Measurement of illness perception and behaviour along a continuum of symptomatic knee osteoarthritis: a transdisciplinary approach

Clayon B. Hamilton
The University of Western Ontario

Supervisor
Dr. Bert M. Chesworth
The University of Western Ontario

Graduate Program in Health and Rehabilitation Sciences

A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

© Clayon B. Hamilton 2015
Measurement of illness perception and behaviour along a continuum of symptomatic knee osteoarthritis: a transdisciplinary approach

(Thesis format: Integrated Article)

by

Clayon B. Hamilton

Graduate Program in Health and Rehabilitation Sciences

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Health and Rehabilitation Sciences

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

© Clayon B. Hamilton 2015
Abstract

Objectives: A multifactorial approach is recommended for the identification/diagnosis, prognosis, and treatment of pain in knee osteoarthritis (OA). One aspect of this approach includes illness perception and behaviour. The purpose of this thesis was to investigate the measurement of illness perception and behaviour along a continuum of symptomatic knee OA, starting from the early symptoms of knee OA.

Methods: Three studies were conducted to fulfill this purpose. The first study was a scoping review that applied an interpretative analysis to validated measures that had been used to assess people with knee pain and/or knee OA. Second was the construct validation of a measure of illness perception and behaviour in people with early symptoms of knee OA and confirmed knee OA. Third was a study of a rat model of post-traumatic knee OA that was undertaken to identify behavioural measures that were significantly different between rats with and without knee OA.

Results: The scoping review identified 16 validated measures that capture components of illness perception and behaviour. Only one measure, the Questionnaire to Identify Knee Symptoms (QuIKS), capture all four components of illness perception and behaviour. In the second study, a version of the QuIKS called the QuIKS-R was found to be unidimensional and to provide interval-level scaling of illness perception and behaviour. In the third study, ipsilateral weight-bearing deficit and vertical activity limitations were identified as two behavioural measures that differed between the rat model of post-traumatic knee OA and control groups.

Conclusions: The three studies in this thesis identified measures that could be important in advancing the identification and care of people with symptoms of knee OA, in terms of clinical care, clinical research with humans and preclinical research with the rat model of post-traumatic knee OA.
Keywords

illness behaviour, knee osteoarthritis, knee pain, outcome assessment, screening, validation
Co-Authorship Statement

Chapter 2 was co-authored by Ming-Kin Wong, Monique A.M. Gignac, Aileen M. Davis, and Bert M. Chesworth. Ming-Kin Wong collaborated on the study design, data collection, and data analysis. Monique A.M. Gignac, Aileen M. Davis, and Bert M. Chesworth participated in the manuscript preparation and submission.

Chapter 3 was co-authored by Monica R. Maly, J. Robert Giffin, Jessica M. Clark, Mark Speechley, Robert J. Petrella, and Bert M. Chesworth. Bert M. Chesworth participated in the data analysis. J. Robert Giffin and Bert M. Chesworth participated in study data collection. All co-authors participated in the study design, and manuscript preparation and submission.

Chapter 4 was co-authored by Micheal A. Pest, Vasek Pitelka, Anusha Ratneswaran, Frank Beier, and Bert M. Chesworth. Vasek Pitelka performed the osteoarthritis induction surgeries on the rats. Micheal A. Pest and Anusha Ratneswaran participated in the histology data collection. Michael A. Pest participated in the histology data analysis. All authors participated in the study design, and manuscript preparation and submission.
Dedication

To my mommy, Consie Hamilton (née Dockery), who through her many sacrifices, hard-work, and love, inspired my desire to attain a good education. To my son, Ceyon Hamilton, and my daughter, Candice Hamilton who I love.

Labor for learning before you grow old
For learning is better than silver or gold
   Silver and gold will vanish away
But a good education will never decay.

A Jamaican poem by an anonymous author
Acknowledgements

Thanks to Dr. Bert Chesworth, my PhD supervisor, who has been a cornerstone in my pursuit of this degree. I am very thankful to have been under his tutelage. Dr. Chesworth’s generosity gave me motivation to persevere through to the completion of my PhD.

I would like to thank my advisory committee members: Dr. Monica Maly, Dr. Frank Beier, and Dr. Aileen Davis. They have mentored, sponsored, and collaborated with me. I feel very privileged to have had the opportunity to be endorsed and guided by them, all of whom rank among the best scientists in their fields and are truly awesome people to know. I look forward to working with them in the future as my ideas mature and my research skills and success as a health scientist blossom.

I am very grateful for the contributions of all my co-authors who collaborated with me in this process of contributing to science with my PhD research. It was an awesome experience to have had the opportunity to work with basic scientists, orthopaedic surgeons, physical therapists, clinical epidemiologists, physical therapy students, and an undergraduate student. I want to thank the surgeons’ assistants at Fowler Kennedy Sport Medicine Clinic who assisted with data collection.

Thank you to all the participants for volunteering and providing their experiences. I hope that your contributions will help to make a positive change to the health of many.

Thank you to the funding agencies and scholarship programs that have supported me: the Canadian Institute of Health Research (CIHR), the Joint Motion Program- a CIHR training program in Musculoskeletal Health Research and Leadership, and the University of Western Ontario. I am especially grateful to the Joint Motion Program and the people behind it that are driving the support and development of leaders in musculoskeletal health research.
Table of Contents

Abstract .................................................................................................................................................. ii
Co-Authorship Statement ................................................................................................................... iv
Dedication ............................................................................................................................................... v
Acknowledgements ............................................................................................................................ vi
Table of Contents ................................................................................................................................ vii
List of Tables ........................................................................................................................................ xi
List of Figures ....................................................................................................................................... xii
List of Appendices ............................................................................................................................. xiii
List of Abbreviations ........................................................................................................................... xiv
Chapter 1 ............................................................................................................................................... 1
  1.1 Knee OA ........................................................................................................................................ 1
  1.2 Impact and management of knee OA in Canada ..................................................................... 3
  1.3 Assessment of symptomatic knee OA ................................................................................... 4
  1.4 Lived experience with symptomatic knee OA ................................................................. 4
  1.5 Measures of illness perception and behaviour .............................................................. 5
  1.6 Rodent models in knee OA research .................................................................................. 6
  1.7 Overarching Objective ...................................................................................................... 8
  1.8 Research plan ....................................................................................................................... 8
  1.9 References ............................................................................................................................ 10
Chapter 2 ........................................................................................................................................... 16
  2.1 Abstract ...................................................................................................................................... 16
  2.2 Introduction ............................................................................................................................ 17
  2.3 Validated measures of illness perception and behaviour .................................................. 17
  2.4 Impact and management of knee OA in Canada ............................................................. 18
  2.5 Assessment of symptomatic knee OA ............................................................................. 19
  2.6 Lived experience with symptomatic knee OA ............................................................... 19
  2.7 Measures of illness perception and behaviour ............................................................... 20
  2.8 Rodent models in knee OA research ................................................................................ 20
  2.9 Overarching Objective ...................................................................................................... 21
  2.10 Research plan ..................................................................................................................... 21
  2.11 References ........................................................................................................................... 23
Chapter 3 ............................................................................................................................................ 25
  3.1 Knee OA .................................................................................................................................... 25
  3.2 Impact and management of knee OA in Canada ............................................................. 26
  3.3 Assessment of symptomatic knee OA ............................................................................. 27
  3.4 Lived experience with symptomatic knee OA ............................................................... 27
  3.5 Measures of illness perception and behaviour ............................................................... 28
  3.6 Rodent models in knee OA research ................................................................................ 28
  3.7 Overarching Objective ...................................................................................................... 29
  3.8 Research plan ....................................................................................................................... 29
  3.9 References ............................................................................................................................ 31
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4.6</td>
<td>Convergent validity</td>
<td>97</td>
</tr>
<tr>
<td>3.5</td>
<td>Discussion</td>
<td>98</td>
</tr>
<tr>
<td>3.6</td>
<td>Limitations and future research</td>
<td>100</td>
</tr>
<tr>
<td>3.7</td>
<td>Conclusions</td>
<td>101</td>
</tr>
<tr>
<td>3.8</td>
<td>References</td>
<td>102</td>
</tr>
<tr>
<td>4</td>
<td>Behavioural measures in a rat model of post-traumatic knee OA</td>
<td>106</td>
</tr>
<tr>
<td>4.1</td>
<td>Abstract</td>
<td>106</td>
</tr>
<tr>
<td>4.2</td>
<td>Introduction</td>
<td>108</td>
</tr>
<tr>
<td>4.3</td>
<td>Methods</td>
<td>110</td>
</tr>
<tr>
<td>4.3.1</td>
<td>Animals</td>
<td>110</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Study design</td>
<td>110</td>
</tr>
<tr>
<td>4.3.3</td>
<td>ACLT + pMMx-induced OA</td>
<td>112</td>
</tr>
<tr>
<td>4.3.4</td>
<td>Structural joint changes</td>
<td>112</td>
</tr>
<tr>
<td>4.3.5</td>
<td>Static weight-bearing</td>
<td>113</td>
</tr>
<tr>
<td>4.3.6</td>
<td>General exploratory motor behaviour</td>
<td>115</td>
</tr>
<tr>
<td>4.3.7</td>
<td>Statistical analysis</td>
<td>119</td>
</tr>
<tr>
<td>4.3.8</td>
<td>Analysis of static weight-bearing</td>
<td>119</td>
</tr>
<tr>
<td>4.3.9</td>
<td>Analysis of exploratory motor behaviour</td>
<td>120</td>
</tr>
<tr>
<td>4.4</td>
<td>Results</td>
<td>120</td>
</tr>
<tr>
<td>4.4.1</td>
<td>Animal characteristics</td>
<td>120</td>
</tr>
<tr>
<td>4.4.2</td>
<td>Structural changes of the joint</td>
<td>121</td>
</tr>
<tr>
<td>4.4.3</td>
<td>The ACLT + pMMx animals demonstrated less ipsilateral static weight-bearing</td>
<td>123</td>
</tr>
<tr>
<td>4.4.4</td>
<td>ACLT+pMMx animals performed less rearing in exploratory motor behaviour testing</td>
<td>125</td>
</tr>
<tr>
<td>4.5</td>
<td>Discussion</td>
<td>128</td>
</tr>
</tbody>
</table>
List of Tables

Table 2.1 Sixteen validated measures that capture components of illness perception and behaviour................................................................. 31

Table 2.2 Summary of publications that used the identified measures................................. 42

Table 3.1 Sample characteristics by study groups .......................................................... 87

Table 3.2 Results from factor analysis using Horn’s parallel analysis............................... 89

Table 3.3 Summary fit statistics from Rasch analysis..................................................... 91

Table 4.1: Repeated Measures ANOVA results for variables of exploratory motor behaviour ................................................................................................................................. 117

Table 4.2: Repeated Measures ANOVA post-hoc testing results for exploratory motor behaviour................................................................................................................................. 127
List of Figures

Figure 2.1 Flow chart of study inclusion and exclusion ............................................................... 29

Figure 2.2 Chart showing the frequency of the four components of illness perception and
behaviour among the charted validated measures as used in the publications. ................. 35

Figure 3.1 Category probability curves of one item from the modifying subscale. .............. 94

Figure 3.2 Fitting persons and items threshold distribution on the same logit scale .......... 96

Figure 4.1: Schematic of experimental protocol ..................................................................... 111

Figure 4.2: Incapacitance Tester. This instrument was used to assess static weight-bearing.
............................................................................................................................................... 114

Figure 4.3: Open-field Tester. Instrument used to capture exploratory motor behaviour. ... 116

Figure 4.4: Evidence of OA in ACLT + pMMx operated rats as shown by histology ...... 122

Figure 4.5: Percent ipsilateral weight-bearing between rat groups ................................. 124

Figure 4.6: Vertical episode count differed between rat groups ....................................... 126

Figure 4.7: No evidence of OA found in the lateral knee joint compartments of ACLT +
pMMx operated rats .............................................................................................................. 132
List of Appendices

Appendix A Questionnaire to Identify Knee Symptoms (QuIKS)-R ........................................... 145

Appendix B Ethics board approval for Chapter 3 ............................................................................ 148

Appendix C Institutional ethics board approval for Chapter 3 .......................................................... 149
## 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>ACLT + pMMx</td>
<td>ACL transection with partial medial meniscectomy</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ASES</td>
<td>Arthritis Self-Efficacy Scale</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CFI</td>
<td>Comparative Fit Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>COPE</td>
<td>Coping Orientation to Problems Experiences inventory</td>
</tr>
<tr>
<td>CPCI</td>
<td>Chronic Pain Coping Inventory</td>
</tr>
<tr>
<td>CSI</td>
<td>Coping Strategies Inventory</td>
</tr>
<tr>
<td>CSQ</td>
<td>Coping Strategies Questionnaire</td>
</tr>
<tr>
<td>DCI</td>
<td>Daily Coping Inventory</td>
</tr>
<tr>
<td>DIF</td>
<td>Differential Item Functioning</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>European Quality of Life 5 Dimensions</td>
</tr>
<tr>
<td>FABQ</td>
<td>Fear Avoidance Beliefs Questionnaire</td>
</tr>
<tr>
<td>HK</td>
<td>Pain-free healthy knees</td>
</tr>
<tr>
<td>Keefe’s method</td>
<td>Keefe’s Pain Behavior Observation Protocol</td>
</tr>
<tr>
<td>KOFBeQ</td>
<td>Knee Osteoarthritis Fears and Beliefs Questionnaire</td>
</tr>
<tr>
<td>KOOS</td>
<td>Knee injury and Osteoarthritis Outcome Score</td>
</tr>
<tr>
<td>KP</td>
<td>Knee pain with no knee OA diagnosis</td>
</tr>
<tr>
<td>IPQ</td>
<td>Illness Perceptions Questionnaire</td>
</tr>
<tr>
<td>IPQ-R</td>
<td>Illness Perceptions Questionnaire-Revised</td>
</tr>
<tr>
<td>MFC</td>
<td>Medial Femoral Condyle</td>
</tr>
<tr>
<td>MTP</td>
<td>Medial Tibial Plateau</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>PASE</td>
<td>Physical Activity Scale for the Elderly</td>
</tr>
<tr>
<td>PBOICIE</td>
<td>Pain Behaviors for Osteoarthritis Instrument for Cognitively Impaired Elders</td>
</tr>
<tr>
<td>PCI</td>
<td>Pain-Coping Inventory</td>
</tr>
<tr>
<td>PCS</td>
<td>Pain Catastrophizing Scale</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>pre-HTO</td>
<td>Scheduled for high tibial osteotomy</td>
</tr>
<tr>
<td>PSI</td>
<td>Person Separation Index</td>
</tr>
<tr>
<td>QuIKS</td>
<td>Questionnaire to Identify Knee Symptoms</td>
</tr>
<tr>
<td>QuIKS-R</td>
<td>Rasch-refined Questionnaire to Identify Knee Symptoms</td>
</tr>
<tr>
<td>( r )</td>
<td>Effect size – Mann Whitney U test</td>
</tr>
<tr>
<td>RMSEA</td>
<td>Root-mean-square error of approximation</td>
</tr>
<tr>
<td>( r_s )</td>
<td>Spearman’s rank correlation coefficient</td>
</tr>
<tr>
<td>SOPA</td>
<td>Survey of Pain Attitudes</td>
</tr>
<tr>
<td>TKR</td>
<td>Total Knee Replacement</td>
</tr>
<tr>
<td>TLI</td>
<td>Tucker-Lewis index</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WAYS</td>
<td>Ways of Coping Scale</td>
</tr>
<tr>
<td>( \chi^2 )</td>
<td>Chi-square</td>
</tr>
</tbody>
</table>
Chapter 1

1 General Introduction

At the foundation of this thesis is the quest for a deeper understanding of the measurement of ‘illness perception and behaviour’ in the experience of symptomatic knee osteoarthritis (OA). According to Petri et al. (2007; p. 163), illness perception as a unique concept can be defined as “the organized cognitive representations or beliefs that patients [or people] have about their illness”.\textsuperscript{1} In general, behaviours are the internally coordinated responses (action or inaction) to internal or external stimuli, with the exclusion of developmental changes.\textsuperscript{2} In contrast, ‘illness perception and behaviour’ is used as a unified concept in this thesis by applying Mechanic’s (1986; p. 1) definition of illness behaviour, which states that “it [illness behaviour] refers to the manner in which individuals monitor their bodies, define and interpret their symptoms, take remedial action, and utilize sources of help as well as the more formal health care system”.\textsuperscript{3}

In this thesis, a transdisciplinary approach was used to study the assessment of illness perception and behaviour along a continuum of symptomatic knee OA. This means the dissertation is comprised of both human and animal studies.

1.1 Knee OA

The knees are among the most common sites of OA. Knee OA is usually debilitating, is characterized by joint deterioration at the level of the articular cartilage as part of the wider disruption of the biology of the whole joint, and can result in varied levels of pain in and/or around the knee, loss of physical functioning, activity limitations, participation restrictions, psychological distress, and reduced quality of life.\textsuperscript{4-6} Recently, the Osteoarthritis Research Society International (OARSI) proposed a standardized definition of OA that reads, “Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity.
The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.\textsuperscript{7, 8}

Knee pain is a reliable indicator of symptomatic knee OA, even when OA-related structural changes of the joint are not present on plain radiographs.\textsuperscript{5, 6, 9, 10} While knee pain is an integral part of the clinical diagnosis of symptomatic knee OA in people aged 40 years and over,\textsuperscript{9, 11} it should be recognized that there is a discordance between the presence of knee pain and radiographic knee OA.\textsuperscript{12, 13} One review found that 15\% to 76\% of people with knee pain had radiographic knee OA, whereas 15\% to 81\% of people with radiographic knee OA had knee pain.\textsuperscript{12} Also, the prevalence of symptomatic knee OA is generally lower than its radiographic counterpart, and the definition of symptomatic knee OA affects estimates of its prevalence.\textsuperscript{9, 14}

The prevalence of symptomatic knee OA varies around the world. The crude prevalence estimates fall between 5.4\% and 24.2\% in adult populations, and prevalence rates are highest in older age groups.\textsuperscript{14} In general, over 10\% but fewer than 25\% of people aged 50 years or more have been reported to have symptomatic knee OA.\textsuperscript{14} For example, in the United States of America (US), symptomatic knee OA is reported to affect about 10\% of men and 13\% of women aged 60 years or more.\textsuperscript{5} Another US study showed that the prevalence of both knee pain and symptomatic knee OA has been on the rise, increasing twofold or more from 1983 through 2005 in a community cohort of people aged over 70 years.\textsuperscript{15} Subsequently, data from a 2007 to 2008 nationwide survey in the US estimated a 13.8\% lifetime risk for symptomatic knee OA in people aged 25 years or more.\textsuperscript{16} Furthermore, the estimated lifetime risk was as low as 0.7\% for non-obese men aged 25 years to 34 years and rose to 32.4\% for obese women aged 85 years or more.
1.2 Impact and management of knee OA in Canada

In Canada, 13% (4.4 million) of the population aged 15 years or more had OA in 2010 with a forecasted increase to 22.9% by 2032.\textsuperscript{17} It has been estimated that $488 billion dollars could potentially be saved in the direct and indirect costs of OA between 2010 and 2040 if adequate pain management strategies for OA are implemented.\textsuperscript{17} Knee OA has had a substantial financial burden on individuals and society. For example, $398 million dollars were spent on acute care during hospitalization for unilateral knee replacements in 2012-2013, making it by far the most costly intervention in Canada for that year.\textsuperscript{18} Accordingly, in the year 2013 to 2014, knee OA was the fifth highest reason for hospitalization, in terms of volume and average length of stay, in Canada.\textsuperscript{19}

No cure currently exists for knee OA.\textsuperscript{20} However, important strategies for combatting symptomatic knee OA include early recognition and application of self-management techniques, and clinical intervention strategies such as exercise, patient education and weight-loss.\textsuperscript{21-29} In line with established clinical guidelines, knee OA is typically treated with various types of conservative treatments, pharmacotherapies, and surgical modalities that are focused on relieving knee pain and discomfort, augmenting functional capacity, maintaining and improving physical activity levels, and thus on improving quality of life.\textsuperscript{21-29}

When less invasive and aggressive therapies fail to resolve the ill-effects of knee OA, total knee replacement (TKR) has become the standard approach for treating end-stage knee OA.\textsuperscript{21-30} Between 2013 and 2014, a total of 59,388 knee replacement surgeries were performed in Canada, which constituted the second most frequently performed surgical intervention in the country, second only to caesarean section.\textsuperscript{19} In that same year, 97.1% of all TKRs were for treating knee OA.\textsuperscript{31} Additionally, compared to five years earlier, 8.5% more total joint replacements were performed, which constituted a 14.8% to 16.0% increase in TKRs among people aged 45 to 64 years, whilst TKR remained most prevalent among those between 65 and 84 years of age.\textsuperscript{31} Yet one Canadian study found that 14% to 28% of people who received primary TKR in Ontario were not satisfied with pain relief and 16% to 30% were not satisfied with their level of function.\textsuperscript{32} Also, one study found a little over 1% to about 7% of artificial knee joints did not survive beyond 10 years.\textsuperscript{33} This raises concerns,
especially given the increase in younger people having the procedure, and the current trend in greater life expectancy and population age in Canada.\textsuperscript{31, 34} The preceding facts reflect the need to implement strategies to detect and manage symptomatic knee OA earlier in primary care practice and in community settings in order to delay or prevent the need for knee replacement surgeries.

