THE ROLE OF SEX AND GENDER IN ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTIVE SURGERY OUTCOME

by

Sabrina M. Kolker

A thesis submitted in conformity with the requirements for the degree of Master of Science Degree
Graduate Department of Health Policy, Management and Evaluation
University of Toronto

© Copyright by Sabrina M. Kolker (2017)
The Role of Sex and Gender In Anterior Cruciate Ligament Reconstructive Surgery Outcome
Sabrina M. Kolker
Master of Science
Department of Health Policy, Management and Evaluation
University of Toronto
2017

Abstract

Similarities and differences between women and men (M/F) in health-related quality of life (HRQoL) and predictors of 1-year HRQoL after anterior cruciate ligament reconstruction (ACLR) were explored for the first time using a Sex and Gender Sensitive Analysis (SGSA). M/F differences in variables representing biological sex (S), gender-based sociocultural factors (G) and both SG were evaluated. Males and females in the cohort (n=121, 18-41 years, 77 males) had good 1-year HRQoL but scores indicated potential for improvement. Bivariate analyses showed minimal differences at baseline; males reported more depressive symptoms. In multi-variable regression, 1-year strength (S), change in pain (SG) and physical function (SG) predicted 1-year HRQoL. While a SGSA provided insight into some sex, gender and SG differences, male/female was not associated with 1-year HRQoL. The results suggest the need for the care team to address the psychological as well as the physical aspects of ACL rehabilitation following ACLR.
Acknowledgments

I would first like to thank my supervisor, Dr. Aileen Davis for her consistent guidance, knowledge and mentorship over the course of this project. Dr. Davis patiently pushed me to do better and her insights and suggestions on countless drafts helped me refine my thoughts in order to achieve this work.

Thank you to my thesis committee members Drs. Jas Chahal and Monique Gignac for their insightful suggestions and commitment to this work. Thank you to Dr. Paul Marks for his support and encouragement and to the Toronto Orthopedics Department as well as the Surgeon Scientist Program for financial support. Thank you to Zach Fishman for his technical support and to Monica Kunz and her team for data support and retrieval.

Thank you to my mom Suzan and sister Magalie for always believing and encouraging me. Without your love, strength and positivity I would not be where I am today. To my extended family and friends, including Isa, Les, Gavin, Josh, Billy and Dave, thank you for taking interest in this thesis and your encouragement. To my husband Larry, thank you for enduring this long process with me and always offering your love and humour. Without you this thesis would not have been possible and I feel so lucky to have you in my life. To my son Liam who was born while writing this thesis, thank you for being the light of my life and filling each day with so much joy.

Finally, thank you to my father Bill, who passed away in 2012 to whom this thesis is dedicated. You are my giant and your humour and grace will always inspire me. I still feel your impact every single day.
# Table of Contents

Chapter 1: Introduction ............................................................................................................. 1

Chapter 2: Background, Rationale, and Objectives ................................................................. 5
  2.1 Preface ............................................................................................................................. 5
  2.2 Anatomy, Biomechanics and Function of the Anterior Cruciate Ligament (ACL) .......................................................... 5
    2.2.1 Anatomy of the ACL ................................................................................................. 5
    2.2.2 ACL Biomechanics and Function ............................................................................. 6
  2.3 Epidemiology of ACL Tears ............................................................................................. 7
    2.3.1 Mechanism of Tears ................................................................................................. 7
    2.3.2 Risk Factors Leading to ACL Tears .......................................................................... 9
  2.4 Management of ACL Tears ............................................................................................. 13
  2.5 Measurement of ACLR Outcomes .................................................................................. 16
    2.5.1 Clinical Measures and Functional Performance Measures of ACLR .................. 16
    2.5.2 Patient Reported Outcomes Measures (PROMS) ................................................ 20
  2.6 Health Related Quality of Life ......................................................................................... 25
    2.6.1 Health Related Quality of Life defined ................................................................. 25
    2.6.2 PROMS Used To Assess ACLR HRQoL ............................................................... 27
    2.6.3 Factors Associated with ACLR HRQoL ............................................................... 36
      2.6.3.1 Patient Characteristics Associated with ACLR HRQoL ................................. 37
      2.6.3.2 Surgical Considerations Associated with ACLR HRQoL ............................. 39
      2.6.3.3 Psychological Factors Associated with ACLR HRQoL ................................. 41
      2.6.3.4 Male/Female as Predictor of ACLR HRQoL ................................................ 44
      2.6.3.5 Additional Independent Variables Included in this Thesis ............................ 47
  2.7 Sex and Gender .............................................................................................................. 48
    2.7.1 Sex and Gender Defined ........................................................................................ 49
    2.7.2 Overview of Sex and Gender Differences and Similarities in Health .................. 49
    2.7.3 Sex and Gender Theory ......................................................................................... 50
      2.7.3.1 Evolutionary Theory ....................................................................................... 51
      2.7.3.2 Cognitive and Social Learning Theory ........................................................... 52
      2.7.3.3 Sociocultural Theory ...................................................................................... 53
    2.7.4 Overview of a Sex and Gender Sensitive Approach in Biological Research and Medical Practice ................................. 55
  2.8 Thesis Rationale ............................................................................................................. 56
  2.9 Conceptual Framework and Objectives ......................................................................... 58
    2.9.1 Conceptual Framework ......................................................................................... 58
    2.9.2 Objectives .............................................................................................................. 59

Chapter 3: Methods ............................................................................................................... 60
  3.1 Preface ........................................................................................................................... 60
LIST OF TABLES

Table 1: Literature Review of ACL Tear Risk Factors ..................................................10
Table 2: Literature Review of Measurement Properties of ACL HRQoL Measurement Instruments in ACLR Cohorts .........................................................33
Table 3: Overall Sample Characteristics and Similarities and Differences Between Males and Females .........................................................................................80
Table 4: Univariable Association of Baseline Independent Variables with Baseline and 1-Year HRQoL .........................................................................................85
Table 5: Multivariable Analysis of Baseline Predictors of Baseline HRQoL ........88
Table 6: Univariable Association of 1-Year Independent Variables with 1-Year HRQoL .................................................................................................................91
Table 7: Multivariable Analysis of Baseline Predictors of 1-Year HRQoL ....93
Table 8: Final Model- Evaluation of Baseline and 1-Year Predictors of 1-Year HRQoL in Multivariable Regression .................................................................96
Table 9: Evaluation of Effect Modification by M/F of Knee Strength, Knee Alignment, Weight Concern, BMI, Pain, Time Spent in High Demand Activities and 1-Year HRQoL .........................................................................................98
LIST OF FIGURES

Figure 1: Conceptual Framework: .................................................................59
Figure 2: Measuring the mechanical axis angle ............................................64
Figure 3: Hypothesized model showing factors predictive of 1-Year HRQoL...102

LIST OF DIAGRAMS

Diagram 1: Summary of analyses used for objectives 2-4..............................75
Diagram 2: Pain scores for Men and Women related to HRQoL at 1-year ........99
# List of Appendices

<table>
<thead>
<tr>
<th>Appendix A:</th>
<th>Example of Physical Activity Categories Based on Type of Activity and Intensity Level ................................................................. 119</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix B:</td>
<td>Assumptions Check for the Multivariable Analysis of Baseline and 1-Year Predictor Variables With 1-Year HRQoL .................................. 120</td>
</tr>
<tr>
<td>Appendix C:</td>
<td>Ethics Approval .................................................................................................................. 124</td>
</tr>
<tr>
<td>Appendix D:</td>
<td>Baseline and 1-Year Univariable Regression for Pain, Weight Concern and Time Participating in High Demand Activities with 1-Year KOOS-QOL .................................................................................. 129</td>
</tr>
<tr>
<td>Appendix E:</td>
<td>Multivariable Analyses of Baseline Variables Predicting 1-Year HRQoL .................................. 130</td>
</tr>
<tr>
<td>Appendix F:</td>
<td>Multivariable Analyses of 1-Year Variables Predicting 1-Year HRQoL .................................. 131</td>
</tr>
</tbody>
</table>
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACL</td>
<td>Anterior Cruciate Ligament</td>
</tr>
<tr>
<td>ACL-QOL</td>
<td>Mohtadi-ACL QOL Questionnaire</td>
</tr>
<tr>
<td>ACLR</td>
<td>Anterior Cruciate Ligament Reconstructive Surgery</td>
</tr>
<tr>
<td>ACS</td>
<td>Acute Coronary Syndrome</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>AP</td>
<td>Anterior posterior</td>
</tr>
<tr>
<td>BP</td>
<td>Bodily Pain</td>
</tr>
<tr>
<td>BPTB</td>
<td>Bone Patellar Tendon Bone</td>
</tr>
<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
</tr>
<tr>
<td>EIS</td>
<td>Exercise Identity Scale</td>
</tr>
<tr>
<td>ES</td>
<td>Effect size</td>
</tr>
<tr>
<td>FP</td>
<td>Functional Performance</td>
</tr>
<tr>
<td>GH</td>
<td>General health</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health Related Quality Of Life</td>
</tr>
<tr>
<td>HT</td>
<td>Hamstring</td>
</tr>
<tr>
<td>IKDC</td>
<td>International Knee Documentation Committee Subjective Knee Form</td>
</tr>
<tr>
<td>KOOS</td>
<td>Knee Injury and Osteoarthritis Outcome Score</td>
</tr>
<tr>
<td>KOOS-QOL</td>
<td>Knee Injury and Osteoarthritis Outcome Score Quality of Life Subscale</td>
</tr>
<tr>
<td>LSI</td>
<td>Limb Symmetry Index</td>
</tr>
<tr>
<td>M/F</td>
<td>Male/Female</td>
</tr>
<tr>
<td>MH</td>
<td>Mental health</td>
</tr>
<tr>
<td>OLHD</td>
<td>One legged hop test for distance</td>
</tr>
<tr>
<td>PF</td>
<td>Physical Function</td>
</tr>
<tr>
<td>PROM</td>
<td>Patient Reported Outcome Measures</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Control Trial</td>
</tr>
<tr>
<td>RE</td>
<td>Role emotional</td>
</tr>
<tr>
<td>ROM</td>
<td>Range of motion</td>
</tr>
<tr>
<td>RP</td>
<td>Role Physical</td>
</tr>
<tr>
<td>SF</td>
<td>Social functioning</td>
</tr>
<tr>
<td>SF-36</td>
<td>36-Item Short Form Health Survey</td>
</tr>
<tr>
<td>SF-8</td>
<td>Medical Outcomes Study 8-Item Short-Form Health Survey</td>
</tr>
<tr>
<td>SG</td>
<td>Sex + Gender</td>
</tr>
<tr>
<td>SGSA</td>
<td>Sex and Gender Sensitive Approach</td>
</tr>
<tr>
<td>VT</td>
<td>Vitality</td>
</tr>
</tbody>
</table>
CHAPTER 1: INTRODUCTION

Among young, active individuals, an anterior cruciate ligament (ACL) tear is known to be one of the most prevalent and debilitating recreation and sport-related injuries. [1-5] ACL reconstructive surgery (ACLR) is often the standard practice of care for patients hoping to return to their pre-injury level of activity. [6] ACLR is aimed at restoring knee stability leading to restored function sufficient to allow resumption of pre-injury activity level [7] and optimizing health-related quality of life (HRQoL). [8] Following ACLR, post-operative impairment-based results including knee laxity and muscle strength are generally favourable. [9, 10] However, other outcomes including return to pre-injury level of activity are not always ideal [9, 11-15] and while reporting of HRQoL outcomes are generally good, [8, 16-20] individuals continue to report deficits in HRQoL. Exploration as to the reasons for patient-reported outcome deficits in HRQoL needs greater attention. In particular, understanding of outcome may be informed by considering whether and how studies have addressed potential differences between the sexes.

It is recognized that women are on average three times more likely to tear their ACL compared to men. [6, 21-28] Reasons for this increase include women having a narrower femoral intercondylar notch disrupting the ACL’s path, [29] hormone level variations [22] that may increase risks of injury, weaker ligaments [23] and an increased deficit in dynamic muscular control of the knee compared to males [30] that can lead to a greater knee abduction moment during impact on landing, described as a “valgus intersegmental torque.” [25, 26, 31]
Given the identified differences in risk of ACL tears, [6, 21-26] anatomy and physiology of the ACL and associated structures of the knee in males and females, [22-26, 29, 31] some literature has evaluated outcomes between males and females. [16, 32-39] However, the influence of sex on outcomes following ACLR remains unclear and inconsistent. Some authors report no differences [32-36, 38] while others report poorer outcomes in female patients. [16, 37-39]

When studies have examined differences in ACLR outcomes between the sexes, these differences are often examined using a single variable defined as male/female (M/F). However, potential differences between women and men can be examined in terms of both “sex” and “gender”. Although the two terms, sex and gender, are frequently acknowledged in health research, they are often used interchangeably. [40] This use of sex and gender leads to confusion about the contributions of sex and gender to overall health and, potentially, missed opportunities and errors made when developing appropriate inferences in health research. [41] Aulakh and Anand [42] found when a sex and gender analysis is performed incorrectly it can result in erroneous results. For example, the results from one study [43] misled researchers to believe that aspirin was only useful for stroke prevention in men. These inaccurate results occurred because the sex and gender analysis was done incorrectly. As a result many women initially missed this important therapy.

Sex differences refer to the biological differences between males and females. [44] The term “gender” refers to potentially different “socially constructed roles and relationships, personality traits, attitudes, behaviours, values, relative power and influence that society ascribes” to men and women. [45] “Female” and “male” are
encompassed within sex categories, whereas “feminine” and “masculine” are gender categories that fall on a spectrum. [46, 47] Applying a sex and gender sensitive approach (SGSA) to health may be informative because many differences between men and women are not due to biology or socio-cultural reasons alone. [40] Instead, differences may be due to a combination of sex and gender factors. However, the challenge remains how to best design and implement SGSA in health research.

Bierman [48] suggests that it is necessary to assess if sex, gender, or both are contributing factors to outcome. Moerman and Van Men-Verhulst have suggested that if a dichotomous variable of M/F (male/female) is used when interpreting the results of a SGSA study using a multivariable approach, the biological and sociocultural complexities webbed within M/F could balance each other out and give the false sense of equality between men and women. [40, 49] Current recommendations for SGSA in health outcomes research indicate that both sex and gender can influence health and illness throughout the lifespan and therefore need to be evaluated. [48, 50, 51]

Recently, health services literature has recommended increased attention be placed on a “whole-person” health care approach. [52-54] Gaining a better understanding of how HRQoL following ACLR may be associated with similarities and differences between men and women and whether some factors can be separated as sex versus gender could aid in more accurately identifying and addressing explanations for similarities and differences between men and women, could enhance a more personalized and tailored care approach if necessary, or even reveal inequalities in care. Moreover, if sex and gender are associated with a range of modifiable factors that are linked to HRQoL, there
is potential to enhance interventions to improve HRQoL outcomes following ACLR, including models of care, policies, management plans and medical interventions.

The overall aim of this research is to examine sex and gender similarities and differences between women and men with ACLR surgery and to examine if these influence HRQoL outcomes 1-year following surgery. In addressing this aim, this thesis is divided into 5 chapters. Chapter 2 provides background information, as well as the rationale and the specific objectives of the thesis. Chapter 3 presents an overview of the methods including an explanation of how variables were derived to represent sex, gender and sex + gender (SG) constructs and Chapter 4 presents the results of the study. The analysis approach first assessed the data to come to a better understanding of how males and females are similar or different with regards to demographics, sex, gender and SG-related factors when they present for ACLR and 1-year following ACLR. The statistical analysis was then geared towards analyzing which factors were predictive of HRQoL. Additionally, exploratory analyses considered the potential interaction of clinically relevant factors and M/F in order to evaluate if male/female moderated the explanatory effects of the variables involved in predicting HRQoL 1-year following ACLR. Finally, a discussion of the study findings, proposed future directions for research and overall conclusions of the thesis are summarized in Chapter 5.
CHAPTER 2: BACKGROUND, RATIONALE, AND OBJECTIVES

2.1 PREFACE

This chapter begins by discussing the anatomy and function of the anterior cruciate ligament (ACL), as well as ACL tear epidemiology, its management and outcomes. Then a literature review of HRQoL and its assessment specific to ACLR are provided followed by a review of factors predictive of HRQoL in ACLR research. A discussion of how sex and gender as potential predictors of HRQoL are incorporated into the thesis follows. First, sex and gender are defined. Second, an overview of a sex and gender sensitive approach (SGSA) is provided to support the methodological approach and analyses undertaken. The chapter concludes with the rationale, conceptual framework, and specific objectives of the thesis.

2.2 ANATOMY, BIOMECHANICS AND FUNCTION OF THE ANTERIOR CRUCIATE LIGAMENT (ACL)

2.2.1 Anatomy of the ACL

The ACL is on average 33mm long and has an average width of 11mm. [54] It is composed of a band of regularly oriented, dense connective tissue connecting the tibia to the femur. [55] The ACL is an intra-articular, extra synovial collagenous structure that develops prior to the knee joint cavity’s actual formation in the 6.5 week old embryo. [56] Running in an oblique direction, the ACL originates from a fossa located on the posteromedial aspect of the lateral femoral condyle and attaches to the tibia just anterior and lateral to the anterior tibial spine. The ACL does not attach to the femur and tibia as a singular cord but rather as a collection of individual fascicles that fan out over a broad,
flattened area. It has been shown, that some ACL fibres may blend with the lateral meniscus in some individuals. [55]

The ACL is composed of fibroblasts surrounded by an extracellular matrix formed by collagen that makes up 75% of the ACL’s dry weight (90% type I, 10% type III). Elastin, proteoglycans and glycoproteins make up a small amount of ACL’s dry weight, while water contributes to about 60% of the ACL’s wet weight.

The middle genicular artery’s ligamentous branches provide the ACL’s primary blood supply, with minor contribution from the medial and lateral branches of the inferior genicular artery. The posterior articular branch of the posterior tibial nerve innervates the ACL. [57] The ACL has three distinct fibre bundles: the anterior-medial, the intermediate and postero-lateral bundles. [58] However, the smaller antero-medial band and the larger postero-lateral portion are the two principle parts. In flexion, the antero-medial (AM) bundle is longest or most tense, while in extension the postero-lateral (PL) bundle is longest or most tense. [59, 60]

2.2.2 ACL Biomechanics and Function

Biomechanical studies consistently support that the primary role of the ACL is to resist anterior tibial translation. [59, 61-65] As the knee moves from extension to increasing degrees of flexion, the AM and PL bundles differentially contribute to anterior tibial restraint. [66] It also has been reported that the ACL serves as a secondary rotatory restraint to external and internal tibial rotation. [67] However, the ACL also works closely with the other anatomical structures in the knee. Together with the posterior cruciate ligament, the bony femoral condyles, the tibial articular surfaces and meniscal cartilage, it determines the normal rolling and gliding mechanisms that contribute to knee
range of motion. [68] Girgis et al.’s 1975 study was one of the first to describe the ACL’s function. [69] They found that by sectioning the ACL, anterior tibial translation, internal rotation and external rotation all increased. Noyes et al. [66, 69] and Kennedy et al. [70] furthered our understanding of the ACL by demonstrating the effect of age, stress and strain on ACL physical properties. Noyes et al. [66, 70, 71] determined the ACL’s ultimate tensile strength to be 1730 Newtons. While Kennedy et al. used older cadaveric specimens and found significantly lower tensile strength values. [72]

2.3 EPIDEMIOLOGY OF ACL TEARS

An ACL tear has been shown to be one of the most prevalent and debilitating recreation- and sport-related injuries. [1-3, 73, 74] The annual incidence of ACL tears is approximately 8 per 1000 people aged 10 to 64 years [75] with most ACL injuries occurring in people in their late teens and early 20s. [28] Being female is a risk factor for sustaining an ACL tear, [24, 25, 76] with the literature indicating that women are two to eight times more likely to tear their ACL compared to men. [6, 21, 22, 24-28] The potential reasons for this are discussed in later sections.

2.3.1 Mechanism of Tears

ACL tears occur in direct contact of the knee, indirect contact and non-contact settings. [77] Approximately 70% of ACL tear injuries occur during non-contact injuries [78, 79] meaning they have occurred in the absence of body-to-body contact. [80] However, ACL tears do not only occur in a sporting environment. Making accidental movements that twist the knee including falling off a ladder, jumping from an extreme height, stepping into a hole, or missing a step on a staircase also can lead to an ACL tear. [81]
The exact mechanism of non-contact ACL injuries is not known; rather several possible contributing factors have been associated with this injury. The most common scenarios resulting in a torn ACL include a change of direction or cutting manoeuvres combined with deceleration, landing from a jump in or near full extension, pivoting with the knee in near full extension and a planted foot. [78, 80, 82, 83] Boden et al. identified this vulnerable landing position and hypothesized that it resulted in a rapid excessive axial loading of the knee. [84] The most frequently reported non-contact ACL injury mechanism is a combination of dynamic valgus rotation where the body weight shifts over the index knee, the plantar surface of the foot fixes flat on a surface and a deceleration with high knee extension torque (with or without perturbation) occurs. [82] Boden et al. report that a flat foot reduces the calf muscle’s ability to absorb energy upon landing resulting in increased impulse to the knee compared to if the knee were flexed. [85] Furthermore, while the lower extremity remains in a vulnerable position, the tibial plateau angle in relation to the femoral condyles also potentially contributes to the ACL injury. [86-88] The body absorbs ground reaction forces (GRFs) when the foot makes contact with the ground. The hip, knee, ankle and foot absorb GRFs during normal landing and deceleration [89] and while walking, the GRFs are equal to the patient’s body weight. However, after jumping into the air and then landing the GRFs increase to greater than 8 times the patient’s body weight. [82] These same GRFs cause the compressive forces that play a critical role in non-contact ACL injuries. Additional ACL tear mechanisms include knee hyperextension and hyperflexion of the leg prior to injury. [82, 90-92] Lastly, a forceful eccentric quadriceps contraction is also thought to result in non-contact ACL injuries. This can occur when an anterior force is placed on the tibia as
a result of an unplanned or disrupted manoeuvre where the anterior vector of a forceful quadriceps contraction in an extended knee occurs. [85, 87] Overall, with respect to quadriceps contraction, studies involving cadaveric specimens demonstrate that forces sustained while landing from a jump are sufficient to injure the ACL as quadriceps contraction significantly reduces injury threshold. [85, 87] The compressive vector of a quadriceps contraction has been shown to be at least twice that of the anterior shear vector [89, 93] and bone bruises seen on magnetic resonance images after non-contact ACL injuries are also consistent with this type of impaction injury. [94] All the above supports the theory that quadriceps contraction contributes to ACL injury by increasing the compressive loads on the tibio-femoral joint. Understanding the mechanism of injury is important. However, it is also critical to understand the many risk factors that preclude an actual ACL injury in order to fully comprehend the factors influencing ACL injury occurrence.

