aguirre A, Emery CA. Outcomes associated with early post-traumatic osteoarthritis and other negative health consequences 3–10 years following knee joint injury in youth sport. Osteoarthritis Cartilage 2015;23:1122–9.
40. Skou ST, Pedersen BK, Abbott JH, Patterson B, Barton C. Physical activity and exercise therapy benefits more than just symptoms and impairments in people with hip and knee osteoarthritis. J Orthop Sports Phys Ther 2018;1–36.
41. Fransen M, McConnell S, Harmer AR, van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015;1:CD004376.
42. Culvenor AG, Crossley KM. Patellofemoral osteoarthritis: are we missing an important source of symptoms after anterior cruciate ligament reconstruction? J Orthop Sports Phys Ther 2016;46:232–4.
43. Culvenor AG, Patterson BE, Guermazi A, Morris HG, Whitehead TS, Crossley KM. Accelerated return to sport after ACL reconstruction and early knee osteoarthritis features at 1 year: an exploratory study. PM R 2018;10:349–56.
44. Sharma L, Nevitt M, Hochberg M, Guermazi A, Roemer FW, Crema M, et al. Clinical significance of worsening versus stable preradiographic MRI lesions in a cohort study of persons at higher risk for knee osteoarthritis. Ann Rheum Dis 2016;75:1630–6.
45. Daniel DM, Malcom LL, Losse G, Stone ML, Sachs R, Burks R. Instrumented measurement of anterior laxity of the knee. J Bone Joint Surg Am 1985;67:720–6.

Appendix J: Chapter 4 Supplementary File A, Relationship between participant characteristics and PROs at one and five years

Supplementary File A, Table 1. Participant characteristics and univariate associations with KOOS and IKDC scores at one year (n=111)*

Participant characteristics at 1 year	1 year PROs*				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport*	*KOOS-QoL*	IKDC
Age at time of surgery, weeks	-0.26 (-0.55, 0.03)	-0.16 (-0.36, 0.04)	**-0.55 (-0.90, -0.20)**	-0.15 (-0.56, 0.25)	**-0.45 (-0.71, -0.20)**
Sex, *(ref female)*	-0.05 (-5.22, 5.13)	0.64 (-2.89, 4.19)	-0.72 (-7.08, 5.64)	2.67 (-4.37, 9.71)	1.45 (-3.18, 6.08)
Participating Level 1 sport pre-injury[◊] *(ref no.)*	-0.54 (-6.11, 5.02)	-0.50 (-4.31, 3.32)	1.99 (-4.85, 8.82)	3.96 (-3.60, 11.52)	1.21 (-3.76, 6.21)
Time injury to surgery, weeks	-0.00 (-0.06, 0.05)	0.02 (-0.02, 0.07)	0.03 (-0.04, 0.09)	-0.06 (-0.14, 0.01)	0.00 (-0.05, 0.05)
Combined injury at time of ACLR~ *(ref no.)*	**-6.57 (-11.41, 1.73)**	-2.36 (-5.76, 1.03)	**-10.40 (-16.23, -4.58)**	-6.65 (-13.35, 0.05)	**-9.00 (-13.15, -4.86)**
Meniscectomy at time of ACLR[¥] *(ref no.)*	**-5.26 (-10.3, -0.18)**	-1.38 (-4.92, 2.15)	**-8.22 (-14.39, -2.05)**	**-7.92 (-14.82, -1.02)**	**-7.00 (-11.45, -2.56)**
Cartilage defect at time of ACLR[¤] *(ref no.)*	**-8.04 (-14.02, -2.06)**	-1.85(-6.07, 2.35)	**-8.71 (-16.11, -1.30)**	**-9.02 (-17.27, -0.78)**	**-10.15 (-15.33, -4.96)**
Returned to Level 1 sports at 1 year post-ACLR[◊] *(ref no.)*	3.45 (-3.46, 10.36)	1.54 (-3.21, 6.30)	3.98 (-4.53, 12.48)	**13.63 (4.51, 22.76)**	**9.05 (3.06, 15.03)**
Body mass Index at 1 year post-ACLR, kg/m^2	-0.22 (-0.84, 0.41)	-0.12 (-0.55, 0.32)	-0.72 (-1.48, 0.04)	0.10 (-0.75, 0.96)	**-0.69 (-1.24, -0.14)**
Anteroposterior laxity between-limb difference at 1 year[ϑ], millimeters	0.79 (-0.47, 2.05)	0.75 (-0.10, 1.61)	1.42 (-0.11, 2.95)	0.18 (-1.54, 1.91)	0.66 (-0.47, 1.79)

*Values represent coefficient and 95% confidence interval. Univariate linear regression was used to determine the relationship between the demographic factor and KOOS and IKDC scores. Values in **bold** represent statistically significant associations ($p<0.05$).
~Participants were defined as a combined injury at 1 and 5 years if they had a significant cartilage lesion/meniscectomy assessed at the time of ACLR.
[◊]Level 1 sport=jumping, cutting, pivoting as per Sports Activity Classification based on Grindem et al. 2012.
[¥]Performed at the time of ACLR.
[¤]Assessed arthroscopically at time of ACLR, cartilage defect defined as Outerbridge (2) grade ≥2 (i.e., at least a partial-thickness defect).
[ϑ] Assessed using a KT-1000 arthrometer.

Supplementary File A, Table 2. Participant characteristics and univariate associations with KOOS and IKDC scores at five years (n=81)

Participant characteristics at 1 year	5 years PROs*				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport/Rec*	*KOOS-QoL*	IKDC
Age at time of surgery, weeks	-0.07 (-0.44, 0.29)	-0.09 (-0.31, 0.12)	-0.04 (-0.44, 0.37)	-0.32 (-0.74, 0.09)	**-0.33 (-0.60, -0.06)**
Sex, *(ref. female)*	3.98 (-2.51, 10.47)	3.78 (-0.07, 7.64)	**7.57 (0.51, 14.64)**	**9.45 (2.16, 16.74)**	4.02 (-0.92, 8.97)
Participating Level 1 sport pre-injury◊ *(ref no.)*	1.45 (-5.43, 8.34)	2.32 (-1.79, 6.45)	0.34 (-7.29, 7.99)	1.29 (-6.68, 9.27)	4.99 (-0.17, 10.17)
Time injury to surgery, weeks	0.00 (-0.07, 0.08)	0.01 (-0.03, 0.06)	0.00 (-0.08, 0.08)	-0.04 (-0.12, 0.05)	0.02 (-0.04, 0.07)
Combined injury at time of ACLR *(ref no.)*	**-6.36 (-12.57, -0.15)**	**-4.63 (-8.32, -0.94)**	-6.42 (-13.24, 0.50)	**-12.71 (-19.51, -5.90)**	**-5.86 (-10.58, -1.15)**
Meniscectomy at time of ACLR¥*(ref no.)*	-3.98 (-10.44, 2.46)	-3.66 (-7.50, 0.17)	-5.63 (-12.75, 1.48)	**-11.29 (-18.40, -4.18)**	-4.21 (-9.12, 0.69)
Cartilage defect at time of ACLR *(ref no.)*	-6.08 (-13.96, 1.79)	-1.55 (-6.36, 3.25)	1.01 (-7.86, 9.88)	-7.89 (-16.98, 1.20)	-5.63 (-11.64, 0.38)
New knee Injuries (either limb) *(ref no.)*	-6.62 (-14.48, 1.22)	**-4.90 (-9.59, -0.21)**	-7.16 (-15.89, 1.56)	**-14.74 (-23.40, -6.09)**	**-6.94 (-12.88, -1.00)**
ACLR limb✪ *(ref no.)*	-5.07 (-15.68, 4.53)	-5.78 (-11.47, -0.09)	-7.99 (-18.57, 2.60)	**-13.75 (-24.53, -2.97)**	-6.47 (-13.76, 0.82)
Contralateral limb★ *(ref no.)*	-7.32 (-19.36, 4.72)	-2.2 (-9.51, 5.11)	-3.96 (-17.42, 9.50	-12.37 (-26.18, 1.42)	-5.83 (-15.08, 3.41)
Returned to Level 1 sports 1 year post-ACLR◊ *(ref no.)*	-0.53 (-8.96, 7.88)	1.62 (-3.43, 6.69)	5.61 (-3.64, 14.87)	7.05 (-2.57, 16.67)	4.20 (-2.19, 10.60)
Body mass Index at 1 year post-ACLR, kg/m^2	-0.44 (-1.29, 0.42)	**-0.73 (-1.22, -0.23)**	**-1.48 (-2.38, -0.58)**	-0.91 (-1.88, 0.07)	**-0.93 (-1.56, -0.30)**
Anteroposterior laxity between-limb difference at 1 yearϑ, millimeters	1.33 (-2.1, 2.87)	0.75 (0.18, 1.69)	1.45 (-0.25, 3.17)	1.44 (-0.35, 3.23)	0.71 (-0.48, 1.91)
KOOS/IKDC 1 year value, raw score out of 100	**0.28 (0.04, 0.53)**	**0.47 (0.30, 0.65)**	**0.31 (0.14, 0.48)**	**0.40 (0.21, 0.60)**	**0.48 (0.33, 0.64)**

* Values represent coefficient and 95% confidence interval. Univariate linear regression was used to determine the relationship between the demographic factor and KOOS and IKDC scores. Values in **bold** represent statistically significant associations (p<0.05).

◊Level 1 sport=jumping, cutting, pivoting as per Sports Activity Classification based on Grindem et al.2012.

~Participants were defined as a combined injury at 1 and 5 years if they had a significant cartilage lesion/meniscectomy assessed at the time of ACLR.

¤ Assessed arthroscopically at time of ACLR, cartilage defect defined as Outerbridge et al. (1961) grade ≥2 (i.e., at least a partial-thickness defect).

✪New (between 1 and 5 years) ACLR limb knee injuries/surgery n=10 (n=3 ACLR revision, n=6 meniscectomy, n=1 lateral collateral ligament sprain).

★New (between 1 and 5 years) contralateral limb knee injuries/surgery n=6 (combined: n=2 ACLR, n=1 meniscectomy; isolated: n=1 ACLR, n=1 meniscectomy, n=1 lateral collateral sprain).

ϑ Assessed using a KT-1000 arthrometer.

Supplementary File A, Table 3. Participant characteristics five years following ACLR and associations with KOOS and IKDC scores at five years (n=75)~

Participant characteristics at 5 years	5 years PROs*				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport/Rec*	*KOOS-QoL*	IKDC
Returned to Level 1 sports at 5 years post-ACLR◊ *(ref no.)*	1.04 (-5.76, 7.84)	2.86 (-1.19, 6.91)	3.46 (-3.16, 10.08)	**8.54 (0.61, 16.47)**	4.82 (-0.27, 9.91)
Body mass Index at 5 years post-ACLR, kg/m²^	-0.41 (-1.39, 0.47)	**-0.56 (-1.08, -0.04)**	**-0.96 (-1.80, -0.12)**	-0.78 (-1.82, 0.27)	**-0.96 (-1.61, -0.32)**

~n=75 participated in PROs and clinical assessment at 5 years.
* Values represent coefficient and 95% confidence interval. Univariate linear regression was used to determine the relationship between the demographic factor and KOOS and IKDC scores. Values in **bold** represent statistically significant associations (p<0.05).
◊ Level 1 sport=jumping, cutting, pivoting as per Sports Activity Classification based on Grindem et al. (2012).

Appendix K: Chapter 4 Supplementary File B, Participant characteristics for those participating and not participating in the five-year assessment

Supplementary File B, Table 1. Demographic and surgical characteristics of those participating and not participating in the five-year assessment

	Not participating at 5 years (n=31)[£]	**Participating in 5-year assessment (n=81)**	
Participant characteristics	*1 year post-ACLR*	*1 year post-ACLR*	*5 years post-ACLR*
Age, median±IQR (range)	27±12 (20-50)	28±14 (19-52)	32±14 (23-56)
Male sex, no. (%)	21 (68%)	50 (62%)	50 (62%)
Sports activity level pre-injury, no. (%)[§]			
Level 1. Jumping, cutting, pivoting sports	25 (81%)	56 (69%)	56 (69%)
Level 2. Lateral movement sports	4 (13%)	19 (23%)	19 (23%)
Level 3. Straight-line activities	2 (6%)	6 (8%)	6 (8%)
Level 4. Sedentary	0 (0%)	0 (0%)	0 (0%)
Sports activity at time of MRI, no. (%)[§]			
Level 1. Jumping, cutting, pivoting sports	8 (26%)	20 (25%)	26 (32%)
Level 2. Lateral movement sports	4 (13%)	10 (12%)	11 (14%)
Level 3. Straight-line activities	7 (23%)	20 (25%)	32 (39%)
Level 4. Sedentary	12 (38%)	31 (38%)	12 (15%)
Surgery delay, median±IQR (range), weeks	12±13 (2.5-241)	14±20 (1-232)	14±20 (1-232)
Body mass index^, median±IQR (range) kg/m^2	25±7 (21-37)	26±4 (19-37)	26±5 (20-35)
Concomitant injuries at time of ACLR, no. (%)			
Medial meniscectomy[¥]	6 (19%)	17 (21%)	17 (21%)
Lateral meniscectomy[¥]	5 (16%)	19 (23%)	19 (23%)
Patellofemoral chondral defect[¤]	3 (10%)	7 (9%)	7 (9%)
Medial tibiofemoral chondral defect[¤]	4 (13%)	8 (10%)	8 (10%)
Lateral tibiofemoral chondral defect[¤]	3 (10%)	4 (5%)	4 (5%)
Anteroposterior laxity between-limb difference^, median±IQR (range), millimetres	1.3±2.5 (-1.9 to 5.0)	1.6±2.6 (-3.75 to 7.17)	n.a

ACLR=anterior cruciate ligament reconstruction; IQR=interquartile range; n.a.=not assessed at 5 years.
§ Activity level classification based on Grindem et al. (2012).
¥ Performed at the time of ACLR.
¤ Outerbridge grade ≥2 assessed arthroscopically.
^Assessed using a KT-1000 arthrometer.

Supplementary File B, Table 2. Imaging results of those participating and not participating in the five-year assessment

	Not participating in 5-year assessment (n=33)	**Participating in 5-year assessment (n=78)**	
	1 year post-ACLR	*1 year post-ACLR*	*5 years post-ACLR**
OA features on MRI, no. (%)*			
Cartilage defect (≥grade 1, full- or partial-thickness)			
Patellofemoral	13 (39%)	37 (48%)	47 (60%)
Medial tibiofemoral	9 (27%)	23 (29%)	28 (36%)
Lateral tibiofemoral	11 (33%)	18 (23%)	26 (33%)
Bone marrow lesion (≥grade 1)			
Patellofemoral	6 (18%)	20 (26%)	18 (23%)
Medial tibiofemoral	4 (12%)	14 (18%)	13 (17%)
Lateral tibiofemoral	8 (24%)	14 (18%)	16 (21%)
Osteophyte (≥grade 2)¶			
Patellofemoral	0 (0%)	3 (4%)	7 (9%)
Medial tibiofemoral	0 (0%)	1 (1%)	10 (12%)
Lateral tibiofemoral	2 (6%)	6 (8%)	9 (12%)
*Meniscal lesion (≥grade 1)^*			
Medial tibiofemoral	**18 (55%)#**	52 (67%)	53 (68%)
Lateral tibiofemoral	20 (60%)	38 (49%)	40 (52%)
Radiographic OA, no. (%)			
Patellofemoral (ACLR | CL limb)	1 (3%) | 2 (6%)	4 (5%) | 2 (3%)	19 (22%) | 5 (6%)
Medial tibiofemoral (ACLR | CL limb)	1 (3%) | 1 (3%)	2 (3%) | 2 (3%)	4 (5%) | 2 (3%)
Lateral tibiofemoral (ACLR | CL limb)	2 (6%) | 0 (0%)	1 (1%) | 1 (1%)	4 (5%) | 1 (1%)

ACLR=anterior cruciate ligament reconstructed limb; CL=contralateral limb.
# Characteristic statistically significant ($p<0.05$) compared with participating group.
^ Meniscal lesion includes tear (vertical/horizontal/complex), maceration (partial/degenerative), or extrusion.
*****Three participants had an MRI on a different scanner at 5 years due to being interstate.
¶ Given that the definition of a definite osteophyte has not been delineated, an osteophyte was considered present when it was scored ≥2.

Appendix L: Chapter 4 Supplementary File C, Patient-reported outcomes at one and five years for all subgroups

Supplementary File C, Table 1. Patient-reported outcomes from one to five years following ACLR for the whole group (n=81)

	Group**	Raw group scores# Median(IQR) | Mean(SD)		Between-group differences^		Absolute change 1-5 years~ Median(IQR) | Mean(SD)	Between-group differences for change ^^
		1 year	5 year	1 year	5 years		
KOOS-Pain	*Whole group*	92(8) | 91(9)	97(8)*| 93(9)			2.6(9.1) | 2.8 (9.1)	
	Isolated	92(10) | 91(10)	99(6)*| 96(5)	0.236	**0.006**	5.1(8.4) | 4.3 (9.3)	0.117
	Combined	92(7) | 90(8)	94(11) | 91(10)			2.6(6.2) | 1.2 (8.8)	
KOOS-Symptoms	*Whole group*	86(18) |84(13)	89(21) | 84(14)			0.1(14.5) | 0.5(16.1)	
	Isolated	88(18) | 85(13)	93(18) | 89(12)	0.236	**0.026**	3.6(13.6) | 2.3 (16.2)	0.319
	Combined	84(21) | 83(12)	82(24) | 81(15)			-0.3(15.8) | -1.3 (15.8)	
KOOS-Sport	*Whole group*	83(15) | 81(17)	90(20)* | 87(16)			5.0(20) | 6.0(18.2)	
	Isolated	90(22) | 85(16)	95(15)* | 91(11)	**0.006**	0.061	0.0(15) | 4.9 (16.3)	0.506
	Combined	75(20) | 76(16)	90(25)* | 84(18)			10.0(19.5) | 7.3 (20.2)	
KOO-QoL	*Whole group*	69(25) | 68(18)	81(25)*| 78(17)			12.5(19) | 10.0(18.9)	
	Isolated	75(19) | 71(16)	88(13)* | 86(11)	0.232	**<0.001**	13.0(25) | 13.7 (16.8)	0.079
	Combined	65(31)| 66(20)	75(25)* | 72(18)			9.4(21.6) |6.3 (20.3)	
IKDC	*Whole group*	86(16) | 84(12)	91(15)* | 88(11)			4.0 (10) | 4.7(10.9)	
	Isolated	87(11) | 88(9)	93(10)*| 92(7)	**0.003**	**0.002**	2.3(10.3) | 3.2 (9.6)	0.241
	Combined	82(25) | 79(13)	89(18)*| 85(13)			6.3(13.1) | 6.2 (12.0)	

** At 1 year; n=40 combined, n=41 isolated. At 5 years; n=46 combined, n=35 isolated.

The majority of KOOS and IKDC scores were non-normally distributed at 1 and 5 years; therefore, median(IQR) was used for analysis in this study.

*Indicates a significant within-group change in KOOS or IKDC score between 1 and 5 years (Wilcoxon signed rank tests for non-parametric data).

^Mann-Whitney U tests were used to compare PROs at 1 and 5 years (non-parametric data) between the combined and isolated groups. Values in **bold** represent statistically significant difference (p<0.05) between groups.

~Absolute change was calculated by subtracting the raw score at 1 year from the raw score at 5 years. A positive value represents an "improved" score (i.e., less knee problems). ^^Independent t-tests (parametric data) were used to compare the absolute change scores between the combined and isolated groups. Values in **bold** represent a statistically significant difference (p<0.05) between groups.

Appendix M: Chapter 4 Supplementary File D, Sensitivity analysis excluding individuals with a secondary injury to the index knee between one and five years

Supplementary File D, Table 1. Sensitivity analysis excluding individuals with a secondary injury (n=10) between one and five years: Number of participants with "acceptable" KOOS and IKDC scores~ (as per **Table 4.2** in thesis)

		Number (%) "acceptable"~		**Between-group differences^**	
Outcome measure (cut-off score)	**Group***	*1 year*	*5 years*	*1 year*	*5 years*
KOOS-Pain (88)	*Whole group*	63 (78)	58 (82)		
	Isolated	33 (80)	33 (94)	0.601	**0.012**
	Combined	30 (75)	25 (69)		
KOOS-Symptom (83)	*Whole group*	47 (58)	41 (58)		
	Isolated	27 (65)	25 (72)	0.180	**0.031**
	Combined	20 (50)	16 (44)		
KOOS-Sport (73)	*Whole group*	60 (75)	63 (89)		
	Isolated	32 (78)	33 (94)	0.455	0.260
	Combined	28 (70)	30 (83)		
KOOS-QoL (73)	*Whole group*	38 (47)	51 (72)		
	Isolated	22 (54)	30 (86)	0.268	**0.017**
	Combined	16 (40)	21 (58)		
IKDC (75)	*Whole group*	62 (77)	62 (88)		
	Isolated	37 (90)	35 (100)	**0.004**	**0.002**
	Combined	25 (63)	27 (75)		

KOOS=Knee injury and Osteoarthritis Outcome Score; IKDC=International Knee Documentation Committee knee evaluation.
~Reported as the number of individuals (%) in the group with a raw score above "acceptable" cut-off using previously published data in ACLR individuals for the KOOS (Ingelsrud et al., 2015) and IKDC (Muller et al., 2016).
*Whole group at 1 year n=81; 5 years n=71. Participants were defined as having a combined injury at 1 year if they had a concomitant injury (significant cartilage lesions/meniscectomy assessed at the time of surgery). Participants with a new knee injury to the ACLR knee between 1 and 5 years post-ACLR were excluded from this sensitivity analysis. All other participants were defined as having an isolated injury. At 1 year; n=40 combined, n=41 isolated. At 5 years; n=36 combined, n=35 isolated.
^ Fisher's exact tests were used to compare the proportions of the isolated and combined groups above the acceptable cut-off value. Values in **bold** represent $p<0.05$.

Supplementary File D, Table 2. Sensitivity analysis excluding individuals with a secondary injury (n=10) between one and five years: Multivariable linear regression analysis of OA features on MRI associated with PROs at one and five years following ACLR˜ (as per **Table 4.3** in thesis)

1 year OA feature on MRI^ (% with feature)~	**5 years PROs****				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport/Rec*	*KOOS-QoL*	*IKDC*
PF Any cartilage (41)	**-8.01 (-15.42, -0.60)**	-3.11 (-6.75, 0.51)	-5.96 (-14.65, 2.73)	-6.20 (-14.16, 1.76)	-2.87 (-7.85, 2.12)
PF Any BML (26)	-4.37 (-11.97, 3.21)	-0.48 (-4.13, 3.16)	-1.10 (-9.85, 7.64)	1.80 (-6.12, 9.71)	-0.39 (-5.29, 4.51)
TF Any cartilage (46)	-1.72 (-8.63, 5.19)	0.74 (-2.60, 4.09)	1.72 (-6.13, 9.57)	3.81 (-3.44, 11.06)	2.12 (-2.45, 6.67)
TF Any BML (31)	1.14 (-6.03, 8.33)	2.06 (-1.37, 5.48)	3.30 (-4.84, 11.44)	-2.13 (-9.67, 5.39)	0.52 (-4.19, 5.22)
Meniscal lesion (77)	-6.58 (-14.79, 1.61)	-0.77 (-4.80, 3.25)	2.81 (-6.71, 12.34)	-2.99 (-13.41, 3.04)	-2.46 (-7.91, 3.00)
5 years OA features on MRI^ (% with feature)~	**5 years PROs***				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport/Rec*	*KOOS-QoL*	*IKDC*
PF Any cartilage (54)	-6.28 (-12.94, 0.37)	-2.27 (-5.81, 1.26)	-2.59 (-10.16, 4.97)	**-11.68 (-19.32, -4.04)**	-2.71 (-7.97, 2.55)
PF Any BML (21)	-0.24 (-8.63, 8.16)	-2.07 (-6.19, 2.06)	0.76 (-8.53, 10.06)	-0.78 (-10.85, 9.29)	-2.72 (-9.18, 3.73)
TF Any cartilage (54)	-1.94 (-8.68, 4.79)	0.35 (-3.18, 3.88)	2.10 (-5.35, 9.56)	**8.73 (0.96, 16.5)**	4.89 (-0.18, 9.96)
TF Any BML (26)	2.04 (-5.84, 9.93)	3.21 (-0.83, 7.26)	8.05 (-0.45, 16.54)	**12.77 (3.90, 21.65)**	**6.01 (0.09, 11.92)**
Meniscal lesion (79)	-7.81 (-16.16, 0.54)	-1.91 (-6.37, 2.56)	0.29 (-9.22, 9.81)	-1.66 (-11.97, 8.64)	-4.10 (-10.69, 2.49)

MRI=magnetic resonance imaging; OA=osteoarthritis; PROs=patient-reported outcomes; KOOS=Knee injury and OA Outcome Score; IKDC= International Knee Documentation Committee knee evaluation; QoL=quality of life; PF= patellofemoral; TF=tibiofemoral; BML=bone marrow lesion.
˜Values represent coefficient and 95% confidence interval. Values in **bold** represent statistically significant associations (p<0.05).
#1 year MRI associations with 1 year PROs, n=111; for 1 year MRI association with 5 years PROs, n=70; for 5 years MRI associations with 5 years PROs, n=68. Participants with a new knee injury to the ACLR knee between 1 and 5 years following ACLR were excluded from this sensitivity analysis.
^Cartilage, BMLs, and meniscal lesions were graded as present if ≥grade 1 in size as per the MRI OA Knee Score (MOAKS). Meniscal lesions include any type of tear, maceration, or extrusion ≥grade 1 in either the medial or lateral tibiofemoral compartment.
*Adjusted for age, sex, body mass index, and presence of a combined injury.
**Adjusted for age, sex, body mass index, presence of a combined injury, and 1 year following ACLR KOOS and IKDC scores.

Appendix N: Chapter 4 Supplementary File E, Unadjusted regression analysis

Supplementary File E, Table 1. Unadjusted linear regression analysis of MRI lesions associated with PROs at one and five years following ACLR~~ (as per **Table 4.3** in thesis)

1 year OA features* (% with feature)~	**1 year PROs**				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport/Rec*	*KOOS-QoL*	IKDC
PF Any cartilage (45)	-2.95 (-7.95, 2.04)	-1.60 (-5.00, 1.80)	2.33 (-8.53, 3.86)	2.68 (-4.19, 9.56)	-3.91 (-8.33, 0.52)
PF Any BML (23)	-2.05 (-7.98, 3.87)	-2.29 (-6.30, 1.73)	**-7.67 (-14.82, -0.52)**	-2.27 (-10.29, 5.76)	-2.43 (-7.69, 2.83)
TF Any cartilage (48)	0.72 (-4.28, 5.73)	0.29 (-3.11, 3.69)	-3.97 (-10.11, 2.17)	0.42 (-6.44, 7.30)	-0.71 (-5.18, 3.75)
TF Any BML (31)	-0.32 (-5.78, 5.15)	0.67 (-3.04, 4.38)	-1.35 (-8.06, 5.35)	-2.20 (-9.58, 5.18)	-0.25 (-5.12, 4.60)
Meniscal lesion (72)	-0.69 (6.27, 4.88)	-1.56 (-5.34, 2.21)	**-6.87 (-13.63, -0.11)**	-2.28 (-9.92, 5.35)	**-5.29 (-10.16, -0.42)**
1 year OA features* (% with feature)~	**5 years PROs**				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport/Rec*	*KOOS-QoL*	*IKDC*
PF Any cartilage (46)	**-9.35 (-15.41, -3.29)**	**-4.50 (-8.21, -0.78)**	**-7.25 (-14.23, -0.27)**	**-10.80 (-17.88, -3.71)**	**-7.03 (-11.72, -2.33)**
PF Any BML (26)	-5.21 (-12.38, 1.96)	-3.10 (-7.41, 1.20)	-5.61 (-13.63, 2.42)	-0.83 (-9.32, 7.65)	-4.33 (-9.86, 1.19)
TF Any cartilage (47)	-6.10 (-12.35, 0.15)	-2.35 (-6.16, 1.45)	-2.82 (-9.95, 4.30)	-2.26 (-9.72, 5.20)	-1.09 (-6.03, 3.85)
TF Any BML (30)	-1.88 (-8.85, 5.08)	1.04 (-3.14, 5.22)	0.89 (-6.91, 8.68)	-4.65 (-12.74, 3.43)	0.35 (-5.03, 5.75)
Meniscal lesion (79)	**-8.95 (-16.51, -1.41)**	-2.54 (-7.20, 2.11)	-1.83 (-10.56, 6.90)	-8.87 (-17.78, 0.04)	**-6.36 (-12.23, -0.49)**
5 years OA features* (% with feature)~	**5 years PROs**				
	KOOS-Symp	*KOOS-Pain*	*KOOS-Sport/Rec*	*KOOS-QoL*	*IKDC*
PF Any cartilage (58)	**-6.89 (-12.79, -0.99)**	-3.61 (-7.45, 0.24)	-5.61 (-12.83, 1.59)	**-14.21 (-20.91, -7.51)**	**-7.13 (-11.91, -2.34)**
PF Any BML (22)	0.64 (-6.39, 7.69)	1.51 (-3.23, 6.26)	1.67 (--6.76, 10.12)	2.92 (-5.63, 11.47)	-2.34 (-8.15, 3.46)
TF Any cartilage (56)	**-6.31 (-12.25, -0.38)**	-3.19 (-7.05, 0.67)	-4.58 (-11.83, 2.67)	-2.29 (-9.71, 5.12)	-1.44 (-6.48, 3.60)
TF Any BML (27)	-1.88 (-8.41, 4.66)	-0.25 (-4.46, 3.97)	2.67 (-5.15, 10.51)	0.79 (-7.18, 8.76)	1.53 (-3.87, 6.94)
Meniscal lesion (81)	**-8.80 (-16.21, -1.38)**	-1.76 (-6.68, 3.16)	-0.86 (-10.01, 8.35)	-6.27 (-15.51, 2.96)	-5.56 (-11.78, 0.67)

MRI=magnetic resonance imaging; OA=osteoarthritis; PROs=patient-reported outcomes; KOOS=Knee injury and OA Outcome Score; IKDC= International Knee Documentation Committee knee evaluation; QoL=quality of life; PF= patellofemoral; TF=tibiofemoral; BML=bone marrow lesion.

~Values are coefficient and 95% CI. Values in **bold** represent statistically significant associations (p<0.05).

*1 year MRI associations with 1 year PROs, n=111; for 1 year MRI association with 5 years PROs, n=80 (n=1 no MRI assessment at 1 year); for 5 years MRI associations with 5 years PROs, n=73 (n=2 no MRI at 5 years; n=5 no BMI (covariate) assessment at 5 years). Refer to **Figure 4.1** for flow of participant recruitment

^Cartilage, BMLs, and meniscal lesions were graded as present if ≥grade 1 in size as per the MRI OA Knee Scoring system. Meniscal lesions include any type of tear, maceration, or extrusion ≥grade 1 in either the medial or lateral tibiofemoral compartment.

Appendix O: Chapter 5 original publication, Physical Therapy in Sport

Physical Therapy in Sport 44 (2020) 67–74

Contents lists available at ScienceDirect

Physical Therapy in Sport

journal homepage: www.elsevier.com/ptsp

Original Research

Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function

Brooke E. Patterson [a], Kay M. Crossley [a], Luke G. Perraton [b], Avnish S. Kumar [a], Matthew G. King [a], Joshua J. Heerey [a], Christian J. Barton [a], Adam G. Culvenor [a, *]

[a] La Trobe Sport and Exercise Medicine Research Centre, School of Allied Health, La Trobe University, Bundoora, Australia
[b] Department of Physiotherapy, School of Primary Health Care, Monash University, Frankston, Australia

ARTICLE INFO

Article history:
Received 9 January 2020
Received in revised form
14 March 2020
Accepted 22 April 2020

Keywords:
Anterior cruciate ligament
Rehabilitation
Functional performance
Limb symmetry index

ABSTRACT

Objective: Evaluate change in functional performance from 1- to 5-years after anterior cruciate ligament reconstruction (ACLR).
Methods: 59 participants (38 men) aged 29 ± 16 years completed three hops and one-leg rise 1- and 5-years following ACLR. Linear mixed-effects models evaluated differences in change between the ACLR and contralateral limbs. Participants were classified with stable, improving or worsening function relative to previously published minimal detectable change thresholds. Healthy controls completed the three hops (n = 41) and one-leg rise (n = 31) as reference data.
Results: The contralateral limb had a significantly greater decrease in functional performance between 1- and 5-years for the three hops, compared to the ACLR limb. Worsening was more common in the contralateral limb than the ACLR limb; resulting in significant improvements in the LSI for the single hop (mean 87% at 1-year to 95% at 5-years), side hop (77%to 86%) and one-leg rise (76% to85%). Performance of both ACLR and contralateral limbs and the LSI remained below the healthy controls.
Conclusion: Functional performance changes differ between limbs between 1- and 5-years post-ACLR. The LSI should not be used in isolation to evaluate functional performance changes after ACLR, as it may overestimate functional improvement, due to worsening contralateral limb function.

1. Introduction

Following anterior cruciate ligament injury and reconstruction (ACLR), functional performance testing is advocated to determine readiness for return-to-sport and mitigate risk of reinjury (Grindem, Arundale, & Ardern, 2018; Kyritsis, Bahr, Landreau, Miladi, & Witvrouw, 2016; van Melick et al., 2016). A limb symmetry index (LSI) is frequently used to describe function of the ACLR limb compared to the contralateral limb, expressed as a percentage (score of ACLR knee divided by contralateral knee, multiplied by 100). An LSI >90% on a functional test battery (e.g. hop tests, muscle strength) frequently defines functional recovery and return-to-sport clearance (Abrams et al., 2014).

Symmetry (>90%) on hop-testing is associated with reduced reinjury risk (Grindem, Snyder-Mackler, Moksnes, Engebretsen, & Risberg, 2016; Kyritsis et al., 2016), better patient-reported symptoms and quality of life (Ericsson, Roos, & Frobell, 2013) and reduced risk of osteoarthritis (OA) (Culvenor et al., 2017; Patterson et al., 2020; Pinczewski et al., 2007). However, the LSI assumes the contralateral limb is the acceptable standard, equivalent to pre-injury status and immune to decline (Benjaminse, Holden, & Myer, 2018; Wellsandt et al., 2017). In reality, bilateral neuromuscular deficits (e.g. muscle strength, activation or size, biomechanics, balance and functional performance) exist following unilateral ACLR (Culvenor et al., 2016a; Gokeler et al., 2017; Ingersoll, Grindstaff, Pietrosimone, & Hart, 2008); hence the LSI may overestimate postoperative knee function (Wellsandt et al., 2017), which is an important consideration given the high risk of second ACL injury (Wiggins et al., 2016). To determine whether the LSI overestimates knee function, it is important to compare raw scores from the ACLR and contralateral limb to healthy uninjured controls,

* Corresponding author. La Trobe Sport & Exercise Medicine Research Centre, School of Allied Health, La Trobe University, Bundoora, 3086, Australia.
E-mail address: A.Culvenor@latrobe.edu.au (A.G. Culvenor).

https://doi.org/10.1016/j.ptsp.2020.04.031
1466-853X/

providing the benchmark for functional performance.

While functional improvements in hop-testing LSI are well documented within the first year following ACLR (Abrams et al., 2014; Nagelli & Hewett, 2017; Thomee et al., 2012), functional changes beyond the period of active rehabilitation (i.e. >1–2 years postoperatively) are less often reported (Oiestad et al., 2010). Specifically, it is not known whether functional LSI changes beyond the initial 1–2 postoperative years are driven by changes in the ACLR or contralateral limb. Evaluating the magnitude of functional performance (e.g. hop distance) in the ACLR and contralateral limb, and as expressed with the LSI over time compared to uninjured controls, is important to understand the longer-term functional burden of ACLR.

The primary aim of the current study was to evaluate the change in functional performance in the ACLR and contralateral limbs from 1- to 5-years post-ACLR to determine the influence on LSI. We hypothesised change in functional performance would differ between the ACLR and contralateral limbs, primarily due to worsening contralateral limb function. Our secondary aim was to compare functional performance at 1- and 5-years post-ACLR with uninjured healthy controls. We hypothesised functional performance in those following ACLR at both time points would be significantly lower than uninjured healthy controls.

2. Methods

2.1. Participants

Adults (aged 18–50 years) who had undergone primary hamstring-autograft ACLR by one of two orthopaedic surgeons were consecutively recruited at their routine 12-month surgical review into this prospective cohort study (Culvenor et al., 2016d). Exclusion criteria at baseline were: i) injury/surgery to the ACLR knee prior to ACL rupture; ii) post-operative injury or follow-up surgery to the ACLR knee; iii) history of contralateral knee injury or surgery; iv) other condition influencing function (e.g. neurological condition, current low back pain); v) pregnant/breastfeeding. Participants attended baseline and follow-up assessments at 1- and 5-years post-ACLR, respectively. Those reporting new injuries to either knee between the 1- and 5-year assessments were excluded.

Two healthy control groups were utilised to provide reference data for the functional performance tests. Asymptomatic uninjured recreational athletes recruited from sporting clubs provided control data for the three hop tests at a single time-point (Perraton et al., 2017). A second asymptomatic uninjured control group of recreational football players provided reference data at a single time-point for the one-leg rise test, as this was not part of our earlier healthy control study. Ethical approval for the ACLR and control cohorts were granted by La Trobe University Human Ethics Committee (No. HEC15-100, HEC16-045 respectively) and University of Melbourne (1136167), and participants provided informed consent.

2.2. Procedures

Four lower-limb functional performance tests were completed at both baseline and follow-up (1- and 5-years post-ACLR, respectively) for the ACLR group, and at one time-point for the healthy controls. Identical methods were used for all participants on both limbs with assessors blind to ACLR limb (elastic bandage over both knees covering scars). Details of the test-battery are provided in Supplementary 1, and were performed based on previously reported methods for the single hop (Gustavsson et al., 2006), triple crossover hop (Reid, Birmingham, Stratford, Alcock, & Giffin, 2007), side hop (Gustavsson et al., 2006), and one-leg rise (Thorstensson, Petersson, Jacobsson, Boegard, & Roos, 2004). Briefly, the single hop assessed the maximum distance (cm) achieved from a stationary position with a balanced landing (Gustavsson et al., 2006). The triple crossover hop assessed the cumulative distance (cm) achieved with three consecutive hops, with each hop crossing over two parallel lines 15 cm apart (Reid et al., 2007). The side hop assessed the number of hops over two parallel lines 40 cm apart in 30 s (Gustavsson et al., 2006). The one-leg rise (Thorstensson et al., 2004), a global measure of lower-limb strength and endurance, was performed from a seated position and standardised height (90° knee flexion). Participants were instructed to rise on one leg as many times as possible (up to 50 repetitions) at a controlled speed (45 beats per minute using a metronome). In addition to functional performance testing, participant age, sex, body mass index (BMI), injury history, and activity level (defined as level 1 pivoting/jumping sports, level 2 lateral movement sports (i.e. tennis), level 3 straight line activities (i.e. running, weight-lifting, cycling), level 4 sedentary) (Grindem, Eitzen, Snyder-Mackler, & Risberg, 2014), was obtained at the 1- and 5-year assessments.

2.3. Statistical analysis

Data were examined for normality and homogeneity of variance. Baseline, follow-up, and 1- to 5-year (absolute) changes (mean ± SD) in ACLR and contralateral limb performance (cm or repetitions) and LSI (%) were calculated. Within the ACLR group, within-limb and LSI changes between 1- and 5-years were evaluated using a paired *t*-test. A linear mixed-effects model incorporating random effects (accounting for between-limb correlation) assessed the difference in change in function (mean difference, 95% confidence interval (CI)) between the ACLR and contralateral limb. The proportion of participants classified as having stable, improving or worsening function between 1- and 5-years relative to previously published minimal detectable change (MDC) thresholds (Haitz, Shultz, Hodgins, & Matheson, 2014; Kockum & Heijne, 2015; Reid et al., 2007) are reported descriptively. To determine healthy control group scores, data from both limbs at the single time-point were averaged on a per-participant basis, and an overall group average calculated (mean ± SD). Linear regression models assessed the differences in functional performance between the ACLR group (separate model for each limb and LSI) at 1- and 5-years post-ACLR and the healthy control group. The model was adjusted for age and BMI, as the ACLR group was significantly older and had a higher BMI ($p < 0.05$). Analyses were performed using Stata V.14.2 with an α level of 0.05.

3. Results

3.1. Participants

Of the 110 participants who were included in our cross-sectional study of function at 1-year post-ACLR (Culvenor et al., 2016d), 74 (67%) were re-tested 5-years postoperatively (5.2 ± 0.2 years). Reasons for dropout (n = 36) included i) unable to contact (n = 9), ii) unable to attend in person (n = 9), iii) declined participation due to time (n = 11), iv) conflict of interest (e.g. participation in another study (n = 5), and v) other condition limiting participation (n = 2). A further 14 participants were excluded due to new knee injury/surgery between 1- and 5-years. One additional participant was excluded due to a previous contralateral knee arthroscope reported at 5-years which was not reported at the 1-year assessment. The 59 ACLR participants (37% women) were (median ± IQR) age 29 ± 16 years at 1-year and 33 ± 16 years at 5-years, with a (mean ± SD) BMI 24.9 ± 3.3 kg/m^2 at 1-year and 25.6 ± 3.6 kg/m^2 at 5-years post-ACLR. Prior to ACL injury, 88% (n = 52) participated in

Level 1 or 2 sports, 12% (n = 7) in Level 3 activities, and no participants were classified as sedentary (Level 4). At 1-year post-ACLR, 34% (n = 20) of ACLR participants played Level 1 or 2 sports, 24% (n = 14) participated in Level 3 activities, and 42% (n = 25) were classified as (Level 4) sedentary. At 5-year follow-up, activity level increased to 41% (n = 24) for Level 1 or 2 sports, 47% (n = 28) for Level 3 activities, and fewer participants (n = 7, 12%) were classified as sedentary. The 41 healthy controls providing hopping reference data were similar in sex distribution (39% female) and BMI (mean ± SD: 24.0 ± 2.6 kg/m^2), but were 5 years younger (median ± interquartile range: 24 ± 3 years) (Perraton et al., 2017). The 31 healthy controls providing one-leg rise test reference data (34% female) were 3 years younger (median ± interquartile range: 26 ± 10 years) with similar BMI (mean ± SD: 24.6 ± 3.1 kg/m^2). At the time of assessment, 74% of the healthy controls were participating in Level 1 or 2 sports.

3.2. ACLR group changes

Functional performance in the ACLR limb did not significantly change between 1- and 5-years, except for the single hop distance, which increased significantly (p = 0.017) (Table 1, Fig. 1). In contrast, contralateral limb performance decreased between 1- and 5-years, and this was significant for the triple crossover (p = 0.004), side hop (p = 0.019), and one-leg rise tests (p = 0.001) (Fig. 1, Table 1). Between 1- and 5-years the contralateral limb had a significantly greater decrease in function compared to the ACLR limb for all functional tests (Table 1). This resulted in the LSI increasing significantly over time for the single hop (p = 0.003), side hop (p < 0.001), and one-leg rise (p = 0.069) (Table 1, Fig. 1).

3.3. Were the ACLR group changes meaningful?

When evaluating each participant's functional change between 1- and 5-years post-ACLR in each limb (e.g. distance hopped) according to MDC thresholds, most participants (63%–85%) had stable function (i.e. increase/decrease < MDC) (Fig. 2). Worsening function (decrease > MDC) was more common across all three hop tests in the contralateral limb (12%–19%) than the ACLR limb (8%–10%). Improvement (increase > MDC) was more common across all three hop tests in the ACLR limb (7%–27%) than the contralateral limb (0%–8%). The LSI improved (increase > MDC) in approximately one-third of participants in the three hop tests (single hop: 41%, triple crossover hop: 25% side hop: 44%) (Fig. 2).

3.4. Comparison to healthy control data

At 1-year post-ACLR, the single hop of the ACLR (p < 0.001) and contralateral limb (p = 0.012) was significantly lower than the healthy controls, with adjustment for age and BMI. No differences between the ACLR or contralateral limbs and healthy control group for the triple crossover, side hop and one-leg rise were observed. At 1-year post-ACLR, the LSI for the single hop (p < 0.001), triple crossover hop (p = 0.003), side hop (p < 0.001) and one-leg rise (p = 0.003) were significantly lower than the healthy controls. At 5-years post-ACLR, the side hop LSI was the only test to be significantly lower (p = 0.016) than the healthy controls. There were no differences between the ACLR and control limbs and healthy controls at 5-years. Healthy control data from the single time-point is presented in Table 2.

4. Discussion

Functional performance changes differ between the index and contralateral limbs during the first 5 years post-ACLR. Although function in the ACLR limb remained relatively stable from 1- to 5-years post-ACLR, with the average change not exceeding MDC thresholds, worsening function in the contralateral limb resulted in statistically significant LSI improvements for the single hop, side hop, and one-leg rise tests. This highlights the limitations of using the LSI in isolation to evaluate functional change, as it may overstate improvements in the ACLR limb.

4.1. Limb symmetry index overestimates function

In the current study, improved LSI between 1- and 5-years post-ACLR was primarily driven by worsening function in the contralateral limb, rather than improved function in the ACLR limb. These

Table 1
Functional performance from 1 to 5-years post-ACLR^.

	1-year	5-year	Change 1 - 5 years	Mean (95%CI) difference in change scores
Single hop (cm)				
ACLR	103.2 (29.7)	109.8 (27.5)	6.5 (20.5)[i]	**−8.3 (-13.4, -3.3)**
Contralateral	118.3 (21.9)	116.5 (26.7)	−1.8 (12.9)	***p* = *0.001***
LSI (%)	86.5 (17.4)	95.4 (18.0)	8.9 (22.4)[i]	NA
Triple crossover hop (cm)				
ACLR	327.7 (100.0)	321.6 (98.9)	−6.1 (59.2)	**−16.4 (-30.0, -2.8)**
Contralateral	363.5 (85.5)	341.0 (90.2)	−22.5 (46.0)[d]	***p* = *0.018***
LSI (%)	89.4 (17.0)	93.2 (16.9)	3.8 (18.5)	NA
Side hop (reps)				
ACLR	24.9 (14.0)	24.0 (14.0)	−0.9 (7.9)	**−3.7 (-5.6, -1.9)**
Contralateral	30.8 (14.0)	26.2 (13.7)	−4.7 (7.9)[d]	***p* = *0.000***
LSI (%)	77.2 (31.2)	85.7 (32.5)	10.4 (26.1)[i]	NA
One-leg rise (reps)				
ACLR	28.1 (18.9)	25.2 (18.4)	−2.8 (14.4)	−1.9 (−4.0, 0.25)
Contralateral	31.9 (17.1)	27.1 (17.7)	−4.8 (13.5)[d]	*p=0.083*
LSI (%)	75.6 (38.9)	85.4 (40.3)	11.1 (37.7)[i]	NA

^n = 59 with functional performance assessment at 1- and 5-years. Values are mean (±standard deviation) unless otherwise indicated. CI = confidence interval; LSI = limb symmetry index; ACLR = anterior cruciate ligament reconstruction.
Bolded values indicate a statistically significant (p < 0.05) difference between the change score for the ACLR and contralateral limb.
[i] Statistically significant (p < 0.05) increase in average group score between 1 and 5 years.
[d] Statistically significant (p < 0.05) decrease in average group score between 1 and 5 years.