### 1.3 Assessment of symptomatic knee OA

It is imperative that symptomatic knee OA is recognized during its early stages, if appropriate primary care interventions are to be effectively utilized. Kittelson et al. (2014) shared their perspective that the future of diagnosis, prognosis and treatment of symptomatic knee OA rests on leveraging the equitable contribution of knee joint pathology, pain neurophysiology, and psychological distress to the phenotypes of pain in knee OA.\textsuperscript{35} Imaging technologies are the standard measures for diagnosing knee OA.\textsuperscript{6, 36} While imaging technologies focus on structural changes at the joint, pain and disability are among the main reasons people with knee OA seek care.\textsuperscript{37} The measurement of knee pain and physical, psychological, and social functioning factors related to knee OA are usually subjective and require self-reporting by the affected individual.\textsuperscript{38-40} Psychological distress (cognitive, psychosocial, and behavioural factors) plays an integral role in the recognition/diagnosis and treatment of symptomatic knee OA, and is consistent with what individuals report about their lived experiences with knee pain/OA.\textsuperscript{41-44}

### 1.4 Lived experience with symptomatic knee OA

During the last decade, several qualitative studies have made important contributions to our understanding of the lived experiences of people with knee pain/OA.\textsuperscript{41-44} A systematic review of qualitative studies on people with OA, with a majority having knee OA, showed that people’s attitudes were influenced by how severe their OA symptoms were, whether their level of function was affected, how much they knew about the disease, and how they perceived others viewed their condition.\textsuperscript{42} Among these people, an overarching theme was
that their decision to seek professional diagnosis was delayed while they self-managed their condition and gathered information through informal rather than formal sources.\textsuperscript{42} Diagnosis was not sought until people reached a critical point. Even then, self-management continued until there was an ‘inevitable’ need for knee joint replacement.\textsuperscript{43} A qualitative meta-synthesis found that the decision to undergo TKR was shaped by one’s experience with pain, the perceived role of health professionals, thoughts on the treatment options and outcomes, the perceived cause of the condition, and social context.\textsuperscript{41} Subsequently, post-surgery recovery outcomes, both short and long term, were thought to be determined by one’s life context and coping strategies.\textsuperscript{41}

In the context of people living in Canada with mild-to-moderate symptomatic knee OA or knee OA-like pain, their attitudes, behaviours, beliefs, intentions, and perceptions are related to how their knee symptoms shape their lived experience.\textsuperscript{45-49} These contextual factors have been implicated in the negative effects of the early symptoms of knee OA, effect such as decreased engagement in meaningful physical activity and social roles, and deteriorated emotional wellbeing.\textsuperscript{45-49} Furthermore, contextual factors were implicated in the evaluation of one’s own health, the search for information, the implementation of self-management strategies, the seeking of lay-person and professional care provider support through interpersonal interactions and for conservative treatment, and finally the seemingly inevitable decision for surgery.\textsuperscript{45-49}

1.5 Measures of illness perception and behaviour

Illness perception and behaviour has been operationalized in many measures that have been used to assess attitudes, behaviours, beliefs, coping strategies, and perceptions related to illness in people with various medical conditions.\textsuperscript{1, 50, 51} Consistent across the studies of its conceptualization and operationalization, is the message of the importance of illness perception and behaviour in the recognition and management of medical conditions, and the demonstration of it having significant associations with physical and psychological adjustments to medical conditions.\textsuperscript{3, 50-52} The measurement of illness perception and behaviour as it relates to knee symptoms could be critical for the implementation of
professional-guided conservative management strategies in early symptomatic knee OA.\textsuperscript{49, 53} For example, one study successfully used ‘illness behaviour’ as the first filter in a model that identified people with hip or knee pain problems within the community who have OA and utilized health care.\textsuperscript{54, 55} Self-report questionnaires such as the Arthritis Self-Efficacy Scale (ASES) have measured the beliefs of people with symptomatic knee OA regarding their ability to manage their pain, the presence of other symptoms, and the performance of certain physical functions.\textsuperscript{56, 57} These beliefs have been important outcomes associated with pain and the level of physical function of people with symptomatic knee OA who participated in various arthritis self-management programs.\textsuperscript{56, 57}

Some questions about the development, progression and treatment of knee OA are too challenging to be conducted using humans due to the cost and time required to monitor people over many years. Using an animal model provides experimental control over the induction of OA with varying degrees of severity and also provides more certainty around the establishment of mild-to-moderate OA structural changes in relatively short timelines. Furthermore, animal samples can be controlled to have high levels of biological homogeneity. These characteristics make animal models attractive for studying the measurement of the joint pathological and the pain neurophysiological aspects of OA, as well as the measurement of the psychological-related components of OA such as changes in behaviour.

### 1.6 Rodent models in knee OA research

Rodent models are commonly used as surrogates for the study of knee OA in humans.\textsuperscript{58} They allow for the experimental study of knee OA in ways that would normally be considered unethical, even impossible in human beings, such as the induction of disease and sacrifice after a therapeutic intervention.\textsuperscript{59} There are several rodent models of knee OA that are based mostly on methods of chemical induction (e.g. mono-sodium iodoacetate) or surgical induction (e.g. anterior cruciate ligament transection).\textsuperscript{58} The surgically-induced rodent models are particularly relevant to the study of post-traumatic knee OA.\textsuperscript{58}
In humans, an anterior cruciate ligament (ACL) tear increases the risk of symptomatic knee OA, with up to 80% of people developing radiographic knee OA and up to 46% developing symptomatic knee OA within 10 to 15 years.\textsuperscript{60-62} People with ACL reconstruction and meniscectomy are more likely to have knee OA than people with ACL reconstruction and a normal meniscus.\textsuperscript{60, 63} Furthermore, there is no convincing evidence that surgical interventions for knee joint injury protect against future knee OA.\textsuperscript{64} Rat models of knee OA that were created through destabilizing the knee joint using ACL transection and meniscectomy have been reported to demonstrate structural joint changes characteristic of knee OA within as little as two weeks after the operation.\textsuperscript{65} Thus, the knee OA pathology and its response to therapy can be studied in a relatively short period of time and without injury to humans.

While pain and disability in humans with knee OA are typically assessed using self-reports and performance-based measures, the histology of joint changes and reflexes evoked by sensory stimuli are usually the primary outcome measures in preclinical rodent models of knee OA.\textsuperscript{39, 66-68} This difference in measuring the effectiveness of therapies challenges the translation of preclinical research to clinical settings, because important components of the phenotype of the condition are not accounted for when evaluating the outcomes of preclinical rodent research.\textsuperscript{67, 69} Behavioural measures of pain in rodent models of knee OA provide a closer and more realistic measure of clinical pain.\textsuperscript{58, 69-72} Therefore, including assessments of behavioural changes, such as changes in physical activity, in preclinical rodent models of knee OA could provide information comparable to self-report or observational methods of illness response in humans.\textsuperscript{67, 69} To fill this gap, the assessment of behavioural alterations such as changes in physical activities, possibly brought on by movement-induced pain, are becoming more of an integral part of assessing the outcomes of experiments using rodent models of knee OA.\textsuperscript{58, 69-73} These behavioural outcomes include measures such as changes in gait, weight-bearing symmetry, and locomotor activity.\textsuperscript{58, 69-73} The inclusion of these measures better account for the complexity that forms the experience of having knee OA. Furthermore, the inclusion of behavioural measures as outcomes in research using rodent models of knee OA is thought to increase the validity of the models.\textsuperscript{69}
1.7 Overarching Objective

Illness perception and behaviour is an important aspect of the lived experience of people with symptomatic knee OA. If properly measured, illness perception and behaviour could help in providing more well-rounded descriptions of an individual with knee pain/OA condition for informing the individual’s therapy. Therefore, the overarching objective of this thesis was to identify measures of illness perception and behaviour used with people that are on a continuum of symptomatic knee OA with a greater emphasis on emergent and early stages of symptomatic knee OA. Also, my transdisciplinary approach sought to identify measures of behaviour in a preclinical rat model of knee OA with joint pathology characteristic of mild-to-moderate knee OA.

1.8 Research plan

A systematic synthesis of the research literature that documents validated measures of illness perception and behaviour in people with knee pain/OA does not exist. Undertaking such a study was considered to be a valuable first step in assessing the need for a measure that captures the illness perception and behaviour of people with emergent or early symptomatic knee OA. It is expected that a measure of illness perception and behaviour could be integral in the recognition of people as members of this population during primary care consultation or in the community and later in the selection of appropriate treatment protocols. Beyond synthesizing the research literature on these measures, an interpretive approach was planned as a part of the methodology of the review. This was planned in order to understand how comprehensively the measures assess illness perception and behaviour.

As a natural extension to the findings of the systematic synthesis, a psychometric evaluation was planned for the Questionnaire to Identify Knee Symptoms (QuIKS) to strengthen its value as an assessment measure of illness perception and behaviour for use to identify people who are experiencing some symptoms consistent with knee OA. This second study was needed to raise its scaling to an interval-level as recommended as a part of the development and validation of measurement methods. In this second study, plans were
made to provide preliminary interpretation of the QuIKS’s interval-level scale using a known-group analysis of people along a continuum of symptomatic knee OA.

The third and final study was planned as a contribution to the development of a more robust rat model of knee OA that integrates behavioural alteration due to knee OA as a component of the model. The plan was to investigate certain behaviours that are an integral part of the human experience of knee OA for their possible use as outcome measures that could be routinely included in studies using a preclinical rat model of post-traumatic knee OA.

The three studies are presented in the next three chapters. Chapter two is a scoping review of validated measures that were interpreted as assessors of illness perception and behaviour in people with knee pain/OA. Chapter three is a version of the QuIKS that provides interval-level scaling for the measurement of illness perception and behaviour for people along a continuum of symptomatic knee OA. Chapter four provides behavioural measures that can form a part of routine outcome measurement in a surgically-induced rat model of post-traumatic knee OA. The final chapter of the thesis provides a discussion of the totality of the research conducted including implications for management for people with knee OA and future research directions.
1.9 References


71. Suokas AK, Sagar DR, Mapp PI, Chapman V, Walsh DA. Design, study quality and evidence of analgesic efficacy in studies of drugs in models of OA pain: a systematic review and a meta-analysis. Osteoarthritis and Cartilage;22(9):1207-23.


Chapter 2

2 Validated measures of illness perception and behaviour

_A version of this chapter is presently under review for publication in a peer-reviewed journal._

2.1 Abstract

**Objective:** To identify validated measures that capture illness perception and behavior and have been used to assess people who have knee pain/osteoarthritis (OA).

**Methods:** A scoping review was performed. Nine electronic databases were searched for records from inception through April 19, 2015. Search terms included illness perception and behavior, knee, pain, osteoarthritis, and their related terms. This review included English language publications of primary data on people with knee pain/OA assessed with validated measures capturing any of four components of illness perception and behavior: _monitor body, define and interpret symptoms, take remedial action, and utilize sources of help_. Initially, one reviewer screened the titles and abstracts of 11,151 publications. Then, two reviewers independently screened the full-text of 153 publications. Subsequently, 71 publications were analyzed. Two reviewers independently charted and coded the measures into the four components.

**Results:** Sixteen measures were identified that capture components of illness perception and behavior in the target population. Coding results indicated that 31, 69, 75 and 31 percent of these measures included the _monitor body, define and interpret symptoms, take remedial action, and utilize sources of help_ components, respectively.

**Conclusions:** Several validated measures were interpreted as capturing some components, and only one measure was interpreted as capturing all of the components of illness perception and behavior in the target population. A measure that comprehensively captures illness perception and behavior could be valuable for informing and evaluating therapy for patients along a continuum of symptomatic knee OA.
2.2 Introduction

Thirteen percent of Canadians had OA in 2010, with a projected increase to 22.9% by 2032.\(^1\) In the United States (US), the estimated lifetime risk of developing symptomatic knee OA is 13.8% for adults aged 25 years and more.\(^2\) People with knee pain and knee OA represent a large and growing global population of people with disability.\(^3,4\) Accordingly, knee OA is the leading cause of chronic disability among community-dwelling older adults, primarily due to knee pain.\(^5,6\) Furthermore, people with symptomatic knee OA may have substantial inter-individual variation in their illness response, such as seeking care and taking medication.\(^7,8\)

A number of theories and models from the behavioural and social sciences identify concepts that are relevant to the ways that individuals with health conditions appraise, evaluate, perceive and respond to illness.\(^9-16\) They include theories related broadly to stress, coping and adaptation; theories that discuss individual differences or personality and its relationship to illness responses, as well as biopsychosocial frameworks or theories that are specific to managing diseases, illnesses or other health problems.\(^9-16\) For example, Mechanic (1986: p.1) defined illness behaviour as “the manner in which persons monitor their bodies, define and interpret their symptoms, take remedial action, and utilize various sources of help including the formal health-care system”.\(^17\) Research on illness perception and behaviour is scattered and segmented in the medical literature, covering concepts such as appraisals, perceptions, coping strategies, care-seeking behaviour, sick roles, and personal difference factors.\(^18-20\) The broad concepts surrounding illness responses fit with the contemporary biopsychosocial framework, which views illness as a complex relationship between biomedical and psychosocial factors.\(^16,20,21\)

Three main models of illness contributed to our understanding of illness perception and behaviour as it applies to knee pain/OA. First is the model of illness behaviour.\(^14\) This model describes different phases in order to explain an individual’s decision-making when seeking relief during illness. These include the recognition, appraisal and labeling of an illness; evaluating the meaning and significance of the illness; responses to health problems such as seeking out and assessing treatment options and weighing the benefits and costs of treatment; and illness management responses or behaviours like selecting and adhering to a
treatment plan. Finally, any new information or health changes are re-evaluated, making the model cyclical as an individual may return to some of the previous phases.\textsuperscript{14}

Second is the common-sense model of illness representation (or Leventhal’s self-regulatory model of illness behaviour).\textsuperscript{16,22} It has several parallels with the model of illness behaviour. For example, both models describe the role of illness history and the somatic self in determining how information about an illness is processed.\textsuperscript{14,16} The common-sense model pays specific attention to the role that internal and external influences play in cognitive and emotional responses to stimuli, in appraisal, and in coping, with particular focus on personality variables or individual difference factors, as well as cultural and interpersonal contexts.\textsuperscript{16} In the common-sense model, cognitive level processes or health threats revolve around five attributes of illness representation: the *identity* of the illness, the *timeline* that describes the duration and pattern of symptoms, the attributable *causes* that elicit symptoms, the perceived *controllability* of the stimuli, and the *imagined consequences* of the illness.\textsuperscript{16}

Third is the model of selective optimization with compensation, which describes a general process of adaptation that can be applied to any illness.\textsuperscript{15,23} The model has previously been described for the adaptation of older adults with OA to disability.\textsuperscript{23} It has three components: selection, the giving up or restriction of activities because of reduced functional capacity; optimization, the individual’s augmentation of their capacity to engage in desired tasks; and compensation, the changing of strategies used to continue engaging in specific tasks despite the loss of capacity.\textsuperscript{23}

Previous reviews have looked at the conceptualization and operationalization of illness perceptions, appraisals and behaviours.\textsuperscript{18-20,24} These reviews have also highlighted their importance in the assessment and management of health conditions by clinicians.\textsuperscript{18-20} Prior and Bond (2013) noted that the primary purpose of the operationalization of illness behaviour is for individual-level assessment of the illness response, and posited the idea that illness behaviour has both covert (affective and cognitive) and overt (observable) aspects.\textsuperscript{20,25} Consistent with this, Sirri et al (2013) argued that illness behaviour unifies diverse concepts in the medical literature that may improve illness recognition and a
patient’s medical care. Moreover, these concepts not only may help clinicians better understand decision making, coping, self-management, and treatment adherence; but they may also be useful as outcome measures of change in perceptions or behaviours after treatment.

In the present study, measures were sought that capture illness perception and behaviour and which could be used during the rehabilitation of people with knee symptoms consistent with symptomatic knee OA. Therefore, the aim of this study was to identify validated measures that capture illness perception and behaviour and were used to assess people who have knee pain/OA.

2.3 Methods

2.3.1 Study design

The published research literature was reviewed using the systematic methodological framework for scoping studies developed by Arksey and O’Malley (2005). This study also incorporated some of the recommendations for its enhancement when used in health research. Following this framework, we: 1) identified the research question, 2) identified relevant publications, 3) selected the qualifying publications, 4) charted the data, 5) collated, summarized, and reported the results, and 6) consulted with stakeholders, which included two experts in psychosocial theory, chronic diseases such as OA, rehabilitation, and measurement.

2.3.1.1 Stage 1: Identification of the research question

First we formulated the following research question: What are the available validated measures of illness perception and behaviour used with people who have knee pain and knee OA? Illness perception and behaviour as a unified concept followed Mechanic’s (1986) definition of illness behaviour. This definition is applicable to clinical management of pain/OA because it encompasses both covert and overt responses to illness.
2.3.1.2 Stage 2: Identification of relevant publications

**Search strategy.** The search strategy was informed by a health sciences librarian. Search was done of all the online records up to October 20, 2014 of nine electronic databases and grey literature, namely: AMED, CINAHL, Cochrane Library, EMBASE, Health and Psychosocial Instruments, Open Grey, ProQuest Research Library (all 65 databases), PubMed, and Web of Knowledge. Using Boolean logic, the search terms included: illness behaviour, knee, pain, and osteoarthritis, each with related terms. Box 2.1 provides a full list of the search terms. One co-author (C.B.H. and M-K.W.) screened the reference list of the publications included in the final selection. Also, the names of the eligible validated measures were used to search for additional relevant publications.
Box 2.1. Search strategy for identifying studies before consultation

- **Databases** (inception to October 14, 2014)
  AMED, CINAHL, Cochrane Library, EMBASE, Health and Psychosocial Instruments, Open Grey, ProQuest Research Library (all 65 databases), PubMed, and Web of Knowledge

- **Search terms**
  [Illness perception and behaviour related terms: “sick role” OR “illness behaviour/behavior” OR “help seeking behaviour/behavior” OR “health seeking behaviour/behavior” OR “information seeking behaviour/behavior” OR “care seeking behaviour/behavior” OR “health care seeking behaviour/behaviour” OR “healthcare seeking behaviour/behavior” OR “self-care” OR “pain behaviour/behavior” OR “self-management” OR “treatment seeking behaviour/behavior” OR “adaptive behaviour/behavior” OR “health care utilization” OR “information seeking” OR “coping behaviour/behavior” OR “coping behavior” OR “illness response” OR “severity of illness index” OR “severity of illness indices” OR “illness experience” OR “treatment adherence” OR “symptoms response” OR “pain response” OR “self-regulation” OR “professional regulation” OR “professional care” OR “self-monitoring”] AND [Knee related terms: “knee” OR “knee joint” OR “patellofemoral joint” OR “tibiofemoral”] AND [The condition related terms: “pain” OR “osteoarthritis” OR “knee osteoarthritis” OR “osteoarthritis, knee”]

- **Journals**
  None searched
2.3.1.3  Stage 3: Study selection

**Inclusion criteria.** We defined the four components of illness perception and behaviour identified within Mechanic’s (1986) definition,\textsuperscript{17} (see Box 2.2.): (i) *Monitor body* means maintaining focus on the occurrence of symptoms and factors contributing to symptom episodes.\textsuperscript{29} (ii) *Define and interpret symptoms* refers to an individual’s attempt to decipher
meaning and place significance on their symptoms including their perceived ability to manage them.²⁹ (iii) *Take remedial action* means applying lay- or professionally-guided care to control one’s symptoms or progression of the disease, such as the avoidance of knee pain triggering activities, the use of pain medication, or self-talk.³⁰,³¹ (iv) *Utilize sources of help* means help through interpersonal interaction with either lay or professional care providers regarding one’s illness or symptoms.³¹,³² We included quantitative studies that reported primary data from people with knee pain/OA, who were assessed with a measure that was previously validated or validated as part of the study. Measures were considered validated if, at the minimum, they had evidence of content validation in any population. Also, each measure had to be available in English and provide an individual-level scoring method. The full version of each validated measure or its validated subsections (e.g. subscales or factors) were eligible. Furthermore, the validated measure had to be interpreted as capturing one or more components of illness perception and behaviour.

**Exclusion criteria.** We excluded animal studies, qualitative studies, and publications that were not available in English. Publications were also excluded when subjects were diagnosed with rheumatoid arthritis, fibromyalgia, generalized pain, generalized OA, or were post-surgical. Also, exclusion during full-text screening focused on the following four criteria: the publication: 1) did not use a validated measure of illness perception and behaviour; 2) did not specify a sample with knee pain and/or knee OA; 3) contained a non-English measure with no evidence of cross-cultural validation with an English language equivalent; and 4) a full-text or measure was not found.
Box 2.2. Definition of illness perception and behaviour components

- **Monitor body** means maintaining focus on the occurrence of symptoms and factors contributing to symptom episodes.
- **Define and interpret symptoms** refers to an individual’s attempt to decipher meaning and place significance on their symptoms including their perceived ability to manage them.
- **Take remedial action** means applying lay- or professionally-guided care to control one’s symptoms or progression of the disease, such as the avoidance of knee pain triggering activities, the use of pain medication, or self-talk.
- **Utilize sources of help** means help through interpersonal interaction with either lay or professional care providers regarding one’s illness or symptoms.
**Screening, full-text and measure review.** All of the retrieved publications were placed in a citation management system. A sample of 300 publications was independently screened by two reviewers (C.B.H. and M-K.W.). This was done to refine the inclusion and exclusion criteria. In a sequential and iterative process, one reviewer (C.B.H.) screened the titles and abstracts of all the initial set of publications retrieved by the search strategy. Some publications were excluded at this stage. We retrieved those publications judged to be possibly eligible. Then, full-text review of the remaining publications was independently performed by two reviewers (C.B.H. and M-K.W.). When the reviewers disagreed on eligibility, advice was sought from a third investigator (B.M.C.), and the decision was made by consensus on whether to include the publication. We then retrieved the measures from the included publications. The final decision to include a publication consisted of analysing each item of the relevant validated measure by assessing how well it fit with the definition of each of the four components.

### 2.3.1.4 Stage 4: Charting the data

A data charting form was developed and used to record key information extracted from the final set of included publications. Two reviewers (C.B.H. and M-K.W.) independently recorded the following information from the included publications:

- Author(s), year of publication, country of study
- Aim of study
- Population
- Methodology
- Name of relevant validated measure

### 2.3.1.5 Stage 5: Collating, summarizing and reporting results

We applied a directed approach to the qualitative content analysis of the text data for each measure by collating, summarizing, and reporting the results in a way that provided a narrative account of the data. Content analysis required analytical re-interpretation of the
items in the validated measures to determine whether they fit with the core concept of illness perception and behaviour. The four components defined above were used as key categories for coding the content of each measure.\textsuperscript{33} Particular attention was placed on identifying any gaps in the measurement of illness perception and behaviour within the target population. We have provided a summary of the included measures. Inter-rater agreement when coding the measures to each component of illness perception and behaviour was calculated using the kappa statistic. Statistically significant ($P < 0.05$) values of kappa from 0.21 to 0.40, 0.41 to 0.60, and 0.61 to 0.80 were interpreted as fair, moderate, and substantial agreement between raters, respectively.\textsuperscript{34}

### 2.3.1.6 Stage 6: Consultation exercise

After the first draft of the manuscript, we sought two experts’ opinion to inform and validate our findings.\textsuperscript{28} We had two consulting researchers: a clinician researcher (A.M.D.) who focuses on OA, measurement, and rehabilitation – particularly related to the experiences of people with early-to-moderate symptoms who are looking to manage and prevent progression; and, a researcher (M.A.M.G.) with a health psychology background in chronic disease, coping and measurement. They reviewed the initial draft of this manuscript, provided insightful critiques and recommendations, and were involved from the preparation of the manuscript through to the final draft submitted for publication.\textsuperscript{27}

After the initial consultation, we performed a second search on April 19, 2015 using the terms listed in Box 2.3. Two key journals were hand-searched: Health Psychology and Journal of Behavioural Medicine. Also, given the new insights from the consultation, the full-text results from before the consultation were rescreened for additional publications and measures.
Box 2.3 Search Strategy for identifying studies after consultation

- **Databases** (inception to April 19, 2015)
  AMED, CINAHL, Cochrane Library, EMBASE, Health and Psychosocial Instruments, Open Grey, ProQuest Research Library (all 65 databases), PubMed, and Web of Knowledge

- **Search terms**
  Search Terms: [**Illness perception and behaviour related terms:** “informal support” OR “support seeking” OR “formal support” OR “illness perceptions” OR “pain perceptions” OR “psychosocial perceptions” OR “health perceptions” OR “illness appraisals” OR “illness evaluations” OR “pain appraisals” OR “illness evaluations” OR “pain appraisals” OR “pain evaluations” OR “illness monitoring” OR “pain monitoring” OR “illness support” OR “adaptation” OR “pain vigilance” OR “illness vigilance”] AND [**Knee related terms:** “knee” OR “knee joint” OR “patellofemoral joint” OR “tibiofemoral”] AND [**The condition related terms:** “pain” OR “knee symptoms” OR “osteoarthritis” OR “knee osteoarthritis”] NOT [“qualitative”]. Where possible the search limits included English Language and Human.