2.3.2 Risk Factors Leading to ACL Tears

ACL injury risk factors can be categorized as intrinsic or extrinsic. [95, 96] Intrinsic factors, referring to those from within the body, include those inherent to the individual including race, hormones, genetic factors, neuromuscular factors and sex. [96] Intrinsic factors also include anatomic variables such as BMI, joint laxity, and knee joint geometry. Extrinsic factors are those that are external to the individual and include level of activity and environmental conditions. Risk factors leading to ACL tears are a well-studied topic and, although not the focus of this thesis, the risk factors described in table 1 provide an overview of the factors leading to ACL tears studied in the literature. When available male versus female differences are described.
### Table 1: Literature Review of ACL Tear Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Author</th>
<th>Study Design</th>
<th>N(%Females)</th>
<th>Age in years (SD or range)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrinsic Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White European/</td>
<td>Trojan et al. [97]</td>
<td>Retrospective Cohort</td>
<td>371(100)</td>
<td>NR</td>
<td>White European American players:</td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 x ↑ risk of tear vs. African American players</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 x ↑ risk vs. other ethnic groups combined</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑LH</td>
<td>Wojtyś et al. [26]</td>
<td>Descriptive study</td>
<td>65(100)</td>
<td>51 non OC users 14 OC users 28+-/10years</td>
<td>Non OC users ↑ ACL tear during ovulatory phase (p&lt;0.001) OC users no significant association between ACL tear and ovulatory phase (p=0.7)</td>
</tr>
<tr>
<td>↑Estrogen (Hypothesized)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑Estrogen</td>
<td>Myklebust et al. [98]</td>
<td>Prospective Cohort: Subgroup analysis of women</td>
<td>Entire Cohort: 33(85) Subgroup with ACL tears: 28(82) 23.4+-/3.9</td>
<td>↑ACL tear risk during week prior to (late luteal) or after start of menstrual period (follicular phase) (p &lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>↑Progesterone (Hypothesized)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑Progesterone</td>
<td>Hewett et al. [99]</td>
<td>Systematic Review</td>
<td>381(100)</td>
<td>25+-/13</td>
<td>↑ACL tears during the Pre-ovulatory (1st half of menstrual cycle)</td>
</tr>
<tr>
<td>↑Relaxin (Hypothesized)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genetic Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of ACL tear</td>
<td>Harner et al. [100]</td>
<td>Retrospective cohort</td>
<td>ACL injured: 31(30) 29.3+-/6.83 Control group: 23(43) 29.39+-/8.48</td>
<td>Family History: ACL tear rate ↑ x 35% in patients with immediate family member with history of ACL tear vs. control group with no family history (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underrepresentation of</td>
<td>Posthumus et al. [101]</td>
<td>Case Control: Subgroup analysis of women</td>
<td>ACL injured: 129(30) 29.8+-/12.1 Control group (no ACL tear): 216(29) 28.2+-/10</td>
<td>ACL injured females: underrepresentation of COL5A1 sequence variants vs. ACL injured males (p=0.006)</td>
<td></td>
</tr>
<tr>
<td>COL5A1 sequence variants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ACL injured females have ↑self-reported family history of ligament injury vs. males (p=0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuromuscular factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased neuromuscular</td>
<td>Hewett et al. [102]</td>
<td>Prospective Cohort</td>
<td>205(100)</td>
<td>9 ACL injured 196 Non-injured</td>
<td>ACL injured knees had ↑in:</td>
</tr>
<tr>
<td>control of lower extremity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Knee abduction</td>
</tr>
<tr>
<td>Risk Factor</td>
<td>Author</td>
<td>Study Design</td>
<td>N(% Females)</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age in years (SD or range)</td>
<td>loading (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 20% ↑ ground reaction forced (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ACL injured knees had ↓ in:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Stance time (16% shorter) vs. uninjured controls</td>
</tr>
<tr>
<td>Weak core muscles leading to instability</td>
<td>Zazulak et al. [103]</td>
<td>Prospective Cohort</td>
<td>Entire cohort: 277(50) ACL tears among cohort: 25(44) 19+/1.8</td>
<td>ACL injured: ↑ in trunk displacement vs. uninjured (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lateral trunk displacement = strongest predictor of ACL injury (p=0.01)</td>
</tr>
<tr>
<td>BMI</td>
<td>Uhorchak et al. [104]</td>
<td>Prospective Cohort</td>
<td>Entire Cohort: 859(15) ACL tears among cohort: 24(33) 17-23</td>
<td>↑BMI = ACL injury risk factor for women (p&lt;0.008), not for men (p=0.137)</td>
<td></td>
</tr>
<tr>
<td>Generalized joint laxity</td>
<td>Myer et al. [105]</td>
<td>Prospective Cohort</td>
<td>Entire Cohort: 1558(100) ACL tears among cohort: 19 17-24</td>
<td>For every 1.3mm ↑ in side to side difference in AP knee displacement = 4-fold ↑ in odds of ACL tear ↑Knee hyperextension = 5x↑ odds of ACL injury</td>
<td></td>
</tr>
<tr>
<td>Knee Joint Geometry: Intercondylar Notch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Women have narrower notch widths compared to males (p&lt;0.04)</td>
</tr>
<tr>
<td>Narrow intercondylar notch width</td>
<td>Uhorchack et al. [104]</td>
<td>Prospective Cohort</td>
<td>Entire Cohort: 859(15) ACL tears among cohort: 24(33) 17-23</td>
<td>↑Relative Risk of ACL tear in women vs. men when notch width 1SD ≤ mean</td>
<td></td>
</tr>
<tr>
<td>Knee Geometry: Tibial Slope</td>
<td>Todd [106]</td>
<td>Case control</td>
<td>ACL injured: 140(32) 24.9+/7.9 Control: 179(30) 25.4+/8.7</td>
<td>↑Tibial slopes in ACL injured group vs. control (p=0.003)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ACL injured females had increased tibial slope compared to control (p=0.002), this difference was not found in ACL injured males vs. control</td>
</tr>
<tr>
<td>ACL size</td>
<td>Chaudhari et al. [107]</td>
<td>Case control</td>
<td>54(37) 33.6</td>
<td>ACL injured: Contralateral ACL volume significantly smaller vs. non ACL</td>
<td></td>
</tr>
<tr>
<td>Risk Factor</td>
<td>Author</td>
<td>Study Design</td>
<td>N(%Females)</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Incidence of ACL injury during competition 30 x ↑ compared to during practice (p=0.013)</td>
<td></td>
</tr>
<tr>
<td>Extrinsic Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity Level</td>
<td>Myklebust et al.[98]</td>
<td>Prospective cohort study</td>
<td>33(85) 23.4 +/- 3.9</td>
<td>Incidence of ACL injury during competition 30 x ↑ compared to during practice</td>
<td></td>
</tr>
<tr>
<td>Environmental Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic floor playing surface</td>
<td>Olsen et al.[108]</td>
<td>Prospective cohort</td>
<td>53 ACL injuries Wooden floors: 12(67) Artificial floors 41(88) 22 +/- 4</td>
<td>Females: Risk of ACL injury 2.35 times ↑ vs. males when playing on synthetic floor</td>
<td></td>
</tr>
<tr>
<td>Increased shoe-surface traction on hard ground surfaces</td>
<td>Orchard et al.[109]</td>
<td>Prospective Cohort</td>
<td>All players in 5520 Australian Football league matches from 1992-1998</td>
<td>↓ Risk of ACL tear (RR= 2.8) in areas with low water evaporation rates and ↑ rainfall</td>
<td></td>
</tr>
</tbody>
</table>

**Findings:**

To summarize there is consistency that being Caucasian, [97] having a family history of ACL tear, [100] decreased neuromuscular control, [103, 110] increased generalized joint laxity, [105] and engaging in a more aggressive activity level during competition compared to practice [98] all increase the risk for ACL injury. Notable for the context of this thesis, females on average have a 3-fold increased risk [6, 21-28] compared to males for ACL tear. Because of this risk to females, ACL studies have looked at males vs. females. Although the magnitude of the risk depends on the risk factor, factors contributing to this increased risk include: hormone level variations, the extent to which each hormone contributes to the increase in ACL tear risk has yet to be concluded. Also, the risk of ACL tear has been shown to vary depending on where a female is in her menstrual cycle. However, elevated estrogen has consistently shown to negatively effect muscle function, ligament and tendon strength. [26, 98, 111] Other risk factors

NR= Not reported
OC= Oral Contraceptive
BMI= Body mass index
SD= Standard Deviation
contributing to a female’s increased risk for ACL tear include: genotype sequence
variant, specifically an underrepresentation of COL5A1 sequence, an important structural
component in ligaments and tendons, [101] increased body mass index (BMI) in females,
[104] a narrow intercondylar notch width, [104] increased tibial slope, [106] and
participating in activity on a synthetic floor. [108]

2.4 MANAGEMENT OF ACL TEARS

ACL tears can be managed with or without surgery and there is debate within the
literature regarding whether individuals should undergo reconstruction versus non-
operative treatment with rehabilitation alone. [112, 113] Although an ACL tear will not
heal on its own, patients often can tolerate the absence of an ACL if they avoid certain
types of manoeuvres including cutting, twisting and pivoting manoeuvres. [113] As a
result a patient’s desired activity level and symptoms of instability have been shown to be
primary determinants for a treatment pathway following ACL injury. [113] In the less
active patient, non-operative management consisting of rehabilitation, bracing if needed
and activity modification has been shown to result in good-to-excellent outcomes. [114,
115] There is also support for non-surgical management involving a structured
neuromuscular rehabilitation program thought to provide an effective recovery for more
active patients with high physical demands including participation in pivoting sports and
lifestyle activities. [116, 117] Furthermore, non-operative management may limit the risk
of degenerative damage in the long term, [117, 118] decreases the risk of operative
complications such as arthrofibrosis, infection, graft failure and donor site morbidity,
pain, and limits the surgical costs associated with operative intervention. [116, 117]
In terms of comparing management approaches, the decision to conservatively manage an ACL injury is primarily dependent on activity, where the best results occur in patients with sedentary lifestyles and who participate in mostly low demand activities.

[119] With respect to this thesis all cohort patients underwent ACLR; therefore the focus will now move to ACLR.

ACLR is advocated by those who ascribe to the belief that it restores tibio-femoral joint kinematics, prevents further meniscal damage, and reduces joint instability risk leading to the possibility of decreased secondary joint damage and the development of osteoarthritis. [116, 117, 120-126] The goal of ACLR is to restore knee stability, improve function for activities of daily living, recreation and sport activities, and prevent future articular cartilage and meniscal deterioration. [127, 128] There are a variety of surgical techniques and a variety of biologic grafts that can be used for reconstruction. Currently, an arthroscopically assisted technique is most commonly used to perform ACLR. [129, 130] Graft choices include either autogenous tissue (central-third bone–patellar tendon–bone (BPTB), hamstring (HT), and quadriceps autografts) or allograft tissue (BTPB, HT, Achilles, tibialis anterior). [130] Despite the plethora of choice in ACLR techniques, the most commonly used graft in Canada for ACLR is the HT autograft, [131] while in the USA, especially among high-level athletes and high-demand patients it is the BPTB autograft. [132-136]

Many consider the BPTB autograft as the gold standard for ACLR for both males and females, [137-141] and it is used as a comparator for other techniques/approaches. [130]

Cohort data from the Norwegian Cruciate Ligament Registry including 3428 patients repaired with BPTB (average age 29 years, 41% females) and 9214 patients repaired with
HT (average age 28.3, 43% females) with a mean follow up of 4 years showed that HT grafts had twice the risk of revision compared to BPTB grafts. [142] As further testament to their strength and durability, BPTB autografts are the most frequently used grafts for ACLR by the National Football League (NFL) (which is male dominated) and by the National Collegiate Athletic Association (NCAA) Division I (which includes both male and female athletes) team physicians. [143] Of note, all of the patients included in this research had their ACL repaired with a BPTB autograft.

Following surgery, patients participate in an intensive period of rehabilitation lasting approximately 6-18 months. The rehabilitation is designed to build strength and enhance flexibility [144] with the goal of resumption of pre-injury level of activity by 12 months after surgery. [7] However, even with good clinical outcomes, and receiving clearance to return to sports and activity from their surgeon many individuals still do not return to their pre-injury levels of activity. [9, 33, 145-147] A study that included 187 competitive and recreational athletes (average age 27.3 years, 33% females) found that despite good to excellent knee outcomes after rehabilitation, only 31% of all study participants (both competitive and recreational athletes) had returned to their pre-injury level of activity 1-year following ACLR. [7] Lentz et al. [148] performed a case control study involving 46 patients (average age 21 years, 49% females) assessing return to sport status at 6 months and 1-year post ACLR. The authors found that those who had not returned to sport were older, had lower quadriceps strength, worse knee function and symptoms, and greater fear of re-injury. Fear of re-injury, which will be more extensively discussed in a later section, and knee functional limitations are both common factors identified with lower
level of return to physical activity inclusive of sporting activities following ACLR. [3, 7, 9, 12, 13, 75]

2.5 MEASUREMENT OF ACLR OUTCOMES

ACLR outcomes have been evaluated with clinical measures, functional tests and patient-reported generic and disease-specific measures covering a wide range of concepts. [149-154] Overall, ACLR clinical outcomes are considered to be excellent with low failure rates (averaging only 3 to 24%). [6, 113, 155-157] A systematic review of forty-eight studies (n=5770; 36% females) with a mean age of 25.1 years and a mean follow-up of 41.5 months following ACLR, reported that 82% returned to some kind of sports participation, 63% returned to their pre-injury level of participation, and 44% returned to competitive sport. [9] Ninety percent achieved normal or near normal knee function based on laxity and strength measures, while 85% achieved normal or near normal knee function based on patient-reported activity measure. Overall ACLR is considered an effective [9] and cost-effective treatment for ACL injury. [158, 159]

The following section briefly reviews the various outcome measures commonly used with ACLR and reports the results of specific ACLR studies based on these outcomes, particularly focusing on results specific to men and women where reported. As HRQoL is the outcome of focus for this thesis, HRQoL is defined and its measurement and the results in people with ACLR are discussed in more detail.

2.5.1 Clinical Measures and Functional Performance Measures of ACLR

Following ACLR standardized outcome measures are used during the rehabilitation process in order to make clinical decisions about individual patient progress and allowing the patient to return to pre-injury activities. [160-162] Criteria for return to sport
following ACL repair often includes full knee active range of motion (ROM), resolution of pain, no joint effusion present, and less than a 15% performance and strength deficit when compared to uninjured knee as measured with the Limb Symmetry Index (LSI).

This section provides a brief overview of the clinical and functional performance measures (FP) used to assess objective outcomes following ACLR and a more in depth review of the objective outcomes pertinent to this thesis.

Clinical Outcomes Measures

Clinical outcome measures in ACLR include physical examination tests such as ROM with an emphasis on terminal knee extension by goniometry, [163] strength measured by manual muscle testing or isokinetic equipment such as a Biodex isokinetic dynamo-meter [149, 164] and radiographic findings. [165] Knee ligamentous laxity is also an important clinical measure and can be measured several ways including manual ligament testing with the anterior drawer test, Lachman test or pivot shift test [166] or with the use of the KT-1000. Although clinical tests to measure ligamentous laxity are useful for treatment, their interpretation can vary among those measuring. [167] Of the validated knee laxity measuring instruments, the KT-1000 is considered the most accurate. [168] The KT-1000 was used to measure knee laxity in the cohort studied in this thesis. It measures the anterior tibia displacement on the operated versus non-operated knee. A difference of >4mm in anterior displacement measured by the KT-1000 has been shown to be associated with suboptimal outcomes. [169] The literature supports the use of the KT-1000 as a reliable method for quantifying antero-posterior laxity in both normal and ACL-deficient knees. [170]. The KT-1000 has also been shown to be a reliable measure in patients following ACLR (ICC= 0.83-0.88). [171] Three studies were identified in the
literature that investigated male/female differences in AP knee laxity measured with the KT-1000 following ACLR. [32, 172, 173] Two studies [172, 173] reported no significant male/female differences in AP knee laxity measured with the KT-1000 at 24-38 months following ACLR. The first of these studies by Wiger et al. [173] examined 429 competitive athletes (aged 16-45 years, 31% females) 21-68 months following ACLR. These authors found that there was no statistically significant difference in AP displacement between females (2mm; range of 5-10mm) and males (1.5mm; range of 4-13mm). A second study by Barber-Westin et al. [172] examined 94 patients (aged 16-54 years, 50% females) two years following ACLR and also found no differences between sexes in knee laxity (p= 0.33). In contrast, Ferrari et al. [32] examined 200 patients (aged 15-55 years, 31% females) and found a significant side-to-side difference in AP translation between males and females. Male study participants presented with a 0.77 ± 2.77 mm side-to-side difference, while the females presented with a 1.73 ± 2.16 mm side-to-side difference (p= 0.014) using the KT-1000 2-8 years following ACLR.

**Functional Performance Measures**

Functional performance (FP) measures objectively quantify function and, in the context of ACLR, the measures evaluate lower extremity demands. [163, 174, 175] The FP used in the thesis cohort was the One Legged Hop Test for Distance (OLHD). Two systematic reviews of various FP after ACLR, [149, 162] found that the OLHD was the most commonly reported test. Hop testing is a practical performance-based outcome measure that requires minimal space, equipment and time to administer. It accurately assesses neuromuscular control, strength and confidence in the limb. [163, 176, 177] The OLHD has demonstrated good to high intra-rater reliability in patients following ACLR.
(ICC= 0.76-0.97) [161, 178] and had a strong positive correlation with isokinetic strength [163] and power. [179]

Performance of the OLHD is often expressed as a percentage of the ACL-reconstructed limb in relation to the non-reconstructed limb, known as the Limb Symmetry Index score (LSI). [161] The “gold standard” criterion is often regarded as having an LSI greater than 85%. [149, 163] This assumes that the uninjured leg is “normal” in strength [163] and that anything less than a 15% deficit in strength between the operated and non-operated knee is acceptable. [180] For example, in a systematic review of 88 studies [162] that included 4927 patients (mean patient age of 26.5 ± 3.4 years, 44% females) the results of the OLHD, as reported by the LSI, improved with increasing time from surgery, with nearly all results greater than 90% 1-year after ACLR. (LSI averaged 87%, 92%, and 94% at 6 months, 1 year, and 2 years respectively following ACLR). Wiger et al. [173] examined 429 competitive athletes (ages 16-45 years, 69% males) 21-68 months following ACLR and found a significant difference in the OLHD performance between males and females. In their study the LSI was 93% (0-116%) for females and 96% (0-130%) for males (p= 0.006).

As evidenced by the above studies, OLHD results are commonly interpreted using the LSI; however, it has been recognized that reporting of the absolute OLHD is also important. [161] For example, Reid et al. [161] examined 42 patients, 27 recreational and 15 competitive athletes (aged 15-45 years, 45% males). The participants performed the OLHD on 3 separate occasions 16 weeks following ACLR and on a fourth occasion 6 weeks later. Reid et al. found the LSI values were similar for test occasions 1 and 2 (82.9+/−15.4% and 82.2+/−12.3% respectively); however, the absolute scores of the
operative limb in isolation were very different on the two occasions (112.0+/−32.5cm and 127.4+/−32.3cm respectively). In Reid et al.’s study looking at LSI in isolation would have masked this improvement in performance. In this thesis absolute values of the OLHD are reported.

2.5.2 Patient Reported Outcomes Measures (PROMS)

Following surgery it is recognized that using PROMs to evaluate outcome is important as patients not only provide valid and reliable insights into their outcomes, but are often the main (or only) source of information about symptoms like pain and participation in activities, as well as satisfaction and HRQoL. [181-184]

A number of valid and reliable knee and condition-specific PROMs have been used to evaluate outcome after ACLR. These include the International Documentation Committee Subjective Knee Evaluation Form (IKDC), a measure of knee function, [185] the Lysholm Knee Scoring Scale, used to evaluate knee symptoms and functional impairments [186] and the Cincinnati, [187] Tegner and Marx [188] knee scoring scales, measures of activity participation. Less commonly used but applicable due to its use in the cohort in this study is the Minnesota Leisure Time Physical Activity Questionnaire. [189] Each of these PROMs is briefly described below with respect to the number of domains they contain, their scoring and their measurement properties in a population of young, healthy adults with ACL deficiency. Additionally, findings describing similarities or differences between men and women when compared using the specific PROMs are provided where available.

In section 2.6.2 PROMs specific to measuring HRQoL, the focus of this thesis, including the KOOS, the SF-36 and Mohtadi-ACL are described in more detail.
**The IKDC**

The IKDC is a 10-item assessment of 3 domains: knee symptoms, sports/daily activities and current knee function. [190] The IKDC was shown to include items important to patients in a cohort study of 58 ACL deficient patients (48% females). [191] IKDC scores range from 0 to 100, with higher scores indicating fewer symptoms and disability and it has demonstrated reliability, validity and responsiveness in people with ACLR. [185] Lentz et al. [37] studied 12 females and 14 males, ages 15-45, 12 months following ACLR (average 48 weeks). Men tended to have higher scores on the IKDC after 12-months follow-up. Other studies demonstrated that IKDC scores improved as time from surgery increased and that there were no differences in self-reported function [32] or IKDC scores between males and females 2 years after ACLR. [33, 34, 38]

**The Lysholm**

The Lysholm Knee Scoring Scale [192] is an 8-item questionnaire administered by a practitioner to assess how knee pain affects the daily life of an ACL deficient patient. [152] A score of 0 represents major disability or symptoms due to knee problems, while a score of 100 represents no disability or knee symptoms. [35] Reliability, validity, and responsiveness have been demonstrated in active patients. [188, 193, 194] In a retrospective cohort study, Teitsma et al. [35] evaluated 1052 patients (average age 28 years, 38% females) with an average age of 28 years at 3, 6, 9 and 12 months post ACLR. At the pre-operative and 3, 6 and 9-month post-operative assessments males had less symptoms and disability compared to females (p≤ 0.001, p≤ 0.001, p≤ 0.001, p=0.005 respectively). However, 12 months after surgery there were no differences between males and females (p= 0.872).
The Cincinnati Knee Scoring System

The Cincinnati knee scoring system was originally introduced in 1983 [195] and has undergone several modifications. The current version assesses 11 functional activities with an emphasis on activity participation. It is a 100-point scoring system that includes evaluation of symptoms (pain, swelling, and giving way) and function (overall, walking, stair climbing, running, and jumping or twisting) where the total score is calculated by summing the specified point values to the individual responses. [38] In addition to the patient-reported component, the Cincinnati scoring system includes a physical examination, a knee laxity assessment and radiographic evidence of degenerative disease. [196] Ott et al.’s [38] retrospective study of 77 females and 74 males with an average age of 24 years and a minimum follow-up of 4 years following ACLR found lower Cincinnati scores (i.e. poorer outcome) for females compared to males (p=0.032). Although the Cincinnati scoring system has been shown to adequately evaluate knee function following ACL reconstruction, [187] it is criticized for being complex and time-consuming. [196] Additionally, Risberg et al. [187] reported in their prospective study of 120 patients with ACLR over a 2 year period that it is more difficult to separate various aspects of knee function using the Cincinnati knee scoring scale compared to the Lysholm and IKDC because the Cincinnati scale uses both manual and instrumented stability testing to assess symptoms and function.

The IKDC, the Cincinnati scoring scale and the Lysholm are interviewer-administered PROMs and it is thought that this mode of data collection introduces bias when applied to individuals with an ACL injury. [149, 197] Also, Rodriguez-Merchan suggested [198] that researchers who are considering using a PROM such as the IKDC for ACLR
outcomes should also include, at a minimum, the KOOS which addresses broader and more pertinent areas of concern to patients following ACLR. These include quality of life and emotional health that are lacking in the IKDC. Furthermore, Roos et al. have suggested that the KOOS is potentially more suitable for patient assessment over longer-term periods as compared to the IKDC. [199] Overall, in the last 10 years, the KOOS and the IKDC are the two measures that are increasingly being used for ACLR outcome evaluation. [149]

**The Tegner Activity Scale**

The Tegner activity scale is the most commonly used activity rating system for patients with various knee disorders. [188, 193, 200, 201] The Tegner was developed to evaluate activity based on work and sports activities and has been shown to be reliable, valid and responsive in patients with ACL injury and following ACLR. [152, 200] The Tegner scores a person’s activity level between 0 and 10, where 0 represents being on sick leave/disabled, 5 represents participation in recreational sports and 10 represents participation in competitive sports at the elite level. [35] The Tegner has acceptable responsiveness when used in early return to function following ACLR. [188] Teitsma et al. [35] surveyed 790 patients (37% females) and found no difference between males and females (p= 0.77) on activity rating as measured by the Tegner scale by 12 months following ACLR.

**The Marx Activity Scale**

The Marx Activity Scale is another PROM assessing patient ability and frequency of activity in 4 categories including running, cutting, pivoting and decelerating activities. [184, 196] Each category is scored on a 5-point scale quantifying the frequency of
participation as less than one time per month (0) to 4 or more times per week (4). A score is given as the sum of the score from the four categories ranging from 0-16 where, for example, a competitive athlete practicing several days a week would receive a score of 16, while a recreational jogger would receive a score of 3. [202] Briggs et al. provided evidence for acceptable test-retest reliability (ICC > 0.70) and expected correlations with other activity scales such as the Tegner. [200] Dunn et al. [202] evaluated 393 people (average age 23 years, 44% female) 2 years following ACLR and found at baseline the median Marx activity level was 12 (range 8-16). Two years following ACLR, the median Marx activity level declined to 9 (3-13) with no significant difference between males and females on the Marx activity level after 2 years (p=0.43) Because the Marx is specific to those activities that challenge a patient with an ACL injury, there is a concern that this scale will not differentiate between those who remain active in non-knee aggravating activities compared to those who give up activities completely due to their injury. [188] As a result, the IKDC has been recommended as a PROM to use along with the Marx when assessing activity level. [188, 201]

**The Minnesota Leisure-Time Physical Activity Questionnaire**

The Minnesota Leisure-Time Physical Activity Questionnaire (MLPAQ) assesses the type, frequency and intensity of involvement in a range of activities in number of hours participated in an activity over a 12-month period. [203] The MLPAQ has been validated in several epidemiological studies and interventions. [189, 204-206] The questionnaire enquires about participation in 54 different activities requiring various levels of physical activity including walking, housework, home repair, caregiving, physical conditioning, individual and team sports, racquet sports, water activities, winter activities and has been
used as a measure of activity in the cohort studied in this thesis in a study by Gignac et al. [207] Seventy seven males and 44 females (average age of 27.6) were assessed prior to their ACLR, then again at 1, 2 and 3 years following their ACLR. [208] Overall, this cohort spent more time participating in “lower risk of knee injury activities” compared to “higher risk knee injury activities” at baseline (311.5 hours versus 192.5 hours). Gignac et al. reported time spent walking and participating in household activities did not significantly change from pre-surgery through years one to three post ACLR (p>0.05). However time spent participating in “lower risk knee activities” did change significantly (p<0.05) from baseline to 1-year post ACLR (311.5 hours to 201.6 hours) as did time spent participating in “higher risk knee activities” (192.6 to 38.5 hours). Results comparing males to females were not reported.

2.6 HEALTH RELATED QUALITY OF LIFE

2.6.1 Health Related Quality of Life defined

HRQoL and quality of life (QOL) are terms that are often used interchangeably, but they are not the same concept. Quality of life (QOL) is a broad multidimensional concept that goes beyond health appraisals and usually includes subjective evaluations of both positive and negative aspects of life like an individual’s financial situation, support, perceptions of the self and participation in a wide range of roles. [208]

Schipper et al. [209] writes that “HRQoL is subjective and multidimensional, encompassing physical and occupational function, psychological state, social interaction and somatic sensation.” HRQoL reflects the way an individual perceives and reacts both to their health as well as to the nonmedical aspects of their lives, which includes health-related factors (physical, functional, emotional, and mental well-being) as well as non-
health-related factors (family, friends, job and other situations in life). [209] When compared to other health outcomes representing disease models, HRQoL generates a more positive, broader concept of health. [210] The complexity of HRQoL is also addressed by the World Health Organization (WHO) that describes HRQoL as encompassing multiple components including an individual’s physical health, psychological state, level of independence and social relationships, as well as their relationship to the salient features of their environment. [211] Health-related factors influence HRQoL including illness, injury and treatment. [212] However, past experiences, present circumstances, and expectations for the future also can influence HRQoL. [213] Perception and achievement of HRQoL is dependent on both the individual’s physical condition and his or her priorities in life.