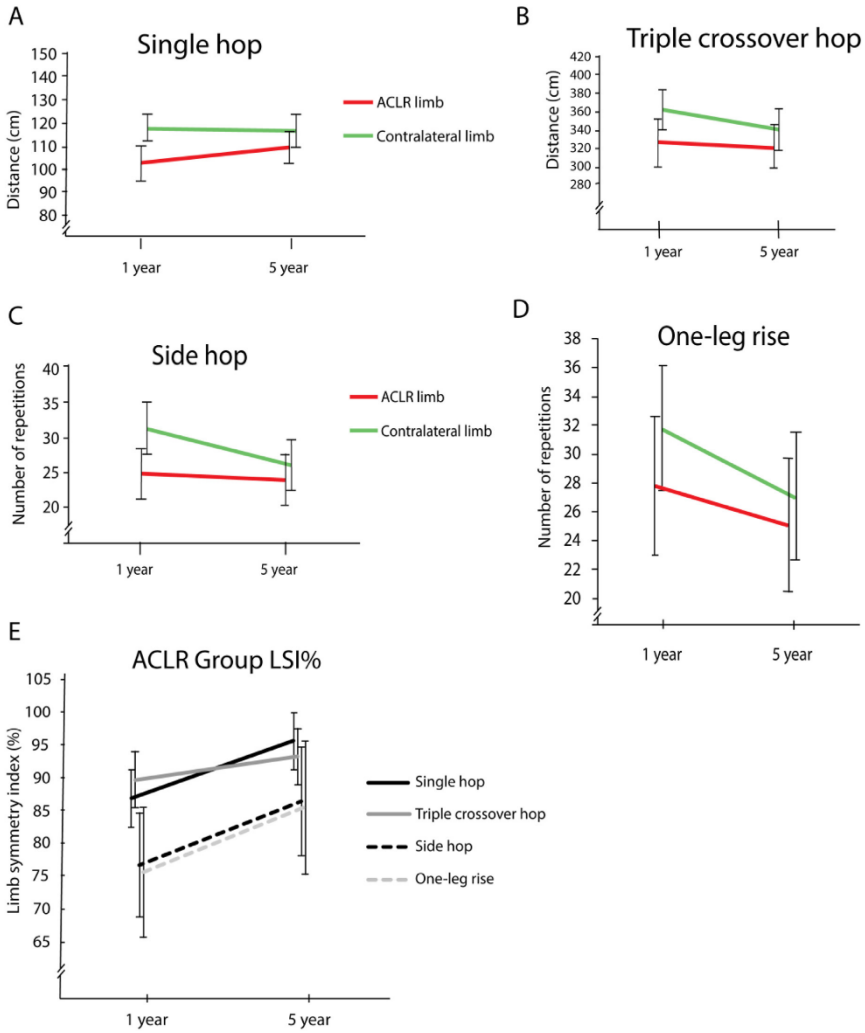


Fig. 1. A-D. Functional performance in the ACLR and contralateral limb at 1- and 5-years post-ACLR~. Limb symmetry index of each functional test in ACLR group at 1- and 5-years post-ACLR~. ~ Values are mean (±standard deviation). ACLR = anterior cruciate ligament reconstruction.

findings extend previous cross-sectional data at 6-months post-ACLR (Wellsandt et al., 2017), which showed that an LSI using the postoperative status of the contralateral limb as a reference over-estimates function (i.e. 57% of individuals achieve >90% LSI) compared to using preoperative contralateral limb function as the reference (i.e. 29% achieve >90% LSI). Combined, it appears that caution must be used when interpreting LSI at a single time-point and over time to determine treatment success and readiness to progress milestones (including clearance for return-to-sport).

4.2. Why does the contralateral limb worsen, and why more so than the ACLR limb?

The contralateral limb had a significantly greater decrease in function on the three hop tests compared to the ACLR limb. Different responses in the ACLR and contralateral limb functional capacity over time is supported by one of the few studies reporting the raw change in hop test performance in both limbs (i.e. distance hopped) after ACLR (Thomee et al., 2012). In that report, the ACLR limb improved by 11 cm (single hop) and 6 repetitions (side hop)

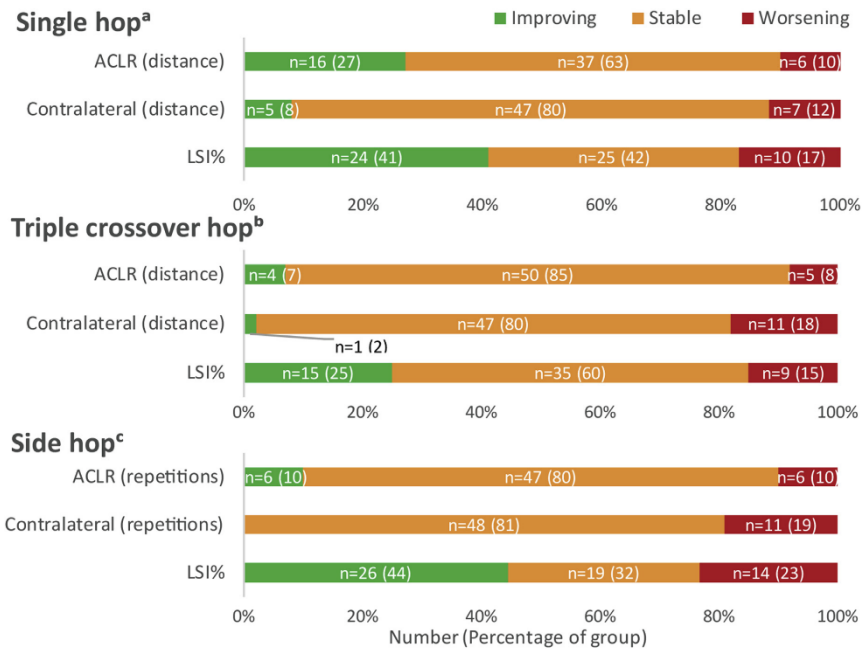


Fig. 2. Number of participants with stable, improving or worsening functional performance between 1 and 5 years post-ACLR, according to the minimal detectable change~.
~The minimal detectable change (MDC) is the smallest change that can be detected by the test beyond measurement error. The results for the OLR are not presented, as there is no known MDC for the OLR. LSI% = limb symmetry index; ACLR = anterior cruciate ligament reconstruction.
[a]MDC for the single hop distance (14 cm) and LSI (8%) is informed by Kockum et al. (Kockum & Heijne, 2015) and Reid et al. (Reid et al., 2007), respectively.
[b]MDC for triple crossover distance (73 cm) and LSI (12%) is informed by Haitz et al. (Haitz et al., 2014) and Reid et al. (Reid et al., 2007), respectively.
[c]MDC for side hop repetitions (n = 11 repetitions) and LSI (10%), is informed by Kockum et al. (Kockum & Heijne, 2015) and Reid et al. (Reid et al., 2007), respectively. The LSI% MDC for the side hop is not specifically reported, therefore, we estimated 10% MDC for side hop (as an average of the 8% and 12% from the single and triple crossover HFD tests).

Table 2
Functional performance for the healthy control groups~.

	Raw score	LSI (%)
Single hop (cm)[a]	135.0 (27.3)	101.8 (5.6)
Triple crossover hop (cm)[a]	392.5 (102.2)	101.4 (6.0)
Side hop (reps)[a]	33.9 (14.5)	108.2 (14.5)
One-leg rise (reps)[b]	31.7 (15.7)	109.0 (36.4)

~Values are mean (±standard deviation) unless otherwise indicated.
[a] n = 41 in healthy control group for three hop tests.
[b] n = 31 in healthy control group for one-leg rise.

from 6 to 12 months postoperatively, with minimal change between 12 and 24 months, while the contralateral limb was stable or declined in both tests (Thomee et al., 2012). Concurrent strength testing demonstrated a deterioration in quadriceps and hamstring strength from 12 to 24 months in the contralateral limb and stable/improving ACLR limb (Thomee et al., 2012). Functional recovery is reported to occur up to 2-years post-ACLR (Abrams et al., 2014; Nagelli & Hewett, 2017), but is often limited to reports of LSI, which concurs with the improving LSI in the current study.

Worsening in the contralateral limb between 1- and 5-years is not entirely due to age-related deterioration in muscle function (Doherty, 2001; Faulkner, Larkin, Claflin, & Brooks, 2007), since muscle mass and strength appears to be maintained until age 40 or 50, especially when regular sporting activity is continued (Culvenor et al., 2016b; Doherty, 2001; Faulkner et al., 2007). In the current study, the proportion of individuals competing in jumping/pivoting sports increased between 1-year (34%) and 5-years (41%) post-ACLR. The proportion of individuals participating in Level 3 activities increased from 24% to 47%, while those classified as sedentary (Level 4) decreased from 42% to 12%, between 1- and 5-years post-ACLR. Overall, 39% (n = 24), increased their activity level on the classification used (Grindem et al., 2014) between 1- and 5-years. Greater worsening of knee function observed in one limb (i.e. the contralateral leg) might be considered surprising since most dynamic activities are performed using both limbs. Patients and therapists may also prioritise rehabilitation of the ACLR limb, neglecting the contralateral limb, despite the known bilateral neuromuscular deficits (Ingersoll et al., 2008), and decline in function due to changing demands from high-level sport to only walking/activities of daily living for 6–12 months. Worsening function in the contralateral limb might reflect deconditioning following rehabilitation cessation, bilateral movement adaptations (e.g. reduced knee flexion moments) (Hart et al., 2016; Pairot-de-Fontenay et al., 2019), or fear of movement (Hart, Culvenor, Guermazi, & Crossley, 2019).

4.3. Should we be using the LSI in clinical practice?

These findings have important implications for current return-to-sport criteria, given they are highly dependent on achieving >90% LSI on a battery of hop tests (Barber-Westin & Noyes, 2011; van Melick et al., 2016). The overestimation of functional ability with the LSI might contribute to the high re-rupture rates (7%) (Wiggins et al., 2016), or high rates of contralateral ACL injury (8%) (Wiggins et al., 2016) if the acceptable LSI results from low contralateral limb function (Webster & Hewett, 2019). In addition to LSI, return-to-sport criteria should also incorporate individual limb performance scores (e.g. distance hopped, or peak muscle power) benchmarked to their body composition (e.g. height), and to age-, sex- and activity-level matched non-injured populations obtained from context-specific databases or peer-reviewed reports (Bennell et al., 1998). In addition to our healthy reference data, other functional reference data are available for the single hop (Baltaci, Yilmaz, & Atay, 2012; Kemp, Schache, Makdissi, Sims, & Crossley, 2013), triple crossover hop (Baltaci et al., 2012; Kockum & Heijne, 2015), and side hop (Kockum & Heijne, 2015). In an ideal (but often unrealistic or uncommon) scenario pre-injury index limb testing data or pre-operative functional testing of the non-injured limb (i.e. prior to deterioration) may be used as the benchmark. Pre-operative function in the non-injured limb as the reference standard for LSI calculations is more sensitive in predicting second ACL injury, compared to using postoperative performance of the non-injured limb at the time of ACLR limb assessment (Wellsandt et al., 2017). Further research is required to determine the best type and combination of assessments and interventions, and their relationship with future injury risk, patient-reported symptoms, function and quality of life.

The benefits of functional performance symmetry (>90%) at 1- and 5-years post-ACLR even after return-to-sport, should not be discounted. However, symmetry should not come at the expense of inadequate or deteriorating performance in the contralateral limb. Given the known associations between reduced strength and function and increased risk of reinjury and OA (Hootman, Fitzgerald, Macera, & Blair, 2004; Oiestad, Juhl, Eitzen, & Thorlund, 2015; Patterson et al., 2020; Segal et al., 2009), restoring or maintaining symmetry and performance should remain an ongoing priority for both limbs regardless of sports participation. Regardless of return-to-sport and ongoing sports participation, asymmetries on hop-testing are relevant to everyday activities such as walking, as less than 90% LSI on hop tests was associated with lower knee loading on the ACLR limb (Gardinier, Di Stasi, Manal, Buchanan, & Snyder-Mackler, 2014; Sritharan et al., 2020), which has been recently linked to OA risk (Wellsandt et al., 2016).

4.4. Clinical implications for functional performance assessment

Hop testing provides a highly accessible, low-cost alternative to isokinetic and biomechanical testing, and has moderate associations with quadriceps peak torque and rate of torque development(Birchmeier et al., 2019) , force control (Perraton et al., 2017), kinetics and kinematics (Perraton et al., 2018). However, due to persistent morphological changes (i.e. quadriceps volume) post-ACLR (Birchmeier et al., 2020), clinicians should endeavour to evaluate isolated quadriceps and hamstring muscle function (e.g. isokinetic testing). Assessment of muscle function and movement quality is important, as some patients can use compensatory mechanisms and sub-optimal kinematics and kinetics to achieve adequate performance in hop tests (Kotsifaki et al., 2020).

Changes in functional performance after ACLR may differ between tasks. The single hop (ACLR limb) was the only test that demonstrated statistically and clinically important improvement in performance (one-third of participants had performance increase > MDC). The majority of participants did not demonstrate clinically meaningful changes in the ACLR or contralateral limb for the triple-crossover hop and side hop (Fig. 2). Improvement in the ACLR limb single hop may reflect a return to sagittal plane activities such as running after ACLR. No change or decrease in function in more dynamic tasks such as the triple crossover and side hop may reflect lack of progression to multidirectional rehabilitation tasks or sport. These findings are supported by our activity level data, whereby only 41% were participating in Level 1 or 2 sports at 5-years, and a larger proportion (47%) were participating in Level 3 (running, cycling, weight-training) activities at 5-years. Test batteries should include different aspects of function (i.e. multiplanar strength, power and endurance), as a single hop alone may overstate functional improvement, particularly if the patient is returning to multi-directional cutting and pivoting sports (Dingenen & Gokeler, 2017).

4.5. Should healthy control data be used as a reference group?

The LSI on all four tests at 1-year post-ACLR was significantly lower than healthy controls but did not generally differ between groups at 5-years. At 1-year post-ACLR, performance on the ACLR and contralateral limb was also lower than healthy controls for all tests, with significant deficits being observed on the single hop test. The ACLR and contralateral limb performance on all tests was also lower than previously published normative values for those aged 18–50 years (Baltaci et al., 2012; Kemp et al., 2013; Kockum & Heijne, 2015). Together, these findings concur with previous research that functional deficits can persist up to 1–2 years post-ACLR (Nagelli & Hewett, 2017; Thomee et al., 2012). Despite this, most supervised rehabilitation ceases before 6-months with little evidence of ongoing plyometric or lower-limb resistance training (Ebert et al., 2017; Greenberg, Greenberg, Albaugh, Storey, & Ganley, 2018). Evidence-based interventions (van Melick et al., 2016) targeting both limbs after ACLR may need to be implemented beyond the typical 6- to 12-month rehabilitation period to restore function and reduce the risk of reinjury (Kyritsis et al., 2016; Wiggins et al., 2016). Beyond the immediate recovery following ACLR, maintenance of lower-limb exercises will also likely benefit function over the lifespan. This is particularly relevant following a joint injury where an elevated risk of early-onset posttraumatic OA exists (Culvenor et al., 2014, 2015; Patterson et al., 2018). It is encouraging that the functional performance in those with an ACLR at 5-years did not generally differ to healthy controls. However, it is likely a sub-group of individuals with inadequate function exists. For example, at 5-years, 54% (n = 32) and 44% (n = 26) of those with an ACLR could not perform >22 one-leg rises on their ACLR and contralateral limb, respectively, placing them at even greater risk of longer-term symptomatic and radiographic OA (Culvenor et al., 2016c; Thorstensson et al., 2004).

4.6. Limitations

Findings from this study should be considered in the context of its limitations. Selection bias may be evident, as those included for the current analysis (n = 59) were older than our original 110 participants (Culvenor et al., 2016d). As a result, our ACLR group was an average 2 years older at baseline than the healthy control group recruited at the time. This was a primarily a result of younger participants being excluded due to a second injury or being lost to follow-up at 5-years due to relocation and time commitments (e.g. work, family, study). Conversely, those motivated to attend follow-up may have knee problems and functional deficits. Importantly,

we adjusted our between-group analyses for differences in age (and BMI). All participants underwent a hamstring-tendon autograft ACLR. While this limits generalisability to other graft types, there are no known differences in hop-test performance or self-reported knee function between graft types (Holm et al., 2010) (Li et al., 2012). Despite this, our cohort is representative of the wider ACLR population, given majority (88%) were participating in cutting/pivoting sports pre-injury with return-to-sport rates similar to large ACL cohorts at comparable follow-up (Ardern, Taylor, Feller, & Webster, 2014).

We did not include a longitudinal follow-up of the healthy control group to demonstrate potential age-related change. However, our comparison of functional performance between the ACLR and healthy control groups included a regression model with adjustment for age and BMI. Additionally, the scores in our healthy controls (single hop: 135 cm, triple crossover-hop: 393 cm, side hop: 34 repetitions) are comparable to hop-test scores for recreational athletes aged 18–50 years (Baltaci et al., 2012; Gustavsson et al., 2006; Kockum & Heijne, 2015). This is post-hoc analysis of a prospective cohort study and no a-priori sample size calculations were performed. While our sample size was sufficiently powered to detect a statistically significant difference in the changes over time between the ACLR and contralateral limb for all hop tests, we may have been underpowered to detect differences between the ACLR and contralateral limbs for the one leg rise test. While the one-leg rise between-limb difference approached statistical significance, the mean difference of 1.9 repetitions is not likely to be clinically significant. Additionally, the one-leg rise on both limbs had floor effects (scored zero) at 1-year (ACLR: n = 8, contralateral: n = 5) and 5-years (ACLR: n = 6 contralateral: n = 5) and ceiling effects (scored 50) at 1-year (ACLR: n = 21, contralateral: n = 23) and 5-years (ACLR: n = 16, contralateral: n = 17), which may have influenced our statistical analyses of change in functional performance.

5. Conclusion

In conclusion, the contralateral limb had a significantly greater decrease in functional performance compared to the ACLR limb for the three hop tests between 1- and 5-years post-ACLR. Worsening function in the contralateral limb combined with a relatively stable ACLR limb resulted in significant improvements in the LSI. Clinicians should be aware the LSI may overstate improvement in functional performance over time Interventions should target dynamic tasks in both the ACLR and contralateral limbs, considering the deficits at 1-year post-ACLR compared to healthy controls (adjusted for age and BMI), and minimal improvement observed over the proceeding 4-years. Exercise-based interventions may need to continue beyond the typical rehabilitation period of 6–12 months to restore or maintain function in both limbs, given the known influence of lower-limb function on future knee symptoms, OA development and quality of life.

Author contributions

BP, AG, and KC conceived and designed the study. AC, LP, BP, MK and JH conducted the data collection. AC, BP, and AK conducted the statistical analysis and interpretation of data, with input from CB and KC. BP, AK and AC drafted the manuscript with input from and CB and KC. All authors have read and approved the final manuscript.

Ethical approval

Ethical approval for the ACLR and control cohorts were granted by La Trobe University Human Ethics Committee (HEC15-100, HEC16-045 respectively) and University of Melbourne (1136167), and participants provided informed consent.

Funding

Brooke Patterson, Adam Culvenor and Christian Barton are recipients of National Health and Medical Research Council awards (post-graduate scholarship No. 1114296, Neil Hamilton Fairley Clinical Fellowship No. 1121173 and MRFF Translating Research Into Practice No. 11163250, respectively). The sponsors were not involved in the design and conduct of this study, in the analysis and interpretation of the data, and in the preparation, review, or approval of the manuscript.

Declaration of competing interest

None.

Acknowledgements

We thank all the participants, orthopaedic surgeons Mr Timothy Whitehead and Mr Hayden Morris for facilitating recruitment, and Olympic Park Sports Medicine Centre for use of their facility for data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ptsp.2020.04.031.

References

Abrams, G. D., Harris, J. D., Gupta, A. K., McCormick, F. M., Bush-Joseph, C. A., Verma, N. N., et al. (2014). Functional performance testing after anterior cruciate ligament reconstruction: A systematic review. *Journal of Orthopaedics and Sports Medicine, 2*(1).

Ardern, C. L., Taylor, N. F., Feller, J. A., & Webster, K. E. (2014). Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: An updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. *British Journal of Sports Medicine, 48*(21), 1543–1552.

Baltaci, G., Yilmaz, G., & Atay, A. O. (2012). The outcomes of anterior cruciate ligament reconstructed and rehabilitated knees versus healthy knees: A functional comparison. *Acta Orthopaedica et Traumatologica Turcica, 46*(3), 186–195.

Barber-Westin, S. D., & Noyes, F. R. (2011). Objective criteria for return to athletics after anterior cruciate ligament reconstruction and subsequent reinjury rates: A systematic review. *The Physician and Sportsmedicine, 39*(3), 100–110.

Benjaminse, A., Holden, S., & Myer, G. D. (2018). ACL rupture is a single leg injury but a double leg problem: Too much focus on 'symmetry' alone and that's not enough! *British Journal of Sports Medicine*.

Bennell, K., Wajswelner, H., Lew, P., Schall-Riaucour, A., Leslie, S., Plant, D., et al. (1998). Isokinetic strength testing does not predict hamstring injury in Australian Rules footballers. *British Journal of Sports Medicine, 32*(4), 309–314.

Birchmeier, T., Lisee, C., Geers, B., & Kuenze, C. (2019). Reactive strength index and knee extension strength characteristics are predictive of single-leg hop performance after anterior cruciate ligament reconstruction. *The Journal of Strength & Conditioning Research, 33*(5), 1201–1207.

Birchmeier, T., Lisee, C., Kane, K., Brazier, B., Triplett, A., & Kuenze, C. (2020). Quadriceps muscle size following ACL injury and reconstruction: A systematic review. *Journal of Orthopaedic Research, 38*(3), 598–608.

Culvenor, A. G., Alexander, B. C., Clark, R. A., Collins, N. J., Ageberg, E., Morris, H. G., et al. (2016). Dynamic single-leg postural control is impaired bilaterally following anterior cruciate ligament reconstruction: Implications for reinjury risk. *Journal of Orthopaedic & Sports Physical Therapy, 46*(5), 357–364.

Culvenor, A. G., Boeth, H., Diederichs, G., Wirth, W., Duda, G., & Eckstein, F. (2016). Longitudinal bone, muscle and adipose tissue changes in physically active subjects - sex differences during adolescence and maturity. *Journal of Musculoskeletal and Neuronal Interactions, 16*(3), 237–246.

Culvenor, A. G., Collins, N. J., Guermazi, A., Cook, J. L., Vicenzino, B., Khan, K. M., et al. (2015). Early knee osteoarthritis is evident one year following anterior cruciate ligament reconstruction: A magnetic resonance imaging evaluation. *Arthritis & Rheumatology (Hoboken, NJ), 67*(4), 946–955.

Culvenor, A. G., Collins, N. J., Guermazi, A., Cook, J. L., Vicenzino, B., Whitehead, T. S., et al. (2016). Early patellofemoral osteoarthritis features one year after anterior cruciate ligament reconstruction: Symptoms and quality of life at three years. *Arthritis Care & Research, 68*(6), 784–792.

Culvenor, A. G., Collins, N. J., Vicenzino, B., Cook, J. L., Whitehead, T. S., Morris, H. G., et al. (2016). Predictors and effects of patellofemoral pain following hamstring-tendon ACL reconstruction. *Journal of Science and Medicine in Sport, 19*(7), 518–523.

Culvenor, A. G., Lai, C. C., Gabbe, B. J., Makdissi, M., Collins, N. J., Vicenzino, B., et al. (2014). Patellofemoral OA is prevalent and associated with worse symptoms and function after hamstring tendon autograft ACL reconstruction. *British Journal of Sports Medicine, 48*(6), 435–439.

Culvenor, A. G., Patterson, B. E., Guermazi, A., Morris, H. G., Whitehead, T. S., & Crossley, K. M. (2017). *Accelerated return to sport after ACL reconstruction and early knee osteoarthritis features at 1 year: An exploratory study.* PM R.

Dingenen, B., & Gokeler, A. (2017). Optimization of the return-to-sport paradigm after anterior cruciate ligament reconstruction: A critical step back to move forward. *Sports Medicine, 47*(8), 1487–1500.

Doherty, T. J. (2001). The influence of aging and sex on skeletal muscle mass and strength. *Current Opinion in Clinical Nutrition and Metabolic Care, 4*(6), 503–508.

Ebert, J. R., Edwards, P., Yi, L., Joss, B., Ackland, T., Carey-Smith, R., et al. (2017). Strength and functional symmetry is associated with post-operative rehabilitation in patients following anterior cruciate ligament reconstruction. *Knee Surgery, Sports Traumatology, Arthroscopy*.

Ericsson, Y. B., Roos, E. M., & Frobell, R. B. (2013). Lower extremity performance following ACL rehabilitation in the KANON-trial: Impact of reconstruction and predictive value at 2 and 5 years. *British Journal of Sports Medicine, 47*(15), 980–985.

Faulkner, J. A., Larkin, L. M., Claflin, D. R., & Brooks, S. V. (2007). Age-related changes in the structure and function of skeletal muscles. *Clinical and Experimental Pharmacology and Physiology, 34*(11), 1091–1096.

Gardinier, E. S., Di Stasi, S., Manal, K., Buchanan, T. S., & Snyder-Mackler, L. (2014). Knee contact force asymmetries in patients who failed return-to-sport readiness criteria 6 months after anterior cruciate ligament reconstruction. *The American Journal of Sports Medicine, 42*(12), 2917–2925.

Gokeler, A., Welling, W., Benjaminse, A., Lemmink, K., Seil, R., & Zaffagnini, S. (2017). A critical analysis of limb symmetry indices of hop tests in athletes after anterior cruciate ligament reconstruction: A case control study. *Orthopaedics & Traumatology: Surgery & Research, 103*(6), 947–951.

Greenberg, E. M., Greenberg, E. T., Albaugh, J., Storey, E., & Ganley, T. J. (2018). Rehabilitation practice patterns following anterior cruciate ligament reconstruction: A survey of physical therapists. *Journal of Orthopaedic & Sports Physical Therapy, 48*(10), 801–811.

Grindem, H., Arundale, A. J., & Ardern, C. L. (2018). Alarming underutilisation of rehabilitation in athletes with anterior cruciate ligament reconstruction: Four ways to change the game. *British Journal of Sports Medicine*.

Grindem, H., Eitzen, I., Snyder-Mackler, L., & Risberg, M. A. (2014). Online registration of monthly sports participation after anterior cruciate ligament injury: A reliability and validity study. *British Journal of Sports Medicine, 48*(9), 748–753.

Grindem, H., Snyder-Mackler, L., Moksnes, H., Engebretsen, L., & Risberg, M. A. (2016). Simple decision rules can reduce reinjury risk by 84% after ACL reconstruction: The Delaware-Oslo ACL cohort study. *British Journal of Sports Medicine, 50*(13), 804–808.

Gustavsson, A., Neeter, C., Thomee, P., Silbernagel, K. G., Augustsson, J., Thomee, R., et al. (2006). A test battery for evaluating hop performance in patients with an ACL injury and patients who have undergone ACL reconstruction. *Knee Surgery, Sports Traumatology, Arthroscopy, 14*(8), 778–788.

Haitz, K., Shultz, R., Hodgins, M., & Matheson, G. O. (2014). Test-retest and interrater reliability of the functional lower extremity evaluation. *Journal of Orthopaedic & Sports Physical Therapy, 44*(12), 947–954.

Hart, H. F., Culvenor, A. G., Collins, N. J., Ackland, D. C., Cowan, S. M., Machotka, Z., et al. (2016). Knee kinematics and joint moments during gait following anterior cruciate ligament reconstruction: A systematic review and meta-analysis. *British Journal of Sports Medicine, 50*(10), 597–612.

Hart, H. F., Culvenor, A. G., Guermazi, A., & Crossley, K. M. (2019). Worse knee confidence, fear of movement, psychological readiness to return-to-sport and pain are associated with worse function after ACL reconstruction. *Physical Therapy in Sport*.

Holm, I., Oiestad, B. E., Risberg, M. A., & Aune, A. K. (2010). No difference in knee function or prevalence of osteoarthritis after reconstruction of the anterior cruciate ligament with 4-strand hamstring autograft versus patellar tendon-bone autograft: A randomized study with 10-year follow-up. *The American Journal of Sports Medicine, 38*(3), 448–454.

Hootman, J. M., Fitzgerald, S., Macera, C. A., & Blair, S. N. (2004). Lower extremity muscle strength and risk of self-reported hip or knee osteoarthritis. *Journal of Physical Activity and Health, 1*(4), 321–330.

Ingersoll, C. D., Grindstaff, T. L., Pietrosimone, B. G., & Hart, J. M. (2008). Neuromuscular consequences of anterior cruciate ligament injury. *Clinics in Sports Medicine, 27*(3), 383–404 (vii).

Kemp, J. L., Schache, A. G., Makdissi, M., Sims, K. J., & Crossley, K. M. (2013). Greater understanding of normal hip physical function may guide clinicians in providing targeted rehabilitation programmes. *Journal of Science and Medicine in Sport, 16*(4), 292–296.

Kockum, B., & Heijne, A. I. (2015). Hop performance and leg muscle power in athletes: Reliability of a test battery. *Physical Therapy in Sport, 16*(3), 222–227.

Kotsifaki, A., Korakakis, V., Whiteley, R., Van Rossom, S., & Jonkers, I. (2020). Measuring only hop distance during single leg hop testing is insufficient to detect deficits in knee function after ACL reconstruction: A systematic review and meta-analysis. *British Journal of Sports Medicine, 54*(3), 139–153.

Kyritsis, P., Bahr, R., Landreau, P., Miladi, R., & Witvrouw, E. (2016). Likelihood of ACL graft rupture: Not meeting six clinical discharge criteria before return to sport is associated with a four times greater risk of rupture. *British Journal of Sports Medicine, 50*(15), 946–951.

Li, S., Chen, Y., Lin, Z., Cui, W., Zhao, J., & Su, W. (2012). A systematic review of randomized controlled clinical trials comparing hamstring autografts versus bone-patellar tendon-bone autografts for the reconstruction of the anterior cruciate ligament. *Archives of Orthopaedic and Trauma Surgery, 132*(9), 1287–1297.

van Melick, N., van Cingel, R. E., Brooijmans, F., Neeter, C., van Tienen, T., Hullegie, W., et al. (2016). Evidence-based clinical practice update: Practice guidelines for anterior cruciate ligament rehabilitation based on a systematic review and multidisciplinary consensus. *British Journal of Sports Medicine, 50*(24), 1506–1515.

Nagelli, C. V., & Hewett, T. E. (2017). Should return to sport be delayed until 2 Years after anterior cruciate ligament reconstruction? Biological and functional considerations. *Sports Medicine, 47*(2), 221–232.

Oiestad, B. E., Holm, I., Aune, A. K., Gunderson, R., Myklebust, G., Engebretsen, L., et al. (2010). Knee function and prevalence of knee OA after ACLR: A prospective study with 10-15 years follow-up. *The American Journal of Sports Medicine, 38*(11), 2201–2210.

Oiestad, B. E., Juhl, C. B., Eitzen, I., & Thorlund, J. B. (2015). Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis and Cartilage, 23*(2), 171–177.

Pairot-de-Fontenay, B., Willy, R. W., Elias, A. R. C., Mizner, R. L., Dube, M. O., & Roy, J. S. (2019). Running biomechanics in individuals with anterior cruciate ligament reconstruction: A systematic review. *Sports Medicine, 49*(9), 1411–1424.

Patterson B, Culvenor AG, Barton CJ, Guermazi A, Stefanik JJ, Morris HG, et al. Poor functional performance 1 year after ACL reconstruction increases the risk of early osteoarthritis progression. BJSM Epub, ahead of print: [17 January 2020]: doi:10.1136/bjsports-2019-101503.2020.

Patterson, B. E., Culvenor, A. G., Barton, C. J., Guermazi, A., Stefanik, J. J., Morris, H. G., et al. (2018). Worsening knee osteoarthritis features on magnetic resonance imaging 1 to 5 Years after anterior cruciate ligament reconstruction. *The American Journal of Sports Medicine, 46*(12), 2873–2883.

Perraton, L., Clark, R., Crossley, K. M., Pua, Y. H., Whitehead, T. S., Morris, H., et al. (2017). Impaired voluntary quadriceps force control following anterior cruciate ligament reconstruction: Relationship with knee function. *Knee Surgery, Sports Traumatology, Arthroscopy, 25*(5), 1424–1431.

Perraton, L. G., Hall, M., Clark, R. A., Crossley, K. M., Pua, Y. H., Whitehead, T. S., et al. (2018). Poor knee function after ACL reconstruction is associated with attenuated landing force and knee flexion moment during running. *Knee Surgery, Sports Traumatology, Arthroscopy, 26*(2), 391–398.

Pinczewski, L. A., Lyman, J., Salmon, L. J., Russell, V. J., Roe, J., & Linklater, J. (2007). A 10-year comparison of ACLR with hamstring tendon and patellar tendon autograft: A controlled, prospective trial. *The American Journal of Sports Medicine, 35*(4), 564–574.

Reid, A., Birmingham, T. B., Stratford, P. W., Alcock, G. K., & Giffin, J. R. (2007). Hop testing provides a reliable and valid outcome measure during rehabilitation after ACLR. *Physical Therapy, 87*(3), 337–349.

Segal, N. A., Torner, J. C., Felson, D., Niu, J., Sharma, L., Lewis, C. E., et al. (2009). Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. *Arthritis & Rheumatism, 61*(9), 1210–1217.

Sritharan, P., Schache, A. G., Culvenor, A. G., Perraton, L. G., Bryant, A. L., & KM, C. (2020). Between-limb differences in patellofemoral joint forces during running 12 to 24 months after unilateral ACL reconstruction. *The American Journal of Sports Medicine* (in press).

Thomee, R., Neeter, C., Gustavsson, A., Thomee, P., Augustsson, J., Eriksson, B., et al. (2012). Variability in leg muscle power and hop performance after anterior cruciate ligament reconstruction. *Knee Surgery, Sports Traumatology, Arthroscopy, 20*(6), 1143–1151.

Thorstensson, C. A., Petersson, I. F., Jacobsson, L. T., Boegard, T. L., & Roos, E. M. (2004). Reduced functional performance in the lower extremity predicted radiographic knee osteoarthritis five years later. *Annals of the Rheumatic Diseases, 63*(4), 402–407.

Webster, K. E., & Hewett, T. E. (2019). What is the evidence for and validity of return-to-sport testing after anterior cruciate ligament reconstruction surgery? A systematic review and meta-analysis. *Sports Medicine, 49*(6), 917–929.

Wellsandt, E., Failla, M. J., & Snyder-Mackler, L. (2017). Limb symmetry indexes can overestimate knee function after anterior cruciate ligament injury. *Journal of Orthopaedic & Sports Physical Therapy, 47*(5), 334–338.

Wellsandt, E., Gardinier, E. S., Manal, K., Axe, M. J., Buchanan, T. S., & Snyder-Mackler, L. (2016). Decreased knee joint loading associated with early knee osteoarthritis after anterior cruciate ligament injury. *The American Journal of Sports Medicine, 44*(1), 143–151.

Wiggins, A. J., Grandhi, R. K., Schneider, D. K., Stanfield, D., Webster, K. E., & Myer, G. D. (2016). Risk of secondary injury in younger athletes after anterior cruciate ligament reconstruction: A systematic review and meta-analysis. *The American Journal of Sports Medicine, 44*(7), 1861–1876.

Original research

Poor functional performance 1 year after ACL reconstruction increases the risk of early osteoarthritis progression

Brooke Patterson ,[1] Adam Geoffrey Culvenor ,[1,2] Christian J Barton ,[1] Ali Guermazi ,[3] Joshua Stefanik,[4] Hayden G Morris,[5] Timothy S Whitehead,[6] Kay M Crossley [1]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjsports-2019-101503).

[1]Sport and Exercise Medicine Research Centre, La Trobe University, Melbourne, Victoria, Australia
[2]Institute of Anatomy, Paracelsus Medical University, Salzburg & Nuremberg, Salzburg, Austria
[3]Department of Radiology, School of Medicine, Boston University, Boston, Massachusetts, USA
[4]Department of Physical Therapy, Movement and Rehabilitation Sciences, Northeastern University, Boston, Massachusetts, USA
[5]The Park Clinic, St Vincent's Private Hospital, Melbourne, Victoria, Australia
[6]Orthosport Victoria, Epworth HealthCare, Richmond, Victoria, Australia

Correspondence to
Professor Kay M Crossley, Sport and Exercise Medicine Research Centre, La Trobe University, Melbourne, VIC 3086, Australia; k.crossley@latrobe.edu.au

Accepted 17 January 2020

To cite: Patterson B, Culvenor AG, Barton CJ, *et al*. *Br J Sports Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjsports-2019-101503

ABSTRACT

Background Not meeting functional performance criteria increases reinjury risk after ACL reconstruction (ACLR), but the implications for osteoarthritis are not well known.

Objective To determine if poor functional performance post-ACLR is associated with risk of worsening early osteoarthritis features, knee symptoms, function and quality of life (QoL).

Methods Seventy-eight participants (48 men) aged 28±15 years completed a functional performance test battery (three hop tests, one-leg-rise) 1 year post-ACLR. Poor functional performance was defined as <90% limb symmetry index (LSI) on each test. At 1 and 5 years, MRI, Knee injury Osteoarthritis Outcome Score (KOOS) and International Knee Documentation Committee (IKDC) subjective form were completed. Primary outcomes were: (i) worsening patellofemoral and tibiofemoral MRI-osteoarthritis features (cartilage, bone marrow lesions (BMLs) and meniscus) and (ii) change in KOOS and IKDC scores, between 1 and 5 years.

Results Only 14 (18%) passed (≥90% LSI on all tests) the functional test battery. Poor functional performance on the battery (all four tests <90% LSI) 1 year post-ACLR was associated with 3.66 times (95% CI 1.12 to 12.01) greater risk of worsening patellofemoral BMLs. A triple-crossover hop <90% LSI was associated with 2.09 (95% CI 1.15 to 3.81) times greater risk of worsening patellofemoral cartilage. There was generally no association between functional performance and tibiofemoral MRI-osteoarthritis features, or KOOS/IKDC scores.

Conclusion Only one in five participants met common functional performance criteria (≥90% LSI all four tests) 1 year post-ACLR. Poor function on all four tests was associated with a 3.66 times increased risk of worsening patellofemoral BMLs, and generally not associated with decline in self-reported outcomes.

INTRODUCTION

Rupture and subsequent reconstruction of the ACL (ACLR) substantially increases the risk of knee osteoarthritis (OA) development and poor quality of life (QoL).[1 2] Yet not everyone after ACLR develops OA; radiographic OA is evident in approximately one-in-two,[3 4] and one-in-three will have symptomatic radiographic OA within 10–15 years of injury.[3 4] MRI can detect OA features within 5 years of ACLR,[5–7] and can be used to identify individuals who may be on an accelerated trajectory towards radiographic, symptomatic OA.[8] Understanding modifiable factors associated with structural changes early after ACLR is a priority to inform secondary OA prevention strategies.

Impaired functional performance, often measured through hop tests, is common following ACLR,[9] and may influence the development of early knee OA and symptoms. Quadriceps weakness is a risk factor for the development of radiographic and/or symptomatic OA, based on the theory of impaired shock absorption, consequent excessive load to joint structures, initiating a degenerative process.[10] Hop-test batteries provide a clinically feasible method to assess multiple aspects of lower-limb muscle function (including quadriceps strength, sensorimotor control) and may indicate reduced ability to control mechanical loading in the knee,[11–13] thus influencing joint degeneration and/or potential symptoms. Functional performance impairments may represent lack of confidence in the limb,[14] and be reflected in reduced physical activity and worse patient-reported outcomes (PROs).

Following ACLR, the link between functional performance and worsening symptomatic and early structural OA outcomes is unclear. While a single hop-for-distance test at 1 year post-ACLR was associated with the presence of tibiofemoral radiographic OA at 10 years,[15] other studies have reported minimal association between postoperative functional performance and future radiographic OA 5–15 years post-ACLR.[4 16 17] Prior studies focus on radiographic tibiofemoral OA, and do not evaluate early structural *change* (ie, worsening) in individual joint features. Despite the patellofemoral joint being burdensome post-ACLR,[18 19] few studies consider the patellofemoral joint structure. Radiographic measures lack the sensitivity to detect early structural changes which are identifiable on MRI over shorter follow-up.[20 21] No studies have reported the relationship between functional performance and early (<5 years) structural changes on MRI in an ACLR population.

Evaluation of risk factors for early OA after ACLR should also include concurrent assessment of change in PROs, given the discordance between knee imaging findings and symptoms.[22 23] Functional performance may possess differing relationships with change in individual early OA features and PROs. Functional performance deficits at the time of return to sport (RTS) are often associated

with worse PROs 2–3 years after ACL injury,[16 24–28] with few studies evaluating the change in PROs beyond 3 years, due to cross-sectional design. It is this change in PROs and structural outcomes that equates to the problematic accelerated trajectory of symptomatic OA in young adults post-ACLR.

If early functional impairments are related to worsening structural or symptomatic OA, functional deficits can be targeted through exercise therapy to halt or slow the trajectory towards radiographic, symptomatic OA. The aims of the current study were to determine if functional performance 1 year post-ACLR is associated with risk of worsening patellofemoral and tibiofemoral MRI-OA features and change in PROs between 1 and 5 years.

METHODS

Study design and participants

A longitudinal prospective cohort study assessed the trajectory of PROs, functional performance and early OA features 1–5 years post-ACLR. Individuals assessed 1 year post-ACLR (ie, baseline for the current study) (n=111; 64% male, median age 27 (range 19–51) years)[5] were eligible for 5-year follow-up. Descriptions of baseline eligibility criteria, ACLR technique and postoperative rehabilitation have been published.[5] Briefly, all participants underwent a primary single-bundle hamstring-tendon autograft ACLR. Exclusion criteria were: knee injury/symptoms prior to ACL injury, >5 years between ACL injury and reconstruction and any secondary injury/surgery to the ACLR knee (between ACLR and 1 year post-ACLR). Participants with a secondary injury between 1 and 5 years were invited to participate in the 5-year assessment, as this is common occurrence and represents the wider ACLR population. Of the 112 participants who completed baseline PROs, 81 (72%) completed PROs at 5 years. Of the 111 who underwent baseline MRI evaluation, 78 (70%) were re-imaged at 5 years (figure 1).

Demographic, injury and surgical factors

Participant age, sex, height, weight, injury history, activity level (defined as level 1 pivoting/jumping sports to level 4 sedentary[29]) was obtained at the 1-year and 5-year assessments. Participants were classified as having a 'combined injury' if they had (at the time of ACLR): (i) significant cartilage defect identified arthroscopically (Outerbridge grade ≥2)[30] or (ii) surgical resection or repair of meniscus. To determine the presence of tibiofemoral and patellofemoral OA in the ACLR limb, posteroanterior and lateral weightbearing, and non-weightbearing skyline views were taken, and graded according the Osteoarthritis Research Society International atlas definitions.[31] Radiographic OA was defined as joint space narrowing of grade ≥2, sum of osteophytes ≥2 or grade 1 osteophyte in combination with grade 1 joint space narrowing.[31]

Functional performance

At 1 and 5 years post-ACLR, participants completed a battery of functional tests in the following order: single-hop, triple-crossover hop, side-hop and one-leg rise. The left leg was always tested first after two to three practice trials. The single-hop assessed the maximum distance (cm) achieved from a stationary position with a balanced landing (≥2 s without placing the other foot to the floor).[32] The triple-crossover hop assessed

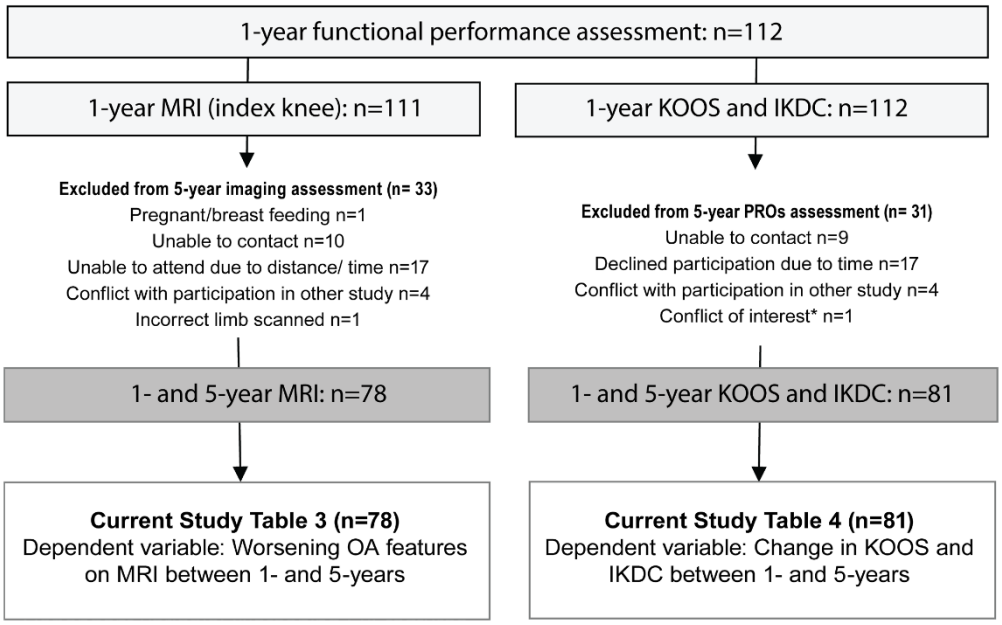


Figure 1 Flow chart of participant recruitment into the study. IKDC, International Knee Documentation Committee; KOOS, Knee injury Osteoarthritis Outcome Score; OA, osteoarthritis. *Participant at 1 year was involved in research team at 5 years.

the cumulative distance (cm) achieved with three consecutive hops with a balanced landing, with each hop crossing over two parallel lines 15 cm apart.[33] Hops were repeated for the single-hop and triple-crossover until three successful trials were recorded, and until no increase in distance was seen, due to the known learning effects.[34] The side-hop assessed the number of hops over two parallel lines 40 cm apart in 30 s.[32] The one-leg rise is the maximum number of times (up to 50) the participant can rise on one leg from 90° knee flexion, at a consistent speed of 45 beats per minute (using a metronome).[35] A hop test or one-leg rise test was scored zero if the participant was unable (due to lack of strength/balance/confidence) to perform one successful trial. The one-leg rise test was stopped if the participant received three warnings for deviating from speed or touching the ground with opposite foot. The one-leg rise was added to the traditional battery of hops as it also assesses endurance, and has been associated with the development of radiographic OA in those with chronic knee pain.[35]

The raw score (ie, distance hopped) and limb symmetry index (LSI) (% score of ACLR knee/contralateral knee) were recorded for each test. Poor functional performance on an individual test was defined as <90% LSI, a common benchmark used to define return-to-sport readiness,[9 36] and is associated with risk of reinjury.[37 38] Poor function on the battery was defined as <90% LSI on all four tests, to specifically capture individuals with poor function.