- **Journals** (Inception to April 24, 2015)
  - Health Psychology
  - Journal of Behavioural Medicine

- **Rescreened full-text results obtained before consultation**
  n = 79
2.4 Results

2.4.1 Data synthesis

Figure 2.1 outlines the data selection process. The searches before the consultation produced 8028 publications, with 6534 publications remaining after the removal of duplicates. Subsequently, 6455 publications that were ineligible were excluded prior to the full-text review. The main reasons for excluding a publication after screening only its title and abstract were that the publication was: an animal study, not written in English, a conference abstract, a study of a post-surgical population, a study involving an excluded disease, not related to knee pain or knee OA, a publication without a measure of the concept, a qualitative study, or a review paper. The searches after consultation produced 4995 publications, and subsequently 4617 publications without duplicates. The full-text of 79 publications (before consultation) and 74 additional publications (after consultation), totaling 153 publications were screened, of which 71 publications and their relevant validated measures had their information charted and analysed.
Figure 2.1 Flow chart of study inclusion and exclusion
2.4.2 Components of illness perception and behaviour in each measure

Table 2.1 shows the 16 validated measures identified in publications between 1987 and 2014. Eleven measures were identified before consultation and five after consultation. The components of these 16 measures are presented in Table 2.1. We included multiple versions or factor structures of some measures, for example the Coping Strategies Questionnaire (CSQ), see Table 2.2 that presents a summary of the measures and how they were used. For other measures, we included only the subscales used in the included publications, such as only the religious coping subscale of the Coping Orientation to Problems Experienced (COPE) inventory.35,36
Table 2.1 Sixteen validated measures that capture components of illness perception and behaviour.

<table>
<thead>
<tr>
<th>Validated measure*</th>
<th>Illness Perception and Behaviour Components</th>
<th>Summary of Population</th>
<th>Number of Articles and Study Locations</th>
<th>Publications</th>
<th>Index Article of measure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monitor Body</td>
<td>Define &amp; Interpret Symptoms</td>
<td>Take Remedial Action</td>
<td>Utilize Sources of Help</td>
<td></td>
</tr>
<tr>
<td>Arthritis Self-Efficacy Scale (ASES)†</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>Painful early/advance knee OA, hip/knee OA, non-acute hip/knee pain, OA-like knee pain</td>
</tr>
<tr>
<td>Chronic Pain Coping Inventory (CPCI)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>Painful hip/knee OA</td>
</tr>
<tr>
<td>Coping Orientation to Problems Experienced (COPE) inventory†</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>Knee OA</td>
</tr>
<tr>
<td>- Religious coping subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coping Strategies Inventory (CSI)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>Knee OA</td>
</tr>
<tr>
<td>Coping Strategies Questionnaire (CSQ)†</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>Hand/hip/knee OA, painful knee OA, painful advance knee OA, hip/knee OA</td>
</tr>
<tr>
<td>Questionnaire/Scale</td>
<td>OA</td>
<td>Hand/hip/knee OA</td>
<td>Knee OA</td>
<td>Study Details</td>
<td>Reference Numbers</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>---------------------</td>
<td>------------------</td>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Daily Coping Inventory (DCI)</td>
<td>x</td>
<td></td>
<td>x x x</td>
<td>OA /US) n=4</td>
<td>108, 109, 115, 116</td>
</tr>
<tr>
<td>Fear Avoidance Beliefs Questionnaire (FABQ)‡</td>
<td>x</td>
<td></td>
<td>x</td>
<td>Knee OA, hip/knee OA n=4 (3=Netherlands, 1=US)</td>
<td>59, 76, 117, 118</td>
</tr>
<tr>
<td>‐physical activity subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keefe’s Pain Behavior Observation Protocol (Keefe’s method)†</td>
<td>x</td>
<td></td>
<td></td>
<td>Knee OA, hip/knee OA n=12 (7=US)</td>
<td>51, 52, 95, 104, 106, 110, 111, 117-120</td>
</tr>
<tr>
<td>Knee Osteoarthritis Fears and Beliefs Questionnaire (KOFBeQ)†</td>
<td>x</td>
<td></td>
<td></td>
<td>Knee OA n=1 (1=France)</td>
<td>50</td>
</tr>
<tr>
<td>Illness Perceptions Questionnaire (IPQ)</td>
<td>x</td>
<td></td>
<td>x</td>
<td>Knee pain, hip/knee pain/OA n=2 (1=Netherlands, 1=UK)</td>
<td>121, 122</td>
</tr>
<tr>
<td>Pain Catastrophizing Scale (PCS)</td>
<td>x</td>
<td></td>
<td></td>
<td>Knee OA, Severe knee OA, advance hip/knee OA n=8 (1=Canada, 1=Japan, 6=US)</td>
<td>100, 115, 116, 123-126</td>
</tr>
</tbody>
</table>

‡ Indicates a subscale of a larger questionnaire.
† Indicates a modified version of an existing questionnaire.
<table>
<thead>
<tr>
<th>Measure Name</th>
<th>x</th>
<th>x</th>
<th>x</th>
<th>Early Painful Knee OA, Hip/OA-related Knee/hip Symptoms</th>
<th>n=12</th>
<th>1=France, 10=Netherlands, 1=Nigeria</th>
<th>76, 117, 127-136</th>
<th>47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain-Coping Inventory (PCI)†</td>
<td></td>
<td></td>
<td>x</td>
<td>Early Painful Knee OA, Hip/OA-related Knee/hip Symptoms</td>
<td>n=1</td>
<td>1=US</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Pain Behaviors for Osteoarthritis Instrument for Cognitively Impaired Elders (PBOICIE)†</td>
<td></td>
<td></td>
<td>x</td>
<td>Knee/hip OA</td>
<td>n=1</td>
<td>1=US</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Questionnaire to Identify Knee Symptoms (QuIKS)†</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>OA-like Knee Pain</td>
<td>n=2</td>
<td>1=Taiwan</td>
<td>37, 137</td>
<td>37</td>
</tr>
<tr>
<td>Survey of Pain Attitudes (SOPA)-35</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>Knee OA</td>
<td>n=1</td>
<td>1=Taiwan</td>
<td>66</td>
<td>48</td>
</tr>
<tr>
<td>Ways of Coping Scale (WAYS)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>Knee Pain</td>
<td>n=1</td>
<td>1=Canada</td>
<td>138</td>
<td>13,49</td>
</tr>
</tbody>
</table>

* The measures are listed in alphabetical order.
† Measure that have been validated in the target population. A brief 6-item version of the ASES has been validated in the target sample.
‡ Only the subscales indicated were charted for each of these measures.
Note: All the self-report questionnaires except the DCI, PBOICIE and QuIKS have been translated and/or validated in languages other than English.
As depicted in Figure 2.2, the coding of the items in the measures indicates that monitor body was represented in 5 (31%) of the 16 measures, and define and interpret symptoms in 11 (69%), take remedial action in 12 (75%) and utilize sources of help in 5 (31%). Of the 16 measures, only the QuIKS included all four components of illness perception and behaviour.37

The inter-rater agreement for the coding of the items in the validated measures included before consultation were: a kappa of 0.43 for utilize sources of help, 0.51 for take remedial action, 0.56 for monitor body and 0.68 for define and interpret symptoms. The consensus discussion resulted in complete agreement between the two reviewers.
Figure 2.2 Chart showing the frequency of the four components of illness perception and behaviour among the charted validated measures as used in the publications.
2.4.3 Measures identified

The measures identified were originally developed to measure illness beliefs, coping strategies/skills/styles, pain behaviour, or self-efficacy. The measures vary in length, and are self-administered questionnaires, except for two that are observation-based. Most have been used many times to assess general and condition-specific populations and have been validated over many versions and in many languages, but further details are beyond the scope of this study. Table 2.2 provides a summary of the publications that used the identified measures. Below is a brief description of each measure, listed in alphabetical order.

The Arthritis Self-Efficacy Scale (ASES) is a 20-item 3-subscale (pain, function, and other symptoms) self-report questionnaire. It was developed in the US in 1987 to evaluate the beliefs individuals with arthritis have about their ability to cope with the consequences of chronic arthritis. Its initial psychometric validation used attendees of an arthritis self-management course. We coded the ASES as capturing the define and interpret symptoms component.

The Chronic Pain Coping Inventory (CPCI) was developed in the US in 1995. It was validated as a measure of behavioural coping strategies (illness-focus, wellness-focus, and other) that could be addressed in multidisciplinary treatment pain programs using people with chronic pain problems. Two versions were developed: a patient self-report version (65 items) and a significant-other observation version (52 items). The patient version has 11 dimensions (guarding, resting, asking for assistance, relaxation, task persistence, exercise/stretch, seeking social support, coping self-statements, opioid medication use, non-steroidal use, and sedative-hypnotic use). The significant-other version lacks the dimension for coping self-statements. After excluding item 65, which covers three dimensions of medication use, the CPCI retained eight subscales. The psychometric properties of this 8-subscale version have been further validated in studies using samples of people attending multidisciplinary pain treatment programs. We coded the measure as take remedial action and utilize sources of help.
The COPE inventory is a 60-item 14-subscale self-report questionnaire about coping strategies and styles.\textsuperscript{35} Its theoretical underpinning are a behavioural self-regulation as well as Lazarus’ model of stress.\textsuperscript{35,42} The COPE was initially developed and validated in the US in 1989 using samples of undergraduate students.\textsuperscript{42} Its 14 subscales are: active coping, planning, suppression of competing activities, restraint coping, seeking social support-instrumental, seeking social support-emotional, positive reinterpretation and growth, acceptance, turning to religion, focus on and venting of emotion, denial, behavioural disengagement, and alcohol-drug disengagement.\textsuperscript{35} Thirteen of its scales measure emotion-focused, problem-focused, and dysfunctional coping responses.\textsuperscript{35} The present review coded the COPE religious coping subscale as \textit{take remedial action}.

The Coping Strategies Inventory (CSI) is a 72-item 14-subscale self-report questionnaire about coping strategies. It was developed and validated in the US in 1985 using samples of undergraduate students.\textsuperscript{40,57} Its 14 subscales are arranged hierarchically into eight primary factors (problem solving, cognitive restructuring, express emotion, social support, problem avoidance, wishful thinking, self-criticism, and social withdrawal), four secondary factors (problem- and emotion-focus engagement and problem- and emotion-focus disengagement) that capture problem/emotion-focus coping and two tertiary factors (engagement and disengagement) that capture approach/avoidance coping.\textsuperscript{40} Twenty-three of its items are from the Ways of Coping Scale (WAYS).\textsuperscript{13,57} The CSI was coded as capturing all the components except \textit{monitor body}.

The CSQ is a 48-item questionnaire that records cognitive and behavioural coping strategies.\textsuperscript{41} Its original version divided the items into three factors (cognitive coping and suppression, helplessness, and diverting attention and praying).\textsuperscript{41} It was developed in the US in 1983 using data from 61 subjects with chronic low back pain.\textsuperscript{41} The majority of CSQ items were coded as \textit{take remedial action}, and a few were coded as \textit{define and interpret symptoms}.

The Daily Coping Inventory (DCI) is a self-report questionnaire consisting of eight single-item categories about coping.\textsuperscript{42} The DCI has an open item asking the respondent to state their ‘most bothersome event or issue of the day’ and eight closed appraisal items.\textsuperscript{42} It was
developed in the US in 1984 using samples of people in the local community to measure cognitive and behavioural coping. In 1992, the DCI was adapted for assessing daily coping with chronic pain in seven categories: distraction, redefinition, direction action, relaxation, emotional expression, seek spiritual comfort, and seek emotional comfort. This newer version of the DCI attained construct validation using 75 adults with rheumatoid arthritis. We coded the DCI with all the components except monitor body.

The Fear Avoidance Beliefs Questionnaire (FABQ) is a 16-item 2-subscale (physical activity and work) self-report questionnaire. It was developed in Scotland in 1993, and is based on theories of fear behaviour, avoidance behaviour, and illness behaviour. Its psychometric properties were validated using patients with lower back pain and/or sciatica in a study of how one’s beliefs affect one’s physical activity and work. It has since been adapted for knee pathology. Only the ‘physical activity’ subscale of the FABQ was included and was coded as monitor body and utilize sources of help.

The Illness Perception Question (IPQ) is a 38-item 5-subscale self-report questionnaire. It was theoretically-based on Leventhal’s self-regulation model of illness behaviour and was constructed to assess the five cognitive attributes of illness representation. It was developed in England and New Zealand in 1994 and was validated using samples of patients in England with diabetes, rheumatoid arthritis, asthma or undergoing dialysis, and patients in New Zealand with chronic fatigue syndrome, chronic pain, or myocardial infarction. Only some samples were used for evaluating each psychometric property. To correct minor psychometric problems in two subscales and add additional subscales which would also cover emotional representation, a revised version (IPQ-R) was developed in 2002 using eight different illness groups. The IPQ-R consists of three sections. We included section two, which is a 38-item 7-dimension measure of timeline acute/chronic, timeline cyclical, consequences, personal control, treatment control, illness coherence, and emotional representations. We coded section two as monitor body and define and interpret symptoms.

Keefe’s Pain Behavior Observation Protocol (Keefe’s method) is a 5-item observation-based measure. It was developed and validated in the US in 1982 using a sample of
patients with back pain. In the original measure, people were asked to sit, recline, stand, walk, and shift, and the frequency of five concomitant behaviours were coded as pain behaviour items. For assessing people with knee OA pain, the five items were modified to guarding, active rubbing, unloading joints, rigidity, and joint-flexing. We coded all five items as take remedial action.

The Knee Osteoarthritis Fears and Beliefs Questionnaire (KOFBeQ) is an 11-item self-report questionnaire that assesses an individual’s fears and beliefs about their knee OA. It was developed in 2013 in France using an empirical approach. Its psychometric properties were tested using a sample of 524 patients with radiographic knee OA. We coded the KOFBeQ as define and interpret symptoms.

The Pain Behaviors for Osteoarthritis Instrument for Cognitively Impaired Elderly (PBOICIE) is a 6-item observation-based measure. It was developed and validated in the US in 2008 and uses the activity protocol from the Keefe’s method but applies a different set of 6 items (excessive stiffness of the affected joint during activities other than walking, shifting weight when seated, massaging affected area, clutching or holding onto affected area, rigid and tense body posture, and clenching teeth). A 10-item version was evaluated in a sample of 32 non-cognitively impaired elderly with knee or hip OA, which resulted in the 6-item PBOICIE. We coded the PBOICIE as take remedial action.

The Pain Catastrophizing Scale (PCS) is a 13-item 3-subscale (rumination, magnification, and helplessness) self-report questionnaire about exaggerated negative affect towards pain. It was developed in Canada in 1995 for clinical and non-clinical populations and includes five items from the catastrophizing subscale of the CSQ. It was initially validated in a series of four studies, of which three used samples of undergraduate students and the other used a sample of people undergoing an electro-diagnostic evaluation. Its psychometric properties were then confirmed using a sample of undergraduate students. The PCS was coded as define and interpret symptoms.

The Pain-Coping Inventory (PCI) is a 33-item self-report questionnaire that records individuals’ cognitive and behavioural pain coping strategies. The original paper on its development was a 1996 publication from the Netherlands and is not available in English.
A follow-up publication in 2003 confirmed its psychometric properties using patients with chronic pain conditions. The conditions specified were rheumatoid arthritis, fibromyalgia, and several location-specific pain syndromes, although they are not specific to the knee. The PCI has two second-order factors that cover six first-order factors: active pain coping (transformation, distraction, and reducing demands) and passive pain coping (retreating, worrying, and resting). The items of the PCI, similar to the CSQ, were predominantly coded as capturing take remedial action. The PCI also had a few items coded as monitor body and define and interpret symptoms.

The QuIKS is a 13-item 4-subscale self-report questionnaire focused on identifying early symptomatic knee OA problems in order to inform conservative intervention. It was developed in Canada, in 2013, using an empirical approach. It demonstrated internal consistency in a sample of people between 40 and 65 years of age with knee pain consistent with knee OA. Its four subscales are: medication [use], monitoring [of knee symptoms], interpreting [ongoing knee symptoms], and modifying [activities in response to knee pain]. The QuIKS was coded as having all four components of illness perception and behaviour.

The Survey of Pain Attitudes (SOPA) underwent preliminary development and psychometric evaluation as a 24-item 5-subscale measure of pain-related beliefs in the US in 1986. However, the development and validation of its original 57-item 7-subscale (pain control, disability, harm, emotion, medication, solicitude, and medical cure) version was informed by cognitive behavioural models and used 241 patients with chronic pain (17% had lower extremity pain, but the knees were not specified). Subsequently, a 35-item version (SOPA-35) was published in 1999. The SOPA-35 has the same seven subscales, and was developed and underwent validation using patients with chronic pain in several body locations, not specifying the knees. In the present review, we included only the control subscale of the SOPA-35 which we coded as all the components except utilize sources of help.

The WAYS is a 66-item self-report questionnaire, whose theoretical underpinning is the coping and stress theory, was developed by Lazarus and Folkman (1984) to record coping and behaviour strategies. Only 50 items are used for scoring. Analyses using a sample
of 150 community dwelling adults derived eight subscales: confrontive coping, distancing, self-controlling, seeking social support, accepting responsibility, escape-avoidance, planful problem solving, and positive reappraisal. Most items were coded as take remedial action, a few items were coded as define and interpret symptoms, and as utilize sources of help (particularly, the items of the seeking social support subscale).
Table 2.2 Summary of publications that used the identified measures