By measuring perceived physical, mental health, and function as important components of health surveillance, HRQoL is generally considered a valid indicator of service needs and intervention outcomes, [214, 215] and is considered an important indicator used to capture the burden of disease or illness. [216] The importance of integrating HRQoL in orthopaedic outcome studies has been recognized as it is thought to contribute to a more complete picture of how the injury/disease influences all areas of life. [17]

Despite the different nuanced definitions of HRQoL mentioned above, Schipper et al.’s definition best underpins this thesis work as it incorporates both biological and sociocultural components, both of which are aspects of SGSA research. HRQoL has been used as the primary outcome of interest in this thesis because it has the potential to
capture the breadth of what a patient recovering from ACLR may experience including the physical, social, mental and functional aspects that hinder optimal quality of life.

2.6.2 PROMS Used To Assess ACLR HRQoL

Both disease-specific and generic instruments have been used to evaluate HRQoL following ACLR. The most commonly used PROMs are the disease-specific KOOS-Quality of Life (KOOS-QOL) subscale of the KOOS, the SF-36, a generic HRQoL assessment tool and the Mohtadi ACL QOL, an ACL-specific HRQoL measure.

The Knee Injury and Osteoarthritis Outcomes Score (KOOS)

The KOOS was designed to evaluate and assess patient opinion about their knee and associated problems. [194, 217, 218] It evaluates pain (KOOS-Pain, 9 items); other symptoms (7 items); Activities of Daily Living (ADL, 17 items); Sport and Recreation function (Sport/Rec, 5 items); and knee-related Quality of Life (KOOS-QOL, 4 items). The KOOS-QOL items have 5 response options scored from zero to four (never, monthly, weekly, daily, constantly) for question 1, from zero to four (not at all, mildly, moderately, severely, totally) for questions 2, 3 and from zero to four (none, mild, moderate, severe, extreme) for question 4. Each subscale is scored separately from zero (extreme knee problems) to 100 (no knee problems). [218] The KOOS has demonstrated reliability, validity and responsiveness over short- and long-term follow-up in patients with ACL injury, meniscal tears and post-traumatic OA. [182, 190, 193, 194, 217, 219, 220] Specific to the KOOS-QOL in the context of ACLR, the subscale has demonstrated test-retest reliability (ICC=0.86-0.89), [218, 221, 222] and responsiveness (Effect Sizes (ES)= 1.65 and 1.36 at 6 months and 1-year post-operatively respectively)[220, 221]. It has demonstrated construct validity against the subscales of the SF-36 including the SF-
36 GH \((r=0.28)\) [220], the SF-36 SF \((r=0.59)\) [221] and the SF-36 PF scale \((r=0.64)\) [222].

Studies vary between time of ACLR and time when HRQoL was assessed with the KOOS-QOL. In a systematic review [8] of 14 studies [17-20, 32, 38, 223-230] HRQoL was examined ≥5 years following ACLR. Five of the studies were randomized control trials, [17, 223, 226, 228, 231] and the other 9 studies were either prospective [226, 227, 230] or retrospective in design [18-20, 32, 38, 224]. Sample sizes ranged from 22-1452 participants. The time range from ACLR to follow-up ranged from 5-18.1 years. Age of the participants ranged from 18 to 42 years. Of these studies, twelve included both men and women, only one study included men [32] and one study did not report on the sex of the participants. [230] The pooled KOOS-QOL summary effect was 74.5 points (95% CI, 68.3-80.7). [8] When comparing these pooled KOOS-QOL values with previously published normative data from a healthy population with no knee symptoms, [229] ACLR patients reported poorer KOOS-QOL scores. [8] In a study from this systematic review that looked at KOOS-QOL score pre-operatively and at 1-year post-operatively, results revealed that patients who underwent ACLR generally reported improved KOOS-QOL compared to their pre-operative scores \(p<0.001\), [230] similar to findings reported in previous literature. [232, 233] Pain as measured with the KOOS pain subscale as well as the KOOS sport/rec subscales were found to have a strong correlation to KOOS-QOL \(\rho=0.85, p=0.003\) and \(\rho=0.7, p=0.04\), respectively). [8] Despite the wide range in follow-up time in these studies, duration of follow-up was not significantly associated with the KOOS-QOL subscale scores \(p=0.19\).
Ageberg et al. [234] examined differences in HRQoL between males and females at 1 and 2 years following ACLR in 5255 participants (52% female) with a mean age of 27 years. Preoperatively, female patients reported worse scores than male patients in 4 of the KOOS subscales (i.e., pain, symptoms, sport/recreation, quality of life subscales). At 1-year post-operatively, female patients reported worse scores than male patients in KOOS pain (mean difference, 1.4; 95% CI, 0.4-2.4) and KOOS sport/rec subscales (mean difference, 2.7; 95% CI, 0.9-4.4). At 2 years post-operatively, females reported worse scores in the KOOS sport/rec (mean difference, 4.4; 95% CI, 2.1-6.7) and KOOS-QOL subscales (mean difference, 2.4; 95% CI, 0.4-4.4). Female patients reported less improvement from 1 to 2 years post-operatively than male patients in the KOOS sport/rec subscale (mean difference, 3.2; 95% CI, 0.3-6.1). [234] This study demonstrates in a large cohort that while there were no significant differences between males and females in HRQoL at 1-year post-operatively, females reported lower HRQoL than males at 2 years follow-up. The reasons for these differences between males and females are unknown but further research that evaluates differences between males and females in factors that impact HRQoL may be informative. See Table 2 for a review of the KOOS measurement properties among ACLR cohorts.

**Shortform-36 (SF-36)**

The SF-36 is a validated [235] and reliable [236] generic HRQoL measure designed for use in a variety of populations. [237] The SF-36 is comprised of 36 items that evaluate eight health dimensions: bodily pain (BP); general health (GH); mental health (MH); physical function (PF); role emotional (RE); role physical (RP); social function (SF); and vitality (VT). Scores can be derived for each dimension or for physical and
mental component scores. [237] The SF-36 has been validated in orthopaedic settings to show changes for groups in physical, mental, and social dimensions for different types of surgery. It has also been validated to make comparisons between surgical groups including ACLR with normative data from populations [238] and to examine HRQoL in individuals with ACL injury and ACLR. [17, 19, 20, 32, 224, 225, 228] Only responsiveness of the 8 subscales has been evaluated in people with ACLR. ES ranged from 0.7 to 1.8 (with the exception of the GH subscale; ES= 0.2) at 6 months follow-up. At two years post ACLR, ES remained large for all subscales (ES ranged from 0.7 to 2.5 with the exception of GH where the ES= 0.1).

In a systematic review of five studies examining HRQoL measured with the SF-36 following ACLR, sample sizes ranged from 22-137 participants with follow up ranging from 5-17 years. Two studies consisted of RCTs [17, 231] comparing hamstring vs. BPTB techniques and although not explicitly stated the results of the two arms were pooled. The other three studies were retrospective cohorts. [19, 32, 224] All but one [32] of the studies included both men and women, with females accounting for 37-57% of the sample in the other studies. The ACLR population described in the 5 studies reported on average higher SF-36 values compared to normative data values at follow-up. The exception was the MH subscale where data for the ACLR group approximated the normative values of 78.7. [239]

In another study Shapiro et al. [240] followed 113 patients (65 male, 48 female with an average age of 30 years) with evaluations pre-operatively and at 6, 12 and 24 months follow-up. They compared the SF-36 subscale scores of those treated with the BPTB ACLR technique versus conservative management (rehabilitation). Despite the scores not
being statistically significant, the authors considered the differences meaningful as changes from baseline to 1-year follow up were greater than 10 points in the PF, RP, BP, VT, SF, RE and MH subscales from baseline to 1-year follow-up. When one looks at the actual change scores that range from 21 in the MH subscale to 67 in the RP subscale, the change scores are quite large. The non-significant findings could be due to the large standard deviation of the score. Although there were several limitations to this study, including the small sample size and relatively short follow-up, it is one of the few studies to look at HRQoL as an outcome longitudinally.

Ochiai et al. [241] prospectively evaluated 81 patients (46 males and 35 females) with a mean age of 27.4 years pre-operatively, at 6 months and 1-year after ACLR. There was a significant improvement at the 6-month and again at the 12-month evaluation in all SF-36 domain scores compared to pre-operative results (p<0.05). During the pre-operative time point the authors found that all subscales except VT and MH were lower than the national standard of 50 for SF-36 subscales used in Japan. The authors concluded that HRQoL assessed by the SF-36 improved significantly following ACLR. They also noted that physical health might be a more significant determinant of HRQoL pre-operatively than mental health. Results were not reported separately for males and females.

Busija et al. reviewed 62 patients’ (50 males, 12 females; age range 18-35) ACLR outcomes 2 years post ACLR in a longitudinal analysis. Despite improvements (ES≥0.80) in physical subscales of the SF-36 (PF, RP BP) between pre- and post-surgical time points, these same subscale scores were still below normative data values from an age- and sex-matched population. [236] While the MH (SF, RE and VT) displayed small (ES= 0.20-0.49) to moderate (ES= 0.50-0.79) effect sizes, these subscales did approach
population normative values following surgery. [238] See Table 2 for a review of the SF-36 measurement properties among ACLR cohorts.

**The Mohtadi ACL QOL**

The Mohtadi-ACL QOL questionnaire (ACL-QOL) is an ACL-specific HRQoL PROM with 31 items distributed across five domains including: the spectrum of symptoms and signs, impact on work, recreation and sport, social activities and emotional issues. [242] Face validity was derived from direct patient input and content validity was established by consensus from 20 surgeons who determined the items included the full spectrum of disease impact in ACL deficient patients. [194, 242] The ACL-QOL has demonstrated test-retest reliability (0.6 and 0.86) [242, 243] construct validity (r= 0.88) [243] and has been found to be responsive to change (ES= 0.61). [242] See table 2 for a review of the ACL-QOL measurement properties in ACLR cohorts.
<table>
<thead>
<tr>
<th>Instrument</th>
<th>Reference</th>
<th>N (# Female)</th>
<th>Patient baseline activity level and/or cohort traits</th>
<th>Age (mean +/-SD)</th>
<th>Subscale</th>
<th>Content validity</th>
<th>Construct validity (Spearman’s correlation coefficient r)</th>
<th>Reliability</th>
<th>Test-retest reliability ICC (95% CI)</th>
<th>Responsiveness ES (0/u time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOOS[244]</td>
<td>ROOS (1998)[220]</td>
<td>21(12)</td>
<td>10 competing in sports, 9 recreational athletes, 2 not active in sports</td>
<td>32+/-NR</td>
<td>Pain</td>
<td>Literature review of patient relevant outcomes, expert panel consultation and pilot study</td>
<td>0.46 (compared to SF-36 BP)</td>
<td>-</td>
<td>0.85 (0.85-0.95)</td>
<td>0.84(6mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptoms</td>
<td></td>
<td>0.29 (compared to SF-36 PF)</td>
<td></td>
<td>0.93(0.75-0.91)</td>
<td>0.87(6mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Activities of Daily Living</td>
<td></td>
<td>0.57 (compared to SF-36 PF)</td>
<td></td>
<td>0.75(0.75-0.91)</td>
<td>0.94(6mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sports and Recreation Function</td>
<td></td>
<td>0.47 (compared to SF-36 PF)</td>
<td></td>
<td>0.81(0.61-0.89)</td>
<td>1.16(6mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>QOL</td>
<td></td>
<td>0.28 (compared to the SF-36 GH)</td>
<td></td>
<td>0.86(0.83-0.95)</td>
<td>1.65(6mo)</td>
</tr>
<tr>
<td>Comins (2008)[245]</td>
<td>200(70)</td>
<td>200 patients tested 20 weeks after ACLR. All patients followed a standardized 16-week rehabilitation protocol. Baseline NR</td>
<td>29.4+/-NR</td>
<td>Pain</td>
<td>-</td>
<td>-</td>
<td>0.80</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptoms</td>
<td></td>
<td>-</td>
<td></td>
<td>0.59</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADLs</td>
<td></td>
<td>0.89</td>
<td></td>
<td>0.89</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sports and Recreation</td>
<td></td>
<td>0.80</td>
<td></td>
<td>0.75</td>
<td>-</td>
</tr>
<tr>
<td>Salavati (2011) [221]</td>
<td>57(18)</td>
<td>Soccer, basketball players, wrestlers</td>
<td>25.6+/-3.4</td>
<td>Pain</td>
<td>-</td>
<td>0.79 (compared to SF-36 BP)</td>
<td>0.91</td>
<td>0.93 (0.91-0.96)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptoms</td>
<td></td>
<td>0.49/0.41 (vs. SF-36 GH/PF)</td>
<td>0.75</td>
<td>0.85(0.81-0.91)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Activities of Daily Living</td>
<td></td>
<td>0.73 (vs. SF-36 PF)</td>
<td>0.96</td>
<td>0.91(0.87-0.93)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sports and</td>
<td></td>
<td>0.72/0.46 (vs. SF-36 PF)</td>
<td>0.86</td>
<td>0.75(0.87-</td>
<td>-</td>
</tr>
<tr>
<td>Instrument</td>
<td>Reference</td>
<td>N (# Female)</td>
<td>Patient baseline activity level and/or cohort traits</td>
<td>Age (mean +/-SD)</td>
<td>Subscale</td>
<td>Content Validity</td>
<td>Construct validity (Spearman’s correlation coefficient r)</td>
<td>Reliability</td>
<td>Responsiveness ES (f/u time)</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------------------------------------------------</td>
<td>-----------------</td>
<td>----------</td>
<td>----------------</td>
<td>------------------------------------------------</td>
<td>------------</td>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td>Busija (2008)[238]</td>
<td>62(12)</td>
<td>- 25.9 (5.1)</td>
<td>-</td>
<td>PF</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.6 (6mo), 1.8 (2yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.9 (6mo), 2.5 (2yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.6 (6mo), 1.7 (2yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.2 (6mo), 0.1 (2yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SF</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.6(6mo), 0.7(2yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.7(6mo), 0.8(2yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.7(6mo), 0.8(2yr)</td>
<td></td>
</tr>
<tr>
<td>Recreation Function</td>
<td>SF-36 PF(SF)</td>
<td>0.92</td>
<td></td>
<td></td>
<td>QOL</td>
<td>0.59(vs. SF-36 SF)</td>
<td>0.74</td>
<td>0.89(0.87-0.92)</td>
<td>ES at 1-year f/u</td>
<td></td>
</tr>
<tr>
<td>QOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain</td>
<td>0.66(vs. SF-36 BP)</td>
<td>0.92</td>
<td>0.86(0.84-0.88)</td>
<td>ES at 1-year f/u</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain</td>
<td>0.65(vs. SF-36 PF)</td>
<td>0.94</td>
<td>0.89(0.88-0.91)</td>
<td>ES at 1-year f/u</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Activities of Daily Living</td>
<td>0.67(vs. SF-36 PF)</td>
<td>0.96</td>
<td>0.93(0.91-0.94)</td>
<td>ES at 1-year f/u</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sports and Recreation Function</td>
<td>0.64(vs. SF-36 PF)</td>
<td>0.95</td>
<td>0.90(0.88-0.92)</td>
<td>ES at 1-year f/u</td>
<td></td>
</tr>
</tbody>
</table>

Paradowski (2013)[222] Polish speaking patients who had undergone ACLR, 6 months structured rehabilitation. Baseline Activity NR.

Mohtadi used paired t test.
<table>
<thead>
<tr>
<th>Instrument</th>
<th>Reference</th>
<th>N (# Female)</th>
<th>Patient baseline activity level and/or cohort traits</th>
<th>Age (mean +/-SD)</th>
<th>Subscale</th>
<th>Content Validity</th>
<th>Construct Validity (Spearman's correlation coefficient r)</th>
<th>Reliability</th>
<th>Responsiveness ES (f/u time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACL-QOL</td>
<td>Lafave (2016)[246]</td>
<td>579 (278)</td>
<td>-</td>
<td>27.8 (6.9)</td>
<td>Questionnaire analyzed as an overall score</td>
<td>0.96</td>
<td>-</td>
<td>0.96</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>Mohtadi (1998)[242]</td>
<td>100(-)</td>
<td>-</td>
<td>18-45 (-)</td>
<td>Questionnaire analyzed as an overall score</td>
<td>Descriptive consensus among surgeons</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Tanner (2007)[194]</td>
<td>58(28)</td>
<td>Tegner activity 5</td>
<td>30.1(-)</td>
<td>Questionnaire analyzed as an overall score</td>
<td>Highest FIP * (compared to IKDC, Cincinnati, Lysholm)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Bryant (2006)[243]</td>
<td>344(130)</td>
<td>-</td>
<td>39(-)</td>
<td>Questionnaire analyzed as an overall score</td>
<td>-</td>
<td>0.88</td>
<td>-</td>
<td>0.86(0.75-0.91)</td>
</tr>
</tbody>
</table>

*NR= Not reported  f/u = follow up

FIP= Frequency Intensity Product: Ideal quality of life measures include questions about symptoms and disabilities with a high* FIP[247] The FIP is calculated by multiplying the number of patients endorsing a question by the mean importance rating of that question[194] * High FIP indicates that a symptom or disability is both frequently experienced and most important to patient
2.6.3 Factors Associated with ACLR HRQOL

In order to better understand outcomes of ACLR surgery, researchers have examined a wide range of pre-and post-operative factors associated with various outcomes. These factors include knee strength [184, 187, 248-251], knee laxity [252, 253], knee alignment [254, 255], body mass index (BMI) [6, 202, 249, 256], age [257, 258], graft choice [259-264], sex [202, 258], smoking [249], baseline activity level [265], pre-operative level of knee function [266], time from injury to surgery. [250, 267-270] Psychological perceptions have also been explored in this context including fear of re-injury [7, 12, 271-273], mental health (e.g., depression) [241] and pain levels with its predictive effect on post-operative disability and knee function [187, 274, 275] However, when focusing on factors predictive of ACLR HRQoL, research has been more limited. It is important to look at these factors and their associations with HRQoL as they potentially can provide a more nuanced view and identify groups of patients who may be at risk for poorer outcomes.

The review of factors that have been explored with respect to ACLR HRQoL is divided into three categories. First, patient characteristics, including patient age [18, 38, 225, 229], knee strength [276], knee laxity [225], BMI [12] and baseline activity level [266] will be discussed. Second, surgical considerations, including time from injury to surgery [277] and graft type [17, 223, 224, 228] will be reviewed. Third, psychological factors such as return to pre-injury level of activity following ACLR [278], fear of re-injury [13], self-efficacy [279] and pain [280] are reviewed. The literature related to male/female [8, 32, 38, 172, 225, 227, 229] as a predictor of HRQoL is then reviewed.
The scope of this review is comprehensive yet focused on examining only factors that have been examined as predictors of HRQoL in ACLR and is not a review of the factors that have been examined in relationship to other ACLR outcomes.

2.6.3.1 Patient Characteristics Associated with ACLR HRQoL

Age

Four studies have investigated the relationship between age at the time of ACL surgery and HRQoL [18, 38, 225, 229] These studies included participants aged 18 to 50 years and found no significant relationship between patient age and HRQoL measured with the KOOS-QOL [18, 225, 229] or the SF-36 subscales. [231] However, Ott et al. [38] did find a difference in their research dividing their cohort recovering from ACLR into three age groups: 12-18 years (42 females, 20 males), 19-24 years (16 females, 20 males) and over 24 years (19 females, 34 males). The time from surgery to follow up was a minimum of two years. When comparing HRQoL between males and females from each age category, males averaged better HRQoL compared to females in both the 12-18 years age category and the over 24 years age category as assessed by the Mohtadi QOL (93.1 vs. 78.2 and 78.5 vs. 70.5 respectively). However in the cohort of 19-24 year olds, females reported better HRQoL compared to males (77.9 vs. 72.7). Among this cohort, the youngest females from the 12-18-age category had the largest discrepancy and poorer HRQoL following ACLR scoring 15 points lower in HRQoL compared to their male counterparts from the same age category. Older females reported less of discrepancy in the over 24 years age category or better HRQoL in the 19-24-age category compared to males.
Knee Strength

Knee strength has been shown to be significantly associated with HRQoL following ACLR, using the SF-36 in a study of 70 Korean participants (mean age 32 years) 1-year following ACLR. [281] Specifically, extensor and flexor knee strength deficits significantly correlated at a modest level (r’s = -.20 to -.39) with several of the SF-36 subscales 1-year following ACLR. The percentage of male versus female participants was not reported.

Knee Laxity

Moller et al. [225] studied 62 patients (30 males and 32 females) with an average age of 27.5 years. They categorized their two follow up periods as “short” (2 years post ACLR) or “long-term” (11.5 years post ACLR). Stepwise logistic regression analyses were used to evaluate the association between the dependent variables (KOOS sport/rec, KOOS-QOL, SF-36 PF, SF-36 RP) and clinical variables, including sagittal knee laxity, muscle peak torque, one-leg hop test, Lysholm score, time between injury and surgery, age and gender. Specific to knee laxity, the Mann-Whitney U test was used to investigate if there was any difference in the KOOS-QOL among patients with a knee laxity side to side difference of ≤3mm compared to those with a side to side difference of ≥3 mm at the 2-year follow up. There were no significant group differences in HRQoL as determined by the KOOS-QOL based on knee laxity, muscle peak torque or the OLHD at 2 years post ACLR. No significant differences were found between males and females.

Body Mass Index

Heijne et al. [12] studied 64 patients (35 males and 29 females) with an average age of 30.1 years 12 months following ACLR. The KOOS sport/rec, the KOOS-QOL, the
OLHD and the Tegner activity scale were used as dependent variables in multiple linear regression analysis. Lower pre-operative BMI was significantly associated with greater post-operative KOOS-QOL at 1-year follow-up. However, similar to many of the studies explored thus far in this thesis, specific differences between males compared to females were not reported.

**Baseline Activity Level**

Mansson et al. [280] evaluated pre-operative activity levels and their association with post-operative HRQoL in a sample of 73 patients (51 males, 22 females) with an average age of 24.6 years. The patients had an average pre-operative Tegner activity level of 4 (1-8). Each participant underwent a physical examination at follow-up an average of 26 months (22-36 months) following ACLR. Predictive factors for HRQoL were explored using the SF-36 and KOOS subscales as dependent variables. All of the SF-36 subscales except for MH were used. The study found that those patients with a higher pre-operative activity level reported greater HRQoL scores at follow-up as measured by the KOOS-QOL ($R^2=0.18$, $\beta=6.8$, $p<0.05$), but not the SF-36. Sex differences were not reported.

**2.6.3.2 Surgical Considerations Associated with ACLR HRQoL**

*Time from ACL injury to surgery*

Frobell et al. [277] followed 120 patients aged 18 to 35 years in a randomized controlled trial looking at early ACLR versus starting rehabilitation with the option of delayed ACLR. The study randomized 61 patients (12 females and 49 males) to the early ACLR intervention group where surgery was performed within 10 weeks after the injury. 59 patients (20 females and 39 males) were randomized to the rehabilitation intervention with optional delayed ACL reconstruction. Participants in this latter group were referred
for ACLR if they chose surgery and if they met pre-specified criteria including self-reported symptomatic ACL instability and a positive pivot shift test. Twenty-three of the 59 patients from the rehabilitation intervention with optional delayed ACLR ended up undergoing ACLR an average of 11.6 months after randomization. Participants were evaluated at 3, 6, 12 and 24 months following randomization. At each follow-up they completed the KOOS-QOL scale. Findings show no significant difference in the two treatment options with the rehabilitation plus early ACLR group’s mean KOOS-QOL score being 67.3 (61.3-73.3) and the rehabilitation plus optional delayed ACLR group’s mean score being 63.0 (56.9-69.2) (p= 0.28). Sex differences were not reported.

Graft Type

Four studies [17, 223, 224, 228] have investigated differences in HRQoL measured with the KOOS-QOL following ACLR using a single or double-looped hamstring tendon autograft or a BPTB autograft. In the first study, 153 patients (42% female) with an average age of 34 years were studied prospectively over an 8-year follow-up. [17] The second study evaluated 93 participants (37% female) with an average age of 34 years and prospectively followed for 7 years post-operatively. [223] In the third study, 19 participants (7% female) with an average age of 28 years were examined retrospectively 9 years following ACLR. [224] Lastly, in the fourth study, 64 participants, (42% females) with an average age of 32 years were followed prospectively for 5 years. [228] At 2 years post ACLR, there was no significant association between graft type and KOOS-QOL outcome. Filbay et al. [8] performed a systematic review of HRQoL after ACLR in 14 studies with a total of 2493 participants (34% female) with a mean age of 34 years (18-42). The systematic review found similar results to the studies mentioned previously with
no significant correlation between graft type and KOOS-QOL at follow-up. Sex differences were not reported.

2.6.3.3 Psychological Factors Associated with ACLR HRQoL

Research has found that psychological perceptions and appraisals are often associated with physiological outcomes and return to sport and activity following ACLR. [7, 9-11, 282-286] The association of psychological factors with HRQoL following ACLR have been explored far less frequently. However, some factors have been evaluated as predictors of HRQoL including returning to pre-injury activity levels or activities [278], fear of re-injury [13, 283, 286-292], self-efficacy [279, 293-297] and pain [2, 12, 272, 291, 292, 298-300].

Return to pre-injury activity levels or activities following ACLR

Christino et al. [278] studied 26 individuals (average age 25.7 years, 50% female) approximately 16.5 (+/-5.9) months following ACLR. Psychological perceptions assessed included internal/external locus of control, mood, and self-esteem. Greater self-esteem was significantly correlated with being more likely to return to pre-injury levels of activity and with higher KOOS-QOL scores. Sex differences were not reported.