MRI-OA features

At 1 and 5 years post-ACLR, participants had unilateral (index) knee MRI scans acquired using a single 3T system (Philips Achieva, The Netherlands), as previously described.[5 7] The three-dimensional proton density-weighted VISTA sequence was acquired at 0.35 mm isotropically (repetition time/echo time (TR/TE) 1300 ms/27 ms, field of view (FOV) 150 mm^2 and echo train length 64 ms) and reconstructed in coronal and axial planes. The sagittal short-tau inversion-recovery sequence was at 2.5 mm thickness, 1.2 mm slice gap and an inversion time of 180 ms was applied with TR/TE 3850 ms/30 ms, FOV 160 mm^2 and voxel size 0.45×0.50×2.5 mm. The axial proton-density turbo spin-echo sequence was obtained with imaging parameters of TR/TE 3850 ms/34 ms, slice thickness 2.5 mm, slice gap 2.0 mm, corresponding voxel size 0.5×0.55×2.5 mm and FOV 140 mm^2. All MRI scans were evaluated using the MRI-OA Knee Score (MOAKS) by a musculoskeletal radiologist (AG) with 19 years' experience of semi-quantitative MRI analysis of knee OA, and established inter-rater and intrarater reliability (kappa=0.61–0.80).[39] The 1-year and 5-year images were read paired (not blinded to time-points), but blind to clinical information. The MOAKS divides the knee into subregions to score specific OA features. For the current study, cartilage defects, bone marrow lesions (BMLs) and meniscal lesions were semi-quantitatively graded.

Four subregions defined the patellofemoral joint (medial and lateral patella, medial and lateral trochlea) and 10 subregions defined the tibiofemoral joint (medial and lateral: femur central and posterior, tibia anterior, central and posterior). For grading of meniscal lesions, six subregions (medial and lateral: anterior, posterior and central) were combined. Cartilage defects and BMLs were graded from 0 to 3 based on size (percentage of surface area relative to each subregion, where 0=none, 1=<33%, 2=33%–66%, 3=>66%). Cartilage defects were also scored on severity based on depth of the lesion (percentage of lesion which is full thickness; 0=no full-thickness loss; 1=<10%; 2=10%–75%; 3=>75%). A meniscal tear was defined as an area of abnormal signal that extends to both meniscal articular surfaces, and meniscal macerations were defined as loss of morphological substance of the meniscus. Meniscal lesions were described as absent or present, and by type (a tear was either vertical, horizontal or complex; and maceration was partial, progressive or complete). These abnormalities were scored according to MOAKS scoring system. Meniscal extrusion was graded by size 0 (<2 mm); 1 (2–2.9 mm); 2 (3–4.9 mm) or 3 (>5 mm) in each of the subregions. Meniscal extrusion, while based on the amount of extrusion in mm, was also scored using the MOAKS.

Worsening OA features in each subregion was defined as any increase in the size or severity of the feature. Therefore, either progression of an OA feature (ie, increase in severity) or a new OA feature (ie, from absent to present) from 1 year to 5 years was classified as worsening. New OA features were defined as those with size=0 at baseline, and size ≥1 at follow-up. Increase in severity was defined as an increase in size or depth of an existing OA feature at 1 year by ≥1 point on the MOAKS. Worsening OA features in the patellofemoral and tibiofemoral compartment was defined as worsening in any corresponding subregion for that compartment, as previously described.[7 40] This definition of worsening is reliable and sensitive to change in ACL-injured patients.[6 7]

Patient-reported outcomes

Participants completed the Knee injury Osteoarthritis Outcome Score (KOOS) and the International Knee Documentation Committee (IKDC) subjective knee form 1 and 5 years post-ACLR, with respect to their knee condition during the previous week. The KOOS and IKDC have established reliability and validity in people with ACL injuries.[41] Four of the five subscales of the KOOS were assessed (activities of daily living subscale excluded due to ceiling effects in ACL populations). They were completed in by pen and paper or via an online portal (MySQL, Oracle, California, USA and Promptus, DS PRIMA, Melbourne, Australia) with matching instructions to the original paper version, as previously described.[22 26] The KOOS and IKDC raw scores were recorded and converted to a percentile score, with 100 being the best possible score (ie, no knee problems). The absolute change (5-year score minus 1-year score) was calculated for each subscale (a negative value indicating worsening knee problems).

Statistical analyses

Generalised linear models with Poisson regression and generalised estimating equations (GEE) (accounting for correlations between subregions within the same participant) assessed whether functional performance at 1 year post-ACLR (both as a dichotomous (poor function≤90% LSI) and a continuous (ACLR limb raw score in cm/repetitions) variable) was associated with risk of worsening MRI-OA features. Risk ratios (RR) and 95% CIs were calculated. A RR >1.0 represents an increased risk of worsening OA features in the presence of poor functional performance (<90% LSI) or a lower functional performance score (ie, fewer repetitions). The GEE regression was adjusted for presence of a combined injury (noted at time of ACLR, or secondary injury to the index knee), 1-year age, sex, height and weight, due to their potential influence on function and MRI-OA features.[7] Linear regression (β, 95% CI) determined the relationship between 1-year functional performance, and change in KOOS/IKDC scores between 1 and 5 years (adjusted for combined injury (noted at time of ACLR, or secondary injury to

Table 1 Participant characteristics at 1 and 5 years post-ACLR*

	Participants at 1 year post-ACLR (n=81)	Participants at 5 years post-ACLR (n=81)
Age, median±IQR years	28±14	32±14
Male sex, no. (%)	50 (62)	50 (62)
Body mass index, median±IQR kg/m^2	25.7±4.2	26.4±5.0
Preinjury activity level 1 sport†, no. (%)	56 (69)	56 (69)
Time injury to surgery, median±IQR weeks	14±20	14±20
Combined injury,‡ no. (%)	40 (49)	46 (57)
New knee injuries, no. (%)	0 (0)§	16 (20)
ACLR limb¶	0 (0)§	10 (11)
Contralateral limb**	0 (0)§	6 (7)
Returned to level 1 sports,† no. (%)	20 (25)	26 (32)
Radiographic OA, no. (%)††	5 (6)	15 (19)
Patellofemoral	4 (5)	14 (18)
Tibiofemoral	2 (3)	6 (8)

*Participant demographics of n=81 completed PROs at 1 and 5 years.
†Level 1 sport=jumping, cutting pivoting as per Sports Activity Classification based on the study by Grindem *et al*.[29]
‡Participants were defined as a combined injury at 1 and 5 years if they had a significant cartilage defect[30] and/or meniscectomy assessed/performed at the time of ACLR. Those who had a secondary injury/surgery to the index knee between 1 and 5 years follow-up were added to the combined injury group at 5 years.
§No new knee injuries were reported at 1 year as this was an exclusion criterion at baseline.
¶5-year new ACLR limb knee injuries/surgery n=10 (n=3 ACLR revision, n=6 meniscectomy, n=1 lateral collateral ligament sprain).
**5-year new contralateral limb knee injuries/surgery n=6 (combined: n=2 ACLR, n=1 meniscectomy, isolated: n=1 ACLR, n=1 meniscectomy, n=1 lateral collateral sprain).
††n=78 completed X-ray evaluation at 1 and 5 years, demographics of these participants have been reported previously.[7]

Table 2 Functional performance 1 year post-ACLR*

	Raw score	LSI %
Single HFD, median±IQR (range) cm	108±40 (3 to 169)	92±15 (4 to 109)
≥90% LSI (n=50/81)	119±27 (71 to 169)	96±6 (90 to 109)
<90% LSI (n=31/81)	85±34 (3 to 142)	79±17 (4 to 88)
Triple-crossover HFD, median±IQR (range) cm	337±130 (0 to 569)†	95±11 (0 to 129)
≥90% LSI (n=55/81)	383±119 (146 to 569)	98±5 (90 to 129)
<90% LSI (n=26/81)	262±83 (0 to 403)	79±11 (0 to 89)
Side-hop, median±IQR (range) reps	25±17 (0 to 63)†	83±28 (0 to 156)
≥90% LSI (n=29/81)	29±13 (14 to 63)	100±11 (90 to 155)
<90% LSI (n=52/81)	23±18 (0 to 51)	70±20 (0 to 89)
OLR, median±IQR (range) reps	26±39 (0 to 50)†	96±40 (0 to 167)
≥90% LSI (n=40/76)	50±8 (5 to 50)	100±0 (92 to 325)
<90% LSI (n=36/76)	12±15 (0 to 43)	59±36 (0 to 89)

*n=81 completed functional performance assessment at 1 year and PROs at 1 and 5 years. n=76 for the one-leg rise as five participants were not included, as they could not perform a valid test on both ACLR and contralateral limb.
†Number of participants with a score of zero for the ACLR limb for the triple-crossover hop (n=1), side-hop (n=5) and one-leg rise (n=8).
ACLR, ACL reconstruction; HFD, hop for distance; LSI, limb symmetry index; OLR, one-leg rise; PRO, patient-reported outcome.

the index or contralateral knee), 1-year age, sex, height, weight and baseline KOOS/IKDC score, due to their potential to influence function and PROs[22]). Analyses were performed using Stata V.14.2 with $\alpha=0.05$.

RESULTS

Demographics of the 81 participants who completed PROs at 1 and 5 years are presented in table 1. Of the 81 participants, 10 (12%) had poor functional performance (<90% LSI) on all four tests, while only 14 (18%) would have passed the test battery (≥90% on all four tests) at 1 year post-ACLR. The proportion of participants with <90% LSI on individual tests, and functional performance outcomes are presented in table 2. Of the 78 participants with radiographs at 5 years, the prevalence of any radiographic OA increased from 6% to 19% between 1 and 5 years (table 1). In those with poor function on the battery at 1 year (n=9/78), 33% (n=3) had patellofemoral or tibiofemoral radiographic OA at 5 years.

Imaging outcomes

Worsening compartment-specific MRI-OA features and radiographic OA prevalence are reported in detail previously.[7] Briefly, patellofemoral and tibiofemoral cartilage worsening (34 (44%) and 16 (21%) participants, respectively) was more common than BML worsening (14 (18%) and 12 (15%) participants, respectively). Seventeen (22%) participants displayed worsening meniscal lesions. Five (6%) participants displayed worsening of all three features, while 20 (26%), 4 (5%) and 7 (9%) had isolated cartilage, BML and meniscal worsening, respectively. Worsening osteophytes were not included in the current study due to low numbers in the patellofemoral (n=7) and tibiofemoral (n=9) compartments.[7]

Functional performance and risk of worsening early OA features

Poor functional performance on the test battery (<90% on all four tests) resulted in an increased risk of worsening patellofemoral BMLs (RR 3.66; 95% CI 1.12 to 12.01) (table 3). The majority (86%) of those with a worsening patellofemoral BML had <90% LSI on the side-hop (figure 2). Individuals with <90% LSI on the triple-crossover hop-for-distance had an increased risk of worsening patellofemoral cartilage lesions (RR 2.09; 95% CI 1.15 to 3.81). Individuals with <90% LSI on the single hop-for-distance, side-hop and one-leg rise had an increased risk of worsening patellofemoral BMLs (RR 4.17, 95% CI 1.37 to 12.72; RR 3.77, 95% CI 1.15 to 12.43 and RR 2.92, 95% CI 1.19 to 7.18, respectively). Fewer side-hop repetitions was associated with an increased risk of worsening patellofemoral BMLs (RR 1.08; 95% CI 1.01 to 1.15). In contrast, fewer one-leg rises was associated with a small reduction in risk of worsening tibiofemoral cartilage lesions (RR 0.96; 95% CI 0.94 to 0.99) (table 3).

Functional performance relationship with KOOS and IKDC

The 1-year and 5-year KOOS and IKDC scores (n=81) have been reported in detail previously.[22] Significant ($p<0.05$) improvement (ie, less knee symptoms, better function and QoL) was observed for all KOOS subscales (except KOOS-Symptoms) and IKDC between 1 and 5 years.[22] The mean±SD changes were: pain: 2.8±9; symptoms: 0.5±16.1; sport: 6.0±18.2; QoL: 10.0±18.9 and IKDC: 4.7±10.9. Generally, functional performance 1 year post-ACLR was not associated with change in KOOS or IKDC scores between 1 and 5 years (table 4). Participants with <90% LSI for the side-hop test had a mean

Table 3 Functional performance at 1 year and risk of worsening early osteoarthritis features up to 5 years*

		Worsening early osteoarthritis features on MRI				
		PF cartilage	PF BML	TF cartilage	TF BML	TF meniscal
		n=34/78 (44%)	n=14/78 (18%)	n=16/78 (21%)	n=12/78 (15%)	n=17/78 (22%)
Single HFD	No. (%)					
Raw score (cm)†		1.00 (0.99 to 1.01)	1.01 (0.98 to 1.03)	0.98 (0.96 to 1.01)	1.00 (0.97 to 1.03)	0.98 (0.96 to 1.02)
Poor function (ref ≥90% LSI)‡	31 (38%)	1.26 (0.66 to 2.41)	**4.17 (1.37 to 12.72)**	0.69 (0.21 to 2.35)	0.68 (0.20 to 2.31)	1.65 (0.62 to 4.44)
Triple-crossover HFD						
Raw score (cm)†		1.00 (1.00 to 1.01)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.01)	0.99 (0.98 to 1.00)
Poor function (ref ≥90% LSI)‡	25 (32%)	**2.09 (1.15 to 3.81)**	2.60 (0.79 to 8.62)	1.02 (0.31 to 3.38)	1.02 (0.29 to 3.57)	1.76 (0.52 to 6.01)
Side-hop						
Raw score (repetitions)†		1.01 (0.98 to 1.05)	**1.08 (1.01 to 1.15)**	0.96 (0.91 to 1.02)	1.00 (0.95 to 1.06)	0.97 (0.92 to 1.02)
Poor function (ref ≥90% LSI)‡	49 (63%)	1.02 (0.51 to 2.03)	**3.77 (1.15 to 12.43)**	1.10 (0.47 to 2.60)	1.69 (0.34 to 8.45)	0.89 (0.35 to 2.28)
One-leg rise						
Raw score (repetitions)†		1.01 (0.99 to 1.02)	1.02 (0.99 to 1.05)	**0.96 (0.94 to 0.99)**	0.99 (0.94 to 1.04)	0.98 (0.95 to 1.02)
Poor function (ref ≥90% LSI)‡	35 (48%)§	1.32 (0.72 to 2.41)	**2.92 (1.19 to 7.18)**	0.30 (0.08 to 1.05)	0.58 (0.19 to 1.78)	0.98 (0.33 to 2.93)
Functional battery‡ (ref ≥90% LSI ≥any one test)						
Poor function all four tests§	9 (12%)	1.99 (0.92 to 4.30)	**3.66 (1.12 to 12.01)**	NA¶	1.32 (0.30 to 5.78)	1.25 (0.32 to 4.88)

Bold values indicate a statistically significant association (p<0.05).
*Values are RR (95% CIs). Analysis performed in n=78 who completed functional assessment at 1 year and MRI and X-ray evaluation at 1 and 5 years. n=73 for the one-leg rise and battery LSI% as five participants were not included, as they could not perform a valid one-leg rise on both ACLR and contralateral limb.
†For continuous exposure variables (raw score in cm or repetitions in ACLR limb), a RR >1 represents greater risk of the MRI-OA feature worsening in the presence of lower functional performance (ie, less distance or fewer repetitions). For example, a one repetition decrease on the side-hop test could be interpreted as having a 8% increased risk of worsening patellofemoral BMLs.
‡For dichotomous exposure variables (poor function defined as <90% LSI), a RR >1 represents a greater risk of the MRI-OA feature worsening in the presence of poor functional performance. For example, individuals with <90% LSI on the one-leg rise were 2.92 times more likely to have worsening patellofemoral BMLs, than those with >90% LSI.
§Poor functional performance was defined as <90% LSI.
¶Unable to perform analysis as all participants with <90% on the functional performance battery had TF cartilage defect worsening.
ACLR, ACL reconstruction; BML, bone marrow lesion; LSI, limb symmetry index; n, number of subregions with feature; N, total number of subregions; PF, patellofemoral; RR, risk ratio; TF, tibiofemoral.

8-points higher KOOS-QoL change value (β: 8.08; 95% CI 1.56 to 14.61).

DISCUSSION

Only one in five participants met common functional performance criteria (≥90% LSI on all hopping, one-leg rise tests) 1 year following ACLR—a time when function is typically expected to be restored. In this first evaluation of the implications of not meeting functional performance criteria on early OA outcomes after ACLR, poor function (<90% LSI) was consistently associated with 2–4 times increased risk of worsening patellofemoral BMLs. While performance on the triple-crossover

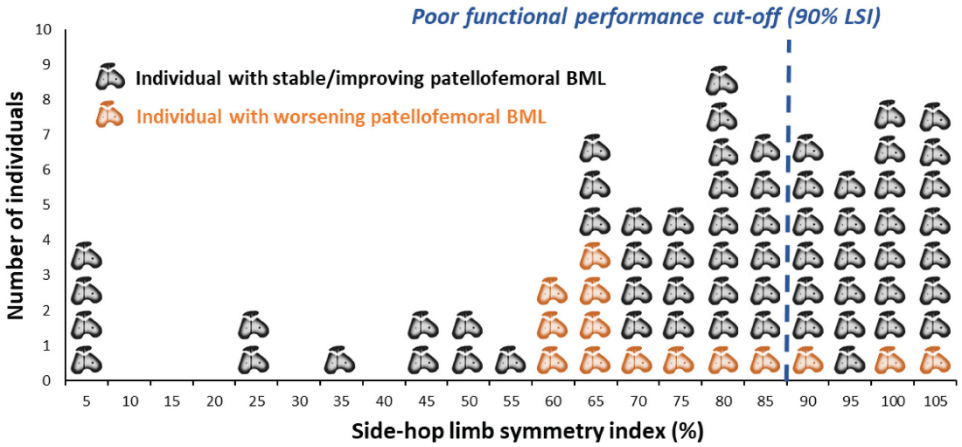


Figure 2 Individuals with and without change in patellofemoral BMLs and respective side-hop limb symmetry index.* *LSI scores are presented in categories of 0%–5%, 5%–10% in increasing increments of 5% for purposes of visualisation. BML, bone marrow lesion; LSI, limb symmetry index.

Table 4 Functional performance at 1 year post-ACLR: relationship with change in KOOS and IKDC between 1 and 5 years*

		Change in KOOS and IKDC between 1 and 5 years				
		KOOS-Symptoms	KOOS-Pain	KOOS-Sport	KOOS-QoL	IKDC
Single HFD	No. (%)					
Raw score (cm)†		0.05 (−0.09 to 0.19)	−0.06 (−0.13 to 0.01)	−0.11 (−0.27 to 0.05)	−0.03 (−0.18 to 0.12)	−0.02 (−0.12 to 0.08)
Poor function (ref >90% LSI)‡	31 (38%)	1.35 (−5.70 to 8.41)	−2.57 (−6.08 to 0.94)	−1.68 (−9.04 to 5.67)	−1.81 (−9.01 to 5.41)	−1.27 (−6.07 to 3.52)
Triple-crossover HFD						
Raw score (cm)†		0.02 (−0.02 to 0.07)	−0.02 (−0.05 to 0.00)	−0.03 (−0.08 to 0.02)	−0.01 (−0.05 to 0.04)	0.00 (−0.03 to 0.03)
Poor function (ref >90% LSI)‡	26 (32%)	2.56 (−4.30 to 9.42)	−3.14 (−6.65 to 0.37)	−3.14 (−6.65 to 0.37)	−3.40 (−10.27 to 3.46)	0.38 (−4.17 to 4.94)
Side-hop						
Raw score (repetitions)†		0.22 (−0.08 to 0.52)	0.06 (−0.22 to 0.10)	−0.07 (−0.40 to 0.27)	0.08 (−0.24 to 0.40)	0.07 (−0.15 to 0.28)
Poor function (ref >90% LSI)‡	52 (64%)	5.50 (−1.23 to 12.24)	2.97 (−0.43 to 6.37)	2.96 (−0.44 to 6.37)	**8.08 (1.56 to 14.61)**	1.27 (−3.08 to 5.63)
One-leg rise						
Raw score (repetitions)†		−0.08 (−0.11 to 0.26)	0.00 (−0.10 to 0.10)	−0.04 (−0.25 to 0.18)	0.09 (−0.10 to 0.29)	0.09 (−0.04 to 0.22)
Poor function (ref >90% LSI)‡	36 (47%)§	2.92 (−3.72 to 9.58)	0.45 (−3.07 to 3.97)	0.45 (−3.08 to 3.97)	6.19 (−0.75 to 13.15)	3.79 (−0.62 to 8.21)
Functional battery‡ (ref ≥90% LSI ≥any 1 test)						
Poor function all four tests§	10 (13%)	−2.78 (−12.44 to 6.88)	−3.00 (−7.80 to 1.79)	0.30 (−11.23 to 11.83)	0.47 (−9.66 to 10.61)	−0.05 (−6.64 to 6.54)

Bold values indicate a statistically significant association (p<0.05).
*Values are beta-coefficient (95% CIs). Analysis performed in n=81 completed functional assessment at 1 year, KOOS and IKDC at 1 and 5 years. n=76 for the one-leg rise and battery LSI% as five participants were not included, as they could not perform a valid one-leg rise on both ACLR and contralateral limb.
†The beta-coefficient represents the adjusted difference in KOOS or IKDC change score per unit decrease in the continuous exposure variables. (ie, cm or number of side-hop repetitions, ACLR limb).
‡The beta-coefficient represents the adjusted difference in KOOS or IKDC in the presence of the dichotomous exposure variables (ie, poor function defined as <90% LSI), eg, those with <90% LSI had on average 8.08 points greater improvement on the KOOS-QoL than those with >90%.
§Poor functional performance was defined as <90% LSI.
ACLR, ACL reconstruction; HFD, hop for distance; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; LSI, limb symmetry index; QoL, quality of life.

hop was also associated with worsening patellofemoral cartilage over the subsequent 4 years, weak/no associations were generally observed between poor function and tibiofemoral cartilage, bone marrow and meniscal lesions and changes in PROs.

Poor function and risk of worsening patellofemoral OA features

Poor functional performance was associated with an increased risk of worsening patellofemoral OA features, particularly BMLs. An LSI <90% on all four tests in the battery was associated with 3.66 times greater risk of worsening patellofemoral BMLs. When considered as a continuous variable (ie, number of repetitions), the side-hop test was associated with worsening patellofemoral BMLs—each one repetition decrease on the side-hop test could be interpreted as having an 8% increased risk of worsening patellofemoral BMLs (RR: 1.08). Given the association of BMLs with incident symptoms, future damage to adjacent features (ie, cartilage) and incident radiographic OA,[8 42 43] these findings may help identify individuals on an accelerated trajectory towards radiographic OA.[8] There is need to validate these findings in larger cohorts and to confirm which factors influence functional recovery. Previous cross-sectional evaluation of this cohort at 1 year post-ACLR found worse hop-test performance at 1 year post-ACLR was associated with patellofemoral pain, kinesiophobia, lower psychological readiness for RTS and worse knee confidence.[14 19] Other factors that have been linked to functional recovery after ACLR, such as motivation, stress and self-efficacy,[44] may also be important to target during supervised rehabilitation[45] to optimise function. Future interventional studies should determine if improving functional performance can positively impact long-term patellofemoral joint health.

Do tibiofemoral and patellofemoral post-traumatic OA have different risk profiles?

Functional performance 1 year post-ACLR had little association with worsening tibiofemoral OA features in the following 4 years, concurring with other studies reporting minimal association between greater postoperative function or muscle strength and tibiofemoral radiographic OA 5–15 years later.[4 17] The tibiofemoral and patellofemoral compartment may have a different association with function for the development of post-traumatic OA. Our results extend those from non-traumatic older OA populations, where lower-limb function (ie, quadriceps muscle strength) was more strongly associated with risk of patellofemoral disease progression than tibiofemoral.[46] In contrast to patellofemoral disease worsening, our results indicate that poorer function (fewer one-leg rises) reduced the risk of tibiofemoral disease worsening. The mechanism underpinning this inverse (and unexpected) relationship is uncertain but is consistent with results in military recruits (aged 18 years), where lower quadriceps strength reduced the incidence of tibiofemoral OA 20 years later.[47] Taken together with demographic and surgical-related factors which display compartment-specific relationships with post-traumatic OA progression,[7 22 48] future studies should evaluate the patellofemoral and tibiofemoral compartments independently to determine distinct risk profiles—particularly as they may have differing impacts on disease burden.[18] For example, patellar alignment (lateral patellar displacement) was weakly associated with worsening patellofemoral cartilage in this cohort,[49] although when added as a covariate to the current statistical models, the relationship between function and worsening patellofemoral bone marrow and cartilage lesions did not change (data not shown). There is emerging appreciation of the greater risk of early[5 7] and long-term radiographic patellofemoral OA,[50] and potential contribution to symptoms,[18] compared with tibiofemoral OA.

Challenges in predicting PROs

Functional performance 1 year post-ACLR was mostly not associated with change in PROs between 1 and 5 years. The only significant finding was that individuals with poor function (<90% LSI) for the side-hop test had an 8-point greater improvement in KOOS-QoL compared with those with good function (<90% LSI). Due to a low proportion (12%) scoring <90% LSI on all four tests, a sensitivity analysis calculated the RRs for poor function (<90% LSI) on *any* one, two or three tests, or *at least* one, two or three tests (ie, at least 2=all participants with two, three or four tests <90% LSI) (see online supplementary file 1). Similarly, poor function at 1 year on *any* or *at least* two tests was associated with 8–12 points greater improvement in KOOS scores. While 8–12 points approaches a clinically meaningful difference for the KOOS (≥8–10 points),[41] these results should be interpreted with caution. Individuals with poor function 1 year post-ACLR have greater potential for future improvement in physical and self-reported function, compared with those who have already restored good function. Only seven (9%) had a KOOS-QoL >90 at 1 year, demonstrating majority of the cohort had not reached a ceiling point, and may continue to improve between 1 and 5 years.

The only other study to evaluate the relationship between function at the time of RTS and PROs beyond 2 years reported conflicting findings.[51] Greater between limb asymmetry on the one-leg rise test 6–15 months post-ACL injury was associated with worse KOOS scores at 5 years.[51] Due to the multifactorial fluctuating nature of life for a young active adult, it is likely many other subjective factors influence change in KOOS and IKDC scores, hence predicting PROs post-ACLR is challenging.[16 52] Further research should consider potential psychosocial and contextual influences on PROs such as fear avoidance, confidence, coping and healthcare utilisation.[53–57]

Limitations

This prospective study lost 31 (28%) participants between 1 and 5 years. However, there were no significant differences in preinjury activity level, age, sex, body mass index or combined injury presence at the time of ACLR, between those who did and did not participate in follow-up.[7] The current study included six (8%) participants who did not participate in jumping or cutting sports preinjury (ie, level 3 or 4),[29] which may influence the raw hop-test scores at 1 year. The current study may have been underpowered to detect potential relationships with functional performance for some outcome variables (ie, tibiofemoral worsening), affecting the statistical stability of some regression models. Future approaches should combine large sets of individual level data from multiple sites to provide sufficient power to detect risk factors and develop a risk profile for early OA development and progression in this young active population. Mechanical (eg, movement patterns,[58] physical activity,[59–61] time from injury to ACLR[7]) and systemic factors (eg, adiposity)[62] may influence the development of post-traumatic OA[61] and warrant consideration in future risk profiles.

The LSI has inherent limitations and may overestimate knee function due to the bilateral neuromuscular deficits observed post-ACLR.[63] Also, discrete cut-offs (ie, >90% LSI) as an independent risk factor may result in overestimation of risk estimates.[64] Therefore, we considered both magnitude of performance as a

continuous outcome (repetitions or distance), as well as symmetry (LSI%), with generally a closer association observed between worsening OA features and dichotomised outcomes (<90% LSI). A floor effect for the functional performance tests should be noted as some participants scored zero on their ACLR limb (table 2), with reasons (anecdotally reported) as lack of physical capability (strength/power/control) or confidence to attempt the task. Future studies should explore reasons for poor functional performance, to better direct intervention strategies.

Clinical considerations

Despite the limitations of the LSI, better limb symmetry in hop tests has been associated with greater likelihood of return-to-sport, and reduced reinjury risk.[38 65] Our results show restoring limb symmetry is also an attractive intervention target, given only 18% 'passed' the test battery (>90% LSI all four tests), and poor function was associated with increased risk of worsening patellofemoral bone marrow and cartilage lesions. Our sensitivity analysis (see online supplementary file 1) demonstrated the highest RRs for worsening patellofemoral cartilage, patellofemoral BMLs, tibiofemoral meniscal lesions were observed when *any* three tests, or *at least* two or three tests were failed (<90% LSI). A battery of tests assessing multiple functional domains (ie, strength, endurance, balance) may better categorise individuals with poor functional performance, and be more predictive of clinical outcomes.[38] Multifaceted neuromuscular deficits may affect joint loading,[12] and consequently joint health. Regardless of return-to-sport aspirations, continuing rehabilitation to achieve 'functional criteria' on a test battery may optimise future joint health. Future studies should continue to investigate the relationship between symptomatic and structural changes in a post-traumatic OA population after ACLR. Underlying early stages of OA without the presence of symptoms may not be 'incidental' in those at risk of OA, and may lead to future symptomatic radiographic OA.[8]

What are the findings?

- Individuals with poor functional performance 1 year following ACL reconstruction (ACLR) had 2–4 times increased risk of worsening patellofemoral bone marrow lesions (BMLs) in the following 4 years.
- Less than one in five passed the functional performance battery (≥90% limb symmetry index on all four tests) 1 year after ACLR, highlighting a need to implement treatments capable of improving functional recovery.
- Poor functional capacity on hop testing and a one-leg rise at 1 year post-ACLR may help identify individuals at an increased risk of worsening patellofemoral BMLs, and developing early onset post-traumatic patellofemoral osteoarthritis.

How might it impact on clinical practice in the future?

- Clinicians should evaluate patient-specific barriers and enablers to implement evidence-based rehabilitation, given only 18% passed the functional test battery at 1 year post-ACLR.
- Regardless of an individual's desire to return-to-sport, restoring lower-limb function may be important to mitigate the risk of future joint degeneration.

CONCLUSION

Only one in five participants met common functional performance criteria (≥90% LSI all four tests) 1 year post-ACLR. Poor function was consistently associated with 2–4 times increased risk of worsening patellofemoral (but not tibiofemoral) BMLs. These results highlight the importance of optimising function beyond the short-term re-injury risk, as functional performance may help identify individuals on an accelerated trajectory towards (patellofemoral) radiographic OA.

Patient and public involvement

There were no funds or time allocated for patient and public involvement so we were unable to involve patients. We have invited patients to our knowledge translation events, to help inform our dissemination strategy and future research questions.

Twitter Brooke Patterson @Knee_Howells and Christian J Barton @DrChrisBarton

Acknowledgements The authors would like to thank all the participants, Imaging@Olympic Park for assistance in obtaining all MRIs and Olympic Park Sports Medicine Centre for use of their facility for clinical data collection.

Contributors BP, AG and KAC conceived and designed the study. HGM and TSW assisted with recruitment of participants. BP, JS and AGC conducted the statistical analysis and interpretation of data, with input from CB and KMC. BP drafted the manuscript with input from AG, CJB, KAC, JS, HGM, TSW and KAC. All authors have read and approved the final manuscript.

Funding Support for this study was provided by Arthritis Australia, La Trobe University Sport, Exercise and Rehabilitation Research Focus Area, the Queensland Orthopaedic Physiotherapy Network, the University of Melbourne (Research Collaboration grant) and the University of British Columbia Centre for Hip Health and Mobility (Society for Mobility and Health). BP was the recipient of the Felice Rosemary-Lloyd Travel Scholarship, which assisted with travel and data analysis to visit coauthor JS at the University of Delaware. BP, AC and CB are recipients of National Health and Medical Research Council awards (post-graduate scholarship No. 1114296, Neil Hamilton Fairley Clinical Fellowship No. 1121173 and MRFF Translating Research into Practice No. 11163250, respectively). JS is supported by a NIH/NIGMS grant U54-GM104941.

Competing interests AG received consulting fees for grading of MRI images at baseline and follow-up. He is a shareholder of Boston Imaging Core Lab (BICL) and a consultant to Merck Serono, Pfizer, GE Healthcare, Galapagos, Roche and TissueGene.

Patient consent for publication Not required.

Ethics approval Ethical approval was granted by the La Trobe University Human Ethics Committee (HEC15-100) and all participants signed informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. Reuse will be permitted by the corresponding author, and can occur up until 2027, which corresponds with the conditions of the La Trobe University Human Ethics committee that indicates data will be kept for at least 10 years following completion of data collection.

ORCID iDs
Brooke Patterson http://orcid.org/0000-0002-6570-5429
Adam Geoffrey Culvenor http://orcid.org/0000-0001-9491-0264
Christian J Barton http://orcid.org/0000-0002-3545-5094
Ali Guermazi http://orcid.org/0000-0002-9374-8266
Kay M Crossley http://orcid.org/0000-0001-5892-129X

REFERENCES

1 Lohmander LS, Östenberg A, Englund M, *et al*. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis Rheum* 2004;50:3145–52.
2 Poulsen E, Goncalves GH, Bricca A, *et al*. Knee osteoarthritis risk is increased 4-6 fold after knee injury – a systematic review and meta-analysis. *Br J Sports Med* 2019;53:1454–63.
3 Lie MM, Risberg MA, Storheim K, *et al*. What's the rate of knee osteoarthritis 10 years after anterior cruciate ligament injury? An updated systematic review. *Br J Sports Med* 2019;53:1162–7.

4 Ølestad BE, Holm I, Gunderson R, *et al*. Quadriceps muscle weakness after anterior cruciate ligament reconstruction: a risk factor for knee osteoarthritis? *Arthritis Care Res* 2010;62:1706–14.
5 Culvenor AG, Collins NJ, Guermazi A, *et al*. Early knee osteoarthritis is evident one year following anterior cruciate ligament reconstruction: a magnetic resonance imaging evaluation. *Arthritis Rheumatol* 2015;67:946–55.
6 van Meer BL, Oei EHG, Meuffels DE, *et al*. Degenerative changes in the knee 2 years after anterior cruciate ligament rupture and related risk factors: a prospective observational follow-up study. *Am J Sports Med* 2016;44:1524–33.
7 Patterson BE, Culvenor AG, Barton CJ, *et al*. Worsening knee osteoarthritis features on magnetic resonance imaging 1 to 5 years after anterior cruciate ligament reconstruction. *Am J Sports Med* 2018;46:2873–83.
8 Sharma L, Nevitt M, Hochberg M, *et al*. Clinical significance of worsening versus stable preradiographic MRI lesions in a cohort study of persons at higher risk for knee osteoarthritis. *Ann Rheum Dis* 2016;75:1630–6.
9 Abrams GD, Harris JD, Gupta AK, *et al*. Functional performance testing after anterior cruciate ligament reconstruction. *Orthop J Sports Med* 2014;2:232596711351830.
10 Øiestad BE, Juhl CB, Eitzen I, *et al*. Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23:171–7.
11 Palmieri-Smith RM, Lepley LK. Quadriceps strength asymmetry after anterior cruciate ligament reconstruction alters knee joint biomechanics and functional performance at time of return to activity. *Am J Sports Med* 2015;43:1662–9.
12 Gardinier ES, Di Stasi S, Manal K, *et al*. Knee contact force asymmetries in patients who failed return-to-sport readiness criteria 6 months after anterior cruciate ligament reconstruction. *Am J Sports Med* 2014;42:2917–25.
13 Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. *Nat Rev Rheumatol* 2016;12:92–101.
14 Hart HF, Culvenor AG, Guermazi A, *et al*. Worse knee confidence, fear of movement, psychological readiness to return-to-sport and pain are associated with worse function after ACL reconstruction. *Physical Therapy in Sport* 2019.
15 Pinczewski LA, Lyman J, Salmon LJ, *et al*. A 10-year comparison of ACLR with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. *Am J Sports Med* 2007;35:564–74.
16 Losciale JM, Bullock G, Cromwell C, *et al*. Hop testing lacks strong association with key outcome variables after primary anterior cruciate ligament reconstruction: a systematic review. *Am J Sports Med* 2019:363546519838794.
17 Wellsandt E, Axe MJ, Snyder-Mackler L. Poor performance on Single-Legged hop tests associated with development of posttraumatic knee osteoarthritis after anterior cruciate ligament injury. *Orthop J Sports Med* 2018;6:232596711881077.
18 Culvenor AG, Lai CCH, Gabbe BJ, *et al*. Patellofemoral osteoarthritis is prevalent and associated with worse symptoms and function after hamstring tendon autograft ACL reconstruction. *Br J Sports Med* 2014;48:435–9.
19 Culvenor AG, Collins NJ, Vicenzino B, *et al*. Predictors and effects of patellofemoral pain following hamstring-tendon ACL reconstruction. *J Sci Med Sport* 2016;19:518–23.
20 Pollard TC, Gwilym SE, Carr AJ. The assessment of early OA. *J Bone Joint Surg Br* 2008;90:411–21.
21 Hunter DJ, Zhang W, Conaghan PG, *et al*. Responsiveness and reliability of MRI in knee osteoarthritis: a meta-analysis of published evidence. *Osteoarthritis Cartilage* 2011;19:589–605.
22 Patterson BE, Culvenor AG, Barton CJ, *et al*. Patient-reported outcomes 1 to 5 years after ACL reconstruction: effect of combined injury, and associations with MRI-defined osteoarthritis features. *Arthritis Care Res* 2019. doi:10.1002/acr.23854. [Epub ahead of print: 14 Feb 2019].
23 Yusuf E, Kortekaas MC, Watt I, *et al*. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis* 2011;70:60–7.
24 Logerstedt D, Grindem H, Lynch A, *et al*. Single-legged hop tests as predictors of self-reported knee function after anterior cruciate ligament reconstruction. *Am J Sports Med* 2012;40:2348–56.
25 Grindem H, Logerstedt D, Eitzen I, *et al*. Single-legged hop tests as predictors of self-reported knee function in nonoperatively treated individuals with anterior cruciate ligament injury. *Am J Sports Med* 2011;39:2347–54.
26 Culvenor AG, Collins NJ, Guermazi A, *et al*. Early Patellofemoral osteoarthritis features one year after anterior cruciate ligament reconstruction: symptoms and quality of life at three years. *Arthritis Care Res* 2016;68:784–92.
27 Menzer H, Slater LV, Diduch D, *et al*. The utility of objective strength and functional performance to predict subjective outcomes after anterior cruciate ligament reconstruction. *Orthop J Sports Med* 2017;5:232596711774475.
28 Bodkin S, Goetschius J, Hertel J, *et al*. Relationships of muscle function and subjective knee function in patients after ACL reconstruction. *Orthop J Sports Med* 2017;5:232596711771904.
29 Grindem H, Eitzen I, Snyder-Mackler L, *et al*. Online registration of monthly sports participation after anterior cruciate ligament injury: a reliability and validity study. *Br J Sports Med* 2014;48:748–53.
30 Marx RG, Connor J, Lyman S, *et al*. Multirater agreement of arthroscopic grading of knee articular cartilage. *Am J Sports Med* 2005;33:1654–7.
31 Altman RD, Hochberg M, Murphy WA, *et al*. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage* 1995;3:3–70.
32 Gustavsson A, Neeter C, Thomeé P, *et al*. A test battery for evaluating hop performance in patients with an ACL injury and patients who have undergone ACL reconstruction. *Knee Surg Sports Traumatol Arthr* 2006;14:778–88.
33 Reid A, Birmingham TB, Stratford PW, *et al*. Hop testing provides a reliable and valid outcome measure during rehabilitation after ACLR. *Phys Ther* 2007;87:337–49.
34 Munro AG, Herrington LC. Between-session reliability of four hop tests and the agility t-test. *J Strength Cond Res* 2011;25:1470–7.
35 Thorstensson CA*et al*. Reduced functional performance in the lower extremity predicted radiographic knee osteoarthritis five years later. *Ann Rheum Dis* 2004;63:402–7.
36 Burgi CR, Peters S, Ardern CL, *et al*. Which criteria are used to clear patients to return to sport after primary ACL reconstruction? A scoping review. *Br J Sports Med* 2019;53:1154–61.
37 Grindem H, Snyder-Mackler L, Moksnes H, *et al*. Simple decision rules can reduce reinjury risk by 84% after ACL reconstruction: the Delaware-Oslo ACL cohort study. *Br J Sports Med* 2016;50:804–8.
38 Kyritsis P, Bahr R, Landreau P, *et al*. Likelihood of ACL graft rupture: not meeting six clinical discharge criteria before return to sport is associated with a four times greater risk of rupture. *Br J Sports Med* 2016;50:946–51.
39 Hunter DJ, Guermazi A, Lo GH, *et al*. Evolution of semi-quantitative whole joint assessment of knee oa: MOAKS (MRI osteoarthritis knee score). *Osteoarthritis Cartilage* 2011;19:990–1002.
40 Runhaar J, Schiphof D, van Meer B, *et al*. How to define subregional osteoarthritis progression using semi-quantitative MRI osteoarthritis knee score (MOAKS). *Osteoarthritis Cartilage* 2014;22:1533–6.
41 Collins NJ, Misra D, Felson DT, *et al*. Measures of knee function: international knee documentation Committee (IKDC) subjective knee evaluation form, knee injury and osteoarthritis outcome score (KOOS), knee injury and osteoarthritis outcome score physical function short form (KOOS-PS), knee outcome survey activities of daily living scale (KOS-ADL), Lysholm knee scoring scale, Oxford knee score (OKS), Western Ontario and McMaster universities osteoarthritis index (WOMAC), activity rating scale (ARS), and Tegner activity score (Tas). *Arthritis Care Res* 2011;63:S208–28.
42 Lo GH, McAlindon TE, Niu J, *et al*. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2009;17:1562–9.
43 Hunter DJ, Zhang Y, Niu J, *et al*. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum* 2006;54:1529–35.
44 Everhart JS, Best TM, Flanigan DC. Psychological predictors of anterior cruciate ligament reconstruction outcomes: a systematic review. *Knee Surg Sports Traumatol Arthrosc* 2015;23:752–62.
45 Ebert JR, Edwards P, Yi L, *et al*. Strength and functional symmetry is associated with post-operative rehabilitation in patients following anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc* 2018;26:2353–61.
46 Culvenor AG, Segal NA, Guermazi A, *et al*. Sex-Specific influence of quadriceps weakness on worsening Patellofemoral and Tibiofemoral cartilage damage: a prospective cohort study. *Arthritis Care Res* 2019;71:1360–5.
47 Turkiewicz A, Timpka S, Thorlund JB, *et al*. Knee extensor strength and body weight in adolescent men and the risk of knee osteoarthritis by middle age. *Ann Rheum Dis* 2017;76:1657–61.
48 van Meer BL, Meuffels DE, van Eijsden WA, *et al*. Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. *Br J Sports Med* 2015;49:975–83.
49 Macri EM, Patterson BE, Crossley KM, *et al*. Does patellar alignment or trochlear morphology predict worsening of patellofemoral disease within the first 5 years after anterior cruciate ligament reconstruction? *Eur J Radiol* 2019;113:32–8.
50 Culvenor AG, Cook JL, Collins NJ, *et al*. Is patellofemoral joint osteoarthritis an under-recognised outcome of anterior cruciate ligament reconstruction? A narrative literature review. *Br J Sports Med* 2013;47:66–70.
51 Ericsson YB, Roos EM, Frobell RB. Lower extremity performance following ACL rehabilitation in the KANON-trial: impact of reconstruction and predictive value at 2 and 5 years. *Br J Sports Med* 2013;47:980–5.
52 An VV, Scholes C, Mhaskar VA, *et al*. Limitations in predicting outcome following primary ACL reconstruction with single-bundle hamstring autograft - A systematic review. *Knee* 2017;24:170–8.
53 Ardern CL, Österberg A, Sonesson S, *et al*. Satisfaction with knee function after primary anterior cruciate ligament reconstruction is associated with self-efficacy, quality of life, and returning to the Preinjury physical activity. *Arthroscopy* 2016;32:1631–8.
54 Ardern CL, Österberg A, Tagesson S, *et al*. The impact of psychological readiness to return to sport and recreational activities after anterior cruciate ligament reconstruction. *Br J Sports Med* 2014;48:1613–9.
55 Feucht MJ, Cotic M, Saier T, *et al*. Patient expectations of primary and revision anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc* 2016;24:201–7.

56 Hart HF, Collins NJ, Ackland DC, *et al*. Is impaired knee confidence related to worse kinesiophobia, symptoms, and physical function in people with knee osteoarthritis after anterior cruciate ligament reconstruction? *J Sci Med Sport* 2015;18:512–7.
57 Grindem H, Arundale AJ, Ardern CL. Alarming underutilisation of rehabilitation in athletes with anterior cruciate ligament reconstruction: four ways to change the game. *Br J Sports Med* 2018;52:1162–3.
58 Culvenor AG, Perraton L, Guermazi A, *et al*. Knee kinematics and kinetics are associated with early patellofemoral osteoarthritis following anterior cruciate ligament reconstruction. *Osteoarthritis Cartilage* 2016;24:1548–53.
59 Culvenor AG, Patterson BE, Guermazi A, *et al*. Accelerated return to sport after anterior cruciate ligament reconstruction and early knee osteoarthritis features at 1 year: an exploratory study. *PM R* 2018;10:349–56.
60 Øiestad BE, Holm I, Risberg MA. Return to pivoting sport after ACL reconstruction: association with osteoarthritis and knee function at the 15-year follow-up. *Br J Sports Med* 2018;52:1199–204.
61 Whittaker JL, Roos EM. A pragmatic approach to prevent post-traumatic osteoarthritis after sport or exercise-related joint injury. *Best Pract Res Clin Rheumatol* 2019;33:158–71.
62 Toomey CM, Whittaker JL, Nettel-Aguirre A, *et al*. Higher fat mass is associated with a history of knee injury in youth sport. *J Orthop Sports Phys Ther* 2017;47:80–7.
63 Wellsandt E, Failla MJ, Snyder-Mackler L. Limb symmetry indexes can overestimate knee function after anterior cruciate ligament injury. *J Orthop Sports Phys Ther* 2017;47:334–8.
64 Carey DL, Crossley KM, Whiteley R, *et al*. Modeling training loads and injuries: the dangers of Discretization. *Med Sci Sports Exerc* 2018;50:2267–76.
65 Ardern CL, Taylor NF, Feller JA, *et al*. Sports participation 2 years after anterior cruciate ligament reconstruction in athletes who had not returned to sport at 1 year: a prospective follow-up of physical function and psychological factors in 122 athletes. *Am J Sports Med* 2015;43:848–56.