<table>
<thead>
<tr>
<th>Author/ Year</th>
<th>Country</th>
<th>Sample*</th>
<th>Aim/Question</th>
<th>Relevant validated measure</th>
<th>Methodology</th>
<th>Measure-Variable Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al. (2014)</td>
<td>Canada</td>
<td>105 OA-like knee pain</td>
<td>Develop QuIKS as a screening tool for early knee OA</td>
<td>QuIKS</td>
<td>Cross-sectional</td>
<td>Independent</td>
<td>Subscales have adequate internal consistency</td>
</tr>
<tr>
<td>Golightly et al. (2014)</td>
<td>US</td>
<td>153 hand/hip/knee OA (82=knee)</td>
<td>Examine associations between pain coping strategies and daily pain diary-based measures</td>
<td>DCI and CSQ</td>
<td>Longitudinal</td>
<td>Independent</td>
<td>Pain coping strategies related to maximum pain and pain range</td>
</tr>
<tr>
<td>Hiramatsu et al. (2014)</td>
<td>Japan</td>
<td>12 knee OA, 11 healthy</td>
<td>Examine cerebral responses to experimental pain</td>
<td>PCS</td>
<td>Cross-sectional (Case-control)</td>
<td>Independent</td>
<td>3 dimensions of catastrophizing (PCS) were significant different between groups.</td>
</tr>
<tr>
<td>Holla et al. (2014)</td>
<td>Netherlands</td>
<td>828 painful early knee OA</td>
<td>Examine predictors and outcomes of avoidance of activities using the</td>
<td>PCI</td>
<td>5-year Longitudinal</td>
<td>Mediator</td>
<td>Knee pain/Vitality predicted pain-related avoidance of activity (PCI) which predicted</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Independent Variables/Measures</td>
<td>Mediation/Association</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>---------------------------------</td>
<td>----------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marcum et al. (2014)</td>
<td>US</td>
<td>190 painful advanced knee OA</td>
<td>Cross-sectional</td>
<td>ASES, CSQ (catastrophizing subscale)</td>
<td>Independent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Functional self-efficacy (ASES) and opioid use were independently associated with gait speed.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marks (2014)</td>
<td>US</td>
<td>17 knee OA, women</td>
<td>Cross-sectional</td>
<td>ASES (Pain and Other symptoms subscales)</td>
<td>Mediator</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain efficacy (ASES) mediated ambulatory capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pisters et al. (2014)</td>
<td>Netherlands</td>
<td>288 hip/knee OA (216 knees)</td>
<td>5-year Longitudinal</td>
<td>PCI (resting subscale)</td>
<td>Independent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduced knee extensor muscle strength mediated avoidance of activity (PCI) effect on limitations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rayahin et al. (2014)</td>
<td>US</td>
<td>212 knee OA</td>
<td>2-year Longitudinal</td>
<td>ASES and PCS</td>
<td>Independent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Higher self-efficacy (ASES) and pain catastrophizing (PCS) were associated with good outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skou et al.</td>
<td>Denmark</td>
<td>79 non-acute hip/knee pain</td>
<td>1-year Longitudinal</td>
<td>ASES</td>
<td>Independent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Self-efficacy predicted pain and quality of life.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Intervention/Outcome</td>
<td>Study Design</td>
<td>Outcome/ Predictor</td>
<td>Findings</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>--------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>--------------------</td>
<td>----------</td>
</tr>
<tr>
<td>2014</td>
<td>Netherlands</td>
<td>313 painful hip/knee OA</td>
<td>Which factors relate to health care use after stepped-care strategy?</td>
<td>PCI</td>
<td>36-week Longitudinal</td>
<td>Independent</td>
<td>Active coping style (PCI) determinant of health care use, but not statistically significant</td>
</tr>
<tr>
<td>2014</td>
<td>US</td>
<td>107 knee OA</td>
<td>Does sensitivity to physical activity predicts psychological factors, response to quantitative sensory testing, and OA-related outcomes?</td>
<td>PCS</td>
<td>Cross-sectional</td>
<td>Dependent (Outcome)</td>
<td>Along with other variables, catastrophizing (PCS) predicted walking performance, self-reported pain and physical function</td>
</tr>
<tr>
<td>2013</td>
<td>US</td>
<td>797 painful knee OA</td>
<td>Are pain coping skills prognostic factor of pain/function changes?</td>
<td>CSQ</td>
<td>1-year Longitudinal</td>
<td>Independent (Predictor)</td>
<td>Constructs in CSQ were prognostic of pain and function</td>
</tr>
<tr>
<td>2013</td>
<td>France</td>
<td>524 knee OA</td>
<td>Develop measure of fears and beliefs held by patients with knee OA</td>
<td>KOFBeQ</td>
<td>Cross-sectional</td>
<td>Independent</td>
<td>Reliable, and obtained content and construct validation</td>
</tr>
<tr>
<td>2013</td>
<td>Nigeria</td>
<td>215 painful</td>
<td>Explore difference in</td>
<td>PCI</td>
<td>Cross-</td>
<td>Dependent</td>
<td>Passive coping (PCI)</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Intervention/Mediation</td>
<td>Methodology</td>
<td>Dependent Variable</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>--------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>(2013)</td>
<td>US</td>
<td>194 knee OA</td>
<td>Identify psychology profile relationship with pain and sensory</td>
<td>CSQ</td>
<td>Cross-sectional</td>
<td>Lower scores on passive dimension of CSQ related to higher optimism</td>
<td></td>
</tr>
<tr>
<td>(2013)</td>
<td>Canada</td>
<td>105 knee OA</td>
<td>Does activity-modifying behavior mediates the relationship between the pain severity with physical function or knee-related quality of life?</td>
<td>QuIKS (Modifying subscale)</td>
<td>Cross-sectional</td>
<td>activity-modifying behavior (QuIKS) mediated pain severity effect on physical function and quality of life</td>
<td></td>
</tr>
<tr>
<td>(2013)</td>
<td>Canada/US/Australia</td>
<td>20 knee OA</td>
<td>Feasibility of a physiotherapist-delivered treatment protocol combining exercise and Pain Coping Skills Training</td>
<td>CSQ, ASES</td>
<td>Intervention (Randomized Control Trial)</td>
<td>Exercise with but not without Pain Coping Skills Training improves pain coping (CSQ). Both improved self-efficacy (ASES) for control of pain management</td>
<td></td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>was higher in males, and related to poorer pain, depression, and physical activity</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Methodology</td>
<td>Outcome/Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riddle and Jensen (2013)</td>
<td>US</td>
<td>873 painful knee OA</td>
<td>Cross-sectional</td>
<td>CSQ (2-item per subscale version)</td>
<td>Construct validity was generally supported (strongest for Catastrophizing and Praying and Hoping subscales), criterion validity depended on criterion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiner et al. (2013)</td>
<td>US</td>
<td>190 painful advanced knee OA</td>
<td>Intervention (Randomized Control Trial)</td>
<td>ASES, CSQ (catastrophizing subscale)</td>
<td>Lower self-efficacy (ASES), depressive symptoms, higher difficulty with daily activity predicted lower likelihood of response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murphy et al.</td>
<td>US</td>
<td>44 painful hip/knee OA</td>
<td>Cross-sectional</td>
<td>CPCI</td>
<td>Guarding (CPCI) related to lower levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Authors</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Measure</td>
<td>Time Period</td>
<td>Design</td>
<td>Findings</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Skou et al. (2012)</td>
<td>Denmark</td>
<td>36 hip/knee OA-related pain</td>
<td>Longitudinal</td>
<td>ASES</td>
<td>3-month</td>
<td>Dependent</td>
<td>Significant improvement on ASES</td>
</tr>
<tr>
<td>Somers et al. (2012)</td>
<td>US</td>
<td>232 knee OA, overweight/obese</td>
<td>Intervention</td>
<td>ASES and CSQ (catastrophizing)</td>
<td>Randomized</td>
<td>Dependent</td>
<td>Significant difference in improvements in self-</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Methodology</td>
<td>Predictor</td>
<td>Effectiveness</td>
<td>Findings</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>Broderick et al. (2011)</td>
<td>US</td>
<td>171 painful hip/knee OA (174=knee)</td>
<td>Cross-sectional</td>
<td>ASES and CSQ</td>
<td>Independent</td>
<td>Control Trial</td>
<td>This predictor of treatment expectation had better adaptive coping (CSQ) associated with better self-efficacy (ASES), quality of life, and psychological function</td>
</tr>
<tr>
<td>Van Dijk et al. (2011)</td>
<td>Netherlands</td>
<td>237 hip/knee OA (174=knee)</td>
<td>Longitudinal</td>
<td>PCI</td>
<td>Independent</td>
<td>Not independent</td>
<td>This predictor of activity limitations had a better adaptive coping (CSQ) associated with better self-efficacy (ASES), quality of life, and psychological function</td>
</tr>
<tr>
<td>Wade et al. (2011)</td>
<td>US</td>
<td>310 severe knee OA</td>
<td>Cross-sectional</td>
<td>PCS</td>
<td>Mediator</td>
<td>Pain catastrophizing (PSC) mediated pain unpleasantness effect on suffering</td>
<td></td>
</tr>
<tr>
<td>Wu et al. (2011)</td>
<td>Taiwan</td>
<td>205 knee OA</td>
<td>Intervention (Treatment-Control Trial)</td>
<td>ASES and SOPA-35 (pain control subscale)</td>
<td>Dependent</td>
<td>Pain beliefs (SOPA-35) and self-efficacy (ASES) improved by program</td>
<td></td>
</tr>
<tr>
<td>Gandhi et al.</td>
<td>Canada</td>
<td>200 advance</td>
<td>Cross-sectional</td>
<td>PCS</td>
<td>Independent</td>
<td>Pain catastrophizing</td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Aim</td>
<td>Design</td>
<td>Pain Coping Strategy</td>
<td>Additional Findings</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>-------------</td>
<td>-----------</td>
<td>--------</td>
<td>----------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>Holla et al. (2010)</td>
<td>Netherlands</td>
<td>1002 early OA-related knee/hip symptoms</td>
<td>Predict 2-year course of activity limitations</td>
<td>PCI</td>
<td>2-year Longitudinal</td>
<td>Pain coping strategy (PCI) associated with higher activity limitations</td>
<td></td>
</tr>
<tr>
<td>Izal et al. (2010)</td>
<td>Spain</td>
<td>104 OA (61.5% knee)</td>
<td>Role of coping strategies in disagreement between radiographic damage and function</td>
<td>CSQ</td>
<td>Cross-sectional</td>
<td>Certain pain coping strategies (CSQ) explain disparity between joint damage and functional impairment</td>
<td></td>
</tr>
<tr>
<td>Mcknight et al. (2010)</td>
<td>US</td>
<td>254 early knee OA</td>
<td>Effect of coping self-efficacy and catastrophizing on physical function</td>
<td>ASES and CSQ (catastrophizing subscale)</td>
<td>9-month Longitudinal</td>
<td>Self-efficacy (ASES) mediated pain catastrophizing (PCS) effect on physical function</td>
<td></td>
</tr>
<tr>
<td>Peat and Thomas (2009)</td>
<td>UK</td>
<td>285 knee pain</td>
<td>Describe the changes of appraisal and behavior that accompanies</td>
<td>CSQ (1 item per subscale version)</td>
<td>18-month Longitudinal</td>
<td>Worsen of pain was accompanied by increased catastrophizing, praying</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Design</td>
<td>Dependent Variable</td>
<td>Study Purpose</td>
<td>Methodology</td>
<td>Conclusion</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------</td>
<td>-------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Scopaz et al. (2009)</td>
<td>US</td>
<td>182 knee OA</td>
<td>Cross-sectional</td>
<td>Independent</td>
<td>Higher fear avoidance beliefs (FABQ) and anxiety related to poorer physical function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones et al. (2008)</td>
<td>UK</td>
<td>939 hip/knee OA</td>
<td>Cross-sectional</td>
<td>Dependent</td>
<td>Race associated with hope and praying (CSQ) but not self-efficacy (ASES)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perrot et al. (2008)</td>
<td>France</td>
<td>4,719 hip/knee OA (2781=knee, 385 = both)</td>
<td>Cross-sectional</td>
<td>Dependent</td>
<td>More passive coping with longer duration of OA. Supported structural and other validation criteria of PCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shelby et al. (2008)</td>
<td>US</td>
<td>192 knee OA</td>
<td>Cross-sectional</td>
<td>ASES=Mediator</td>
<td>Self-efficacy was a significant mediator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Participants</td>
<td>Research Question</td>
<td>Design</td>
<td>Measure/Method</td>
<td>Analysis</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>--------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tsai et al. (2008)</td>
<td>US</td>
<td>7 cognitively impaired elder, then 32 elders with hip/knee OA</td>
<td>Develop and do psychometric testing of PBOICIE</td>
<td>Keefe's method, PBOICIE</td>
<td>Cross-sectional</td>
<td>Dependent</td>
<td>PBOICE significantly associated with Keefe's method, discriminate pain behaviors before and after analgesic use. Internal consistency not acceptable</td>
</tr>
<tr>
<td>Wright et al. (2008)</td>
<td>US</td>
<td>275 early knee OA</td>
<td>Which psychological factors with disease severity factors best account for levels of pain and function?</td>
<td>ASES</td>
<td>24-month Longitudinal</td>
<td>Mediator</td>
<td>Higher self-efficacy mediated resilience effect on lower pain and better physical function</td>
</tr>
<tr>
<td>Fraenkel et al. (2007)</td>
<td>US</td>
<td>105 OA-like knee pain</td>
<td>Efficacy of a computer tool to improve informed</td>
<td>ASES</td>
<td>Intervention (Randomized Control Trial)</td>
<td>Dependent</td>
<td>Self-efficacy (ASES) higher with intervention</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Country</td>
<td>Sample Size</td>
<td>Condition</td>
<td>Research Question</td>
<td>Measure(s)</td>
<td>Study Design</td>
<td>Role</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
<td>-------------</td>
<td>-----------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>------</td>
</tr>
<tr>
<td>Maly et al. (2007)</td>
<td>Canada</td>
<td>54</td>
<td>Knee OA</td>
<td>Does self-efficacy mediate the effect of age, psychosocial, impairment, and mechanical factors on walking performance?</td>
<td>ASES (function subscale)</td>
<td>Cross-sectional</td>
<td>Mediator</td>
</tr>
<tr>
<td>Marks (2007)</td>
<td>US</td>
<td>100</td>
<td>Knee OA</td>
<td>Examine strength of the relationship between walking ability and certain psychological factors</td>
<td>ASES</td>
<td>Cross-sectional</td>
<td>Independent</td>
</tr>
<tr>
<td>Botha-Scheepers et al. (2006)</td>
<td>Netherlands</td>
<td>316</td>
<td>Hip/Knee OA</td>
<td>Is the association between impairments and activity limitations modified by illness perception and mental health?</td>
<td>IPQ (revised version IPQ-R)</td>
<td>Cross-sectional</td>
<td>Moderator</td>
</tr>
<tr>
<td>Emery et al. (2006)</td>
<td>US</td>
<td>62</td>
<td>Knee OA</td>
<td>Relationship between baseline pain coping and pain catastrophizing on changes in</td>
<td>DCI and PCS</td>
<td>Cross-sectional</td>
<td>Independent</td>
</tr>
<tr>
<td>Authors</td>
<td>Location</td>
<td>Sample Size</td>
<td>Study Aim</td>
<td>Test Measure(s)</td>
<td>Study Design</td>
<td>Dependent Variable(s)</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Maly et al. (2006)</td>
<td>Canada</td>
<td>54 knee OA</td>
<td>Determine factors related to self-efficacy for physical task</td>
<td>ASES (Function subscale)</td>
<td>Cross-sectional</td>
<td>51% of variance in functional self-efficacy (ASES) explained by knee stiffness, hamstrings strength, age, depression scores, but not pain, anxiety, joint space, and body weight.</td>
<td></td>
</tr>
<tr>
<td>Mitchell et al. (2006)</td>
<td>UK</td>
<td>231 knee pain</td>
<td>Investigate treatment of knee pain in primary care</td>
<td>IPQ</td>
<td>Cross-sectional</td>
<td>Illness beliefs (IPQ) predicted consultation with GP and referral to rheumatology services</td>
<td></td>
</tr>
<tr>
<td>Heuts et al. (2005)</td>
<td>Netherlands</td>
<td>273 hip/knee OA</td>
<td>Efficacy of self-management program</td>
<td>ASES (Function subscale)</td>
<td>Intervention (Randomized Control Trial)</td>
<td>Functional self-efficacy (ASES) improvement not significantly different between groups</td>
<td></td>
</tr>
<tr>
<td>France et al. (2004)</td>
<td>US</td>
<td>74 post-menopausal</td>
<td>Relationship between pain behavior,</td>
<td>DCI, PCS</td>
<td>Cross-sectional</td>
<td>More emotion-focus coping (DCI) or pain</td>
<td></td>
</tr>
<tr>
<td>Researcher(s) / Year</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Methods</td>
<td>Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>---------</td>
<td>----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harrison (2004)</td>
<td>US</td>
<td>50 knee OA</td>
<td>Cross-sectional</td>
<td>Relationship among knee OA grade, pain, balance, and self-efficacy</td>
<td>ASES (function subscale)</td>
<td>Categorizing (PSC) related to more arthritis pain and less pain tolerance</td>
<td></td>
</tr>
<tr>
<td>Keefe et al. (2004a)</td>
<td>US</td>
<td>64 women and 36 men with knee OA</td>
<td>Dependent</td>
<td>Gender difference in pain, mood, and pain coping</td>
<td>CSQ (catastrophizing subscale and coping efficacy subscale) and DCI</td>
<td>Self-efficacy and pain accounted for 74% of variance in functional difficulty</td>
<td></td>
</tr>
<tr>
<td>Keefe et al. (2004b)</td>
<td>US</td>
<td>72 married patients with painful knee OA and their spouse</td>
<td>Dependent</td>
<td>Test separate and combined effects of spouse-assisted pain coping skills training and exercise training</td>
<td>ASES and CSQ</td>
<td>Problem-focus coping (DCI) used more by women.</td>
<td></td>
</tr>
<tr>
<td>Jensen et al. (2003)</td>
<td>US</td>
<td>87 knee OA (from Keefe et al. 1996)</td>
<td>Intervention</td>
<td>Develop and validate brief versions of pain-related beliefs and coping scales</td>
<td>ASES and CSQ</td>
<td>Combined interventions improve pain coping (CSQ) and self-efficacy (ASES)</td>
<td></td>
</tr>
</tbody>
</table>

ASES = Arthritis Self-Efficacy Scale, CSQ = Coping Strategies Questionnaire, DCI = Difficulties Coping Index.
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sample Size</th>
<th>Methodology</th>
<th>Variables</th>
<th>Design</th>
<th>Group</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma et al. (2003)</td>
<td>US</td>
<td>257 knee OA</td>
<td>Identify factors that predict poor physical function</td>
<td>ASES (function subscale)</td>
<td>3-year Longitudinal</td>
<td>Independent</td>
<td>Self-efficacy along with other variables protected against poor physical function scores</td>
</tr>
<tr>
<td>Steultjens et al. (2001)</td>
<td>Netherlands</td>
<td>190 hip/knee OA (119 Knee OA)</td>
<td>Role of coping styles as prospective determinants of pain and disability</td>
<td>FABQ (physical activity subscale) and PCI</td>
<td>36-week Longitudinal</td>
<td>Independent</td>
<td>For knee OA, only resting (PCI) at baseline predicted disability at follow-up, and pain transformation (PCI) was determinant of pain. For hip, none significant.</td>
</tr>
<tr>
<td>Hopman-Rock et al. (2000)</td>
<td>Netherlands</td>
<td>56 knee/hip OA, 49 controls</td>
<td>Evaluate self-management program</td>
<td>ASES</td>
<td>Intervention (Control Trial)</td>
<td>Dependent</td>
<td>Self-efficacy (ASES) significantly related group x time effect</td>
</tr>
<tr>
<td>Rapp et al.</td>
<td>US</td>
<td>394 knee pain</td>
<td>Evaluate relationship</td>
<td>CSQ</td>
<td>Cross-</td>
<td>Independent</td>
<td>Pain coping skills</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Country</td>
<td>Participants</td>
<td>Methodology</td>
<td>Intervention</td>
<td>Dependent</td>
<td>Outcome</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>---------</td>
<td>--------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>2000</td>
<td>Keefe et al.</td>
<td>US</td>
<td>88 painful knee OA</td>
<td>Sectional</td>
<td>ASES, CSQ, Keefe's method</td>
<td>Independent/Dependent</td>
<td>Improved self-efficacy and coping at 6 months. Improved self-efficacy and pain behavior at 12 months</td>
</tr>
<tr>
<td>1999</td>
<td>Hopman-Rock and Kraaimaat</td>
<td>Netherlands</td>
<td>157 knee/hip pain in last month</td>
<td>Cross-sectional</td>
<td>PCI</td>
<td>Mediator</td>
<td>Pain coping (PCI) mediated pain chronicity effect on physical disability</td>
</tr>
<tr>
<td>1998</td>
<td>Sullivan et al.</td>
<td>US</td>
<td>92 painful knee OA</td>
<td>Treatment-Control</td>
<td>ASES (pain and other symptoms subscales)</td>
<td>Dependent</td>
<td>Gains on both subscales were not significant between groups</td>
</tr>
<tr>
<td>1998</td>
<td>van Baar et al.</td>
<td>Netherlands</td>
<td>201 hip/knee OA</td>
<td>Randomized Control Trial</td>
<td>FABQ (physical activity subscale)</td>
<td>Dependent</td>
<td>Scores not different between intervention and control</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Population</td>
<td>Methodology</td>
<td>Primary Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>------------------</td>
<td>-------------------------------</td>
<td>------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Baar <em>et al.</em> (1998)</td>
<td>Netherlands</td>
<td>200 knee/hip OA (112=knees)</td>
<td>Examine the extent to which various factors affect pain and disability</td>
<td>FABQ (physical activity subscale), Keefe's method, and PCI</td>
<td>Cross-sectional</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FABQ and PCI= Independent Keefe's Method= Dependent</td>
<td>Retreating (PCI) predicted pain</td>
<td></td>
</tr>
<tr>
<td>Keefe <em>et al.</em> (1997)</td>
<td>US</td>
<td>130 knee OA</td>
<td>Examine relationship between pain coping strategies and self-efficacy</td>
<td>ASES and CSQ</td>
<td>Cross-sectional</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CSQ= Independent ASES= Dependent</td>
<td>Different coping strategies predicted lower/higher self-efficacy</td>
<td></td>
</tr>
<tr>
<td>Keefe <em>et al.</em> (1996)</td>
<td>US</td>
<td>88 knee OA</td>
<td>Determine the effect of spouse-assisted pain-coping skills training several physical and psychological disability, pain-coping and pain behavior</td>
<td>ASES, CSQ, Keefe's method</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dependent</td>
<td>Improved psychological disability scores, self-efficacy and certain coping strategies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Independent</td>
<td>Constructs in CSI were related to future psychological well-</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Group</td>
<td>Study Description</td>
<td>Intervention Type</td>
<td>Study Design</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Fry and Wong (1991)</td>
<td>Canada</td>
<td>69 knee pain</td>
<td>Determine the effect of matching pain management training and individual differences on coping style</td>
<td>WAYS</td>
<td>Cross-sectional</td>
<td>Matches between coping styles (WAYS) with intervention types were effective</td>
<td></td>
</tr>
<tr>
<td>Keefe et al. (1990a)</td>
<td>US</td>
<td>99 knee OA</td>
<td>Does cognitive-behavioral intervention to improve pain coping skills reduce pain, physical and psychological disability, and pain behavior?</td>
<td>Keefe's method and CSQ</td>
<td>Intervention</td>
<td>Pain-coping skills training had improved pain and psychological disability scores</td>
<td></td>
</tr>
<tr>
<td>Keefe et al. (1990b)</td>
<td>US</td>
<td>99 knee OA</td>
<td>6 months follow-up of pain-coping skills training</td>
<td>Keefe's method and CSQ</td>
<td>Intervention (Randomized Control Trial)</td>
<td>Deterioration in gains in psychology ability, and trend towards improvement in physical ability</td>
<td></td>
</tr>
<tr>
<td>Keefe et al. (1987a)</td>
<td>US</td>
<td>87 painful knee OA</td>
<td>Provide descriptive data on behavior patterns and functional</td>
<td>Keefe's method and CSQ</td>
<td>Cross-sectional</td>
<td>Guarded movement (Keefe's Protocol) was most frequent pain behavior. Pain control</td>
<td></td>
</tr>
</tbody>
</table>
impairment and rational thinking (CSQ) were predictive of functional impairment

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population</th>
<th>Methodology</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keefe et al. (1987b)</td>
<td>US</td>
<td>51 painful knee OA</td>
<td>CSQ</td>
<td>Independent</td>
<td>Coping attempts, pain control and rational thinking (CSQ) accounted for 60% of variance in CSQ scores. Higher pain control and rational thinking predicted better pain, health status, and psychological distress scores.</td>
</tr>
</tbody>
</table>

*Most samples composed of older adults, usually aged ≥40 year or ≥50 years.*
2.5 Discussion

To our knowledge, this is the first attempt to identify and analyse the content of published validated measures that can be interpreted as capturing components of illness perception and behaviour in people who have knee pain/OA. The primary finding was that most existing measures did not capture all four components of illness perception and behaviour. The one that did, the QuIKS, was the most recently developed of all the measures. The QuIKS is one of only seven measures identified in this review that have been validated using people with knee pain/OA, see Table 2.1.

Our findings demonstrated that most of the included measures do not operationalize all four components of illness perception and behaviour. The validated measures focus more on capturing *take remedial action*. This seems to be reflective of several measures capturing cognitive and/or behavioural coping strategies, including the COPE, CPCI, CSQ, CSI, DCI, and PCI. Conversely, only 31% of the measures were identified to have items that capture *monitor body* or *utilize sources of help*. One could argue that *utilize sources of help* is a very unique concept and that our search was aimed at support-seeking rather than the support literature. However, other questionnaires fitting this concept did come up in our search, but they did not have an individual-level scoring method, were open-ended questions, were checklists, or were comprised of a single question about the number of visits to a clinician.

We included only one subscale from each of the COPE, FABQ and SOPA-35 because that was the portion of these questionnaires used in the included publications. The other items of these measures could be explored to determine how comprehensively each full measure operationalizes the concept of illness perception and behaviour. The suitability of the full version of these measures might vary with clinical scenarios, such as the temporal dimensions of a person’s condition, and with the measurement purpose, such as for diagnosis, evaluation, or prognosis. Therefore, future research could investigate the validity of the full version of these measures for use in assessing people who have knee pain/OA.
With respect to our findings, it can be reasoned that scores on validated measures that are missing components of illness perception and behaviour provide an incomplete description and insight into an individual’s response to his or her symptoms. The measures identified have been previously demonstrated to be predictive of pain level, disability, activity limitations, psychological functioning (e.g. depression) and physical functioning in the target population. Particularly, the ASES and CSQ have been richly used in many roles as independent, mediator, moderator, and dependent variables in studies on the target population, see Table 2. A measure covering the four components may provide sufficient information regarding a person’s response to their knee pain/OA to adequately inform therapy.

While the QuIKS captures all four components, it has only undergone content validation and had its internal consistency confirmed in people with early symptoms of knee OA. More aspects of validation are required to provide confidence that the QuIKS is psychometrically sound and related to physical and psychological adjustments to knee pain/OA. Alternatively, an additional measure capturing all four components of illness perception and behaviour could be developed by combining items from some of the included measures, and then validated for people with symptomatic knee OA.

The assessment of illness perception and behaviour is applicable to the recognition of illness and the implementation of the medical management of disability. As noted by Sirri et al. (2013: p.79), illness behaviour is a concept that delineates “prognosis and therapeutic differences” among people with “deceptively” similar diagnoses. Therefore, illness perception and behaviour may become important in explaining the discordance between the pain symptoms and the biologic evidence of knee OA, such as was previously demonstrated using the CSQ. For example, patients with similar structural knee joint changes and pain levels may require different treatment approaches if their levels of illness perception and behaviour are different. Identifying illness perception and behaviour issues that clinicians should address, could help direct clinical resources such as patient education and structured interventions to improve an individual’s health.
Caution is advised regarding the use of the identified measures in the target population where they have not undergone validation. Many of the measures were developed and have been validated in a sample that was not identified as including people with knee pain/OA. For example some were developed and validated using samples of undergraduate psychology students,\textsuperscript{35,46,64} general population from the community,\textsuperscript{49} and people with various chronic conditions.\textsuperscript{39,53} Also, whilst measures validated in populations affected by OA in other joints are likely applicable to knee OA, their psychometric properties might be different for people with knee OA.\textsuperscript{76}

### 2.6 Study limitations

This review has some limitations. First, given the large variety of terms related to illness perception and behaviour, it is possible that relevant terms were missed. Therefore validated measures used with the target population may have been overlooked. Also, two measures were not included because they were not made available by the developer or publisher by the end of this study.\textsuperscript{77,78} Second, the definitions used for each of the four components of illness perception and behaviour were developed for this study.\textsuperscript{17} So, the focus was on responses to illness and not all the different factors that may shape illness responses (e.g., optimism and mastery). It is likely that there may be many more components and antecedents to illness perception and behaviour, such as psychological function (depression), anxiety and optimism. Alternate definitions could be considered for the four components, which would possibly change the coding of the included measures.