Fear of Re-Injury

A fear of re-injury has often been assessed in research as a potential barrier to a return to pre-injury levels of activity following ACLR. [13, 283, 286-290] In a retrospective comparative study investigating the rate of return to sport and activity after ACLR, Flanigan et al. interviewed 135 patients 12-25 months following ACLR. The study sample consisted of 67 men (mean age 29.16 ± 10.62 years) and 68 women (mean age 27.53 ± 10.24 years). Sixty-two of the 135 patients (46%) returned to their pre-injury
levels (returners) while the remaining 73 patients did not (54%) (Non-returners). Fear of re-injury was the most common reason cited by the non-returners for not returning to their pre-injury level of activity (38 of the 73 non-returners or 52%) regardless of sex (51% of women compared to 53% of men, P > 0.05). [287]

Kvist et al. [13] followed 62 patients (45% females) with an average age of 27 years in a prospective study to evaluate if fear of re-injury measured with the Tampa Scale of Kinesiophobia (TSK) was significantly associated with returning to pre-ACLR activity level at 3 years following ACLR. Kinesiophobia has been described by Kori et al. [301] as, “as excessive, irrational and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or re-injury”. Kinesiophobia has also been described as leading to an avoidance-behaviour, namely the expectation that movement can cause re-injury and thus increase suffering. [13, 289, 290] The Kvist et al., study found that greater fear of movement was associated with lower KOOS-QOL and with being less likely to return to pre-injury levels of activity. Of interest is that some psychological characteristics like locus of control and self-esteem are likely to be relatively stable over time and not change. Other perceptions like a fear of re-injury may vary with time. In a study of 77 men and 44 women, a longitudinal study of activity post ACLR found that perceptions of a fear of re-injury decreased significantly in the first year post-ACLR and then remained relatively stable over the next two years. [288] Individuals with the greatest decrease in fear of re-injury were most likely to return to activities. However, when the researchers included perceptions of the importance of exercise to participants, fears of re-injury were less relevant and importance of exercise was associated with increased involvement in activities. [288] Chmielewski et al. studied
60 men and 37 women at different time points following ACLR in a cross sectional study. [291, 292] In their study three patient groups were formed based on time from ACLR: group 1, less than 90 days (n= 39); group 2, 91 to 180 days (n= 31) and group 3, 181 to 372 days (n= 27). Results from the Chmielewski et al. study found TSK scores were highest among group 1 participants compared to group 3 (p<0.05) indicating fear of re-injury levels declined with time among this cohort.

**Self-Efficacy of Knee function**

Self-efficacy refers to the confidence an individual has that he or she can behave in ways that will help manage difficulties. [295-297] It has been widely studied in a range of health studies and interventions, including how to better understand rehabilitation behaviours after sport-related injuries. [279, 293, 295-297] Thomee et al. developed a knee self-efficacy scale (K-SES) [294] and administered it to 38 individuals (13 females and 25 males; mean age 29.6 years) pre-operatively and 1-year following ACLR. [279] Results found that greater pre-operative self-efficacy was significantly associated with greater KOOS-QOL at 1-year post surgery controlling for age, gender and pre-injury level of activity. Differences between males and females were not reported.

**Pain**

Higher levels of perceived pain also have been associated with poorer HRQoL [302] and pain is often assessed in ACLR studies. [2, 12, 272, 298-300] Heijne et al. [12] studied 64 patients (45% females; average age 30.1 years) 12 months following ACLR. Controlling for a number of other clinical factors, a low degree of pre-operative knee pain was the strongest predictor for greater HRQoL. Differences between males compared to females were not reported.
Chmielewski et al. examined change in pain levels over time in a cross sectional study of 3 patients groups (group 1, less than 90 days from ACLR (n= 39); group 2, 91 to 180 days from ACLR (n= 31) and group 3, 181 to 372 days from ACLR (n= 27)). Pain was measured using a single item from the Medical Outcomes Study 8-Item Short-Form Health Survey (SF-8). The SF-8 bodily pain ratings range from 0 to 5 where a higher score indicates more pain. Group 1 averaged a rating of 1.8 on the SF-8; group 2 averaged 1.2 and group 3 averaged 0.6 (p<0.001). They concluded that bodily pain lessened as more time elapsed from ACLR among this cohort.

2.6.3.4 Male/Female as Predictor of ACLR HRQoL

Barber-Westin et al.’s [172] study was the first to compare ACLR results between males and females. Their research included 94 patients (47 of each sex) with a mean age of 29 years (range of 15-54 years). Similarities and differences in complications and outcomes 2 years (range of 22-35 months) following ACLR were examined. The authors found no statistically significant differences in post-surgery complications, AP knee displacement, patellofemoral crepitus, quadriceps and hamstring strength, knee articular cartilage deterioration, subjective complaints such as pain, or sports activity level differences between men and women. HRQoL was not included as an outcome in their study.

Other research has found contradictory findings. In Filbay et al.’s review of five studies [8] that included an investigation of the relationship of M/F with HRQoL outcomes after ACLR [32, 38, 225, 227, 229] only one study [32] reported a difference. Ferrari et al. [32] conducted a retrospective case review of 200 patients (31% females; average age 28 years) examining ACLR outcomes at 36 to 70 months follow-up.
Because pre-operative SF-36 data were not available, the authors compared post-surgery SF-36 subscale scores with gender-matched controls. Women scored higher on the SF-36 Role Physical, Bodily Pain and General Health subscales compared to female normative data than did males with male normative data. There were no significant differences between men and women in HRQoL in the other five studies reviewed and that used the SF-36, KOOS-QOL, or ACL-QOL to evaluate HRQoL. [8, 38, 225, 227, 229]

Ryan et al. [303] systematically reviewed six studies [16, 38, 39, 172, 304, 305] of 5410 patients (42% females; average age 28 years) and reported on M/F HRQoL results 2-7 years following ACLR. Outcomes were mostly similar in men and women patients in each of these studies with the exception of Ageberg et al.’s [16] retrospective cohort study. One of the largest retrospective studies to analyze M/F differences in ACLR outcomes, Ageberg et al. obtained data on 4438 patients (44% females; average age 27 years) pre-operatively and at 1 and 2 years following ACLR from the Swedish knee ligament registry. Preoperatively, women had significantly worse outcomes in four of the five KOOS subscales following ACLR compared to men, including worse pain (F= 73.2 vs. Mean= 75.1), symptoms (F= 67.5, Mean= 68.9), sport/REC (F= 38, Mean= 42.7) and QOL (F= 31.9 vs. Mean= 34). The largest pre-operative M/F difference was in the KOOS Sport/Rec subscale. 1-year post-operatively, women continued to report worse scores compared to males in KOOS pain and KOOS Sport/Rec, again with the largest difference in the KOOS Sport/Rec. Two years post-operatively, women reported worse scores than male patients in the KOOS Sport/Rec and KOOS-QOL subscales. The authors found no differences between men and women in changes in KOOS scores over time from the pre-operative to 1-year post-operative time points.
In summary, a number of variables have been examined as predictors of HRQoL in ACLR research. Preoperatively, lower levels of knee pain, lower BMI, higher levels of activity level, and greater self-efficacy have all been associated with greater HRQoL post-operatively. Greater knee strength, lower fear of re-injury and return to pre-injury activity all measured post-operatively have also been found to be associated with improved HRQoL outcomes following ACLR. The relationship of age with HRQoL outcomes is inconsistent. Finally, graft type, time from injury to-surgery as well as degree of knee laxity have not been found to be significant predictors of ACLR HRQoL outcomes. With respect to similarities and differences between men and women, three of the eleven studies in this review reported some differences in ACLR HRQoL outcomes. [13, 38, 225] No significant M/F differences in knee laxity [225] or in fear of re-injury [13] were found.

In studies examining men and women in the context of ACLR HRQoL [8, 16, 38, 39, 172, 225, 227, 229, 304, 305] some significant differences between men and women were reported among younger women (<18 years) who had poorer HRQoL following ACLR compared to women ages 19-24 who were found to have better HRQoL compared to their male counterparts of the same age. [38] Also of note is the literature examining ACLR HRQoL has a number of limitations. Pre-operative factors are largely evaluated with limited examination of changes over the course of recovery from ACLR. Second, research is limited examining outcomes and their predictors separately for men and women at different time points. Similarities and differences also have not been examined using a sex-gender sensitive analysis that can help understand the experiences between women and men in a more nuanced way.
2.6.3.5 Additional Independent Variables Included in this Thesis

In addition to some of the variables described in previous research, this thesis examines the association of mental health, physical functioning, exercise importance, exercise commitment and weight concern with HRQoL. Reasons for their inclusion are briefly discussed below.

Mental Health Relationship to HRQoL

Mental health is an important component of HRQoL. The Center for Disease Control writes that, “By measuring perceived physical and mental health as well as function as an important component of health surveillance, HRQoL is generally considered a valid indicator of service needs and intervention outcomes.”[214] More specific to ACL research, Christino et al. [278] noted that psychological factors are often significantly associated with various aspects of ACLR recovery and ACL injury including anxiety, pain response, mood disturbance and depression. Greater depressive symptoms have been found to be associated with poorer HRQoL in all domains. [306] Furthermore, cross sectional studies have found lower depressive symptoms among men and women who are physically active compared to those who are more sedentary. [307, 308] However, to date there is no literature investigating the association of mental health like negative mood and its association with HRQoL in ACLR research.

Physical Functioning

Although physical functioning has not been looked at with respect to HRQoL in samples of individuals with ACLR, as noted earlier knee functional limitation is often associated with lower return to physical activity following ACLR. [3, 7, 9, 12, 13, 75] In Ferrari et al.’s [32] study, no significant difference was found between men and women
in their SF-36 PF scores following ACLR. However, their focus was on examining the scores of men and women compared to normative data available for each sex and they lacked SF-36 PF baseline data. In this thesis, both pre-operative and 1-year follow-up SF-36 PF scores for men and women will be compared as potential predictors of HRQoL following ACLR.

**Exercise Importance, Exercise Commitment and Weight Concern**

A number of studies have emphasized that HRQoL is not only associated with an individual’s physical condition but also their perceptions and priorities. [309] Therefore, this thesis also includes perceptions of exercise importance, exercise commitment and weight concerns. Only two studies [207, 310] have addressed the importance of exercise in those with an ACL injury. In one study of 77 men and 44 women assessed pre-operatively and then yearly for three years, the researchers found that the importance of exercise was relatively stable over time and did not decrease with injury or surgery. Individuals with higher perceived exercise importance engaged in significantly more physical activities than those with lower perceived exercise importance. [207] Similar findings have been found in other injury research. [311-314] However, the association of exercise importance, commitment to exercise and weight concerns have not been examined with HRQoL and studies have not examined similarities and differences in these perceptions between men and women.

**2.7 SEX AND GENDER**

As described earlier, few studies have examined similarities and differences between men and women related to ACLR and HRQoL and those that do have yielded few or inconsistent findings. Moreover, few studies have examined HRQoL 1-year post-ACLR
using diverse clinical and personal factors. Identifying factors, especially modifiable factors could help optimize or improve outcomes. Implementing a sex-gender sensitive approach (SGSA) may also tease apart important differences that may have been overlooked in previous studies. In the following section sex and gender will be defined and discussed in terms of gender theory.

2.7.1 Sex and Gender Defined

The Canadian Institutes of Health Research (CIHR) refers to sex as: “A set of biological attributes in humans and animals. It is primarily associated with physical and physiological features, including sex chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy.” [315] In contrast, gender is “[a] person's self-representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation.” [50] Furthermore, “…gender is rooted in biology and shaped by environment and experience.” [50] Health Canada defines gender as: “The array of socially constructed roles and relationships, personality traits, attitudes, behaviours, values, relative power and influence that society ascribes to the two sexes on a differential basis. Gender roles and characteristics do not exist in isolation, but are defined in relation to one another and through the relationships between women and men, girls and boys.” [316] Feminine and masculine are gender categories. [46]

2.7.2 Overview of Sex and Gender Differences and Similarities in Health

Although differences between the concepts of sex and gender have been studied in the social and behavioural sciences, researchers across a wide range of disciplines often use a dichotomous variable - male/female - in their analyses and do not differentiate between
the concepts of sex and gender or variables that may relate to them. However, there are research studies that have adopted sex and gender analyses in areas like health intervention and health care system utilization, as well as chronic pain studies. [317, 318] To date, there are no studies examining ACL injury and ACLR outcomes from a sex and gender sensitive focus.

Sex and gender may relate to disease progression in terms of the aetiology, diagnosis, progression, prevention, treatment, and health outcomes of disease, as well as health-seeking behaviours and exposure to risk. [319] Sex has been hypothesized to play a role in the aetiology, onset, and progression of disease; gender has been discussed in terms of symptom recognition, severity of disease, access, quality, and compliance with care, as well as disease burden and management. [318, 320] Different theories have been put forward in an attempt to explain similarities and differences between men and women. It is beyond the scope of this thesis to provide a detailed overview of sex and gender as discussed in evolutionary psychology, cognitive and social learning theory, and sociocultural theory. However, the next section provides a brief overview designed to highlight essential elements of each theory as they pertain to health outcome research.

2.7.3 Sex and Gender Theory

Krieger notes that the word ‘gender’ was introduced in English as an alternative to ‘sex’ in the 1970s and was integral to the women’s movement, which debated whether observed differences in social roles, performances and non-reproductive health status was due to innate biological differences (i.e., ‘sex’) or to culturally bound conventions about norms within relationships between women, men, boy and girls. [321] Although much has been written on why it is important to distinguish between ‘gender’ and ‘sex’, [322-
there has been a lack of clear conceptual models that consider both, simultaneously, in order to determine whether they are relevant to diverse outcomes, including outcomes related to health treatments and interventions.

Hyde [325] proposes that gender differences and similarities can be explained by three overarching theories: Evolutionary; Cognitive social learning; and Sociocultural theory.

2.7.3.1 Evolutionary Theory

Buss and Schmidt [326] suggest evolutionary selection is based on assumptions that males and females have different adaptive behaviours and strategies for maximizing the number of genes that are passed on to the next generation, which leads to key psychological gender differences. Integral to this argument is Darwin’s concept of sexual selection, consisting of two processes. First, members of one gender (usually men) historically compete, often aggressively, among themselves in order to win the privilege to mate with the other gender (usually women). The other gender (usually women) decides which male they are willing to mate with. Studies testing the hypotheses generated in evolutionary theory are difficult to design. One study by Carre et al. [327] randomly assigned men and women to groups where they would experience a series of victories or defeats while playing a video game. The researchers assessed aggressive behaviour and examined hormone levels. Winning produced elevated testosterone concentrations in men, but not in women.

Buss et al.’s evolutionary theory also highlights gender differences in parental investment, speculating that women have greater parental investment compared to men. They theorize that because women must invest one of their limited number of ova (compared to the millions of sperm men produce every day), as well as the nine months
invested in gestation, women have a greater investment in the well-being of their children compared to men. [326, 328]

There are, however, opposing arguments to evolutionary theory. For example, evolutionary theory would predict that men would increase their chances of reproduction and fitness by having sex with many women. Pedersen et al. [329] interviewed men and women, asking about the number of sexual partners they desired in their lifetime. Both men and women reported wanting a single mutually exclusive partner, refuting this hypothesis based on evolutionary theory.

Critics of evolutionary perspectives suggest that it lacks the status of a theory because there is so little that can be done to test the hypotheses in this area. [330] Evidence for or against the theory can often be explained by other factors [331] and there is often little relevance to health. [329] Instead, the focus is generally on interpersonal relationships including reasons for mate selection and parental behaviour.

2.7.3.2 Cognitive and Social Learning Theory

Another theory explaining gender differences is Bussey and Bandura’s cognitive and social learning theory. Bussey and Bandura [296, 332-335] expanded on learning theory, which emphasized rewards and punishments, and speculated that much of the behaviour of boys and girls was learned through observation of men and women as role models. As a child grows older their behaviour becomes less controlled by externally imposed reinforcements and punishments for correct role behaviour and more internally controlled and self-regulated. Else-Quest et al. [336] found that even if a girl’s math performance was equal to that of a boy’s, she was significantly more likely to have lower confidence in her mathematic skills. An advantage of social learning theories is that they can explain
changes in norms and roles over time as boys and girls adopt new role models. To date, there is little research suggesting relevance to other health-outcome models. However, if male and female role models emulate behaviours to a greater or lesser extent (e.g., previously injured male professional athletes return to sports more frequently than female professional athletes), there is the potential for social learning theory to have relevance to health outcomes like ACLR. Additional research is needed in this area.

2.7.3.3 Sociocultural Theory

Eagly and Wood developed sociocultural theory as an alternative to evolutionary theory. [337-342] They speculate that society’s traditional division of labour contributes to gender differences. Biological differences between men and women, including size and strength differences, as well as a woman’s capacity to bear and nurse children all contribute to the division of labour by gender. Historically, men’s larger size and greater strength, which led them to participate in more physical activities like warfare also led to increased status and wealth and, in turn, power over women. Pool et al. [343] conducted research showing that men who identified themselves with traditional “male” roles were significantly more likely to tolerate higher levels of painful stimuli than other men, who had similar pain tolerance levels as women. Other studies have found male respondents reported less pain and had higher pain thresholds when tested by a female examiner, perhaps masking their pain to impress the female examiner. [344] Similarly, female respondents had lower pain thresholds and reported more pain with attractive male examiners, perhaps adopting traditional female subordinate roles and seeking attention from their male counterparts. [257]
Similar to the other theories, there is little data supporting hypotheses stemming from sociocultural theory in health research. However, Borkhoff et al. [317] found that women were more concerned about surgery interfering with their caregiving roles, the length of time required for recovery and the burden placed on others for supportive care during the recovery period than men. As a result, women were less likely to undergo total joint arthroplasty, despite being approved as surgical candidates. In other research, women without a partner have been found to have poorer health outcomes [345] and to be more likely to engage in unhealthy behaviours. [346] Sociocultural theories have remained of interest, especially as cultural norms have changed in many developing countries, particularly around education and work. [255, 261-264]

With respect to ACLR post-operative outcomes, sociocultural theory holds promise in explaining potential similarities and differences between women and men. For example, it may be that women have greater fear of re-injury than men and that this may impact their perceived HRQoL if they are unable to return to their pre-injury level of activity to the same extent as men. It may also be that men may value exercise and sport more as a traditional role and this may lead them to view an ACL injury as more disruptive and as having a greater negative impact on their HRQoL than women. Or, it may be that women potentially place more importance on exercise and body image in order to maintain a lean physique due to societal pressures. And, because they are unable to remain as physically active after their ACL injury and during ACLR rehabilitation, women may experience greater negative psychological effects and poorer HRQoL. Alternatively, women and men who participate in sports and an active lifestyle may be different from many of their counterparts and exhibit more similarities than differences in their responses to their ACL
injury, treatment and subsequent HRQoL. The SGSA used in this thesis may help us better answer these questions that have yet to be addressed in people with ACLR.

2.7.4 Overview of a Sex and Gender Sensitive Approach in Biological Research and Medical Practice

A sex-gender sensitive analysis (SGSA), “is an approach which systematically enquires about biological (sex-based) and sociocultural (gender-based) differences between women and men, boys and girls, without presuming that any differences exist.” [347] Many research and governmental organizations also have recognized the importance of applying a SGSA in health research. [348] For example, the National Institutes of Health (NIH) note that both sex and gender, “play a role in how health and disease processes differ among individuals, and consideration of these factors in research studies informs the development and testing of preventive and therapeutic interventions in both sexes.” [349] Since 2010, the CIHR also has stated that sex and gender analyses should be included in health research. [350]

Sex analyses in research include reporting the sex (male/female) of the participant and analyzing data and reporting similarities and differences by sex. [351] Analyses are often relatively simple and dichotomize male and female into two groups. [352] Gender, by contrast, is not as well understood and methods for measuring gender are not agreed upon, especially for statistical analyses. [351] In 1981 the Bem Sex Role Inventory [353] (BSRI) was the first measurement tool designed to measure varying degrees of masculinity and femininity within a person. The theory underlying the measure posited that people acquire and display traits, behaviours, and attitudes that complement their gender identity and that this could be described by the concepts of femininity and masculinity. [354] Since its inception, the BSRI’s ability to measure masculinity and
femininity has been questioned because of shifts in gender roles and stereotypes. Moreover, Heilbrun suggested measuring gender not as a single continuum, but as two separate and independent dimensions with individuals potentially being able to score high (or low) on both. Pelletier et al. have criticized these approaches suggesting there is a too large a focus on personality traits with too little emphasis on culture and phase of life. Pelletier et al. recommend selecting gender variables based on gender roles, gender identity, gender relations and institutionalized gender. Using this method, Pelletier et al. examined associations among gender, sex and cardiovascular risk factors in patients with Acute Coronary Syndrome (ACS). Their findings showed no sex differences, but gender was significantly related to cardiovascular risk. That is, being male or female did not predict those patients who were likely to relapse or die within 12 months from ACS. However, individuals with a higher gender-based “femininity” composite score (regardless of whether they were male or female) were more likely to suffer a recurrence of ACS. As shown by the Pelletier study, sex and gender may be related to health and illness. Sex and gender sensitive research can elucidate these relationships and inform differences and similarities in the healthcare needs of men and women.

2.8 THESIS RATIONALE

The overall aim of this thesis is to enhance our understanding of HRQoL and the factors associated with HRQoL after ACLR. In particular, this research examines HRQoL 1-year post-ACLR surgery with a view to disentangle similarities and differences related to sex and gender. Sex – biological differences between men and women – has received the most attention in ACLR research up until now. Although often
categorized as binary for medical outcome analysis (e.g. male/female), attributes of sex and gender are multidimensional, dynamic and interactive. In developing a sex and gender conceptual framework for health research, Johnson et al. note that, “...the binary variable of “male” and “female” derived from most questionnaires is useful for a beginning exploration of difference between males and females. Once, established we need to move beyond description and ask about whether the observed difference is caused by biological or social factors. It is in this exploration of the causal mechanism of difference and uniqueness where more refined definitions of sex and gender are required.”[41] By using a SGSA that accounts not only for the impact of sex but also recognizes the impact of social and environmental factors by including gender in the analysis, we may enhance our understanding of differences in health perception and behaviours and how these may cause differences in HRQoL outcomes between men and women following ACLR.

A SGSA approach allows for a novel method to analyze variables. Potential significant findings may bring light to modifiable factors that if addressed can improve outcomes that otherwise may be missed or overlooked applying this novel approach.

Very few studies assessed shorter-term (e.g. 1 to 2 years) HRQoL outcomes following ACLR. Instead, ACLR research more commonly has focused on physical outcomes that potentially require longer follow-up periods to allow for differences to present and the HRQoL outcomes have been included as secondary outcomes. However, it is important to look at shorter time periods of follow up because this is potentially when modifications can be made to improve post-operative outcomes.
This thesis applied a SGSA to examine how men and women were similar or different with respect to their demographics and with respect to variables related to sex, gender and sex + gender (SG) in a sample of people who have undergone ACLR. The 1-year post-operative time point was examined to explore if men and women’s demographics and variables representing sex, gender and SG were similar pre-operatively (baseline) and at 1-year. Analyses then considered which baseline and 1-year sex, gender, and SG factors were associated with HRQoL 1-year following ACLR. Finally, exploratory analyses examining whether the relationship of predictor variables (i.e. knee strength, knee alignment, weight concern, BMI, pain and time spent participating in high demand activities) and 1-year HRQoL was similar or different for men and women was undertaken by exploring if the predictor/HRQoL effect was modified by sex.

The findings from this thesis have the potential to help better understand the differences and similarities between men and women presenting for ACLR, as well as in developing a better understanding of the relationship between HRQoL and patient-related factors following ACLR. This could assist in improved and tailored care during the ACLR rehabilitation process potentially leading to better HRQoL outcomes for men and women.

2.9 CONCEPTUAL FRAMEWORK AND OBJECTIVES

This thesis is grounded in a conceptual framework to inform the selection and grouping of potential factors representing sex, gender and SG factors.

2.9.1 Conceptual Framework

There are three categories of variables that need to be considered in developing a conceptual framework for an SGSA: variables that reflect biological sex (S), variables
that reflect gender (G), and variables that may be a combination of both sex and gender (SG) (see Figure 1). SG variables represent those that include both sex and gender components. This framework underpins the objectives of the thesis and the approach to the study. A description of the variables used in this thesis and their hypothesized relationship to sex, gender or both sex and gender are presented in the methods section.

Figure 1: Conceptual Framework:

![Conceptual Framework](image)

### 2.9.2 Objectives

The overall objective of this research is to evaluate sex, gender, and sex/gender factors associated with HRQoL following ACLR to better understand potentially modifiable factors that might be targets for intervention.

The specific objectives are:

1. To investigate whether there is a difference in the profile/characteristics of men and women who underwent ACLR, specifically related to biological sex and sociocultural gender factors.
2. To examine whether factors related to pre-operative (i.e., baseline) HRQoL were similar to factors related to HRQoL 1-year following ACLR.
3. To examine what factors are predictive of HRQoL 1-year following ACLR.
4. In exploratory analysis, to evaluate if the variable M/F moderates the association of independent variables and HRQoL 1-year following ACLR.
CHAPTER 3: METHODS

3.1 PREFACE

This chapter describes the methodology used in this study. The overall study design, setting and description of the population of interest are provided, as well as details about the research procedure, methods for variable selection and analyses.

3.2 RESEARCH DESIGN

This research project is a secondary analysis of a prospective cohort of people who underwent ACLR. The original study was a longitudinal follow-up spanning five years. The longitudinal data used in this study reflects the period from when the patient was post-injury but pre-operative, referred to as “baseline,” to 1-year follow-up post ACLR surgery.