Appendix Q: Chapter 6 Supplementary File A, Sensitivity analysis

Chapter 6 Supplementary File A, Table 1. Functional performance at one year and risk of worsening early osteoarthritis features up to five years˜

		Worsening osteoarthritis features on MRI^				
		PF Cartilage	**PF BML**	**TF Cartilage**	**TF BML**	**TF Meniscal**
		n=136/312(44%)	*n=56/780 (18%)*	*n=160/780 (21%)*	*n=120/780 (15%)*	*n=102/468 (22%)*
Functional battery (ref ≥90% LSI all tests; n=13(18%)	n (%) meeting criteria	Ref ≥90%LSI all 4	Ref ≥90%LSI all 4	Ref ≥90%LSI all 4	Ref ≥90%LSI all 4	Ref ≥90%LSI all 4
Poor function any 3 tests*	*13(18%)*	1.37 (0.34, 5.51)	**3.95 (1.02, 15.36)**	0.85 (0.16, 4.61)	1.56 (0.16, 14.62)	1.77 (0.41, 7.59)
Poor function any 2 tests*	*19(26%)*	1.70 (0.53, 5.45)	1.44 (0.23, 9.03)	2.84 (0.92, 8.74)	1.10 (0.10, 11.74)	1.24 (0.28, 5.40)
Poor function any 1 test*	*19(26%)*	1.18 (0.32, 4.31)	0.31 (0.03, 3.26)	3.41 (0.78, 14.86)	2.83 (0.20, 40.15)	1.11 (0.26, 4.83)
Poor function ≥ 3 tests*	*60(83%)*	1.40 (0.74, 2.66)	**5.65 (1.87, 16.99)**	0.42 (0.12, 1.54)	1.03 (0.30, 3.52)	1.49 (0.53, 4.12)
Poor function ≥ 2 tests*	*41(56%)*	1.49 (0.77, 2.90)	**6.92 (1.87, 21.22)**	1.04 (0.22, 4.91)	0.64 (0.23, 1.78)	1.41 (0.52, 3.82)
Poor function ≥ 1 test*	*22(30%)*	1.21 (0.58, 2.56)	2.24 (0.56, 8.98)	1.52 (0.54, 4.26)	0.72 (0.15, 3.49)	1.23 (0.42, 3.66)

LSI=limb symmetry index; BML=bone marrow lesion; PF=patellofemoral; TF=tibiofemoral; MRI=magnetic resonance imaging.
˜Values are risk ratios (95% confidence intervals). Analysis performed in n=73; 5 participants were not included as they could not perform a valid test on both the ACLR and contralateral limb for the one-leg rise.
^A risk ratio >1 represents a greater risk of the OA feature worsening in the presence of poor functional performance. For example, individuals with <90% LSI on the one-leg-rise were 3.67 times more likely to have worsening patellofemoral BMLs, than those with >90% LSI. **Bold** values indicate a statistically significant association (p<0.05).
*Poor functional performance was defined as <90% LSI.

Chapter 6 Supplementary File A, Table 2. Functional performance at one year post-ACLR: Relationships with change in KOOS and IKDC between one and five years~

		Change in KOOS and IKDC between 1 and 5 years^				
		KOOS-Symptoms	**KOOS-Pain**	**KOOS-Sport**	**KOOS-QoL**	**IKDC**
Functional battery (ref ≥90% LSI all tests; n=14(18%)	n (%) meeting criteria					
Poor function all 4 tests*	*10(13%)*	2.94 (-8.83, 14.72)	-1.11 (-7.33, 5.11)	5.53 (-9.27, 20.33)	4.78 (-7.68, 17.25)	3.19 (-4.68, 11.07)
Poor function any 3 tests*	*14(18%)*	8.27 (-2.72, 19.27)	1.71 (-4.01, 7.45)	3.24 (-8.62, 15.10)	1.97 (-9.09, 13.04)	1.12 (-5.82, 8.06)
Poor function any 2 tests*	*20(27%)*	**10.45 (0.31, 20.59)**	4.01 (-1.27, 9.30)	7.49 (-3.49, 1848)	**11.75 (1.79, 21.70)**	**8.79 (2.50, 15.07)**
Poor function any 1 test*	*18(24%)*	0.52 (-9.35, 10.41)	1.19 (4.01, 6.38)	4.34 (-6.43, 15.12)	1.72 (-8.18, 11.63)	0.46 (-5.73, 6.67)
Poor function ≥ 3 tests*	*24 (32%)*	0.87 (-6.74, 8.50)	-1.63 (-5.44, 2.27)	-0.64 (-8.96, 7.68)	-2.84 (-10.77, 5.07)	-2.43 (-7.53, 2.68)
Poor function ≥ 2 tests*	*44 (58%)*	**7.89 (0.60, 15.18)**	1.64 (-2.15, 5.44)	3.46 (-4.45, 11.36)	6.78 (-0.42, 13.97)	**5.34 (0.67, 10.02)**
Poor function ≥ 1 test*	*62 (82%)*	5.04 (-3.36, 13.44)	1.72 (-2.63, 6.08)	5.06 (-3.87, 13.98)	5.20 (-3.40, 13.79)	3.30 (-2.20, 8.85)

LSI=limb symmetry index; KOOS=Knee injury and Osteoarthritis Outcome Score; QoL= quality of life; IKDC= International Knee Documentation Committee subjective knee evaluation.
~Values are beta co-efficient (95% confidence intervals). Analysis performed in n=76; 5 participants were not included as they could not perform a valid test on both the ACLR and contralateral limb for the one-leg rise.
* Poor functional performance was defined as <90% LSI.
^The beta coefficient represents the adjusted difference in KOOS or IKDC in the presence of the dichotomous exposure variables (i.e., poor function defined as <90% LSI).
For example, those with <90% LSI had on average 7.89 points greater improvement on the KOOS-QoL than those with >90%. **Bold** values indicate a statistically significant association (p<0.05).

Appendix R: Chapter 8 Supplementary File A – CONSORT checklist

CONSORT checklist of information to include when reporting a pilot trial*

Section/topic and item No	Standard checklist item	Extension for pilot trials	Section where item is reported
Title and abstract			
1a	Identification as a randomised trial in the title	Identification as a pilot or feasibility randomised trial in the title	8.1
1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	NA
Introduction			
Background and objectives:			
2a	Scientific background and explanation of rationale	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	8.2
2b	Specific objectives or hypotheses	Specific objectives or research questions for pilot trial	8.2
Methods			
Trial design:			
3a	Description of trial design (such as parallel, factorial) including allocation ratio	Description of pilot trial design (such as parallel, factorial) including allocation ratio	8.3.1 8.3.5
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	8.3.4
Participants:			
4a	Eligibility criteria for participants		8.3.3
4b	Settings and locations where the data were collected		8.3.2
4c		How participants were identified and consented	8.3.1 8.3.2
Interventions:			
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered		8.4 Appendix S Appendix T
Outcomes:			
6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	8.5 8.6
6b	Any changes to trial outcomes after the trial commenced, with reasons	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	
6c		If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	8.5 Table 8.2
Sample size:			
7a	How sample size was determined	Rationale for numbers in the pilot trial	8.8
7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:			
Sequence generation:			
8a	Method used to generate the random allocation sequence		8.3.5
8b	Type of randomisation; details of any restriction (such as blocking and block size)	Type of randomisation(s); details of any restriction (such as blocking and block size)	
Allocation concealment mechanism:			
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		
Implementation:			
10	Who generated the random allocation sequence, enrolled participants, and assigned participants to interventions		
Blinding:			
11a	If done, who was blinded after assignment to interventions (eg, participants, care providers, those assessing outcomes) and how		8.3.5
11b	If relevant, description of the similarity of interventions		
Analytical methods:			
12a	Statistical methods used to compare groups for primary and secondary outcomes	Methods used to address each pilot trial objective whether qualitative or quantitative	8.5
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable	
Results			
Participant flow (a diagram is strongly recommended):			
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	Figure 8.1 Table 8.2 Table 8.4
13b	For each group, losses and exclusions after randomisation, together with reasons		Figure 8.1 Table 8.2 Table 8.4
Recruitment:			

14a	Dates defining the periods of recruitment and follow-up		8.3.3
14b	Why the trial ended or was stopped	Why the pilot trial ended or was stopped	
Baseline data:			
15	A table showing baseline demographic and clinical characteristics for each group		Table 8.3
Numbers analysed:			
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Figure 8.1 Table 8.2 Table 8.4
Outcomes and estimation:			
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	8.9 Table 8.2 Table 8.4
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable	
Ancillary analyses:			
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	Results of any other analyses performed that could be used to inform the future definitive trial	Table 8.2 -
Harms:			
19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)		Table 8.2
19a		If relevant, other important unintended consequences	
Discussion			
Limitations:			
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	8.10
Generalisability:			
21	Generalisability (external validity, applicability) of the trial findings	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	8.10
Interpretation:			
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	8.10
22a		Implications for progression from pilot to future definitive trial, including any proposed amendments	
Other information			
Registration:			
23	Registration number and name of trial registry	Registration number for pilot trial and name of trial registry	8.3.1
Protocol:			
24	Where the full trial protocol can be accessed, if available	Where the pilot trial protocol can be accessed, if available	
Funding:			
25	Sources of funding and other support (such as supply of drugs), role of funders		
26		Ethical approval or approval by research review committee, confirmed with reference number	8.3.1

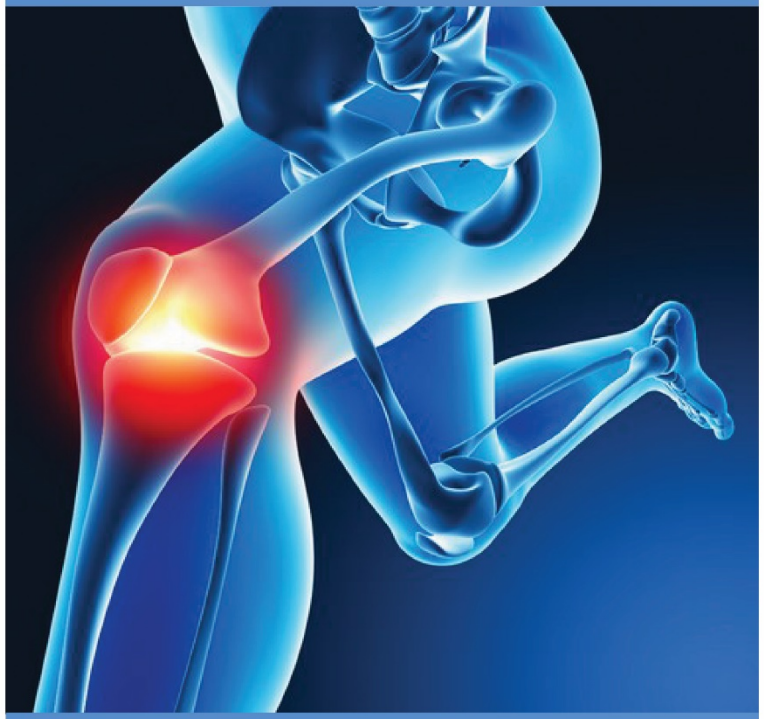
*Here a pilot trial means any randomised study conducted in preparation for a future definitive RCT, where the main objective of the pilot trial is to assess feasibility.

Appendix S: Chapter 8 Supplementary File B – Physiotherapy manual

To download the PDF of the **physiotherapy intervention manual** please click here.

PROJECT DETAILS

An exploration of the feasibility of a randomised clinical trial for physiotherapy intervention in patients at high risk of early-onset knee osteoarthritis and symptomatic decline following anterior cruciate ligament reconstruction.



Investigators: Ms Brooke Patterson, Professor Kay Crossley, Dr Adam Culvenor, and Dr Christian Barton.

If you have any questions relating to the project please contact Chief Investigator – Professor Kay Crossley. This project is approved by the La Trobe Human Ethics Committee (HEC-16-077)

Please remember – investigator Brooke Patterson is blinded to patient group

INTRODUCTION

This exercise-therapy and education protocol is a guide for treating physiotherapists in a pilot randomised controlled trial who are treating individuals who have undergone ACL reconstruction 12-15 months prior and have been identified at risk of early osteoarthritis progression and symptomatic decline. The guide contains both our intervention (lower-limb focussed) and control (trunk-focussed) protocols.

The lower-limb focussed program *(note patient-facing name: "Kangaroo")* is based on the best available evidence and by a group of experienced clinician researchers in the ACL and musculoskeletal field. People following ACLR continue to have persistent lower -imb neuromuscular deficits, do not return to sport, and have reduced quality of life. Rehabilitation requires great commitment from the patient and the therapist, and there are multiple areas to work on and monitor.

Every patient is different and the purpose of this guide is not to produce a recipe, as it allows for varying levels of ability and goals. We have chosen key areas or "tasks" that we believe are most important to recovery in this population, with each task having multiple phases to allow for individualisation.

This exercise therapy and education protocol for the trunk-focussed group *(note patient facing name: "Devil") is* outlined on Page 17-19

Brooke Patterson Dr Adam Culvenor

Professor Kay Crossley Dr Christian Barton

La Trobe University Sports and Exercise Medicine Centre

For further information and many more sports medicine related topics visit: http://semrc.blogs.latrobe.edu.au

PHYSIOTHERAPY PROGRAM: TASK PROJECT (Group: Kangaroo) Participant ID:

This booklet contains:

- Exercise protocol and progressions
- Physiotherapist clinical notes and attendance record
- Educational resources and handouts
- **Other resources you may need:**
- Administrative procedures physiotherapy handbook

OVERVIEW OF PROGRAM (lower-limb focussed ntervention)

1. General

This exercise therapy and education program is designed for every patient to progress at his or her own pace and ability. Patients are to attend 8 face-to-face physiotherapy sessions of 30 minutes duration. Therapists are to use the treatment sessions to progress through each "task" (target area) individually ensuring that the patient is challenged and working towards a strength and/or power dosage as recommended by resistance training principles.

2. Exercise therapy protocol

These "tasks" comprise of various muscle groups and movements that must be targeted after ACL reconstruction. Each task has at least 3 phases of difficulty, and guides for progression criteria. Patients can be on different phases of difficulty for different tasks. I.e. Phase 1 of balance, and Phase 3 of calf.

TASK 1: Movement rretraining (walk – run – jump- land – cut)

TASK 2: Squat

TASK 3: Balance

TASK 4: Hip stabilisers

TASK 5: Calf

TASK 6: Trunk

TASK 7: Hip extensors

TASK 8: Cardiovascular/sport

It may not be appropriate for patients to be completing exercises in all tasks - use clinical reasoning to prescribe exercises based on the patient's needs, goals and level of adherence.

3. Independent Exercise Program

Encourage patients to complete the exercise-therapy program a minimum 3x week. Use clinical reasoning if appropriate to prescribe more or less and combine with sporting activities.

OVERVIEW OF PROGRAM

4. Manual therapy

If appropriate you may perform manual therapy if impairments such as pain, swelling, range of motion or joint mobility is affecting the patient's ability to perform the exercises. Please follow the treatment algorithm on Page 14.

Prescribing other mobility and stretching exercises may be appropriate if you deem range of motion or muscle length is affecting the patient's ability to perform an exercise (i.e. hip flexor/quadriceps length affecting bridge

5 Education

It is important to educate the patients on the level of commitment required to benefit from a resistance training program, achieve adequate physical and psychological criteria to return to sport, and independently manage their knee joint health in the long term. Remind patients of the following expectations, and provide them with the handouts (Page20 to 34) as you deem appropriate.

Time:
Exercises at least 3 x week.
Dependent on the level of recovery, ability, and goals of the individual.

Equipment:
When they will need to access the gym.

Return to sport:
Does the patient want to get back to previous level of activity? When?
Based on achievement of specific goals (strength, level of functioning), not time.

Clinicians should follow the guide for return to running and return to sport outlined on Page 35-36. Each of the outcome measures related to the criteria are outlined on Page 37-44.

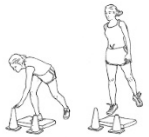
Provide patients with the leaflets on Page to 20-34 and provide face-to-face education as appropriate.

TASK 1: MOVEMENT RETRAINING					Physiotherapy Log
	Straight Line	Landing	Lateral	Multidirectional	
Phase 1	"Walking drills" Normal gait	"Landing technique" Walk through and teach key points	"Lateral movement technique" Walk through and teach key points	See Video: Cutting technique Walk through and teach key points	Session (_): Date: Phase + Dosage:
Dosage*	Complete 10 minutes of 1:1 movement technique with physio At home: 10 sets of 5 (rest 30s), daily				
Phase 2	"Running program" (see Task 8)	"Jump series" (Increase height/length) with: - On spot - Forwards - On to step - Off step (progress to with a jump)	"Lateral movement technique" Progress through the following - Step lateral, shift weight and touch cone - Moving sidesteps – without resistance, with theraband, increase speed - Bounding side to side	"Agility Program" 45 – 90 – 135 – 180 degree cuts	Session (_): Date: Phase + Dosage: Session (_): Date: Phase + Dosage:
Dosage*	As per Task 8 graduated	5 sets of 5 reps max effort BW (rest 60s) max effort. 3 x week		As per program on Task 8 graduated	Session (_): Date: Phase + Dosage:
Phase 3	Sprinting program (see Task 8) "Running program" PHYSITRACK	"Hop series" - as per jump series above	"Side jump series" - Increase speed/decrease contact time - Over hurdles/step	Multidirectional and unanticipated – Including individual & partner skill drills	Session (_): Date: Phase + Dosage:
Dosage*	As per Task 8 graduated	5 sets of 5 reps max effort BW (rest 60s. 3 x week)		As per program on Task 8 graduated	
Phase 4	Acceleration/ Deceleration/ program (see Task 8) "Running program" PHYSITRACK	Any advanced landing specific to sport and integrate sport specific skills	"Side hop series" - Increase speed / decrease contact time - Over hurdles/step	Integrate into non contact training drills	Session (_): Date: Phase + Dosage: Session (_): Date: Phase + Dosage:
Dosage*	As per Task 8 graduated	5 sets of 5 reps max effort BW (rest 60s) 3 x week		As per program on Task 8 graduated	Session (_): Date: Phase + Dosage:

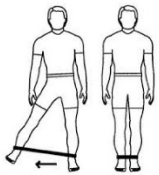
*Pass once completed set dosage + correct technique/functional alignment/area of fatigue, nil response of pain (<2/10) or swelling.

TASK 2: SQUATS		Physiotherapy Log
Phase 1	Wall Sit Progress: - Depth 30 - 90 degrees**	Session (_): Date: Phase + Dosage:
Dosage	3 sets of 60s isometric (rest 60s) BW. 3 x week	Session (_): Date: Phase + Dosage:
Progress to Phase 2*	Able to DL BW Squat x 15 <2/10 pain OR Wall Sit to 90 degrees	
Phase 2	Squatting Series** Double leg Options - "Squat" - "Squat" – dumbells "Squat" – barbell back squat	Session (_): Date: Phase + Dosage:
	Single Leg Options - "Single Leg Rise" assisted - "Single Leg Rise" unassisted - "Single Leg Rise" with external load (5 - 15kg) - "Single leg squat" +/- load	Session (_): Date: Phase + Dosage: Session (_): Date: Phase + Dosage:
Dosage **3 x week**	3 x 10-12 reps (3s down, 0 hold, 2s up) (60s rest) Fatigue at 12 reps Can be doing DL and SL exercise coinciding 3 x week : Double leg 3 x week: Single leg	Session (_): Date: Phase + Dosage:
Progress to Phase 3*	Able to squat DL Body Weight external load	
Phase 3	Squatting Series (Power)** As above different dosage Advanced – jump / hop with smith machine bar / load	Session (_): Date: Phase + Dosage:
Dosage **3 x week**	5-10 repetitions, 3-5 sets (2s down, 0 hold, 1s up) (60-90s rest) Progress load as appropriate Note: Patient can be doing DL and SL strengthening at the same time. For example, Phase 2 (double or single) exercise in the same session or 2 x week Phase 2, and 1 x week Phase 3	Session (_): Date: Phase + Dosage:

*Pass once completed set dosage + correct technique/functional alignment/area of fatigue, nil response of pain (<2/10) or swelling.
**Depth as appropriate for patient (their anatomy/ROM, goals, pathology)

TASK 3: BALANCE		Description of Exercise	Physiotherapy Log
Phase 1	"SLS" (Eyes Open -> Eyes Closed)	Focus on early awareness of: - Foot control - Gluteal activation and pelvic position - Alignment of shoulder, hip, knee, foot	Session (_): Date: Phase + Dosage:
Dosage	3 x 30s hold each side (0s rest). Daily#		
Progress to Phase 2*	15s eyes closed each side good control, no loss of balance		
Phase 2	"SLS Bosu" (Eyes Open -> Closed) Bosu ball/foam/Pillow at home		Session (_): Date: Phase + Dosage:
Dosage	3 x 30s hold each side (0s rest). Daily#		
Progress to Phase 3*	15s eyes closed each leg good control, no loss of balance		Session (_): Date: Phase + Dosage:
Phase 3	"Balance and reach" - Hand to cones /throwing task - Toe to cones - Progress distance appropriate to patient size - Progress to foam		Session (_): Date: Phase + Dosage:
Dosage	3 x 10 touches each side (2s down 2s up) (0s rest). Minimum 3 x week		
Progress to Phase 4*	10 each side with good control, no loss of balance		Session (_): Date: Phase + Dosage:
Phase 4	"Advanced Balance series 1 or 2" (can vary it) i) Various balancing on ½ foam roller / beam ii) +/- Skills iii) Up to discretion of physio – make sport specific Alternatives on Physitrack – "curtsy slide' "Jump on off bosu"		Session (_): Date: Phase + Dosage:
Dosage	3 x 60s duration (60s rest). Minimum 3 x week		
Ongoing progression *	Continue to challenge patient as appropriate or specific to their sport.		Session (_): Date: Phase + Dosage: Session (_): Date: Phase + Dosage:

*Pass once completed set dosage + correct technique/functional alignment/area of fatigue, nil response of pain (<2/10) or swelling.
#In Physitrack "add exercise" go to appropriate balance exercise and click add to specific "off" days – usually 2,4,6,7.

TASK 4: Hip		Description of Exercise	Physiotherapy Log
Phase 1	Side-lying hip abduction Progress: - Theraband resistance (Yellow – Green – Blue) and length	 *Emphasise posterior pelvic tilt* *"Heel behind hip"/don't let leg drift forward* *trunk position/don't let back push into ground*	Session (_): Date: Phase + Dosage:
Dosage	3 x 10-12 (3s up, 1s hold, 3s down) each side to 45 degrees (swap 0s rest) Load: BW or theraband to fatigue at 12 reps/12RM If BW - 5 x week Theraband – 3 x week		Session (_): Date: Phase + Dosage:
Progress to Phase 2*	3 x 10-12 blue theraband (15cm length when tied) to 30 degrees		Session (_): Date: Phase + Dosage:
Phase 2	Standing Hip Abduction Resisted Progress: - Theraband resistance (Yellow – Green – Blue) and length	*Light upper limb support allowed* 	
Dosage	3 x 10-12 (3s out, 1s hold, 3s in) each side to 30 degrees (swap 0s rest) Load: BW or theraband to fatigue at 12 reps/12RM 3 x week		Session (_): Date: Phase + Dosage:
Progress to Phase 3*	3 x 10-2 blue theraband (15cm length when tied) to 30 degrees		Session (_): Date: Phase + Dosage:
Phase 3	Standing Hip Abduction Cables Progress: - External load	Alternatively gold/silver theraband can provide sufficient resistance 	
Dosage **3 x week**	3 x 8-10 (3s up, 1s hold, 3s down) each side to 30 degrees (swap 0s rest) Load: BW or theraband to fatigue at 10 reps/10RM	*Light upper limb support allowed*	Session (_): Date: Phase + Dosage: Session (_): Date: Phase + Dosage: Session (_): Date: Phase + Dosage:

**Pass once completed set dosage + correct technique/functional alignment/area of fatigue, nil response of pain (<2/10) or swelling.
**If struggling with activation, give as 7x week activation work (i.e. pillow between legs). Adjust accordingly in Physitrack 7x week for this exercise

TASK 5: Calf		Description of Exercise	Physiotherapy Log
Phase 1	"Calf Raise" Bilat - BW Double Leg "Soleus Raise" – BW Double Leg	*Emphasise medial calf /foot intrinsic/Pushing through big toe* *Focus on technique, foot control* *Note focus on patient deficits and bias knee extended vs knee flexed as appropriate*	Session (_): Date: Phase + Dosage:
Dosage	3 x 30 (2s up 1s hold 2s down) (Rest 30s) Full available ROM 5 x week 3 sessions: KE 2 sessions: KF (or vice versa depending on patient)		Session (_): Date: Phase + Dosage:
Progress to Phase 2*	3 x 20 body weight correct fatigue area and form		
Phase 2	"SL Calf Raise" - Body Weight "SL Soleus Raise" – Body Weight		Session (_): Date: Phase + Dosage:
Dosage	3 x 15 - 30 (2s up 1s hold 2s down) (Rest 30s) Full available ROM 3 x week /every 2nd day 2 sessions: KE 1 sessions: KF (or vice versa depending on patient)		Session (_): Date: Phase + Dosage:
Progress to Phase 3*	1. 3 x 25 BW 2. >95% LSI (max reps compared side to side)		
Phase 3	"SL Calf Raise - off Step" (Body Weight) "SL Soleus Raise - off Step" (Body Weight)		Session (_): Date: Phase + Dosage:
Dosage **3 x week**	3 x 10-12 (2s up 1s hold 2s down) (Rest 30s) 3 x week/every 2nd day 2 sessions: KE 1 sessions: KF (or vice versa depending on patient)		Session (_): Date: Phase + Dosage:
Progress to Phase 4*	1. 3 x 25 BW 2. >95% LSI (max reps compared side to side)		Session (_): Date: Phase + Dosage:
Phase 4	"SL Calf Raise off Step" with external load "SL Soleus Raise off Step" with external load	Note: option for Smith Machine Seated for soleus	
Dosage	3 x 12 (2s up, 1s hold, 2s down) (Rest 30s) Full available ROM 3 x week /every second day 2 sessions: KE 1 sessions: KF (or vice versa depending on patient)		Session (_): Date: Phase + Dosage:
Ongoing progressions	Continue to build load to maintain dosage 3 8-12RM		

*Pass once completed set dosage + correct technique/functional alignment/area of fatigue, nil response of pain (<2/10) or swelling.

TASK 6: TRUNK^		Physiotherapy Log
Phase 1	Bench Plank – 45 degrees – 30 degrees Progress: - Height of bench (45 – 30 – 15 degrees) to elbows on ground (0 degrees body angle)	Session (_): Date: Phase + Dosage:
Dosage	3 x 60s isometric hold (60s rest) 3 x week/every 2nd day	
Progress to Phase 2*	60s elbows on ground /0 degrees body angle with good trunk control	Session (_): Date: Phase + Dosage:
Phase 2	"Elbow Plank" Progress: - Push Up Plank - Push Up Plank with hip knee drive (+/-)theraband	Session (_): Date: Phase + Dosage:
Dosage	3 x 60s isometric hold (60s rest) 3 x week/every 2nd day Knee drive – 3 x 10 reps each side (2s out 2s in)	
Progress to Phase 2*	60s on knee drive with theraband	Session (_): Date: Phase + Dosage:
Phase 3	"Side plank series" (start on knees) Progress: - On toes and elbow - On toes and hand	Session (_): Date: Phase + Dosage:
Dosage	3 x 60s isometric hold (60s rest) 3 x week/every 2nd day	
Progress to Phase 2*	60s on toes with arm and leg raise	Session (_): Date: Phase + Dosage:
Phase 4	Rotational trunk series - Palov press or rotations with theraband or cable - Side plank with rotation with weight Other Physitrack options – cable woodchop	Session (_): Date: Phase + Dosage:
Dosage	3 x 12 reps (2s out, 2s in) (60s rest) 3 x week/every 2nd day	
Ongoing Progressions*	Continue to challenge patient as appropriate or specific to their sport.	Session (_): Date: Phase + Dosage:

**Pass once completed set dosage + correct technique/functional alignment/area of fatigue, nil response of pain (<2/10) or swelling.

Key points as per video:
- *Keep pelvis tucked/squeeze gluts*
- *Sink shoulder blades*
- *Neck neutral*
- *Reinforce into functional movements and activities*

TASK 7: Gluteal/Hamstring		Physiotherapy Log
Phase 1	Double Leg Bridge	Session (_): Date: Phase + Dosage:
Dosage	Activation: 3 x 15 reps (2s up, 2s down) + 20s hold (30s rest) 7 x week#	
Progress to Phase 2*	Feeling gluteals working for 3 x 20 DL Feels gluteals > hamstring working in SL trial	Session (_): Date: Phase + Dosage:
Phase 2	Single Leg bridge Progress: - Assisted to unassisted	
Dosage	3 x 15 reps (2s up, 2s hold 2s down) (60s rest) 3 x week/ every 2nd day	Session (_): Date: Phase + Dosage:
Progress to Phase 3*	Full height: 1. >95% LSI 2. > 15 reps max 3. Fatigue - mainly gluteals	Session (_): Date: Phase + Dosage:
Phase 3	Hamstring Bridge series (on bench) Progress: Double – single	
Dosage	3 x 15 (2s up, 2s down) (60s rest) 3 x week / every 2nd day	
Progress to Phase 4*	3 x 15 single leg	Session (_): Date: Phase + Dosage:
Phase 4	Hamstring Ball Curl series Progress:Double – single Combine with DL- do 3 SL and 9 DL	
Dosage	3 x 12 (2s out, 0 hold 2s in) (60s rest) 3 x week / every 2nd day	Session (_): Date: Phase + Dosage:
Phase 5	Nordics Progress: Assisted (theraband) – unassisted	
Dosage	3 x 4-6 (2s out, hold 2, 2s in) 3 x week / every 2nd day	Session (_): Date: Phase + Dosage:
Ongoing Progressions*	To physio discretion according to patient needs	Session (_): Date: Phase + Dosage:

*Pass once completed set dosage + correct technique/functional alignment/area of fatigue (as per video), nil response of pain (<2/10) or swelling.

#In Physitrack still delete Days 2, 4, 6, 7 still, then "Add exercise" go to exercise and click add to specific "off" days usually 2,4,6,7.

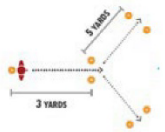
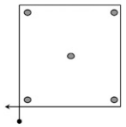
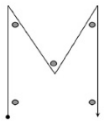
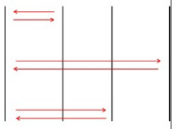
TASK 8: Sport Specific/Cardiovascular^		Description of Exercise	Physiotherapy Log
Phase 1	**Non-impact cross training**	Walking Bike Swimming Cross Trainer Deep water jogging Rowing	Session (_): Date: Phase + Dosage:
	Phase 1.1 10 mins		
	Phase 1.2 20 mins		
	Phase 1.3 30 mins		
	Phase 1.4 30 mins (inc 5x60s high intensity, 90s rest)		
	Phase 1.5 30 mins (inc 5x2mins high intensity, 120s rest)		
	Phase 1.6 45 mins with 15 mins high intensity	PLUS Non-impact Sport Specific Skills	Session (_): Date: Phase + Dosage:
Progress to Phase 2*	Return to Running Outcome Measures (See section 4.6)		
Phase 2*	**Running + Agility Program**	Note: distance/time can be catered to individual needs/sport At least one rest day between sessions	
	Phase 2.1 Run 15 minutes + 30 mins Phase 1		
	Phase 2.2 Run 20 minutes + 25 mins Phase 1	**Running progressions:** 1. Walk: jog (5:1, 4:2, 3:3, 2:4, 1:5) 2. Continuous	Session (_): Date: Phase + Dosage:
	Phase 2.3 Run 30 minutes + 20 mins Phase 1		
	Phase 2.4 Run 45 minutes inc 10 mins high intensity/agility	**High intensity progressions** Total time (10-20 minutes) can be made up of: 1. Straight line efforts 2. Straight line acceleration/deceleration 3. Agility program (example attached)	
	Phase 2.5 Run 50 minutes inc 20 mins high intensity/agility		Session (_): Date: Phase + Dosage:
Progress to Phase 3*	>90% Return to Sport Score		
Phase 3	**Non-Contact Training**	*Straight line efforts* Moderate speed i.e. 14 – 16km/hr or 75% High speed i.e. 16 – 20km/hr or 80-90% Sprint i.e. 20-23km/hr or 100%	
	Phase 3.1 Sport 15 minutes + 30 mins Phase 2 running		
	Phase 3.2 Sport 20 minutes + 25 mins Phase 2 running	Progress through levels Once completed 2 sessions at 100%move to next level. (120s rest btw sets)	Session (_): Date: Phase + Dosage:
	Phase 3.3 Sport 30 minutes + 20 mins Phase 2 running		
	Phase 3.4 Sport 45 minutes including 15 mins high intensity running /agility	Level 1: 2 x 200m on 90 secs, Repeat x 2 sets Level 2: 3 x 200m on 90 secs, Repeat x 2 sets Level 3: 3 x 200m, on 90 secs, Repeat x 3 sets	
	Phase 3.5 Sport 50 minutes including 20 mins high intensity running + 10 minutes low intensity running	*Acceleration/Deceleration:* As above with 2 x 40m spurts of 100% (accel at cone, decel at cone) 40m 100% 40m 100% 200m	Session (_): Date: Phase + Dosage:
Progress to Phase 4*	>95% RETURN TO SPORT SCORE		
Phase 4	**Full training**	Level 4: Complete Level 3, then 2 x 200m on 90secs with accel/decel, x 2 sets Level 5: Complete Level 3, then 3 x 300m, on 90secs with accel/decel, x 2 sets	
	Full training up to 1 hour 3 x week (no match play)		
	Full training up to 1.5 hour 3 x week (no match play)	Level 6: Complete Level 3, then 3 x 300m, on 90secs with accel/decel, x 3 sets	Session (_): Date: Phase + Dosage:
	Full training including match play up to 4 x week	Level 7: Complete as above, but with backpedal x 2 (3rd cone to 2nd cone, then 5th to 4th) (120s rest btw sets)	
Progress to Phase 5*	Dosage, nil adverse effects		
Phase 5	**Return to match play**	***Agility*** - See attached section: Note must have completed straight-line accel/decel Level 4 before can start 70% agility runs.	
	Match play 45-60 minutes x 1 week		Session (_): Date: Phase + Dosage:
	Full match load 60 minutes + 1 x week		
	Monitor for adverse effects		

*Pass once completed set dosage + correct technique/functional alignment/area of fatigue, nil response of pain (<2/10) or swelling.

ON PHYSITRACK – add the type of CVS exercise I.e. bike or running then add manually what running etc they are doing

AGILITY PROGRAM – on physitrack

Distance can be varied according to individual sport/fitness level

Drill	Angle Progressions	Speed % Max	Dosage
Phase 1 	45 degrees	70 80 90 100	3 X 5 3 X 4 3 X 3 3 X 2
Phase 2 	90 degrees	70 80 90 100	3 X 5 3 X 4 3 X 3 3 X 2 +/- 2 x 2 minutes skipping/ladder
Phase 3 	135 degrees	70 80 90 100	3 X 5 3 X 4 3 X 3 3 X 2 +/- 2 x 2 minutes skipping/ladder
Phase 4 	180 degrees	70 80 90 100	3 X 5 3 X 4 3 X 3 3 X 2 +/- 2 x 2 minutes skipping/ladder
Phase 5 - Walking grapevine 20m - Increased speed grapvine 20m - "S" bends - Run backwards 10m, turn and go R or L (anticipated – unanticipated)	Pivoting/twisting	70 80 90 100	X 6
Phase 6  	Multidirectional & unanticipated - Reaction ball Partner mirroring - Partner skill work non contact i.e. basketball defensive slides against ball carrier - Partner skill work contact i.e. basketball boxing out	70 80 90 100	10 - 20 minutes Integrate into individual skill and partner drills

TREATMENT GUIDE FOR TIER 1 – PASSIVE THERAPY

Target for treatment	Technique	Aim	Description	Dosage	Home Exercises	Timeline
Overactive secondary stabilisers	Soft tissue massage and trigger point release of pes anserine group, adductor group, vastus lateralis, rectus femoris, popletius, gastrocnemius group, hamstring group, gluteal/ITB	Address soft tissue restrictions with the aim of: Reducing pain Increasing knee joint range of movement Improving muscle activation Improving symptoms during function	Sustained digital pressure to each trigger point with the muscle positioned on stretch OR Massage longitudinally along the muscle belly	30-60 seconds digital pressure per trigger point 2-5 minutes of massage per muscle	Self release/trigger point/stretching of appropriate muscle group Foam Roller – 2 x 10 each muscle group. 2-3 x daily Spikey Ball- 3 x 30s each point. 2-3 x daily Stretching – 3 x 30s each group 2-3 x daily	As required/until passed Tier 1 criteria to enter Tier 2 Rehab Program. See Assessment Log Book for guidance.
Swelling/ Effusion	Patient education	Determine aggravating factors Educate about management of aggravating and addressing contributing factors	Education: Swelling vs joint effusion, inflammatory factors and cartilage Contributing factors to joint load	NA	Reducing aggravating factors to allow joint to settle Address contributing factors (range, strength, biomechanics)	
"PFJ" Anterior knee pain or stiffness felt on palpation	PFJ mobilisation techniques Taping techniques	Address PFJ mobility restrictions to improve knee joint range of movement, pain, muscle activation Alleviate PFJ contact pressure with taping, reduction of aggravation factors	Lateral-medial glides, grade 111 or IV in position of restriction i.e. sidelying 30 degrees Taping: rigid, kinesiology techniques	3-5 sets of 30-60 seconds	Self mobilisation/release of appropriate soft tissue structures Self taping Reducing aggravating factors/addressing contributing factors as above	
ROM	Various: Inc knee extension/flexion range of motion by addressing appropriate contributing factor:	Bony end feel Soft tissue soft end feel/muscle protective	Treat with respect STW as per above OR Hold relax techniques OR Gr II or IV physiological mobilisation	NA 2-5 minutes 3-5 sets, 30s hold 3-5 sets of 30-60s	Range of motion exercises at discretion of physiotherapist - AROM 5 daily x 20 - Prone Leg hang Self release if muscle protective	
Muscle weakness -Quad - Glut - Calf - Hamstring	Activation techniques	Improve activation through hands on feedback, taping	Therapist and patient hands on touch to muscle activation in sitting, bridging exercises Kinesiology active taping	2-5 minutes	- Quads activation/STS practice 3 x 20 (DL –SL) - Bridging 3 x 20 (DL-SL) - Calf Raises 3 x 20 (DL-SL) - SL Stance 3 x 30s (EO-EC)	
Gait	Re-education techniques	Determine any biomechanical deficiencies. I.e. Dec KE stance, Dec KF swing. Assess in part practice, compare to other side	Education about gait deficiencies and how leads to increased PFJ pressure and break down components Video/mirror feedback/part practice	2-5 minutes	Gait part practice – whole practice. I.e. stance with theraband / inner range quads control. Progress to step up. 3 x 8	

PHYSIOTHERAPY PROGRAM: TASK PROJECT (Group: Devil) Participant ID:

This booklet contains:

- Trunk strengthening exercise therapy protocol
- Physiotherapist clinical notes and attendance record
- Educational resources and handouts
- **Other resources you may need:**
- Administrative procedures physiotherapy handbook

OVERVIEW OF PROGRAM

General overview
The control group intervention consists of standardised trunk strengthening, stretching and education.

Patients are to attend physiotherapy appointments as per the intervention group (8 sessions of 30 minutes duration

Whilst this is a "control group" we ask that you deliver this intervention with equal enthusiasm as the targeted ACL-specific protocol, and educate the participants on the value of trunk strength and lumbo-pelvic control for lower limb neuromuscular function, biomechanics and sport performance.

- **Trunk strengthening**
- **Stretching**
- **Education**

1. Exercise-therapy protocol
Choose a minimum of three trunk exercises. Progress each patient according to their level of ability through the trunk strengthening exercises. They require minimal to no equipment. (Page 16)

2. Stretching
Lower limb and lumbo-thoracic stretches and mobility appropriate for the patient should be prescribed (Page 17)

Participants are encouraged to perform the exercises independently 3 times per week, and record their adherence via Physiapp.

3. Education
Education topics for the control group are outlined on Page 20. As the control group contains only trunk strength, patients are not educated on the importance of strengthening other muscle groups and specific return to sport criteria. However, if wishing to return to sport they are encouraged to receive advice and clearance from their surgeon.

TRUNK STRENGTH		Description of Exercise Program	Physiotherapy Log
Exercise 1	"Active alternate UL and LL extensions over ball" - Or in "4 point kneeling"	Even though this is the control group ensure remain positive about the effectiveness of trunk strengthening, education and stretching program First 5 sessions use exercises 1 E 3 Big appropriate difficulty of that exercise for patient Make sure they get a good work out within the session – perform 3 sets of each of the 3 exercises. Education re trunk and pelvic position and relationship to muscle function and lower limb biomechanics Demonstrate pelvic position in lying and standing + Patient practice **Education re exercise program:** - Progress as able to achieve technique and dosage - Minimum 3 x week	Session (_): Date: Phase: Assessment:
	Arm Lift – Leg Lift – Arm and Leg Lift *Alternate/fun challenge in session: Both Arms and Legs*		Session (_): Date: Phase: Assessment:
Dosage	3 x 30 - 60 seconds		
PASS	Dosage with good control Arm & Leg Lift		
Exercise 2	"Dead bugs" Toe taps – leg extension		Session (_): Date: Phase: Assessment:
	Alternate/fun challenge in session: ball between legs and pass to hands		
Dosage	3 x 30 - 60 seconds		
PASS	Dosage with good control on toes		Session (_): Date: Phase: Assessment:
Exercise 3	Plank series - "30 degree bench plank" - "Elbow plank" - "Plank in push up position" - "Plank – one arm row"		
	Alternate/fun challenge: Ball roll outs		Session (_): Date: Phase: Assessment:
Dosage	3 x 30 - 60 seconds		
PASS	Dosage with good control		Session (_): Date: Phase: Assessment:
Exercise 4	"Anti rotation series in standing" - Palov press - Rotation with theraband then cable		
Dosage	3 x 30 - 60 seconds		Session (_): Date: Phase: Assessment:
PASS	Dosage with good control		
Exercise 5	*Free choice trunk exercise*		
	According to patient needs		
Dosage	3 x 30 - 60 seconds		Session (_): Date: Phase: Assessment
PASS	Dosage with good control		

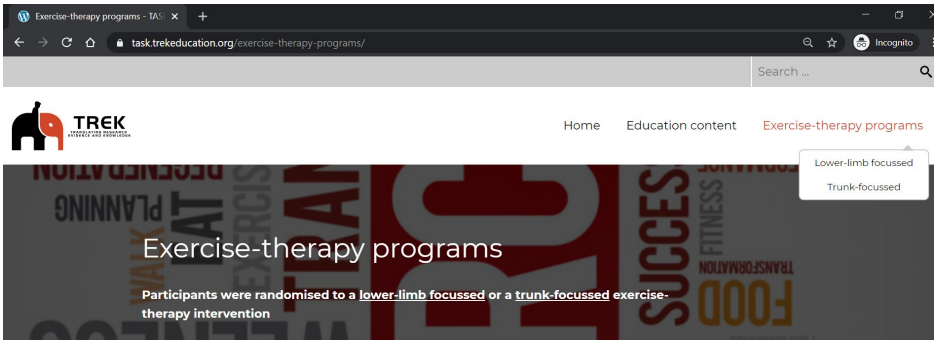
Stretching and mobility

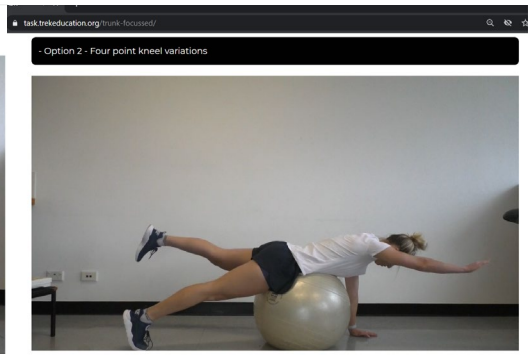
- *Education to patient - to improve joint and muscle mobility*
- *Choose most appropriate for patient*

Physio to circle most appropriate for individual patient	**Options (type name into physitrack)**	**Dosage**	**Description**
	1. Side-lying thoracic rotations 2. Thoracic foam roll 3. Quadriceps stretch 4. Hip flexor stretch 5. Hamstring stretch 6. Gluteal myofascial release with ball 7. Rotational spine stretch 8. Calf stretching standing (gastrocs) 9. Soleus stretching	As appropriate to patient	See videos on Physitrack

Appendix T: Chapter 8 Supplementary File C–Intervention material

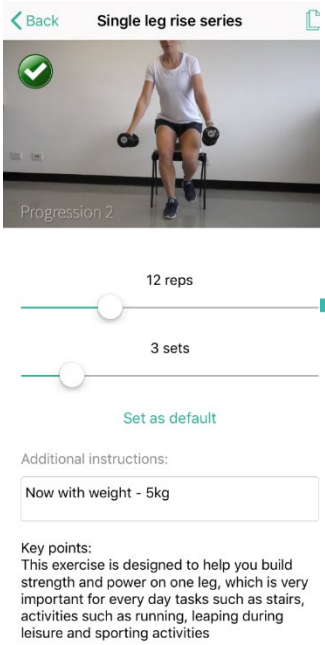
Go to the website to view the videos of the **lower-limb-focussed** and **trunk-focussed** **exercise therapy** program. **(www.task.trekeducation.org)**

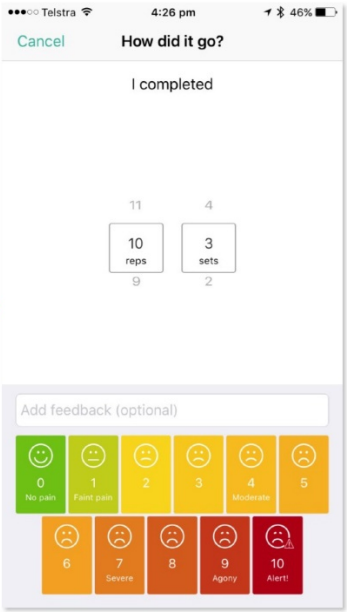


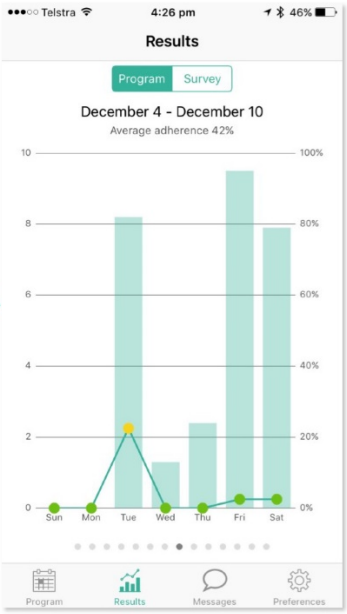


The exercise videos with detailed descriptions, were uploaded to PhysiApp© for participants

PhysiApp®







The **education** leaflets can be viewed on the website here, and are shown below:

LA TROBE UNIVERSITY

PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

1. What does the surgery involve?

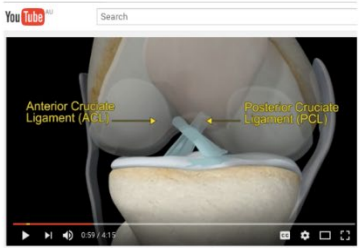
This education leaflet is designed to give you a brief and basic overview of anterior cruciate ligament reconstructive surgery

Every patient, injury and surgeon is different therefore please consult your health professional for further individual detail

Further information related to this topic can be found at:

semrc.blogs.latrobe.edu.au

For a great visual summary of ACL reconstructive surgery go to the following YouTube® video
"ACL Surgery – 3D Reconstruction"



LA TROBE UNIVERSITY

PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

Main Graft Types

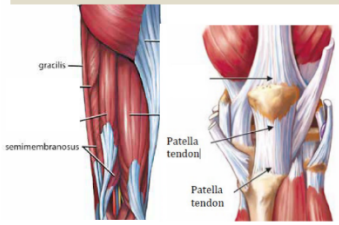
Autograft

- Tendon comes from you (hamstring or patella tendon)
- Risk of rejection is low due to tissue being native (from you)

Preference

- Surgeon/patient dependent but outcomes are similar regardless
- E.g. patella may be preferred if previous hamstring injuries

Hamstring and Patella Tendon Grafts



Back of knee Front of knee

What to expect after surgery

It is normal to experience in the first few weeks:

- Pain, swelling, muscle wastage, stiffness

You will be given advice about:

- Use of crutches
- Pain medication
- Ice, elevation and compression
- Gentle exercise vs rest

Other injuries

The difference between meniscus and cartilage

"*Cartilage*" refers to the "articular cartilage," the smooth protective covering over the bone

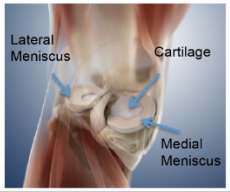
The "*meniscus*" are different types of shock absorbing cartilage. They are the "C" shaped discs that sit inside the knee.