### 2.7 Conclusions

Several validated measures capture the components of illness perception and behaviour defined in this study, but most do not capture \textit{monitor body} or \textit{utilize sources of help}. Only the QuIKS captures all four components. We recommend that it undergo further validation of its psychometric properties in the target population.
2.8 References


Chapter 3

3 Interval-level measure of illness perception and behaviour

A version of this chapter is presently under review for publication in a peer-reviewed journal.

3.1 Abstract

Objective: The Questionnaire to Identify Knee Symptoms (QuIKS) was recently developed to promote activity by screening for key lived experiences (i.e., illness perception and behavior) in people with osteoarthritis (OA) –like knee pain. The main purpose of this study was to evaluate measurement properties of the QuIKS using Rasch analysis in a sample of people with knee pain symptoms consistent with symptomatic knee OA.

Methods: This study used cross-sectional data. The sample included 200 people along the following knee health continuum: pain-free healthy knees (n=55) from a university community, knee pain with no knee OA diagnosis (n=111) from a university-affiliated medical clinic, and patients with surgeon-diagnosed symptomatic knee OA awaiting high tibial osteotomy (n=34) from a sports medicine surgical clinic. The 13-item QuIKS was evaluated for its factor structure, item- and person-fit, an item’s category response structure, differential item functioning, local item dependency, unidimensionality, and test precision. Subsequently, the QuIKS underwent known-groups analysis and convergent validity with the Knee injury and Osteoarthritis Outcome Score (KOOS).

Results: In the QuIKS, each item’s category response structure was modified. Local item dependency informed the formation of four testlets. This refined QuIKS obtained summary fit to the Rasch model, unidimensionality, reliability (person separation index = 0.82) and interval-level scoring. Subsequently, the Rasch-refined QuIKS (QuIKS-R) demonstrated excellent known-groups validity and good convergent validity with the KOOS (Spearman’s rho = 0.45-0.77).
**Conclusions:** The QuIKS-R provides interval-level quantification of illness behavior in people with knee pain symptoms consistent with symptomatic knee OA. Its scores may help clinicians to identify important issues to address in therapy for people with early symptoms of symptomatic knee OA.
3.2 Introduction

Symptomatic knee OA is a chronic degenerative joint disease that leads to activity limitations, performance restrictions, and reduced quality of life.\textsuperscript{1-4} In the US, the lifetime risk of developing symptomatic knee OA is up to 23.9\%, depending on one’s sex, age, and obesity status.\textsuperscript{3} The lived experience of knee pain in people with knee OA is considered to be a biopsychosocial phenomenon.\textsuperscript{4-8}

Studies have linked illness perception and behaviour to knee OA-related disability in the pre-diagnosis stage and early stages of knee OA, and in people with recently diagnosed symptomatic knee OA.\textsuperscript{4-8} Illness perception and behaviour can be considered to have four components, each component corresponding to a clause in the definition that follows. Using Mechanic’s (1986) definition of illness behaviour, illness perception and behaviour is defined as “the manner in which persons monitor their bodies, define and interpret their symptoms, take remedial action, and utilize various sources of help as well as the more formal health-care system”.\textsuperscript{9} Illness perception and behaviour is promoted as a health construct.\textsuperscript{10, 11} When operationalized, it can identify issues that clinicians should address with patients to facilitate management of symptoms.\textsuperscript{10, 11}

Quantifying illness perception and behaviour, whether adaptive or maladaptive, may be useful in facilitating early recognition and management of knee OA symptoms to aid in the delay or prevention of long term disability. Several generic measures of illness perception and behaviour exist.\textsuperscript{10, 11} These measures include the Illness Behavior Questionnaire, Symptoms Response Scale, Scale for the Assessment of Illness Behavior, and Illness Cognition Scale, to name just a few.\textsuperscript{11} No generic measure of illness perception and behaviour has been specifically validated for knee pain and knee OA. Thus, their application to knee pain problems is questionable. For example, the Illness Behavior Questionnaire assesses several dimensions of abnormal illness behaviour and is currently the most widely used of these measures.\textsuperscript{12, 13} While it has a strong focus on the affective and cognitive aspects of illness, it overlooks overt aspects which are more applicable to physical health management.\textsuperscript{10, 11} The concept of illness perception and behaviour has been operationalized as coping strategies in other measures, such as the commonly used Coping Strategies Questionnaire.\textsuperscript{10, 14} However, we searched the literature and found the measures
of coping strategies are limited in their coverage across the four components (i.e., full definition) of illness perception and behaviour. More specifically, these measures provide a fairly incomplete picture of a patient’s illness perception and behaviour. This limitation in these measures could affect a clinician’s ability to make an informed decision about the management of a patient’s knee pain and knee OA-related symptoms. On the other hand, the QuIKS was specifically developed for clinical use in assessing a patient’s responses to their knee pain and knee OA-related symptoms. Furthermore, the contents of the QuIKS covers all four components of illness perception and behaviour and could better identify important issues to address in therapy.

The QuIKS is a 13-item self-administered discriminative questionnaire. It was developed using a mixed-methods approach, which aligns with recommendations by Velozo et al. (2012) for scale development. First, its items were generated through grounded theory qualitative research using one-on-one interviews of people with recently diagnosed knee OA or undiagnosed symptoms consistent with knee OA. This was followed by a consensus of rheumatology experts, then item reduction and internal consistency evaluation. Velozo et al. also recommended using Rasch analysis to determine whether a measure captures a unidimensional construct. However, this last recommendation has not yet been conducted for the QuIKS and therefore is the main purpose of this paper.

In Rasch analysis, observed data are expected to fit the probabilistic relationship within and between person estimates and item estimates as specified in the Rasch measurement model. Consequently, a questionnaire with data that fits the Rasch model has a unidimensional construct, thereby having interval-level measurement properties as recommended for questionnaire measures. The current study sought to evaluate the factor structure, the items’ category response structure, item- and person-fit, differential item functioning, local item dependence, overall fit, unidimensionality, and the test precision of the QuIKS using Rasch analysis. The secondary purpose was to subsequently evaluate the known-groups validity and the convergent validity of the Rasch-refined QuIKS.
3.3 Methods

3.3.1 Design

This study used cross-sectional data. We recruited subjects into three distinct groups along the following knee health continuum: pain-free healthy knees (HK), knee pain with no knee OA diagnosis (KP), and surgeon-diagnosed knee OA scheduled for high tibial osteotomy (pre-HTO). Subjects in the HK group self-reported no knee pain in the past three years and were between the ages of 20-40 years. Subjects in the KP group had verbally complained of knee pain lasting two or more weeks to their family physician within the previous three years as recorded in their medical chart and were between the ages of 40-65 years. Subjects in the pre-HTO group were between the ages of 40-65 years. The prevalence of knee OA increases with age. Therefore, the HK group was younger than the two involved groups and less likely to have knee OA. The HK group was recruited (March 2011 to January 2012) from a university community through posted paper notices. The KP group was retrospectively collected from data collected (April to August 2009) through a university-affiliated medical clinic using mailed questionnaires as previously described. The pre-HTO group was prospectively collected (March 2011 to January 2012) through a university-affiliated sports medicine clinic using mailed questionnaires. Each subject had to be fluent in English to participate in this study. We excluded persons with gout, rheumatoid arthritis, chronic low back pain, foot or hip pain, major co-morbidities, previous knee arthroplasty, or high tibial osteotomy. These exclusion criteria helped to ensure that the knee pain and the illness experiences of the subjects were consistent with symptomatic knee OA. Ethics approval was granted by Western University’s Health Sciences Research Ethics Board, see Appendix B. Each participant provided written informed consent.

3.3.2 Participants

The total sample was 200 subjects along the knee health continuum. The HK, KP, and pre-HTO group had 55, 111, and 34 subjects, respectively.
3.3.3 Outcome measures

The sample descriptive data included sex, age, body mass index (BMI), affected knee (unilateral, bilateral, or none), family history of arthritis (yes or no), and history of knee injury (yes or no). To indicate the structural severity of knee OA, a single rater recorded the Kellgren and Lawrence grade from standard weight-bearing radiographs of each symptomatic knee in the pre-HTO group. A Kellgren and Lawrence grade of 0, 1, 2, 3, and 4, represented normal, doubtful, minimal, moderate, and severe knee (tibiofemoral) OA, respectively.

3.3.3.1 The QuIKS

We analysed the QuIKS, but data were collected on its 35-item prototype questionnaire (as in the initial validation of the questionnaire) to allow for consistency of data collection across the study groups. The QuIKS has 13 items and four subscales, and each item has a 5-point rating scale. Each of its four subscales captures one or more components of illness perception and behaviour. Some items use an adjectival scale to quantify frequency (0 = never, 4 = always), while others use Likert responses ranging from strongly disagree (0) to strongly agree (4). The 3-item medication subscale captures medication usage to relieve knee pain, reflecting self-care and professional-guided care. The 3-item monitoring subscale captures a person’s awareness of their knee symptoms, reflecting illness recognition and evaluation. The 4-item interpreting subscale captures one’s understanding of one’s symptoms, reflecting information and health-care seeking, and illness recognition and labeling. The 3-item modifying subscale captures an individual’s changes or intention to change engagement in activity in order to avoid progressive knee damage, reflecting the principles of selection of, optimization of, and compensation for activity engagement. However, since each subscale may be the operationalization of one or more components of illness perception and behaviour, combining these subscales into a single measure might reflect a higher-order construct of illness perception and behaviour. This higher-order construct would be expected to be unidimensional. When normalized, the summative total score of the subscales of the QuIKS varies from 0-100 (worst to best state).
3.3.3.2 The KOOS

The KOOS is a 42-item knee-specific self-administered questionnaire.\(^{24}\) It captures health status in the following five subscales: pain, other symptoms, activities of daily living, sport and recreation function, and knee-related quality of life.\(^{24}\) The total score of each subscale was normalized to a 0-100 scale (extreme to no problems). The KOOS has been widely used and has demonstrated validity, reliability and responsiveness for adults of all ages with acute and chronic knee pain problems; i.e. knee injury and osteoarthritis.\(^{25, 26}\) The KOOS was chosen to demonstrate the convergent validity of the QuIKS because both measures have a similar target population. However, the KOOS evaluates symptoms severity, function, activity, and quality of life, whereas the QuIKS evaluates the illness perception and behaviour related to one’s knee pain symptoms.

3.3.4 Data analysis

3.3.4.1 Sample characteristics

Descriptive characteristics were summarized for the knee health groups. The Shapiro-Wilk test evaluated the normality of the data within each group of knee health. Factor analysis and Rasch analysis used only the KP and pre-HTO groups combined (\(n = 145\)), because scores within the HK group were extreme and would not contribute to these analyses. Most data analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, Illinois).

3.3.4.2 Factor analysis

As recommended by Tennant and Pallant (2006),\(^{27}\) Horn’s parallel analysis was performed to determine the number of factors to extract from the QuIKS prior to its Rasch analysis.\(^{27}\) This determined whether the QuIKS had only a single dominant construct as required for proceeding to Rasch analysis.\(^{27}\) Horn’s parallel analysis uses principal components analysis (PCA) with Monte Carlo simulation to determine the number of factors in a dataset. It identifies the number of factors with an empirical eigenvalue greater than the
corresponding eigenvalue generated from 1000 random datasets at a 95% confidence level.\textsuperscript{28} Horn’s parallel analysis is more accurate than other forms of factor analysis, such as the eigenvalues-greater-than-one rule and the scree plot.\textsuperscript{28} Following parallel analysis, PCA with varimax rotation determined the percentage variance explained by each factor.

### 3.3.4.3 Rasch analysis

A Rasch analysis approach was used to evaluate the fit of the data collected by the QuIKS to the Rasch mathematical model.\textsuperscript{29,30} The RUMM2030 software (RUMM Laboratories, Perth, Australia) was used, which is a sophisticated and widely used software that is specialized for Rasch analysis. An estimated minimum sample size of 144 subjects was adequate for Rasch analysis for items calibration with ±0.05 logits at 95% confidence even if the scale is poorly targeted.\textsuperscript{31} However a minimum sample size of 100 subjects is considered to be adequate in most cases at this confidence level.\textsuperscript{31}

We hypothesized that the QuIKS would contain a unidimensional dominant construct, conceptualized as illness perception and behaviour that represented the key experiences consistent with symptomatic knee OA. We used the following 12 steps and previously published fit criteria for the Rasch model to investigate this hypothesis.\textsuperscript{30}

Step 1: to evaluate goodness-of-fit, the data were divided into two class intervals using the subjects’ total scores. Step 2: a Fishers Likelihood test was performed. If significant ($P <0.05$ with Bonferroni correction for the number of items), it would suggest that the partial credit model version of the Rasch model should be used.\textsuperscript{32} Step 3: data for misfitted subjects, those with residual values outside ±2.5, were removed to allow for an accurate estimation of the questionnaire’s measurement properties. Step 4: response categories of the individual items were expected to be sequentially ordered. Disorder occurred when any response category for an item always had less than 50% probability of being endorsed when compared to each adjacent response category. When disordered response categories were identified, the response structure of the rating scale was corrected by combining two or more adjacent response categories. Step 5: the fit of each item was evaluated. Items
misfitted the model if their residual value was above +2.5 and/or had a significant chi-square ($\chi^2$, $P < 0.05$ with Bonferroni correction for the number of items in the questionnaire). Any misfitted item was deleted because it did not align with the construct captured collectively by the other items. All the preceding steps were iterative.

Step 6: the remaining data were evaluated for summary fit with the Rasch model as defined by a non-significant item-trait interactive $\chi^2$ ($P < 0.05$ with Bonferroni correction), mean person- and mean item- residual value (standard deviation) of ~0 (~1). Step 7: each item was examined for differential item functioning (DIF) across two subject characteristics considered clinically relevant to the experience of illness perception and behaviour: sex (male/female) and body mass index (i.e., BMI cut point obese [$\geq 30$ kg/m$^2$]/not obese) using two separate two-way analysis of variance (ANOVA) procedures. In each two-way ANOVA, the two independent variables were the subjects’ overall construct estimate divided into two class intervals and a subject characteristic. Each item had one mean score for the subjects in each class interval which formed the dependent variable. An item with DIF does not provide consistent estimation of the construct across the categories of the subject characteristics for subjects with equal overall estimates.$^{30}$ Step 8: item pairs with their residual correlation > 0.2 after mathematically removing the dominant construct, were considered to have displayed local item dependency, which means that those items were associated beyond the dominant construct in the questionnaire.$^{33}$ Such items were combined into a testlet.$^{33}$

A testlet is a group of two or more very closely associated items that give a similar estimate of a subject’s level of the construct. Testlets are sub-constructs of a scale, whereas subscales may or may not be sub-constructs. Step 9: the misfitting subjects’ data (from step 3) were re-entered and the changes to the QuIKS in step 1 to 6 were repeated. This allowed all subjects who fit the Rasch-refined QuIKS to be accounted for in the subsequent steps of Rasch analysis. Step 10: we formally evaluated whether the dominant construct was unidimensional.

Unidimensionality is a vital component for interval-level measurement. In the context of testlets, the construct was the common variance (A) among the testlets.$^{33, 34}$ Each subject
had an estimate generated for two exclusive sets of items, using the Smith method. The two estimates for each subject were then compared using an independent $t$-test.

Unidimensionality was confirmed if less than 5% of subjects had significant $t$-scores, as estimated by the lower bound of a binomial 95% confidence interval. Step 11: reliability (or scale precision) was then evaluated using the Person Separation Index (PSI). A PSI value of 0.8 indicated the questionnaire can distinguish subjects in up to three levels of the dominant construct, which is the minimum acceptable level for a measurement scale. Step 12: targeting of the sample by the refined QuIKS was evaluated. This step investigated whether the spectrum of the construct captured by the refined QuIKS covered the spread of the construct in the sample. Ideally, the difficulty thresholds of the items should be adequately spread to capture the quantity of construct in every subject. Statistically, this was indicated by a mean person estimate (standard deviation) of $\sim1$ ($\sim0$) when the mean item estimate was zero on the same logit (log-odd units) scale of the dominant construct. Also in this step, the estimate of each testlet was determined. This allowed us to determine the hierarchical order of the testlets on the dominant construct based on their logit scores. Lower logit scores represented the tendency of an item or testlet to capture lower levels of the dominant construct. A floor effect and ceiling effect were 15% or more subjects with the maximum or minimum scores, respectively. If the QuIKS was adequately validated by Rasch analysis, we adapted a conversion formula, and transformed its summative total raw scores to interval-level scores.

### 3.3.4.4 Confirmatory factory analysis

This was performed to test the factor structure in the Rasch-refined QuIKS. Version 7.3 of the Mplus software (Muthén & Muthén, Los Angeles, California) was used. Model fit was evaluated using the following fit indices and cut-off criteria for adequate fit; comparative fit index (CFI, $>0.90$), the Tucker-Lewis index (TLI, $>0.90$), and the root-mean-square error of approximation (RMSEA, $<0.08$).
3.3.4.5 Known-groups analysis

We hypothesized that the total scores from the Rasch-refined QuIKS would be significantly higher for the HK versus the KP group (n = 166), and higher for the KP versus the pre-HTO group (n = 145) with at least a moderate effect size. The estimated sample size was 52 subjects per group for a moderate effect size.\(^1\) We used the Kruskal-Wallis H test (the non-parametric version of a 1-way ANOVA) with the Mann-Whitney U test (the non-parametric version of an independent \(t\)-test) for post-hoc testing because the data had a non-normal distribution. Effect size \((r)\) from the Mann-Whitney test was calculated as \(r = z/\sqrt{n}\) and then converted to Cohen’s \(d = 2r/\sqrt{(1 - r^2)}\), where \(z\) was the \(z\)-score value obtained from the Mann-Whitney test and \(n\) was the total sample used in the analysis.\(^2\) A Cohen’s \(d\) of 0.41 was considered small and the minimum effect size for a clinically relevant effect, 1.15 and \(\geq 2.70\) were moderate and strong effects, respectively.\(^3\) The 95% confidence interval (CI) of Cohen’s \(d\) was calculated as \(d \pm 1.96\times\text{Standard Error}.\(^4\)

3.3.4.6 Convergent validity

We hypothesized that a moderate correlation would be observed between scores on the Rasch-refined QuIKS and each subscale of the KOOS. This hypothesis was based on reasoning that the KOOS subscales should be moderately related to a measure that identifies responses to early symptoms of knee OA. Spearman correlation coefficients \((r_s)\) quantified these relationships. The HK group was excluded to prevent errors in \(r_s\) that would be caused by their extreme scores. Moderate correlation of \(r_s \geq 0.5\) supported convergent validity.\(^5\) This analysis required an estimated sample size of 129 subjects, calculated using an \(r_s\) of 0.7 (95% CI = 0.5 to 0.9) at an alpha value of 0.05, which was adequately met by the present study sample.\(^6\)
3.4 Results

3.4.1 Sample characteristics

Response rate was 63.0% for the KP and pre-HTO group, and not applicable to the HK group. The sample characteristics are summarized in Table 3.1.

3.4.2 Number of factors

Table 3.2 shows the results of Horn’s parallel analysis. Only the first factor had an empirical eigenvalue (5.97) that was greater than the corresponding randomly generated eigenvalue (1.67). These results indicated a single factor solution for the QuIKS which explained 45.9% of the total variance in its score.
<p>| Characteristics | Known Groups |
|----------------|
| | Healthy Knees, Knee Pain, Knee Osteoarthritis (pre-HTO), Knee Pain and pre-HTO, |
| | n = 55 | n = 111 | n = 34 | n = 145 |
| Age, years | 24.7 (4.4) | 52.1 (6.8) | 48.9 (6.5) | 51.3 (6.8) |
| Sex | | | | |
| Female (%) | 35 (63.6) | 62 (55.4) | 9 (36.0) | 71 (49.0) |
| BMI, kg/m² | | | | |
| mean (SD) | 22.9 (3.1) | 28.1 (9.1) | 29.1 (4.7) | 28.3 (8.3) |
| Affected knee | | | | |
| Unilateral (%) | 1 (1.8) | 61 (55.0) | 18 (52.9) | 79 (54.5) |
| Bilateral (%) | 4 (7.3) | 49 (44.1) | 16 (47.1) | 65 (44.8) |
| None (%) | 50 (90.0) | 1 (0.9) | 0 | 1 (0.7) |
| Family history of arthritis | | | | |
| Yes (%) | 23 (42.6) | 52 (46.8) | 11 (33.3) | 63 (43.4) |
| History of knee injury | | | | |
| Yes (%) | 3 (5.5) | 77 (69.4) | 23 (71.9) | 100 (69.0) |
| History of knee pain | | | | |
| Yes (%) | 2 (3.6) | 51 (45.9) | 32 (100) | 83 (57.2) |
| Kellgren and Lawrence Grade, Number of knees with | | | | |
| Grade 0/1/2/3/4 | -- | -- | 0/10/20/11/4 | -- |
| KOOS, range = 0-100 (worst to best state), median (IQR) | | | | |
| Other symptoms | 100 (7.1) | 53.6 (19.6) | 37.5 (29.5) | 53.6 (21.4) |
| Pain | 100 (2.8) | 80.6 (27.8) | 48.6 (23.6) | 72.2 (30.6) |</p>
<table>
<thead>
<tr>
<th></th>
<th>100 (0)</th>
<th>89.7 (23.2)</th>
<th>58.8 (27.7)</th>
<th>80.9 (29.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL</td>
<td>100 (0)</td>
<td>75.0 (40.0)</td>
<td>17.5 (39.1)</td>
<td>58.0 (50.0)</td>
</tr>
<tr>
<td>Sport &amp; Recreation</td>
<td>100 (0)</td>
<td>68.8 (31.3)</td>
<td>15.6 (31.3)</td>
<td>56.3 (43.8)</td>
</tr>
<tr>
<td>QOL</td>
<td>100 (0)</td>
<td>68.8 (31.3)</td>
<td>15.6 (31.3)</td>
<td>56.3 (43.8)</td>
</tr>
</tbody>
</table>

Missing data †n=1, ‡n=3, †‡n=4, †§n=9, †║n=2.