3.3 SETTING

Surgery and data collection took place from April 2005- June 2007 at Sunnybrook Hospital, a tertiary care center in Toronto, Ontario, Canada.

3.4 PARTICIPANTS

The sample included 121 individuals between the ages of 18 to 41 years. Of the 121 participants, 44 were women and 77 were men. All were less than 3 months from injury at the time of surgery with the exception of patients with meniscal tears who had a “locked knee” and required meniscal repair. These individuals were given an additional four to six weeks to regain range of knee motion before ACLR. Eligibility for the cohort included: no previous knee surgery or ACL injury; no other bone pathology; no pre-
existing arthritis; and, no major systemic disease. All patients had a BPTB autograft ACLR technique using a transtibial technique performed by a single surgeon.

3.5 RESEARCH PROCEDURE

The primary objective of the original study was to identify risk factors predicting osteoarthritis (OA) progression after knee injury and to develop a predictive algorithm for OA progression based on the risk factors. Within 6 weeks of their ACL injury, all patients had an initial clinic visit where they were screened for eligibility, provided study consent, and completed a questionnaire with demographic information and several patient-reported outcomes measures (PROMs). At 1-year following surgery, measures of knee laxity, knee strength, height and weight were recorded. Study respondents also completed the same PROMs they had completed prior to their surgery.

All participants in the original study were included in the current research. Potential variables predictive of 1-year health-related quality of life (HRQoL) were examined with a sex and gender lens and classified as primarily reflecting sex, gender or sex + gender (SG). All variables were assessed at baseline and 1-year when available.

3.6 PRIMARY OUTCOME MEASURE

The primary outcome for this study was knee-specific HRQoL as measured by the Knee Osteoarthritis Outcome Score Quality of Life subscale (KOOS-QOL) at 1-year following ACLR. The KOOS-QOL subscale is comprised of 4 questions with five possible response options scored from zero to four (never, monthly, weekly, daily, constantly) for the first question and from zero to four (none, mild, moderately, severely, totally) for questions 2, 3 and 4. The KOOS-QOL subscale score was calculated based on
the developer’s scoring guidelines with higher values representing better quality of life on a 0-100 scale. [364]

3.7 INDEPENDENT VARIABLES

3.7.1 Determining Sex, Gender and SG Variables

Participants indicated whether they were male or female. In addition, drawing on research discussing sex and gender sensitive analyses, any variables that had a biological basis were categorized as “sex” variables and variables referring to non-biological aspects of being man or woman were categorized as “gender”. [357] However, some variables had research available that suggested they included both sex and gender components that were too complex to tease apart. These variables were labeled as SG variables.

3.7.2 Sex Variables

Variables representing “sex” included knee strength, knee laxity and alignment.

3.7.2.1 Knee Strength

Knee strength is dependent on the proportion of lean body tissue and body structure. [365] Strength may be affected by social factors such as diet and exercise. However, because individuals in this study mostly did not participate in high-level or professional level activity, strength was deemed to be more representative of biological differences than a combination of sex and gender differences. Strength was measured with the one-legged hop test for distance (OLHD). [149] Participants were asked to hop for distance on their surgical knee and the average distance of the three hops was measured in millimeters. Knee strength was analyzed as a continuous variable.
3.7.2.2 Knee Laxity

Knee laxity also was categorized as a sex-based variable. Knee laxity has been found to be greater in females than males [366, 367] and sex hormones are thought to be the primary contributor to these differences. [368] Knee laxity was measured with the KT-1000 using a 30 lb. force averaged over three trials on both the surgical and non-surgical knee. Knee laxity was quantified as the difference between the surgical and non-surgical knee and was analyzed as a categorical variable. Based on clinical judgement, -7mm to -3.01 mm was considered “tight”, -3 mm to +3 mm was considered “normal” and a measurement of greater than +3 mm was considered to represent “laxity”.

3.7.2.3 Knee Alignment

Knee alignment refers to the degree of knee varus or valgus. Sex differences in distal femoral valgus have been reported, with females displaying a greater prevalence of valgus (knock kneed) alignment than males. This difference has been largely attributed to femoral geometry. [369] Although the origin of this difference in geometry between men and women is unknown, there has been speculation that it may be the result of sex-related differences in femoral bowing. [369, 370]

The mechanical axis (MA) measured on a full-limb radiograph is the gold standard method for assessing knee alignment. [370] To measure the MA, three landmarks on each lower extremity radiograph were identified, drawing on the work of Specogna et al. [371] and Paley [372]. First, hip center was defined by placing four points along the outside of the femoral head at approximately 90-degree arcs and creating two lines by connecting opposing points with a line. The point where the two lines intersected was identified as the hip center. The center of the ankle was determined based on a method also previously
described in the literature [371, 373] by drawing a line tangent to the tibial plafond’s most distal point to form the superior aspect of the talar dome. Once the talar dome was determined, a point along this line located at 50% of the talar dome was used as the ankle center. Finally, the center of the knee was found using a method described in the literature by using the midpoints of the tibial spine tips in the horizontal plane, then extrapolating that point to the surface of the intercondylar eminence. [371, 374] The MA angle was defined as the angle formed by the line drawn from the center of the hip to the center of the knee and the line drawn from the center of the ankle to the center of the knee. By convention, if the patient demonstrated a varus deformity, the mechanical axis was reported in “negative” degrees. [371, 375] Figure 2 below shows how alignment was found.

Figure 2: Measuring the mechanical axis angle: The mechanical axis angle of the lower limb is the angle formed by a line connecting the center of the ankle to the center of the knee and a line connecting the center of the hip to the center of the knee.
3.7.3 Gender Variables

Variables representing “gender” were modeled after the four dimensions outlined by the Women’s Health Research Network of the Canadian Institutes of Health [376]:

i. Gender Roles: Represent the behavioural ‘norms’ that are often applied to men and women in society and which are thought to influence individuals’ everyday actions, expectations, and experiences. Critics often describe gender roles as unnecessarily categorizing and potentially controlling individuals within institutions such as the family, the labour force, or the educational system;

ii. Gender identity: Describes whether people see themselves as female or male and is thought to affect an individual’s feelings and behaviours;

iii. Gender relations: Refers to how people are treated by others based on their ascribed ‘gender’;

iv. Institutionalized gender: Reflects the distribution of power between men and women in political, educational and social institutions in society. Institutionalized aspects of gender are also thought to shape social norms that define, reproduce, and often justify different expectations and opportunities for men and women.

Gender variables were represented by perceptions of a fear of re-injury, perceived importance of exercise, commitment to exercise, weight concerns, time spent on household and caregiving activities and time spent participating in low demand and walking activities.
3.7.3.1 Fear of Re-injury

Fear of re-injury was assessed using a single item from the 32-item Mohtadi-ACL QOL questionnaire. Participants were asked, “How fearful are you of re-injuring your knee?” with responses ranging from 0= extremely fearful to 100= no fear at all. [182, 242]

Fear of re-injury was classified as a gender variable because it appears to have no biological basis and is a behaviour that may be shaped by society, including gender identity and gender relations.

3.7.3.2 Body Image

Traditionally, the ideals women and men use to judge their appearances differ. Research suggests women tend to strive for a body type characterized by low body fat and that they are more critical and dissatisfied with their appearance while men tend to prefer a muscular ideal body type and often have a more positive body image. [377] Body image has been found to be associated with HRQoL and related to physical inactivity, [378, 379] unhealthy eating, [380, 381] and weight gain. [382, 383] It is unclear whether body image is related to HRQoL among men and women following ACLR, as it has not been studied to date.

The motivations people have to exercise are varied and despite the many physical [384, 385] and psychological [386, 387] benefits linked with exercise, potential negative outcomes associated with particular motivations for exercise exist. [388] For example, those who exercise for appearance motives as oppose to health motives have shown higher levels of body dissatisfaction, poorer body image, decrease self-esteem and decreased psychological wellbeing. [389-391]
Variables including exercise importance, commitment to exercise and weight concern will represent the concept of body image in this thesis. These variables were categorized as gender variables and were measured using individual questions from the Exercise Identity Scale (EIS). [392] The EIS is a PROM made up of twenty-two questions. This includes 9 “identity” questions measured on a 5-point Likert scale, 8 “commitment” questions and 5 “beliefs” questions both measured on a 1-10 scale. A higher score reflects greater agreement with the question being asked. In this thesis one question from each of the EIS “identity”, “commitment” and “beliefs” categories were used to evaluate exercise importance, commitment to exercise and weight concern respectively.

3.7.3.2.1 Exercise Importance

Participants were asked their agreement with the item, “I need to exercise to feel good about myself”. Responses ranged from 1-5 where 1= strongly disagree, 2= disagree, 3= undecided, 4= agree and 5= strongly agree.

3.7.3.2.2 Commitment to Exercise

Respondents were asked, “Do you continue to exercise at times when you feel tired or unwell”. Responses ranged from 0-10 where 0= never, and 10= always.

3.7.3.2.3 Weight Concern

Participants were asked the extent to which the following statement was true, “If I do not exercise I will become overweight”. Responses ranged from 0-10 where 0= “I do not believe this question at all” to 10= “I am completely convinced this thought is true”.

3.7.3.3 Activity Variables

Baseline and 1-year activity level was determined using the Minnesota Leisure-Time Physical Activity Questionnaire (MLPAQ). The MLPAQ is a validated [189] and widely
used questionnaire [204] designed to assess type, frequency and intensity of involvement in 54 different activities. [203] The 54 activities range from walking, individual and team sports, racquet sports, water activities, physical conditioning, winter sports and activities, housework, home repair and caregiving. [288] Drawing on research from Ratzlaff et al., activities were divided into Sports/Recreation, Occupation and Household activity. [393] In order to take into account the intensity level of each activity, [316] activities were further categorized as: I) Household activities; II) Walking activities; III) High Demand Sports/Leisure activity; IV) Low Demand Sports/Leisure activity; and, V) Caregiving activities. Participants recorded the average number of times per month they performed the activity (0-30), the average number of minutes per episode (no limit) and the number of months in 1-year that they participated in each activity. The average number of times the activity was performed in a month was multiplied by the number of months the activity was performed during the year all multiplied by the average number of minutes per episode. The total minutes was then converted into hours in order to capture the number of hours an activity was performed during the previous year at baseline and at the 1-year follow up point. To take into account that the sample was young, with relatively few domestic obligations, three categories of activity were created:

i. Caregiving + Household activities  
ii. Low demand+ Walking activities= Walking and Low Demand  
iii. High Demand Sports/Leisure Activities= High Demand

Specific activities included in each category of Household and Caregiving Activities and Walking and Low Demand Activities are detailed in Appendix A.

Time spent participating in high demand sports and leisure activities were considered as SG variable. More information about this variable is provided below.
3.7.4 Sex and Gender Variables

Disentangling biological attributes due to sex from sociocultural attributes due to gender was complex for some variables. Similar to other research, [44] variables considered as a product of both sex and gender were labeled as “SG” variables. They included: Body Mass Index (BMI), Pain, Physical Function, Time Spent Participating in High Demand Activities and Mental Health.

3.7.4.1 BMI

BMI is calculated as kg/m\(^2\) and is a SG variable because it is associated with both biological and social components. Overall, adult males tend to be taller than adult females. [394] This height difference between sexes is due to both sex chromosomal differences [395] and hormonal differences. [396] Height, weight and body mass index also are associated with environmental factors including diet, exercise, and living conditions. [40, 397]

3.7.4.2 Pain

Pain was also categorized as a SG variable as it is related to biological and social factors. Studies find that women report a greater frequency of musculoskeletal pain compared to men. [398] Women are thought to experience more pain due to biological functioning, including liver metabolism, immune responses [399] and hormonal changes [400] and they have been found to be more willing/able to express their pain compared to men, possibly related to social conditioning and cultural upbringing. [401]

Pain was assessed using the nine items from the KOOS pain subscale (KOOS-P), which assessed the frequency and degree of pain in the previous week. [220] Patients were asked to rate the amount of pain they experienced performing certain activities on a
scale from zero to four where 0= none, 1= mild, 2= moderate, 3= severe and 4= extreme. These activities include twisting/pivoting, straightening, bending, walking on flat surface, going up or down stairs, at night while in bed and sitting or lying and standing upright. Scores were converted to a 0-100 scale to reflect the direction of pain based on the developers scoring guidelines where 0= extreme problems and 100= no problems. [364]

3.7.4.3 Physical Function

Physical function was categorized as an SG variable because it comprises biologically based strength to perform an activity as well as sociocultural aspects, including beliefs about one’s ability to perform activities and expectations from others about performance. [402] Physical Functioning was measured using the Physical Functioning Subscale from the SF-36 (PF). The PF consists of 10 questions related to commonly performed activities of daily living (including stair climbing, dressing, lifting/carrying groceries, bending, kneeling and bathing). Participants were asked if their health limited them from performing the activities. For example, “Does your health limit you in vigorous activities? If so, how much?” Perceived limitations were scored as: 1= yes, limited a lot; 2= yes, limited a little; or 3= no, not limited at all. Raw scores were summed and then standardized on a 0 to 100 scale based on the developer’s scoring guidelines, [237] with 0 indicating extreme limitations and 100 indicating no limitations.

3.7.4.4 Time Spent Participating in High Demand Activities

The amount of time respondents reported participating in high demand activities was calculated using the MLPAQ as previously described in section 3.7.3.3. This was considered an SG variable because themes of biological factors including strength may be involved, as well as gender roles, pain tolerance, psychological motivation to return to
previous level of activity, and importance of sport/leisure in one's daily routine. See Appendix A for activities that were categorized as high demand.

### 3.7.4.5 Mental Health

Mental health was measured using the SF-36 Mental Health Subscale (MH) consisting of five items that assess nervousness, sadness, calmness, mood and happiness. [237] Participants rated the frequency they experienced each item during the previous four weeks on a 6 point-Likert scale where 1= all of the time, 2= most of the time, 3= a good bit of the time, 4= some of the time, 5= a little of the time and 6= none of the time. For example, ‘How much of the time, in the last 4 weeks, have you felt so down in the dumps that nothing could cheer you up?’ A total score was computed by summing then transforming the five-item scores into a single score between 0= lowest mental health to 100= highest mental health based on the developer’s scoring guidelines. [403, 404]

### 3.7.5 Other Variables

Information on age, defined in years at the time of ACLR, was collected and analyzed as a continuous variable.

### 3.8 DATA MANAGEMENT

Raw data were stored in Microsoft excel format. All data were cleaned and coded for subsequent analyses. The data were then inspected for missing values. Preliminary frequency inspection revealed that there was less than 6% missing data for all variables. For this missing data, mean values were imputed. [405] KOOS-QOL guidelines suggest that aggregate scores are possible if 50% of questions are completed. [364]

For missing activity level values, imputation was based on participant activity level trends at baseline. For example, six individuals had no data for activity level recorded for
1-year following surgery. The activities each individual participated in at baseline were analyzed and, based on these activities, the average for that particular activity at 1-year was imputed. For example, if in the baseline data the participant swam, then an average for swimming at 1-year was imputed. However, if that same participant did not participate in martial arts at baseline, they were given a “0” time spent in this activity at 1-year. This assumed similar behaviour at 1-year compared to the year prior to the surgery. It was applied for the 6 respondents missing values for activity at 1-year to allow for these individuals to be included in data analyses.

One participant also indicated that they participated in an activity for 12 months, but they omitted the number of times per month and number of minutes per time. In this scenario, the average value recorded by the other participants for that particular activity and the average number of days and average number of minutes based on other participant input was used and then imputed for this participant.

3.9 DATA ANALYSIS

All statistical analyses were performed using SPSS v.23 (SPSS Inc., Chicago, IL, USA).

Descriptive statistics, means and frequencies, of each sex, gender and SG variable at baseline and 1-year was performed. Then, bivariate analyses was used to investigate whether there was a difference in the profile of men and women who underwent ACLR at baseline and 1-year (Objective 1). Mean scores and standard deviations were used for continuous variables; frequencies and proportions were used for categorical variables. Differences between males and females were evaluated using independent Student’s t-tests for continuous variables and Chi Square tests for the categorical variables. The
continuous variables demonstrated normal distributions (Shapiro Wilk value >0.05) in the study sample and therefore nonparametric tests were not required.

To address objectives 2 and 3 factors predictive of baseline HRQoL and 1-year HRQoL were evaluated with linear regression analyses. The analyses included four steps. First, potential co-linearity among independent variables was examined and univariable regression analyses were carried out to identify significant associations with baseline HRQoL (Step II.1 from Diagram 1). Variables significant at p < 0.10 were carried forward to multivariable analyses, a practice that has been used in other research [12] to maintain a broad inclusion of variables in analyses. Second, multivariable analyses were conducted adjusting for age as a covariate to assess the relationship between baseline variables and baseline KOOS-QOL (Step II.2 from Diagram 1). To address objective 3 a similar analytical process was used. Univariable regression analyses were conducted to examine baseline predictors of 1-year KOOS-QOL with any baseline variable significant at p < 0.10 carried forward to multivariable analyses. (Step II.3 from Diagram 1) The relationship between baseline variables and 1-year KOOS-QOL was then assessed using multivariable regression analyses.

Potential predictors of 1-year HRQoL were also evaluated. For the final model, multivariable analysis was performed to examine both baseline and 1-year predictors of 1-year KOOS-QOL (Step III.2 from Diagram 1).

In evaluating predictors of 1-year HRQoL, there were three independent variables measured at baseline and at 1-year that were significantly associated with 1-year KOOS-QOL at p < .10. Because both the baseline and 1-year variable were significant, correlations were assessed. If the baseline and 1-year assessment were highly correlated
(Pearson’s r >0.7) [406] only the baseline variable was included in the final model. [407] If the two time points were not highly correlated, then the baseline time point was subtracted from the 1-year time point score to create a change score for use in further analyses. Male/female (M/F) was retained in multivariable analyses regardless of its significance in univariable analyses because it was a key variable of interest.

All assumptions were verified including independence of residuals, linear relationship between the dependent and independent variables, homoscedasticity and co-linearity.

Finally, to address the fourth objective, an exploratory analysis was conducted to examine whether being male or female moderated the relationship of significant predictors with 1-year HRQoL scores. Moderation was examined by including the predictor variable, Male/Female, and the interaction term of the predictor variable with male/female (Step IV.2 from Diagram 1). Interactions were explored independently because of limited power based on the available sample size and not having any previous knowledge about possible relationships.
3.9.1 Sample Size

This is a secondary analysis of data from a longitudinal study with an available sample size of 121 respondents. Therefore, to maximize power for the analyses no more than, fourteen independent variables of interest were identified a priori; 3 representing sex, 6 representing gender and 5 representing SG. Literature estimates of the number of participants needed per predictor variable to ensure a stable solution in a multiple regression analysis range from 5-15 outcome data points per variable. [408-410] Using a conservative estimate of 10 respondents per variable yielded a sample size of 140 needed for analyses. Although the actual sample size was 121 respondents it was anticipated not all independent variables examined would be significant in univariable analyses. As a
result, not all variables would be carried forward in further analyses. Therefore, the available sample size of 121 was considered adequate to prevent over fitting of the models in multiple regression analyses.

3.9.2 Ethics

Ethics approval was obtained from Sunnybrook Hospital (Toronto, Canada) for the original study at each time point data were collected, as well as for this thesis. Ethics approval was also obtained from the University of Toronto (Toronto, Canada) for the thesis (See Appendix C).
CHAPTER 4: RESULTS

4.1 PREFACE

This chapter begins with a description of the study participants. An assessment of data quality is then presented. Then, the findings related to differences in sex, gender and SG factors between males and females at baseline and 1-year are reported. This is followed by a description of the results from univariable and multivariable regression analyses with 1-year HRQOL as the outcome.

4.2 DESCRIPTIVE CHARACTERISTICS OF STUDY PARTICIPANTS

At baseline, there were 121 participants, 77 men and 44 women (36%) ranging in age from 17-41 (mean= 27.3 years, SD= 6.1). Males average age ranged from 17-39 years (mean= 27.3 years, SD= 5.9) and females average age ranged from 18-41 years (mean= 27.3, SD= 6.6). More than half of the cohort (53.8%) reported their ACL injury occurred while participating in skiing, soccer and basketball; 19% reported their injury occurred as part of a university/college team; while the rest identified themselves either as recreational (53.7%), amateur (19.8%) or professional/minor professional athletes (7.4%). [207] At 1-year, three participants had dropped out of the study and an additional three participants were missing three or more items on their 1-year KOOS-QOL score, precluding calculation of a summary score. This left a final sample of 115 participants available for multivariable analyses.

In examining the sex, gender and SG variables and outcomes in Table 1, the results from the 1-year sex related knee laxity results indicate that the majority of the cohort (78.1%) had “normal” knee laxity by 1-year indicating a positive surgical outcome. Overall this cohort’s BMI, a SG-related variable, remained constant from baseline
(24.88) to 1-year (24.95). Gender variables examined were fear of re-injury, exercise importance, exercise commitment and weight concerns. Fear of re-injury variable scores indicated modest levels of fear of re-injury at baseline (22.82) and a reduced fear of re-injury at 1-year (51.01). Exercise importance scores indicated that most respondents valued exercise and reported that they needed to exercise to feel good about themselves with average total scores of 4 out of 5 at baseline and 3.83 out of 5 at 1-year. In terms of exercise commitment, respondents indicated overall modest agreement with items asking whether they continued to exercise when tired or unwell with average scores of 5.72 out of 10 at baseline and 5.37 out of 10 at 1-year. Participants were somewhat in agreement that they will become overweight if they did not exercise at baseline with an average score of 6.12 out of 10. This belief was relatively similar at 1-year with average scores of 5.7 out of 10.

The sample spent the least amount of time at baseline participating in high demand physical activities (293.12 hours), a SG-related variable, compared to household and caregiving activities (317.55 hours) and low demand and walking activities (655.16 hours), which were both classified as gender-related variables. The pattern of activity was maintained at 1-year; although time spent participating in high demand physical activities was reduced (80.93 hours). Household and caregiving activities at 1-year were 303.05 hours and low demand and walking activities were 574.91 hours. The largest change in activity level occurred in high demand activities as the cohort decreased by 213 hours, compared to an 81 hour decrease in low demand activities and a 14 hour decrease in household/caregiving activities from baseline to 1-year. Participants reported overall improvement from baseline to 1-year in knee pain as it decreased from 66.94 to 87.53
over 1-year and physical function improved from 73.04 to 90.93 over 1-year as well. Participant mental health scores also increased from 70.18 to 79.04 as measured by the SF-36 from baseline to 1-year respectively. Although HRQoL scores represented by their 1-year KOOS-QOL improved to an average of 64.98 from an average baseline score of 28.36, they represent a perception of a moderately good quality of life on a score from 0 - 100 (See Table 3).
Table 3: Overall Sample Characteristics and Similarities and Differences Between Males and Females (n= 115)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/-SD</td>
<td>+/-SD</td>
<td>+/-SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(min.-max)</td>
<td>(min-max)</td>
<td>(min-max)</td>
<td></td>
</tr>
</tbody>
</table>

**SEX VARIABLES**

**Knee Strength** (surgical knee hop average distance (avg. of 3 hops) in mm)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>1313.03</td>
<td>1456.76</td>
<td>1057.13</td>
</tr>
<tr>
<td></td>
<td>+/-366.99</td>
<td>+/-354.60</td>
<td>+/-222.09</td>
</tr>
<tr>
<td></td>
<td>(0.00-1313.03)</td>
<td>(0.00-2002.33)</td>
<td>(448.67-1408.33)</td>
</tr>
</tbody>
</table>

**Knee Laxity** (frequency(%))

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Not available</td>
</tr>
<tr>
<td>Year 1</td>
<td>-7 to -3.01 “Tight” 21(18.4%) 11(15.1%) 10(24.4%)</td>
</tr>
<tr>
<td></td>
<td>-3 to +3 “Normal” 89(78.1%) 61(83.6%) 28(68.3%)</td>
</tr>
<tr>
<td></td>
<td>&gt;=+3 “Lax” 5(4.3%) 2(2.7%) 3(7.3%)</td>
</tr>
</tbody>
</table>

**Alignment Angle** (Varus (-), Valgus (+))

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-0.018</td>
<td>-0.79</td>
<td>1.35</td>
</tr>
<tr>
<td></td>
<td>+/-4.83</td>
<td>+/-4.75</td>
<td>+/-4.73</td>
</tr>
<tr>
<td></td>
<td>(-9.30-9.38)</td>
<td>(-8.84-9.38)</td>
<td>(-9.30-8.50)</td>
</tr>
</tbody>
</table>

**GENDER VARIABLES**

**FEAR OF REINJURY** (“How fearful are you of reinjuring your knee”)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22.82</td>
<td>20.99</td>
<td>26.02</td>
</tr>
<tr>
<td></td>
<td>+/-23.31</td>
<td>+/-23.05</td>
<td>+/-23.69</td>
</tr>
<tr>
<td></td>
<td>(0-90)</td>
<td>(0-90)</td>
<td>(0-89)</td>
</tr>
<tr>
<td>Year 1</td>
<td>51.01</td>
<td>50.27</td>
<td>52.34</td>
</tr>
<tr>
<td></td>
<td>+/-32.20</td>
<td>+/-32.77</td>
<td>+/-31.52</td>
</tr>
<tr>
<td></td>
<td>(0-100)</td>
<td>(0-100)</td>
<td>(0-100)</td>
</tr>
</tbody>
</table>

**Exercise Importance** (“I need to exercise to feel good about myself”)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.00</td>
<td>3.82</td>
<td>4.32</td>
</tr>
<tr>
<td></td>
<td>+/-1.06</td>
<td>+/-1.11</td>
<td>+/-0.88</td>
</tr>
<tr>
<td></td>
<td>(1-5)</td>
<td>(1-5)</td>
<td>(2-5)</td>
</tr>
<tr>
<td>Year 1</td>
<td>3.83</td>
<td>3.69</td>
<td>4.07</td>
</tr>
<tr>
<td></td>
<td>+/-1.11</td>
<td>+/-1.12</td>
<td>+/-1.07</td>
</tr>
<tr>
<td></td>
<td>(1-5)</td>
<td>(1-5)</td>
<td>(2-5)</td>
</tr>
</tbody>
</table>

**Commitment to Exercise** (“Do you continue to exercise when you feel tired or unwell”)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5.71</td>
<td>5.97</td>
<td>5.25</td>
</tr>
<tr>
<td></td>
<td>+/-2.631</td>
<td>+/-2.61</td>
<td>+/-2.64</td>
</tr>
<tr>
<td></td>
<td>(0-10)</td>
<td>(0-10)</td>
<td>(0-10)</td>
</tr>
<tr>
<td>Year 1</td>
<td>5.37</td>
<td>5.58</td>
<td>5.00</td>
</tr>
</tbody>
</table>

**Chi Square: 4.67, p= 0.09**
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/-SD</td>
<td>+/-SD</td>
<td>+/-SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(min-max)</td>
<td>(min-max)</td>
<td>(min-max)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/-2.73</td>
<td>+/-2.68</td>
<td>+/-2.82</td>
<td>p = 0.27</td>
</tr>
<tr>
<td></td>
<td>(0-10)</td>
<td>(0-10)</td>
<td>(0-10)</td>
<td></td>
</tr>
</tbody>
</table>

**Weight Concern** (*“If I do not exercise I will become overweight”*)

0= I do not believe this thought at all 10= I am completely convinced this is true

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Males</th>
<th>Females</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5.70</td>
<td>5.61</td>
<td>5.86</td>
<td></td>
</tr>
<tr>
<td>+/-SD</td>
<td>+/-3.39</td>
<td>+/-3.55</td>
<td>+/-3.15</td>
<td></td>
</tr>
<tr>
<td>(min-max)</td>
<td>(0-10)</td>
<td>(0-10)</td>
<td>(0-10)</td>
<td></td>
</tr>
</tbody>
</table>

**Time spent on household and caregiving activities** (measured in hours)

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Baseline</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>317.55</td>
<td>-0.85</td>
<td>0.39</td>
</tr>
</tbody>
</table>
| +/-SD  | 300.91+/-
| (min-max) | 291.76(1-1719) |            |         |
|         | +/-284.10 | (+/-271.0(31-1312) |         |         |
|         | 346.6    | (+/-3.31 |         |         |
|         | (0-10)   | (0-10)   |         |         |

**Time spent participating in low demand and walking activities** (measured in hours)

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Baseline</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>655.16</td>
<td>0.65</td>
<td>0.52</td>
</tr>
<tr>
<td>+/-SD</td>
<td>673.35</td>
<td>(+/-393.27</td>
<td></td>
</tr>
<tr>
<td>(min-max)</td>
<td>(41-2470)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>623.32</td>
<td>(+/-430.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0-10)</td>
<td>(0-10)</td>
<td></td>
</tr>
</tbody>
</table>

**SEX + GENDER VARIABLES**

**BMI**

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Baseline</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>24.88</td>
<td>4.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+/-SD</td>
<td>25.81</td>
<td>(+/-3.28</td>
<td></td>
</tr>
<tr>
<td>(min-max)</td>
<td>(16.93-35.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>23.27</td>
<td>(+/-3.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(16.27-32.79)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pain (KOOS)**

0= extreme pain 10= No pain

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Baseline</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>66.94</td>
<td>0.76</td>
<td>0.45</td>
</tr>
<tr>
<td>+/-SD</td>
<td>67.71</td>
<td>(+/15.02</td>
<td></td>
</tr>
<tr>
<td>(min-max)</td>
<td>(31.11-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65.58</td>
<td>(+/-14.31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-30.56-93.75)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Physical Functioning (SF-36 scale)**

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Baseline</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>73.04</td>
<td>-0.61</td>
<td>0.54</td>
</tr>
<tr>
<td>+/-SD</td>
<td>72.06</td>
<td>(+/-24.74</td>
<td></td>
</tr>
<tr>
<td>(min-max)</td>
<td>(5-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74.77</td>
<td>(+/-24.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5-100)</td>
<td>(15-100)</td>
<td></td>
</tr>
</tbody>
</table>

**Time Spent participating in High Demand Activities** (measured in hours)

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Baseline</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>293.12</td>
<td>-1.89</td>
<td>0.06</td>
</tr>
<tr>
<td>+/-SD</td>
<td>257.66</td>
<td>(+/-205.09</td>
<td></td>
</tr>
<tr>
<td>(min-max)</td>
<td>(50-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>355.18</td>
<td>(+/-364.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(50-100)</td>
<td>(70-100)</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Total Mean +/-SD (min-max)</td>
<td>Males Mean +/-SD (min-max)</td>
<td>Females Mean +/-SD (min-max)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Year 1</td>
<td>80.93 +/-135.52 (0-1360)</td>
<td>79.56 +/-139.80 (0-1179)</td>
<td>83.32 +/-129.23 (0-615)</td>
</tr>
<tr>
<td>Mental Health (SF-36 Scale)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70.18 +/-17.17 (16-100)</td>
<td>67.78 +/-18.03 (16-96)</td>
<td>74.38 +/-14.81 (40-100)</td>
</tr>
<tr>
<td>Year 1</td>
<td>79.04 +/-14.88 (32-100)</td>
<td>78.03 +/-16.09 (32-100)</td>
<td>80.88 +/-12.38 (52.00-96.00)</td>
</tr>
<tr>
<td>KOOS-QOL Composite Score (0=Problems, 100= No Problems)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.36 +/-16.06 (0-68.75)</td>
<td>27.60 +/-16.45 (0-68.75)</td>
<td>29.68 +/-15.43 (0-56.25)</td>
</tr>
<tr>
<td>Year 1</td>
<td>64.98 +/-17.72 (6.25-100)</td>
<td>64.9 +/-18.74 (6.25-100)</td>
<td>65.13 +/-16.04 (25-100)</td>
</tr>
<tr>
<td>Age</td>
<td>27.30 +/-6.14 (17-41)</td>
<td>27.27 +/-5.89 (17-39)</td>
<td>27.34 +/-6.64 (18-41)</td>
</tr>
</tbody>
</table>

**BOLD=** Variable meets cut point where p-value ≤0.05 indicating a significant difference between males and females.

<table>
<thead>
<tr>
<th>Covariate</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>27.30 +/-6.14 (17-41)</td>
<td>27.27 +/-5.89 (17-39)</td>
<td>27.34 +/-6.64 (18-41)</td>
<td></td>
</tr>
</tbody>
</table>
4.2.1 Overall Differences Between Men and Women

At baseline, statistically significant differences between men and women were found in knee alignment, exercise importance, BMI and mental health. Men had more varus alignment, whereas women had more valgus alignment at baseline ($t = -2.31$, $p = 0.02$). Women more strongly agreed that exercise was important to feel good about themselves compared to men at baseline ($t = 2.56$, $p = 0.01$). However, this difference was no longer statistically significant at 1-year ($t = -1.76$, $p = 0.08$). Examination of BMI showed statistically significant differences between men and women at baseline ($t = 0.53$, $p<0.001$) and 1-year ($t = 4.99$, $p<0.001$) with men being more overweight (mean BMI baseline = 25.8; 1-year = 26.13) compared to women (mean BMI baseline = 23.27; 1-year = 22.86). Although overall mental health was relatively high for men and women, at baseline men had significantly lower mental health scores with a mean of 67.68 compared to women with a mean of 74.38 on the SF-36 mental health subscale ($t = -2.17$, $p = 0.03$). Finally, at 1-year, men had significantly better knee strength with a surgical knee hop distance of 1.45m compared to 1.05m for women ($t = 6.52$, $p<0.001$). Men also spent significantly more time participating in low demand and walking activities compared to women at 1-year ($t = 2.08$, $p = 0.04$).

The extent of knee laxity at 1-year (baseline data not available), fear of re-injury, commitment to exercise, weight concern, time spent on household and caregiving activities, pain, time spent in high demand activities all at baseline and 1-year were not statistically different between men and women. Additionally, men and women were similar in their mental health scores at 1-year. Finally, men and women were similar in KOOS-QOL scores at baseline and 1-year following ACLR.
4.3 EVALUATING THE RELATIONSHIP OF PREDICTORS AND HRQOL

4.3.1 Relationship Between Baseline Sex, Gender and SG Related Variables and Baseline HRQoL

Table 4 presents the findings for baseline sex, gender, and SG-related variables used in the univariable regression analyses examining the relationship between baseline predictors and baseline KOOS-QOL. No sex-related baseline variables were significantly related to baseline KOOS-QOL. Among the gender variables, baseline fear of re-injury ($\beta = 0.32, p<0.001$), exercise importance ($\beta = -3.92, p<0.01$) and perceived weight concern ($\beta = -1.37, p<0.01$) were significantly associated with baseline KOOS-QOL.

More precisely, less fear of re-injury was associated with better baseline HRQoL whereas greater agreement with the statement that individuals needed exercise to feel good about themselves was associated with poorer baseline HRQoL. Similarly, greater agreement with that statement that if one did not exercise he or she would become overweight was associated with poorer baseline HRQoL.
<table>
<thead>
<tr>
<th>Baseline Independent Variable</th>
<th>Baseline KOOS-QOL (Dependent Variable)</th>
<th>Year 1 KOOS-QOL (Dependent Variable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstandardized Beta (95% CI)</td>
<td>F value</td>
</tr>
<tr>
<td>Sex Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>Not Available</td>
<td>Not Available</td>
</tr>
<tr>
<td>Laxity</td>
<td>Not Available</td>
<td>Not Available</td>
</tr>
<tr>
<td>Alignment</td>
<td>0.36 (-0.26-0.98)</td>
<td>1.29</td>
</tr>
<tr>
<td>Gender Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear of Re-Injury</td>
<td>0.32 (0.20-0.43)</td>
<td>31.76</td>
</tr>
<tr>
<td>Exercise Importance</td>
<td>-3.92 (-6.58- -1.25)</td>
<td>11.53</td>
</tr>
<tr>
<td>Commitment to Exercise</td>
<td>-0.71 (-1.81- -0.39)</td>
<td>1.63</td>
</tr>
<tr>
<td>Weight Concern</td>
<td>-1.37 (-2.17- -0.57)</td>
<td>3.39</td>
</tr>
<tr>
<td>Time Spent on Household/Caregiving Activities</td>
<td>0.002 (-0.01-0.012)</td>
<td>0.17</td>
</tr>
<tr>
<td>Time spent on Low Demand/Walking Activities</td>
<td>0.00 (-0.01-0.01)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex and Gender Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.85 (-1.68- -0.02)</td>
<td>4.12</td>
</tr>
<tr>
<td>Pain</td>
<td>0.53 (0.36-0.78)</td>
<td>37.91</td>
</tr>
<tr>
<td>Physical Function</td>
<td>-0.01 (-0.14-0.11)</td>
<td>0.05</td>
</tr>
<tr>
<td>Time Spent in High Demand Activities</td>
<td>-0.01 (-0.02-0.00)</td>
<td>4.00</td>
</tr>
<tr>
<td>Mental Health</td>
<td>0.40 (-0.13-0.21)</td>
<td>0.22</td>
</tr>
<tr>
<td>Baseline Independent Variable</td>
<td>Baseline KOOS-QOL (Dependent Variable)</td>
<td>Year 1 KOOS-QOL (Dependent Variable)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Unstandardized Beta (95% CI)</td>
<td>F value</td>
</tr>
<tr>
<td>M/F</td>
<td>2.10 (-3.93-8.11)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

**Covariates**

<table>
<thead>
<tr>
<th>Baseline KOOS-QOL</th>
<th>N/A</th>
<th>0.52</th>
<th>32.51</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>-0.37 (-0.83-0.10)</td>
<td>2.38</td>
<td><strong>0.10</strong></td>
<td>0.15</td>
</tr>
</tbody>
</table>

**BOLD= Indicates P value ≤ 0.1 where this variable was carried forward to further analyses**
Among the baseline SG-related variables, BMI ($\beta = -0.85$, $p < 0.04$), pain ($\beta = 0.53$, $p < 0.01$) and time participating in high demand activities at baseline ($\beta = -0.01$, $p < 0.04$) were significantly related to baseline KOOS-QOL. More specifically, at baseline, elevated BMI was associated with poorer HRQoL, less pain was associated with greater HRQoL and more time spent in high demand activities was associated with poorer HRQoL.

When model assumptions were evaluated, no violations precluded multivariable modeling (see Appendix B for an example of the assumptions check used in the final model).

Table 5 presents the predictor variables associated with baseline KOOS-QOL at $p < 0.10$ that were included in the multivariable modeling. They were baseline: fear of re-injury, exercise importance, weight concern, BMI, pain, time spent in high demand activities and age as a covariate. After adjusting for age, fear of re-injury ($\beta = 0.23$, $p < 0.001$), exercise importance ($\beta = -2.65$, $p = 0.04$) and pain ($\beta = 0.38$, $p < 0.001$) were significantly associated with baseline HRQoL. Specifically less fear of re-injury and less pain were associated with better baseline HRQoL and the more the participant agreed they needed to exercise to feel good about themselves was related to poorer HRQoL. Male/female was not statistically significant in predicting baseline KOOS-QOL ($p = 0.18$).
<table>
<thead>
<tr>
<th>Baseline Independent Variable</th>
<th>Unstandardized Beta</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear of Re-Injury</td>
<td>0.23</td>
<td>0.13-0.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise Importance</td>
<td>-2.65</td>
<td>-5.11-0.18</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight Concern</td>
<td>-0.34</td>
<td>-1.15-0.46</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Sex and Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.17</td>
<td>-0.95-0.61</td>
<td>0.66</td>
</tr>
<tr>
<td>Pain</td>
<td>0.38</td>
<td>0.22-0.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time Spent in High Demand Activities</td>
<td>-0.01</td>
<td>-0.01-0.03</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Male/Female</strong></td>
<td>3.62</td>
<td>-1.69-8.93</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS-QOL</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.36</td>
<td>-0.75-0.03</td>
<td>0.07</td>
</tr>
</tbody>
</table>

$R^2 = 0.45$

Bold= P value statistically significant p ≤ 0.05
4.3.2 Relationship Between Baseline Sex, Gender, and SG Related Variables and 1-Year HRQoL

Table 4 presents the univariable regression analyses for baseline sex, gender and SG variables and their relationship with 1-year HRQoL. No sex related baseline variables were significantly associated with 1-year HRQoL. Baseline fear of re-injury (β= 0.27, p<0.001), a gender-related variable, and baseline pain (β= 0.49, <0.001), a SG-related variable were both significantly associated with at 1-year HRQoL after adjusting for age (p= 0.58) and baseline HRQoL (p<0.001). Specifically, lower baseline fear of re-injury and having less baseline pain was associated with better 1-year HRQoL. Similar to the previous analyses, the variable male/female was not significantly associated with 1-year HRQoL.

4.3.3 Relationship Between 1-Year Sex, Gender, and SG Related Variables and 1-year HRQoL

Table 6 presents the findings for 1-year sex, gender and SG variables used in the univariable regression analysis to examine the relationship between 1-year predictors and 1-year HRQoL. Among the sex-related variables, 1-year knee strength was significantly associated with 1-year HRQoL (β= 0.02, p <0.001). Among the gender-related variables, 1-year weight concern was significantly associated with 1-year HRQoL (β= -1.40, p<0.01). Several 1-year SG-related variables were significantly associated with 1-year HRQoL, including pain (β=1.11, p<0.001), physical function (β= 0.24, p= 0.04) and time spent participating in high demand activities (β= 0.03, p= 0.02). That is, greater knee strength, less knee pain, improved physical function and more time spent in high demand activities at 1-year were associated with greater HRQoL. At 1-year, being more likely to
believe that if one did not exercise, he or she would become overweight was associated with poorer HRQoL.
Table 6: Univariable Association of 1-Year Independent Variables with 1-Year HRQoL (III.1)

<table>
<thead>
<tr>
<th>Year 1 Independent Variables</th>
<th>Unstandardized Beta</th>
<th>Confidence Interval</th>
<th>F value</th>
<th>Analysis P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>0.02</td>
<td>0.02-0.10</td>
<td>14.15</td>
<td>\textless 0.001</td>
</tr>
<tr>
<td>Laxity</td>
<td>3.75</td>
<td>3.61-11.11</td>
<td>1.02</td>
<td>0.31</td>
</tr>
<tr>
<td>Alignment</td>
<td>Not Available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear of Re-Injury</td>
<td>0.05</td>
<td>-0.05-0.15</td>
<td>0.89</td>
<td>0.35</td>
</tr>
<tr>
<td>Exercise Importance</td>
<td>-1.42</td>
<td>-4.40-1.55</td>
<td>0.90</td>
<td>0.34</td>
</tr>
<tr>
<td>Commitment to Exercise</td>
<td>0.52</td>
<td>-0.69-1.73</td>
<td>0.72</td>
<td>0.40</td>
</tr>
<tr>
<td>Weight Concern</td>
<td>-1.40</td>
<td>-2.33-0.45</td>
<td>8.53</td>
<td>0.01</td>
</tr>
<tr>
<td>Time Spent on Household/Caregiving Activities</td>
<td>0.004</td>
<td>-0.08-0.017</td>
<td>0.41</td>
<td>0.52</td>
</tr>
<tr>
<td>Time spent on Low Demand/Walking Activities</td>
<td>0.01</td>
<td>-0.01-0.02</td>
<td>2.82</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Sex and Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.43</td>
<td>-1.32-0.47</td>
<td>0.90</td>
<td>0.34</td>
</tr>
<tr>
<td>Pain</td>
<td>1.11</td>
<td>0.88-1.38</td>
<td>90.8</td>
<td>\textless 0.001</td>
</tr>
<tr>
<td>Physical Function</td>
<td>0.24</td>
<td>0.00-0.49</td>
<td>3.94</td>
<td>0.04</td>
</tr>
<tr>
<td>Time Spent in High Demand Activities</td>
<td>0.03</td>
<td>0.005-0.05</td>
<td>5.63</td>
<td>0.02</td>
</tr>
<tr>
<td>Mental Health</td>
<td>0.17</td>
<td>-0.04-0.39</td>
<td>2.50</td>
<td>0.10</td>
</tr>
<tr>
<td>M/F</td>
<td>0.23</td>
<td>-6.60-7.06</td>
<td>0.005</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS-QOL</td>
<td>0.52</td>
<td>0.34-0.70</td>
<td>32.5</td>
<td>\textless 0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.15</td>
<td>-0.39-0.69</td>
<td>0.31</td>
<td>0.58</td>
</tr>
</tbody>
</table>

BOLD= Indicates P value \( \leq 0.1 \) where variable was carried forward to further analyses
Separate Multivariable regression models were run investigating baseline predictors as predictors of 1-year HRQoL and 1-year independent variables as predictors of 1-year HRQoL separately (See Appendix E and F). Only baseline KOOS-QOL was a significant predictor of ($\beta=0.34$, $p=0.01$) 1-year HRQoL. Significant 1-year variables predicting 1-year HRQoL included knee strength ($\beta=0.01$, $p=0.03$), weight concern ($\beta=-1.08$, 0.01), pain ($\beta=0.87$, $p<0.001$) and physical function ($\beta=0.23$, $p=0.01$). Overall, better knee strength, less weight concern, less pain and better physical function at 1-year follow-up and greater HRQoL at baseline were associated with greater 1-year HRQoL.

4.3.4 Final Model: Evaluation of Baseline and 1-Year Predictors of 1-Year HRQoL

All 1-year predictor variables with $p<0.1$ level were carried forward from the univariable regression analyses (Table 6). All baseline predictor variables from the multivariable analyses examining the relationship between baseline predictors and 1-year KOOS-QOL (Table 7) with $p<0.05$ were also carried forward to this final model for analyses.
Table 7: Multivariable Analysis of Baseline Predictors of 1-Year HRQoL (II.4)

<table>
<thead>
<tr>
<th>Baseline Independent Variables</th>
<th>Year 1 KOOS-QOL (Dependent Variable)</th>
<th>Unstandardized Beta</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear of Re-Injury</td>
<td>0.15</td>
<td>-0.00-0.29</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Exercise Importance</td>
<td>-1.06</td>
<td>-4.22-2.09</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Weight Concern</td>
<td>0.08</td>
<td>-0.85-1.00</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td><strong>Sex and Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0.23</td>
<td>0.01-0.47</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Time Spent in High Demand Activities</td>
<td>0.003</td>
<td>-0.01-0.01</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>-0.73</td>
<td>-6.94-5.48</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS-QOL</td>
<td>0.32</td>
<td>0.08-0.57</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.32</td>
<td>-0.19-0.83</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

$R^2 = 0.54$

Bold= P value statistically significant $p \leq 0.05$
Given that both the baseline and 1-year data for three variables, namely pain, weight concern and time participating in high demand activities were significantly associated with 1-year HRQOL, the magnitude of the correlation between the baseline and 1-year data was evaluated to provide guidance for inclusion of these variables in the multivariable model (See Appendix D). The Pearson correlation coefficients between baseline and 1-year for pain was \( r = 0.45 \), weight concern was \( r = 0.72 \) and time participating in high demand activities was \( r = 0.33 \). A change score was calculated for pain and time spent participating in high demand sports because the baseline and 1-year values were not highly correlated \( (r<0.7) \). Because of the high correlation and hence collinearity [406] between baseline and 1-year weight concern, only baseline weight concern was modeled with multivariable analysis.

The variables included in the final model analysis consisted of: 1-year strength (sex-related variable); the gender-related variables baseline fear of re-injury, baseline weight concern, 1-year walking and low demand activities; and the SG-related variables change in pain, 1-year physical function, change in time spent participating in high demand activities, and 1-year mental health. The model also included M/F, baseline KOOS-QOL, and age. Model assumptions were evaluated and no violations precluded multivariable modeling (Appendix B)

In the final multivariable model (Table 8) examining predictors of 1-year HRQOL, five variables were significant: 1-year knee strength \( (\beta = 0.02, p = 0.01) \), change in pain \( (\beta = 0.44, p<0.001) \), 1-year physical function \( (\beta = 0.27, p = 0.02) \), baseline KOOS-QOL \( (\beta = 0.50, p<0.001) \) and age \( (\beta = 0.58, p = 0.01) \). That is, greater knee strength at 1-year, larger decrease in pain, better 1-year physical functioning, older age and better baseline
QOL were associated with greater 1-year HRQoL. M/F was not statistically significant (p= 0.22).

The variables explained 44% of the variability in the 1-year KOOS-QOL score (adjusted R^2). The adjusted R square is an estimate of the effect size; at 0.44 this is a “medium” effect size. [406]
**Table 8:** Final Model- Evaluation of Baseline and 1-Year Predictors of 1-Year HRQoL in Multivariable Regression

**Independent Variables**

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Beta</th>
<th>Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year Knee Strength</td>
<td>0.02</td>
<td>0.01-0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL Fear of Re-Injury</td>
<td>0.07</td>
<td>-0.05-0.20</td>
<td>0.24</td>
</tr>
<tr>
<td>BL Weight concern</td>
<td>0.12</td>
<td>-0.64-0.89</td>
<td>0.75</td>
</tr>
<tr>
<td>1-Year Time spent on Low Demand/Walking Activities</td>
<td>0.004</td>
<td>-0.002-0.01</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Sex and Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change Pain</td>
<td>0.44</td>
<td>0.23-0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-Year Physical Function</td>
<td>0.27</td>
<td>0.07-0.47</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Change Time Spent in High Demand Activities</td>
<td>0.01</td>
<td>-0.003-0.02</td>
<td>0.16</td>
</tr>
<tr>
<td>1-Year Mental Health</td>
<td>0.04</td>
<td>-0.13-0.22</td>
<td>0.62</td>
</tr>
<tr>
<td>Male/Female</td>
<td>4.86</td>
<td>-1.43-11.61</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL KOOS QOL</td>
<td>0.52</td>
<td>0.31-0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.55</td>
<td>0.11-0.92</td>
<td><strong>0.010</strong></td>
</tr>
</tbody>
</table>

R^2 = 0.44
BL= Baseline
**Bold= P value statistically significant p≤0.05**

**Note:** The independent variables evaluated in this model included statistically significant baseline independent variables carried forward from model II.4 and statistically significant 1-year independent variables carried forward from III.1. Also included were the covariates including baseline KOOS-QOL and Age
In summary, in this multivariable analysis three variables were significant including the sex-related variable 1-year strength, SG-related change in pain (described above), 1-year physical function and the covariates BL KOOS-QOL and age. Specifically, greater 1-year knee strength and greater 1-year physical functioning were independently associated with greater 1-year HRQoL. Neither, M/F or variables representing gender were significant (Table 8).

4.4 EVALUATING WHETHER MALE/FEMALE MODERATES THE RELATIONSHIP OF KEY VARIABLES AND 1-YEAR HRQOL

Table 9 presents the results of the analyses evaluating potential effect modification of male/female and 1-year clinically important variables (i.e. strength, alignment, weight concern, BMI, pain, time spent in high demand activities) with HRQOL at 1-year.
Table 9: Evaluation of Effect Modification by M/F of Knee Strength, Knee Alignment, Weight Concern, BMI, Pain, Time Spent in High Demand Activities and 1-Year HRQoL (IV.2)

<table>
<thead>
<tr>
<th>Year 1 Interaction Terms</th>
<th>Unstandardized Beta</th>
<th>Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODEL 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year Knee Strength</td>
<td>-0.02</td>
<td>-0.03—0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male/Female</td>
<td>-23.07</td>
<td>-52.70—6.57</td>
<td>0.30</td>
</tr>
<tr>
<td>Strength Interaction</td>
<td>0.01</td>
<td>-0.012—0.04</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>MODEL 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL Knee Alignment</td>
<td>0.48</td>
<td>-0.39—1.35</td>
<td>0.28</td>
</tr>
<tr>
<td>Male/Female</td>
<td>-2.13</td>
<td>-9.11—4.86</td>
<td>0.55</td>
</tr>
<tr>
<td>Alignment Interaction</td>
<td>-0.39</td>
<td>-1.83—1.04</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>MODEL 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year Weight Concern</td>
<td>1.32</td>
<td>0.18—2.47</td>
<td>0.02</td>
</tr>
<tr>
<td>Male/Female</td>
<td>-2.09</td>
<td>-15.70—11.52</td>
<td>0.76</td>
</tr>
<tr>
<td>Weight Concern Interaction</td>
<td>0.22</td>
<td>-1.83—2.28</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>MODEL 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year BMI</td>
<td>1.03</td>
<td>-0.11—2.18</td>
<td>0.08</td>
</tr>
<tr>
<td>Male/Female</td>
<td>43.76</td>
<td>-9.12—96.63</td>
<td>0.10</td>
</tr>
<tr>
<td>BMI Interaction Term</td>
<td>-1.74</td>
<td>-3.94—0.46</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>MODEL 5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year Pain</td>
<td>1.30</td>
<td>0.99—1.61</td>
<td>0.00</td>
</tr>
<tr>
<td>Male/Female</td>
<td>4.17</td>
<td>-3.56—11.89</td>
<td>0.29</td>
</tr>
<tr>
<td>Pain Interaction Term</td>
<td>-0.44</td>
<td>-0.90—0.02</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>MODEL 6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year Time Spent in High Demand Activities</td>
<td>-0.04</td>
<td>-0.07—0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Male/Female</td>
<td>-3.33</td>
<td>-11.21—4.54</td>
<td>0.40</td>
</tr>
<tr>
<td>Time Spent in High Demand Activities Interaction</td>
<td>0.04</td>
<td>-0.01—0.09</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**BOLD**= Approaching statistical significance resulting in further exploration

Because the analysis was exploratory and there was limited power due to the relatively small sample size, each interaction term was examined individually. None of the individual models resulted in statistically significant interactions. However, there was a
trend for 1-year pain and male/female to interact, p= 0.06. To further explore this finding, 1-year pain was dichotomized at the median and was graphed for males and females, examining 1-year HRQoL (See Diagram 2).

Diagram 2: Pain scores for Men and Women related to HRQoL at 1-year

The results indicate that at low pain levels men and women had similar and relatively high HRQoL at 1-year follow-up. At higher levels of pain, there was worse HRQoL, with some indications that men had poorer HRQoL than women.
CHAPTER 5: DISCUSSION

5.1 PREFACE

This chapter presents the key findings of the thesis. Discussion of how the use of a SGSA enhanced understanding of the research and findings is presented followed by presentation of the findings of the thesis objectives in the context of the literature. Next, study limitations are outlined followed by clinical implications and strategies for knowledge translation. Finally, directions for future research are presented.

5.2 KEY FINDINGS FROM THIS THESIS

The overall aim of this thesis was to examine factors associated with HRQoL 1-year after ACLR using a SGSA to disentangle whether and how sex and gender are associated with HRQoL. In keeping with previous research, [230, 232, 233] both males and females from the cohort reported relatively high levels of HRQoL 1-year following ACLR. However, their HRQoL scores were on average 29/100 points below scores from healthy populations, [411] suggesting that there is potential for improvement in HRQoL following ACLR. Improving HRQoL requires an understanding of potentially modifiable factors associated with this outcome.

Applying a SGSA approach to ACLR and HRQoL in men and women post ACL surgery, this research found no significant difference between males and females in HRQoL at baseline. However, several baseline factors including greater fear of re-injury (gender-related variable), exercise importance (gender-related variable) and pain (SG-related variable) were associated with lower baseline HRQoL. At the 1-year follow-up in the final model, greater 1-year knee strength (sex-related variable), larger decrease in
pain (SG-related variable), greater 1-year physical function (SG-related variable), greater baseline HRQoL and younger age were associated with higher 1-year follow-up HRQoL.

Both sex and gender-related variables have been found to be associated with health and illness [412] and a SGSA perspective was useful because it provided a rationale and guide for categorizing variables in new ways, reflecting both biological and sociocultural aspects of sex and gender. Overall, the findings highlight that although there were few overall differences between men and women, both sex-and gender-related factors were associated with HRQoL at 1-year after ACLR. This may open new avenues of research and help to tailor interventions more directly to the needs of men and women. For example, there is a recognized biological difference in strength between men and women so the goals for the expected outcomes for knee strength attainment post-operatively should be specific to men and women in order to maximize HRQoL post-operatively.

Figure 3 presents a diagrammatic presentation of the statistically significant predictors of 1) baseline; and, 2) 1-year HRQoL. Although this full model needs to be tested in future research, the suggested predictors of each of baseline and 1-year HRQoL identified in this thesis may be important for improving 1-year HRQoL after ACLR. Many of these factors, such as knee strength, pain, fear of re-injury and exercise importance may be amenable to modification. Additionally, given baseline HRQoL predicts 1-year HRQoL factors associated with baseline HRQoL may also be targets that ultimately improve 1-year HRQoL through baseline HRQoL.
5.3 Advantages and Challenges of Applying a SGSA

Applying a SGSA approach was advantageous for variable selection. It provided guidance for the inclusion of predictor variables representing potential biological, psychological and sociocultural determinants and provided more depth and breadth to the understanding of factors associated with HRQoL. By embarking on this research with a sex and gender perspective, variable selection resulted in the inclusion of variables not previously explored to better understand HRQoL after ACLR. In particular, analyses included variables exploring exercise importance, fear of re-injury and mental health. These helped to shed new light on perceptions associated with HRQoL and moved the research beyond clinical and functional measures that have commonly been relied upon in previous ACLR research. [6, 278, 286, 413]
A SGSA approach also provided guidance for the multivariable analyses. Variables of interest were selected to represent sex, gender and SG a priori. As the literature has noted, [44, 60] when M/F as a variable is not significant in a multivariable model, there may still be other sex- or gender-related predictor variables in the model that provide insight into outcomes of interest. In this thesis, despite M/F being carried forward through each regression, it was not statistically significant in the final analysis. However, other variables included in the SGSA including sex-related knee strength, gender-related exercise importance and SG-related pain were significantly associated with HRQoL 1-year following ACLR. Although past publications from other conditions such as cardiovascular disease, have provided guidance in categorizing variables using a sex-gender approach, [338, 357, 358] many of the variables from these publications were not available in this thesis.

Categorizing all variables as reflecting either sex or gender also was not a straightforward exercise. Attempting to disentangle biological attributes due to sex from sociocultural attributes due to gender was complex for some variables. In addition, there are limited examples to draw from in the literature that prove relevant to ACLR. As a result some variables were categorized as SG as they best reflected both biological sex and sociocultural components. For example, some research has suggested that pain, [324, 400, 401] BMI, [40, 397] physical function, [402] and mental health [414] include both sex and gender components. Further research aimed at understanding if variables represent sex-, gender- or sex-gender-related concepts will be important to increase our understanding of these concepts. Through repeated studies we may come to better understand if there are male and female differences related to sex and gender. If no
differences are found with these repeated studies it may be that the underlining categorization of sex-, gender- or sex-gender for a particular variable is not meaningful.

Another way that studies can assess whether gender is relevant is to look at measures that consider masculinity and femininity. As noted in the background chapter, Pelletier et al. [357] developed a measure assessing masculinity and femininity to be administered to a group of patients with coronary vascular disease (CVD). In developing this scale they selected a number of variables that were subjected to principle component analysis to develop a reduced set of variables. This reduced set of variables was used to develop a propensity score. This propensity score was then renamed the gender score where higher values on the scale represented greater femininity and it was used to look at the degree of femininity and masculinity among men and women with CVD. Their findings showed no sex differences between men and women, but gender was significantly related to cardiovascular risk. That is, being male or female did not predict those patients who were likely to relapse or die within 12 months from acute coronary syndrome (ACS). However, individuals with a higher gender-based “femininity” score (regardless of whether they were male or female) were more likely to suffer a recurrence of ACS. Pelletier and colleagues concluded that the patient’s gender-related characteristics might be useful in understanding differences in cardiovascular disease. [357] As yet, no ACLR literature has applied measures of masculinity and femininity to examine outcomes like HRQoL. Using Pelletier’s et al.’s methodology as a model, future prospective research could combine findings from this thesis with additional variables based on previous sex and gender research to create a gender score. This gender score could then be used to
more fully examine the effects of gender and its relationship to HRQoL within an ACLR population.

5.4 SAMPLE AND OUTCOMES INCLUDED IN THIS STUDY

5.4.1 The Sample

This research followed a sample of patients post ACLR surgery to examine pre-operative and 1-year post-operative outcomes. The parent study was not designed to specifically examine sex and gender similarities and differences. The sample was adequate in terms of having men and women and allowing for a SGSA. However, despite women being on average three times more likely to tear their ACL compared to men, [6, 21-26, 28] the data available for this thesis had 30% more men in the cohort compared to women. In future research it would be helpful to have a great number of participants, particularly women in order to ensure power to detect sex and gender differences.

The average age of the cohort was 27.3 years (range 17-41 years). This is consistent with most ACL research that includes a younger population with an age range of 15-45 years. [17-20, 32, 223, 224, 226, 227, 231] ACL injuries occur more often in younger populations due to their more active lifestyle and participation in sports. [415] However, as average age and life expectancy rise, there has been an increase in the rate of ACL injuries in people over-40 years of age. [415, 416] It, therefore, would also be helpful in future studies to include a greater age range as physical activity levels are rising in older populations. [415]

5.4.2 The Study Outcome

This thesis measured HRQoL at 1-year post ACLR using the KOOS-QOL as the outcome of interest. There have been very few studies that have used the KOOS-QOL to
examine HRQoL in the context of ACLR pre-operatively and then 1-year post-operatively. [16, 230, 232, 233] Most ACLR studies examine longer-term post-operative HRQoL, usually more than two years from the time of surgery. [17-20, 32, 38, 223, 224, 226, 227, 229-231] Ageberg et al.’s study [16] is one of the few studies to measure ACLR HRQoL with the KOOS-QOL pre-operatively and then 1-year post-operatively, the same time points used in this thesis. Ageberg et al.’s study had a much larger sample size compared to this thesis with 4438 participants and had a more balanced male/female ratio with 44% females compared to 37% females in this thesis. Despite these differences both studies had similar HRQoL findings. In both studies males and females showed marked improvement in HRQoL from baseline to 1-year following ACLR. Also similar was that Ageberg et al.’s cohort scored well below population HRQoL normative values with an average of 32/100 points below that of healthy controls,[411] suggesting that, similar to this thesis, there is potential for improvement in HRQoL following ACLR. Although there were differences in number of participants between the two studies, the similar findings gives more confidence in this thesis’ findings and suggests the results of this thesis might be generalizable.

As a measurement of ACLR HRQoL in a SGSA, the KOOS-QOL subscale has several strengths. First, it is a relatively short scale with four items specific to the knee. These items enquire about knee awareness, need for lifestyle modifications, lack of confidence and general difficulty. [217] Each item includes content that is applicable to an ACL injured population. Second, both women and men were included in the development of the items and testing of the KOOS’ measurement properties. [220] Third, the format is user friendly and takes a short amount of time to complete. [364] Lastly, it has excellent
measurement properties with high responsiveness [217] and has been shown to be both
valid and reliable when measuring HRQoL after ACLR. [221]

Despite these strengths, the KOOS-QOL does not include extensive inquiry into the
psychosocial aspects of an ACL injury; instead its focus is more physical in nature. With
respect to choosing a measurement tool, research has noted that there is a trade-off
between providing detailed coverage of a few topics and covering many topics more
broadly that translates into precision versus comprehensiveness. [417] As the KOOS-
QOL includes only four items, it may not be comprehensive enough to capture sex and
gender differences. This research like other research [16] did not find any HRQoL
differences between men and women. Because HRQoL is a diverse concept, had we used
another measurement tool we may have found differences between men and women. For
example the ACL QOL developed by Mohtadi includes psychosocial items. [72]
However the challenge with the ACL QOL is it has multiple subscales, it is long, has low
reliability (ICC= 0.6) and is still missing content on roles. [242, 246] While every
measurement tool can be criticized, the KOOS-QOL was valuable as an outcome for this
thesis and should be recommended for future research.

Another measurement consideration in the context of sex- and gender-based
approaches is the mode in which data are collected. There is some evidence that the data
collected in surveys differs from that collected in interviews. For example, research on
pain [49, 418, 419] has shown that men may provide additional information regarding the
emotional component of their pain in an interview setting compared to survey data. [419]
A more complete assessment of HRQoL in ACLR should include not only physical,
functional, emotional, and mental well-being aspects of HRQoL, but also consider how
data are collected.

5.5 PROFILE OF MEN AND WOMEN AT BASELINE AND VARIABLES
RELATED TO BASELINE HRQOL

Overall the characteristics and profile of men and women on baseline sex, gender and
SG variables was very similar. The few differences found at baseline included that
women had greater valgus alignment (sex-related), they more strongly agreed that they
needed to exercise to feel good about themselves (gender-related), they had lower BMI
(SG-related) and they had higher scores in mental health (SG-related).

In the multivariable analysis of baseline predictors of baseline HRQoL, no sex-related
variables were statistically significant. However, gender-related variables including
baseline fear of re-injury and baseline exercise importance, as well as the SG-related
variable pain were all statistically significant predictors of baseline HRQoL.

Women had greater valgus alignment, which is in keeping with the literature. [369] It
has been suggested that women with greater valgus knee alignment tend to have a larger
Q angle, [420] making them more susceptible to ACL tears. [370, 421] Although there
were sex differences in alignment, and this is a variable of interest clinically, it was not a
variable that predicted HRQoL. Based on the results of this study, it is unlikely to explain
HRQoL.

At baseline, women more strongly agreed that they needed to exercise to feel good
about themselves, an item included in the study to measure exercise importance. This is
in keeping with some theoretical work, including Cash’s theory [377] that women tend to
strive for a thin ideal and a body type characterized by lower body fat such that they tend
to exercise even when sick, injured, tired or unwell out of fear of gaining weight. This
study adds to the literature in linking perceptions of exercise importance to perceptions of HRQoL in a sample of individuals with ACLR. The finding that the perceived value of exercise differed between men and women suggests additional research examining exercise perceptions in more detail may be warranted. Also, because exercise importance was a predictor of baseline HRQoL, how men and women value exercise may be a key component in recovery from ACLR and their subsequent HRQoL.

Men had higher BMI values compared to women at both baseline and 1-year post-operatively. It is unclear if these differences in BMI between men and women (differences of 2.54 at baseline and 3.27 at 1-year) are clinically meaningful. Additionally, any differences in BMI are challenging. Although it is used as a surrogate marker for body fat, differences between men and women may occur because BMI does not measure percentage body fat (PBF) directly, poorly distinguishing between total body fat and total body lean tissue. On average women have greater amounts of total body fat compared to muscle than do men for an equivalent BMI. [422, 423] Men’s increased muscul arity [424] can cause them to have an elevated BMI without taking into account their relative proportion of muscle within their body mass. Although there were differences between men and women in BMI, this factor was not significant in multivariate analyses predicting baseline HRQoL.

Men had lower scores on the SF-36 mental health subscale score compared to women at baseline. At 1-year these differences disappeared. This is one of the first studies in the ACLR literature that has examined mental health using the SF-36 mental health subscale during the 1-year post-operative time period. The SF-36 mental health subscale has been shown to be a sensitive instrument used to screen for depression. [425] Although the
reasons for the difference in mental health scores between men and women at baseline are unknown, some literature has evaluated the association of depression and identity in other populations. For example, sociocultural theory has suggested that an important component of men’s identities is related to their physicality. [337, 340] An injury may temporarily threaten that identity or the social network that men may have built around sports participation. Other literature, although not in people with ACLR, has examined the association between depression and pain coping strategies and suggested that men have poorer coping skills in managing pain compared to women. This may also explain their lower mental health scores. [318, 418, 419, 426-430] At the same time, differences between men and women were small and disappeared over time. This suggests that mental health differences may be temporary and disappear as individuals recover from their injury and surgery. Notably, mental scores were not significantly associated with HRQoL. Additional research that explores mental health and the potential reasons for differences, including perceived identity, depressed mood following an injury, and pain coping strategies between men and women is warranted. Additionally, research linking these factors to HRQoL is required.

Although there were no sex differences in the gender-related variable fear of re-injury and the SG-related variable pain, both these variables were statistically significant predictors of baseline HRQoL in multivariable analysis. In knee OA literature, [431-434] the association between pain and fear of re-injury has been explored and higher levels of knee pain have been associated with greater fear of re-injury. Perhaps a similar phenomenon occurs among this cohort of ACL injured patients prior to undergoing ACLR. That is, the pain that results from acutely injuring their ACL may drive the fear of
re-injury during the pre-operative phase. However, in this research pain and fear of re-injury were not highly correlated (see Appendix B) which could counter this argument. Future research that further explores the relationship between fear of re-injury and pain and their influence on HRQoL after ACLR should be conducted.

5.6 PROFILE OF MEN AND WOMEN AT 1-YEAR AND VARIABLES RELATED TO 1-YEAR HRQOL

There were also few statistically significant differences between men and women at 1-year following ACLR. The few differences found at 1-year included that men reported greater knee strength (sex-related variable); greater time spent participating in low demand and walking activities (gender-related variable) and, as discussed above, greater BMI (SG-related variable) compared to women.

For the most part, results related to differences between males and females regarding knee strength and BMI are in keeping with previous studies as described above. [173, 276] Men spent more time participating in low demand and walking activities but there were no significant differences between men and women in time spent on household and caregiving activities at 1-year. Based on the sociocultural theory, women might have been expected to report more time spent on these traditionally female roles. [435] Possible reasons for the finding in this thesis include that men and women are more similar in many of their roles than previously thought. It may also be that the relatively young age of participants meant that they had fewer caregiving responsibilities at this time of their lives. Unfortunately, no data on marital status or number of dependents was available. Such information would be helpful in understanding the time commitments a patient recovering from ACLR may have in caring for others and should be included in future research.
While there were differences between men and women in the above-mentioned 1-year variables, of these, only 1-year knee strength (a sex-related variable) was significantly associated with 1-year HRQoL. There were differences in strength between males and females. However, given the function and demands of the knee musculature that suggest that strength in and of itself is important in HRQoL, the interrelationships among sex, knee strength and HRQoL are not entirely clear. Additional research teasing these variables apart would be helpful. While a variable can be categorized as a sex or gender variable, this does not necessarily mean that sex or gender are relevant in explaining the findings.

In the multivariable analysis results of baseline predictors of 1-year HRQoL, baseline fear of re-injury and baseline pain remained predictors of 1-year HRQoL while exercise importance was not statistically significant. A possible explanation for this difference is that while baseline fear of re-injury, exercise importance and pain might all appear to affect baseline HRQoL, at 1-year the patients may have developed different priorities. [436] Another explanation is that patients may have realized their physical limits due to ACLR rehabilitation and adjusted their exercise regimen accordingly. Due to these potential changes in behaviour, it may be that patients no longer placed as much importance on exercise to feel good about themselves at 1-year as they did during the acute injury phase. Additional longitudinal data asking about changes to behaviour and the importance of activities would help illuminate these findings in greater detail.

One of the few studies to investigate pain as a predictor of HRQoL following ACLR found similar results to this thesis. [12] That is, less knee pain was associated with better 1-year HRQoL as measured by the KOOS-QOL. Studies [12, 437] suggest patients with
an absence of or with minor pre-surgical knee pain experience less post-operative knee pain such that they are better able to participate in their rehabilitation program following ACLR. Returning to pre-injury level of activity was associated with higher self-esteem [278] and higher self-esteem has been associated with greater KOOS-QOL scores. [278] However, more research needs to be undertaken before the association between returning to pre-injury level of activity and higher post-operative HRQoL is clearly understood.

Fear of re-injury also has been examined as a pre-operative predictor of post-operative HRQoL following ACLR. In accordance with this thesis’ results, researchers found lower pre-operative fear of re-injury was associated with better post-operative HRQoL. [13] Because of the predictive association with HRQoL in both this thesis and other research, further prospective studies investigating the relationship between level of knee pain and fear of re-injury is warranted in order to improve our understanding of ways to improve HRQoL.

Finally, exploratory analyses were conducted in an attempt to evaluate if the variable male/female moderated the association of independent variables and HRQoL 1-year following ACLR, but no significant results were found. These analyses were limited by a small sample size and should be further explored in future research by increasing sample size with similar numbers of men and women. Additionally, a prospective study will allow for variable selection that is supported by prior literature and a conceptual framework informing the study.

5.7 STRENGTHS AND LIMITATIONS

One of the main strengths of this thesis was the application of a sex and gender framework that used a SGSA approach throughout the planning, design, analysis, and
interpretation of this study. As noted previously, this research considered important sociocultural aspects that may otherwise have been overlooked in order to assess predictors of HRQoL. Other strengths include that a range of variables that potentially assess sex, gender, or both sex + gender were available in the dataset and could be examined in relation to HRQoL. This enabled the study to not only gain insight into HRQoL post ACLR surgery, but also better understand factors related to HRQoL.

There are also limitations to this study that need to be noted. They include that the study was a secondary analysis and the data were not collected for the primary purpose of evaluating sex and gender as predictors of HRQoL. This limited the derivation of the variables representing sex and gender to the existing data. Potentially important variables such as those related to women and men’s roles within their family (e.g. caregiving) and society (e.g. employment) could not be examined, as well as a wide range of attitudes and perceptions about the meaning of having an ACL injury, the value of exercise, and factors related to individuals' identity. Qualitative research might be particularly valuable in gaining more depth and breadth into sex and gender factors related to HRQoL post ACL injury that might be important to evaluate as predictors of HRQoL in quantitative studies.

Finally, this cohort was recruited from a single surgeon’s practice and a single surgical technique was used to reconstruct the ACL. While the characteristics of the sample are similar to those reported in the literature, this single site recruitment may limit generalizability of the findings. Additional research with larger and more diverse samples is needed.
5.8 CLINICAL IMPLICATIONS AND KNOWLEDGE TRANSLATION

This study provides novel information regarding HRQoL in patients following ACLR that may be useful to clinicians. Clinicians need greater awareness that, although HRQoL improves over a 1-year period following ACLR, it often remains lower than that of healthy controls. Clinicians should also be aware that ACLR HRQoL at 1-year post-surgery is predicted not only by clinical features (e.g., knee strength) but also by psychosocial factors such as pain perceptions and physical function. Currently, ACLR rehabilitation programs are mostly focused on the physical aspects of these variables, and less focused on the fact that pain and function may have psychosocial aspects or might be related to sex and gender. [16, 32] Based on findings from this study, the allied care team should broaden their awareness and consider addressing mental health and exercise identity/importance issues as important to rehabilitation and subsequent HRQoL.

The novel method of applying a SGSA to an ACLR cohort also provides valuable insight for physicians and members of the allied health care team interested in improving HRQoL after ACLR. While patients have previously been examined as being M/F in ACLR research, often the contribution of sociocultural aspects of variables and their relationship to outcome have not been considered. It is important to not only recognize the biological differences between men and women, but also to recognize the importance of sociocultural factors like pain perceptions that may or may not affect men and women differently. This thesis highlights the need to consider the whole person in order to develop the best care plans after ACLR. This is important because, as this study found, even if there are no group differences between men and women, there may be sex or gender-related issues that can enhance our understanding of HRQoL or treatment and
interventions to improve HRQoL. By applying a SGSA in research, individual aspects of sex and gender can be identified and considered in ways that may have otherwise been missed if a single variable examining male/female were examined alone.

In the context of these clinical implications the challenge becomes how to disseminate the thesis findings. While information can be provided through publication in peer-reviewed journals, incorporation into the education of health professionals through educational rounds and, ideally, curricula will be key dissemination activities to uptake.

Integration of the potential influences of sex and gender into the medical and physical therapy curricula would ensure students are comfortable with the definitions of sex (biological) and gender (sociocultural). Finally, in the context of graduate and post-graduate research studies, researchers need to be encouraged to include equal numbers of women and men in their studies, and, where appropriate, ensure that men are not portrayed as the prototype of normal. [438-440]

5.9 FUTURE RESEARCH

Directions for future research should focus on optimizing HRQoL. Critical to interventions aimed at achieving this is a better understanding of modifiable factors that are potential treatment targets. A prospective study should include diverse samples with comparable numbers of men and women and relevant sex, gender and SG variables. This includes asking patients details about the perceived impact of an injury on their identity, social life, and goals and values, as well as information on domestic roles, type of employment, type of care giving responsibilities, number of children/dependents and marriage status to identify the impact of these aspects on HRQoL following ACLR. Evaluating these gender related aspects may help researchers better understand the
psychological, physical, emotional and social similarities and differences men and women experience following ACLR. Together this may help us better understand the nuances of sex and gender and potential targets for interventions.

Other potential targets for intervention may also be found by evaluating indirect as well as direct associations (such as that depicted in Figure 3) and examined in longitudinal studies so as to better tease apart the causal relationship between potential modifiable factors and outcomes. For example by decreasing fear of re-injury during the pre-surgical period it may benefit both baseline and possibly benefit 1-year HRQoL. As noted previously, other indirect factors may be targets for intervention to help increase HRQoL following ACLR.

Lastly, other outcomes including graft failure and development of knee OA would benefit from a SGSA. For example, a systematic review [303] demonstrated there was no difference in ACL graft failure risk between men and women. This review did not consider potentially important sociocultural aspects such as differences in activity levels between men and women that may have influenced the results. Although these two outcomes likely need a long follow-up in order to detect difference, a longitudinal design using a SGSA may help to better tease apart a causal relationship.

5.10 CONCLUSION

Using a SGSA to examine post-operative ACL HRQoL, this study identified both sex and gender factors associated with 1-year HRQoL that would not have been considered as relevant if differences between men and women had been examined as a single variable. The study’s results also highlight the need for the care team to address sociocultural aspects of an injury and its recovery, as well as physical aspects of injuries
and ACL rehabilitation following ACLR. This study found that men and women had improved HRQoL 1-year after ACLR. However, comparison with population data suggests there remains room for improvement in HRQoL post ACLR. By studying sex and gender we may come to better understand the composite of effects from both sex and gender on ACLR recovery and rehabilitation. As a result patients may more easily and more successfully be treated when recovering from ACLR, leading to improved HRQoL for both men and women.
### Appendix A: Example of Physical Activity Categories Based on Type of Activity and Intensity Level

<table>
<thead>
<tr>
<th>Household and Caregiving Activities</th>
<th>Low Demand and Walking Activities</th>
<th>High Demand Sports and Leisure Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeding/Planting</td>
<td>Walking for pleasure</td>
<td>Dancing</td>
</tr>
<tr>
<td>Spading/Digging</td>
<td>Walking for exercise</td>
<td>Martial Arts</td>
</tr>
<tr>
<td>Raking</td>
<td>Using the stairs</td>
<td>Jogging or Running</td>
</tr>
<tr>
<td>Shovelling Snow</td>
<td>Hiking, carrying &lt;20lbs</td>
<td>Aerobic classes</td>
</tr>
<tr>
<td>Pushing Lawn Mower</td>
<td>Hiking, carrying &gt;20lbs</td>
<td>Aerobics at home</td>
</tr>
<tr>
<td>Light Housekeeping</td>
<td>Horseback riding</td>
<td>Table tennis/ ping pong</td>
</tr>
<tr>
<td>Washing Windows</td>
<td>Cycling to work for pleasure</td>
<td>Badminton</td>
</tr>
<tr>
<td>Scrubbing Floors</td>
<td>Swimming</td>
<td>Tennis Singles</td>
</tr>
<tr>
<td>Lifting Laundry, boxes, bags</td>
<td>Aqua fitness Class</td>
<td>Tennis Doubles</td>
</tr>
<tr>
<td>Painting</td>
<td>Weight training at home</td>
<td>Squash/Racquetball</td>
</tr>
<tr>
<td>Carpentry</td>
<td>Weight training at gym</td>
<td>Waterskiing</td>
</tr>
<tr>
<td>Lifting a dependent</td>
<td>Golfing- pulling clubs on cart</td>
<td>Skiing downhill</td>
</tr>
<tr>
<td>Assisting a dependent with bathing</td>
<td>Golfing- riding power cart</td>
<td>Skiing cross country</td>
</tr>
<tr>
<td></td>
<td>Bowling</td>
<td>Ice Skating (not hockey)</td>
</tr>
<tr>
<td></td>
<td>Sailing</td>
<td>Soccer</td>
</tr>
<tr>
<td></td>
<td>Canoeing/Kayaking</td>
<td>Ultimate Frisbee</td>
</tr>
<tr>
<td></td>
<td>Rowing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scuba Diving</td>
<td>Basketball</td>
</tr>
<tr>
<td></td>
<td>Snorkelling</td>
<td>Volleyball</td>
</tr>
<tr>
<td></td>
<td>Fishing from a boat</td>
<td>Hockey</td>
</tr>
<tr>
<td></td>
<td>Fishing standing on shore/dock</td>
<td>Snowboarding</td>
</tr>
<tr>
<td></td>
<td>Sledding/ Tobogganing</td>
<td></td>
</tr>
</tbody>
</table>
Appendix B: Assumptions Check for the Multivariable Analysis of Baseline and 1-Year Predictor Variables With 1-Year HRQoL

The following assumptions were checked:

1. Independence of observations:

<table>
<thead>
<tr>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>Durbin-Watson</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.71</td>
<td>0.51</td>
<td>0.44</td>
<td>12.80</td>
<td>1.99</td>
</tr>
</tbody>
</table>

There was independence of the residuals, as assessed by a Durbin-Watson statistic of 1.99 where a value of approximately 2 indicates that there is no correlation between residuals.[441]

2. Linear relationship between the dependent variable and the independent predictor variables:

Upon visual inspection of each of the generated partial regression plots it was concluded that a linear relationship existed between each independent variable and the dependent variable.

3. By plotting the studentized residuals against the unstandardized predicted homoscedasticity it was confirmed the spread of the residuals did not increase over the range of the dependent variable’s predicted values. Therefore, the assumption of homoscedasticity was not violated.

4. Based on the Correlations table below none of the independent variables were correlated >0.7 indicating there were no concerns with multicollinearity.
Correlations between independent variables of interest:

| Variable                                      | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 | YI= Year 1 |
|-----------------------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 1-Year Strength                               | 1.00       | 0.10       | -0.12      | -0.21      | -0.26      | 0.09       | -0.01      | 0.08       | -0.07      | 0.53       | -0.18      | -0.19      |
| BL Fear of Re-injury                          | 0.10       | 1.00       | 0.01       | -0.23      | 0.08       | 0.21       | 0.16       | 0.14       | -0.16      | 0.09       | -0.48      | -0.04      |
| BL Exercise Importance                        | -0.12      | 0.01       | 1.00       | 0.42       | 0.00       | -0.11      | -0.07      | -0.14      | -0.08      | 0.21       | 0.27       | 0.18       |
| BL Weight Concern                             | -0.21      | -0.23      | 0.41       | 1.00       | -0.19      | 0.12       | -0.15      | -0.14      | -0.05      | 0.13       | 0.30       | 0.15       |
| 1-Year Time Spent on Low Demand/Walking Activities | 0.26       | 0.08       | -0.19      | -0.19      | 1.00       | -0.11      | -0.18      | -0.22      | 0.01       | -0.19      | -0.05      | -0.22      |
| Change Pain                                   | 0.09       | 0.21       | -0.12      | -0.12      | -0.11      | 1.00       | 0.11       | 0.12       | -0.07      | 0.03       | -0.46      | -0.07      |
| 1-Year Physical Function                      | -0.01      | 0.16       | -0.15      | -0.15      | -0.18      | 0.11       | 1.00       | 0.00       | 0.00       | -0.12      | -0.10      | -0.13      |
| Change Time Spent in High Demand Activities   | 0.08       | 0.14       | -0.14      | -0.14      | -0.22      | 0.12       | 0.00       | 1.00       | 0.07       | -0.08      | -0.32      | 0.13       |
| 1-Year Mental Health                          | -0.07      | 0.16       | -0.08      | -0.05      | 0.01       | -0.07      | 0.00       | -0.7       | 1.00       | 0.13       | -0.14      | -0.16      |
| Male/Female                                   | -0.53      | 0.09       | 0.21       | 0.13       | -0.19      | 0.03       | 0.12       | -0.08      | 0.13       | 1.00       | -0.04      | 0.00       |
| BL KOOS-QOL                                   | -0.18      | -0.48      | 0.27       | 0.29       | -0.05      | -0.46      | -0.11      | -0.32      | -0.14      | -0.04      | 1.00       | 0.18       |
| Age                                           | -0.19      | -0.04      | -0.18      | -0.15      | -0.22      | -0.07      | -0.13      | 0.13       | -0.16      | 0.00       | 0.18       | 1.00       |

BL= Baseline  
YI= Year 1
By consulting the Tolerance and VIF value table below, no VIF was greater than 10 and all tolerance values were greater than 0.1, indicating that there was no co-linearity between the independent variables in the data set.

Co-linearity Check

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tolerance</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year Strength</td>
<td>0.62</td>
<td>1.61</td>
</tr>
<tr>
<td>BL Fear of Re-injury</td>
<td>0.69</td>
<td>1.44</td>
</tr>
<tr>
<td>BL Exercise Importance</td>
<td>0.70</td>
<td>1.43</td>
</tr>
<tr>
<td>BL Weight Concern</td>
<td>0.70</td>
<td>1.42</td>
</tr>
<tr>
<td>1-Year Time Spent on Low Demand/Walking Activities</td>
<td>0.74</td>
<td>1.36</td>
</tr>
<tr>
<td>Change Pain</td>
<td>0.75</td>
<td>1.34</td>
</tr>
<tr>
<td>1-Year Physical Function</td>
<td>0.87</td>
<td>1.15</td>
</tr>
<tr>
<td>Change Time Spent in High Demand Activities</td>
<td>0.78</td>
<td>1.28</td>
</tr>
<tr>
<td>1-Year Mental Health</td>
<td>0.89</td>
<td>1.12</td>
</tr>
<tr>
<td>Male/Female</td>
<td>0.63</td>
<td>1.59</td>
</tr>
<tr>
<td>Baseline KOOS-QOL</td>
<td>0.51</td>
<td>1.97</td>
</tr>
<tr>
<td>Age</td>
<td>0.81</td>
<td>1.23</td>
</tr>
</tbody>
</table>

5. Upon review of the standardized residuals all the cases in this data set had standardized residuals less than +/- 3 standard deviations and therefore this assumption was satisfied. Leverage points were assessed. All leverage values were assessed and although 3 values fell above the desired level of 0.2. However, because their values were <0.5 these cases were kept for the analysis due to the relatively small sample size. Additionally, upon inspection of Cook’s distance for each case as a measure of influence there were no values above 1 therefore indicating none of the cases were influential.

6. Finally residuals were checked to ensure they were normally distributed. Upon inspection of the standardized residuals histogram the standardized residuals appeared to approximate a normal distribution.

Further, the P-P plot shown below demonstrates that although the points are not aligned perfectly along the diagonal line, they were in close enough proximity to the line to confirm the assumption of normality.
Final Model Multivariable Assumptions Check summary
The data met all the assumptions except the 1-year KOOS-QOL composite score was not normally distributed (Shapiro Wilks <0.05). However, the literature has shown assuming Kurtosis is not extreme (from -1 to 2) and sample size is not small (<=5) that even moderate departures from normality are acceptable. [442] Kurtosis for the outcome was 1.05 and the sample size was 115 participants and therefore the analysis was carried out.

Assumptions check for the multivariable analysis involving baseline predictors of baseline HRQoL
Similarly, to the final model, the data met all the assumptions with the exception of the KOOS-QOL baseline composite score that was not normally distributed (Shapiro Wilks <0.05). However, as mentioned above, the literature has shown that, assuming Kurtosis is not extreme (from -1 to 2) and sample size is not small (<=5), that moderate departures from normality are acceptable. [442] The Kurtosis was -0.64 and the sample size was 115 participants therefore the analysis proceeded as planned.
Appendix C: Ethics Approval

PROTOCOL REFERENCE # 31936

July 23, 2015

Dr. Aileen Davis
DEPT OF PHYSICAL THERAPY
FACULTY OF MEDICINE

Dr. Sabrina Koller
DEPT OF PHYSICAL THERAPY
FACULTY OF MEDICINE

Dear Dr. Davis and Dr. Sabrina Koller,

Re: Administrative Approval of your research protocol entitled, "The effects of sex and gender on anterior cruciate ligament reconstructive surgery outcome"

We are writing to advise you that the Office of Research Ethics (ORE) has granted administrative approval to the above-named research protocol. The level of approval is based on the following role(s) of the University of Toronto (University), as you have identified with your submission and administered under the terms and conditions of the affiliation agreement between the University and the associated TAHSN hospital:

- Graduate Student research - hospital-based only
- Storage or analysis of De-identified Personal Information (data)

This approval does not substitute for ethics approval, which has been obtained from your hospital Research Ethics Board (REB). Please note that you do not need to submit Annual Renewals, Study Completion Reports or Amendments to the ORE unless the involvement of the University changes so that ethics review is required. Please contact the ORE to determine whether a particular change to the University's involvement requires ethics review.

Best wishes for the successful completion of your research.

Yours sincerely,

[Signature]

Dario Kuzmanovic
REB Manager
To: Dr. Paul Marks
Orthopedic Surgery
Room MG 350

From: Dr. Brian J. Murray

Date: June 8, 2015

Subject: The Role of Sex and Gender in Anterior Cruciate Ligament Reconstructive Surgery Outcome

Project Identification Number: 197-2015
Approval Date: June 8, 2015
Expiry Date: June 8, 2016

The Research Ethics Board of Sunnybrook Health Sciences Centre has conducted a Delegated Board review of the research study referenced above and approved the involvement of human participants. Quorum for approval did not involve a member associated with this study.

The approval of this study includes the following documents:
- Protocol dated May 10, 2015
- Data Elements (received May 15, 2015)

☑ The Sunnybrook REB has determined that an Informed Consent Form (ICF) is not required for this study; consent requirements, if applicable, have been otherwise dealt with in accordance with Article 3.7 and/or 3.12 and/or 5.5 of TCPS2.

As Principal Investigator you are responsible for the ethical conduct of this study which may be subject to review by the Quality Assurance and Education Program. The study must comply with current legislation outlined in the Ontario Personal Health Information Protection Act (PHIPA) and all acts, regulations, guidelines and policies that govern this research. The REB requires immediate notification of internal serious adverse events and significant deviations, submission of a renewal form prior to the approval expiry date, and notification of study closure.

The REB and Research Ethics Office are in support of facilitating the progress of ethical research and thank you in advance for your efforts to protect research participants. Best wishes for a successful project.

Brian J. Murray, MD FRCP(C) D,ABSMM OR Philip C. Hébert, MD PhD FCFPC
Chair, Research Ethics Board Vice-Chair, Research Ethics Board

The Research Ethics Board of Sunnybrook Health Sciences Centre operates in compliance with the Tri-Council Policy Statement 2nd edition, ICH GCP Guidelines, Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, and Part 3 of the Medical Devices Regulations. All Health Canada regulated trials at Sunnybrook are conducted by a Qualified Investigator.

Fully affiliated with the University of Toronto
The Renewal Form is an application for continuing ethics approval and must be submitted for review and approval prior to the study's expiry date. Ethics approval expires each subsequent year from the day REB approval was initially granted unless otherwise indicated by the Sunnybrook REB. Failure to submit this form prior to the expiry date signifies that the study does not have REB approval and all research activities must be suspended. Conducting research without REB approval may result in a notice of non-compliance involving corrective action, up to and including, termination of the research study.

Principal Investigator (PI): Dr. Paul Marks

REB Project Identification Number (PIN): 197-2015

Full Study Title: The Role of Sex and Gender in Anterior Cruciate Ligament Reconstructive Surgery Outcome

1. Date of initial Sunnybrook REB approval (dd/mmm/yyyy).
   June 8, 2015

2. Type of REB review requested. (Final decision rests with the REB Chair.)
   ☑ Delegated Review    ☐ Full Board Review

3. Is this an Industry-Sponsored/Supported study?
   ☐ YES (If YES, complete the table below.) ☑ NO (If NO, proceed to question 4.)

<table>
<thead>
<tr>
<th>Invoicing Information for Industry-Sponsored/Supported Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A fee of $500 Cdn is invoiced for all Industry-Sponsored/Supported Studies applying for continuing ethics approval.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Invoice to the Following Company:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Name:</td>
</tr>
<tr>
<td>Telephone:</td>
</tr>
<tr>
<td>Street Address:</td>
</tr>
<tr>
<td>City:</td>
</tr>
<tr>
<td>Country:</td>
</tr>
<tr>
<td>E-mail:</td>
</tr>
<tr>
<td>Suite:</td>
</tr>
<tr>
<td>Province/State:</td>
</tr>
<tr>
<td>Postal/Zip Code:</td>
</tr>
</tbody>
</table>

4. Is this study open for enrollment at Sunnybrook?  ☐ YES ☑ NO

If YES, attach a copy of the current Informed Consent Form(s).
5. How many participants at Sunnybrook:

<table>
<thead>
<tr>
<th>Were planned for enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were consented</td>
</tr>
<tr>
<td>Were enrolled</td>
</tr>
<tr>
<td>Are currently receiving study treatment/intervention</td>
</tr>
<tr>
<td>Completed study treatment/intervention &amp; are currently on follow-up</td>
</tr>
<tr>
<td>Completed study treatment/intervention &amp; follow-up</td>
</tr>
<tr>
<td>Withdrew consent</td>
</tr>
<tr>
<td>Were planned for inclusion in a chart review (retrospective or prospective)</td>
</tr>
<tr>
<td>Were included in a chart review (retrospective or prospective)</td>
</tr>
</tbody>
</table>

6. Have all Serious Adverse Events (SAEs) experienced by a Sunnybrook participant been reported to the REB?  

☐ YES ☐ NO, will submit immediately ☐ NO SAEs have occurred

7. In the opinion of the PI, is there a concern or trend in the SAEs that have occurred with Sunnybrook participants?  

☐ YES ☒ NO ☐ NO SAEs have occurred

If YES, provide details and action taken.

8. Have all significant protocol deviations/violations been reported to the REB?  

☐ YES ☐ NO, will submit immediately ☒ NO significant deviations/violations to report

9. Since the last REB approval, is there any new ethical or scientific information outside of a protocol amendment that would be relevant to the continuing review of this study?  

☐ YES ☒ NO

If YES, provide details.

10. Since the last REB approval, is there any change in the conflict of interest information provided to the REB for any of the investigators, study staff or members of their immediate family?  

☐ YES ☒ NO

If YES, provide details.
11. Person completing this form.

<table>
<thead>
<tr>
<th>Title: Dr.</th>
<th>First Name: Sabrina</th>
<th>Last Name: Kolker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dept/Div:</td>
<td>Institution: Sunnybrook Hospital</td>
<td></td>
</tr>
<tr>
<td>Full Address: 993 Dovercourt Road</td>
<td>Room Number:</td>
<td></td>
</tr>
<tr>
<td>Telephone: 416 705 1375</td>
<td>Extension:</td>
<td></td>
</tr>
<tr>
<td>E-mail:</td>
<td><a href="mailto:sabrina.kolker@sunnybrook.ca">sabrina.kolker@sunnybrook.ca</a></td>
<td></td>
</tr>
</tbody>
</table>

12. Statement of Principal Investigator (PI).

I assume full responsibility for the scientific and ethical conduct of this study and agree to conduct this study in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Human Subjects (TCPS), Personal Health Information Protection Act (PHIPA) and any other relevant regulations or guidelines. I certify that all researchers and personnel involved in this study at this institution are appropriately qualified and trained to fulfill their role in this study.

[Signature]  
[Date: Apr 19, 2016]

Research Ethics Office Use Only

The Sunnybrook REB has reviewed the information provided and confirms that this study has obtained ethics approval by way of:

☒ [ ] Delegated Review

☐ [ ] Full Board Review — Date of Full Board meeting:

This study is only approved for the following period:

[ ] Jun 6, 2016 to Jun 6, 2017

[Signature]  
Chair/Vice-Chair, Research Ethics Board
Appendix D: Baseline and 1-Year Univariable Regression for Pain, Weight Concern and Time Participating in High Demand Activities with 1-Year KOOS-QOL

<table>
<thead>
<tr>
<th>Variable used in analysis</th>
<th>Baseline Unstandardized Beta (CI)</th>
<th>1-Year Unstandardized Beta (CI)</th>
<th>Correlation Between Baseline and 1-Year: ( r ) values</th>
<th>Variable used in analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>-0.49 (-0.69 - -0.28)</td>
<td>-1.11 (-1.34 - -0.88)</td>
<td>0.45</td>
<td>Change score</td>
</tr>
<tr>
<td>Weight Concern</td>
<td>-0.72 (-1.65 - 0.22)</td>
<td>-1.39 (-2.33 - -0.45)</td>
<td>0.72</td>
<td>Baseline Weight Concern</td>
</tr>
<tr>
<td>Times spent on high demand activities</td>
<td>-0.01 (-0.02-0.003)</td>
<td>0.03 (0.005-0.05)</td>
<td>0.33</td>
<td>Change Score</td>
</tr>
</tbody>
</table>
Appendix E: Multivariable Analyses of Baseline Variables Predicting 1-Year HRQoL

<table>
<thead>
<tr>
<th>Baseline Predictor Variables</th>
<th>Unstandardized Beta</th>
<th>Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL Strength</td>
<td>Not Available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL Laxity</td>
<td>Not Available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL Alignment</td>
<td>-0.38</td>
<td>-1.02-0.27</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Gender Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL Fear of Re-Injury</td>
<td>0.10</td>
<td>-0.05-0.26</td>
<td>0.20</td>
</tr>
<tr>
<td>BL Exercise Importance</td>
<td>0.03</td>
<td>-3.35-3.42</td>
<td>0.98</td>
</tr>
<tr>
<td>BL Commitment to Exercise</td>
<td>0.31</td>
<td>-0.92-1.54</td>
<td>0.62</td>
</tr>
<tr>
<td>BL Weight Concern</td>
<td>-0.37</td>
<td>-1.41-0.67</td>
<td>0.49</td>
</tr>
<tr>
<td>BL Time Spent on Household/Caregiving Activities</td>
<td>0.003</td>
<td>-0.01-0.01</td>
<td>0.57</td>
</tr>
<tr>
<td>BL Time spent on Low Demand/Walking Activities</td>
<td>0.002</td>
<td>-0.01-0.10</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Sex and Gender Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL BMI</td>
<td>-0.32</td>
<td>-1.31-0.67</td>
<td>0.53</td>
</tr>
<tr>
<td>BL Pain</td>
<td>0.16</td>
<td>-0.08-0.40</td>
<td>0.18</td>
</tr>
<tr>
<td>BL Physical Function</td>
<td>-0.02</td>
<td>-0.17-0.13</td>
<td>0.77</td>
</tr>
<tr>
<td>BL Time Spent in High Demand Activities</td>
<td>-0.02</td>
<td>-0.01-0.01</td>
<td>0.72</td>
</tr>
<tr>
<td>BL Mental Health</td>
<td>0.02</td>
<td>-0.16-0.20</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Covariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS-QOL Baseline</td>
<td>0.34</td>
<td>0.09-0.59</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Age</td>
<td>0.22</td>
<td>-0.32-0.76</td>
<td>0.42</td>
</tr>
</tbody>
</table>

BL = Baseline
R² = 0.29
BOLD indicates significance p<0.05
Appendix F: Multivariable Analyses of 1-Year Variables Predicting 1-Year HRQoL

<table>
<thead>
<tr>
<th>1-Year Predictor Variables</th>
<th>Unstandardized Beta</th>
<th>Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year Strength</td>
<td>0.01</td>
<td>0.001-0.02</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>1-Year Laxity</td>
<td>-3.37</td>
<td>-8.35-1.61</td>
<td>0.18</td>
</tr>
<tr>
<td>Alignment</td>
<td>Not Available</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year Fear of Re-Injury</td>
<td>-0.02</td>
<td>-0.09-0.05</td>
<td>0.52</td>
</tr>
<tr>
<td>1-Year Exercise Importance</td>
<td>0.36</td>
<td>-1.84-2.56</td>
<td>0.75</td>
</tr>
<tr>
<td>1-Year Commitment to Exercise</td>
<td>0.52</td>
<td>-0.34-1.39</td>
<td>0.23</td>
</tr>
<tr>
<td>1-Year Weight Concern</td>
<td>-1.08</td>
<td>-1.85-0.32</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>1-Year Time Spent on Household/Caregiving Activities</td>
<td>-0.003</td>
<td>-0.01-0.01</td>
<td>0.53</td>
</tr>
<tr>
<td>1-Year Time spent on Low Demand/Walking Activities</td>
<td>0.003</td>
<td>-0.003-0.01</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Sex and Gender Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year BMI</td>
<td>0.63</td>
<td>-0.13-1.39</td>
<td>0.10</td>
</tr>
<tr>
<td>1-Year Pain</td>
<td>0.87</td>
<td>0.65-1.09</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>1-Year Physical Function</td>
<td>0.23</td>
<td>0.07-0.40</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>1-Year Time Spent in High Demand Activities</td>
<td>0.01</td>
<td>-0.01-0.02</td>
<td>0.42</td>
</tr>
<tr>
<td>1-Year Mental Health</td>
<td>-0.04</td>
<td>-0.20-0.12</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Covariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS-QOL Baseline</td>
<td>0.38</td>
<td>0.24-0.52</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Age</td>
<td>0.33</td>
<td>-0.06-0.73</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**R² = 0.69**

**BOLD indicates significance**
CHAPTER 6: REFERENCES

31. Stijak L, Radonjic V, Nikolic V, Blagojevic Z, Aksic M, Flipovic B. Correlation between the morphometric parameters of the anterior cruciate ligament and the


176. Petsching R, Baron R, Albrecht M. The relationship between isokinetic quadriceps strength test and hop tests for distance and one legged vertical jump test


320. Van Vollenhoven R. Sex differences in rheumatoid arthritis: more than meets the eye. BMC Health Serv Res. 2009;7:12.


Consideration of Sex as a Biological Variable in NIH- Funded Research [Internet]. 2015. NOT-OD-15-102; June 9, 2015


Schiebinger L, STefanik M. Gender Matters in Biological Research and Medical Practice. Journal of the American College of Cardiology. 2016;67(2).