Injuries to the cartilage and/or the meniscus commonly occur at the same time as injury to the ACL.

Other surgeries

Repair vs resection

Damage to cartilage or meniscus may be repaired using a variety of fixation methods (stiches/anchors). If this is not possible it may be left, or taken out/"resected"



Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

2. Rehabilitation & Return to Sport

This education leaflet is designed to give you a brief and basic overview of the rehabilitation and return to sport process following anterior cruciate ligament reconstruction

Every patient, injury and surgeon is different therefore please consult your health professional for further individual detail

Further information related to this topic can be found at: semrc.latrobe.edu.au

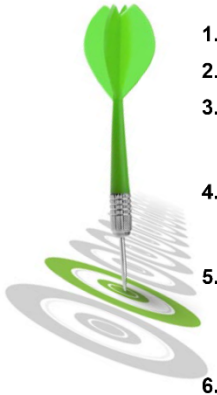
Rehabilitation following anterior cruciate ligament reconstruction is challenging and at times you may wish to discontinue for a variety of reasons (cost, time, ability to self manage, decreased motivation)

You should continue formal rehabilitation with a health professional until your operated leg is as strong as your other leg (if not stronger) to reduce the risk of re-injury and possibly future joint health

LA TROBE UNIVERSITY
PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

Return to Sport Criteria

Returning to sport with ongoing strength and movement deficits may place you at risk of abnormal joint/muscle loading, or reinjury. It is therefore important to continue to see your health professional for assessment and treatment of strength/movement deficits.



1. Nil to minimal **pain** and **swelling**
2. **Full range of motion**
3. "**Full" strength** of all muscle groups (= >95% of opposite side & >values for non injured people). This includes calf, quadriceps, hamstring, gluteals and trunk muscles.
4. "**Restored" function and movement.** I.e. walking, running, jumping, landing/cutting. This is not only how far you can run or hop but normal "movement patterns"
5. **Completed a graded return to activity.** I.e. - cardiovascular exercise non-impact exercise – running – speed/agility – modified – full training – match simulation – return to games. No more than 10% increase each week
6. **Psychological readiness** (see leaflet no. 4)

Your physiotherapist will assist you in assessing these items formally. Achieving all of these criteria typically takes 12 months, however it can take up to 2 years.

What if I do not want to return to sport?

- This is a completely justified decision, however restoring full symmetry in strength and function is still important for future joint health.
- Restoring all movements is also important as it may required in a social setting (i.e. playing sport with family/children)

Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

3. Can I prevent future injury?

This education leaflet is designed to give you a brief and basic overview of injury prevention following anterior cruciate ligament reconstruction

Injury prevention does not just refer to acute injuries or re-rupture of the ACL, injury prevention is important for prevention of meniscus, cartilage wear and tear and all lower limb joint health.

Further information related to this topic can be found at:

semrc.blogs.latrobe.edu.au

Topics covered will include:

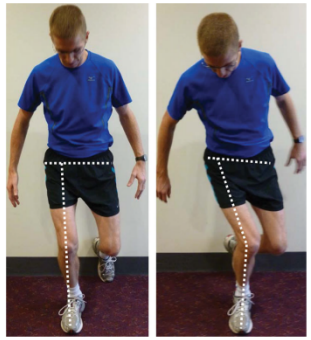
- Risk factors for re injury
- What is it and how do I do injury prevention?
- For how long?

LA TROBE UNIVERSITY
PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

Risk factors for re-injury

1. Returning to sport too early and not meeting "discharge criteria" prior to return to sport (see leaflet no.2)

2. "Altered movement patterns." People who sustain a second knee injury (re-injury/opposite leg ACL injury) land differently compared to those who do not sustain a second injury. These may include the movement patterns displayed below



A large part of rehabilitation should include retraining any poor movement patterns – see your health professional

Injury Prevention Key Point 1:

Ongoing Rehabilitation

A large part of injury prevention is maintaining an ongoing strength and conditioning program

2-3 x week to maintain strength & movement patterns in combination with your leisure activities.

The types of exercises you perform may change over your life (see your health professional for program check ups if you have symptoms/functional ability changes)

FOR LIFE?! Strength exercises are important to continue not only for general health but to optimize loads for joint health.

2 – 3 x week in combination with sport/leisure activities

Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

Injury Prevention Key Point 2: Injury Prevention Warm Up Programs

As well as performing your regular strength and control exercises, it is important to incorporate an **injury prevention warm up**" to fire up muscles/movement patterns before activity/sport.

Some of these programs have great videos, posters and manuals

1. **PEP program: http://smsmf.org/files/PEP_Program_04122011.pdf**
2. **FIFA 11+ program: http://f-marc.com/11plus/exercises/**
3. **Footy First program: https://footyfirstaustralia.wordpress.com/footyfirst-video-footage/**

Get your sporting club implementing them!

Injury Prevention Key Point #3

A large part of injury prevention also includes managing fatigue and load through your body. Some key things to consider may include:

- **Body weight management**
- **Load management**: Avoid large changes in intensity, type or duration of sport/exercise (no more than 10% increase per week). A simple way to measure this is through "RPE = rating of perceived exertion" x minutes of session. I.e. 7/10 difficult session x 60 minutes = 230. If you did exact session 3 x week. Total load for week = 3 x 230 = 690. Could increase to 760 next week.
- **Eat well** (see health professional if unsure)
- **Sleep well**

Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

LA TROBE UNIVERSITY
PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

4. Psychological Impact of Injury

This education leaflet is designed to give you a an insight into the psychological impact of anterior cruciate ligament reconstructive surgery can have

Injury will challenge each individual in different ways and if you are unsure how to best tackle any issues, please consult a qualified health professional

Further information related to this topic can be found at:

semrc.blogs.latrobe.edu.au

Topics covered include:
- Common struggles
- Psychological readiness for sport
- Resources available

LA TROBE UNIVERSITY

PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

Psychological Impact

Fear of re-injury and a lack of trust in your reconstructed knee is very common and you may be having some of the negative thoughts below. However, building strength, and gradually increasing the demands you place on your knee, realistic goal setting, will help you to feel in control.

"It is always in the back of my mind"

"I have changed the way I move and play to reduce the risk of getting injured again"

"I will never be able to ever perform the same"

What can I do about it?

- **Support** from coaches, teammates. Being involved in other ways.
- **Positive** attitude/outlook/mood and motivation toward rehabilitation and return to sport, performance and skills
- Setting **realistic goals** –short and long term with your rehabilitation team along the way is important to aid in **expectations** and prevent dissatisfaction.

Resources you can use:

- Peers that have had an ACL injury
- Your physiotherapist
- Qualified psychologist
- Online website resource created by Daniel Menzel to inspire local sports people: http://www.mtmf.com.au

Am I psychologically ready?

1. Prior to return to sport - **physical AND psychological readiness**

2. **ACL specific return to sport after injury questionnaire (ACL – RSI).** Assesses emotions, confidence in performance, and fear of reinjury

See attached copy/smartphone app

People who return to pre injury activity level score significantly higher on the ACL RSI

ACL RSI

Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

LA TROBE UNIVERSITY

PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

ACL – RSI (RETURN TO SPORT INDEX)

1. Are you confident that you can perform at your previous level of sport participation?

Not at all confident — Fully confident

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

2. Do you think you are likely to re-injury your knee by participating in your sport?

Extremely likely — Not likely at all

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

3. Are you nervous about playing your sport?

Extremely nervous — Not nervous at all

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

4. Are you confident that your knee will not give way by playing your sport?

Not at all confident — Fully confident

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

5. Are you confident that you could play your sport without concern for your knee?

Not at all confident — Fully confident

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

6. Do you find it frustrating to have to consider your knee with respect to your sport?

Extremely frustrating — Not at all frustrating

☐ 0 ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

ACL – RSI continued

7. Are you fearful of re-injuring your knee by playing your sport?

Extremely fearful										No fear at all
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	10	20	30	40	50	60	70	80	90	100

8. Are you confident about your knee holding up under pressure?

Not at all confident										Fully confident
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	10	20	30	40	50	60	70	80	90	100

9. Are you afraid of accidentally injuring your knee by playing your sport?

Extremely afraid										Not at all afraid
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	10	20	30	40	50	60	70	80	90	100

10. Do thoughts of having to go through surgery and rehabilitation prevent you from playing your sport?

All of the time										None of the time
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	10	20	30	40	50	60	70	80	90	100

11. Are you confident about your ability to perform well at your sport?

Not at all confident										Fully confident
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	10	20	30	40	50	60	70	80	90	100

12. Do you feel relaxed about playing your sport?

Not at all relaxed										Fully relaxed
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	10	20	30	40	50	60	70	80	90	100

Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

LA TROBE UNIVERSITY
PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

5. Things to look out for

This education leaflet is designed to give you a brief and basic overview of signs and symptoms to look out for following anterior cruciate ligament reconstructive surgery

Every patient, injury and surgeon is different therefore please consult your health professional for further individual detail

Further information related to this topic can be found at:

semrc.blogs.latrobe.edu.au

Many people experience new symptoms and change in function of their knee, and it is important to know that this is normal and common after ACL reconstructive surgery.

LA TROBE UNIVERSITY

PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

Future symptoms – am I at risk?

Some people experience changes in symptoms and function in the early years following their surgery, where as others it occurs much later and others not at all. It is poorly understood what puts people into these categories. And it is likely that a large variety of factors play a part in the development of symptoms.

Key things to watch for

- New or change in pain, swelling or stiffness (at rest, during or after activity)
- Giving way
- People stating you are limping whilst walking
- Altered muscle strength or weakness

What is osteoarthritis? Will I get it?

Knee osteoarthritis (OA) is a common musculoskeletal condition with incidence increasing with age.

Isn't it just a normal part of ageing?
Now that you have had an ACL injury and surgery your knee is at greater risk of osteoarthritis (OA) development at an earlier age

Does surgery reduce my risk of OA?
No, it restores the stability of the knee joint but it does not reduce the risk of OA.

Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

LA TROBE UNIVERSITY

PATIENT EDUCATION
ANTERIOR CRUCIATE
LIGAMENT RECONSTRUCTION

OSTEOARTHRITIS – General Population

Knee OA (on X-ray)
1% aged between 25 - 34 years
15 – 30% aged 55 years
50% aged > 75 years

- Cartilage begins to thin
- Small bone spurs/cysts
- Space between joint becomes smaller

Knee pain/symptoms
<1% aged 25 - 34 years
20% aged 55 years
25% aged > 75 years

- Pain,
- Stiffness,
- Swelling,
- Loss of strength/function

THESE DO NOT ALWAYS MATCH UP
I.e. you can have degenerative changes on X-ray but NO symptoms or vice

OSTEOARTHRITIS – Following ACL Reconstruction

OA after ACL reconstruction is common and NOT always associated with symptoms

- 1 year following ACL reconstruction: 5% (I.e. aged 18 – 40)
- 15 years following ACL reconstruction: 50% (I.e. aged 35 – 60)

What can I do about it?

- **Graded exercises and return to activity** following injury is important to ensure the knee joint is gradually loaded.
- Progression based on **achieving strength/functional goals** not a time point
- Continue **seeing health care professional** until all deficits are restored
- Keep strong and maintain good function
- **Healthy diet and weight** (seek professional help if unsure)

Further information

Website/Blog
semrc.blogs.latrobe.edu.au/category/acl

Facebook
facebook.com/latrobesemrc

Twitter
twitter.com/LaTrobeSEM

Appendix U: Chapter 8 Supplementary File D – Participant feedback

Questions each participant (n=23) was asked at follow-up

1. Were you aware which intervention group you were in? Did you think you were in the control group?
2. Do you have any feedback on the exercise program (specifically the content, and any barriers to completing the program in own time)?
3. Do you have any feedback on the exercise program delivery (specifically the physiotherapist, duration and frequency of appointments, and any barriers to attending physiotherapy)?
4. Do you have any feedback on Physiapp?
5. Do you have any feedback on the trial as whole? (i.e., would you participate again, recruitment methods)?

1. Were you aware which intervention group you were in? Did you think you were in the control group?

ID#	
1	Wasn't sure
2	My initial concern was that if I was in control group or not. But I wasn't sure.
3	No
4	No
5	No
6	No
7	No
8	No
12	No
13	No
14	No
15	No
16	I had fair idea early on I might be in the control group; however, I thought it was a valid treatment
17	No
18	No
19	No
20	I thought was in the control group/standard program against a new innovative program, but I wasn't worried what group was in
22	No
24	No
25	No, as I felt like I needed the core strength once I started
26	Didn't know didn't think about it
28	Didn't know, wasn't concerned
30	No

2. Do you have any feedback on the exercise program (specifically the content, and any barriers to completing the program in own time)?

ID#	
1	The exercises were good additions to the current program, sometimes I would do my own program sometimes I would do the trial exercises
2	-
3	Too much, especially every day, not striving for elite sport, exercise 3 x week running in off days. Hard to fit it in
4	All got too much, life and work and study and travel
5	I felt benefit of core strength for work (standing all day bar work)
6	Difficult to find motivation as didn't feel was assisting knee, but overall gradual build into hockey confidence and knee coping better and better
7	Too many exercises time constraints
8	It was good
12	Great to see progression in exercises and have consistent physiotherapy monitoring at this time-point otherwise would have just continued and done nothing
13	Type of exercise needs to take into account activities that doing throughout the day. I am squatting all day at work,
14	Wasn't sure exercises were going to help knee
15	Good, challenging progressing all the time, 1 rep max squat improvement 105-135 very happy with that
16	Felt was improved deficiencies in core strength, which helped with LBP, golf swing, standing for longer periods at work, and tightness through hip flexors, good workout, good variety of different muscles and positions
17	Felt personalised and modified to make challenging for me, core strength useful for my sport/throwing athletics,
18	Good exercises
19	Didn't notice much improvement but wasn't working hard on the exercises
20	I struggled with motivation at the end as I was doing the same exercises, bored, felt wasn't progressing, as wasn't able to move forward before reaching a certain weight. Felt a bit limited by being in a trial that exercises couldn't be individualised for me
22	Felt was catered to me and specific to ACL
24	Good to begin with then felt bit boring as same exercise just increased weight
25	Really good exercises have taken photos of them all to continue doing them
26	Loved variety of exercises, but it was time consuming, I hated the bridges, favourite exercise was jumping and hopping
28	Good variety and always challenging
30	Good amount of exercises 1-hour sessions, good how was progressing each week initially, felt good to squat and increase the weight to almost body weight and see tangible improvements, would be better if there was a home option for every exercise as only couple needed gym could do most at home didn't seem worth it, bit boring in the end same exercises just more weight would like variety.

3. **Do you have any feedback on the exercise program delivery (specifically the physiotherapist, duration and frequency of appointments, and any barriers to attending physiotherapy)?**

ID#	
1	physio good at giving demonstrations
2	Dave was excellent
3	physio really good in terms of explanation, need time to be able to fully understand what meant to do at home or more regular check-ups as forget and couldn't interpret exercise program
4	Dave was excellent but overall got too much and wasn't priority at the time due to work, study, and travel commitments
5	difficulty with doing exercises and attending appointments due to newborn, work, lacking motivation to return-to-sport
6	nil
7	good explanation of why core was needed
8	some of the instructions on video hard to understand, can't remember which ones
12	good
13	good demo and explanations
14	nil
15	structure and timing no issue, 30 mins enough, 1 week initially good, 2-3 weeks then suitable
16	Dave was great, explaining reasons for exercises and simple instructions
17	structure was good, enough time
18	good spacing of appointments, more the better
19	3 weeks too long, need motivation, 30 mins good, difficulty with missing school and work to make appointments
20	30-40 mins was enough time to go through everything
22	30 mins enough time, structure good able to self-progress
24	Dave was great, worked really well to update program on app if it was just an increase in weight
25	good amount of time and constantly challenged
26	Dave very accommodating, right amount of appointments once a week for any longer would be too much and inconvenient, 30 mins enough time
28	good structure of appointments, enough time
30	3-4 months good, feel like need to learn how to self-manage now with guidance as required, 6 days a week exercises too much. Will struggle once go back to work, spacing of appts good. Not as rigid for 3-week follow-ups if need to come in for a question

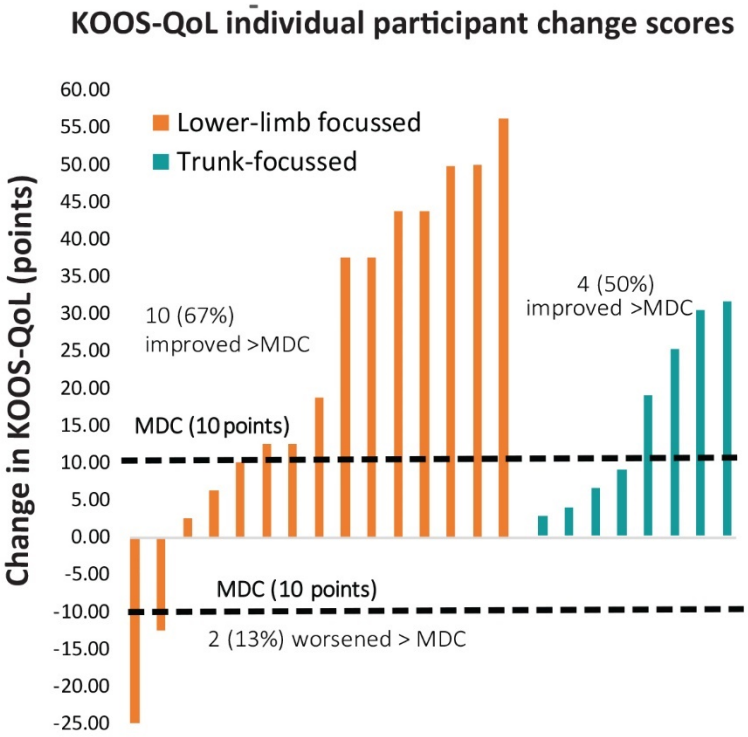
4. Do you have any feedback on Physiapp©?

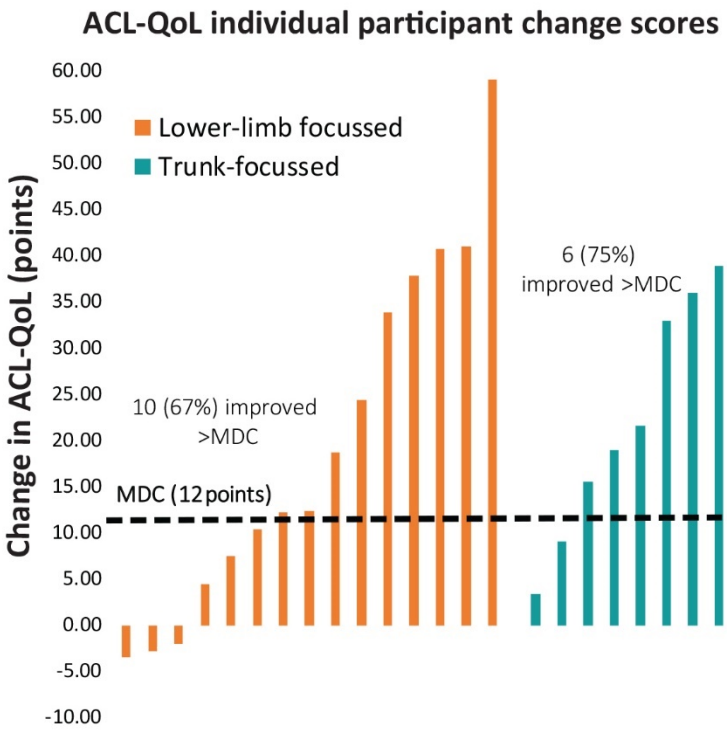
ID#	
1	too hard and clunky
2	good for accountability, useful for exercise technique
3	little bit clunky, not updating all the time, like the pain and additional comments section, number of sets and reps confusing and to do each side or not, videos really good, bit too wordy descriptions
4	too much to have to fill out all the time
5	remembering to fill out an issue
6	nil
7	good, easy to use
8	easy to use, kept accountable
12	good easy to use intuitive, great to keep track of progression, unable to change comments section
13	clunky, not updating, have to log in and out again, videos good but music irritating, technique good vs bad really good
14	good
15	good at times, frustrating at times, especially if got a new program/program ended. Videos and instructions good for new exercises
16	bit clunky, didn't always load and update, also hard to go back and enter retrospectively, videos good reminder for new exercises
17	couldn't go back and enter in completion, would like to enter 1 x week, didn't always have phone, videos and text useful to make individualised comments
18	useful videos and instructions
19	instructions helpful, clear reps and sets, no technical issues
20	really liked the app, no issues, something good would be an idea of how long they should take, best order of exercises, amount of rest time
22	couldn't go back more than 5 days to enter in, used the text more than the videos, good to track progress and help with motivation, individual notes good
24	great, used text rather than videos as reception not great and videos used battery, no issues with filling in compliance, ability to have order of exercises would be good as figured out was better to do gluteal stuff first before squats
25	used paper logbook, liked this, would just take photo of it and then fill it in later
26	trouble with writing comments on specific exercises, video and written instructions very good, used both, clear on reps and sets, sometimes too much info/contradicting what Physio was saying on the written instructions
28	Some difficulty at times with new program loading and going back to enter in completion of exercises
30	Great! Loved the app for self-monitoring and motivation. Issue with messaging not directly linking to the exercise referring to. Would be great to be able to continue using independently.

5. **Do you have any feedback on trial as a whole (i.e., would you participate again, recruitment methods)?**

ID#	
1	overall happy with program; however, didn't feel like it helped with pain or range of motion, improved strength, still lacking confidence to go bush walking
2	Excellent result improvement in all measures, would participate again, going to miss not having the accountability
3	expectations should be set by surgeon - so much more to it than what they say, overall, I felt like I got stronger, but sickness, other injuries (sesamoiditis) got in way of making more progress and doing exercises. I had a much better physiotherapy experience in terms of treating whole body not just the knee.
4	nil
5	nil
6	nil
7	overall happy with program, felt was beneficial. Function likely improved from increased basketball 1 - 4 x week and gradual loading back into basketball, pain settling to manageable level
8	overall was doing quite well until strained hamstring in basketball 6 weeks ago. Found that my body awareness was quite poor, I found it difficult to be able to correct techniques very well
12	overall good improvement in measures, very happy with program and progress, plans to continue to increase running and maintain gym program and see PT as required
13	overall felt good improvement in feeling of the knee and strength, hope to continue doing the program, will likely come back and see Nick for clearance for RTS, pes anserine pain flare up
14	nil
15	
16	overall good to be a part of
17	overall felt improvements and increased confidence in knee with time. Core strength helped athletics, going to netball tryouts on Monday
18	overall felt good improvement in strength and reduced amount of "instability" and effusions, will continue to do strengthening exercises, some pain with exercises but would settle back to norm
19	nil
20	overall noticed significant decrease in pain, increase in strength and really enjoyed being a part of the trial
22	overall very glad participated, overall improvement in pain and strength
24	overall felt really improved confidence and ability to do full moves at cheerleading and noticeable decrease in pain
25	overall have I learnt that needs to me that is ready to return-to-sport, not the surgeon saying graft is okay
26	would like to return to tennis and skiing, get into some kind of sport for competitive needs, start yoga/Pilates
28	aiming to go to world champs athletics
30	overall very happy with improvements in pain and everyday activities, would like to be able to increase running tolerance and confidence in skiing. Worried about how will go without the motivation of the trial, the app, the physio

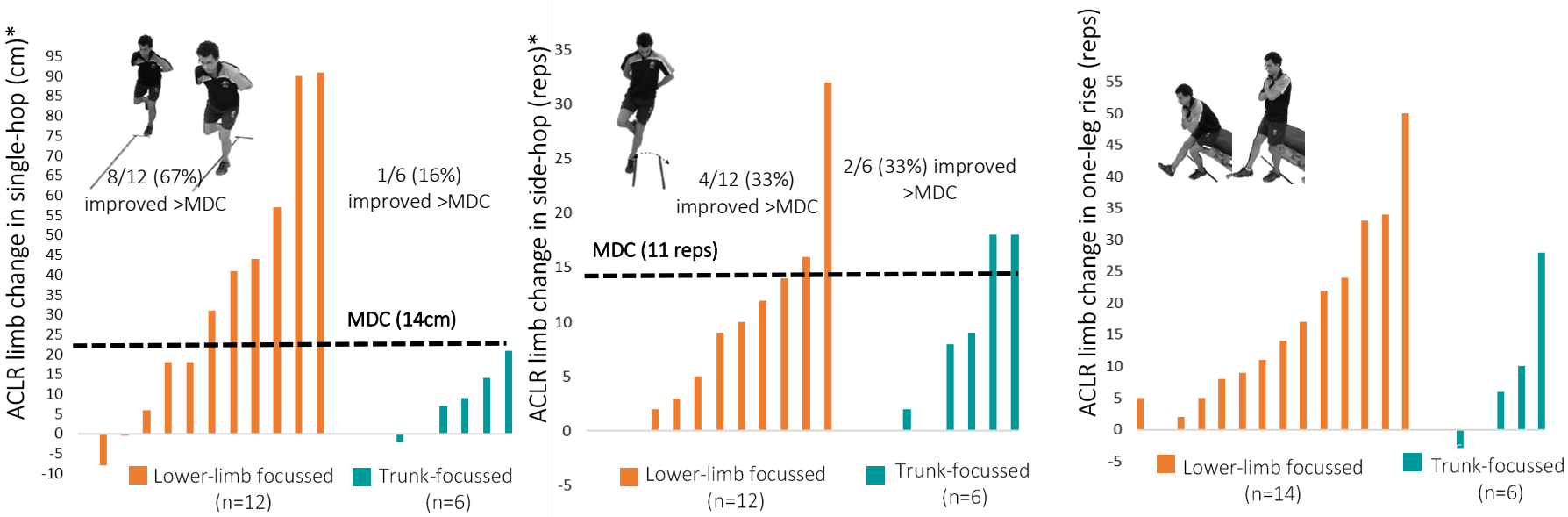
Appendix V: Chapter 8 Supplementary File E – Secondary outcomes





Supplementary File E, Figure 1. Individual participant changes for the KOOS-QoL and ACL-QOL

KOOS=Knee injury and Osteoarthritis Outcome Score; ACL-QoL=Anterior Cruciate Ligament Quality of Life survey; MID=minimal important difference for KOOS-QoL (10 points) and ACL-QOL (12 points).



Supplementary File E, Figure 2. Individual participant changes for the functional performance in the ACLR limb

MDC=minimal detectable change for the single-hop (14 cm) and side-hop (11 repetitions) from Kockum et al. (2015). No known MIC for the one-leg rise.
~n=20 out of 23 completed follow-up functional performance assessment (n=2 overseas, n=1 work commitments).
* single-hop and side-hop, n=18 (n=2 could not complete the hop tests at follow-up as they were still recovering from adverse events; n=1 hamstring strain, n=1 ankle sprain).

Appendix W: Replication and copyright permissions for published papers

---

STUDY 1 (CHAPTER 3)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2018). Worsening Knee Osteoarthritis Features on Magnetic Resonance Imaging 1 to 5 Years After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med, 46*(12), 2873-2883.

This publication is able to be reproduced within this thesis plain text format, but not the final published PDF. This is in accordance with the SAGE publications' re-use guidelines outlined, with key points highlighted below

---

SAGE's Author Archiving and Re-Use Guidelines

These guidelines should be followed by authors of Contributions published in a SAGE subscription journal, including authors whose Contributions were published under a previous version of the author guidelines. For a list of exceptions to these guidelines, please see below.

Three versions of the Contribution are referenced in these guidelines:

Original Submission: the version submitted by the author before peer review
Accepted Manuscript: version updated to include the author's revisions after peer review, prior to any typesetting for the journal. This is often the version accepted by the editor
Final Published PDF: copy-edited and typeset Publisher's PDF, published on the journal's website

Green Open Access: SAGE's Archiving and Sharing Policy

You may share the **Original Submission** or **Accepted Manuscript** at any time and in any format. Your sharing of the **Original Submission** or **Accepted Manuscript** may include posting a downloadable copy on any website, saving a copy in any repository or network, sharing a copy through any social media channel, and distributing print or electronic copies.

You may use the **Final Published PDF** (or **Original Submission** or **Accepted Manuscript**, if preferred) in the following ways:

- in relation to your own teaching, provided that any electronic distribution maintains restricted access
- to share on an individual basis with research colleagues, provided that such sharing is not for commercial purposes
- in your dissertation or thesis, including where the dissertation or thesis will be posted in any electronic Institutional Repository or database
- in a book authored or edited by you, at any time after the Contribution's publication in the journal.

Provided that:

- Access to the Original Submission and Accepted Manuscript is provided at no charge.
- Any re-use terms for users of websites and repositories (where your **Original Submission** or **Accepted Manuscript** are posted) are restricted to non-commercial and no derivative uses.
- You may not post the **Final Published PDF** on any unrestricted website or repository without permission from SAGE.
- You may not republish or translate any version of your Contribution in another journal without prior permission from SAGE.
- The journal as the original publication of your Contribution is appropriately credited by including the full citation information each time your Contribution, or excerpts, are further distributed or re-used:

STUDY 2 (CHAPTER 4)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., & Crossley, K.M. (2020). Patient-Reported Outcomes One to Five Years After Anterior Cruciate Ligament Reconstruction: The Effect of Combined Injury and Associations With Osteoarthritis Features Defined on Magnetic Resonance Imaging. *Arthritis Care Res, 72*(3), 412-422.

STUDY 3 (CHAPTER 5)

Patterson, B.E., Crossley, K.M., Perraton, L.G., Kumar, A.S., King, M.G., Heerey, J.J., Barton, C.J., & Culvenor, A.G. (2020). Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function. *Physical Therapy in Sport, 44*, 67-74.

STUDY 4 (CHAPTER 6)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2020). Poor functional performance 1 year after ACL reconstruction increases the risk of early osteoarthritis progression. *Br J Sports Med, 54*(9), 546-553.

Appendix X: Confirmation of authorship

STUDY 1 (CHAPTER 3)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2018). Worsening Knee Osteoarthritis Features on Magnetic Resonance Imaging 1 to 5 Years After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med, 46*(12), 2873-2883.

As the primary supervisor, I certify that Brooke Patterson has made the following contributions:

- Research question design
- Obtained ethics approval
- Recruitment
- Grading of radiographs
- Data collection and management
- Data analysis and visualisation
- Writing of the manuscript
- Study administration

Professor Kay Crossley 4th December 2020

STUDY 2 (CHAPTER 4)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., & Crossley, K.M. (2020). Patient-Reported Outcomes One to Five Years After Anterior Cruciate Ligament Reconstruction: The Effect of Combined Injury and Associations With Osteoarthritis Features Defined on Magnetic Resonance Imaging. *Arthritis Care Res, 72*(3), 412-422.

As the primary supervisor, I certify that Brooke Patterson has made the following contributions:

- Research question design
- Obtained ethics approval
- Development of protocol and procedures
- Recruitment
- Data collection and management
- Data analysis and visualisation
- Writing of the manuscript
- Study administration

Professor Kay Crossley 4th December 2020

STUDY 3 (CHAPTER 5)

Patterson, B.E., Crossley, K.M., Perraton, L.G., Kumar, A.S., King, M.G., Heerey, J.J., Barton, C.J., & Culvenor, A.G. (2020). Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function. *Physical Therapy in Sport, 44*, 67-74.

As the primary supervisor, I certify that Brooke Patterson has made the following contributions:

- Research question design
- Obtained ethics approval
- Development of protocol and procedures
- Recruitment
- Data collection and management
- Data analysis and visualisation
- Writing of the manuscript
- Study administration

Professor Kay Crossley 4th December 2020

STUDY 4 (CHAPTER 6)

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2020). Poor functional performance 1 year after ACL reconstruction increases the risk of early osteoarthritis progression. *Br J Sports Med, 54*(9), 546-553.

As the primary supervisor, I certify that Brooke Patterson has made the following contributions:

- Research question design
- Obtained ethics approval
- Recruitment
- Data collection and management
- Data analysis and visualisation
- Writing of the manuscript
- Study administration

Professor Kay Crossley 4th December 2020

STUDY 5 (CHAPTER 8)

Exercise therapy and education for individuals with persistent symptoms 1 year following ACLR: A pilot RCT

As the primary supervisor, I certify that Brooke Patterson has made the following contributions:

- Research question design
- Obtained funding and ethics approval
- Recruitment
- Data collection and management
- Data analysis and visualisation
- Writing of the manuscript
- Study administration

Professor Kay Crossley 4th December 2020

List of References

Aboagye, E. (2017). Valuing Individuals' Preferences and Health Choices of Physical Exercise. *Pain and Therapy, 6*(1), 85-91. doi:10.1007/s40122-017-0067-4

Abrams, G., Harris J., Gupta, A., McCormick F., Bush-Joseph C., Verma N., Cole B., & Bach R. (2014). Functional Performance Testing After Anterior Cruciate Ligament Reconstruction: A Systematic Review. *Orthop J Sports Med, 2*(1). doi:10.1177/2325967113518305

Ackerman, I., Kemp J.L, Crossley K.M, Culvenor A.G, & Hinman R.S. (2017). Hip and Knee OA Affects Younger People Too. *J Orthop Sports Phys Ther, 47*(2), 67-79. doi:10.2519/jospt.2017.7286

Ackerman I., Pratt C., Gorelik A., & Liew D. (2018). Projected Burden of OA and Rheumatoid Arthritis in Australia. *Arthritis Care Res, 70*(6), 877-883. doi:10.1002/acr.23414

Ageberg, E. (2002). Consequences of a ligament injury on neuromuscular function and relevance to rehabilitation — using the ACL-injured knee as model. *J Electromyogr Kinesiol, 12*(3), 205-212. doi:10.1016/s1050-6411(02)00022-6

Ageberg, E., & Roos, E.M. (2015). Neuromuscular exercise as treatment of degenerative knee disease. *Exerc Sport Sci Rev, 43*(1), 14-22. doi:10.1249/JES.0000000000000030

Ageberg, E., Roos, H.P., Silbernagel, K.G., Thomee, R., & Roos, E.M. (2009). Knee extension and flexion muscle power after anterior cruciate ligament reconstruction with patellar tendon graft or hamstring tendons graft: a cross-sectional comparison 3 years post surgery. *Knee Surg Sports Traumatol Arthrosc, 17*(2), 162-169. doi:10.1007/s00167-008-0645-4

Ageberg, E., Thomeé, R., Neeter, C., Silbernagel, K.G., & Roos, E.M. (2008). Muscle strength and functional performance in patients with anterior cruciate ligament injury treated with training and surgical reconstruction or training only: A two to five-year followup. *Arthritis Rheum, 59*(12), 1773-1779. doi:10.1002/art.24066

Ageberg, E., Zatterstrom, R., Friden, T., & Moritz, U. (2001a). Individual factors affecting stabilometry and one-leg hop test in 75 healthy subjects, aged 15-44 years. *Scan J Med Sci Sport, 11*(1), 47-53. doi:10.1034/j.1600-0838.2001.011001047.x

Ageberg, E., Zatterstrom, R., Moritz, U., & Friden, T. (2001b). Influence of supervised and nonsupervised training on postural control after an acute anterior cruciate ligament rupture: a three-year longitudinal prospective study. *J Orthop Sports Phys Ther, 31*(11), 632-644. doi:10.2519/jospt.2001.31.11.632

Agree Collaboration. (2003). Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care, 12*(1), 18-23. doi:10.1136/qhc.12.1.18

Ahldén, M., Samuelsson, K., Sernert, N., Forssblad, M., Karlsson, J., & Kartus, J. (2012). The Swedish National Anterior Cruciate Ligament Register. *Am J Sports Med, 40*(10), 2230-2235. doi:10.1177/0363546512457348

Ajrawat, P., Dwyer, T., Whelan, D., Theodoropoulos, J., Murnaghan, L., Bhargava, M., Ogilvie-Harris, D., & Chahal, J. (2019). A Comparison of Quadriceps Tendon Autograft With Bone-Patellar Tendon-Bone Autograft and Hamstring Tendon Autograft for Primary Anterior Cruciate Ligament Reconstruction. *Clinical Journal of Sport Medicine*, 1. doi:10.1097/jsm.0000000000000765

Ajuied, A., Wong, F., Smith, C., Norris, M., Earnshaw, P., Back, D., & Davies, A. (2014). Anterior cruciate ligament injury and radiologic progression of knee osteoarthritis: a systematic review and meta-analysis. *Am J Sports Med, 42*(9), 2242-2252. doi:10.1177/0363546513508376

Allen, K.D., Choong, P.F., Davis, A.M., Dowsey, M.M., Dziedzic, K.S., Emery, C., Hunter, D.J., Losina, E., Page, A.E., Roos, E.M., Skou, S.T., Thorstensson, C.A., van der Esch, M., & Whittaker, J.L. (2016). Osteoarthritis: Models for appropriate care across the disease continuum. *Best Pract Res Clin Rheumatol, 30*(3), 503-535. doi:10.1016/j.berh.2016.09.003

Almangoush, A., & Herrington, L. (2014). Functional Performance Testing and Patient Reported Outcomes following ACL Reconstruction: A Systematic Scoping Review. *International Scholarly Research Notices, 2014*, 1-14. doi:10.1155/2014/613034

Altman, R.D., & Gold, G.E. (2007). Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage, 15 Suppl A*, A1-56. doi:10.1016/j.joca.2006.11.009

Altman, R.D., Hochberg, M., Murphy, W.A., Jr., Wolfe, F., & Lequesne, M. (1995). Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage, 3 Suppl A*, 3-70.

American College of Sports Medicine. (2009). American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc, 41*(3), 687-708. doi:10.1249/MSS.0b013e3181915670

Amin, S., Baker, K., Niu, J., Clancy, M., Goggins, J., Guermazi, A., Grigoryan, M., Hunter, D.J., & Felson, D.T. (2009). Quadriceps strength and the risk of cartilage loss and symptom progression in knee osteoarthritis. *Arthritis and rheumatism, 60*(1), 189-198. doi:10.1002/art.24182

Amin, S., LaValley, M.P., Guermazi, A., Grigoryan, M., Hunter, D.J., Clancy, M., Niu, J., Gale, D.R., & Felson, D.T. (2005). The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. *Arthritis and rheumatism, 52*(10), 3152-3159. doi:10.1002/art.21296

An, V.V., Scholes, C., Mhaskar, V.A., Hadden, W., & Parker, D. (2017). Limitations in predicting outcome following primary ACL reconstruction with single-bundle hamstring autograft — A systematic review. *The Knee, 24*(2), 170-178. doi:10.1016/j.knee.2016.10.006

Anderson, A.F., Irrgang, J.J., Kocher, M.S., Mann, B.J., Harrast, J.J., & International Knee Documentation, C. (2006). The International Knee Documentation Committee Subjective Knee Evaluation Form: normative data. *Am J Sports Med, 34*(1), 128-135. doi:10.1177/0363546505280214

Anderson, J.A., Little, D., Toth, A.P., Moorman, C.T., 3rd, Tucker, B.S., Ciccotti, M.G., & Guilak, F. (2014). Stem cell therapies for knee cartilage repair: the current status of preclinical and clinical studies. *Am J Sports Med, 42*(9), 2253-2261. doi:10.1177/0363546513508744

Anderson, M.J., Browning, W.M., 3rd, Urband, C.E., Kluczynski, M.A., & Bisson, L.J. (2016). A Systematic Summary of Systematic Reviews on the Topic of the Anterior Cruciate Ligament. *Orthop J Sports Med, 4*(3), 2325967116634074. doi:10.1177/2325967116634074

Andrade, R., Pereira, R., van Cingel, R., Staal, J.B., & Espregueira-Mendes, J. (2019). How should clinicians rehabilitate patients after ACL reconstruction? A systematic review of clinical practice guidelines (CPGs) with a focus on quality appraisal (AGREE II). *Br J Sports Med*. doi:10.1136/bjsports-2018-100310

Andriacchi, T.P., Briant, P.L., Bevill, S.L., & Koo, S. (2006). Rotational changes at the knee after ACL injury cause cartilage thinning. *Clin Orthop Relat Res, 442*, 39-44. doi:10.1097/01.blo.0000197079.26600.09

Andriacchi, T.P., Griffin, T.M., Loeser, R.F., Chu, C.R., Roos, E.M., Hawker, G.A., Erhart-Hledik, J.C., & Fischer, A.G. (2020). Bridging Disciplines as a pathway to Finding New Solutions for Osteoarthritis a collaborative program presented at the 2019 Orthopaedic Research Society and the Osteoarthritis Research Society International. *Osteoarthritis and Cartilage Open, 2*(1), 100026. doi:10.1016/j.ocarto.2020.100026

Anstey, D.E., Heyworth, B.E., Price, M.D., & Gill, T.J. (2012). Effect of timing of ACL reconstruction in surgery and development of meniscal and chondral lesions. *Phys Sportsmed, 40*(1), 36-40. doi:10.3810/psm.2012.02.1949

Antosh, I.J., Svoboda, S.J., Peck, K.Y., Garcia, E.J., & Cameron, K.L. (2018). Change in KOOS and WOMAC Scores in a Young Athletic Population With and Without Anterior Cruciate Ligament Injury. *Am J Sports Med, 46*(7), 1606-1616. doi:10.1177/0363546518768753

Ardern, C.L., Osterberg, A., Sonesson, S., Gauffin, H., Webster, K.E., & Kvist, J. (2016). Satisfaction With Knee Function After Primary Anterior Cruciate Ligament Reconstruction Is Associated With Self-Efficacy, Quality of Life, and Returning to the Preinjury Physical Activity. *Arthroscopy, 32*(8), 1631-1638 e1633. doi:10.1016/j.arthro.2016.01.035

Ardern, C.L., Osterberg, A., Tagesson, S., Gauffin, H., Webster, K.E., & Kvist, J. (2014a). The impact of psychological readiness to return-to-sport and recreational activities after anterior cruciate ligament reconstruction. *Br J Sports Med, 48*(22), 1613-1619. doi:10.1136/bjsports-2014-093842

Ardern, C.L., Taylor, N.F., Feller, J.A., & Webster, K.E. (2014b). Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. *Br J Sports Med, 48*(21), 1543-1552. doi:10.1136/bjsports-2013-093398

Ardern, C.L., Taylor, N.F., Feller, J.A., Whitehead, T.S., & Webster, K.E. (2015). Sports Participation 2 Years After Anterior Cruciate Ligament Reconstruction in Athletes Who Had Not Returned to Sport at 1 Year: A Prospective Follow-up of Physical Function and Psychological Factors in 122 Athletes. *Am J Sports Med, 43*(4), 848-856. doi:10.1177/0363546514563282

Arroll B, Robb G, & Sutich E. (2003). The diagnosis and management of soft tissue knee injuries: internal derangements. 1–100.

Arundale, A.J.H., Capin, J.J., Zarzycki, R., Smith, A., & Snyder-Mackler, L. (2018). Functional and Patient-Reported Outcomes Improve Over the Course of Rehabilitation: A Secondary Analysis of the ACL-SPORTS Trial. *Sports health*, 1941738118779023. doi:10.1177/1941738118779023

Ashigbi, E.Y.K., Banzer, W., & Niederer, D. (2020). Return-to-sport Tests' Prognostic Value for Reinjury Risk after Anterior Cruciate Ligament Reconstruction. *Med Sci Sports Exerc, 52*(6), 1263-1271. doi:10.1249/mss.0000000000002246

Avery, K.N.L., Williamson, P.R., Gamble, C., O'Connell Francischetto, E., Metcalfe, C., Davidson, P., Williams, H., & Blazeby, J.M. (2017). Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open, 7*(2), e013537. doi:10.1136/bmjopen-2016-013537

Baltaci, G., Yilmaz, G., & Atay, A.O. (2012). The outcomes of anterior cruciate ligament reconstructed and rehabilitated knees versus healthy knees: a functional comparison. *Acta orthopaedica et traumatologica turcica, 46*(3), 186-195.