BMI, Body mass index
KOOS, Knee injury and Osteoarthritis Outcome Score
ADL, Activities of Daily Living
QOL, Quality of Life
IQR, Inter-quartile range

Kellgren and Lawrence grade severity: 0 (normal) is no OA; 1 (doubtful) is possible joint space narrowing and osteophytes, 2 (minimal) is definite joint space narrowing and osteophyte, 3 (moderate) is definite joint space narrowing, multiple osteophytes, some sclerosis and possible bone contour deformity, 4 (severe) is marked joint space narrowing, large osteophytes, severe sclerosis and definite bone contour deformity.20
Table 3.2 Results from factor analysis using Horn’s parallel analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Empirical Eigenvalue (95% CI)</th>
<th>Randomly Generated Eigenvalue</th>
<th>Percent Variance Explained based on empirically generated eigenvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>5.97 (5.02, 6.92)</td>
<td>1.67</td>
<td>45.9</td>
</tr>
<tr>
<td>2</td>
<td>1.35 (1.13, 1.57)</td>
<td>1.49</td>
<td>10.4</td>
</tr>
<tr>
<td>3</td>
<td>1.22 (1.03, 1.41)</td>
<td>1.36</td>
<td>9.3</td>
</tr>
<tr>
<td>4</td>
<td>1.12 (0.94, 1.30)</td>
<td>1.26</td>
<td>8.6</td>
</tr>
<tr>
<td>5</td>
<td>0.69 (0.58, 0.80)</td>
<td>1.18</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*Only factor suitable for extraction from the QuIKS.
3.4.3 Data fit to the Rasch model

Rasch analysis used the partial credit model. The main results of the Rasch analysis are summarized in Table 3.3. Initially, the QuIKS did not fit the Rasch model. Therefore, its measurement properties were refined through eight rounds of Rasch analysis. One set of modifications or data manipulation was performed in each round of Rasch analysis, guided by information obtained in the preceding rounds.
<table>
<thead>
<tr>
<th>Version</th>
<th>Data changes</th>
<th>Sample size</th>
<th>Item-trait interaction</th>
<th>Item fit residual</th>
<th>Person fit residual</th>
<th>PSI</th>
<th>Significant t-tests, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>( \chi^2 ) Value (df)</td>
<td>P value</td>
<td>Mean SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>None</td>
<td>145</td>
<td>73.512 (13) *</td>
<td>0.000</td>
<td>0.49 1.84</td>
<td>-0.22</td>
<td>1.18 0.89 7.0</td>
</tr>
<tr>
<td>Run 2</td>
<td>Deleted 8 misfit persons</td>
<td>137</td>
<td>72.550 (13)</td>
<td>0.000</td>
<td>0.43 1.93</td>
<td>-0.14</td>
<td>1.01 0.90 5.2</td>
</tr>
<tr>
<td>Run 3</td>
<td>Rescored all items</td>
<td>137</td>
<td>19.693 (13)</td>
<td>0.103</td>
<td>-1.01 1.21</td>
<td>-0.66</td>
<td>1.29 0.89 1.6</td>
</tr>
<tr>
<td>Run 4 *</td>
<td>Deleted 20 misfit persons</td>
<td>117</td>
<td>16.105 (13)</td>
<td>0.243</td>
<td>-0.58 1.12</td>
<td>-0.41</td>
<td>1.08 0.90 4.8</td>
</tr>
<tr>
<td>Run 5</td>
<td>Formed 4 testlets</td>
<td>117</td>
<td>0.937 (4)</td>
<td>0.92</td>
<td>0.26 0.72</td>
<td>-0.35</td>
<td>0.87 0.84 1.3</td>
</tr>
<tr>
<td>Run 6 *</td>
<td>Used initial data, rescored all items</td>
<td>145</td>
<td>19.480 (13)</td>
<td>0.108</td>
<td>-1.07 1.33</td>
<td>-0.70</td>
<td>1.33 0.89 4.3</td>
</tr>
<tr>
<td>Run 7</td>
<td>Formed the 4 testlets again</td>
<td>145</td>
<td>3.546 (4)</td>
<td>0.47</td>
<td>0.02 0.85</td>
<td>-0.45</td>
<td>0.89 0.83 2.9</td>
</tr>
<tr>
<td>Run 8</td>
<td>Deleted 1 misfit persons</td>
<td>144</td>
<td>3.612 (4)</td>
<td>0.46</td>
<td>0.03 0.85</td>
<td>-0.43</td>
<td>0.86 0.82 2.9</td>
</tr>
<tr>
<td>Rasch-Refined</td>
<td>Deleted 3 persons with incomplete data</td>
<td>141</td>
<td>3.613 (4)</td>
<td>0.46</td>
<td>0.00 0.87</td>
<td>-0.44</td>
<td>0.86 0.82 3.0</td>
</tr>
</tbody>
</table>

\* Significant after \( P < 0.05 \) with Bonferroni correction for the number of items in the analysis. \* Had local item dependency. Criteria of fit to Rasch Model: minimum sample size of \( n = 108 \), PSI (Person Separation Index) \( \geq 0.80 \) for reliability assessment by measurement scale, \( P \)-value of \( \chi^2 > 0.05 \) [Bonferroni-adjusted], Items- and Persons- Fit Residual Mean \( \sim 0 \) and SD (Standard Deviation) \( \sim 1 \), less than 5% significant t-test.
Eight items had disordered thresholds. There was equitable utilization of response categories across most items. The exceptions were items of the medications subscale, for which the subjects predominantly endorsed the ‘None – 0’ category. Rescoring the category response structure of all 13 items from five-level to three-level numeric response categories resolved all threshold disorders. In this new category response structure, the middle three response options have the same value (e.g. 0-1-2-3-4 became 0-1-1-1-2), thus assigning an equal score for the three inner response categories. As an example, figure 3.1 depicts the category probability curves of one item of the modifying subscale before and after being rescored. There was no DIF.

The residual correlation matrix of the items indicated that the four subscales had local item dependency, which grouped the items into their respective subscales. Only one pair of items of the interpreting subscale had residual correlations >0.2, but its items were still considered a subscale because their residuals were most correlated with each other. The results from Horn’s parallel analysis, coupled with these results, suggested that the dominant construct in the QuIKS is a higher-order factor, while its subscales are lower-order factors. Existing theory, prior research and the preceding results in this study guided our decision to form four testlets corresponding to the original four subscales. There was a large proportion of common variance (A = 0.93) among the testlets, which indicated that a single dominant construct (i.e., illness perception and behaviour) was captured by the QuIKS. Finally, data for four subjects were removed; one subject with an individual data pattern that misfitted the Rasch model and three subjects who each had data missing for one item.
Figure 3.1 Category probability curves of one item from the modifying subscale - ‘I participate in certain activities less often to avoid aggravating my knees’ before formation of testlets. Panel A depicts disordered response category thresholds. Panel B depicts the item’s response scale after the three inner response categories were rescored to have an equal value of one, thus creating a logical and sequential ordering of its thresholds.
This refined QuIKS conformed to the expectations of summary fit to the Rasch model, as revealed by a non-significant item-trait interaction $\chi^2$, see Table 3.3. Only 3.0% of subjects had significant independent $t$-tests, confirming the unidimensionality of the illness perception and behaviour construct in the refined QuIKS. This Rasch-refined QuIKS had a PSI of 0.82, which is adequate to distinguish up to three distinct levels of illness perception and behaviour. Figure 3.2 depicts findings that suggested the Rasch-refined QuIKS was suitable for assessing the subjects, because the mean (SD) person estimate was 0.08 (1.19) with an item estimate mean of 0.00. The subscales of the Rasch-refined QuIKS had a hierarchical order from less to more illness perception and behaviour in logit scores as follows: monitoring (-0.886), modifying (-0.192), interpreting (-0.112) and medication (1.19). There were no floor or ceiling effects. The Appendix provides the Rasch-refined QuIKS. A table at the bottom of the Rasch-refined QuIKS (see Appendix A) provides the interval level scores (vary 0 to 100) that correspond to the total raw scores (vary 0 to 26).
Figure 3.2 Fitting persons and items threshold distribution on the same logit scale.

The distribution of the subjects’ estimate of illness perception and behaviour is in the upper histogram, with increasing illness perception and behaviour from left to right on the x-axis. The distribution of the 13 items threshold estimate is the lower histogram, with higher illness perception and behaviour from left to right on the x-axis.
3.4.4 Factor structure of QuIKS

Results from confirmatory factor analysis substantiated the results from the Horn’s parallel analysis and Rasch analysis. We tested the one-dominant construct (second-order factor) and four-testlet (first order factors) structure of the 13-item Rasch-refined QuIKS, and the data showed adequate fit to the model \([\text{CFI} = 0.94, \text{TLI} = 0.92, \text{and RMSEA} = 0.08 (95\% \text{ CI} = 0.06-0.10)\]. Thus, the Rasch-refined QuIKS conformed to a unidimensional model.

3.4.5 Known-groups validity

The Kruskal-Wallis H test, where \(H\) is the test statistic, revealed that the total scores on the Rasch-refined QuIKS were significantly different among the three knee-health groups (\(H = 123.01, df = 2, \text{and } P < 0.001\)), with a median (inter-quartile range) of 100.0 (12.7) for HK, 52.9 (21.4) for KP, and 29.7 (13.8) for pre-HTO. There was a statistically significant moderate effect size between the HK and KP groups \((n = 166)\) with Cohen’s \(d = 2.20 (95\% \text{ CI} = 1.81-2.60), z = -9.615, \text{and } P < 0.001\), which indicated less illness perception and behaviour in the HK group compared to the KP group. There was a significant moderate effect size between the KP and pre-HTO groups \((n = 145)\) with Cohen’s \(d = 1.32 (95\% \text{ CI} = 0.99-1.66), z = -6.641, \text{and } P < 0.001\).

3.4.6 Convergent validity

The QuIKS had a statistically significant moderate correlation \((r_s = 0.45-0.77)\) with each KOOS subscale. Its lowest correlation was with the KOOS-other symptoms \((r_s = 0.45)\), followed by the KOOS-sports and recreation function \((r_s = 0.65)\), the KOOS-activities of daily living \((r_s = 0.70)\), the KOOS-Pain \((r_s = 0.72)\), and its highest correlation was with the KOOS-quality of life \((r_s = 0.77)\).
3.5 Discussion

Our findings affirmed all the hypotheses in this study. An updated version of the QuIKS, called the QuIKS-R, was adequately validated using information from Rasch analysis. The results suggest that the QuIKS-R encapsulates all four of its subscales into a unidimensional measure of illness perception and behaviour that captures the key experiences of knee pain symptoms that are consistent with knee OA. For clinicians and researchers, these findings mean that ratings on the QuIKS-R can be validly summed, much like marks on a ruler. First, calculate the total raw score, then use the conversion table at the bottom of the QuIKS-R (see Appendix A) to obtain the corresponding interval-level (final) total score. These interval-level scores represent an individual’s level of illness perception and behaviour. To the best of our knowledge, the QuIKS-R would be the first unidimensional measure designed to quantify illness perception and behaviour specifically for people with early symptoms of symptomatic knee OA.\textsuperscript{10,11}

It made conceptual sense to condense the three middle response categories of each item, given the descriptors used for these categories. In the medication subscale we combined ‘Rarely’, ‘Sometimes’, and ‘Often’. We did this because it might have been difficult for subjects to recall their illness response and then choose a response category that best classified their experience. It is possible that the subjects did not use a consistent pattern when selecting between ‘Rarely’ and ‘Sometimes’ and between ‘Sometimes’ and ‘Often’. Perhaps more clearly defined descriptors, for example, ‘Rarely = 1 to 3 times per week’, ‘Sometimes = 4 to 6 times per week’, and ‘Often = 7 to 9 times per week’ would remove ambiguity from among these categories.\textsuperscript{47} Furthermore, the other 10 items used five-point Likert scales with a ‘Neutral’ midpoint. The rescoring of these items could be explained in the context of the long history of debate on the implication of midpoints in rating scales.\textsuperscript{48} A midpoint, such as ‘Neutral’, is sometimes misinterpreted or selected in a biased way,\textsuperscript{48} however, its removal might push some respondents to choose adjacent categories, reducing the reliability and validity of the measure.\textsuperscript{48} Therefore, scoring the midpoint in the same manner as its adjacent categories was deemed a good solution for these two issues.

This study suggests that the level of illness perception and behaviour increased as individuals moved from the monitoring, to the modifying, then the interpreting, and finally
to the medication subscale. This pattern means that subjects tended to indicate higher ratings on the monitoring subscale compared to the medication subscale. This pattern fits with the model of illness behaviour, the latter being a representation of the decision-making process during an illness. This model employs nine stages, starting from illness recognition and labeling to the application of treatment with consequential re-evaluation of the illness state by the individual, in an iterative process. Furthermore, the model of selective optimization with compensation also offers a theoretical basis for some of the items in the QuIKS-R, as it provides an explanation of the process of adaptation in people with knee pain problems. For example, in the early stages of symptomatic knee OA, one would expect that a person might make the decision to stop engaging in a favorite activity because of their knee pain (selection), change their exercise routine because of the knee problem (compensation), and take medication before engaging in an activity to prevent pain (optimization). For clinicians these findings mean that scores on the QuIKS-R capture on a continuum illness perception and behaviour of people with knee pain symptoms that are consistent with knee OA.

Forming testlets to obtain unidimensionality demonstrated that the subscales of the QuIKS are sub-constructs of illness perception and behaviour. When measuring a construct, measures with fewer items tend to have higher accuracy but lower precision. By forming the testlets, we were able to capitalize on the accuracy of the subscales while also capitalizing on the precision of the full questionnaire, thereby providing more information about an individual’s level of illness perception and behavior in a single score. It is worth noting that the individual testlets should not be used for score interpretation. Only the total scores from all 13 items of the QuIKS-R should be interpreted, and this interpretation should be in the context of the higher-order construct of illness perception and behaviour.

The QuIKS-R discriminated between the study groups. The pre-HTO group had the highest level of illness perception and behaviour, followed by the KP, then the HK group, with a significant between-group difference of at least a moderate effect size. There are no previous studies of the QuIKS with which to compare these findings. However, population-based reference data of each subscale of the KOOS supports the values obtained in the present study. For example, the KOOS-pain median score for the KP and pre-HTO
groups were 80.6 and 48.6 respectively, and 97.2 for people aged 35 to 54 years in a population-based group.\textsuperscript{50} This is logical given that the prevalence of symptomatic knee OA increases with age and OA-related knee pain usually becomes more severe over time.\textsuperscript{3, 52} A lower correlation between the QuIKS-R and the KOOS-other symptom subscale, when compared to the QuIKS-R’s correlation with the other KOOS subscales, could mean that the level of illness perception and behaviour in the study population was less related to other joint impairments but highly related to activity limitations and knee-related quality of life. For clinicians, these findings mean that the QuIKS-R may be useful in discouraging physical activity limitations and helpful in promoting or maintaining quality of life in patients with knee pain symptoms consistent with knee OA.

One of the main advantages of the QuIKS-R over the original 13-item QuIKS is the unidimensionality it gained after the ambiguity was removed from the rating scale of each item. This finding suggests that the QuIKS-R has an improved ability to discriminate compared to its predecessor. Also, along with its validity specifically for people with OA-like knee pain, a main advantage of the QuIKS-R over other measures of illness perception and behaviour is its proposed ‘unified construct of illness perception and behaviour’.

\subsection*{3.6 Limitations and future research}

A limitation of this study was that the subjects in the KP group did not receive a medical diagnosis, so their knee pathology could be unrelated to knee OA. Also, while known-group (discriminative) validation supported the QuIKS-R ability to discriminate the level of illness perception and behaviour between the healthy group and two severely involved groups, this information might not be useful for a clinician’s assessment of individual patients. Future studies should use a larger sample and evaluate the predictive validity of the QuIKS-R in identifying subjects with OA-like knee pain who are at greatest risk for physical activity limitations.
3.7 Conclusions

The QuIKS-R is a unidimensional measurement scale that provides an interval-level score of illness perception and behaviour in persons with knee pain symptoms consistent with symptomatic knee OA. Scores on the QuIKS-R that represent more illness perception and behaviour, also mean that a patient is more aware of and affected by their knee pain, and has tried more to remedy their condition. This information might be useful for clinicians in guiding pain management interventions by identifying important issues to address in the therapy of people experiencing early symptoms of symptomatic knee OA.
3.8 References


Chapter 4

4 Behavioural measures in a rat model of post-traumatic knee OA

This chapter was reprinted with permission. A version of this chapter has been published as:

doi:10.1016/j.joca.2015.03.001.

4.1 Abstract

Objective: This study used a rat model of post-traumatic knee OA created by anterior cruciate ligament transection with partial medial meniscectomy (ACLT + pMMx). In this model, mild to moderate structural changes that are typical of knee OA have been observed within two and eight weeks post-surgery. The aim was to determine whether pain-related behaviours can distinguish between an ACLT + pMMx and a sham surgery group.

Design: Three-month old male Sprague-Dawley rats underwent ACLT + pMMx on their right hindlimb within two groups of $n = 6$ each, and sham surgery within two groups of $n = 5$ each. Assessments evaluated percent ipsilateral weight-bearing for static weight-bearing and 18 different variables of exploratory motor behaviour at multiple time points between one and eight weeks post-surgery. Histology was performed on the right hindlimbs at four and eight weeks post-surgery.

Results: Histology confirmed mild to moderate knee OA changes in the ACLT + pMMx group and the absence of knee OA changes in the sham group. Compared to the sham group, the ACLT + pMMx group had significantly lower percent ipsilateral weight-bearing from one through eight weeks post-surgery. Compared to the sham group, the ACLT + pMMx group had significantly lower vertical activity (episode count, time, and count) values.
**Conclusions:** These findings suggest that ipsilateral weight-bearing deficit and vertical activity limitations resulted from the presence of knee OA-like changes in this model. When using the ACLT + pMMx-induced rat model of knee OA, percent ipsilateral weight-bearing and vertical activity distinguished between rats with and without knee OA changes. These variables may be useful outcome measures in preclinical research performed with this experimental post-traumatic knee OA model.
4.2 Introduction

The clinical presentation of knee OA typically involves chronic pain and physical disability.\textsuperscript{1} Pain does not always accompany knee OA, but symptomatic knee OA is very prevalent.\textsuperscript{2,3} For example, the lifetime risk of developing symptomatic knee OA in the US has been estimated to vary between 9.6\% and 23.9\%, depending on a person’s age, sex, and obesity status.\textsuperscript{3} In humans, the presence of OA pain is associated with negative outcomes such as activity limitations, participation restrictions, and reduced quality of life\textsuperscript{1}. These symptoms may be observed as behavioural changes, beginning at the early stages of the disease before diagnosis, and continuing through to its late stages.\textsuperscript{4-6}

Several rat models of OA serve as surrogates to the disease in humans, and are useful in preclinical studies on pharmacology and pathophysiology of the disease.\textsuperscript{7} Chemical (particularly, monosodium iodoacetate - MIA) and surgical induction methods are the two most commonly used to create experimental knee OA models with rats.\textsuperscript{7,8} The surgical induction methods are particularly suited for studying post-traumatic knee OA.

In humans, previous ligamentous knee joint injury, such as an ACL tear, is a major risk factor for knee OA.\textsuperscript{9} In most instances, an ACL tear is accompanied by a meniscal tear.\textsuperscript{10} On average, 50\% of individuals develop knee OA within 10 to 20 years after an ACL tear.\textsuperscript{10,11}

We used a preclinical rat model of post-traumatic knee OA created by ACL transection with partial medial menisectomy (ACLT + pMMx).\textsuperscript{12-15} The model acts by destabilizing the joint and disrupting its biomechanics, and thus has high clinical relevance in the study of knee OA.\textsuperscript{12} This model’s changes in joint structure and gene expression have been well characterized in previous studies.\textsuperscript{12-15} Histology and micro-computed tomography (\textmu CT) of the knee joints have demonstrated the presence of changes that were characteristic of mild to moderate knee OA in the ACLT + pMMx rats between two and eight weeks post-surgery.\textsuperscript{12} The structural changes have been determined to be similar to early stage knee OA in humans.\textsuperscript{12} In rat models of post-traumatic knee OA, some aspects of their pain-related behaviours have been characterized, such as weight-bearing deficit and gait changes.\textsuperscript{7} However, static weight-bearing and exploratory motor behaviour (spontaneous
locomotor activities) have not been previously published for this particular model, to the best of our knowledge.

The assessment of pain and physical function are vital components of the clinical assessment of patients with symptomatic knee OA. The assessment of pain-related behaviour is becoming more popular in rat models of OA because of its utility for increasing the translatability of animal studies to human clinical settings. This increased popularity is made evident by the recent special issue from the journal Osteoarthritis and Cartilage on ‘Pain in Osteoarthritis’ and other recent publications. Most of this published work has been done with MIA induced rat models of OA that induce mechanical allodynia, which is common in painful non-injured sites in humans. Exploratory motor behaviour, as investigated in the present study, has not been previously published for any rat model of post-traumatic knee OA but has been used with other post-surgery rodent models. Exploratory motor behaviour was recently characterized for a mouse model of post-traumatic knee OA by testing spontaneous locomotor activity in an open field tester. The investigators found no difference between the model and sham groups, which might be a consequence of the period of assessment or the variables of exploratory motor behaviour that were studied. Other studies using rat models of knee OA have observed certain characteristics of activity limitation such as reduced locomotion, rearing and climbing. Pain-related behaviour exhibited by a rat model of OA is dependent on the type rather than the extent of joint damage.

Therefore, the aim of this study was to determine whether static weight-bearing and variables of exploratory motor behaviour in rats can be used to distinguish between an ACLT + pMMx-induced rat model of post-traumatic knee OA and a sham surgery control.
4.3 Methods

4.3.1 Animals

All experimental procedures were conducted in accordance with protocols approved by the University of Western Ontario Animal Care and Use Committee in agreement with federal regulations (Animal protocol No. 2007-045). Subjects were male Sprague-Dawley rats (Charles River Laboratories, St. Constant, Quebec, Canada) that arrived at 10 weeks old and weighed between 301g to 325g. The rats were caged doubly and then singly after surgery in a ventilated animal room with controlled temperature (20°C to 25°C) and controlled humidity (40% to 60%). They were placed on a 12 hour light/dark cycle starting at 7 am and received food and water ad libitum.

4.3.2 Study design

Figure 4.1 is a schematic of the experiment protocol. Rats were randomly allocated to the two main study groups, two alternate groups, and a naïve group (n = 5). The alternate ACLT + pMMx and sham groups were sacrificed at four weeks post-surgery, and the main study groups and the naïve group were sacrificed at eight weeks post-surgery by CO₂ asphyxiation. Hindlimbs were harvested, then fixed in 4% paraformaldehyde overnight, and decalcified for four days in Formical-2000 (Decal Chemical Corp.) for later histological assessment. The alternate groups were treated in the same manner as the main study groups, including behaviour assessments.
Figure 4.1: Schematic of experimental protocol. Three months old male Sprague–Dawley rats were acclimatized for 1 week. They then underwent ACLT + pMMx ($n = 6$), sham surgery ($n = 5$), or were naïve ($n = 5$). At the same time, a drug delivery pump with distilled water as vehicle was installed under the skin in the mid-saggital region of the back. Pump revision surgery was done at 4 weeks after induction surgery to install a newly filled pump to replace the exhausted pump. The rats were followed for 8 weeks after ACLT + pMMx or sham surgery, and static weight-bearing and exploratory motor behaviour was assessed at five and three post-surgery time points, respectively. Two alternate groups were followed for 4 weeks post-surgery, to access early knee structural changes.
4.3.3 ACLT + pMMx-induced OA

The ACLT + pMMx group \((n = 6)\) had surgery to their right hindlimb to induce the model of post-traumatic knee OA using a well-established protocol previously described, without forced mobilization following surgery.\(^{12-15,23}\) The sham group \((n = 5)\) had surgery only to visualize the ACL and medial meniscus of the right hindlimb. Additionally, to emulate the experimental conditions of pre-clinical drug treatment trials, an osmotic minipump (Alzet 2ML4) filled with sterile distilled water was surgically installed subcutaneously between the scapulae of each rat in both the ACLT + pMMx and sham groups.\(^24\) A similar surgery was performed four weeks later, to replace the now exhausted pumps with fresh units. During surgery all rats were anaesthetized via isoflurane inhalation. Analgesic buprenorphine \((50\mu g/kg)\) was injected subcutaneously. This was done once pre-emptively during the surgery and once every 8 hours up to 48 hours following the surgery.