Barber-Westin, S.D., & Noyes, F.R. (2011). Objective criteria for return to athletics after anterior cruciate ligament reconstruction and subsequent reinjury rates: a systematic review. *Phys Sportsmed, 39*(3), 100-110. doi:10.3810/psm.2011.09.1926

Barenius, B., Forssblad, M., Engstrom, B., & Eriksson, K. (2013). Functional recovery after anterior cruciate ligament reconstruction, a study of health-related quality of life based on the Swedish National Knee Ligament Register. *Knee Surg Sports Traumatol Arthrosc, 21*(4), 914-927. doi:10.1007/s00167-012-2162-8

Barenius, B., Ponzer, S., Shalabi, A., Bujak, R., Norlen, L., & Eriksson, K. (2014). Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: a 14-year follow-up study of a randomized controlled trial. *Am J Sports Med, 42*(5), 1049-1057. doi:10.1177/0363546514526139

Baumgart, C., Schubert, M., Hoppe, M.W., Gokeler, A., & Freiwald, J. (2017). Do ground reaction forces during unilateral and bilateral movements exhibit compensation strategies following ACL reconstruction? *Knee Surg, Sports Traum, Arthrosc, 25*(5), 1385-1394. doi:10.1007/s00167-015-3623-7

Bedson, J., & Croft, P.R. (2008). The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskeletal Disorders, 9*(1), 116. doi:10.1186/1471-2474-9-116

Behm, D.G., Faigenbaum, A.D., Falk, B., & Klentrou, P. (2008). Canadian Society for Exercise Physiology position paper: resistance training in children and adolescents. *Applied Physiology, Nutrition, and Metabolism, 33*(3), 547-561. doi:10.1139/h08-020

Belk, J.W., Kraeutler, M.J., Carver, T.J., & McCarty, E.C. (2018). Knee Osteoarthritis After Anterior Cruciate Ligament Reconstruction With Bone-Patellar Tendon-Bone Versus Hamstring Tendon Autograft: A Systematic Review of Randomized Controlled Trials. *Arthroscopy, 34*(4), 1358-1365. doi:https://dx.doi.org/10.1016/j.arthro.2017.11.032

Belk, J.W., Kraeutler, M.J., Houck, D.A., & McCarty, E.C. (2019). Knee Osteoarthritis After Single-Bundle Versus Double-Bundle Anterior Cruciate Ligament Reconstruction: A Systematic Review of Randomized Controlled Trials. *Arthroscopy, 35*(3), 996-1003. doi:https://dx.doi.org/10.1016/j.arthro.2018.10.127

Bell, D.R., Pfeiffer, K.A., Cadmus-Bertram, L.A., Trigsted, S.M., Kelly, A., Post, E.G., Hart, J.M., Cook, D.B., Dunn, W.R., & Kuenze, C. (2017). Objectively Measured Physical Activity in Patients After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med, 45*(8), 1893-1900. doi:10.1177/0363546517698940

Benjaminse, A., Holden, S., & Myer, G.D. (2018). ACL rupture is a single leg injury but a double leg problem: too much focus on 'symmetry' alone and that's not enough! *Br J Sports Med*. doi:10.1136/bjsports-2017-098502

Bennell, K., Wajswelner, H., Lew, P., Schall-Riaucour, A., Leslie, S., Plant, D., & Cirone, J. (1998). Isokinetic strength testing does not predict hamstring injury in Australian Rules footballers. *Br J Sports Med, 32*(4), 309-314. doi:10.1136/bjsm.32.4.309

Bennell, K.L., van Ginckel, A., Kean, C.O., Nelligan, R.K., French, S.D., Stokes, M., Pietrosimone, B., Blackburn, T., Batt, M., Hunter, D.J., Spiers, L., & Hinman, R.S. (2016). Patient Knowledge and Beliefs About Knee Osteoarthritis After Anterior Cruciate Ligament Injury and Reconstruction. *Arthritis Care Res (Hoboken), 68*(8), 1180-1185. doi:10.1002/acr.22794

Bennell, K.L., Wrigley, T.V., Hunt, M.A., Lim, B.W., & Hinman, R.S. (2013). Update on the role of muscle in the genesis and management of knee osteoarthritis. *Rheum Dis Clin North Am, 39*(1), 145-176. doi:10.1016/j.rdc.2012.11.003

Besier, T.F., Lloyd, D.G., & Ackland, T.R. (2003). Muscle activation strategies at the knee during running and cutting maneuvers. *Med Sci Sports Exerc, 35*(1), 119-127. doi:10.1097/00005768-200301000-00019

Bieler, T., Sobol, N.A., Andersen, L.L., Kiel, P., Lofholm, P., Aagaard, P., Magnusson, S.P., Krogsgaard, M.R., & Beyer, N. (2014). The effects of high-intensity versus low-intensity resistance training on leg extensor power and recovery of knee function after ACL-reconstruction. *BioMed research international, 2014*, 278512. doi:10.1155/2014/278512

Birchmeier, T., Lisee, C., Geers, B., & Kuenze, C. (2019a). Reactive Strength Index and Knee Extension Strength Characteristics Are Predictive of Single-Leg Hop Performance After Anterior Cruciate Ligament Reconstruction. *J Strength Cond Res, 33*(5), 1201-1207. doi:10.1519/JSC.0000000000003102

Birchmeier, T., Lisee, C., Kane, K., Brazier, B., Triplett, A., & Kuenze, C. (2019b). Quadriceps Muscle Size Following ACL Injury and Reconstruction: A Systematic Review. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. doi:10.1002/jor.24489

Blagojevic, M., Jinks, C., Jeffery, A., & Jordan, K.P. (2010). Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage, 18*(1), 24-33. doi:10.1016/j.joca.2009.08.010

Bodkin, S., Goetschius, J., Hertel, J., & Hart, J. (2017). Relationships of Muscle Function and Subjective Knee Function in Patients After ACL Reconstruction. *Orthop J Sports Med, 5*(7), 2325967117719041. doi:10.1177/2325967117719041

Bremander, A.B., Dahl, L.L., & Roos, E.M. (2007). Validity and reliability of functional performance tests in meniscectomized patients with or without knee osteoarthritis. *Scand J Med Sci Sports, 17*(2), 120-127. doi:10.1111/j.1600-0838.2006.00544.x

Brewer, B.W., Cornelius, A.E., Van Raalte, J.L., Petitpas, A.J., Sklar, J.H., Pohlman, M.H., Krushell, R.J., & Ditmar, T.D. (2003). Age-Related Differences in Predictors of Adherence to Rehabilitation After Anterior Cruciate Ligament Reconstruction. *J Athl Train, 38*(2), 158-162.

Brewer, B.W., Van Raalte, J.L., Cornelius, A.E., Petitpas, A.J., Sklar, J.H., Pohlman, M.H., Krushell, R.J., & Ditmar, T.D. (2000). Psychological factors, rehabilitation adherence, and rehabilitation outcome after anterior cruciate ligament reconstruction. *Rehabil Psychol, 45*(1), 20-37. doi:10.1037/0090-5550.45.1.20

Bricca, A., Juhl, C.B., Steultjens, M., Wirth, W., & Roos, E.M. (2018). Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: a systematic review of randomised controlled trials. *Br J Sports Med*. doi:10.1136/bjsports-2017-098661

Buckwalter, J.A., Mankin, H.J., & Grodzinsky, A.J. (2005). Articular cartilage and osteoarthritis. *Instr Course Lect, 54*, 465-480.

Burgi, C.R., Peters, S., Ardern, C.L., Magill, J.R., Gomez, C.D., Sylvain, J., & Reiman, M.P. (2019). Which criteria are used to clear patients to return-to-sport after primary ACL reconstruction? A scoping review. *Br J Sports Med*. doi:10.1136/bjsports-2018-099982

Cameron, K.L., Thompson, B.S., Peck, K.Y., Owens, B.D., Marshall, S.W., & Svoboda, S.J. (2013). Normative values for the KOOS and WOMAC in a young athletic population: history of knee ligament injury is associated with lower scores. *Am J Sports Med, 41*(3), 582-589. doi:10.1177/0363546512472330

Capin, J.J., Khandha, A., Zarzycki, R., Arundale, A.J.H., Ziegler, M.L., Manal, K., Buchanan, T.S., & Snyder-Mackler, L. (2018). Gait mechanics and tibiofemoral loading in men of the ACL-SPORTS randomized control trial. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. doi:10.1002/jor.23895

Capin, J.J., Zarzycki, R., Ito, N., Khandha, A., Dix, C., Manal, K., Buchanan, T.S., & Snyder-Mackler, L. (2019). Gait Mechanics in Women of the ACL-SPORTS Randomized Control Trial: Interlimb Symmetry Improves Over Time Regardless of Treatment Group. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. doi:10.1002/jor.24314

Carey, D.L., Crossley, K.M., Whiteley, R., Mosler, A., Ong, K.L., Crow, J., & Morris, M.E. (2018). Modeling Training Loads and Injuries: The Dangers of Discretization. *Medicine and science in sports and exercise, 50*(11), 2267-2276. doi:10.1249/Mss.0000000000001685

Chalmers, P.N., Mall, N.A., Moric, M., Sherman, S.L., Paletta, G.P., Cole, B.J., & Bach, B.R., Jr. (2014). Does ACL reconstruction alter natural history?: A systematic literature review of long-term outcomes. *J Bone Joint Surgery, 96*(4), 292-300. doi:10.2106/JBJS.L.01713

Chaudhari, A.M.W., Briant, P.L., Bevill, S.L., Koo, S., & Andriacchi, T.P. (2008). Knee Kinematics, Cartilage Morphology, and Osteoarthritis after ACL Injury. *Med Sci Sports Exerc, 40*(2), 215-222. doi:10.1249/mss.0b013e31815cbb0e

Chen, A.T., Shrestha, S., Collins, J.E., Sullivan, J.K., Losina, E., & Katz, J.N. (2020). Estimating contextual effect in nonpharmacological therapies for pain in knee osteoarthritis: a systematic analytic review. *Osteoarthritis and Cartilage, 28*(9), 1154-1169. doi:10.1016/j.joca.2020.05.007

Chen, T., Wang, S., Li, Y., Ai, C., Jiang, F., & Chen, S. (2019). Radiographic Osteoarthritis Prevalence Over Ten Years After Anterior Cruciate Ligament Reconstruction. *Int J Sports Med, 40*(11), 683-695. doi:10.1055/a-0902-8539

Chmielewski, T.L., Hurd, W.J., Rudolph, K.S., Axe, M.J., & Snyder-Mackler, L. (2005). Perturbation training improves knee kinematics and reduces muscle co-contraction after complete unilateral anterior cruciate ligament rupture. *Phys Ther, 85*(8), 740-749; discussion 750-744.

Chu, C.R., Williams, A.A., Coyle, C.H., & Bowers, M.E. (2012). Early diagnosis to enable early treatment of pre-osteoarthritis. *Arthritis Res Ther, 14*(3), 212. doi:10.1186/ar3845

Chu, I.J.H., Lim, A.Y.T., & Ng, C.L.W. (2018). Effects of meaningful weight loss beyond symptomatic relief in adults with knee osteoarthritis and obesity: a systematic review and meta-analysis. *Obes Rev, 19*(11), 1597-1607. doi:10.1111/obr.12726

Church, S., & Keating, J.F. (2005). Reconstruction of the anterior cruciate ligament: timing of surgery and the incidence of meniscal tears and degenerative change. *J Bone Joint Surg Br, 87*(12), 1639-1642. doi:10.1302/0301-620X.87B12.16916

Cinque, M.E., Dornan, G.J., Chahla, J., Moatshe, G., & LaPrade, R.F. (2018). High Rates of Osteoarthritis Develop After Anterior Cruciate Ligament Surgery: An Analysis of 4108 Patients. *Am J Sports Med, 46*(8), 2011-2019. doi:10.1177/0363546517730072

Claes, S., Hermie, L., Verdonk, R., Bellemans, J., & Verdonk, P. (2013). Is osteoarthritis an inevitable consequence of anterior cruciate ligament reconstruction? A meta-analysis. *Knee Surg Sports Traumatol Arthrosc, 21*(9), 1967-1976. doi:10.1007/s00167-012-2251-8

Clark, A.L., Leonard, T.R., Barclay, L.D., Matyas, J.R., & Herzog, W. (2006). Heterogeneity in patellofemoral cartilage adaptation to anterior cruciate ligament transection; chondrocyte shape and deformation with compression. *Osteoarthritis Cartilage, 14*(2), 120-130. doi:10.1016/j.joca.2005.08.016

Collette, M., Courville, J., Forton, M., & Gagniere, B. (2012). Objective evaluation of anterior knee laxity; comparison of the KT-1000 and GNRB(R) arthrometers. *Knee Surg Sports Traumatol Arthrosc, 20*(11), 2233-2238. doi:10.1007/s00167-011-1869-2

Collins, J.E., Katz, J.N., Dervan, E.E., & Losina, E. (2014). Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis and Cartilage, 22*(5), 622-630. doi:10.1016/j.joca.2014.03.009

Collins, N.J., Barton, C.J., van Middelkoop, M., Callaghan, M.J., Rathleff, M.S., Vicenzino, B.T., Davis, I.S., Powers, C.M., Macri, E.M., Hart, H.F., de Oliveira Silva, D., & Crossley, K.M. (2018). 2018 Consensus statement on exercise therapy and physical interventions (orthoses, taping and manual therapy) to treat patellofemoral pain: recommendations from the 5th International Patellofemoral Pain Research Retreat, Gold Coast, Australia, 2017. *Br J Sports Med, 52*(18), 1170-1178. doi:10.1136/bjsports-2018-099397

Collins, N.J., Misra, D., Felson, D.T., Crossley, K.M., & Roos, E.M. (2011). Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken), 63 Suppl 11*, S208-228. doi:10.1002/acr.20632

Collins, N.J., Prinsen, C.A., Christensen, R., Bartels, E.M., Terwee, C.B., & Roos, E.M. (2016). Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. *Osteoarthritis Cartilage, 24*(8), 1317-1329. doi:10.1016/j.joca.2016.03.010

Conaghan, P. (2006). Is MRI useful in osteoarthritis? *Best Pract Res Clin Rheumatol, 20*(1), 57-68. doi:10.1016/j.berh.2005.08.003

Cooper, C., Snow, S., McAlindon, T.E., Kellingray, S., Stuart, B., Coggon, D., & Dieppe, P.A. (2000). Risk factors for the incidence and progression of radiographic knee osteoarthritis. *Arthritis Rheum, 43*(5), 995. doi:10.1002/1529-0131(200005)43:5<995::aid-anr6>3.0.co;2-1

Cooper, R.L., Taylor, N.F., & Feller, J.A. (2005a). A randomised controlled trial of proprioceptive and balance training after surgical reconstruction of the anterior cruciate ligament. *Res Sports Med, 13*(3), 217-230. doi:10.1080/15438620500222547

Cooper, R.L., Taylor, N.F., & Feller, J.A. (2005b). A systematic review of the effect of proprioceptive and balance exercises on people with an injured or reconstructed

anterior cruciate ligament. *Res Sports Med, 13*(2), 163-178. doi:10.1080/15438620590956197

Coronado, R.A., Bird, M.L., Van Hoy, E.E., Huston, L.J., Spindler, K.P., & Archer, K.R. (2018). Do psychosocial interventions improve rehabilitation outcomes after anterior cruciate ligament reconstruction? A systematic review. *Clin Rehabil, 32*(3), 287-298. doi:10.1177/0269215517728562

Costa-Paz, M., Muscolo, D.L., Ayerza, M., Makino, A., & Aponte-Tinao, L. (2001). Magnetic resonance imaging follow-up study of bone bruises associated with anterior cruciate ligament ruptures. *Arthroscopy, 17*(5), 445-449. doi:10.1053/jars.2001.23581

Cox, C.L., Huston, L.J., Dunn, W.R., Reinke, E.K., Nwosu, S.K., Parker, R.D., Wright, R.W., Kaeding, C.C., Marx, R.G., Amendola, A., McCarty, E.C., & Spindler, K.P. (2014). Are articular cartilage lesions and meniscus tears predictive of IKDC, KOOS, and Marx activity level outcomes after anterior cruciate ligament reconstruction? A 6-year multicenter cohort study. *Am J Sports Med, 42*(5), 1058-1067. doi:10.1177/0363546514525910

Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., Bridgett, L., Williams, S., Guillemin, F., Hill, C.L., Laslett, L.L., Jones, G., Cicuttini, F., Osborne, R., Vos, T., Buchbinder, R., Woolf, A., & March, L. (2014). The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis, 73*(7), 1323-1330. doi:10.1136/annrheumdis-2013-204763

Crossley, K.M., Patterson, B.E., Culvenor, A.G., Bruder, A.M., Mosler, A.B., & Mentiplay, B.F. (2020). Making football safer for women: a systematic review and meta-analysis of injury prevention programmes in 11 773 female football (soccer) players. *Br J Sports Med, 54*(18), 1089-1098. doi:10.1136/bjsports-2019-101587

Csintalan, R.P., Inacio, M.C., & Funahashi, T.T. (2008). Incidence rate of anterior cruciate ligament reconstructions. *The Permanente journal, 12*(3), 17-21.

Culvenor, A., & Barton, C. (2017). It is time to stop wasting time and money debating graft types and surgical approaches for ACL injuries: The secret probably lies in optimising rehabilitation. Retrieved from https://blogs.bmj.com/bjsm/2017/09/20/. Accessed 7 July 2020

Culvenor, A., Collins, N., Vicenzino, B., Cook, J., Whitehead, T., Morris, H., & Crossley, K. (2014a). Factors associated with anterior knee pain 12 months follow hamstring tendon autograft ACL reconstruction. *Journal of Science and Medicine in Sport, 18, Supplement 1*, e44. doi:http://dx.doi.org/10.1016/j.jsams.2014.11.243

Culvenor, A.G., Alexander, B.C., Clark, R.A., Collins, N.J., Ageberg, E., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2016a). Dynamic Single-Leg Postural Control Is Impaired Bilaterally Following Anterior Cruciate Ligament Reconstruction: Implications for Reinjury Risk. *J Orthop Sports Phys Ther, 46*(5), 357-364. doi:10.2519/jospt.2016.6305

Culvenor, A.G., Boeth, H., Diederichs, G., Wirth, W., Duda, G., & Eckstein, F. (2016b). Longitudinal bone, muscle and adipose tissue changes in physically active subjects - sex differences during adolescence and maturity. *J Musculoskelet Neuronal Interact, 16*(3), 237-246.

Culvenor, A.G., Collins, N.J., Guermazi, A., Cook, J.L., Vicenzino, B., Khan, K.M., Beck, N., Van Leeuwen, J., & Crossley, K.M. (2015a). Early Knee Osteoarthritis Is Evident One Year Following Anterior Cruciate Ligament Reconstruction: A Magnetic Resonance Imaging Evaluation. *Arthritis & Rheumatology, 67*(4), 946-955. doi:10.1002/art.39005

Culvenor, A.G., Collins, N.J., Guermazi, A., Cook, J.L., Vicenzino, B., Whitehead, T.S., Morris, H.G., & Crossley, K.M. (2016c). Early Patellofemoral Osteoarthritis Features One Year After Anterior Cruciate Ligament Reconstruction: Symptoms and Quality of Life at Three Years. *Arthritis Care Res (Hoboken), 68*(6), 784-792. doi:10.1002/acr.22761

Culvenor, A.G., Collins, N.J., Vicenzino, B., Cook, J.L., Whitehead, T.S., Morris, H.G., & Crossley, K.M. (2016d). Predictors and effects of patellofemoral pain following hamstring-tendon ACL reconstruction. *Journal of Science and Medicine in Sport, 19*(7), 518-523. doi:10.1016/j.jsams.2015.07.008

Culvenor, A.G., Cook, J.L., Collins, N.J., & Crossley, K.M. (2013). Is patellofemoral joint osteoarthritis an under-recognised outcome of anterior cruciate ligament reconstruction? A narrative literature review. *Br J Sports Med, 47*(2), 66-70. doi:10.1136/bjsports-2012-091490

Culvenor, A.G., & Crossley, K.M. (2016). Patellofemoral Osteoarthritis: Are We Missing an Important Source of Symptoms After Anterior Cruciate Ligament Reconstruction? *J Orthop Sports Phys Ther, 46*(4), 232-234. doi:10.2519/jospt.2016.0603

Culvenor, A.G., Eckstein, F., Wirth, W., Lohmander, L.S., & Frobell, R. (2019a). Loss of patellofemoral cartilage thickness over 5 years following ACL injury depends on the initial treatment strategy: results from the KANON trial. *Br J Sports Med, 53*(18), 1168-1173. doi:10.1136/bjsports-2018-100167

Culvenor, A.G., Engen, C.N., Oiestad, B.E., Engebretsen, L., & Risberg, M.A. (2015b). Defining the presence of radiographic knee osteoarthritis: a comparison between the Kellgren and Lawrence system and OARSI atlas criteria. *Knee Surg Sports Traumatol Arthrosc, 23*(12), 3532-3539. doi:10.1007/s00167-014-3205-0

Culvenor, A.G., Lai, C.C., Gabbe, B.J., Makdissi, M., Collins, N.J., Vicenzino, B., Morris, H.G., & Crossley, K.M. (2014b). Patellofemoral OA is prevalent and associated with worse symptoms and function after hamstring tendon autograft ACL reconstruction. *Br J Sports Med, 48*(6), 435-439. doi:10.1136/bjsports-2013-092975

Culvenor, A.G., Oiestad, B.E., Hart, H.F., Stefanik, J.J., Guermazi, A., & Crossley, K.M. (2019b). Prevalence of knee osteoarthritis features on magnetic resonance imaging in asymptomatic uninjured adults: a systematic review and meta-analysis. *Br J Sports Med, 53*(20), 1268-1278. doi:10.1136/bjsports-2018-099257

Culvenor, A.G., Patterson, B.E., Guermazi, A., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2017a). Accelerated return-to-sport after ACL reconstruction and early knee osteoarthritis features at 1 year: an exploratory study. *PM R*. doi:10.1016/j.pmrj.2017.09.005

Culvenor, A.G., Perraton, L., Guermazi, A., Bryant, A.L., Whitehead, T.S., Morris, H.G., & Crossley, K.M. (2016e). Knee kinematics and kinetics are associated with early patellofemoral osteoarthritis following anterior cruciate ligament reconstruction. *Osteoarthritis Cartilage*. doi:10.1016/j.joca.2016.05.010

Culvenor, A.G., Ruhdorfer, A., Juhl, C., Eckstein, F., & Øiestad, B.E. (2017b). Knee Extensor Strength and Risk of Structural, Symptomatic, and Functional Decline in Knee Osteoarthritis: A Systematic Review and Meta-Analysis. *Arthritis Care Res, 69*(5), 649-658. doi:10.1002/acr.23005

Culvenor, A.G., Schache, A.G., Vicenzino, B., Pandy, M.G., Collins, N.J., Cook, J.L., & Crossley, K.M. (2014c). Are knee biomechanics different in those with and without patellofemoral osteoarthritis after anterior cruciate ligament reconstruction? *Arthritis Care Res (Hoboken), 66*(10), 1566-1570.

Culvenor, A.G., Segal, N.A., Guermazi, A., Roemer, F., Felson, D.T., Nevitt, M.C., Lewis, C.E., & Stefanik, J.J. (2019c). Sex-Specific Influence of Quadriceps Weakness on Worsening Patellofemoral and Tibiofemoral Cartilage Damage: A Prospective Cohort Study. *Arthritis Care Res (Hoboken), 71*(10), 1360-1365. doi:10.1002/acr.23773

Daniel, D.M., Malcom, L.L., Losse, G., Stone, M.L., Sachs, R., & Burks, R. (1985). Instrumented measurement of anterior laxity of the knee. *J Bone Joint Surg, 67*(5), 720-726.

Daniel, D.M., Stone, M.L., Dobson, B.E., Fithian, D.C., Rossman, D.J., & Kaufman, K.R. (1994). Fate of the ACL-injured patient. A prospective outcome study. *Am J Sports Med, 22*(5), 632-644. doi:10.1177/036354659402200511

Davies-Tuck, M.L., Wluka, A.E., Wang, Y., English, D.R., Giles, G.G., & Cicuttini, F. (2009). The natural history of bone marrow lesions in community-based adults with no clinical knee osteoarthritis. *Ann Rheum Dis, 68*(6), 904-908. doi:10.1136/ard.2008.092973

Davies, G.J., McCarty, E., Provencher, M., & Manske, R.C. (2017). ACL Return-to-sport Guidelines and Criteria. *Current Reviews in Musculoskeletal Medicine, 10*(3), 307-314. doi:10.1007/s12178-017-9420-9

De Oliveira Silva, D., Pazzinatto, M.F., Rathleff, M.S., Holden, S., Bell, E., Azevedo, F., & Barton, C. (2020). Patient Education for Patellofemoral Pain: A Systematic Review. *J Orthop Sports Phys Ther, 50*(7), 388-396. doi:10.2519/jospt.2020.9400

Della Villa, F., Buckthorpe, M., Grassi, A., Nabiuzzi, A., Tosarelli, F., Zaffagnini, S., & Della Villa, S. (2020). Systematic video analysis of ACL injuries in professional male football (soccer): injury mechanisms, situational patterns and biomechanics study on 134 consecutive cases. *Br J Sports Med*, bjsports-2019-2011. doi:10.1136/bjsports-2019-101247

Dillon, C.F., Rasch, E.K., Gu, Q., & Hirsch, R. (2006). Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. *J Rheumatol, 33*(11), 2271-2279.

Ding, C., Cicuttini, F., Scott, F., Boon, C., & Jones, G. (2005). Association of prevalent and incident knee cartilage defects with loss of tibial and patellar cartilage: a longitudinal study. *Arthritis and rheumatism, 52*(12), 3918-3927. doi:10.1002/art.21474

Ding, C., Jones, G., Wluka, A.E., & Cicuttini, F. (2010). What can we learn about osteoarthritis by studying a healthy person against a person with early onset of disease? *Curr Opin Rheumatol, 22*(5), 520-527. doi:10.1097/BOR.0b013e32833b90e9

Ding, C., Martel-Pelletier, J., Pelletier, J.P., Abram, F., Raynauld, J.P., Cicuttini, F., & Jones, G. (2007). Knee meniscal extrusion in a largely non-osteoarthritic cohort: association with greater loss of cartilage volume. *Arthritis Res Ther, 9*(2), R21. doi:10.1186/ar2132

Dingenen, B., & Gokeler, A. (2017). Optimization of the Return-to-Sport Paradigm After Anterior Cruciate Ligament Reconstruction: A Critical Step Back to Move Forward. *Sports Med, 47*(8), 1487-1500. doi:10.1007/s40279-017-0674-6

Doherty, T.J. (2001). The influence of aging and sex on skeletal muscle mass and strength. *Current Opinion in Clinical Nutrition and Metabolic Care, 4*(6), 503-508. doi:Doi 10.1097/00075197-200111000-00007

Driban, J.B., Eaton, C.B., Lo, G.H., Ward, R.J., Lu, B., & McAlindon, T.E. (2014). Association of knee injuries with accelerated knee osteoarthritis progression: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken), 66*(11), 1673-1679. doi:10.1002/acr.22359

Ebert, J.R., Edwards, P., Yi, L., Joss, B., Ackland, T., Carey-Smith, R., Buelow, J.U., & Hewitt, B. (2018). Strength and functional symmetry is associated with post-operative rehabilitation in patients following anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc, 26*(8), 2353-2361. doi:10.1007/s00167-017-4712-6

Eckstein, F., Wirth, W., Lohmander, L.S., Hudelmaier, M.I., & Frobell, R.B. (2015). 5-year followup of knee joint cartilage thickness changes after acute rupture of the ACL. *Arthritis & rheumatology (Hoboken, NJ), 67*(1), 152-161. doi:10.1002/art.38881

Ehde, D.M., Dillworth, T.M., & Turner, J.A. (2014). Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. *Am Psychol, 69*(2), 153-166. doi:10.1037/a0035747

Eldridge, S.M., Chan, C.L., Campbell, M.J., Bond, C.M., Hopewell, S., Thabane, L., Lancaster, G.A., & group, P.c. (2016). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ, 355*, i5239. doi:10.1136/bmj.i5239

Elm, E.V., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., & Vandenbroucke, J.P. (2007). Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ, 335*(7624), 806-808. doi:10.1136/bmj.39335.541782.ad

Emery, C.A., Whittaker, J.L., Mahmoudian, A., Lohmander, L.S., Roos, E.M., Bennell, K.L., Toomey, C.M., Reimer, R.A., Thompson, D., Ronsky, J.L., Kuntze, G., Lloyd, D.G., Andriacchi, T., Englund, M., Kraus, V.B., Losina, E., Bierma-Zeinstra, S., Runhaar, J., Peat, G., Luyten, F.P., Snyder-Mackler, L., Risberg, M.A., Mobasheri, A., Guermazi, A., Hunter,

D.J., & Arden, N.K. (2019). Establishing outcome measures in early knee osteoarthritis. *Nat Rev Rheumatol, 15*(7), 438-448. doi:10.1038/s41584-019-0237-3

Engelen-Van Melick, N., Van Cingel, R.E.H., Tijssen, M.P.W., & Nijhuis-Van Der Sanden, M.W.G. (2013). Assessment of functional performance after anterior cruciate ligament reconstruction: a systematic review of measurement procedures. *Knee Surg, Sports Traum, Arthrosc, 21*(4), 869-879. doi:10.1007/s00167-012-2030-6

Englund, M., Roos, E.M., & Lohmander, L.S. (2003). Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. *Arthritis and rheumatism, 48*(8), 2178-2187. doi:10.1002/art.11088

Ericsson, Y.B., Roos, E.M., & Frobell, R.B. (2013). Lower extremity performance following ACL rehabilitation in the KANON-trial: impact of reconstruction and predictive value at 2 and 5 years. *Br J Sports Med, 47*(15), 980-985. doi:10.1136/bjsports-2013-092642

Escamilla, R.F., Fleisig, G.S., Zheng, N., Barrentine, S.W., Wilk, K.E., & Andrews, J.R. (1998). Biomechanics of the knee during closed kinetic chain and open kinetic chain exercises. *Med Sci Sports Exerc, 30*(4), 556-569. doi:10.1097/00005768-199804000-00014

Escobedo, E.M., Hunter, J.C., Zink-Brody, G.C., Wilson, A.J., Harrison, S.D., & Fisher, D.J. (1996). Usefulness of turbo spin-echo MR imaging in the evaluation of meniscal tears: comparison with a conventional spin-echo sequence. *AJR Am J Roentgenol, 167*(5), 1223-1227. doi:10.2214/ajr.167.5.8911185

Everhart, J.S., Best, T.M., & Flanigan, D.C. (2015). Psychological predictors of anterior cruciate ligament reconstruction outcomes: a systematic review. *Knee Surg Sports Traumatol Arthrosc, 23*(3), 752-762. doi:10.1007/s00167-013-2699-1

Faulkner, J.A., Larkin, L.M., Claflin, D.R., & Brooks, S.V. (2007). AGE-RELATED CHANGES IN THE STRUCTURE AND FUNCTION OF SKELETAL MUSCLES. *Clinical and Experimental Pharmacology and Physiology, 34*(11), 1091-1096. doi:10.1111/j.1440-1681.2007.04752.x

Felson, D.T., Chaisson, C.E., Hill, C.L., Totterman, S.M., Gale, M.E., Skinner, K.M., Kazis, L., & Gale, D.R. (2001). The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med, 134*(7), 541-549.

Felson, D.T., Naimark, A., Anderson, J., Kazis, L., Castelli, W., & Meenan, R.F. (1987). The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis and rheumatism, 30*(8), 914-918. doi:10.1002/art.1780300811

Felson, D.T., Niu, J., Guermazi, A., Roemer, F., Aliabadi, P., Clancy, M., Torner, J., Lewis, C.E., & Nevitt, M.C. (2007). Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. *Arthritis and rheumatism, 56*(9), 2986-2992. doi:10.1002/art.22851

Felson, D.T., Zhang, Y., Hannan, M.T., Naimark, A., Weissman, B., Aliabadi, P., & Levy, D. (1997). Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis and rheumatism, 40*(4), 728-733. doi:10.1002/art.1780400420

Feucht, M.J., Cotic, M., Saier, T., Minzlaff, P., Plath, J.E., Imhoff, A.B., & Hinterwimmer, S. (2016). Patient expectations of primary and revision anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc, 24*(1), 201-207. doi:10.1007/s00167-014-3364-z

Filbay, S.R., Ackerman, I.N., Dhupelia, S., Arden, N.K., & Crossley, K.M. (2018a). Quality of Life in Symptomatic Individuals After Anterior Cruciate Ligament Reconstruction, With and Without Radiographic Knee Osteoarthritis. *J Orthop Sports Phys Ther, 48*(5), 398-408. doi:10.2519/jospt.2018.7830

Filbay, S.R., Ackerman, I.N., Russell, T.G., & Crossley, K.M. (2017a). Return-to-sport matters-longer-term quality of life after ACL reconstruction in people with knee difficulties. *Scand J Med Sci Sports, 27*(5), 514-524. doi:10.1111/sms.12698

Filbay, S.R., Ackerman, I.N., Russell, T.G., Macri, E.M., & Crossley, K.M. (2014). Health-related QoL after ACLR: a systematic review. *Am J Sports Med, 42*(5), 1247-1255. doi:10.1177/0363546513512774

Filbay, S.R., Andersson, C., Ardern, C., Gauffin, H., & Kvist, J. (2018b). Patient-reported outcome 32 to 37 years following surgically treated or non-surgically treated acute anterior cruciate ligament injury. *Osteoarthritis and Cartilage, 26*, S52-S53. doi:10.1016/j.joca.2018.02.117

Filbay, S.R., Crossley, K.M., & Ackerman, I.N. (2016). Activity preferences, lifestyle modifications and re-injury fears influence longer-term quality of life in people with knee symptoms following anterior cruciate ligament reconstruction: a qualitative study. *J Physiother, 62*(2), 103-110. doi:10.1016/j.jphys.2016.02.011

Filbay, S.R., Culvenor, A.G., Ackerman, I.N., Russell, T.G., & Crossley, K.M. (2015). Quality of life in anterior cruciate ligament-deficient individuals: a systematic review and meta-analysis. *Br J Sports Med, 49*(16), 1033-1041. doi:10.1136/bjsports-2015-094864

Filbay, S.R., & Grindem, H. (2019). Evidence-based recommendations for the management of anterior cruciate ligament (ACL) rupture. *Best Pract Res Clin Rheumatol, 33*(1), 33-47. doi:10.1016/j.berh.2019.01.018

Filbay, S.R., Roos, E.M., Frobell, R.B., Roemer, F., Ranstam, J., & Lohmander, L.S. (2017b). Delaying ACL reconstruction and treating with exercise therapy alone may alter prognostic factors for 5-year outcome: an exploratory analysis of the KANON trial. *Br J Sports Med, 51*(22), 1622-1629. doi:10.1136/bjsports-2016-097124

Flanigan, D.C., Everhart, J.S., Pedroza, A., Smith, T., & Kaeding, C.C. (2013). Fear of reinjury (kinesiophobia) and persistent knee symptoms are common factors for lack of return-to-sport after anterior cruciate ligament reconstruction. *Arthroscopy, 29*(8), 1322-1329. doi:10.1016/j.arthro.2013.05.015

Fox, M.G. (2007). MR imaging of the meniscus: review, current trends, and clinical implications. *Magn Reson Imaging Clin N Am, 15*(1), 103-123. doi:10.1016/j.mric.2007.02.004

Fransen, M., McConnell, S., Harmer, A.R., Van der Esch, M., Simic, M., & Bennell, K.L. (2015). Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev, 1*, CD004376. doi:10.1002/14651858.CD004376.pub3

Frobell, R.B. (2011). Change in Cartilage Thickness, Posttraumatic Bone Marrow Lesions, and Joint Fluid Volumes After Acute ACL Disruption. *J Bone Joint Surg, 93*(12), 1096-1103. doi:10.2106/jbjs.j.00929

Frobell, R.B., Le Graverand, M.P., Buck, R., Roos, E.M., Roos, H.P., Tamez-Pena, J., Totterman, S., & Lohmander, L.S. (2009). The acutely ACL injured knee assessed by MRI: changes in joint fluid, bone marrow lesions, and cartilage during the first year. *Osteoarthritis Cartilage, 17*(2), 161-167. doi:10.1016/j.joca.2008.06.020

Frobell, R.B., Roos, E.M., Roos, H.P., Ranstam, J., & Lohmander, L.S. (2010). A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med, 363*(4), 331-342. doi:10.1056/NEJMoa0907797

Frobell, R.B., Roos, H.P., Roos, E.M., Roemer, F.W., Ranstam, J., & Lohmander, L.S. (2015). Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. *Br J Sports Med, 49*(10), 700. doi:10.1136/bjsports-2014-f232rep

Furlan, A.D., Pennick, V., Bombardier, C., van Tulder, M., & Editorial Board, C.B.R.G. (2009). 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976), 34*(18), 1929-1941. doi:10.1097/BRS.0b013e3181b1c99f

Gabler, C.M., Jacobs, C.A., Howard, J.S., Mattacola, C.G., & Johnson, D.L. (2016). Comparison of Graft Failure Rate Between Autografts Placed via an Anatomic Anterior Cruciate Ligament Reconstruction Technique: A Systematic Review, Meta-analysis, and Meta-regression. *Am J Sports Med, 44*(4), 1069-1079. doi:10.1177/0363546515584043

Gagnier, J.J., Shen, Y., & Huang, H. (2018). Psychometric Properties of Patient-Reported Outcome Measures for Use in Patients with Anterior Cruciate Ligament Injuries: A Systematic Review. *JBJS Rev, 6*(4), e5. doi:10.2106/JBJS.RVW.17.00114

Galea-O'Neill, R.J., Bruder, A.M., Goulis, J., & Shields, N. (2019). Modifiable factors and their association with self-reported knee function and activity after anterior cruciate ligament

reconstruction: a systematic review and meta-analysis. *Physiother Theory Pract*, 1-14. doi:10.1080/09593985.2019.1655821

Garber, C.E., Blissmer, B., Deschenes, M.R., Franklin, B.A., Lamonte, M.J., Lee, I.M., Nieman, D.C., & Swain, D.P. (2011). Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults. *Med Sci Sports Exerc, 43*(7), 1334-1359. doi:10.1249/mss.0b013e318213fefb

Gardinier, E.S., Di Stasi, S., Manal, K., Buchanan, T.S., & Snyder-Mackler, L. (2014). Knee contact force asymmetries in patients who failed return-to-sport readiness criteria 6 months after anterior cruciate ligament reconstruction. *Am J Sports Med, 42*(12), 2917-2925. doi:10.1177/0363546514552184

Glyn-Jones, S., Palmer, A.J., Agricola, R., Price, A.J., Vincent, T.L., Weinans, H., & Carr, A.J. (2015). Osteoarthritis. *Lancet, 386*(9991), 376-387. doi:10.1016/S0140-6736(14)60802-3

Goddard, K., Roberts, C.-M., Byron-Daniel, J., & Woodford, L. (2020). Psychological factors involved in adherence to sport injury rehabilitation: a systematic review. *International Review of Sport and Exercise Psychology*, 1-23. doi:10.1080/1750984x.2020.1744179

Goff A.J., Page W.S., & Clark N.C. (2018). Reporting of acute programme variables and exercise descriptors in rehabilitation strength training for tibiofemoral joint soft tissue injury: A systematic review. *Phys Ther Sport*, 34:227-37.

Gokeler, A., Hof, A.L., Arnold, M.P., Dijkstra, P.U., Postema, K., & Otten, E. (2010). Abnormal landing strategies after ACL reconstruction. *Scand J Med Sci Sports, 20*(1), e12-19. doi:10.1111/j.1600-0838.2008.00873.x

Gokeler, A., Welling, W., Benjaminse, A., Lemmink, K., Seil, R., & Zaffagnini, S. (2017). A critical analysis of limb symmetry indices of hop tests in athletes after anterior cruciate ligament reconstruction: A case control study. *Orthop Traumatol Surg Res, 103*(6), 947-951. doi:10.1016/j.otsr.2017.02.015

Goldring, S.R. (2008). The role of bone in osteoarthritis pathogenesis. *Rheum Dis Clin North Am, 34*(3), 561-571. doi:10.1016/j.rdc.2008.07.001

Granan, L.-P., Forssblad, M., Lind, M., & Engebretsen, L. (2009). The Scandinavian ACL registries 2004–2007: baseline epidemiology. *Acta Orthopaedica, 80*(5), 563-567. doi:10.3109/17453670903350107

Granan, L.P., Bahr, R., Steindal, K., Furnes, O., & Engebretsen, L. (2008). Development of a national cruciate ligament surgery registry: the Norwegian National Knee Ligament Registry. *Am J Sports Med, 36*(2), 308-315. doi:10.1177/0363546507308939

Green, B., Bourne, M.N., van Dyk, N., & Pizzari, T. (2020). Recalibrating the risk of hamstring strain injury (HSI) - A 2020 systematic review and meta-analysis of risk factors for index and recurrent HSI in sport. *Br J Sports Med, doi: 10.1136/bjsports-2019-100983*. doi:10.1136/bjsports-2019-100983

Greenberg, E.M., Greenberg, E.T., Albaugh, J., Storey, E., & Ganley, T.J. (2018). Rehabilitation Practice Patterns Following Anterior Cruciate Ligament Reconstruction: A Survey of Physical Therapists. *J Orthop Sports Phys Ther, 48*(10), 801-811. doi:10.2519/jospt.2018.8264

Grindem, H., Arundale, A.J., & Ardern, C.L. (2018). Alarming underutilisation of rehabilitation in athletes with anterior cruciate ligament reconstruction: four ways to change the game. *Br J Sports Med*. doi:10.1136/bjsports-2017-098746

Grindem, H., Eitzen, I., Snyder-Mackler, L., & Risberg, M.A. (2014). Online registration of monthly sports participation after anterior cruciate ligament injury: a reliability and validity study. *Br J Sports Med, 48*(9), 748-753. doi:10.1136/bjsports-2012-092075

Grindem, H., Granan, L.P., Risberg, M.A., Engebretsen, L., Snyder-Mackler, L., & Eitzen, I. (2015a). How does a combined preoperative and postoperative rehabilitation programme influence the outcome of ACL reconstruction 2 years after surgery? A comparison between patients in the Delaware-Oslo ACL Cohort and the Norwegian National Knee Ligament Registry. *Br J Sports Med, 49*(6), 385-389. doi:10.1136/bjsports-2014-093891

Grindem, H., Logerstedt, D., Eitzen, I., Moksnes, H., Axe, M.J., Snyder-Mackler, L., Engebretsen, L., & Risberg, M.A. (2011). Single-legged hop tests as predictors of self-reported knee function in nonoperatively treated individuals with anterior cruciate ligament injury. *Am J Sports Med, 39*(11), 2347-2354. doi:10.1177/0363546511417085

Grindem, H., Risberg, M.A., & Eitzen, I. (2015b). Two factors that may underpin outstanding outcomes after ACL rehabilitation. *Br J Sports Med, 49*(22), 1425. doi:10.1136/bjsports-2015-095194

Grindem, H., Snyder-Mackler, L., Moksnes, H., Engebretsen, L., & Risberg, M.A. (2016). Simple decision rules can reduce reinjury risk by 84% after ACL reconstruction: the Delaware-Oslo ACL cohort study. *Br J Sports Med, 50*(13), 804-808. doi:10.1136/bjsports-2016-096031

Grip, H., Tengman, E., & Hager, C.K. (2015). Dynamic knee stability estimated by finite helical axis methods during functional performance approximately twenty years after anterior cruciate ligament injury. *J Biomech, 48*(10), 1906-1914. doi:10.1016/j.jbiomech.2015.04.016

Gudbergsen, H., Bartels, E.M., Krusager, P., Waehrens, E.E., Christensen, R., Danneskiold-Samsoe, B., & Bliddal, H. (2011). Test-retest of computerized health status questionnaires frequently used in the monitoring of knee osteoarthritis: a randomized crossover trial. *BMC Musc Disord, 12*, 190. doi:10.1186/1471-2474-12-190

Gustavsson, A., Neeter, C., Thomee, P., Silbernagel, K.G., Augustsson, J., Thomee, R., & Karlsson, J. (2006). A test battery for evaluating hop performance in patients with an ACL injury and patients who have undergone ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc, 14*(8), 778-788. doi:10.1007/s00167-006-0045-6

Haberfield, M., Patterson, B., Crossley, K., Bruder, A., Guermazi, A., Whitehead, T., Morris, H., & Culvenor, A. (2020). Should return to pivoting sport be advocated in the secondary prevention of osteoarthritis after anterior cruciate ligament reconstruction? A prospective cohort study with MRI, radiographic and symptomatic outcomes. *Osteoarthritis and Cartilage* (under review).

Hagino, T., Ochiai, S., Senga, S., Yamashita, T., Wako, M., Ando, T., & Haro, H. (2015). Meniscal tears associated with anterior cruciate ligament injury. *Archives of Orthopaedic and Trauma Surgery, 135*(12), 1701-1706. doi:10.1007/s00402-015-2309-4

Haitz, K., Shultz, R., Hodgins, M., & Matheson, G.O. (2014). Test-retest and interrater reliability of the functional lower extremity evaluation. *J Orthop Sports Phys Ther, 44*(12), 947-954. doi:10.2519/jospt.2014.4809

Hamilton, R.T., Shultz, S.J., Schmitz, R.J., & Perrin, D.H. (2008). Triple-hop distance as a valid predictor of lower limb strength and power. *J Athl Train, 43*(2), 144-151. doi:10.4085/1062-6050-43.2.144

Hamrin Senorski, E., Svantesson, E., Baldari, A., Ayeni, O.R., Engebretsen, L., Franceschi, F., Karlsson, J., & Samuelsson, K. (2019). Factors that affect patient reported outcome after anterior cruciate ligament reconstruction-a systematic review of the Scandinavian knee ligament registers. *Br J Sports Med, 53*(7), 410-417. doi:10.1136/bjsports-2017-098191

Hamrin Senorski, E., Svantesson, E., Beischer, S., Grassi, A., Krupic, F., Thomee, R., & Samuelsson, K. (2018). Factors Affecting the Achievement of a Patient-Acceptable Symptom State 1 Year After Anterior Cruciate Ligament Reconstruction: A Cohort Study of 343 Patients From 2 Registries. *Orthop J Sports Med, 6*(4), 2325967118764317. doi:10.1177/2325967118764317

Hanna, F.S., Teichtahl, A.J., Wluka, A.E., Wang, Y., Urquhart, D.M., English, D.R., Giles, G.G., & Cicuttini, F.M. (2009). Women have increased rates of cartilage loss and progression of cartilage defects at the knee than men: a gender study of adults without clinical knee osteoarthritis. *Menopause, 16*(4), 666-670.

Hanypsiak, B.T., Spindler, K.P., Rothrock, C.R., Calabrese, G.J., Richmond, B., Herrenbruck, T.M., & Parker, R.D. (2008). Twelve-year follow-up on anterior cruciate ligament

reconstruction: long-term outcomes of prospectively studied osseous and articular injuries. *Am J Sports Med, 36*(4), 671-677. doi:10.1177/0363546508315468

Harkey, M.S., Luc, B.A., Golightly, Y.M., Thomas, A.C., Driban, J.B., Hackney, A.C., & Pietrosimone, B. (2015). Osteoarthritis-related biomarkers following anterior cruciate ligament injury and reconstruction: a systematic review. *Osteoarthritis Cartilage, 23*(1), 1-12. doi:10.1016/j.joca.2014.09.004

Harris, K.P., Driban, J.B., Sitler, M.R., Cattano, N.M., Balasubramanian, E., & Hootman, J.M. (2017). Tibiofemoral Osteoarthritis After Surgical or Nonsurgical Treatment of Anterior Cruciate Ligament Rupture: A Systematic Review. *Journal of Athletic Training, 52*(6), 507-517. doi:https://dx.doi.org/10.4085/1062-6050-49.3.89

Hart, H.F., Collins, N.J., Ackland, D.C., & Crossley, K.M. (2015). Is impaired knee confidence related to worse kinesiophobia, symptoms, and physical function in people with knee osteoarthritis after anterior cruciate ligament reconstruction? *J Sci Med Sport, 18*(5), 512-517. doi:http://dx.doi.org/10.1016/j.jsams.2014.09.011

Hart, H.F., Culvenor, A.G., Collins, N.J., Ackland, D.C., Cowan, S.M., Machotka, Z., & Crossley, K.M. (2016). Knee kinematics and joint moments during gait following anterior cruciate ligament reconstruction: a systematic review and meta-analysis. *Br J Sports Med, 50*(10), 597-612. doi:10.1136/bjsports-2015-094797

Hart, H.F., Culvenor, A.G., Guermazi, A., & Crossley, K.M. (2020). Worse knee confidence, fear of movement, psychological readiness to return-to-sport and pain are associated with worse function after ACL reconstruction. *Phys Ther Sport, 41*, 1-8. doi:10.1016/j.ptsp.2019.10.006

Hart, J.M., Ko, J.W., Konold, T., & Pietrosimone, B. (2010). Sagittal plane knee joint moments following anterior cruciate ligament injury and reconstruction: a systematic review. *Clin Biomech (Bristol, Avon), 25*(4), 277-283. doi:10.1016/j.clinbiomech.2009.12.004

Hartigan, E., Axe, M.J., & Snyder-Mackler, L. (2009). Perturbation training prior to ACL reconstruction improves gait asymmetries in non-copers. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society, 27*(6), 724-729. doi:10.1002/jor.20754

He, X., Leong, H.T., Lau, O.Y., Ong, M.T., & Yung, P.S. (2020). Altered Neuromuscular Activity of the Lower-Extremities During Landing Tasks in Patients With Anterior Cruciate Ligament Reconstruction: A Systematic Review of Electromyographic Studies. *Journal of sport rehabilitation*, 1-10. doi:10.1123/jsr.2019-0393

Heijne, A., Hagstromer, M., & Werner, S. (2015). A two- and five-year follow-up of clinical outcome after ACL reconstruction using BPTB or hamstring tendon grafts: a prospective intervention outcome study. *Knee Surg Sports Traumatol Arthrosc, 23*(3), 799-807. doi:10.1007/s00167-013-2727-1

Herbert, R. (2019). Research Note: Significance testing and hypothesis testing: meaningless, misleading and mostly unnecessary. *J Physiother, 65*(3), 178-181. doi:10.1016/j.jphys.2019.05.001

Herbst, E., Hoser, C., Hildebrandt, C., Raschner, C., Hepperger, C., Pointner, H., & Fink, C. (2015). Functional assessments for decision-making regarding return-to-sports following ACL reconstruction. Part II: clinical application of a new test battery. *Knee Surg Sports Traumatol Arthrosc, 23*(5), 1283-1291. doi:10.1007/s00167-015-3546-3

Herzog, W., Adams, M.E., Matyas, J.R., & Brooks, J.G. (1993). Hindlimb loading, morphology and biochemistry of articular cartilage in the ACL-deficient cat knee. *Osteoarthritis Cartilage, 1*(4), 243-251. doi:10.1016/s1063-4584(05)80330-9

Higgins, J.P.T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions*. Retrieved from Available from www.handbook.cochrane.org.

Hoffmann, T.C., Glasziou, P.P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D.G., Barbour, V., Macdonald, H., Johnston, M., Lamb, S.E., Dixon-Woods, M., McCulloch, P., Wyatt, J.C., Chan, A.W., & Michie, S. (2014). Better reporting of interventions: template

for intervention description and replication (TIDieR) checklist and guide. *BMJ, 348*, g1687. doi:10.1136/bmj.g1687

Holm, I., Oiestad, B.E., Risberg, M.A., & Aune, A.K. (2010). No difference in knee function or prevalence of osteoarthritis after reconstruction of the anterior cruciate ligament with 4-strand hamstring autograft versus patellar tendon-bone autograft: a randomized study with 10-year follow-up. *Am J Sports Med, 38*(3), 448-454. doi:10.1177/0363546509350301

Holm, I., Oiestad, B.E., Risberg, M.A., Gunderson, R., & Aune, A.K. (2012). No differences in prevalence of osteoarthritis or function after open versus endoscopic technique for anterior cruciate ligament reconstruction: 12-year follow-up report of a randomized controlled trial. *Am J Sports Med, 40*(11), 2492-2498. doi:10.1177/0363546512458766

Hunter, D.J., Altman, R.D., Cicuttini, F., Crema, M.D., Duryea, J., Eckstein, F., Guermazi, A., Kijowski, R., Link, T.M., Martel-Pelletier, J., Miller, C.G., Mosher, T.J., Ochoa-Albiztegui, R.E., Pelletier, J.P., Peterfy, C., Raynauld, J.P., Roemer, F.W., Totterman, S.M., & Gold, G.E. (2015). OARSI Clinical Trials Recommendations: Knee imaging in clinical trials in osteoarthritis. *Osteoarthritis Cartilage, 23*(5), 698-715. doi:10.1016/j.joca.2015.03.012

Hunter, D.J., & Bierma-Zeinstra, S. (2019). Osteoarthritis. *Lancet, 393*(10182), 1745-1759. doi:10.1016/S0140-6736(19)30417-9

Hunter, D.J., Conaghan, P.G., Peterfy, C.G., Bloch, D., Guermazi, A., Woodworth, T., Stevens, R., & Genant, H.K. (2006a). Responsiveness, effect size, and smallest detectable difference of Magnetic Resonance Imaging in knee osteoarthritis. *Osteoarthritis Cartilage, 14 Suppl A*, A112-115. doi:10.1016/j.joca.2006.02.027

Hunter, D.J., Guermazi, A., Lo, G.H., Grainger, A.J., Conaghan, P.G., Boudreau, R.M., & Roemer, F.W. (2011a). Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthritis Cartilage, 19*(8), 990-1002. doi:10.1016/j.joca.2011.05.004

Hunter, D.J., Lo, G.H., Gale, D., Grainger, A.J., Guermazi, A., & Conaghan, P.G. (2008). The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston Leeds Osteoarthritis Knee Score). *Ann Rheum Dis, 67*(2), 206-211. doi:10.1136/ard.2006.066183

Hunter, D.J., Zhang, W., Conaghan, P.G., Hirko, K., Menashe, L., Li, L., Reichmann, W.M., & Losina, E. (2011b). Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. *Osteoarthritis Cartilage, 19*(5), 557-588. doi:10.1016/j.joca.2010.10.029

Hunter, D.J., Zhang, W., Conaghan, P.G., Hirko, K., Menashe, L., Reichmann, W.M., & Losina, E. (2011c). Responsiveness and reliability of MRI in knee osteoarthritis: a meta-analysis of published evidence. *Osteoarthritis Cartilage, 19*(5), 589-605. doi:10.1016/j.joca.2010.10.030

Hunter, D.J., Zhang, Y., Niu, J., Goggins, J., Amin, S., LaValley, M.P., Guermazi, A., Genant, H., Gale, D., & Felson, D.T. (2006b). Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis and rheumatism, 54*(5), 1529-1535. doi:10.1002/art.21789

Ingelsrud, L.H., Granan, L.P., Terwee, C.B., Engebretsen, L., & Roos, E.M. (2015). Proportion of Patients Reporting Acceptable Symptoms or Treatment Failure and Their Associated KOOS Values at 6 to 24 Months After Anterior Cruciate Ligament Reconstruction: A Study From the Norwegian Knee Ligament Registry. *Am J Sports Med*. doi:10.1177/0363546515584041

Irrgang, J.J., Anderson, A.F., Boland, A.L., Harner, C.D., Kurosaka, M., Neyret, P., Richmond, J.C., & Shelborne, K.D. (2001). Development and validation of the international knee documentation committee subjective knee form. *Am J Sports Med, 29*(5), 600-613.

Irrgang, J.J., Anderson, A.F., Boland, A.L., Harner, C.D., Neyret, P., Richmond, J.C., & Shelbourne, K.D. (2006). Responsiveness of the International Knee Documentation Committee

Subjective Knee Form. *Am J Sports Med, 34*(10), 1567-1573. doi:10.1177/0363546506288855

Irrgang, J.J., Ho, H., Harner, C.D., & Fu, F.H. (1998). Use of the International Knee Documentation Committee guidelines to assess outcome following anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc, 6*(2), 107-114. doi:10.1007/s001670050082

Janssen, K.W., Orchard, J.W., Driscoll, T.R., & van Mechelen, W. (2012). High incidence and costs for ACLR performed in Aust. from 2003-2008: time for an ACL register by Scandinavian model? *Scand J Med Sci Sports, 22*(4), 495-501. doi:10.1111/j.1600-0838.2010.01253.x

Javaid, M.K., Lynch, J.A., Tolstykh, I., Guermazi, A., Roemer, F., Aliabadi, P., McCulloch, C., Curtis, J., Felson, D., Lane, N.E., Torner, J., & Nevitt, M. (2010). Pre-radiographic MRI findings are associated with onset of knee symptoms: the most study. *Osteoarthritis Cartilage, 18*(3), 323-328. doi:10.1016/j.joca.2009.11.002

Jerosch, J., Castro, W.H., & Assheuer, J. (1996). Age-related magnetic resonance imaging morphology of the menisci in asymptomatic individuals. *Arch Orthop Trauma Surg, 115*(3-4), 199-202.

Johnston, P.T., McClelland, J.A., & Webster, K.E. (2018). Lower Limb Biomechanics During Single-Leg Landings Following Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-Analysis. *Sports Med, 48*(9), 2103-2126. doi:10.1007/s40279-018-0942-0

Jones, M.H., & Spindler, K.P. (2017). Risk factors for radiographic joint space narrowing and patient reported outcomes of post-traumatic osteoarthritis after ACL reconstruction: Data from the MOON cohort. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society, 35*(7), 1366-1374. doi:10.1002/jor.23557

Jonsson, H., Riklund-Ahlstrom, K., & Lind, J. (2004). Positive pivot shift after ACL reconstruction predicts later osteoarthrosis: 63 patients followed 5-9 years after surgery. *Acta Orthop Scand, 75*(5), 594-599. doi:10.1080/00016470410001484

Jordan, J.M., Helmick, C.G., Renner, J.B., Luta, G., Dragomir, A.D., Woodard, J., Fang, F., Schwartz, T.A., Abbate, L.M., Callahan, L.F., Kalsbeek, W.D., & Hochberg, M.C. (2007). Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *J Rheumatol, 34*(1), 172-180.

Jung, J.Y., Yoon, Y.C., Kwon, J.W., Ahn, J.H., & Choe, B.K. (2009). Diagnosis of internal derangement of the knee at 3.0-T MR imaging: 3D isotropic intermediate-weighted versus 2D sequences. *Radiology, 253*(3), 780-787. doi:10.1148/radiol.2533090457

Kamper, S.J., Maher, C.G., & Mackay, G. (2009). Global rating of change scales: a review of strengths and weaknesses and considerations for design. *J Man Manip Ther, 17*(3), 163-170. doi:10.1179/jmt.2009.17.3.163

Katsuragi, J., Sasho, T., Yamaguchi, S., Sato, Y., Watanabe, A., Akagi, R., Muramatsu, Y., Mukoyama, S., Akatsu, Y., Fukawa, T., Endo, J., Hoshi, H., Yamamoto, Y., Sasaki, T., & Takahashi, K. (2015). Hidden osteophyte formation on plain X-ray is the predictive factor for development of knee osteoarthritis after 48 months--data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage, 23*(3), 383-390. doi:10.1016/j.joca.2014.11.026

Kaur, M., Ribeiro, D.C., Theis, J.-C., Webster, K.E., & Sole, G. (2016). Movement Patterns of the Knee During Gait Following ACL Reconstruction: A Systematic Review and Meta-Analysis. *Sports Med, 46*(12), 1869-1895. doi:10.1007/s40279-016-0510-4

Kellgren, J.H., & Lawrence, J.S. (1957). Radiological assessment of osteo-arthrosis. *Ann Rheum Dis, 16*(4), 494-502.

Kemp, J.L., Coburn, S.L., Jones, D.M., & Crossley, K.M. (2018b). The Physiotherapy for Femoroacetabular Impingement Rehabilitation STudy (physioFIRST): A Pilot Randomized Controlled Trial. *J Orthop Sports Phys Ther, 48*(4), 307-315. doi:10.2519/jospt.2018.7941

Kemp, J.L., Schache, A.G., Makdissi, M., Sims, K., & Crossley, K.M. (2013). Greater understanding of normal hip physical function may guide clinicians in providing targeted rehabilitation programmes. *J Sci Med Sport, 16*, 292-296.

Kockum, B., & Heijne, A.I. (2015). Hop performance and leg muscle power in athletes: Reliability of a test battery. *Phys Ther Sport, 16*(3), 222-227. doi:10.1016/j.ptsp.2014.09.002

Koli, J., Multanen, J., Kujala, U.M., Häkkinen, A., Nieminen, M.T., Kautiainen, H., Lammentausta, E., Jämsä, T., Ahola, R., Selänne, H., Kiviranta, I., & Heinonen, A. (2015). Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. *Med Sci Sports Exerc, 47*(9), 1767-1774. doi:10.1249/mss.0000000000000629

Kornaat, P.R., Ceulemans, R.Y., Kroon, H.M., Riyazi, N., Kloppenburg, M., Carter, W.O., Woodworth, T.G., & Bloem, J.L. (2005). MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. *Skeletal Radiol, 34*(2), 95-102. doi:10.1007/s00256-004-0828-0

Kotsifaki, A., Korakakis, V., Whiteley, R., Van Rossom, S., & Jonkers, I. (2020). Measuring only hop distance during single leg hop testing is insufficient to detect deficits in knee function after ACL reconstruction: a systematic review and meta-analysis. *Br J Sports Med, 54*(3), 139-153. doi:10.1136/bjsports-2018-099918

Kruse, L.M., Gray, B., & Wright, R.W. (2012). Rehabilitation after anterior cruciate ligament reconstruction: a systematic review. *J Bone Joint Surgery, 94*(19), 1737-1748. doi:10.2106/JBJS.K.01246

Kuenze, C., Pietrosimone, B., Lisee, C., Rutherford, M., Birchmeier, T., Lepley, A., & Hart, J. (2019). Demographic and surgical factors affect quadriceps strength after ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc, 27*(3), 921-930. doi:10.1007/s00167-018-5215-9

Kujala, U.M., Jaakkola, L.H., Koskinen, S.K., Taimela, S., Hurme, M., & Nelimarkka, O. (1993). Scoring of patellofemoral disorders. *Arthroscopy, 9*(2), 159-163.

Kvist, J., Osterberg, A., Gauffin, H., Tagesson, S., Webster, K., & Ardern, C. (2013). Translation and measurement properties of the Swedish version of ACL-Return-to-sports after Injury questionnaire. *Scand J Med Sci Sports, 23*(5), 568-575. doi:10.1111/j.1600-0838.2011.01438.x

Kyritsis, P., Bahr, R., Landreau, P., Miladi, R., & Witvrouw, E. (2016). Likelihood of ACL graft rupture: not meeting six clinical discharge criteria before return to sport is associated with a four times greater risk of rupture. *Br J Sports Med, 50*(15), 946-951. doi:10.1136/bjsports-2015-095908

Lafave, M.R., Hiemstra, L., Kerslake, S., Heard, M., & Buchko, G. (2017). Validity, Reliability, and Responsiveness of the Anterior Cruciate Ligament Quality of Life Measure: A Continuation of Its Overall Validation. *Clin J Sport Med, 27*(1), 57-63. doi:10.1097/JSM.0000000000000292

Lancaster, G.A., Dodd, S., & Williamson, P.R. (2004). Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract, 10*(2), 307-312. doi:10.1111/j.2002.384.doc.x

LaPrade, R.F., Burnett, Q.M., 2nd, Veenstra, M.A., & Hodgman, C.G. (1994). The prevalence of abnormal magnetic resonance imaging findings in asymptomatic knees. With correlation of magnetic resonance imaging to arthroscopic findings in symptomatic knees. *Am J Sports Med, 22*(6), 739-745. doi:10.1177/036354659402200603

Laxdal, G., Kartus, J., Ejerhed, L., Sernert, N., Magnusson, L., Faxen, E., & Karlsson, J. (2005). Outcome and risk factors after anterior cruciate ligament reconstruction: a follow-up study of 948 patients. *Arthroscopy, 21*(8), 958-964. doi:10.1016/j.arthro.2005.05.007

Lebel, B., Hulet, C., Galaud, B., Burdin, G., Locker, B., & Vielpeau, C. (2008). Arthroscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone autograft: a minimum 10-year follow-up. *Am J Sports Med, 36*(7), 1275-1282. doi:10.1177/0363546508314721

Lee, T.Q., Morris, G., & Csintalan, R.P. (2003). The influence of tibial and femoral rotation on patellofemoral contact area and pressure. *J Orthop Sports Phys Ther, 33*(11), 686-693. doi:10.2519/jospt.2003.33.11.686

Lee, Y.S., Jeong, Y.M., Sim, J.A., Kwak, J.H., Kim, K.H., Nam, S.W., & Lee, B.K. (2013). Specific compartmental analysis of cartilage status in double-bundle ACL reconstruction patients: a comparative study using pre- and postoperative MR images. *Knee Surg Sports Traumatol Arthrosc, 21*(3), 702-707. doi:10.1007/s00167-012-2046-y

Lentz, T.A., Tillman, S.M., Indelicato, P.A., Moser, M.W., George, S.Z., & Chmielewski, T.L. (2009). Factors associated with function after anterior cruciate ligament reconstruction. *Sports health, 1*(1), 47-53. doi:10.1177/1941738108326700

Lepley, A.S., Pietrosimone, B., & Cormier, M.L. (2018). Quadriceps Function, Knee Pain, and Self-Reported Outcomes in Patients With Anterior Cruciate Ligament Reconstruction. *J Athl Train, 53*(4), 337-346. doi:10.4085/1062-6050-245-16

Lepley, L.K. (2015). Deficits in Quadriceps Strength and Patient-Oriented Outcomes at Return to Activity After ACL Reconstruction: A Review of the Current Literature. *Sports health, 7*(3), 231-238. doi:10.1177/1941738115578112

Lepley, L.K., & Palmieri-Smith, R.M. (2015). Quadriceps Strength, Muscle Activation Failure, and Patient-Reported Function at the Time of Return to Activity in Patients Following Anterior Cruciate Ligament Reconstruction: A Cross-sectional Study. *J Orthop Sports Phys Ther, 45*(12), 1017-1025. doi:10.2519/jospt.2015.5753

Li, R.T., Lorenz, S., Xu, Y., Harner, C.D., Fu, F.H., & Irrgang, J.J. (2011a). Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. *Am J Sports Med, 39*(12), 2595-2603. doi:10.1177/0363546511424720

Li, S., Chen, Y., Lin, Z., Cui, W., Zhao, J., & Su, W. (2012). A systematic review of randomized controlled clinical trials comparing hamstring autografts versus bone-patellar tendon-bone autografts for the reconstruction of the anterior cruciate ligament. *Arch Orthop Trauma Surg, 132*(9), 1287-1297. doi:10.1007/s00402-012-1532-5

Li, S., Su, W., Zhao, J., Xu, Y., Bo, Z., Ding, X., & Wei, Q. (2011b). A meta-analysis of hamstring autografts versus bone-patellar tendon-bone autografts for reconstruction of the anterior cruciate ligament. *Knee, 18*(5), 287-293. doi:10.1016/j.knee.2010.08.002

Li, X., Kuo, D., Theologis, A., Carballido-Gamio, J., Stehling, C., Link, T.M., Ma, C.B., & Majumdar, S. (2011c). Cartilage in anterior cruciate ligament-reconstructed knees: MR imaging T1{rho} and T2--initial experience with 1-year follow-up. *Radiology, 258*(2), 505-514. doi:10.1148/radiol.10101006

Li, Y.L., Ning, G.Z., Wu, Q., Wu, Q.L., Li, Y., Hao, Y., & Feng, S.Q. (2014). Single-bundle or double-bundle for anterior cruciate ligament reconstruction: a meta-analysis. *Knee, 21*(1), 28-37. doi:10.1016/j.knee.2012.12.004

Lie, M.M., Risberg, M.A., Storheim, K., Engebretsen, L., & Oiestad, B.E. (2019). What's the rate of knee osteoarthritis 10 years after anterior cruciate ligament injury? An updated systematic review. *Br J Sports Med*. doi:10.1136/bjsports-2018-099751

Liebl, H., Joseph, G., Nevitt, M.C., Singh, N., Heilmeier, U., Subburaj, K., Jungmann, P.M., McCulloch, C.E., Lynch, J.A., Lane, N.E., & Link, T.M. (2015). Early T2 changes predict onset of radiographic knee osteoarthritis: data from the osteoarthritis initiative. *Ann Rheum Dis, 74*(7), 1353-1359. doi:10.1136/annrheumdis-2013-204157

Lien-Iversen, T., Morgan, D.B., Jensen, C., Risberg, M.A., Engebretsen, L., & Viberg, B. (2020). Does surgery reduce knee osteoarthritis, meniscal injury and subsequent complications compared with non-surgery after ACL rupture with at least 10 years follow-up? A systematic review and meta-analysis. *Br J Sports Med, 54*(10), 592-598. doi:10.1136/bjsports-2019-100765

Lind, M., Menhert, F., & Pedersen, A.B. (2009). The first results from the Danish ACL reconstruction registry: epidemiologic and 2 year follow-up results from 5,818 knee ligament reconstructions. *Knee Surg, Sports Traum, Arthrosc, 17*(2), 117-124. doi:10.1007/s00167-008-0654-3

Lisee, C., Lepley, A.S., Birchmeier, T., O'Hagan, K., & Kuenze, C. (2019a). Quadriceps Strength and Volitional Activation After Anterior Cruciate Ligament Reconstruction: A Systematic

Review and Meta-analysis. *Sports health, 11*(2), 163-179. doi:10.1177/1941738118822739

Lisee, C., Slater, L., Hertel, J., & Hart, J.M. (2019b). Effect of Sex and Level of Activity on Lower-Extremity Strength, Functional Performance, and Limb Symmetry. *Journal of sport rehabilitation, 28*(5), 413-420.

Liu-Ambrose, T., Taunton, J.E., MacIntyre, D., McConkey, P., & Khan, K.M. (2003). The effects of proprioceptive or strength training on the neuromuscular function of the ACL reconstructed knee: a randomized clinical trial. *Scand J Med Sci Sports, 13*(2), 115-123. doi:10.1034/j.1600-0838.2003.02113.x

Liu, L., Ishijima, M., Kaneko, H., Sadatsuki, R., Hada, S., Kinoshita, M., Aoki, T., Futami, I., Yusup, A., Arita, H., Shiozawa, J., Takazawa, Y., Ikeda, H., & Kaneko, K. (2017). The MRI-detected osteophyte score is a predictor for undergoing joint replacement in patients with end-stage knee osteoarthritis. *Mod Rheumatol, 27*(2), 332-338. doi:10.1080/14397595.2016.1206509

Lo, G.H., McAlindon, T.E., Niu, J., Zhang, Y., Beals, C., Dabrowski, C., Le Graverand, M.P., Hunter, D.J., & Group, O.A.I.I. (2009). Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis Cartilage, 17*(12), 1562-1569. doi:10.1016/j.joca.2009.06.006

Loeser, R.F., Beavers, D.P., Bay-Jensen, A.C., Karsdal, M.A., Nicklas, B.J., Guermazi, A., Hunter, D.J., & Messier, S.P. (2017). Effects of dietary weight loss with and without exercise on interstitial matrix turnover and tissue inflammation biomarkers in adults with knee osteoarthritis: the Intensive Diet and Exercise for Arthritis trial (IDEA). *Osteoarthritis Cartilage, 25*(11), 1822-1828. doi:10.1016/j.joca.2017.07.015

Logerstedt, D., Grindem, H., Lynch, A., Eitzen, I., Engebretsen, L., Risberg, M.A., Axe, M.J., & Snyder-Mackler, L. (2012). Single-legged hop tests as predictors of self-reported knee function after anterior cruciate ligament reconstruction: the Delaware-Oslo ACL cohort study. *Am J Sports Med, 40*(10), 2348-2356. doi:10.1177/0363546512457551

Logerstedt, D.S., Scalzitti, D., Risberg, M.A., Engebretsen, L., Webster, K.E., Feller, J., Snyder-Mackler, L., Axe, M.J., & McDonough, C.M. (2017). Knee Stability and Movement Coordination Impairments: Knee Ligament Sprain Revision 2017. *J Orthop Sports Phys Ther, 47*(11), A1-A47. doi:10.2519/jospt.2017.0303

Lohmander, L.S., Englund, P.M., Dahl, L.L., & Roos, E.M. (2007). The long-term consequence of ACL and meniscus injuries: OA. *Am J Sports Med, 35*(10), 1756-1769. doi:10.1177/0363546507307396

Lohmander, L.S., Ostenberg, A., Englund, M., & Roos, H. (2004). High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis and rheumatism, 50*(10), 3145-3152. doi:10.1002/art.20589

Losciale, J.M., Bullock, G., Cromwell, C., Ledbetter, L., Pietrosimone, L., & Sell, T.C. (2019). Hop Testing Lacks Strong Association With Key Outcome Variables After Primary Anterior Cruciate Ligament Reconstruction: A Systematic Review. *Am J Sports Med*, 363546519838794. doi:10.1177/0363546519838794

Luc, B., Gribble, P.A., & Pietrosimone, B.G. (2014). Osteoarthritis prevalence following anterior cruciate ligament reconstruction: a systematic review and numbers-needed-to-treat analysis. *J Athl Train, 49*(6), 806-819. doi:10.4085/1062-6050-49.3.35

Lyman, S., Koulouvaris, P., Sherman, S., Do, H., Mandl, L.A., & Marx, R.G. (2009). Epidemiology of anterior cruciate ligament reconstruction: trends, readmissions, and subsequent knee surgery. *J Bone Joint Surgery, 91*(10), 2321-2328. doi:10.2106/JBJS.H.00539

Macri, E.M., Felson, D.T., Zhang, Y., Guermazi, A., Roemer, F.W., Crossley, K.M., Khan, K.M., & Stefanik, J.J. (2017). Patellofemoral morphology and alignment: reference values and dose-response patterns for the relation to MRI features of patellofemoral osteoarthritis. *Osteoarthritis Cartilage, 25*(10), 1690-1697. doi:10.1016/j.joca.2017.06.005

Macri, E.M., Patterson, B.E., Crossley, K.M., Stefanik, J.J., Guermazi, A., Blomqwist, E., Khan, K.M., Whitehead, T.S., Morris, H.G., & Culvenor, A.G. (2019). Does patellar alignment or trochlear morphology predict worsening of patellofemoral disease within the first 5 years after anterior cruciate ligament reconstruction? *Eur J Radiol, 113*, 32-38. doi:10.1016/j.ejrad.2019.01.033

Madry, H., van Dijk, C.N., & Mueller-Gerbl, M. (2010). The basic science of the subchondral bone. *Knee Surg Sports Traumatol Arthrosc, 18*(4), 419-433. doi:10.1007/s00167-010-1054-z

Makris, E.A., Hadidi, P., & Athanasiou, K.A. (2011). The knee meniscus: Structure–function, pathophysiology, current repair techniques, and prospects for regeneration. *Biomaterials, 32*(30), 7411-7431. doi:10.1016/j.biomaterials.2011.06.037

Malfait, A.M. (2016). Osteoarthritis year in review 2015: biology. *Osteoarthritis and Cartilage, 24*(1), 21-26. doi:10.1016/j.joca.2015.09.010

Mall, N.A., Chalmers, P.N., Moric, M., Tanaka, M.J., Cole, B.J., Bach, B.R., Jr., & Paletta, G.A., Jr. (2014). Incidence and trends of anterior cruciate ligament reconstruction in the United States. *Am J Sports Med, 42*(10), 2363-2370. doi:10.1177/0363546514542796

Markatos, K., Kaseta, M.K., Lallos, S.N., Korres, D.S., & Efstathopoulos, N. (2013). The anatomy of the ACL and its importance in ACL reconstruction. *Eur J Orthop Surg Traumatol, 23*(7), 747-752. doi:10.1007/s00590-012-1079-8

Markhardt, B.K., Li, G., & Kijowski, R. (2018). The Clinical Significance of Osteophytes in Compartments of the Knee Joint With Normal Articular Cartilage. *AJR Am J Roentgenol, 210*(4), W164-W171. doi:10.2214/AJR.17.18664

Marx, R.G., Connor, J., Lyman, S., Amendola, A., Andrish, J.T., Kaeding, C., McCarty, E.C., Parker, R.D., Wright, R.W., Spindler, K.P., & Multicenter Orthopaedic Outcomes, N. (2005). Multirater agreement of arthroscopic grading of knee articular cartilage. *Am J Sports Med, 33*(11), 1654-1657. doi:10.1177/0363546505275129

Menzer, H., Slater, L.V., Diduch, D., Miller, M., Norte, G., Goetschius, J., & Hart, J.M. (2017). The Utility of Objective Strength and Functional Performance to Predict Subjective Outcomes After Anterior Cruciate Ligament Reconstruction. *Orthop J Sports Med, 5*(12), 2325967117744758. doi:10.1177/2325967117744758

Messier, S.P., Beavers, D.P., Mihalko, S.L., Miller, G.D., Lyles, M.F., Hunter, D.J., Carr, J.J., Eckstein, F., Guermazi, A., Loeser, R.F., & DeVita, P. (2020). The effects of intensive dietary weight loss and exercise on gait in overweight and obese adults with knee osteoarthritis. The Intensive Diet and Exercise for Arthritis (IDEA) trial. *J Biomech, 98*, 109477. doi:10.1016/j.jbiomech.2019.109477

Messier, S.P., Gutekunst, D.J., Davis, C., & DeVita, P. (2005). Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis and rheumatism, 52*(7), 2026-2032. doi:10.1002/art.21139

Messier, S.P., Legault, C., Loeser, R.F., Van Arsdale, S.J., Davis, C., Ettinger, W.H., & DeVita, P. (2011). Does high weight loss in older adults with knee osteoarthritis affect bone-on-bone joint loads and muscle forces during walking? *Osteoarthritis Cartilage, 19*(3), 272-280. doi:10.1016/j.joca.2010.11.010

Meuffels, D.E., Poldervaart, M.T., Diercks, R.L., Fievez, A.W., Patt, T.W., Hart, C.P.V.D., Hammacher, E.R., Meer, F.V.D., Goedhart, E.A., Lenssen, A.F., Muller-Ploeger, S.B., Pols, M.A., & Saris, D.B.F. (2012). Guideline on anterior cruciate ligament injury. *Acta Orthopaedica, 83*(4), 379-386. doi:10.3109/17453674.2012.704563

Middleton, K.K., Hamilton, T., Irrgang, J.J., Karlsson, J., Harner, C.D., & Fu, F.H. (2014). Anatomic anterior cruciate ligament (ACL) reconstruction: a global perspective. Part 1. *Knee Surg Sports Traumatol Arthrosc, 22*(7), 1467-1482. doi:10.1007/s00167-014-2846-3

Miller, R.E., Tran, P.B., Obeidat, A.M., Raghu, P., Ishihara, S., Miller, R.J., & Malfait, A.-M. (2015). The Role of Peripheral Nociceptive Neurons in the Pathophysiology of Osteoarthritis Pain. *Current Osteoporosis Reports, 13*(5), 318-326. doi:10.1007/s11914-015-0280-1

Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gotzsche, P.C., Devereaux, P.J., Elbourne, D., Egger, M., Altman, D.G., & Consort. (2012). CONSORT 2010 explanation and elaboration:

updated guidelines for reporting parallel group randomised trials. *Int J Surg, 10*(1), 28-55. doi:10.1016/j.ijsu.2011.10.001

Mohr, A., Roemer, F.W., Genant, H.K., & Liess, C. (2003). Using fat-saturated proton density-weighted MR imaging to evaluate articular cartilage. *AJR Am J Roentgenol, 181*(1), 280-281; author reply 281-282. doi:10.2214/ajr.181.1.1810280a

Mohtadi, N. (1998). Development and validation of the quality of life outcome measure (questionnaire) for chronic anterior cruciate ligament deficiency. *Am J Sports Med, 26*(3), 350-359.

Mohtadi, N.G., & Chan, D.S. (2018). Return to Sport-Specific Performance After Primary Anterior Cruciate Ligament Reconstruction: A Systematic Review. *Am J Sports Med, 46*(13), 3307-3316. doi:10.1177/0363546517732541

Moller, E., Weidenhielm, L., & Werner, S. (2009). Outcome and knee-related quality of life after anterior cruciate ligament reconstruction: a long-term follow-up. *Knee Surg Sports Traumatol Arthrosc, 17*(7), 786-794. doi:10.1007/s00167-009-0788-y

Montalvo, A.M., Schneider, D.K., Silva, P.L., Yut, L., Webster, K.E., Riley, M.A., Kiefer, A.W., Doherty-Restrepo, J.L., & Myer, G.D. (2018). 'What's my risk of sustaining an ACL injury while playing football (soccer)?' A systematic review with meta-analysis. *Br J Sports Med*. doi:10.1136/bjsports-2016-097261

Moses, B., Orchard, J., & Orchard, J. (2012). Systematic review: Annual incidence of ACL injury and surgery in various populations. *Res Sports Med, 20*(3-4), 157-179. doi:10.1080/15438627.2012.680633

Mouarbes, D., Menetrey, J., Marot, V., Courtot, L., Berard, E., & Cavaignac, E. (2019). Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-analysis of Outcomes for Quadriceps Tendon Autograft Versus Bone-Patellar Tendon-Bone and Hamstring-Tendon Autografts. *Am J Sports Med*, 363546518825340. doi:10.1177/0363546518825340

Mulford, J.S., Hutchinson, S.E., & Hang, J.R. (2013). Outcomes for primary anterior cruciate reconstruction with the quadriceps autograft: a systematic review. *Knee Surg Sports Traumatol Arthrosc, 21*(8), 1882-1888. doi:10.1007/s00167-012-2212-2

Muller, B., Yabroudi, M.A., Lynch, A., Lai, C.L., van Dijk, C.N., Fu, F.H., & Irrgang, J.J. (2016). Defining Thresholds for the Patient Acceptable Symptom State for the IKDC Subjective Knee Form and KOOS for Patients Who Underwent ACL Reconstruction. *Am J Sports Med, 44*(11), 2820-2826. doi:10.1177/0363546516652888

Multanen, J., Nieminen, M.T., Häkkinen, A., Kujala, U.M., Jämsä, T., Kautiainen, H., Lammentausta, E., Ahola, R., Selänne, H., Ojala, R., Kiviranta, I., & Heinonen, A. (2014). Effects of High-Impact Training on Bone and Articular Cartilage: 12-Month Randomized Controlled Quantitative MRI Study. *J Bone Miner Res, 29*(1), 192-201. doi:10.1002/jbmr.2015

Munro, A.G., & Herrington, L.C. (2011). Between-session reliability of four hop tests and the agility T-test. *J Strength Cond Res, 25*(5), 1470-1477. doi:10.1519/JSC.0b013e3181d83335

Munugoda, I.P., Beavers, D.P., Wirth, W., Aitken, D.A., Loeser, R.F., Miller, G.D., Lyles, M., Carr, J.J., Guermazi, A., Hunter, D.J., Messier, S.P., & Eckstein, F. (2020). The effect of weight loss on the progression of meniscal extrusion and size in knee osteoarthritis: a post-hoc analysis of the Intensive Diet and Exercise for Arthritis (IDEA) trial. *Osteoarthritis Cartilage, 28*(4), 410-417. doi:10.1016/j.joca.2020.01.006

Myers, B.A., Jenkins, W.L., Killian, C., & Rundquist, P. (2014). Normative data for hop tests in high school and collegiate basketball and soccer players. *Int J Sports Phys Ther, 9*(5), 596-603.

Nagai, K., Nakamura, T., & Fu, F.H. (2018). The diagnosis of early osteoarthritis of the knee using magnetic resonance imaging. *Annals of Joint, 3*, 110-110. doi:10.21037/aoj.2018.12.05

Nagelli, C.V., & Hewett, T.E. (2017). Should Return to Sport be Delayed Until 2 Years After Anterior Cruciate Ligament Reconstruction? Biological and Functional Considerations. *Sports Med, 47*(2), 221-232. doi:10.1007/s40279-016-0584-z

Nakamae, A., Engebretsen, L., Bahr, R., Krosshaug, T., & Ochi, M. (2006). Natural history of bone bruises after acute knee injury: clinical outcome and histopathological findings. *Knee Surg Sports Traumatol Arthrosc, 14*(12), 1252-1258. doi:10.1007/s00167-006-0087-9

National Health Medical Research Council. (2007). *National statement on ethical conduct in human research*. Canberra: Australian Research Council

Neeter, C., Gustavsson, A., Thomee, P., Augustsson, J., Thomee, R., & Karlsson, J. (2006). Development of a strength test battery for evaluating leg muscle power after ACL injury and reconstruction. *Knee Surg Sports Traumatol Arthrosc, 14*(6), 571-580. doi:10.1007/s00167-006-0040-y

Negahban, H., Mazaheri, M., Kingma, I., & van Dieen, J.H. (2014). A systematic review of postural control during single-leg stance in patients with untreated anterior cruciate ligament injury. *Knee Surg Sports Traumatol Arthrosc, 22*(7), 1491-1504. doi:10.1007/s00167-013-2501-4

Neogi, T., Bowes, M.A., Niu, J., De Souza, K.M., Vincent, G.R., Goggins, J., Zhang, Y., & Felson, D.T. (2013). Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the osteoarthritis initiative. *Arthritis and rheumatism, 65*(8), 2048-2058. doi:10.1002/art.37987

Nguyen, J., Marx, R., Hidaka, C., Wilson, S., & Lyman, S. (2017). Validation of electronic administration of knee surveys among ACL-injured patients. *Knee Surg Sports Traumatol Arthrosc, 25*(10), 3116-3122. doi:10.1007/s00167-016-4189-8

Nielsen, R.O., Shrier, I., Casals, M., Nettel-Aguirre, A., Moller, M., Bolling, C., Bittencourt, N.F.N., Clarsen, B., Wedderkopp, N., Soligard, T., Timpka, T., Emery, C., Bahr, R., Jacobsson, J., Whiteley, R., Dahlstrom, O., van Dyk, N., Pluim, B.M., Stamatakis, E., Palacios-Derflingher, L., Fagerland, M.W., Khan, K.M., Ardern, C.L., & Verhagen, E. (2020). Statement on methods in sport injury research from the 1st METHODS MATTER Meeting, Copenhagen, 2019. *Br J Sports Med*. doi:10.1136/bjsports-2019-101323

Norte, G.E., Hertel, J., Saliba, S.A., Diduch, D.R., & Hart, J.M. (2018). Quadriceps Function and Patient-Reported Outcomes After Anterior Cruciate Ligament Reconstruction in Patients With or Without Knee Osteoarthritis. *J Athl Train, 53*(10), 965-975. doi:10.4085/1062-6050-170-17

Noyes, F.R., Barber, S.D., & Mangine, R.E. (1991). Abnormal lower limb symmetry determined by function hop tests after anterior cruciate ligament rupture. *Am J Sports Med, 19*(5), 513-518.

Nussbaum, R., Kelly, C., Quinby, E., Mac, A., Parmanto, B., & Dicianno, B.E. (2019). Systematic Review of Mobile Health Applications in Rehabilitation. *Arch Phys Med Rehabil, 100*(1), 115-127. doi:10.1016/j.apmr.2018.07.439

O'Halloran, P.D., Blackstock, F., Shields, N., Holland, A., Iles, R., Kingsley, M., Bernhardt, J., Lannin, N., Morris, M.E., & Taylor, N.F. (2014). Motivational interviewing to increase physical activity in people with chronic health conditions: a systematic review and meta-analysis. *Clin Rehabil, 28*(12), 1159-1171. doi:10.1177/0269215514536210

O'Keeffe, M., Hayes, A., McCreesh, K., Purtill, H., & O'Sullivan, K. (2017). Are group-based and individual physiotherapy exercise programmes equally effective for musculoskeletal conditions? A systematic review and meta-analysis. *Br J Sports Med, 51*(2), 126-132. doi:10.1136/bjsports-2015-095410

Oei, E.H.G., Van Tiel, J., Robinson, W.H., & Gold, G.E. (2014). Quantitative Radiologic Imaging Techniques for Articular Cartilage Composition: Toward Early Diagnosis and Development of Disease-Modifying Therapeutics for Osteoarthritis. *Arthritis Care Res, 66*(8), 1129-1141. doi:10.1002/acr.22316

Oiestad, B.E., Holm, I., Aune, A.K., Gunderson, R., Myklebust, G., Engebretsen, L., Fosdahl, M.A., & Risberg, M.A. (2010a). Knee function and prevalence of knee OA after ACLR: a prospective study with 10-15 years follow-up. *Am J Sports Med, 38*(11), 2201-2210. doi:10.1177/0363546510373876

Oiestad, B.E., Holm, I., Engebretsen, L., Aune, A.K., Gunderson, R., & Risberg, M.A. (2013). The prevalence of patellofemoral osteoarthritis 12 years after anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc, 21*(4), 942-949. doi:10.1007/s00167-012-2161-9

Oiestad, B.E., Holm, I., Engebretsen, L., & Risberg, M.A. (2011). The association between radiographic knee OA and knee symptoms, function and quality of life 10-15 years after ACLR. *Br J Sports Med, 45*(7), 583-588. doi:10.1136/bjsm.2010.073130

Oiestad, B.E., Holm, I., Gunderson, R., Myklebust, G., & Risberg, M.A. (2010b). Quadriceps muscle weakness after anterior cruciate ligament reconstruction: a risk factor for knee osteoarthritis? *Arthritis Care Res (Hoboken), 62*(12), 1706-1714. doi:10.1002/acr.20299

Oiestad, B.E., Holm, I., & Risberg, M.A. (2018). Return to pivoting sport after ACL reconstruction: association with osteoarthritis and knee function at the 15-year follow-up. *Br J Sports Med*. doi:10.1136/bjsports-2017-097718

Oiestad, B.E., Juhl, C.B., Eitzen, I., & Thorlund, J.B. (2015). Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis Cartilage, 23*(2), 171-177. doi:10.1016/j.joca.2014.10.008

Outerbridge, R.E. (1961). The etiology of chondromalacia patellae. *J Bone Joint Surg Br, 43-B*, 752-757.

Pairot-de-Fontenay, B., Willy, R.W., Elias, A.R.C., Mizner, R.L., Dube, M.O., & Roy, J.S. (2019). Running Biomechanics in Individuals with Anterior Cruciate Ligament Reconstruction: A Systematic Review. *Sports Med, 49*(9), 1411-1424. doi:10.1007/s40279-019-01120-x

Palmieri-Smith, R.M., & Lepley, L.K. (2015). Quadriceps Strength Asymmetry After Anterior Cruciate Ligament Reconstruction Alters Knee Joint Biomechanics and Functional Performance at Time of Return to Activity. *Am J Sports Med*. doi:10.1177/0363546515578252

Palmieri-Smith, R.M., & Thomas, A.C. (2009). A neuromuscular mechanism of posttraumatic osteoarthritis associated with ACL injury. *Exerc Sport Sci Rev, 37*(3), 147-153. doi:10.1097/JES.0b013e3181aa6669

Palmieri-Smith, R.M., Villwock, M., Downie, B., Hecht, G., & Zernicke, R. (2013). Pain and effusion and quadriceps activation and strength. *J Athl Train, 48*(2), 186-191. doi:10.4085/1062-6050-48.2.10

Pan, J., Pialat, J.B., Joseph, T., Kuo, D., Joseph, G.B., Nevitt, M.C., & Link, T.M. (2011). Knee cartilage T2 characteristics and evolution in relation to morphologic abnormalities detected at 3-T MR imaging: a longitudinal study of the normal control cohort from the Osteoarthritis Initiative. *Radiology, 261*(2), 507-515. doi:10.1148/radiol.11102234

Panzer, S., Augat, P., Atzwanger, J., & Hergan, K. (2012). 3-T MRI assessment of osteophyte formation in patients with unilateral anterior cruciate ligament injury and reconstruction. *Skeletal Radiol, 41*(12), 1597-1604. doi:10.1007/s00256-012-1445-y

Papalia, R., Torre, G., Vasta, S., Zampogna, B., Pedersen, D.R., Denaro, V., & Amendola, A. (2015). Bone bruises in anterior cruciate ligament injured knee and long-term outcomes. A review of the evidence. *Open Access J Sports Med, 6*, 37-48. doi:10.2147/OAJSM.S75345

Paradowski, P.T., Bergman, S., Sunden-Lundius, A., Lohmander, L.S., & Roos, E.M. (2006). Knee complaints vary with age and gender in the adult population. Population-based reference data for the Knee injury and Osteoarthritis Outcome Score (KOOS). *BMC Musculoskelet Disord, 7*, 38. doi:10.1186/1471-2474-7-38

Patel, S.A., Hageman, J., Quatman, C.E., Wordeman, S.C., & Hewett, T.E. (2014). Prevalence and Location of Bone Bruises Associated with Anterior Cruciate Ligament Injury and Implications for Mechanism of Injury: A Systematic Review. *Sports Med, 44*(2), 281-293. doi:10.1007/s40279-013-0116-z

Paterno, M.V., Schmitt, L.C., Ford, K.R., Rauh, M.J., Myer, G.D., Huang, B., & Hewett, T.E. (2010). Biomechanical measures during landing and postural stability predict second anterior cruciate ligament injury after anterior cruciate ligament reconstruction and return to sport. *Am J Sports Med, 38*(10), 1968-1978. doi:10.1177/0363546510376053

Patterson, B., Crossley, K., Culvenor, A., & Barton, C. (2016). *Shared decision making rarely occurs during return to sport following anterior cruciate ligament reconstruction.* Paper presented at the XXVI International Conference of Sport Rehabilitation and Traumatology Football Medicine Strategies, Barcelona, Spain, .

Patterson, B., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2020a). Poor functional performance 1 year after ACL reconstruction increases the risk of early osteoarthritis progression. *Br J Sports Med, 54*(9), 546-553. doi:10.1136/bjsports-2019-101503

Patterson, B.E., Crossley, K.M., Perraton, L.G., Kumar, A.S., King, M.G., Heerey, J.J., Barton, C.J., & Culvenor, A.G. (2020b). Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function. *Phys Ther Sport, 44*, 67-74. doi:10.1016/j.ptsp.2020.04.031

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., & Crossley, K.M. (2020c). Patient-Reported Outcomes One to Five Years After Anterior Cruciate Ligament Reconstruction: The Effect of Combined Injury and Associations With Osteoarthritis Features Defined on Magnetic Resonance Imaging. *Arthritis Care Res, 72*(3), 412-422. doi:10.1002/acr.23854

Patterson, B.E., Culvenor, A.G., Barton, C.J., Guermazi, A., Stefanik, J.J., Morris, H.G., Whitehead, T.S., & Crossley, K.M. (2018). Worsening Knee Osteoarthritis Features on Magnetic Resonance Imaging 1 to 5 Years After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med, 46*(12), 2873-2883. doi:10.1177/0363546518789685

Peat, G., Thomas, E., Handy, J., Wood, L., Dziedzic, K., Myers, H., Wilkie, R., Duncan, R., Hay, E., Hill, J., Lacey, R., & Croft, P. (2006). The Knee Clinical Assessment Study – CAS(K). A prospective study of knee pain and knee osteoarthritis in the general population: baseline recruitment and retention at 18 months. *BMC Musculoskeletal Disorders, 7*(1). doi:10.1186/1471-2474-7-30

Pereira, D., Peleteiro, B., Araújo, J., Branco, J., Santos, R.A., & Ramos, E. (2011). The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis and Cartilage, 19*(11), 1270-1285. doi:10.1016/j.joca.2011.08.009

Perraton, L., Clark, R., Crossley, K., Pua, Y.H., Whitehead, T., Morris, H., Telianidis, S., & Bryant, A. (2017). Impaired voluntary quadriceps force control following anterior cruciate ligament reconstruction: relationship with knee function. *Knee Surg Sports Traumatol Arthrosc, 25*(5), 1424-1431. doi:10.1007/s00167-015-3937-5

Perraton, L.G., Clark, R.A., Crossley, K.M., Pua, Y.H., Whitehead, T.S., Morris, H.G., Culvenor, A.G., & Bryant, A.L. (2019). Greater knee flexion excursion/moment in hopping is associated with better knee function following anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc, 27*(2), 596-603. doi:10.1007/s00167-018-5197-7

Perraton, L.G., Hall, M., Clark, R.A., Crossley, K.M., Pua, Y.H., Whitehead, T.S., Morris, H.G., Culvenor, A.G., & Bryant, A.L. (2018). Poor knee function after ACL reconstruction is associated with attenuated landing force and knee flexion moment during running. *Knee Surg Sport Tr A, 26*(2), 391-398. doi:10.1007/s00167-017-4810-5

Perriman, A., Leahy, E., & Semciw, A.I. (2018). The Effect of Open- Versus Closed-Kinetic-Chain Exercises on Anterior Tibial Laxity, Strength, and Function Following Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-analysis. *J Orthop Sports Phys Ther, 48*(7), 552-566. doi:10.2519/jospt.2018.7656

Peterfy, C.G., Guermazi, A., Zaim, S., Tirman, P.F., Miaux, Y., White, D., Kothari, M., Lu, Y., Fye, K., Zhao, S., & Genant, H.K. (2004). Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. *Osteoarthritis Cartilage, 12*(3), 177-190. doi:10.1016/j.joca.2003.11.003

Petersen, W., Taheri, P., Forkel, P., & Zantop, T. (2014). Return to play following ACL reconstruction: a systematic review about strength deficits. *Archives of Orthopaedic and Trauma Surgery, 134*(10), 1417-1428. doi:10.1007/s00402-014-1992-x

Pinczewski, L.A., Lyman, J., Salmon, L.J., Russell, V.J., Roe, J., & Linklater, J. (2007). A 10-year comparison of ACLR with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. *Am J Sports Med, 35*(4), 564-574. doi:10.1177/0363546506296042

Pizzari, T., McBurney, H., Taylor, N.F., & Feller, J.A. (2002). Adherence to anterior cruciate ligament rehabilitation: A qualitative analysis. *Journal of sport rehabilitation, 11*(2), 90-102. doi:DOI 10.1123/jsr.11.2.90

Pizzari, T., Taylor, N.F., McBurney, H., & Feller, J.A. (2005). Adherence to rehabilitation after anterior cruciate ligament reconstructive surgery: Implications for outcome. *Journal of sport rehabilitation, 14*(3), 201-214.

Pollard, T.C., Gwilym, S.E., & Carr, A.J. (2008). The assessment of early OA. *J Bone Joint Surg Br, 90*(4), 411-421. doi:10.1302/0301-620X.90B4.20284

Potter, H.G., Jain, S.K., Ma, Y., Black, B.R., Fung, S., & Lyman, S. (2012). Cartilage injury after acute, isolated ACL tear: immediate and longitudinal effect with clinical/MRI follow-up. *Am J Sports Med, 40*(2), 276-285. doi:10.1177/0363546511423380

Poulsen, E., Goncalves, G.H., Bricca, A., Roos, E.M., Thorlund, J.B., & Juhl, C.B. (2019). Knee osteoarthritis risk is increased 4-6 fold after knee injury - a systematic review and meta-analysis. *Br J Sports Med*. doi:10.1136/bjsports-2018-100022

Powers, C.M. (2003). The Influence of Altered Lower-Extremity Kinematics on Patellofemoral Joint Dysfunction: A Theoretical Perspective. *J Orthop Sports Phys Ther, 33*(11), 639-646. doi:10.2519/jospt.2003.33.11.639

Prodromos, C.C., Han, Y., Rogowski, J., Joyce, B., & Shi, K. (2007). A meta-analysis of the incidence of anterior cruciate ligament tears as a function of gender, sport, and a knee injury-reduction regimen. *Arthroscopy, 23*(12), 1320-1325 e1326. doi:10.1016/j.arthro.2007.07.003

Punzi, L., Galozzi, P., Luisetto, R., Favero, M., Ramonda, R., Oliviero, F., & Scanu, A. (2016). Post-traumatic arthritis: overview on pathogenic mechanisms and role of inflammation. *RMD Open, 2*(2), e000279. doi:10.1136/rmdopen-2016-000279

Quatman, C.E., Hettrich, C.M., Schmitt, L.C., & Spindler, K.P. (2011). The clinical utility and diagnostic performance of magnetic resonance imaging for identification of early and advanced knee osteoarthritis: a systematic review. *Am J Sports Med, 39*(7), 1557-1568. doi:10.1177/0363546511407612

Quatman, C.E., Quatman-Yates, C.C., & Hewett, T.E. (2010). A 'plane' explanation of anterior cruciate ligament injury mechanisms: a systematic review. *Sports Med, 40*(9), 729-746. doi:10.2165/11534950-000000000-00000

Rambaud, A.J.M., Ardern, C.L., Thoreux, P., Regnaux, J.-P., & Edouard, P. (2018). Criteria for return to running after anterior cruciate ligament reconstruction: a scoping review. *Br J Sports Med, 52*(22), 1437-1444. doi:10.1136/bjsports-2017-098602

Read, P., Mc Auliffe, S., Wilson, M.G., & Myer, G.D. (2020). Better reporting standards are needed to enhance the quality of hop testing in the setting of ACL return to sport decisions: a narrative review. *Br J Sports Med*. doi:10.1136/bjsports-2019-101245

Reid, A., Birmingham, T.B., Stratford, P.W., Alcock, G.K., & Giffin, J.R. (2007). Hop testing provides a reliable and valid outcome measure during rehabilitation after ACLR. *Phys Ther, 87*(3), 337-349. doi:10.2522/ptj.20060143

Reinke, E.K., Spindler, K.P., Lorring, D., Jones, M.H., Schmitz, L., Flanigan, D.C., An, A.Q., Quiram, A.R., Preston, E., Martin, M., Schroeder, B., Parker, R.D., Kaeding, C.C., Borzi, L., Pedroza, A., Huston, L.J., Harrell, F.E., Jr., & Dunn, W.R. (2011). Hop tests correlate with IKDC and KOOS at minimum of 2 years after primary ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc, 19*(11), 1806-1816. doi:10.1007/s00167-011-1473-5

Relph, N., Herrington, L., & Tyson, S. (2014). The effects of ACL injury on knee proprioception: a meta-analysis. *Physiotherapy, 100*(3), 187-195. doi:10.1016/j.physio.2013.11.002

Renstrom, P., Ljungqvist, A., Arendt, E., Beynnon, B., Fukubayashi, T., Garrett, W., Georgoulis, T., Hewett, T.E., Johnson, R., Krosshaug, T., Mandelbaum, B., Micheli, L., Myklebust, G., Roos, E., Roos, H., Schamasch, P., Shultz, S., Werner, S., Wojtys, E., & Engebretsen, L.

(2008). Non-contact ACL injuries in female athletes: an International Olympic Committee current concepts statement. *Br J Sports Med, 42*(6), 394-412. doi:10.1136/bjsm.2008.048934

Reynoldson, C., Stones, C., Allsop, M., Gardner, P., Bennett, M.I., Closs, S.J., Jones, R., & Knapp, P. (2014). Assessing the Quality and Usability of Smartphone Apps for Pain Self-Management. *Pain Med, 15*(6), 898-909. doi:10.1111/pme.12327

Riboh, J.C., Hasselblad, V., Godin, J.A., & Mather, R.C., 3rd. (2013). Transtibial versus independent drilling techniques for anterior cruciate ligament reconstruction: a systematic review, meta-analysis, and meta-regression. *Am J Sports Med, 41*(11), 2693-2702. doi:10.1177/0363546513506979

Riemann, B.L., & Lephart, S.M. (2002). The sensorimotor system, part I: the physiologic basis of functional joint stability. *J Athl Train, 37*(1), 71-79.

Riley, R.D., Hayden, J.A., Steyerberg, E.W., Moons, K.G., Abrams, K., Kyzas, P.A., Malats, N., Briggs, A., Schroter, S., Altman, D.G., Hemingway, H., & Group, P. (2013). Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med, 10*(2), e1001380. doi:10.1371/journal.pmed.1001380

Riordan, E.A., Little, C., & Hunter, D. (2014). Pathogenesis of post-traumatic OA with a view to intervention. *Best Practice & Research Clinical Rheumatology, 28*(1), 17-30. doi:10.1016/j.berh.2014.02.001

Risberg, M.A., Grindem, H., & Oiestad, B.E. (2016a). We Need to Implement Current Evidence in Early Rehabilitation Programs to Improve Long-Term Outcome After Anterior Cruciate Ligament Injury. *J Orthop Sports Phys Ther, 46*(9), 710-713. doi:10.2519/jospt.2016.0608

Risberg, M.A., Moksnes, H., Storevold, A., Holm, I., & Snyder-Mackler, L. (2009). Rehabilitation after anterior cruciate ligament injury influences joint loading during walking but not hopping. *Br J Sports Med, 43*(6), 423-428. doi:10.1136/bjsm.2008.056846

Risberg, M.A., Oiestad, B.E., Gunderson, R., Aune, A.K., Engebretsen, L., Culvenor, A., & Holm, I. (2016b). Changes in Knee Osteoarthritis, Symptoms, and Function After Anterior Cruciate Ligament Reconstruction: A 20-Year Prospective Follow-up Study. *Am J Sports Med, 44*(5), 1215-1224. doi:10.1177/0363546515626539

Rochcongar, G., Cucurulo, T., Ameline, T., Potel, J.F., Dalmay, F., Pujol, N., Sallé De Chou, É., Lutz, C., Ehkirch, F.P., Le Henaff, G., Laporte, C., Seil, R., Gunepin, F.X., & Sonnery-Cottet, B. (2015). Meniscal survival rate after anterior cruciate ligament reconstruction. *Orthopaedics & Traumatology: Surgery & Research, 101*(8), S323-S326. doi:10.1016/j.otsr.2015.09.005

Roemer, F.W., Frobell, R., Lohmander, L.S., Niu, J., & Guermazi, A. (2014). Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS): Longitudinal MRI-based whole joint assessment of anterior cruciate ligament injury. *Osteoarthritis Cartilage, 22*(5), 668-682. doi:10.1016/j.joca.2014.03.006

Roemer, F.W., Guermazi, A., Javaid, M.K., Lynch, J.A., Niu, J., Zhang, Y., Felson, D.T., Lewis, C.E., Torner, J., Nevitt, M.C., & investigators, M.S. (2009). Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss: the MOST Study. A longitudinal multicentre study of knee osteoarthritis. *Ann Rheum Dis, 68*(9), 1461-1465. doi:10.1136/ard.2008.096834

Roemer, F.W., Kwoh, C.K., Hannon, M.J., Crema, M.D., Moore, C.E., Jakicic, J.M., Green, S.M., & Guermazi, A. (2011). Semiquantitative assessment of focal cartilage damage at 3T MRI: a comparative study of dual echo at steady state (DESS) and intermediate-weighted (IW) fat suppressed fast spin echo sequences. *Eur J Radiol, 80*(2), e126-131. doi:10.1016/j.ejrad.2010.07.025

Roemer, F.W., Kwoh, C.K., Hannon, M.J., Hunter, D.J., Eckstein, F., Fujii, T., Boudreau, R.M., & Guermazi, A. (2015). What comes first? Multitissue involvement leading to radiographic osteoarthritis: magnetic resonance imaging-based trajectory analysis over four years in the osteoarthritis initiative. *Arthritis & rheumatology (Hoboken, NJ), 67*(8), 2085-2096. doi:10.1002/art.39176

Rooney, J. (2016). *Churchill report: Investigation of contemporary conservative management programs for anterior cruciate ligament knee injuries.* Retrieved from

Roos, E.M., & Arden, N.K. (2016). Strategies for the prevention of knee osteoarthritis. *Nat Rev Rheumatol, 12*(2), 92-101. doi:10.1038/nrrheum.2015.135

Roos, E.M., & Dahlberg, L. (2005). Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis and rheumatism, 52*(11), 3507-3514. doi:10.1002/art.21415

Roos, E.M., & Lohmander, L.S. (2003). The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes, 1*, 64. doi:10.1186/1477-7525-1-64

Roos, E.M., Roos, H.P., Lohmander, L.S., Ekdahl, C., & Beynnon, B.D. (1998). Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther, 28*(2), 88-96. doi:10.2519/jospt.1998.28.2.88

Rosso, F., Bonasia, D.E., Cottino, U., Cambursano, S., Dettoni, F., & Rossi, R. (2018). Factors Affecting Subjective and Objective Outcomes and Return to Play in Anterior Cruciate Ligament Reconstruction: A Retrospective Cohort Study. *Joints, 6*(1), 23-32. doi:10.1055/s-0038-1636931

Rothrauff, B.B., Jorge, A., de Sa, D., Kay, J., Fu, F.H., & Musahl, V. (2020). Anatomic ACL reconstruction reduces risk of post-traumatic osteoarthritis: a systematic review with minimum 10-year follow-up. *Knee Surg, Sports Traum, Arthrosc, 28*(4), 1072-1084. doi:https://dx.doi.org/10.1007/s00167-019-05665-2

Rotterud, J.H., Sivertsen, E.A., Forssblad, M., Engebretsen, L., & Aroen, A. (2013). Effect of meniscal and focal cartilage lesions on patient-reported outcome after anterior cruciate ligament reconstruction: a nationwide cohort study from Norway and Sweden of 8476 patients with 2-year follow-up. *Am J Sports Med, 41*(3), 535-543. doi:10.1177/0363546512473571

Runhaar, J., Schiphof, D., van Meer, B., Reijman, M., Bierma-Zeinstra, S.M., & Oei, E.H. (2014). How to define subregional OA progression using semi-quantitative MRI Osteoarthritis Knee Score. *Osteoarthritis Cartilage, 22*(10), 1533-1536. doi:10.1016/j.joca.2014.06.022

Salmon, L.J., Russell, V.J., Refshauge, K., Kader, D., Connolly, C., Linklater, J., & Pinczewski, L.A. (2006). Long-term outcome of endoscopic anterior cruciate ligament reconstruction with patellar tendon autograft: minimum 13-year review. *Am J Sports Med, 34*(5), 721-732. doi:10.1177/0363546505282626

Sanders, T.L., Maradit Kremers, H., Bryan, A.J., Larson, D.R., Dahm, D.L., Levy, B.A., Stuart, M.J., & Krych, A.J. (2016). Incidence of Anterior Cruciate Ligament Tears and Reconstruction: A 21-Year Population-Based Study. *Am J Sports Med, 44*(6), 1502-1507. doi:10.1177/0363546516629944

Sarraj, M., Coughlin, R.P., Solow, M., Ekhtiari, S., Simunovic, N., Krych, A.J., Macdonald, P., & Ayeni, O.R. (2019). Anterior cruciate ligament reconstruction with concomitant meniscal surgery: a systematic review and meta-analysis of outcomes. *Knee Surg, Sports Traum, Arthrosc, 27*(11), 3441-3452. doi:10.1007/s00167-019-05389-3

Scanlan, S.F., Chaudhari, A.M., Dyrby, C.O., & Andriacchi, T.P. (2010). Differences in tibial rotation during walking in ACL reconstructed and healthy contralateral knees. *J Biomech, 43*(9), 1817-1822. doi:10.1016/j.jbiomech.2010.02.010

Schelin, L., Tengman, E., Ryden, P., & Häger, C. (2017). A statistically compiled test battery for feasible evaluation of knee function after rupture of the Anterior Cruciate Ligament – derived from long-term follow-up data. *PLoS One, 12*(5), e0176247. doi:10.1371/journal.pone.0176247

Schmitt, L.C., Paterno, M.V., Ford, K.R., Myer, G.D., & Hewett, T.E. (2015). Strength Asymmetry and Landing Mechanics at Return to Sport after Anterior Cruciate Ligament Reconstruction. *Med Sci Sports Exerc, 47*(7), 1426-1434. doi:10.1249/mss.0000000000000560

Segal, N.A., & Glass, N.A. (2011). Is Quadriceps Muscle Weakness a Risk Factor for Incident or Progressive Knee Osteoarthritis? *The Physician and Sportsmedicine, 39*(4), 44-50. doi:10.3810/psm.2011.11.1938

Shaerf, D.A., Pastides, P.S., Sarraf, K.M., & Willis-Owen, C.A. (2014). Anterior cruciate ligament reconstruction best practice: A review of graft choice. *World J Orthop, 5*(1), 23-29. doi:10.5312/wjo.v5.i1.23

Sharma, L., Chmiel, J.S., Almagor, O., Dunlop, D., Guermazi, A., Bathon, J.M., Eaton, C.B., Hochberg, M.C., Jackson, R.D., Kwoh, C.K., Mysiw, W.J., Crema, M.D., Roemer, F.W., & Nevitt, M.C. (2014). Significance of preradiographic magnetic resonance imaging lesions in persons at increased risk of knee osteoarthritis. *Arthritis & rheumatology (Hoboken, NJ), 66*(7), 1811-1819. doi:10.1002/art.38611

Sharma, L., Nevitt, M., Hochberg, M., Guermazi, A., Roemer, F.W., Crema, M., Eaton, C., Jackson, R., Kwoh, K., Cauley, J., Almagor, O., & Chmiel, J.S. (2016). Clinical significance of worsening versus stable preradiographic MRI lesions in a cohort study of persons at higher risk for knee osteoarthritis. *Ann Rheum Dis, 75*(9), 1630-1636. doi:10.1136/annrheumdis-2015-208129

Shea, K.G., Carey, J.L., Richmond, J., Sandmeier, R., Pitts, R.T., Polousky, J.D., Chu, C., Shultz, S.J., Ellen, M., Smith, A., LaBella, C.R., Anderson, A.F., Musahl, V., Meyer, G.D., Jevsevar, D., Bozic, K.J., Shaffer, W., Cummins, D., Murray, J.N., Patel, N., Shores, P., Woznica, A., Martinez, Y., Gross, L., & Sevarino, K. (2015). The american academy of orthopaedic surgeons evidence-based guideline on management of anterior cruciate ligament injuries. *J Bone Joint Surgery, 97*(8), 672-674.

Shiomi, T., Nishii, T., Tanaka, H., Yamazaki, Y., Murase, K., Myoui, A., Yoshikawa, H., & Sugano, N. (2010). Loading and knee alignment have significant influence on cartilage MRI T2 in porcine knee joints. *Osteoarthritis and Cartilage, 18*(7), 902-908. doi:10.1016/j.joca.2010.05.002

Skou, S.T., Pedersen, B.K., Abbott, J.H., Patterson, B., & Barton, C. (2018). Physical Activity and Exercise Therapy Benefit More Than Just Symptoms and Impairments in People With Hip and Knee Osteoarthritis. *J Orthop Sports Phys Ther, 48*(6), 439-447. doi:10.2519/jospt.2018.7877

Skou, S.T., & Roos, E.M. (2017). Good Life with osteoArthritis in Denmark (GLA:D): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC Musculoskelet Disord, 18*(1), 72. doi:10.1186/s12891-017-1439-y

Slade, S.C., Dionne, C.E., Underwood, M., & Buchbinder, R. (2016). Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. *Br J Sports Med, 50*(23), 1428-1437. doi:10.1136/bjsports-2016-096651

Slater, L.V., Hart, J.M., Kelly, A.R., & Kuenze, C.M. (2017). Progressive Changes in Walking Kinematics and Kinetics After Anterior Cruciate Ligament Injury and Reconstruction: A Review and Meta-Analysis. *J Athl Train, 52*(9), 847-860. doi:10.4085/1062-6050-52.6.06

Smith, H.C., Vacek, P., Johnson, R.J., Slauterbeck, J.R., Hashemi, J., Shultz, S., & Beynnon, B.D. (2012). Risk factors for anterior cruciate ligament injury: a review of the literature-part 2: hormonal, genetic, cognitive function, previous injury, and extrinsic risk factors. *Sports health, 4*(2), 155-161. doi:10.1177/1941738111428282

Smith, T.O., Postle, K., Penny, F., McNamara, I., & Mann, C.J. (2014). Is reconstruction the best management strategy for anterior cruciate ligament rupture? A systematic review and meta-analysis comparing anterior cruciate ligament reconstruction versus non-operative treatment. *Knee, 21*(2), 462-470. doi:10.1016/j.knee.2013.10.009

Sonin, A.H., Pensy, R.A., Mulligan, M.E., & Hatem, S. (2002). Grading articular cartilage of the knee using fast spin-echo proton density-weighted MR imaging without fat suppression. *AJR Am J Roentgenol, 179*(5), 1159-1166. doi:10.2214/ajr.179.5.1791159

Sonnery-Cottet, B., Saithna, A., Quelard, B., Daggett, M., Borade, A., Ouanezar, H., Thaunat, M., & Blakeney, W.G. (2019). Arthrogenic muscle inhibition after ACL reconstruction: a

scoping review of the efficacy of interventions. *Br J Sports Med, 53*(5), 289-298. doi:10.1136/bjsports-2017-098401

Spahn, G., Schiltenwolf, M., Hartmann, B., Grifka, J., Hofmann, G.O., & Klemm, H.T. (2016). [The time-related risk for knee osteoarthritis after ACL injury. Results from a systematic review]. *Orthopade, 45*(1), 81-90. doi:10.1007/s00132-015-3170-4

Spindler, K.P., Huston, L.J., Chagin, K.M., Kattan, M.W., Reinke, E.K., Amendola, A., Andrish, J.T., Brophy, R.H., Cox, C.L., Dunn, W.R., Flanigan, D.C., Jones, M.H., Kaeding, C.C., Magnussen, R.A., Marx, R.G., Matava, M.J., McCarty, E.C., Parker, R.D., Pedroza, A.D., Vidal, A.F., Wolcott, M.L., Wolf, B.R., & Wright, R.W. (2018). Ten-Year Outcomes and Risk Factors After Anterior Cruciate Ligament Reconstruction: A MOON Longitudinal Prospective Cohort Study. *Am J Sports Med, 46*(4), 815-825. doi:10.1177/0363546517749850

Spindler, K.P., Huston, L.J., Wright, R.W., Kaeding, C.C., Marx, R.G., Amendola, A., Parker, R.D., Andrish, J.T., Reinke, E.K., Harrell, F.E., Jr., Group, M., & Dunn, W.R. (2011). The prognosis and predictors of sports function and activity at minimum 6 years after anterior cruciate ligament reconstruction: a population cohort study. *Am J Sports Med, 39*(2), 348-359. doi:10.1177/0363546510383481

Sritharan, P., Schache, A.G., Culvenor, A.G., Perraton, L.G., Bryant, A.L., & Crossley, K.M. (2020). Between-Limb Differences in Patellofemoral Joint Forces During Running at 12 to 24 Months After Unilateral Anterior Cruciate Ligament Reconstruction. *Am J Sports Med, 48*(7), 1711-1719. doi:10.1177/0363546520914628

Stanton, T.R., Karran, E.L., Butler, D.S., Hull, M.J., Schwetlik, S.N., Braithwaite, F.A., Jones, H.G., Moseley, G.L., Hill, C.L., Tomkins-Lane, C., Maher, C., & Bennell, K. (2020). A pain science education and walking program to increase physical activity in people with symptomatic knee osteoarthritis: a feasibility study. *PAIN Reports, 5*(5), e830. doi:10.1097/pr9.0000000000000830

Stefanik, J.J., Gross, K.D., Guermazi, A., Felson, D.T., Roemer, F.W., Zhang, Y., Niu, J., Segal, N.A., Lewis, C.E., Nevitt, M., & Neogi, T. (2015). The relation of MRI-detected structural damage in the medial and lateral patellofemoral joint to knee pain: the Multicenter and Framingham Osteoarthritis Studies. *Osteoarthritis Cartilage, 23*(4), 565-570. doi:10.1016/j.joca.2014.12.023

Stefanik, J.J., Guermazi, A., Roemer, F.W., Peat, G., Niu, J., Segal, N.A., Lewis, C.E., Nevitt, M., & Felson, D.T. (2016). Changes in patellofemoral and tibiofemoral joint cartilage damage and bone marrow lesions over 7 years: the Multicenter Osteoarthritis Study. *Osteoarthritis Cartilage, 24*(7), 1160-1166. doi:10.1016/j.joca.2016.01.981

Stefanik, J.J., Niu, J., Gross, K.D., Roemer, F.W., Guermazi, A., & Felson, D.T. (2013). Using magnetic resonance imaging to determine the compartmental prevalence of knee joint structural damage. *Osteoarthritis Cartilage, 21*(5), 695-699. doi:10.1016/j.joca.2013.02.003

Stefanik, J.J., Zhu, Y., Zumwalt, A.C., Gross, K.D., Clancy, M., Lynch, J.A., Frey Law, L.A., Lewis, C.E., Roemer, F.W., Powers, C.M., Guermazi, A., & Felson, D.T. (2010). Association between patella alta and the prevalence and worsening of structural features of patellofemoral joint osteoarthritis: the multicenter osteoarthritis study. *Arthritis Care Res (Hoboken), 62*(9), 1258-1265. doi:10.1002/acr.20214

Su, F., Hilton, J.F., Nardo, L., Wu, S., Liang, F., Link, T.M., Ma, C.B., & Li, X. (2013). Cartilage morphology and T1rho and T2 quantification in ACL-reconstructed knees: a 2-year follow-up. *Osteoarthritis Cartilage, 21*(8), 1058-1067. doi:10.1016/j.joca.2013.05.010

Suter, E., & Herzog, W. (2000). Does muscle inhibition after knee injury increase the risk of osteoarthritis? *Exerc Sport Sci Rev, 28*(1), 15-18.

Sutherland, K., Clatworthy, M., Fulcher, M., Chang, K., & Young, S. (2019). Marked increase in the incidence of anterior cruciate ligament reconstructions in young females in New Zealand. *ANZ J Surg*. doi:10.1111/ans.15404

Sward, P., Kostogiannis, I., Neuman, P., Von Porat, A., Boegard, T., & Roos, H. (2010). Differences in the radiological characteristics between post-traumatic and non-traumatic knee osteoarthritis. *Scand J Med Sci Sports, 20*(5), 731-739. doi:10.1111/j.1600-0838.2009.01000.x

Swirtun, L.R., Eriksson, K., & Renstrom, P. (2006). Who chooses anterior cruciate ligament reconstruction and why? A 2-year prospective study. *Scand J Med Sci Sports, 16*(6), 441-446. doi:10.1111/j.1600-0838.2005.00505.x

te Wierike, S.C., van der Sluis, A., van den Akker-Scheek, I., Elferink-Gemser, M.T., & Visscher, C. (2013). Psychosocial factors influencing the recovery of athletes with anterior cruciate ligament injury: a systematic review. *Scand J Med Sci Sports, 23*(5), 527-540. doi:10.1111/sms.12010

Thomas, A.C., Hubbard-Turner, T., Wikstrom, E.A., & Palmieri-Smith, R.M. (2017). Epidemiology of Posttraumatic Osteoarthritis. *J Athl Train, 52*(6), 491-496. doi:10.4085/1062-6050-51.5.08

Thomas, A.C., Villwock, M., Wojtys, E.M., & Palmieri-Smith, R.M. (2013). Lower extremity muscle strength after anterior cruciate ligament injury and reconstruction. *J Athl Train, 48*(5), 610-620. doi:10.4085/1062-6050-48.3.23

Thomee, R., Neeter, C., Gustavsson, A., Thomee, P., Augustsson, J., Eriksson, B., & Karlsson, J. (2012). Variability in leg muscle power and hop performance after anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc, 20*(6), 1143-1151. doi:10.1007/s00167-012-1912-y

Thorlund, J.B., Roos, E.M., Goro, P., Ljungcrantz, E.G., Gronne, D.T., & Skou, S.T. (2020). Patients use fewer analgesics following supervised exercise therapy and patient education: an observational study of 16 499 patients with knee or hip osteoarthritis. *Br J Sports Med*. doi:10.1136/bjsports-2019-101265

Thorstensson, C.A., Petersson, I.F., Jacobsson, L.T., Boegard, T.L., & Roos, E.M. (2004). Reduced functional performance in the lower extremity predicted radiographic knee osteoarthritis five years later. *Ann Rheum Dis, 63*(4), 402-407.

Toigo, M., & Boutellier, U. (2006). New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. *Eur J Appl Physiol, 97*(6), 643-663. doi:10.1007/s00421-006-0238-1

Toomey, C.M., Whittaker, J.L., Nettel-Aguirre, A., Reimer, R.A., Woodhouse, L.J., Ghali, B., Doyle-Baker, P.K., & Emery, C.A. (2017). Higher Fat Mass Is Associated With a History of Knee Injury in Youth Sport. *J Orthop Sports Phys Ther, 47*(2), 80-87. doi:10.2519/jospt.2017.7101

Trigsted, S.M., Cook, D.B., Pickett, K.A., Cadmus-Bertram, L., Dunn, W.R., & Bell, D.R. (2018). Greater fear of reinjury is related to stiffened jump-landing biomechanics and muscle activation in women after ACL reconstruction. *Knee Surg, Sports Traum, Arthrosc, 26*(12), 3682-3689. doi:10.1007/s00167-018-4950-2

Truong, L.K., Mosewich, A.D., Holt, C.J., Le, C.Y., Miciak, M., & Whittaker, J.L. (2020). Psychological, social and contextual factors across recovery stages following a sport-related knee injury: a scoping review. *Br J Sports Med, doi: 10.1136/bjsports-2019-101206*. doi:10.1136/bjsports-2019-101206

Tubach, F., Dougados, M., Falissard, B., Baron, G., Logeart, I., & Ravaud, P. (2006). Feeling good rather than feeling better matters more to patients. *Arthritis Rheum, 55*(4), 526-530. doi:10.1002/art.22110

Tubach, F., Ravaud, P., Baron, G., Falissard, B., Logeart, I., Bellamy, N., Bombardier, C., Felson, D., Hochberg, M., van der Heijde, D., & Dougados, M. (2005). Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. *Ann Rheum Dis, 64*(1), 34-37. doi:10.1136/ard.2004.023028

Turkiewicz, A., Timpka, S., Thorlund, J.B., Ageberg, E., & Englund, M. (2017). Knee extensor strength and body weight in adolescent men and the risk of knee osteoarthritis by middle age. *Ann Rheum Dis, 76*(10), 1657-1661. doi:10.1136/annrheumdis-2016-210888

Turpeinen, J.T., Freitas, T.T., Rubio-Arias, J.A., Jordan, M.J., & Aagaard, P. (2020). Contractile rate of force development after anterior cruciate ligament reconstruction-a comprehensive review and meta-analysis. *Scand J Med Sci Sports*. doi:10.1111/sms.13733

Undheim, M.B., Cosgrave, C., King, E., Strike, S., Marshall, B., Falvey, E., & Franklyn-Miller, A. (2015). Isokinetic muscle strength and readiness to return to sport following anterior cruciate ligament reconstruction: is there an association? A systematic review and a protocol recommendation. *Br J Sports Med, 49*(20), 1305-1310. doi:10.1136/bjsports-2014-093962

Van de Velde, S.K., Gill, T.J., DeFrate, L.E., Papannagari, R., & Li, G. (2008). The effect of anterior cruciate ligament deficiency and reconstruction on the patellofemoral joint. *Am J Sports Med, 36*(6), 1150-1159. doi:10.1177/0363546508314404

Van Ginckel, A., Verdonk, P., & Witvrouw, E. (2013). Cartilage adaptation after anterior cruciate ligament injury and reconstruction: implications for clinical management and research? A systematic review of longitudinal MRI studies. *Osteoarthritis and Cartilage, 21*(8), 1009-1024. doi:10.1016/j.joca.2013.04.015

van Meer, B.L., Meuffels, D.E., van Eijsden, W.A., Verhaar, J.A., Bierma-Zeinstra, S.M., & Reijman, M. (2015). Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. *Br J Sports Med*. doi:10.1136/bjsports-2013-093258

van Meer, B.L., Meuffels, D.E., Vissers, M.M., Bierma-Zeinstra, S.M., Verhaar, J.A., Terwee, C.B., & Reijman, M. (2013). Knee injury and Osteoarthritis Outcome Score or International Knee Documentation Committee Subjective Knee Form: which questionnaire is most useful to monitor patients with an anterior cruciate ligament rupture in the short term? *Arthroscopy, 29*(4), 701-715. doi:10.1016/j.arthro.2012.12.015

van Meer, B.L., Oei, E.H., Meuffels, D.E., van Arkel, E.R., Verhaar, J.A., Bierma-Zeinstra, S.M., & Reijman, M. (2016). Degenerative Changes in the Knee 2 Years After Anterior Cruciate Ligament Rupture and Related Risk Factors: A Prospective Observational Follow-up Study. *Am J Sports Med, 44*(6), 1524-1533. doi:10.1177/0363546516631936

van Melick, N., van Cingel, R.E., Brooijmans, F., Neeter, C., van Tienen, T., Hullegie, W., & Nijhuis-van der Sanden, M.W. (2016). Evidence-based clinical practice update: practice guidelines for anterior cruciate ligament rehabilitation based on a systematic review and multidisciplinary consensus. *Br J Sports Med, 50*(24), 1506-1515. doi:10.1136/bjsports-2015-095898

van Middelkoop, M., Bennell, K.L., Callaghan, M.J., Collins, N.J., Conaghan, P.G., Crossley, K.M., Eijkenboom, J., van der Heijden, R.A., Hinman, R.S., Hunter, D.J., Meuffels, D.E., Mills, K., Oei, E.H.G., Runhaar, J., Schiphof, D., Stefanik, J.J., & Bierma-Zeinstra, S.M.A. (2018). International patellofemoral osteoarthritis consortium: Consensus statement on the diagnosis, burden, outcome measures, prognosis, risk factors and treatment. *Semin Arthritis Rheum, 47*(5), 666-675. doi:10.1016/j.semarthrit.2017.09.009

van Saase, J.L., van Romunde, L.K., Cats, A., Vandenbroucke, J.P., & Valkenburg, H.A. (1989). Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis, 48*(4), 271-280. doi:10.1136/ard.48.4.271

Walker, A., Hing, W., & Lorimer, A. (2020). The Influence, Barriers to and Facilitators of Anterior Cruciate Ligament Rehabilitation Adherence and Participation: a Scoping Review. *Sports Med - Open, 6*(1). doi:10.1186/s40798-020-00258-7

Wang, H.J., Ao, Y.F., Chen, L.X., Gong, X., Wang, Y.J., Ma, Y., Leung, K.K., & Yu, J.K. (2011). Second-look arthroscopic evaluation of the articular cartilage after primary single-bundle and double-bundle anterior cruciate ligament reconstructions. *Chinese medical journal, 124*(21), 3551-3555.

Wang, J., Antony, B., Zhu, Z., Han, W., Pan, F., Wang, X., Jin, X., Liu, Z., Cicuttini, F., Jones, G., & Ding, C. (2015). Association of patellar bone marrow lesions with knee pain, patellar

cartilage defect and patellar cartilage volume loss in older adults: a cohort study. *Osteoarthritis Cartilage, 23*(8), 1330-1336. doi:10.1016/j.joca.2015.02.018

Wang, L.-J., Zeng, N., Yan, Z.-P., Li, J.-T., & Ni, G.-X. (2020). Post-traumatic osteoarthritis following ACL injury. *Arthritis Res Ther, 22*(1). doi:10.1186/s13075-020-02156-5

Wang, X., Bennell, K.L., Wang, Y., Wrigley, T.V., Van Ginckel, A., Fortin, K., Saxby, D.J., Cicuttini, F.M., Lloyd, D.G., Vertullo, C.J., Feller, J.A., Whitehead, T., Gallie, P., & Bryant, A.L. (2019). Tibiofemoral joint structural change from 2.5 to 4.5 years following ACL reconstruction with and without combined meniscal pathology. *BMC Musculoskelet Disord, 20*(1), 312. doi:10.1186/s12891-019-2687-9

Wang, X., Wang, Y., Bennell, K.L., Wrigley, T.V., Cicuttini, F.M., Fortin, K., Saxby, D.J., Van Ginckel, A., Dempsey, A.R., Grigg, N., Vertullo, C., Feller, J.A., Whitehead, T., Lloyd, D.G., & Bryant, A.L. (2017). Cartilage morphology at 2-3 years following anterior cruciate ligament reconstruction with or without concomitant meniscal pathology. *Knee Surg Sports Traumatol Arthrosc, 25*(2), 426-436. doi:10.1007/s00167-015-3831-1

Wang, Y., Ding, C., Wluka, A.E., Davis, S., Ebeling, P.R., Jones, G., & Cicuttini, F.M. (2006). Factors affecting progression of knee cartilage defects in normal subjects over 2 years. *Rheumatology (Oxford), 45*(1), 79-84. doi:10.1093/rheumatology/kei108

Watt, F.E., Corp, N., Kingsbury, S.R., Frobell, R., Englund, M., Felson, D.T., Levesque, M., Majumdar, S., Wilson, C., Beard, D.J., Lohmander, L.S., Kraus, V.B., Roemer, F., Conaghan, P.G., Mason, D.J., Arthritis Research, U.K.O., & Crystal Disease Clinical Study Group Expert Working, G. (2019). Towards prevention of post-traumatic osteoarthritis: report from an international expert working group on considerations for the design and conduct of interventional studies following acute knee injury. *Osteoarthritis Cartilage, 27*(1), 23-33. doi:10.1016/j.joca.2018.08.001

Webster, K.E., & Feller, J.A. (2011). Alterations in joint kinematics during walking following hamstring and patellar tendon ACLR. *Clin Biomech (Bristol, Avon), 26*(2), 175-180. doi:10.1016/j.clinbiomech.2010.09.011

Webster, K.E., Feller, J.A., & Lambros, C. (2008). Development and preliminary validation of a scale to measure the psychological impact of returning to sport following anterior cruciate ligament reconstruction surgery. *Phys Ther Sport, 9*(1), 9-15. doi:10.1016/j.ptsp.2007.09.003

Webster, K.E., & Hewett, T.E. (2018). A Meta-analysis of Meta-analyses of Anterior Cruciate Ligament Injury Reduction Training Programs. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. doi:10.1002/jor.24043

Webster, K.E., & Hewett, T.E. (2019). What is the Evidence for and Validity of Return-to-Sport Testing after Anterior Cruciate Ligament Reconstruction Surgery? A Systematic Review and Meta-Analysis. *Sports Med, 49*(6), 917-929. doi:10.1007/s40279-019-01093-x

Webster, K.E., Nagelli, C.V., Hewett, T.E., & Feller, J.A. (2018). Factors Associated With Psychological Readiness to Return to Sport After Anterior Cruciate Ligament Reconstruction Surgery. *Am J Sports Med, 46*(7), 1545-1550. doi:10.1177/0363546518773757

Wellsandt, E., Axe, M.J., & Snyder-Mackler, L. (2018). Poor Performance on Single-Legged Hop Tests Associated With Development of Posttraumatic Knee Osteoarthritis After Anterior Cruciate Ligament Injury. *Orthop J Sports Med, 6*(11), 2325967118810775. doi:10.1177/2325967118810775

Wellsandt, E., Failla, M.J., & Snyder-Mackler, L. (2017). Limb Symmetry Indexes Can Overestimate Knee Function After Anterior Cruciate Ligament Injury. *J Orthop Sports Phys Ther, 47*(5), 334-338. doi:10.2519/jospt.2017.7285

Wellsandt, E., Gardinier, E.S., Manal, K., Axe, M.J., Buchanan, T.S., & Snyder-Mackler, L. (2016). Decreased Knee Joint Loading Associated With Early Knee Osteoarthritis After Anterior Cruciate Ligament Injury. *Am J Sports Med, 44*(1), 143-151. doi:10.1177/0363546515608475

Welsh, R.P. (1980). Knee joint structure and function. *Clin Orthop Relat Res*(147), 7-14.

White, D.K., Zhang, Y., Niu, J., Keysor, J.J., Nevitt, M.C., Lewis, C.E., Torner, J.C., & Neogi, T. (2010). Do worsening knee radiographs mean greater chances of severe functional limitation? *Arthritis Care Res (Hoboken), 62*(10), 1433-1439. doi:10.1002/acr.20247

Whittaker, J.L., & Roos, E.M. (2019). A pragmatic approach to prevent post-traumatic osteoarthritis after sport or exercise-related joint injury. *Best Pract Res Clin Rheumatol, 33*(1), 158-171. doi:10.1016/j.berh.2019.02.008

Whittaker, J.L., Toomey, C.M., Nettel-Aguirre, A., Jaremko, J.L., Doyle-Baker, P.K., Woodhouse, L.J., & Emery, C.A. (2019). Health-related Outcomes after a Youth Sport-related Knee Injury. *Med Sci Sports Exerc, 51*(2), 255-263. doi:10.1249/MSS.0000000000001787

Whittaker, J.L., Toomey, C.M., Woodhouse, L.J., Jaremko, J.L., Nettel-Aguirre, A., & Emery, C.A. (2018). Association between MRI-defined osteoarthritis, pain, function and strength 3-10 years following knee joint injury in youth sport. *Br J Sports Med, 52*(14), 934-939. doi:10.1136/bjsports-2017-097576

Whittaker, J.L., Woodhouse, L.J., Nettel-Aguirre, A., & Emery, C.A. (2015). Outcomes associated with early post-traumatic osteoarthritis and other negative health consequences 3-10 years following knee joint injury in youth sport. *Osteoarthritis Cartilage, 23*(7), 1122-1129. doi:10.1016/j.joca.2015.02.021

Wiggins, A.J., Grandhi, R.K., Schneider, D.K., Stanfield, D., Webster, K.E., & Myer, G.D. (2016). Risk of Secondary Injury in Younger Athletes After Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-analysis. *Am J Sports Med, 44*(7), 1861-1876. doi:10.1177/0363546515621554

Wijayaratne, S.P., Teichtahl, A.J., Wluka, A.E., Hanna, F., Bell, R., Davis, S.R., Adams, J., & Cicuttini, F.M. (2008). The determinants of change in patella cartilage volume--a cohort study of healthy middle-aged women. *47*(9), 1426-1429. doi:10.1093/rheumatology/ken244

Willy, R.W., Hoglund, L.T., Barton, C.J., Bolgla, L.A., Scalzitti, D.A., Logerstedt, D.S., Lynch, A.D., Snyder-Mackler, L., & McDonough, C.M. (2019). Patellofemoral Pain. *J Orthop Sports Phys Ther, 49*(9), CPG1-CPG95. doi:10.2519/jospt.2019.0302

Wilson, K., & Brookfield, D. (2009). Effect of Goal Setting on Motivation and Adherence in a Six-Week Exercise Program. *International Journal of Sport and Exercise Psychology, 7*(1), 89-100. doi:10.1080/1612197x.2009.9671894

Wright, J.G., Swiontkowski, M.F., & Heckman, J.D. (2003). Introducing levels of evidence to the journal. *J Bone Joint Surgery, 85*(1), 1-3.

Wright, R.W., Gill, C.S., Chen, L., Brophy, R.H., Matava, M.J., Smith, M.V., & Mall, N.A. (2012). Outcome of revision anterior cruciate ligament reconstruction: a systematic review. *J Bone Joint Surgery, 94*(6), 531-536. doi:10.2106/JBJS.K.00733

Wright, R.W., Magnussen, R.A., Dunn, W.R., & Spindler, K.P. (2011). Ipsilateral graft and contralateral ACL rupture at five years or more following ACL reconstruction: a systematic review. *J Bone Joint Surgery, 93*(12), 1159-1165. doi:10.2106/JBJS.J.00898

Wright, R.W., Preston, E., Fleming, B.C., Amendola, A., Andrish, J.T., Bergfeld, J.A., Dunn, W.R., Kaeding, C., Kuhn, J.E., Marx, R.G., & et al. (2008). A systematic review of anterior cruciate ligament reconstruction rehabilitation: part II: open versus closed kinetic chain exercises, neuromuscular electrical stimulation, accelerated rehabilitation, and miscellaneous topics. *Journal of knee surgery, 21*(3), 225-234.

Wunschel, M., Leichtle, U., Obloh, C., Wulker, N., & Muller, O. (2011). The effect of different quadriceps loading patterns on tibiofemoral joint kinematics and patellofemoral contact pressure during simulated partial weight-bearing knee flexion. *Knee Surg Sports Traumatol Arthrosc, 19*(7), 1099-1106. doi:10.1007/s00167-010-1359-y

Xergia, S.A., Pappas, E., Zampeli, F., Georgiou, S., & Georgoulis, A.D. (2013). Asymmetries in functional hop tests, lower extremity kinematics, and isokinetic strength persist 6 to 9 months following anterior cruciate ligament reconstruction. *J Orthop Sports Phys Ther, 43*(3), 154-162. doi:10.2519/jospt.2013.3967

Xu, L., Hayashi, D., Roemer, F.W., Felson, D.T., & Guermazi, A. (2012). Magnetic resonance imaging of subchondral bone marrow lesions in association with osteoarthritis. *Semin Arthritis Rheum, 42*(2), 105-118. doi:10.1016/j.semarthrit.2012.03.009

Yabroudi, M.A., & Irrgang, J.J. (2013). Rehabilitation and return to play after anatomic anterior cruciate ligament reconstruction. *Clin Sports Med, 32*(1), 165-175. doi:10.1016/j.csm.2012.08.016

Yoo, J.D., Papannagari, R., Park, S.E., DeFrate, L.E., Gill, T.J., & Li, G. (2005). The effect of anterior cruciate ligament reconstruction on knee joint kinematics under simulated muscle loads. *Am J Sports Med, 33*(2), 240-246.

Yusuf, E., Kortekaas, M.C., Watt, I., Huizinga, T.W., & Kloppenburg, M. (2011). Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis, 70*(1), 60-67. doi:10.1136/ard.2010.131904

Zanetti, M., Pfirrmann, C.W.A., Schmid, M.R., Romero, J., Seifert, B., & Hodler, J. (2003). Patients with Suspected Meniscal Tears: Prevalence of Abnormalities Seen on MRI of 100 Symptomatic and 100 Contralateral Asymptomatic Knees. *American Journal of Roentgenology, 181*(3), 635-641. doi:10.2214/ajr.181.3.1810635

Zbrojkiewicz, D., Vertullo, C., & Grayson, J. (2018). Increasing rates of anterior cruciate ligament reconstruction in young Australians, 2000-2015. *Med J Australia, 208*(8), 354-358. doi:10.5694/mja17.00974

Zhang, W., Nuki, G., Moskowitz, R.W., Abramson, S., Altman, R.D., Arden, N.K., Bierma-Zeinstra, S., Brandt, K.D., Croft, P., Doherty, M., Dougados, M., Hochberg, M., Hunter, D.J., Kwoh, K., Lohmander, L.S., & Tugwell, P. (2010). OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage, 18*(4), 476-499. doi:10.1016/j.joca.2010.01.013

Zhang, Y., Nevitt, M., Niu, J., Lewis, C., Torner, J., Guermazi, A., Roemer, F., McCulloch, C., & Felson, D.T. (2011). Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arth rheum, 63*(3), 691-699. doi:10.1002/art.30148

Zhu, Z., Laslett, L.L., Han, W., Antony, B., Pan, F., Cicuttini, F., Jones, G., & Ding, C. (2017). Associations between MRI-detected early osteophytes and knee structure in older adults: a population-based cohort study. *Osteoarthritis Cartilage, 25*(12), 2055-2062. doi:10.1016/j.joca.2017.09.005

Zwolski, C., Schmitt, L.C., Quatman-Yates, C., Thomas, S., Hewett, T.E., & Paterno, M.V. (2015). The influence of quadriceps strength asymmetry on patient-reported function at time of return to sport after anterior cruciate ligament reconstruction. *Am J Sports Med, 43*(9), 2242-2249. doi:10.1177/0363546515591258