4.3.4 Structural joint changes

Animals from the main ACLT+pMMx group and sham group were sacrificed eight weeks post-surgery for histology assessments. The alternate groups were followed for four weeks post-surgery before their knee joints were harvested for histology to confirm the presence of early OA-related structural changes. Harvested limbs were processed and embedded in paraffin wax following fixation and decalcification. Serial frontal sections were cut spanning the loading portion of the ipsilateral (right) knee joint. Sections were stained from six different depths spanning approximately 1200µm of the joint, using 0.04% toluidine blue.\(^{25}\) Structural joint changes were assessed by using the Osteoarthritis Research Society International (OARSI) guidelines for histomorphometry and pathology scoring by a blinded scorer (M.A.P.).\(^{26}\) This guideline is an ordinal grading system in which lower scores represent less cartilage degeneration.\(^{26}\) Grading was performed for three zones for each of medial tibial plateau (MTP) and the medial femoral condyle (MFC). For each, the grades have numeric values of 0, 1, 2, 3, 4, and 5 with the corresponding descriptors being none, minimal \((5-10\%)\), mild \((11-25\%)\), moderate \((26-50\%)\), marked \((51-75\%)\), and severe \((more than 75\%)\) respectively. The final cartilage degeneration score for the MTP and for
the MFC was calculated by summing the scores from the three zones of each respective anatomic site.\textsuperscript{26}

\section*{4.3.5 Static weight-bearing}

Static weight-bearing was a construct of weight-bearing deficit between the ipsilateral (right) and contralateral hindlimbs when a rat was stationary.\textsuperscript{7, 22} This was assessed during the 12 hour light phase at one, two, four, six, and eight weeks post-surgery using an Incapacitance Tester (Linton Instrumentation, Norfolk, UK) shown in Figure 4.2, with the exception of the six weeks’ time point for the naïve group. During the assessment procedure, each rat was habituated to a relatively static position in a conventional restrainer and separate transducers recorded the average weight on each hindlimb over five seconds for five trials. Changes in the hind paw weight-bearing distribution between the left (contralateral control) and right (ipsilateral) hindlimbs were utilized as an index of joint pain-like symptoms in the knees that had surgery to induce the model of knee OA. Therefore, as a likely indicator of OA pain, percent ipsilateral weight-bearing was subsequently calculated as weight on the ipsilateral hindlimb divided by weight on both hindlimbs multiplied by 100 as per.\textsuperscript{27} The average percent ipsilateral weight-bearing per rat at each time point was used in the statistical analyses.
Figure 4.2: Incapacitance Tester. This instrument was used to assess static weight-bearing.
General exploratory motor behaviour

Exploratory motor behaviour is a common construct that has been used in numerous pharmacologic and non-pharmacologic studies including small animal research dating back to the 1950s.\textsuperscript{28, 29} It captures spontaneous locomotor activity within a given space and is related to self-motivation and curiosity.\textsuperscript{7, 17, 28} Exploratory motor behaviour was assessed during the dark phase in an unlit animal room using an open field tester (AccuScan Instruments, Omnitech Electronic, Columbus, OH) with a transparent Plexiglas cage (height = 33 cm, width = 42 cm, and length = 42 cm), see Figure 4.3. The cage had three pairs of sensors. Each pair of sensors had 16 infrared light beams, equally spaced, that detected activity when broken. Two pairs of sensors captured activity in the horizontal plane at the base of the cage, and one pair captured vertical activity at 19 cm above the base of the cage. Data were automatically uploaded into a computer using the accompanying software. During the assessment, the computer screen was covered to minimize exposing the rats to illumination. Exploratory motor behaviour assessment was started at four weeks post-surgery, after allowing sufficient time for early stage knee OA-like structural joint changes to begin and post-surgery pain to dissipate. Each rat explored the open field for 30 minutes at four, six and eight weeks post-surgery. However, this assessment was done only at eight weeks post-surgery for the naïve group. Eighteen different variables of exploratory motor behaviour were captured, encompassing frequency counts and duration of horizontal, sedentary, stereotypic, revolution movement and vertical activities (see Table 4.1 for complete list). Disturbance of the rats was avoided during the assessments to avoid influencing their movement.
Figure 4.3: Open-field Tester. This instrument was used to assess exploratory motor behaviour.
<table>
<thead>
<tr>
<th>Variable*</th>
<th>Main Effects</th>
<th>Interaction Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group F(1,8), P-Value</td>
<td>Time F(2, 16), P-Value</td>
</tr>
<tr>
<td>Ambulatory Activity Count</td>
<td>3.61, 0.09</td>
<td>2.06, 0.16</td>
</tr>
<tr>
<td>Ambulatory Activity Time</td>
<td>5.13x10^{-3}, 0.99</td>
<td>4.93, 0.02</td>
</tr>
<tr>
<td>Ambulatory Episode Count</td>
<td>0.040, 0.85</td>
<td>12.1, &lt;0.001</td>
</tr>
<tr>
<td>Horizontal Activity Count</td>
<td>3.55, 0.10</td>
<td>1.99, 0.17</td>
</tr>
<tr>
<td>Locomotor Clockwise Revolutions</td>
<td>1.67, 0.219</td>
<td>3.58, 0.05</td>
</tr>
<tr>
<td>Locomotor Counter-Clockwise Revolutions</td>
<td>0.300, 0.60</td>
<td>6.45, 0.01</td>
</tr>
<tr>
<td>Movement Episode Count</td>
<td>0.389, 0.55</td>
<td>0.937, 0.41</td>
</tr>
<tr>
<td>Movement Time</td>
<td>2.66, 0.14</td>
<td>0.731, 0.50</td>
</tr>
<tr>
<td>Rest Episode Count</td>
<td>0.419, 0.54</td>
<td>0.922, 0.42</td>
</tr>
<tr>
<td>Rest Time</td>
<td>2.67, 0.14</td>
<td>0.725, 0.50</td>
</tr>
<tr>
<td>Total Distance</td>
<td>0.336, 0.578</td>
<td>6.07, 0.01</td>
</tr>
<tr>
<td>Stereotypic Activity Count</td>
<td>0.021, 0.89</td>
<td>2.06, 0.16</td>
</tr>
<tr>
<td>Stereotypic Episode Count</td>
<td>0.027, 0.87</td>
<td>1.81, 0.20</td>
</tr>
<tr>
<td>Stereotypic Episode Activity Count</td>
<td>2.99, 0.12</td>
<td>1.18, 0.20</td>
</tr>
<tr>
<td>Stereotypy Time</td>
<td>0.457, 0.52</td>
<td>4.48, 0.03</td>
</tr>
<tr>
<td>Vertical Activity Count</td>
<td>14.2, 0.005</td>
<td>3.29, 0.06</td>
</tr>
<tr>
<td>Vertical Activity Time</td>
<td>16.4, 0.004</td>
<td>10.1, 0.002</td>
</tr>
<tr>
<td>Vertical Activity Episode Count</td>
<td>16.7, <strong>0.004</strong></td>
<td>7.53, <strong>0.005</strong></td>
</tr>
</tbody>
</table>

* Distance is in centimeters, time is in seconds, count and revolution are in numbers.

Bolded $P$-values are significant at $P < 0.05$.

Only the three vertical activity groups showed a statistically significant main effect between the rat groups, while seven variables had a statistically significant main effect by time, of which two had a significant interaction effect.
4.3.7 Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences v.20 (SPSS Inc. Chicago, Illinois) and GraphPad Prism® v4 (San Diego, California). Graphs were constructed in GraphPad Prism® using means and their corresponding 95% confidence intervals (CI).

Each dependent variable was a continuous variable, and had independence of observation at each time point in this study. The following tests of the underlying assumptions of the statistical analyses were performed and the data properties confirmed, unless otherwise stated below. Any outliers in the data, for each dependent variable within each group, were identified using the outlier labeling rule with the $k$ coefficient = 2.2. Normality of the data distribution was assessed using the Shapiro-Wilk test of normality. Homogeneity of variance was assessed using Levene’s test for homogeneity of variance during the analysis of variance (ANOVA) and Student’s unpaired $t$-test. Sphericity was assessed using Mauchly’s test of sphericity during two-way repeated measures ANOVA. Differences between groups were based on statistical significance. In all analyses, statistical significance was tested with a two-tailed $P < 0.05$ with adjustment for multiple comparisons where applicable, such as Tukey’s post hoc test after one-way ANOVA and Bonferroni’s multiple comparison test that had one family with a family-wise alpha of 0.05 for each variable tested at each time point.

4.3.8 Analysis of static weight-bearing

We hypothesized that, from one through eight weeks post-surgery, percent ipsilateral weight-bearing would have significantly lower values for the ACLT + pMMx group compared to the sham group. This hypothesis was tested using two-way repeated measures ANOVA, with post-surgery time point and rat group as the two independent variables, and percent ipsilateral weight-bearing as the dependent variable. This was followed by Student’s unpaired $t$-test of the main effects by rat group, one-way ANOVA with Tukey’s post-hoc testing of main effects by post-surgery time, and univariate parsing of interaction effects to evaluate static weight-bearing between and within the ACLT + pMMx and sham.
groups across the time points. If a significant difference was found between the rat groups in the preceding analysis, Bonferroni’s multiple comparison test in GraphPad Prism® was used to evaluate whether percent ipsilateral weight-bearing values in the ACLT + pMMx and sham groups were significantly different from the values in the naïve group at four and eight weeks post-surgery.

4.3.9 **Analysis of exploratory motor behaviour**

For each of the 18 exploratory motor behaviour variables, we hypothesized that at four and eight weeks post-surgery, their values would have a statistically significant difference between and within the ACLT + pMMx and sham groups. Each hypothesis was tested using two-way repeated measures ANOVA as described for static weight-bearing. Each exploratory motor behaviour variable was a dependent variable. If the values of a variable were significantly different between the ACLT + pMMx and sham groups, Bonferroni’s multiple comparison test in GraphPad Prism®, evaluated whether their values in the ACLT + pMMx and sham groups were significantly different from values in the naïve group at eight weeks post-surgery.

Any dependent variable that had a significant difference between the ACLT + pMMx and sham groups was subsequently evaluated for association with OARSI cartilage degeneration scores at four and eight weeks post-surgery using Spearman’s correlation coefficient ($r_s$). Values range from 0 to ±1, with $r_s = -1$ or 1 representing stronger correlations.

4.4 **Results**

4.4.1 **Animal characteristics**

At surgery, the rats were about three months old with a mean (95% CI) weight of 409 (393-426)g, 401 (386-415)g, and 390 (371-409)g for the ACLT + pMMx, sham, and naïve groups respectively. There was no significant difference between the rat groups at surgery,
or at four weeks and eight weeks post-surgery. Data of one rat from the ACLT + pMMx group was removed due to significant upper outlier values on the three vertical activity variables. Therefore, each group had 5 rats. Data from each dependent variable were approximately normally distributed at each time point.

### 4.4.2 Structural changes of the joint

Evidence of cartilage degeneration (red arrowheads, [Figure 4.4(A)]) and osteophyte development (yellow asterisks, [Figure 4.4(A)]) that were indicative of knee OA-like changes, was found in the medial compartment of ipsilateral knee joints of the ACLT + pMMx animals but not in the sham animals at four and eight weeks post-surgery. The OARSI scores of cartilage degeneration showed a significant difference ($P < 0.005$, Mann-Whitney test) between the ACLT + pMMx and sham groups in both the medial tibial plateau (MTP) and medial femoral condyle (MFC). These groups’ respective mean scores of MTP degeneration at four weeks post-surgery were 4.2 (2.9-5.5) and 0.07 (-0.12-0.25) and at eight weeks post-surgery were 6.0 (3.8-8.2) and 0.27 (0.15-0.38). These groups’ respective mean scores of MFC degeneration at four weeks post-surgery were 3.4 (2.3-4.5) and 0.10 (-0.09- 0.29) and at eight weeks post-surgery were 5.8 (3.1-8.6) and 0.07 (-0.05-0.18) [Figure 4.4(B) and Figure 4.4(C)]. Minor cartilage degeneration was observed in the lateral compartments of the ACLT + pMMx operated animals with significant differences compared to the sham animals [Supplementary data, Figure 4.5 (A, B)]. Evidence of minor fibrosis was identified in the medial but not the lateral synovium of the ACLT + pMMx animals [Supplementary data, Figure 4.5(C)].
Figure 4.4: Evidence of OA in ACLT + pMMx operated rats as shown by histology

(A) Representative toluidine blue stained sections of knee joints demonstrates histological changes congruent with early to mid OA in ACLT + pMMx (n = 6) but not sham operated animals (n = 5). Cartilage degeneration (red arrowheads) and osteophyte development (yellow asterisks) are indicated. (B) At 4 and (C) 8 weeks post-surgery, ACLT + pMMx rats showed significantly higher OARSI cartilage degeneration scores in the MTP and MFC of operated knee joints. **P < 0.005, Mann–Whitney statistical test. The values are presented as mean with 95% CI for each study group. T = medial tibia, F = medial femur.
4.4.3  The ACLT + pMMx animals demonstrated less ipsilateral static weight-bearing

Development of pain-like symptoms following ACLT + pMMx was supported by the static weight-bearing analysis (Figure 4.5). The ACLT + pMMx group had significantly lower percent ipsilateral weight-bearing when compared to the sham group. During the two-way ANOVA, sphericity was assumed (Mauchly’s W = 0.257, \( P = 0.478 \)), but the Greenhouse-Geisser’s F values were used. Percent ipsilateral weight-bearing showed a significant interaction effect between post-surgery time and rat group (\( F(2.95, 23.61) = 5.59, P = 0.005 \)), and a significant main effect by rat group (\( F(1, 8) = 161.26, P < 0.001 \)) and by time (\( F(2.95, 23.61) = 13.1, P < 0.001 \)). Student’s unpaired t-tests with normality and equal variance assumed, showed that the ACLT + pMMx group had significantly lower percent ipsilateral weight-bearing at each post-surgery time point when compared to the sham control (Figure 4.5). One-way ANOVA with Tukey’s post-hoc testing showed that percent ipsilateral weight-bearing in the ACLT + pMMx group was significantly lower for week one compared to the other follow-up weeks (\( F(2.74, 10.96) = 7.60, P = 0.006 \)), but not among the other weeks (\( P > 0.05 \)). Whereas, in the sham group, percent ipsilateral weight-bearing was significantly higher at six weeks post-surgery compared to one week and four weeks post-surgery (\( F(2.56, 10.24) = 10.7, P = 0.002 \)). However, the percent ipsilateral weight-bearing of the sham group was always equal to or greater than 50%.

Bonferroni’s multiple comparison test demonstrated that the mean percent ipsilateral weight-bearing of the naïve group was not significantly different from the ACLT + pMMx group at four weeks (\( t = 2.75, \text{adjusted } P = 0.103 \)), but was significantly higher than the ACLT + pMMx group at eight weeks post-surgery (\( t = 3.06, \text{adjusted } P = 0.020 \)). Also, the mean percent ipsilateral weight-bearing of the naïve group was not significantly different from the sham group at both four weeks (\( t = 0.658, \text{adjusted } P = 1.00 \)) and eight weeks post-surgery (\( t = 0.059, \text{adjusted } P = 1.00 \)).
Figure 4.5: Percent ipsilateral weight-bearing between rat groups. Percent ipsilateral weight-bearing assessed static weight-bearing as a likely indicator of pain. Percent ipsilateral weight-bearing was consistently statistically significantly lower for the ACLT/pMMx rats when compared to the sham operated rats. *At each time point, the groups had statistically significant difference at adjusted $P < 0.001$. The values are presented as means with 95% CI for each study group at each assessed post-surgery time point.
4.4.4 ACLT+pMMx animals performed less rearing in exploratory motor behaviour testing

Of the 18 variables of exploratory motor behaviour investigated, a significant difference between the rat groups was only observed for the three variables that captured vertical (or rearing) activity. Seven variables had a significant main effect by post-surgery time, and two variables had a significant interaction effect (Table 4.1). For group effects, Student’s unpaired t-tests showed that the ACLT + pMMx group had significantly lower vertical activity (episode count, time in seconds, and count) values at each of the assessment time points (Figure 4.4, Table 4.2). Only the sham group had a significant difference between time points, as observed where stereotypic activity time was different between week six and eight. Furthermore, for the sham group, six out of the other seven variables (the exception being total distance) had a significant difference between four weeks and eight weeks post-surgery (Table 4.2). Parsing of the two interaction effects revealed no additional significant difference between the groups at each time point.
Figure 4.6: Vertical episode count differed between rat groups. Vertical episode count was one of eighteen variables used to assess dynamic pain-related behaviour. It is one of the three vertical activity variable that consistently showed statistically significantly lower values for the ACLT + pMMx rats when compared to the sham operated rats from 4 through 8 weeks post-surgery. *At each time point, the groups had statistically significant difference at adjusted $P < 0.05$. The values are presented as means with 95% CI for each study group at each assessed post-surgery time point.
Table 4.2: Repeated Measures ANOVA post-hoc testing results for exploratory motor behaviour

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Post-surgery time, Sham and ACLT+pMMx group mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 4</td>
</tr>
<tr>
<td>Ambulatory Activity Count</td>
<td>1479 (-982 to 3940)</td>
</tr>
<tr>
<td>Ambulatory Activity Time†</td>
<td>4 (-47 to 55)</td>
</tr>
<tr>
<td>Ambulatory Episode Count†</td>
<td>-9 (-22 to 4)</td>
</tr>
<tr>
<td>Horizontal Activity Count</td>
<td>1462 (-1036 to 3961)</td>
</tr>
<tr>
<td>Locomotor Clockwise Revolutions</td>
<td>3 (-20 to 25)</td>
</tr>
<tr>
<td>Locomotor Counter-Clockwise Revolutions†</td>
<td>14 (-4 to 32)</td>
</tr>
<tr>
<td>Movement Episode Count</td>
<td>-16 (-61 to 29)</td>
</tr>
<tr>
<td>Movement Time</td>
<td>72 (-94 to 238)</td>
</tr>
<tr>
<td>Rest Episode Count</td>
<td>-16 (-61 to 29)</td>
</tr>
<tr>
<td>Rest Time</td>
<td>-72 (-238 to 94)</td>
</tr>
<tr>
<td>Total Distance</td>
<td>983 (-1996 to 3963)</td>
</tr>
<tr>
<td>Stereotypic Activity Count</td>
<td>-17 (-147 to 113)</td>
</tr>
<tr>
<td>Stereotypic Episode Activity Count</td>
<td>1029 (-956 to 3014)</td>
</tr>
<tr>
<td>Stereotypic Episode Count</td>
<td>-3 (-50 to 45)</td>
</tr>
<tr>
<td>Stereotypy Time‡</td>
<td>-5 (-29 to 19)</td>
</tr>
<tr>
<td>Vertical Activity Count†</td>
<td>449 (156 to 747)</td>
</tr>
<tr>
<td>Vertical Activity Time†</td>
<td>143 (42 to 244)</td>
</tr>
<tr>
<td>Vertical Episode Count†</td>
<td>66 (24 to 109)</td>
</tr>
</tbody>
</table>

* Distance is in centimeters, time is in seconds, count and revolution are in numbers.
† Statistically significant difference between week 4 and week 8 for the sham operated rats.
‡ Statistically significant difference between week 6 and week 8 for the sham operated rats.
§ Bonferroni’s multiple comparison test showed statistical significance between group differences at adjusted $P < 0.05.$
Bonferroni’s multiple comparison test showed that at eight weeks post-surgery, compared to the naïve group, the ACLT+pMMx group had a significantly lower vertical activity episode count ($t = 2.85$, adjusted $P = 0.029$) and vertical activity count ($t = 0.015$, adjusted $P = 0.019$), but similar vertical activity time ($t = 2.164$, adjusted $P = 0.103$). Whereas, Bonferroni’s multiple comparison test showed that at eight weeks post-surgery compared to the naïve group, the sham group had a similar vertical activity episode count ($t = 0.757$, adjusted $P = 0.927$), vertical activity count ($t = 0.757$, adjusted $P = 0.927$), and vertical activity time ($t = 0.267$, adjusted $P = 1.00$).

The OARSI cartilage degeneration scores for MTP and MFC association with percent ipsilateral weight-bearing and the variables of vertical activity were investigated. At eight weeks post-surgery, moderate to strong correlations were observed, which were in most cases statistically significant for MTP and for MFC with percent ipsilateral weight-bearing ($r_s = -0.71$, $P = 0.022$; $r_s = -0.65$, $P = 0.040$), vertical activity episode count ($r_s = -0.71$, $P = 0.020$; $r_s = -0.83$, $P = 0.003$), vertical activity time ($r_s = -0.70$, $P = 0.024$; $r_s = -0.54$, $P = 0.105$), and vertical activity count ($r_s = -0.59$, $P = 0.072$; $r_s = -0.68$, $P = 0.030$). The correlations at four weeks post-surgery were similar. The negative $r_s$ values indicated lower OARSI scores were correlated with higher percentage ipsilateral weight-bearing and higher vertical activity values.

### 4.5 Discussion

Our findings demonstrated that percentage ipsilateral weight-bearing and vertical (rearing) activity, based on statistical significance, differed between the ACLT + pMMx induced model of post-traumatic knee OA and sham surgery rats. Our data show that these two behaviours were moderately to strongly associated with the presence of mild to moderate osteoarthritic structural joint changes.\textsuperscript{12} Thus, the above findings provide evidence that these behaviours are consistent with symptoms of post-traumatic knee OA, and may be adequate for use to distinguish between rats with and without knee OA-like changes when using the ACLT + pMMx rat model.
It is common among research studies to find significant ipsilateral weight-bearing deficits in a knee OA rat model group when it is compared to a control group. Most studies of rat models of post-traumatic knee OA have assessed weight-bearing during the gait cycle of rats, and therefore, would not measure static weight-bearing. Most other studies that did assess static weight-bearing and demonstrated a statistically significant weight bearing deficit on the ipsilateral hindlimb used MIA-induced OA rat models. Studies that have assessed static weight-bearing for experimental models of post-traumatic knee OA either found no significant weight-bearing deficit or showed a significant difference while using short follow-up periods of usually up to four weeks post-surgery. Such short periods would only capture the very beginning stages of knee OA-like changes in the ACLT + pMMx rat model.

As far as we know, this is the first study to report on exploratory motor behaviour using the open field tester to assess rats with experimentally induced post-traumatic knee OA-like changes. The findings indicated that vertical (rearing) activity in the context of spontaneous locomotor activity may be useful in distinguishing between rats with and without ACLT + pMMx-induced knee OA-like changes. Findings of previous studies are conflicted on the utility of vertical activity in distinguishing between a post-traumatic model of knee OA and control groups in mice. One study found a significant difference in rearing activity between mice in a naïve group and a surgically destabilized medial meniscus induced model of knee OA at 16 weeks post-surgery. However, that study’s behavioural assessment was very lengthy, as it lasted 15 hours and used the Laboratory Animal Behavior Observation Registration and Analysis System (LABORAS) which utilizes vibration and force signals to detect exploratory motor behaviour. On the other hand, a 30 minute assessment in an open field tester found no significant difference in rearing time up to 12 weeks post-surgery between a bilateral cruciate ligament injury mouse model and a sham surgery group. Thus, the present study may be the first to provide support for vertical activity as a measure to distinguish between rats of a post-traumatic model of knee OA and control groups.

Vertical activity may be likened to sit-to-stand activity in humans, which is a valuable performance-based clinical measure of physical function in people with knee OA. Compared to age and gender-matched controls, humans with early stage medial knee OA
have been reported to put less weight on their affected side when transitioning from a sitting to a standing position.\textsuperscript{37} Interestingly, these individuals with knee OA reported no pain at the time of assessment, but had previously been symptomatic.\textsuperscript{37} Therefore, a weight-bearing deficit could be related not only to pain but also to limb strength.\textsuperscript{38} However, another study in humans showed that knee OA-related pain is moderately correlated with the time taken to perform the sit-to-stand activity.\textsuperscript{39} Thus, knee OA-related pain may be associated with a decrease in the number of vertical activity episodes performed within a given period of time.

Using sham surgery as a control allowed for most of the difference between the groups to be attributable to the ACLT + pMMx surgery, and consequently to knee OA changes. The naïve control, further substantiated the strength of our results, by showing a statistically significant difference with the ACLT + pMMx group, but not with the sham control. Assessment of exploratory motor behaviour began at four weeks post-surgery, after allowing post-surgical pain to dissipate and for early stage knee OA-like changes to be established\textsuperscript{12}. Furthermore, in the present study, the sham group did not develop OA-like structural changes compared to the development of OA-like changes in older middle-aged (12 months old) sham-operated rats in a previous study.\textsuperscript{40}

There were some limitations to this study. First, the ACL of the ACLT + pMMx rats were not reconstructed. Therefore interpreting whether the behavioural changes were independent of joint instability and attributable only to symptomatic knee OA-like changes is difficult.\textsuperscript{7} Second, values for some of the behavioural variables had high within-group variation. Thus, some statistical analyses may have been too underpowered to detect a statistically significant difference between the study groups for variables of exploratory motor behaviour other than the three vertical activity variables. In a future study, this limitation might be investigated by using larger group sizes and a longer duration for exploratory motor behaviour assessment. Also, another indication that a future study may benefit from a larger sample size was evident in the results of the static weight-bearing assessment where the naïve group’s ipsilateral weight bearing was higher than the ACLT + pMMx group at week 4 and week 8 post-surgery, but the difference was not statistically significant at week 4 post-surgery (i.e., adjusted $P = 0.103$). While, the naïve group had
almost identical scores to the sham group at both week 4 and week 8 post-surgery, as is made clear by the adjusted $P$-value of 1.0. Third, a drug delivery pump was installed, which makes our findings limited to conditions under which a similar approach is used for drug delivery. Efforts were taken to reduce the trauma involved in pump installation. However, it is possible that these surgeries, and the short term analgesics which followed may influence long term pain pathways. Fourth, changes in exploratory motor behaviour could reflect pain but also other disturbances. Finally, the assessor of the behavioural outcomes was not blinded to group allocation, which might have allowed some observer bias when measuring differences in ipsilateral percent weight-bearing between study groups. Future studies could use a blinded assessor when performing these assessments.

### 4.6 Conclusions

This study demonstrated that percent ipsilateral weight-bearing and three vertical activity variables (i.e. vertical activity count, vertical activity time, and vertical activity episode count) are useful measures to distinguish rats with and without ACLT + pMMx-induced post-traumatic knee OA-like changes. Our data suggest that these behavioural assays can be added as valuable functional outcome measures in studies using rat models of OA; however, their relevance for translational studies of new experimental treatments needs to be further evaluated.

### 4.7 Acknowledgements

C. B. H., M. A. P., and A. R. are supported in part by the Joint Motion Program— a Canadian Institute of Health Research (CIHR) Training Program in Musculoskeletal Health Research and Leadership. C. B. H. and M.A. P. are supported by CIHR doctoral scholarships. A.R. is supported by a doctoral fellowship from The Arthritis Society/Canadian Arthritis Network. F.B. is the Canada Research Chair in Musculoskeletal Research. Rat studies were supported by a CIHR grant (MOP 86574) to F.B.
4.8 Supplementary data

The following is the supplementary data related to this chapter:

Figure 4.7: No evidence of OA found in the lateral knee joint compartments of ACLT + pMMx operated rats

(A) Representative toluidine blue stained sections of knee joints demonstrates healthy lateral compartment cartilage in anterior cruciate ligament transection and partial medial meniscectomized (ACLT + pMMx, $n = 6$) and sham operated animals ($n = 5$). (B) At 4 and
(C) 8 weeks post-surgery, ACLT + pMMx rats showed very minor but statistically significantly higher OARSI cartilage degeneration scores in the lateral tibial plateau (LTP) and lateral femoral condyle (LFC) of operated knee joints. (D) Representative toluidine blue stained sections of the medial knee joint synovium shows minor fibrosis in ACLT + pMMX rats. (E) Representative toluidine blue stained sections of the lateral knee joint synovium shows comparable histology between ACLT + pMMX and sham operated rats. *$P < 0.05$, **$P < 0.005$, Mann–Whitney statistical test. The values are presented as mean with 95% CI for each study group. T = lateral tibia, F = lateral femur.
4.9 References


Chapter 5

5 General Discussion

In recent years, several studies have been published that investigated the identification, treatment and lived experiences of symptomatic knee OA to gain a better understanding of how to prevent or reduce its ill-effects and progression.1-4 These ill-effects include increasing pain, physical activity limitations, physical dysfunction, psychological dysfunction, and loss of quality of life.5 At present, there seems to be no single solution; but the progress that has been made demonstrates the importance of a multifactorial approach to the identification/diagnosis and treatment of symptomatic knee OA.5,6

Three domains that can be used to characterize phenotypes of pain in knee OA have previously been identified.6 These three domains highlight distinct characteristics of symptomatic knee OA that can be used in identifying, providing prognoses and treating knee OA.6 These three domains are “knee pathology, psychological distress, and pain neurophysiology” as stated by Kittelson et al. (2013: p. 422).6 Of particular importance to the research presented in this thesis was the psychological distress domain, because of its consistency with the definition used for illness perception and behaviour in this thesis.6

5.1 Measures of illness perception and behaviour

Chapter two of this thesis showed that 16 validated measures of illness perception and behaviour have been previously used to assess people with knee pain/OA. These measures fit with Kittelson et al’s examples of measures of psychological distress—measures of fear-avoidance beliefs, pain catastrophizing, self-efficacy, and coping.6 This means that the identified measures fit within the psychological distress domain used to define phenotypes of pain in knee OA. This supports the importance of the findings in chapter two, showing chapter two is a useful source of information that summarizes measures in the psychological distress domain that can be useful in therapy and research of people who have knee pain/OA. By using a novel strategy of applying four components derived from the definition used for illness perception and behaviour,11 my research was able to highlight
the measures’ comprehensiveness in operationalizing the concept in the 16 measures. Thus, chapter two is a useful resource for clinicians and researchers when they are selecting measures to assess illness perception and behaviour in people with knee pain/OA. However, users of these measures are recommended to delve deeper into research on the measurement properties of each measure before making their final decision to use any of the 16 measures.¹²

In chapter two, the primary findings indicated that the QuIKS was the only validated measure that captures all four components of illness perception and behaviour in the target sample. This finding supports the QuIKS’s potential to be an important measure in identifying and providing prognoses for people with early symptoms of knee OA. The QuIKS could be used alongside measures of knee pain and knee pathology to describe the phenotype of knee pain in individuals with early symptoms of knee OA. The diverse ways in which the measures of illness perception and behaviour have been used to account for changes in pain, physical activity, physical function, psychological function, and quality of life for people with knee pain/OA speaks to the importance of pursuing future work on the measurement properties of the QuIKS. When the scoping review was conducted, only one study had been published about the measurement properties of the QuIKS, and the publication provided content validation and proof of internal consistency.⁸ Also, there was another study which provided construct validation for one of its four subscales.¹³ Therefore, other measurement properties of the QuIKS needed to be evaluated before it can be used during the care of people with the early symptoms of knee OA.

### 5.2 Interval-level measure of illness perception and behaviour

In chapter three, construct validation was provided for the QuIKS beyond the published works identified in chapter two. More specifically, a Rasch-refined version of the QuIKS (QuIKS-R) was developed which has interval-level scaling of illness perception and behaviour in people with knee pain/OA. The interval-level scaling of illness perception and behaviour by the QuIKS-R is important because it allows for making interpretation on the
relative distance between scores. This kind of interpretation is not recommended when using nominal-level and ordinal-level scaling of measurement which are lower levels of measurements compared to interval-level measurement. Interestingly, none of the other 15 validated measures of illness perception and behaviour included in the scoping review obtained validation using Rasch analysis. Based on the findings in chapter two and chapter three, the QuIKS-R is the first measure to demonstrate interval-level scaling for illness perception and behaviour among people with knee pain/OA. This is significant, as it puts the QuIKS-R at the forefront of measures with sound measurement properties that can be used to discriminate illness perception and behaviour among persons with knee pain/OA.

5.3 Behavioural measures in a rat model of knee OA

A rat model was studied for this thesis at the stages of OA where structural changes in the knee joint were characteristic of mild-to-moderate knee OA in humans. In chapter four, ipsilateral weight-bearing deficit and vertical activity limitations were identified as two behaviours that could potentially enhance the translatability of results from preclinical rat model research into clinical research settings. The knee pathology and pain neurophysiology domains of this rat model of post-traumatic knee OA have already been well characterized in other studies.\(^{14-17}\) The two behaviours that were identified as a part of this thesis could be considered to fit in the *take remedial action* component of illness perception and behaviour, based on the reasoning that these two behaviours might reflect strategies the rats took to avoid knee symptoms. Furthermore, these two behaviours fall under the psychological distress domain of phenotypes of pain in knee OA. Thus, they strengthen this post-traumatic knee OA model for use in preclinical research, because now all three domains of the phenotypes of pain in knee OA are covered by the rat model.

5.4 Limitations

There are limitations across the three studies in this thesis. Regarding chapter two, the four components of illness perception and behaviour are not directly part of a theoretical framework and have not been individually studied and validated. Such validation may
require expert opinion. However, experts consulted on the scoping review were satisfied with the formulation of the components and their definitions. Furthermore, the components and their definitions were informed by prior work on the conceptualization of illness perception, on the conceptualization of illness behaviour, on people’s lived experience with knee pain/OA, and were also informed by general theories and models related to how people respond to being ill.7,11,18-20

Regarding chapter three, the results of the psychometric properties of the QuIKS-R are promising, but have not been verified in an independent sample. It is for this reason that a team of researchers and I presently engaged in ‘The QuIKS Knee Study’, which is presented in the future directions section that follows in this chapter. The QuIKS Knee Study is being conducted to provide further construct validation to, and interpretation of, scores on the QuIKS-R.

Regarding chapter four, more work needs to be done to provide conclusive findings on the behavioural measures utility in preclinical trials using the rat model of post-traumatic knee OA, such as determining whether these behaviours are removed with the use of pain medication. Such a study would provide more evidence that would verify or refute the interpretation that these behavioural outcomes were related to pain in knee OA.

5.5 Clinical implications

There are several clinical implications of the findings presented in this thesis. The scoping review presented in chapter two provides an interpretive review of measures that may be useful in a multifactorial approach to assessing the phenotype of pain in people with symptoms of knee OA. The QuIKS-R, presented in chapter three, is a new and promising tool for assessment within the psychological distress domain of people with early symptoms of knee OA. Therefore the QuIKS-R could be crucial in identifying issues that clinicians could address during therapy for people with early symptoms of knee OA. Ideally it would be used during the initial consultation between the patient and the clinician. Also, the QuIKS-R could be used to identify people in the community with emergent chronic OA-like pain who could benefit from conservative treatment such as
education and exercise. The rat model study presented in chapter four was a ‘bedside-to-bench’ work, which used knowledge from human research to inform the investigation of behaviours related to knee OA in a rat model of post-traumatic knee OA. Therefore, preclinical work performed using this model might be better translated into clinical settings, given that the behavioural factors in the model are now better understood.

5.6 Future directions: The QuIKS Knee Study

Currently, we are engaged in an ongoing research project called The QuIKS Knee Study. The project is investigating the ability of the QuIKS-R to identify people with OA-like knee pain who are more likely to have decreased physical activity, physical function, and health-related quality of life. This further validation of the QuIKS-R may prove it to be a useful measure for identifying, providing prognoses, and informing the therapy of people with knee OA-like symptoms. The QuIKS-R was created through Rasch analysis of data from the original 13-item QuIKS, data which were collected using a 35-item prototype questionnaire. Therefore, it is very important that the QuIKS-R undergo this independent validation with the new data being collected from its target population using this 13 item version.
5.7 References


Appendices

Appendix A Questionnaire to Identify Knee Symptoms (QuIKS)-R

**Questionnaire to Identify Knee Symptoms-R (QuIKS-R)**

**Instructions**

Tick one box to answer each question. If you are unclear about how to answer a question, please give your best answer.

**Medications**

The following statements describe things you might do to manage your knee pain with medications.

Tick the box that best describes how often each statement applies to you in the last 2 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I take pills before I do some activities to prevent knee pain.</td>
<td>□ 0</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 2</td>
</tr>
<tr>
<td>2. I take pills after I do some activities to reduce knee pain.</td>
<td>□ 0</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 2</td>
</tr>
<tr>
<td>3. I carry pills with me just in case my knees start to hurt.</td>
<td>□ 0</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 2</td>
</tr>
</tbody>
</table>

**Monitoring**

The following statements describe how you may monitor your knee symptoms.

Tick the box that best describes your agreement with each of the following statements in the last 2 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. I notice knee pain when kneeling.</td>
<td>□ 0</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 2</td>
</tr>
<tr>
<td>5. My knees feel stiff after sitting or standing for long periods of time.</td>
<td>□ 0</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 1</td>
<td>□ 2</td>
</tr>
</tbody>
</table>
6. My knees hurt after sitting or standing for long periods of time.

Interpreting

The following statements describe how you may interpret your ongoing knee symptoms.

Tick the box that best describes your agreement with each of the following statements in the last 2 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. I talk to family and friends about things I can do about my knee problems.</td>
<td>□₀</td>
<td>□₁</td>
<td>□₁</td>
<td>□₁</td>
<td>□₂</td>
</tr>
<tr>
<td>8. I consult my doctor about my knee problems.</td>
<td>□₀</td>
<td>□₁</td>
<td>□₁</td>
<td>□₁</td>
<td>□₂</td>
</tr>
<tr>
<td>9. I suspect my knee problems are the result of getting older.</td>
<td>□₀</td>
<td>□₁</td>
<td>□₁</td>
<td>□₁</td>
<td>□₂</td>
</tr>
<tr>
<td>10. I suspect my knee problems are arthritis.</td>
<td>□₀</td>
<td>□₁</td>
<td>□₁</td>
<td>□₁</td>
<td>□₂</td>
</tr>
</tbody>
</table>

Modifying

The following statements describe how you may modify activities in response to knee pain.

Tick the box that best describes your agreement with each of the following statements in the last 2 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. I participate in certain activities less often to avoid aggravating my knees.</td>
<td>□₀</td>
<td>□₁</td>
<td>□₁</td>
<td>□₁</td>
<td>□₂</td>
</tr>
<tr>
<td>12. I am considering stopping a favorite activity due to my knees.</td>
<td>□₀</td>
<td>□₁</td>
<td>□₁</td>
<td>□₁</td>
<td>□₂</td>
</tr>
<tr>
<td>13. I am considering changing my exercise routine due to my knee problems.</td>
<td>□₀</td>
<td>□₁</td>
<td>□₁</td>
<td>□₁</td>
<td>□₂</td>
</tr>
</tbody>
</table>
The conversion table below is for Clinicians Use Only

QuIKS-R raw total score = ____________  QuIKS-R final score = ____________

Conversion Table

<table>
<thead>
<tr>
<th>Total Raw Score</th>
<th>Final Score</th>
<th>Total Raw Score</th>
<th>Final Score</th>
<th>Total Raw Score</th>
<th>Final Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>9</td>
<td>66.2</td>
<td>18</td>
<td>29.7</td>
</tr>
<tr>
<td>1</td>
<td>94.8</td>
<td>10</td>
<td>59.2</td>
<td>19</td>
<td>26.7</td>
</tr>
<tr>
<td>2</td>
<td>90.6</td>
<td>11</td>
<td>52.9</td>
<td>20</td>
<td>23.8</td>
</tr>
<tr>
<td>3</td>
<td>87.3</td>
<td>12</td>
<td>48.2</td>
<td>21</td>
<td>20.9</td>
</tr>
<tr>
<td>4</td>
<td>84.4</td>
<td>13</td>
<td>44.5</td>
<td>22</td>
<td>17.9</td>
</tr>
<tr>
<td>5</td>
<td>81.6</td>
<td>14</td>
<td>41.2</td>
<td>23</td>
<td>14.9</td>
</tr>
<tr>
<td>6</td>
<td>78.6</td>
<td>15</td>
<td>38.3</td>
<td>24</td>
<td>11.4</td>
</tr>
<tr>
<td>7</td>
<td>75.3</td>
<td>16</td>
<td>35.4</td>
<td>25</td>
<td>6.6</td>
</tr>
<tr>
<td>8</td>
<td>71.2</td>
<td>17</td>
<td>32.6</td>
<td>26</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix B Ethics board approval for Chapter 3

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Bert Chesworth
Review Number: 17740E
Review Level: Delegated
Approved Local Adult Participants: 140
Approved Local Minor Participants: 0
Protocol Title: Item reduction, validation, and test-retest reliability of the Questionnaire to Identify Knee Symptoms (QUINS): A new clinical screening tool.
Department & Institution: Epidemiology & Biostatistics, University of Western Ontario
Sponsor:
Ethics Approval Date: March 25, 2011
Expiry Date: August 31, 2012
Documents Reviewed & Approved & Documents Received for Information:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Comments</th>
<th>Version Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>UWO Protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Pre-notice</td>
<td></td>
</tr>
<tr>
<td>Letter of Information &amp; Consent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Reminder 1 and Reminder 2</td>
<td></td>
</tr>
<tr>
<td>Letter of Information &amp; Consent</td>
<td>HK Group</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Reminder - HK Group</td>
<td></td>
</tr>
<tr>
<td>Advertisement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research

Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the North American Council for Clinical Practice Standards: Consolidated Guidelines, and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approved date noted above. The membership of this REB also complies with the membership requirements for REBs as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require and updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The UWO HSREB is registered with the U.S. Department of Health & Human Services under the IRB registry number #351006.

Signature

Ethics Officer to Contact for Further Information

[Signature]

This is an official document. Please retain the original in your files.

The University of Western Ontario
Office of Research Ethics
Room 5150, Support Services Building • London, Ontario • CANADA • N6A 3K7
P: 519-661-3036 • F: 519-850-2466 • ethics@uwwo.ca • www.uwo.ca/research/ethics
Appendix C Institutional ethics board approval for Chapter 3

Clinical Research Impact at Fowler Kennedy Sports Medicine Clinic

Title: Item reduction, validation, and test-retest reliability of the Questionnaire to Identify Knee Pain Symptoms (QuIKS): A new clinical screening tool.

Research Ethics Board Number: 17740E

Principal Investigator: Dr. Bert Cherworth, bcherwor@uwoc.ca

Student Researcher/Study Coordinator: Clayon Hamilton, chaml7@uwoc.ca

Summary of Study

The study is developing, validating & assessing reliability of a pre-diagnosed knee OA screening tool (QuIKS). The study includes 3 groups (n=52) of persons at distinct positions along the natural history of OA disease: (1) pain-free healthy knees (HK) - no OA, to be recruited by posters notices on Western’s campus. (2) knee pain problems (KP) but no OA (data already collected). (3) patients with knee OA awaiting HTO (pre-HTO) at Fowler Kennedy Clinic, to be recruited by mailed letters.

For validation purposes, recruits would answer the QuIKS and two self-report questionnaires commonly used in the clinical setting. A subset of HK group participants (n=27) and pre-HTO participants would be asked to complete forms twice (test-retest reliability). Also, the Kellgren-Lawrence OA grade will be obtained from the x-ray database (PACS).

Researchers Interaction with Fowler Kennedy Clinic

The primary interaction will be with the administrative assistant of the following orthopaedic surgeons: Doctors Robert Giffin, Marie-Eve Lebel, Robert Litchfield, and Kevin Willits. These orthopaedic surgeons will facilitate access to their patients through their administrative assistant. Interaction to retrieve names and mailing address of each potential participant will be with the administrative assistant of each orthopaedic surgeon once per week on the day stated below in the table:

<table>
<thead>
<tr>
<th>Administrative Assistant</th>
<th>Orthopaedic Surgeon</th>
<th>Surgical Booking Review Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anne</td>
<td>Dr. Kevin Willits</td>
<td>Tuesday</td>
</tr>
<tr>
<td>Cheryl</td>
<td>Dr. Robert Giffin</td>
<td>Tuesday</td>
</tr>
<tr>
<td>Jennie</td>
<td>Dr. Marie-Eve Lebel</td>
<td>Thursday</td>
</tr>
<tr>
<td>Sue</td>
<td>Dr. Bob Litchfield</td>
<td>Thursday</td>
</tr>
</tbody>
</table>

The administrative assistants will give the study coordinator (Clayon Hamilton) access to the Surgical Booking Schedule of each surgeon. Clayon will review the Surgical Booking Schedule once per week to look for scheduled HTO patients. He will not discuss booking dates with patients. If a patient asks Clayon questions about their surgery or surgery date while he is corresponding with them about his project, he will refer them back to their surgeon or administrative assistant. Clayon will work with Ian Jones in the WOBL laboratory to obtain and score the Kellgren-Lawrence OA grade for the symptomatic knee of study participants.

Anne (for Dr. Kevin Willits) Date
Cheryl (for Dr. Robert Giffin) Date
Jennie (for Dr. Marie-Eve Lebel) Date
Dianne Bryant, PhD Date
Ian Jones (WOBL Lab) Date
# Curriculum Vitae

**Name:** Clayon B. Hamilton

**Post-secondary Education and Degrees:**

- **Ph.D. in Health and Rehabilitation Science (2011 - 2015)**
  - University of Western Ontario
  - London, Ontario, Canada

  Health Sector Stream, MBA Program (Certificate of Completion, 2013 - 2014)
  - Richard Ivey School of Business, University of Western Ontario
  - London, Ontario, Canada

- **M.Sc. in Health and Rehabilitation Science (2009 - 2011)**
  - University of Western Ontario
  - London, Ontario, Canada

  - Northern Caribbean University
  - Manchester, Jamaica, West Indies

**Honours and Awards:**

- **CIHR- Doctoral Research Award**
  - May 2013 - Jul 2015

  CIHR Graduate Fellowship in Musculoskeletal Health Research and Leadership [Doctoral]
  - Sept 2011 - Aug 2015

  CIHR Graduate Fellowship in Musculoskeletal Health Research and Leadership [Masters]
  - Jan 2011 - Aug 2011

**Related Work Experience:**

- **Research Assistant**
  - South West LHIN, London, Ontario, Canada

- **Graduate Teaching Assistant**
  - University of Western Ontario, London, Canada
Peer-reviewed Publications:


Technical Reports: