IS CARDIOMETABOLIC RISK ASSOCIATED WITH PHYSICAL FUNCTION IN THE TOTAL KNEE AND HIP ARTHROPLASTY POPULATION?

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

The purpose of this study was to determine the association of each of five cardiometabolic risk factors (diabetes, hypertension, elevated triglycerides, low high density lipoproteins, obesity), and MetS (three or more risk factors present) with the level of physical function 1) prior to surgery in patients with TKA/THA surgery and 2) 6 weeks postsurgery in patients with TKA/THA surgery, controlling for age, sex, physical activity, and comorbidity.

Patient physical function data were retrospectively extracted from a clinical orthopedic database between September of 2008 and November of 2010. Comorbidities were obtained by chart abstraction. Patients were ≥40 years old with a primary total hip or knee arthroplasty. Relationships between MetS and its individual components, and physical function were completed using the Lower Extremity Function Scale (LEFS) and SF-36 physical component score (PCS). Covariates were age, sex, comorbidities, and physical activity.

Preoperatively, a total of 174 TKA and 112 THA candidates were included. For TKA candidates, mean LEFS scores were significantly ($p<0.001$) lower for patients with MetS (30.0, SD 14.2) than without MetS (39.9, SD 16.0). In TKA cohort, MetS remained significantly associated with reduced lower-extremity physical function; additionally, female sex, chronic back pain and insomnia significantly reduced preoperative lower-extremity physical function, in the adjusted analysis. For THA

candidates, adjusted analysis found MetS and being female were significantly ($p<0.05$) associated with worse lower-extremity physical function.

Postoperatively, 170 and 111 patients with a total knee and total hip arthroplasty were included. In the adjusted analysis: Diabetes, chronic back pain and presurgical physical function remained significantly associated with reduced postoperative lower-extremity physical function. For THA, being female, chronic back pain and presurgical physical function were significantly ($p<0.05$) associated with worse physical health. MetS was not significantly associated with postoperative physical function (PCS or LEFS) in the THA/TKA population.

This study provides evidence that MetS, back pain, and insomnia are modifiable conditions that influence preoperative physical function while back pain, diabetes and preoperative physical function are modifiable conditions that influence postoperative physical function. MetS was not associated with postoperative physical function in either the TKA or THA cohort.

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CHAPTER 1

INTRODUCTION

This chapter is composed of two sections. The first section is a brief overview of what is known about the postsurgical recovery of patients with total knee or total hip arthroplasty (TJR). The second section is an introduction to the Health Outcomes in the Arthroplasty Population project, an overview of the development and implementation of patient outcomes into routine clinical practice.

1.1 Review of the literature

Osteoarthritis (OA) is the most frequently reported condition utilizing TJR for management of pain and disability. There is generally a high success rate with TJR yet there is approximately 15% -30% of the TJR population that is not satisfied with their surgical outcome. Clarification of the expected postoperative recovery and determining what factors are related to recovery pattern is required to better understand how TJR patient outcomes can be improved. Many patient related factors have been investigated to predict TJR outcome. Specifically, comorbidity is one patient factor that has been poorly measured and documented in the TJR population. The high prevalence of comorbidity in the OA population may indeed impact the outcome after TJR as these

comorbidities are not modified by the TJR surgical procedure and may contribute to the compromised TJR success rate.

1.1.1 Osteoarthritis

Osteoarthritis (OA) is highly prevalent,[1-2] incurs substantial costs and functional challenges. Most people live for many years with OA which gradually worsens. The clinical symptoms are dominated by pain and functional impairment that includes joint stiffness and dysfunction most commonly related to the joints of hip, knee, hand, foot and spine.[3] This leads to impaired performance in the workplace; 25% of patients cannot perform their main activities of daily life, which often leads to social isolation and depression.[4-5] More than 13% of Americans aged 55 to 64 years and more than 17% of Americans aged 65 to 74 years, have pain and functional limitations related to knee OA.[1] In addition to the direct costs incurred due to health care utilization in diagnosis and treatment of OA, indirect costs are incurred by both patients and their caregivers related to absence from loss of work days due to treatment, reduced effectiveness at work and losses attributable to the disease preventing persons from working at, or taking, better paying jobs, early retirement and loss of selfesteem and other psychological difficulties.[6]

1.1.2 Total knee and hip arthroplasty

Management of end stage OA often results in a patient undergoing a total knee or total hip arthroplasty (TJR). In 2006, 454,000 primary total knee and 232,000 total hip arthroplasty surgeries were performed.[7] The estimated total hospital cost for joint replacements in 2004 was $30 billion. When evaluating surgically related outcomes, TJR

is seen as an effective intervention, there is a low rate of mortality and few severe adverse outcomes associated with the surgery.[8-11] Studies have shown that TJR's improve patient's health related quality of life(QoL), reduce pain and increase functional capacity.[12-16] Yet, about 15-30% of patients report little or no improvement after surgery or are unsatisfied with the results.[17-22] The number of TJR's is predicted to increase such that by the year 2030 there will be over 3.5 million procedures completed per year.[7] Although TJR is one of the most clinically successful and cost-effective interventions in medicine[23-26] due to the high the number of TJR procedures predicted to increase there could conceivably be a substantial proportion of the population who report little or no improvement. Thus, understanding determinants of patient success or nonimprovement is essential.

1.1.3 Recovery after total joint replacement

The pattern of recovery after TJR is an important aspect of the rehabilitative phase after surgery which provides guidance to patients, caregivers and medical staff. Interpretation of the physical function pattern of recovery has been convoluted due to varying time points being evaluated (early, short and long) and multiple outcomes.

Postoperative functional ability has been evaluated with different outcomes such as quadriceps strength,[27] quality of life,[28] disability[29-31] and physical performance measures[30, 32] thereby making comparisons difficult. Recently, Kennedy et al. (2006) graphed physical function in the early phase of recovery (with 15 weeks after surgery) and showed that recovery was nonlinear with an accelerated rate of recovery occurring in the first 6-9 weeks followed by a slower rate of recovery and a plateau occurring about 12

weeks after surgery.[33] Similar results were seen in studies which with 1-2 year follow-up time periods of recovery were graphed.[31, 34] These studies provide an excellent visualization as to what recovery looks like in a controlled research setting. Confirmation that the pattern of recovery is similar in the actual clinical setting, where patients are not recruited and methodologically scheduled for follow-up appointments, is yet to be determined. To understand what is happening in the rehabilitation phase after TJR, we have completed preliminary analysis of patterns of recovery within the usual physical therapy practice setting evaluating the pattern of recovery of those with total hip replacement (THR) that have functional outcome measurements for at least three physical therapy visits. Using the minimally clinically important difference (MCID) as the measure of change, patient self-reported functional evaluation measures showed that 65% of the postoperative THR patients had achieved significant amount of improvement from their first appointment whereas 32% of the THR did not change and 3% were worse than their first appointment. Further, preliminary examination of patient characteristics (age, gender, time from surgery and the number of visits) indicated that there may be a differences between changers and nonchangers.[35] Mixed-model nonlinear graphing of this population resulted in a similar recovery pattern illustrated by Kennedy et al.(2006) although the patients in the actual clinical practice started with a lower functional outcome at initiation and had a lower functional outcome at discharge.[33] Useful as a guideline, these recovery curves also show that the accuracy of the predicted recovery for an individual patient may be due to the various patient related factors that contribute to TJR recovery due to the large amount of variation seen in the rate of recovery. The clinical data in this preliminary work have selection bias, as these patients are only those

who attend physical therapy; there is a gap in knowing how many people after surgery receive outpatient physical therapy and the pattern of recovery for all patients.

1.1.4 Factors relating to recovery

Determining what characteristics provide the best predictor of recovery is inconclusive. Understanding what characteristics affect the patient's recovery pattern and functional outcome would provide important information in the management of the postoperative TJR patient. Patient related factors such as demographic variables (age, weight and sex), medical variables (diagnosis, comorbid conditions and ambulatory status), patient satisfaction, physical function and health related quality of life (QoL) have all been investigated with inconsistent results. There is limited consensus on what factors affect outcome. Variables that have achieved some consensus on postsurgical outcome are sex; preoperative physical function and health status; and whether the patient undergoes a unilateral or bilateral procedure.[13, 27, 29-30, 36-43]

1.1.5 Importance of comorbidities

Comorbidity is one patient characteristic that has not been well studied in the TJR population. Comorbidity is defined as the co-occurrence of two or more diseases in the same individual.[44] Comorbidities have shown to increase the risk of major health-related outcomes (disability or mortality), higher health care utilization and expenditures.[45] OA is one of the diseases with the highest rate of comorbidity[46-48] and patients with OA have a significantly higher risk of developing comorbidity than non-OA patients.[49-50] Generally, there is no increased risk of mortality related to OA but there is moderate

evidence of increased cause-specific mortality among persons with OA compared with the general population from cardiovascular and gastrointestinal disorders. Risk factors for mortality in persons with OA included an increased burden of osteoarthritis, advanced age and presence of comorbid conditions.[51]

As previously established, people with OA have increased disability. Similarly, people with comorbidity have increased disability[52-57] Understanding how comorbidities may influence TJR functional outcomes is important to the recovery process and may help to explain the faction of people not satisfied or report limited change after the pain from OA is removed with joint replacement.

1.1.6 Measuring comorbidity

In the TJR population measurement of comorbidity has mainly been used to control for confounding, estimating the risk of death, complications and costs. Rarely has comorbidity been used as a predictor of functional outcome. Measures of comorbidity can be as simple as a count of the number of comorbid diseases present [46, 58] or the measure can be a more comprehensive index that accounts for disease severity. Comorbidity measurement approaches used in the TJR literature are varied and inconsistent. Measures of comorbidity have not been developed for an OA or TJR population and often the population that was used in the development is not comparable to the TJR population or does not include conditions that are important to the TJR population. For example, the Charlson Comorbidity Index (CCI) was developed to measure the relative mortality risk for people aged more than 65.[59] The CCI is composed of 22 medical conditions each assigned with a weight scale ranging from 1 to 6

depending on the risk of dying. The final CCI score is the sum of the weights assigned to 22 predetermined clinical conditions, a higher score correlates with greater burden of comorbidities and can be used to predict one year mortality.[59] Some studies which have counted the number of comorbidities and then establish cut points that do not support the prevalence of comorbidity in the OA population nor are standardized to allow for comparison across studies cut points. For example, one study established cut off values of comorbidity as 'none' and equal to or greater than 1. The expected prevalence of comorbidity is underrepresented compared to what is noted in the OA population. Verification of the prevalent comorbidities in the TJR population and valid measures of comorbidity are needed in the TJR population.[29] In addition, often only a summed value was provided for a dichotomized variable without any indication of which conditions were included in the sum or the number of conditions reviewed. There has been only one study which has specifically studied the impact of specific comorbidities on QoL.[60] This study was a cross-sectional survey of 293 veteran men who had undergone a primary TKA. Health status information was collected 2-3 years after surgery using the Short Form-36 for veterans (SF-36 V) while comorbidity information was acquired from the Veterans Affairs database probably at the time of surgery. Multivariate linear regression was used to assess associations between individual component scores of the Short Form-36 for veterans (SF-36 V) and the two summary scores (physical component (PCS) and mental component (MCS)) and five comorbidities (chronic obstructive pulmonary disease (COPD)/asthma, diabetes, depression, hypertension and heart disease). Results indicate that medical and psychiatric comorbidity are negatively associated with mental/emotional QoL, individual comorbidities have different affects on QoL and that a

greater number of conditions negatively impacts both physical and mental/emotional QoL.

Four areas have been highlighted establishing comorbidity as an area requiring further research in the TJR population, summarized as follows: 1) there is a high prevalence of comorbidity established in OA population but limited studies have investigated comorbidity for those undergoing TJR surgery, 2) there are few standardized conditions and comorbidity indexes used in the measurement of comorbidity in the TJR population, 3) comorbidity is often used as a means for adjusting for common diseases rather than being used to provide consideration for the impact the specific comorbidity may have on TJR functional outcome and 4) there has only been one study that has specifically investigated the association of comorbidity and functional outcome although this study has some methodological problems.

1.1.7 Cardiometabolic risk factors

Cardiometabolic risk (CMR) is defined by the American Heart Association as major risk factors (RF) that significantly increase the risk of heart and blood vessel disease and are classified as modifiable (diabetes, obesity, hypertension, inflammation and anticoagulation, abnormal lipid metabolism, physical inactivity, smoking) and non-modifiable risk factors (age, gender, race, ethnicity and family history).[61] The relationship of OA and cardiovascular disease (CVD) is twofold. First, the most common comorbidity for people with OA is CVD.[49] Second, recent research suggests the etiology between OA and CVD are as associated disease pathways with differing outcomes mainly as a result from the inflammation process within the body.[62] The expected

outcome after TJR is to have relief of pain and regain functional ability. If these CMR factors are prevalent in the TJR population these CMR factors may be contributing to the dissatisfaction or lack of improvement in the TJR population even after the OA related impairments and disabilities have been remedied with TJR. Limited studies have specifically investigated these CMR factors and their affect on TJR outcome and are briefly reviewed here.

Diabetes and obesity are the most researched of the CMR risk factors in the TJR population and have mixed findings reported. Some studies have shown that those with diabetes (DM) are more likely to be discharged to a rehabilitation center rather than going directly home and have slower rates of progression after surgery but at one year after surgery patients with DM appear have the same level of function as those without DM. When functional outcomes are evaluated 3-8 years after TKA surgery patients with diabetes are associated with both worse functional and better knee function than those without DM.[63-64] Differences between those with and without DM are noted when outcomes are evaluated during the hospital stay which have shown increased odds of stroke, pneumonia and transfusion and often have more complications in those with DM than those without DM resulting in increased utilization of resources and cost.[65-67]

The effect of obesity on recovery is inconclusive. Studies have shown TJR patients who are obese have increased complications but the effect on functional outcome is unknown,[67-69] while other studies show that obesity is negatively correlated with functional score[70] and yet other studies are unclear or show no effect for short-term and long-term outcomes.[13, 38-39, 71-72] The perplexity with obesity may be the other conditions that are often associated with obesity such as hypertension (HTN), lipid metabolism and

inflammation.

Of the remaining modifiable risk factors, one study has investigated hypertension (HTN)[67] and one study investigated physical activity[73] in the TJR population. There are no reports of the effect of lipid metabolism and inflammation on the outcome of TJR. HTN has been shown to be a major risk factor for complications after TJR, an independent predictor of postoperative complications and nonhomebound discharge but has not specifically been assessed with functional outcome.[67]

Reports on the amount of physical activity (PA), a critical component in the rehabilitation phase after TJR and a modifiable risk factor, are limited in TJR literature. Wegenmaker et al.(2008) found that THA patients in Holland are at least as physically active as a normative population after THA. It is unknown whether similar findings would apply to a USA population.[73]

The clustering of CMR factors (central adiposity, elevated fasting glucose, hypertension and dyslipidemia defined by high serum triglycerides and low high-density lipoprotein cholesterol) is referred to as metabolic syndrome. Metabolic syndrome, is increasing in prevalence and appears to be related to the increased risk of developing CVD and diabetes yet the contribution of metabolic syndrome towards cardiovascular risk has been debated over the last few years.[74] There is agreement regarding the important independent contribution each CMR risk factor takes in cardiovascular health. A lack of consensus remains regarding the effect of the sum of these individual risk factors and their added contribution towards defining cardiovascular risk. Many of the traditional cardiovascular risk factors (age, sex, cigarette smoking and low-density lipoprotein cholesterol levels) established in large part by the Framingham Heart Study

(Framingham Risk Index), are not included in the metabolic syndrome definition and thus metabolic syndrome cannot be used to predict absolute risk. Quantification of metabolic syndrome has led to different definitions of metabolic syndrome and recently has led to a Joint Scientific Statement summarizing the accepted present definition of metabolic syndrome.[74-76] Recently, there have been findings on the effect of specific comorbidities and the clustering of CMR factors in the TJR population.[77-79] [62, 77, 79] One study by Gandhi et al. (2007) assessed the prevalence and implications of metabolic syndrome in the TJR population.[77] Of the 1231 patients who underwent primary hip and knee surgery, 24.4% (n=300) were found to have metabolic syndrome. There is some indication that the clustering CMR factors may contribute to postoperative CV complications. The contribution of CMR factors to other TJR is yet to be determined.

1.1.8 Conclusion

In summary, the population with OA is aging and they are undergoing TJR surgery with an unknown number of comorbidities. Presently, 15-30% of the TJR population is not satisfied with their outcome postsurgery. In the next 30 years, an exponential increase in TJR is predicted; therefore it is important to identify those that are at risk for poor outcomes to maximize the resources available and to benchmark clinical practice. I propose that by understanding the recovery pattern in clinical setting, quantifying the comorbidity within the TJR population and specifically analyzing how these comorbidities impact on the recovery process we may estimate another major contributor to the recovery process for those undergoing TJR surgery.

1.2 Health outcomes in the arthroplasty population

An integral aspect of my PhD experience has been the development of the Health Outcomes in the Arthroplasty Population (HOAP) program. The HOAP program was initiated as a combined venture with the Department of Physical Therapy, the University Orthopedic Center (UOC) Physical Therapy department, UOC Total Joint Team and myself, with the mission to improve patient outcomes using evidence-based practice. This was part of a practice-wide effort to improve patient outcomes after total joint replacement.

To be able to improve patient outcomes we needed to know what the patient outcomes were in this clinical setting. Important key points for the development and implementation of HOAP were to integrate into the existing clinical practice routine without disruption of patient flow, or extra patient burden (i.e., extra time or paperwork), to use existing personal and integrate physical therapy with the total joint program team to facilitate cross professional communication.

The development and implementation of the HOAP program contained five distinct phases. In the first phase, existing clinical systems and processes were evaluated. Decisions were made to complement, modify and enhance the present system. For example, the data collection process for physician reported measures was changed from retrospective chart audit to residents and fellows collecting patient information directly on standardized forms at the time of service.

Understanding patient outcomes from a patients' perspective was set as a high priority. In the second phase (February-September 2008), decisions were made regarding the type of self-report measures that would be implemented to understand the patients'

perspective regarding their clinical outcomes. Based on these decisions, a booklet of questionnaires was developed and pilot tested.

The third phase (November 2008-February 2009) was the development and implementation of *Joint Camp,* a preoperative educational component provided to patients on a weekly basis. The content was developed by physical therapists and the antithrombosis group with input from HOAP team. Also at this time, we initiated performance measures (6-minute walk test and timed stairs) for those attending *Joint Camp* so that physical performance patient outcomes could be tracked.

The fourth (June 2009-present) and fifth (Dec 2009) phases involved the development and implementation of the process to gather physical performance measures postoperatively at 6 weeks and 6 months, respectively.

All data gathered in the HOAP program were collected in an ACCESS database that I serve as the data administrator. The primary data source for this project was based on this clinical outcomes database.

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CHAPTER 2

THE EFFECT ON COMORBIDITY AND PAIN IN PATIENTS WITH OSTEOARTHRITIS

Carmen Kirkness, Junhua Yu, Carl Asche

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OUTCOMES AND ECONOMICS IN PAIN AND PALLIATIVE CARE

The Effect on Comorbidity and Pain in Patients with Osteoarthritis

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ABSTRACT. Comorbidities can affect how patients experience pain associated with chronic disease. Despite numerous studies on the association of pain with chronic conditions, few account for the multiple comorbidities associated with the highly prevalent chronic disease osteoarthritis (OA). OA generally is not lethal but it greatly impacts health care utilization and costs mainly primarily due to pain and disability. This paper describes how comorbidities impact OA pain reporting. We identified the common comorbidities associated with OA and examined the comorbidity measures utilized to identify the comorbidities. Using the identified comorbidities, we related how they may contribute to the pain experience for OA patients. We describe how OA treatment and multiple comorbidities may impact on treatment decisions.

KEYWORDS. chronic disease, comorbidity, osteoarthritis, pain

Many chronic disorders, including cardiovascular disease, asthma, cancer, diabetes, arthritis, and obesity, are progressive and often incurable. Approximately 133 million Americans, 46% of the population, live with one or more chronic diseases,[1] whereas projections estimate that 49% of the population will have at least one chronic disease by 2030.[2] The number of Americans aged 65 and over is projected to increase from 35 million to 71 million by 2030,[3] with a concomitant rise in the number of people living with chronic diseases. This has major implications for both health care services and their associated costs.

Chronic diseases require long-term management and regular monitoring by health professionals.[4,5] The United States spends 75%

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of its $1.9 trillion budget in health care expenditures on chronic diseases each year.[6,7] On average, health care for chronic disease patients costs $6032 per year, five times higher than cost for people without chronic disease.[6] The high prevalence of chronic disease in the workforce translates to increased costs for employers. Direct costs to employers include physician visits, hospital care, and pharmacotherapy. The indirect costs associated with lost productivity due to morbidity and premature death due to chronic conditions in 1990 were estimated to be $234 billion in addition to the $425 billion for direct health care costs.[8]

Reportedly, 61.4 million insured people and 11.4 million people without health insurance have at least one chronic disease.[9] The 2001 Medicare Health Outcomes Survey reported that more than 75% of the respondents had at least one chronic disorder, the most common of which were hypertension (56.6%), arthritis of the hip or knee (39.7%), and arthritis of the hand or wrist (33.3%).[10]

Chronic disease tends to become more common with age. Almost 75% of Americans aged 65 and over have at least one chronic illness.[11] About 50% have at least two chronic illnesses.[11] The presence of multiple chronic conditions increases with age and is associated with a decline in health outcomes, including quality of life, mobility, functional ability, increased hospitalizations, psychological distress, mortality, and the use of health care resources.[12,13] Persons with two or more comorbidities accounted for 26% of the population but 50% of the overall health care costs.[14] Patients with more than four complications and comorbidities generated $5667 loss per patient from the perspective of Medicare reimbursement perspective.[15]

This paper describes osteoarthritis as an example of non–life-threatening chronic disease with multiple comorbidities. These include obesity, hypertension, diabetes, and cardiovascular disease, all of which are associated with pain. The objective of this paper is to characterize the relationship between the burden of medical comorbidities and the reporting of pain in osteoarthritis patients.

OSTEOARTHRITIS AND PAIN

Osteoarthritis (OA) is highly prevalent,[16,17] incurs substantial costs, and causes symptoms and functional challenges, but generally is not lethal. Most people live for many years with OA, which gradually worsens. In American, 27 million people age 25 and over are living with osteoarthritis and 70% of people over the age of 70 have x-ray evidence of the disease.[18] Of those over age 70, only half ever develop symptoms.[18] OA is characterized by degeneration of articular cartilage, synovitis, remodeling of subchondral bone, and atrophy/weakness of joint muscles.[19] The clinical symptoms are dominated by pain and functional impairment that includes joint stiffness and dysfunction most commonly related to the joints of hip, knee, hand, foot, and spine.[20] This leads to impaired performance in the workplace, and 25% of patients cannot perform their main activities of daily life, which often leads to social isolation and depression.[21,22] More than 13% of Americans aged 55 to 64 years, and more than 17% of Americans aged 65 to 74 years, have pain and functional limitations related to knee OA.[23] In addition to the direct costs due to health care utilization in the diagnosis and treatment of OA, indirect costs are incurred by patients and their caregivers due to absence from loss of work days due to treatment; reduced effectiveness at work, and losses attributable to the disease preventing persons from working at, or taking, better paying jobs; early retirement; loss of self-esteem; and other psychological difficulties.[24] One study reported that in the United States, Canada, the United Kingdom, France, and Australia, the direct and indirect costs of OA account for 1% to 2.5% of gross national product.[25] Using a detailed, open-ended resource utilization questionnaire, another study concluded that the estimated annual indirect costs of an OA patient was $880, including lost time doing chores, time lost from work, and support person time lost from work.[26]

PAIN AND DISABILITY— OSTEOARTHRITIS COMORBIDITIES

OA is one of the diseases with the highest rate of comorbidity[27–29] and it is the leading cause of disability in older persons.[27,30] Comorbidity is best described as the total burden of illnesses across multiple potential conditions unrelated to the patient's principle or target diagnosis.[27,31,32] Patients with OA have a significantly higher

risk of developing comorbidity than non-OA patients.[33,34] Comorbidity has a negative impact on physical health, emotional, cognitive, and functional status that goes beyond the mere combined sum effect of each individual disease.[35–38] There is a documented relationship between comorbidity and disability in general populations.[39–44] For example, after adjustment for sociodemographic characteristics, functional and cognitive status, and several biomarkers, indicators of comorbidity were significantly and independently associated with the risk of disability.[45] It is not known if there is comorbidity specific to patients with OA and if so, how that might contribute to the overall impact of OA.

Reported OA comorbidities are chronic conditions that regularly worsen and may eventually cause death. In a study of 29,132 patients aimed to describe the Italian approach to OA management, Caporali and colleagues[49] showed that the proportion of OA patients with the presence of one or more comorbidities was as high as 85% the study population. Hospital-based studies focusing on OA comorbidity documented those to include hypertension, cardiovascular diseases (CVD), obesity, respiratory diseases, diabetes, peptic ulcer disease, and renal disease.[27–29,33,46–50] Adequate assessment of comorbidities is essential for characterizing the overall health status in the OA population.

DIFFICULTY IN MEASURING COMORBIDITY

Assessing the coexistence of multiple chronic diseases in the same individual has led to increasing interest in the measurement of comorbidity. Current comorbidity measurement approaches are varied and inconsistent possibly due to the nature of the primary disease and the outcome of interest. One of the difficulties in measuring comorbidity is accounting for the severity of the presenting medical conditions. A patient suffering concurrently from OA and hypertension does not have the same burden of illness as does a patient with OA and asthma. Measures of comorbidity can be as simple as a count of the number of comorbid diseases present[27,49] or can be a more comprehensive index that accounts for disease severity.

Deciding what comorbidity measure to use requires consideration of many factors. Understanding how the comorbidity measure was developed is instrumental. A measure using a weighted system based on the relative risk of dying, indicating that all conditions do not carry the same impact, has quite a different impact on those with OA than a measure using a weighted system based on mobility. Thus, the outcome the measure is designed needs to be taken into account.[51] Second, it is important have a comparable population for which the measure is designed for use. If the goal is to assess the comorbidity of a community-dwelling OA patient, the measure needs to be developed in a similar population. For example, using a measure designed for long-stay nursing home residents could provide differences in conditions that are weighted most heavily. In addition, measures may only be validated in the population they have been tested and not sensitive to differences in comorbidity in another population.[52] It is important to ensure that the comorbidities being measured are conditions important to the primary condition. Some measures may be limited to a certain number of conditions deemed important, whereas others incorporate all conditions regardless of their relevance to OA.[52] The source of data will influence the measures to utilize.[52] Measures of comorbidity are often ascertained from source data such as medical records in electronic databases, medical charts, and physical examinations,[53,54] but community-based survey measures have often relied on self-reported symptoms using personal interviews or written questionnaires.[55,56] However, some limitations of those methods should be noted. Although self-reports of some chronic conditions are substantially accurate when compared with physician diagnoses,[57–59] the self-reported prevalence of chronic conditions is subject to recall bias and may not reflect the true prevalence. Furthermore, reporting also can be affected by respondents' knowledge, manifestations of the illness in everyday life, patients' willingness to report the condition, and frequency of contact with a physician.[60] Because calculations of the indices are based on the weights assigned to clinical conditions selected from a predefined list by each method, the indices might fall short of comprehensive due to the fact that some diseases originally exclude from this list may also explain the severity of the multiple diseases of patients.

HOW COMORBIDITY IS ASSESSED IN OSTEOARTHRITIS

Comorbidity measures used in the OA population for assessing the burden of accompanying illness in OA are reviewed to illustrate how, within the same population, various comorbidity measures identify different prevalent disease conditions. A literature search in Medline and CINAHL using the key words "osteoarthritis" and "comorbidity/comorbidities" produced 303 abstracts, of which 15 potentially relevant articles were retrieved and reviewed. A total of eight articles specific to OA are shown in Table 1, summarizing the study population, measures of comorbidity used, age, and disease area of study population, and the outcome of the measure. Four indices were used in the various studies, including the Charlson Comorbidity Index (CCI),[61] the Elixhauser Index,[36] the Cumulative Illness Rating Scale (CIRS),[62] and the Index of Coexistent Diseases (ICED).[63] The CCI is composed of 19 medical conditions,[61] each assigned with a weight scale ranging from 1 to 6 with a total maximum possible score of 33. The final CCI score is the sum of the weights assigned to 19 predetermined clinical conditions.[61] Higher scores correlate with greater burdens of comorbidities. Because the weights in the original CCI coding system was developed to measure the relative mortality risk for people aged more than 65,[61,64] different adaptations of CCI to obtain measure of comorbidities have used different weights depending on the specific interests of the studies.[65] The Elixhauser Index is similar to the CCI but was developed to be more comprehensive in the comorbidities assessed in an administrative data source.[36] The Elixhauser Index includes 30 categories of comorbid illness that are identified using ICD-9-CM diagnosis codes. The CIRS is also a comprehensive comorbidity index,[62] and takes into account impairment in 13 or 14 organ systems depending on the version (Cardiac, Vascular, Hematological, Respiratory, Ophthalmological-ORL, Upper gastrointestinal, Lower gastrointestinal, Hepatic-pancreatic, Renal, Genitourinary, Musculoskeletal-tegumental, Neurological, and Psychiatric). Each organ system is given a score from 0 (no organ impairment) to 4 (extremely severe organ impairment). The total CIRS score is the sum of severity scores assigned to each organ domain. Other than the total CIRS score, three indices often are used to measure comorbidity. These are the severity index (sum score on the CIRS divided by morbidity count), the number of diseases on which the patients scored 2 or higher (moderate or more severe comorbidity), and a simple total generated from summing the number of categories endorsed.[38,55] Likewise, modifications might be necessary when it is felt to better reflect the variety of organ impairment in the population studied.[38] The ICED measures the physiological severity of comorbidity as well as general physical impairment. The ICED measures 14 categories of coexistent conditions and physical impairment that combine to form four levels of an ordinal scale that is clinically meaningful. ICED is practical in a clinical setting as the data sources used are laboratory tests, signs, and symptoms.[66] RxRisk-V was developed using pharmacy data from VA medication records and was designed to predict health care expenditures.[67] There are 45 indicators for general drug categories and these indicator variables are summed to create the total RxRisk-V score. The RxRisk-V comorbidity index provides a reliable and valid pharmacy based method to better understand chronic disease burden of treated populations.[68]

Given the evidence of increasing prevalence of comorbidity with age, it is not surprising that most of the comorbidity measures were obtained among the OA patients were more than 50 years old. However, the research has adapted those indices differently to quantify the burden of the comorbid conditions depending on the data used to construct the measures and the purpose of study. For example, Dominick and coworkers[69] used the Elixhauser method based on separate indicator variables for 30 different diagnoses as well as pharmacy data (RxRisk-V) to measure comorbidity, which turned out to be better predictors of health care resources use among OA patients than CCI. The Index of Coexistent Disease (ICED) is as powerful as CCI in predicting mortality of OA patients.[63] This can be partly explained by the fact that ICED[70] differs from the others in that it incorporates two major dimensions: the physiologic severity of each chronic comorbid condition and an assessment of the impairment or disability. In sum, few studies have paid attention to the selection of measures of comorbidity and the impacts of different measures on research results.

TABLE 1. Comparing Comorbidity Measures Used in Osteoarthritis Studies

Author, year	Measure of comorbidities	Study population and OA site	Age of population	Top 3 Comorbidities Identified
Van Dijk et al., 2008[55]	Counts of diseases based on CIRS	288 patients Knee/hip OA	66 (8.7)	
	a. % with specified comorbidity			1. Eye, ear, nose, throat & larynx diseases (96.1%) 2. Cardiac (54%) 3. Endocrine and metabolic disease (46%)
	b. Patients scored 1+ or 2+ on CIRS			1. 1+ CIRS diseases (98.6%) 2. 2+ CIRS diseases (84.4%)
Juhakoski Tenhonen et al., 2008[56]	Counts of disease Heart or coronary diseases, pulmonary disease, diabetes and other	120 patients Hip OA	66.7 (6.5)	1. 0 chronic disease (41.5%) 2. 1 chronic disease (44.9%) 3. ≥2 chronic diseases (13.6%)
Leong Farrell et al., 2007[38]	CIRS score	168/562 patients had OA pain 394/562 patients with other chronic disease	76.3 (6.9)	1. Cardiac (54.4%) 2. Gastrointestinal (35.9%) 3. Respiratory (18.0%)
Williams Dunning et al., 2007[115]	a. Counts of comorbidities	20 patients Hip/knee OA	67.05 (6.62)	1. Vascular (90%) 2. Genitourinary (85%) 3. Respiratory (70%)
	b. CIRS–Geriatric score based on Medical records			1. 4–8 chronic diseases (80%) 2. 9–13 chronic diseases (20%)
Rosemann Laux et al., 2007[116]	Counts of conditions High blood pressure (HBP), diabetes, heart insufficiency (HI), coronary vessel disease (CVD), etc.	1021 patients Knee/hip OA	66.1 (15.1)	1. HBP (55.2%) 2. Elevated cholesterol (36.1%) 3. Diabetes (17.3%)
Saltzman Zimmerman et al., 2006[117]	Counts of conditions 9 major systemic comorbidities	195 patients Ankle OA	53.4 (14.6)	1. 0 chronic disease (43.6%) 2. 1 chronic diseases (26.2%) 3. 2 chronic diseases (19.5%)
Salaffi Carotti et al., 2005[118]	a. The sum of the comorbidity among nine conditions Hypertension, myocardial infarction, lower extremity arterial disease, major neurologic problem, diabetes, etc.	244 patients Knee/hip OA	67.8 for hip OA 68.4 for knee OA	1. Cardiac (29.2%) 2. Respiratory (14.5%) 3. Metabolic (11.5%)
Dominick Dudley et al., 2005[69]	a. Charlson score	306 patients Any type of OA	59.8 (14.2)	1. Diabetes without complications (19.9%) 2. Chronic pulmonary disease (12.8%) 3. Malignancies (10.1%)
	b. RxRisk-V			1. Ischemic heart disease/hypertension (38.2%) 2. Gastric acid disorder (35.6%) 3. Congestive heart failure/hypertension (29.4%)

(*Continued on next page*)

TABLE 1. (*Continued*)

Author, year	Measure of comorbidities	Study population and OA site	Age of population	Top 3 Comorbidities Identified
	c. Elixhauser method			1. Hyperlipidemia (61.2%) 2. Rheumatoid arthritis/collagen vascular disease (18.4%) 3. Diabetes without complications (16.8%)
Kadam Jordan et al., 2004[27]	a. Counts of non-musculoskeletal conditions	11375 patients Any type of OA	50+	1. Obesity (2.25)‡ 2. Gastritis (1.98) 3. Phlebitis (1.80)
Jones Voaklander et al., 2003.[119]	a. Counts of comorbid conditions	276 patients Knee OA	69.2 (9.2)	1. Hypertension (39%) 2. Back pain (26%)
Gabriel Crowson et al., 1999[63]	a. Index of Coexistent Diseases (ICED)	441 patients Any type of OA	70.7	1. 0–1 chronic disease (36.0%) 2. 2 chronic diseases (48.1%) 3. 3–4 chronic diseases (15.9%)
	b. Charlson index			1. 0 chronic disease (0%) 2. 1–2 chronic diseases (71.1%) 3. 3+ chronic diseases(28.9)

‡The numbers are the odds ratio calculated between OA patients versus non-OA controls adjusting for age, sex, and social class.

OSTEOARTHRITIS, COMORBIDITY, AND PAIN

Chronic or persistent pain due to OA is one of the most common pain conditions affecting Americans today.[71] Pain results from deterioration within the joint capsule, ligaments and insertions, periosteum and subchondral bone, and synovium.[72,73] The exact source of pain is often unclear in the OA individual patient.[73,74] According to one hypothesis, the loss of articular cartilage in OA may start as a focal lesion and progressively affect specific joint compartments, ultimately inducing alterations in articulating surfaces[75] and leading to progressive loss of cartilage.[76] Although the etiology of OA is not entirely clear, its development appears to depend on the interaction of various factors, including age, female gender, genetics, metabolism, and biomechanical factors (e.g., obesity, joint malformation or hyperlaxity, intensive sporting activities, and trauma).[77–80] Because the management of OA pain has become an increasing burden on our healthcare system and a challenging problem on the public health agenda, there is a growing need to better understand the pain experience of patients with OA and to investigate potential factors that modify it. Little attention has been devoted to the relationship between pain report and the burden of medical comorbidities[38] and few studies have investigated the relationship between the comorbidity and pain in patients with OA to date.[55]

There is a consensus that comorbidity is closely associated with significantly worse pain and increased the likelihood of disability among OA patients regardless of age and gender.[49,81] However, variations in the strength of the association have been reported. For example, several studies found the evidence of a linear relationship between comorbid conditions and the severity of hip joint pathology and its associated disability.[28,82,83] Another study showed that pain severity was greater when two or more comorbidities were present.[84] In contrast, Leong et al. demonstrated a nonlinear relationship between comorbidity and severity of self-reported pain: the patients did not experience significantly elevated pain until the number of medical comorbidities exceeded four.[38] The mechanism of the increased pain burden from OA and comorbid conditions is unknown. One possible explanation is that impairment due to one disease may exacerbate that due to another: for example, the pain associated with hip OA may be exacerbated by diabetic neuropathy, and diabetic neuropathy may influence the progression of hip OA.[84] Alternatively, the impact of one disease may increase vulnerability to another.[27] Additional factors such as psychological impairment,

socioeconomic status, age, and others[85] may play a role in the burden on disease. However, there are relatively few research data on the potential pain impact of a single comorbidity such as obesity and CVD for OA patients as opposed to the overall comorbidity. This may be due to inherent difficulty in sorting out the relevant causes of correlated diseases in OA patients. A recent study showed that the incidence of OA pain increased with the degree of overweight and the association seemed particularly strong between obesity and OA of the knee.[86] Interestingly, in a hip OA population, no significant correlation has been found between body mass index (BMI) and self-reported pain in a study.[56] Thus far, only tentative explanations have been proposed about the mechanisms relating obesity to OA pain. Joints of obesity patients have to bear greater dynamic stress, which promotes cartilage disruption; moreover, obese patients have a higher bone mass, which may increase stiffness in subchondral bone and facilitate cartilage breakdown.[46] It seems that increased BMI is a causal factor of OA; however, there are opinions that are highly speculative of this conclusion that because obesity itself could be the consequence of a sedentary lifestyle induced by OA pain.[84] Another possible explanation is that the borderline obese patients were significantly more likely than the nonobese patients to report chronic medical conditions,[87,88] which may induce more pain experienced by obese OA patients. In contrast, increased pain thresholds or lower pain ratings have been reported in patients with hypertension. It might be possible that elevated blood pressure in OA patients is associated with reduced pain sensitivity. Although several underlying mechanisms responsible for diminished pain perception associated with hypertension have been proposed, studies on the effects of hypertension on the burden of the pain are too few to ascertain whether in human essential hypertension increased pain threshold is secondary to elevated blood pressure or whether both depend on some common mechanism.[89] Similarly, few studies have elucidated the impact of CVD on self-reported pain. An analysis of National Health and Nutrition Examination Survey found that persons with knee OA plus baseline heart disease had a much greater likelihood of subsequent disability than those without neither OA nor heart disease, followed by the combinations of knee OA plus pulmonary disease.[43] Although there is credible evidence that people with OA are at higher risk for CVD than the general population,[33] the pain burden in OA patients due to CVD has rarely been examined mainly because the etiology of the association between arthritis and CVD is not fully understood.[90] No conclusive evidence has been found that OA increases the likelihood of developing CVD risk factors or CVD. On the contrary, most investigators tend to believe that CVD and OA may represent separate end points of similar pathological process.[91]

CURRENT CLINICAL GUIDELINES

Although there is no known cure for OA,[92] the goals of treatment in OA have focused on decreasing pain, and improving joint movement because disease burden is primarily related to pain occurrence, frequently leading to functional disability. Like the other pain therapy, OA pain relief therapy has been developed in the context of symptomatic treatment (through modulation of aberrant function, that is, neural excitability) and disease modification (through neural restoration of physiological pain processing).[19] The guideline published by the American College of Rheumatology (ACR)[93,94] in 1995 outlined the use of nonpharmacologic modalities and pharmacotherapy. Medications commonly used are acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), mild opioids, corticosteroids, topical analgesics, and intra-articular injection of hyaluronic acid (sodium hyaluronate). Surgical intervention in some cases will be considered only after the failure of nonsurgical treatment.

For many OA patients with mild-to-moderate joint pain, simple analgesics such as acetaminophen and NSAIDs are recommended. Opioid therapy may be considered in OA patients with severe pain when NSAIDs or tranmadol are inefficacious or not tolerated.[95] Topical analgesics, such as capsaicin cream or topical NSAIDs, are frequently prescribed as monotherapy or adjunctive treatment, especially in hand or knee OA.[96] Intra-articular administration of glucocorticoids has been beneficial in treating acute episodes of pain, especially when there is evidence of inflammation and joint effusion.[97] There are also a few potential disease-modifying OA drugs with some suggestion of

disease-modifying effects.[95] They include metalloproteinase inhibitors,[98] growth factors and cytokine manipulation,[99] genetic therapy,[100] and sulfated and nonsulfated sugars.[101]

Nonpharmacologic modalities have also been integrated into OA management strategies. Aerobic and strengthening exercises are core recommendations in all guidelines for the management of patients with hip or knee OA.[102–104] In addition, studies have been underscoring the importance of improved communication and education in decreasing pain and improving function in patients with OA.[105,106] Therefore, patient education and, where appropriate, education of the patient's family, friends, or other caregivers are also considered important instruments for behavior interventions for patients with OA.

What complicate the treatment of OA are additional considerations involved in a practitioner's decision to treat the individual OA patient with existing comorbidities and concomitant therapy. For example, it is concerned that analgesic and anti-inflammatory treatments may interact with CVD and antihypertensive drugs concurrently used by OA patients suffering from those chronic disease or be contraindicated in those patients.[107] Clinical evidence suggests a drug interaction between OA therapy (ibuprofen, rofecoxib, acetaminophen, or diclofenac) and low-dose aspirin (used to protect patients at risk for CVD such as acute myocardial infraction, ischemic stroke, angina, or peripheral arterial disease) involving ibuprofen interfering with aspirin's inhibitory effects on platelet aggregation.[108,109] Furthermore, patients with known CVD on low-dose aspirin with pretreatment of ibuprofen had a significantly higher risk of all cause mortality and cardiovascular mortality than patients taking aspirin alone.[109] It is not surprising that previous research has noted that the presence of a coexistent disease and/or its chronic pharmacological treatment may influence the prescription of pharmacological and non-pharmacological therapy targeted at OA.[49]

In contrast, there is no direct evidence concerning contraindications to nondrug interventions of strengthening or aerobic exercise in patients with hip or knee OA. A minority of intervention trials of exercise in hip or knee OA report adverse events in detail but the frequency of minor adverse events related to the intervention such as exacerbation of pain ranges from 0% to 11.8%.[110] It is generally believed that exercise appears to be a safe intervention mainly because the number of contraindications is relatively few.

As mentioned above, older OA patients are particularly susceptible to comorbidities. In a random sample of 1912 study objects of different ages, the older age group reported pain of significantly longer duration and had a higher percentage of chronic diseases associated with pain than the younger group.[111] Because both OA and other chronic diseases increase with advancing age, it is likely that OA and other comorbidities will occur simultaneously in many patients. It is also likely that OA patients may take medications to treat other medical conditions at the same time.[112] With the growth of the elderly population and the prevalence of OA pain in this age group, older OA patients with comorbidities will be expected to be referred to specialty pain clinics and programs in all developed societies.

Given the multiple underlying mechanisms of pain experience as well as the substantial comorbidity associated with OA, effective pharmacotherapy requires a coordinated interdisciplinary approach that takes into account intersecting comorbidities.[34,104,113] There is an urgent need for diverse medical and allied health providers to work collaboratively to develop comprehensive strategies based on a variety of best-evidence treatment options.[114] On the other hand, with such OA patient heterogeneity in terms of chronic disease profile, it is no easy task to identify "tailor-made" appropriate pharmacotherapy. It is important to ascertain whether the pain in a given patient is represented simply by the OA by or whether there also are other contributing underlying conditions. As a result, it would seem worthwhile to advance research in any potential relationship between the presence of medical comorbidities and the phenomenology of pain in OA patients.

CONCLUSION

The scarcity of literature related to this area is evident in our review of comorbidities common to OA. It was difficult to correlate articles related to comorbidities as there were different measurements (e.g., CCI, varying depictions of simple counts) used in studies. Providing adequate assessment of comorbidities is essential in understanding the role conditions secondary

to OA contribute to pain and aid in the management of the multiple conditions. Future research needs to consider comorbidities based not only on mortality but also on a more suitable measure for a disease that affects quality of life and disability. Comorbidity has been shown to be closely associated with increased pain and disability among OA patients independent of age and gender. Common comorbidities of OA may affect pain in different ways, e.g., increased pain threshold (HTN) and increased pain (obesity), and other conditions (CVD) that are prevalent in this population may be associated with pain, but to what extent is unknown. At a minimum, in the pharmacotherapy management of OA, the number and type of comorbidities identified require consideration in light of the adverse events that can occur with medications typically used (i.e., analgesic and anti-inflammatory treatments).

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CHAPTER 3

OBSERVATIONAL STUDY OR RANDOMIZED CLINICAL TRIALS: CHALLENGES IN MEASURING CHANGE

3.1 Abstract

Evaluating whether a person has changed with treatment is a fundamental aspect of physical therapy practice and research. Historically, randomized clinical trials have been the primary source of evidence to evaluate treatment effectiveness. More recently, a complementary method, observational study designs, has become more prevalent in physical therapy to evaluate the effectiveness of interventions due to the availability and introduction of registry and electronic database information. Understanding the assumptions, limitations and specific analysis strategies unique to data gathered using observational study designs is necessary to provide accurate assessments of the effectiveness of physical therapy interventions. The purpose of this paper is to review the traditional techniques used to analyze the measurement of change due to physical therapy interventions in randomized trials and to discuss alternative analysis methods developed for use in observational studies. Traditional data analysis techniques may not be suitable for data used from registries and databases. New methods in design and analysis, such as hierarchical linear modeling and propensity score matching, are advances that can provide more accurate methods to report and evaluate change in observational studies.

3.2 Introduction

The availability and use of electronic databases are increasing in physical therapy.[4, 7] Interpreting the data available from databases requires considerations and techniques that may be unfamiliar in physical therapy. Therefore, there is a need for attention to be given to the methodological issues involved. To provide accurate evidence of the effectiveness of physical therapy, it is essential to accurately match the study design to the subsequent analysis. Each study design presents with unique sets of assumptions, limitations and specific analysis strategies most appropriate for handling these considerations. Inappropriate use of analysis techniques that are not matched to the study design from which data are collected can lead to biased conclusions that may erroneously support ineffective physical therapy techniques or deny potentially effective techniques.

The goal of any study design is to maximize the degree of internal validity (the best approximation of the truth) and external validity (ability to generalize to the affected population) to answer the study question. Detailed definitions of statistical terms are presented in Table 3.1. Studies with a high degree of internal validity may be able to evaluate a treatment effect in a controlled research setting, but this high degree of control may not be suitable for extrapolating to patients in the clinical practice setting.[6] The randomized clinical trial (RCT) is the classic study design for maximizing internal validity because this design is conducted within a clinical setting that is controlled, to a certain extent, by enrolling patients who meet prespecified criteria and provide informed consent. Controlled settings and more homogeneous patient samples in RCTs may not

Table 3.1 Statistical terms

Statistical Term	Definition
Randomized control trial	participants are randomly allocated to an intervention(s) in a controlled setting prior to the intervention being evaluated
Observational study design	observation or measurement of outcomes without impacting the outcome using an intervention
Efficacy	the ability of an intervention to produce the desired beneficial effect under ideal circumstances
Effectiveness	the degree to which action(s) achieves the intended health result under normal or usual circumstances
Internal validity	the degree which the experimental treatment makes a difference in the specific setting
External validity	the degree the results are generalizable to the affected population
Confounding	a situation in which the estimated intervention effect is biased because of some difference between the comparison groups apart from the planned interventions such as baseline characteristics, prognostic factors, or concomitant interventions. For a factor to be a confounder, it must differ between the comparison groups and predict the outcome of interest
Covariates	a variable that is possibly predictive of the outcome under study
Regression to the mean	a variable is extreme on its first measurement, it will tend to be closer to the average on a second measurement
Selection bias	a systematic error in creating intervention groups, causing them to differ with respect to prognosis. The groups differ in measured or unmeasured baseline characteristics because of the way in which participants were selected for the study or assigned to their study groups
Treatment effect	a measure of the difference in outcome between intervention groups
Directional bias	results of a study systematically deviate in one direction from the truth because of nonrandom factors (i.e., overestimate or underestimate)

reflect "real-world" clinical circumstances, limiting the external validity of RCT results. A key distinguishing feature of RCTs is random (i.e., chance) assignment of participants to treatment which optimally balances treatment groups for all possible differences that could impact outcomes other than the treatment itself.[34] In contrast, observational study designs often involve the collection of data within clinical settings that are more typical of routine practice and are more inclusive of all patients within those settings. Observational designs therefore typically have high external validity and are more generalizable to the general population. Observational studies do not use random processes to assign patients to treatment groups, creating the possibility that groups of patients receiving different treatments also differ on other important variables (e.g., duration of symptoms, age, etc.) that could partially, or wholly, explain any differences in outcomes between treatment groups. In this way, observational studies may lack sufficient internal validity to interpret their results as conclusive. Although vastly different in their execution both the RCT and observational study design can be used to evaluate the effectiveness of different treatments.[25]

Recently, national initiatives to routinely gather outcomes electronically in clinical practice have been introduced.[3] The use of electronic databases presents new opportunities for physical therapists to contribute important evidence towards the quality of care and evaluate what is occurring in clinical practice. Understanding the differences between information gathered in usual clinical practice (observational design) and information from a controlled study will assist physical therapists to critically examine the evidence presented from different study designs.

The purpose of this perspective paper is to review the techniques used to analyze the measurement of change within an RCT and to discuss alternative techniques developed for use in observational studies. The objectives will be as follows: 1) to identify threats to internal and external validity, 2) to describe two specific study designs used to evaluate change, 3) to describe the analysis techniques used to measure change in RCT and extrapolate their usefulness in observational studies and 4) to introduce newer approaches in study design and the evaluation of change in observational studies.

3.2.1 Threats to internal validity

Limiting the threats to the internal validity and potential sources of bias in a study can achieve the best approximation of the true difference between groups. Confounding, selection bias and regression to the mean are threats to internal validity that can be found in both RCT and observational study designs.

Confounding is the potential that another variable outside the study variables is associated to both the treatment and the outcome,[10] resulting in an unfair comparison of groups. Some commonly identified confounders are age, sex, or prognostic factors other than the ones under study (e.g., comorbidities, duration of symptoms, etc.). When confounders are known and measured in a study, their effects can be identified in the analysis.[10] In addition, there are hidden confounders that may be unknown to the investigators and unmeasured. Hidden confounders are present in every study, but because their identity is unknown they cannot be accounted for in the analysis. Their contribution to the outcome cannot be ascertained; thus this lack of control is a threat to the internal validity.[18, 30] Regardless of study design, when confounding factors are

known, design and statistical analysis methods can be used to 'control' the effects of confounding to permit valid comparisons between groups. For example, excluding potential participants that have the confounding factor (restriction), stratifying participants by the factor (adjustment, standardization) and mathematical modeling (regression) are some of the techniques that are used to control for known confounders. However, only random assignment can control for the effects of unknown confounders.

Selection bias can occur as a result of the study design or analysis and is defined as differences "in measured and unmeasured baseline characteristics because of the way in which participants were selected for the study or assigned to their study groups". [2] When participants are randomly assigned to a study group the assumption is that baseline characteristics will be equally distributed between groups. If participants are not randomly assigned, there may be a systematic reason that participants were assigned to a study group (e.g., healthier patients may be assigned to the more intensive treatment). When there is no randomization, group differences are expected resulting in selection bias. Selection bias can also occur if groups within the study differ in participant follow-up rates. Loss to follow-up occurs in virtually any study; however, if loss to follow-up is associated with factors specific to one treatment group, selection bias results. For example, there may be bias when participants who had undergone total hip arthroplasty have their function evaluated at a clinic visit once a month over the first 6 months of recovery. Those with high function may find it easy to physically get to the evaluations early in the recovery period and may discontinue evaluations scheduled later in the recovery period because of their high function. Selection bias would result if those with low function continued to be followed because they still had remaining functional

limitations whereas those with higher levels of function may not be motivated to return for follow-up care due to lack of functional limitations. The study would represent only those with lower function and over-represent those with low-function. In addition, selection bias can result during the analysis if there are missing data and analysis is performed only on those with complete data. Many data analysis techniques require an entire case to be excluded from analysis if any data point is missing. If there is a high proportion of data excluded from the analysis or if the missing data are distributed differently between groups, selection bias is possible.

A common occurrence in all clinical studies is the threat of regression to the mean; an "observable phenomenon" not related to the treatment effect.[19] Regression to the mean occurs when there is a tendency for participants who score below the average on a measure to improve the next time and conversely, those who scored above the average on the measure to decline. The more a participant deviates from the group mean on a measure, the greater the tendency to regress to the mean will be (i.e., it will appear as these participants change the most). Randomization allows equal distribution of patients who are above average and below average on important measures to each group, thereby minimizing the likelihood that regression to the mean could explain outcome differences between groups.[19] If the randomization procedure, by chance, causes an imbalance in the variables related to the outcome across the treatment groups, regression to the mean may still influence the results.[19] In observational study design where groups may be naturally occurring, apparent differences between groups may be influenced by different rates of regression to the mean.[19]

3.2.2 Threats to external validity

External validity relates to the extent to which the results can be generalized to another situation, population, setting or time period.[10] Maximizing the external validity in a study can provide the best approximation of what is occurring in the real world by establishing if the results from studies with high internal validity can be replicated in usual clinical practice and what these results mean in the real world. Low generalizability in a study can be a result of very specific or restrictive criteria for subject inclusion, measurement instruments, or treatment procedures. For example, restrictive inclusion criteria could yield a group of participants with a better than average prognosis who may react differently to a treatment than a more inclusive group of people. External validity could also be compromised if treatment procedures are delivered by highly trained individuals whose skill in applying a particular treatment may not be viewed as typical of most clinicians. Finally, the process of requiring an informed consent introduces a bias by the potential for subjects who agree to participate may be different than those that refuse to participate. Further, participation in an experiment can result in participants behaving differently had they not been involved in the study ('Hawthorne Effect').[20] As a result, the study's generalizability may be compromised because the study results may not be applicable to the nonexperimental setting.

Study design is a trade-off between internal and external validity which can span a continuum from highly favoring internal validity or external validity, to attempt for a more balanced approach. When a study is designed with focus on one validity element, the other validity element is compromised (i.e., a high focus on internal validity will

result in lower external validity). Ideally, high levels of both internal and external validity are desired but no single study design accomplishes this.

3.3 Randomized clinical trial

The RCT study design is used in the evaluation of change to determine whether a difference exists between two or more groups.[13] The cornerstone of the RCT study design is random assignment of participants to groups, which should create balanced treatment groups.[34] Randomization is assumed to create two groups with equivalent baseline characteristics, reducing selection bias and equally distributing hidden variables, thereby controlling the effects of confounding.[34] Even when randomization is used to assign participants to treatment groups, the possibility remains that the groups could be unbalanced in a meaningful way. This could occur by chance, particularly in RCTs with small sample sizes. Aspects of how randomization is conducted within a study may also be responsible for the failure to produce balanced groups. In particular, it is important that the sequence of randomization is concealed from persons involved in the study (i.e., participants, clinicians, investigators, administrators).[10] If the randomization sequence is revealed, there is the potential of selection bias and the possibility groups will differ in characteristics. Successful participant randomization is important as it creates unbiased comparison between groups, providing a valid basis for statistical tests of significance.[1]

In addition to randomization, the RCT study design creates similar treatment groups, to reduce confounding, follow-up time points and study variables. In the RCT, restrictions are imposed on the participants recruited by very precise inclusion and exclusion criteria. Further, to reduce the possibility of selection bias during participant

follow-up, group balance is maintained after randomization by a process called blinding. Blinding is defined as the concealment of the assigned treatment group from the patient, the investigator and the outcomes assessor. Blinding to the treatment group encourages all groups should be followed with equal rigor because knowledge about which intervention each participant is receiving can misrepresent results or conclusions. Finally, high control is maintained over the treatment, treatment delivery and delivery time by strict study protocols to provide similar treatment for all study participants.

The high level of control in a RCT reduces bias and increases the internal validity allowing causal interpretations to be made on the study population. The restrictions imposed on the RCT have the potential to reduce the level of external validity, causing these types of studies to be limited in their ability to generalize to the affected population.[6]

3.4 Observational study design

By design, an observational study lacks randomization in treatment assignment[34] and requires the observation or measurement of outcomes without impacting the outcome.[13] Studies using this design have advantages as the population being studied can be diverse, treatments are more likely to be delivered in a manner consistent with clinical practice, treatments that may be unethical to withhold in a RCT study design can be investigated and these designs can be used to model outcomes in usual practice.

Although the lack of control imposed in observational study designs can enhance external validity, these approaches create biases that limit internal validity. The primary reason for the reduced internal validity is the lack of randomization. There is selection

bias in observational studies because participants are not randomly assigned to a treatment group but instead have either chosen their own treatment, or their treatment has been imposed upon them (i.e., clinician, family, setting). The reasons certain participants chose or receive a certain treatment are difficult to account for and if these reasons also affect the outcome, direct comparison of the groups may result in biased conclusions. When there is no randomization, group differences are expected, introducing a risk that the difference in outcomes could be due to the initial differences between patient groups.[34] This selection bias results in incorrect treatment effect inferences because of the increased threats to internal validity.[12, 30]

The lack of randomization also results in the potential for the hidden variables to be unequal between groups resulting in confounding.[13, 18, 30] In studies that use a secondary data source such as a database, these hidden variables present a problem because the choice of data elements in a preexisting database is limited to that which has already been collected and often does not include an element that may be desired.[27] Randomization is the only strategy to manage hidden variables. The nonrandomization process in observational studies introduces a risk that the difference in outcomes could be due to the differences between patient groups.

The participants in observational studies often have few restrictions placed upon their inclusion, allowing a diverse population with a broad spectrum of disease severity[13] and attend multiple visits at varying time points. This lack of restriction can lead to a loss of control over variables external to the study. As a result, there is an increase in the possibility of confounding and low internal validity but also an increase in the generalizability (external validity) to the affected population.

Recent developments in the design of observational studies can assist in minimizing threats to internal validity without using randomization. Matching is a well known strategy to manage confounding due to nonrandomization. An advanced matching strategy, the propensity score methodology, was developed to create groups that were similar to those found when a randomization process is used. [5, 31, 34] The groups created by the propensity score can be statistically analyzed with the same assumptions and rules that apply to an RCT.[5, 31, 34]

The propensity score is the predicted probability of being in the treatment group(versus control) given the individuals characteristics.[5] When there are a large number of confounders (i.e., age, gender, comorbidities), matching on confounders is difficult. Propensity score matching provides an alternative to individual matching by using a group assessment.[17, 32] The propensity score uses all of the participants' characteristics (covariates) and reduces these covariates to a single, individual score. If participants have similar propensity scores, then they have similar probabilities of receiving the treatment given the measured confounders.[31-32]

An example of propensity score matching was used by George et al. (2008) to investigate the effects of total knee arthroplasty (TKA) on physical functioning in the older population.[9] Using Medicare claims data (n=12,500), 259 participants with osteoarthritis of the knee who received a TKA were matched, using a propensity score based on demographic characteristics, comorbid conditions and baseline function, to 1816 participants who did not receive a TKA. The estimated treatment effect demonstrated improvements in physical function for those with a TKA.[9]

3.5 Potential problems in statistical analysis

To achieve a robust evaluation of change occurring with treatment, it is essential that the type of study (i.e., observational or RCT) and the research question being investigated match the data analysis technique. When the same analysis techniques are used to evaluate change without consideration of study design, misinterpretation of results may occur due to the potential of bias, confounding and regression to the mean. A review of the methods and statistical techniques historically associated with each study design is necessary to understand how recently developed procedures are applied to the evaluation of change. [35] Recent advances in methodological and statistical techniques are not yet common, but are highly applicable to research related to physical therapy treatments.[35]

The absolute difference, percentage change and baseline adjustment are established statistical analysis techniques used to evaluate group differences at two or more time points (repeated measures). In an RCT study design, these techniques can minimize error and avoid overestimation of group differences. In contrast, use of these techniques with observational study designs may result in artificial treatment effects due to group differences related to extraneous variables. The lack of randomization of participants in an observational study complicates the evaluation of change and requires statistical analysis techniques that deviate from the analysis techniques performed with randomized clinical trial designs.[25]

3.5.1 Absolute difference

The absolute difference (change score) is computed as the posttreatment score subtracted from the pretreatment score and is used to examine whether two groups differ in their mean change over time. The absolute difference does not control for group differences at baseline but rather asks a question "Do these groups differ in their average change?" The absolute difference is appropriate with data derived from a RCT or observational study.

3.5.2 Percentage change

Percentage change (i.e., relative difference) is a unitless number expressed as a fraction of improvement [(baseline score – posttest score)/baseline score X 100]. It is a description of a percentage gain or loss from the initial value on a particular outcome. The main benefit of using the percentage change score may be the ease in the interpretation of change. For example, to describe functional level change after total hip arthroplasty(THA) the following statement could be said using percentage change analysis *On average, the functional level increased 10% for young people after THR, whereas it increased 30% for older people*. Whereas using the absolute difference to describe the same population may result in a less intuitive description: On average the functional level increased 10 units for young people after THA, whereas it increased 20 units for older people.

In general, the percentage change score performs poorly when there are differences at baseline. Similar to the absolute difference, there may be confounding

present because of other measured or unmeasured variables not controlled for in the analysis.

3.5.3 Baseline adjustment

Baseline adjustment uses the pretreatment score as a covariate in a regression equation to compare changes between groups. When groups are randomly allocated, the groups are assumed to be equal at baseline. If by chance there are differences at baseline, using the baseline measure as a covariate reduces between-subject variability (i.e., error variance-differences due to chance) and statistically creates more similar groups for comparison. When the baseline value is used as a covariate, the question being asked becomes conditional; given that all groups have the same baseline value, are there differences between groups?[8]

In observational studies, baseline differences are expected due to the nonrandomized selection. There is controversy whether or not to adjust for baseline difference with those against the use of baseline adjustment with nonrandomized groups[11, 15, 28] and those that recommend its use with caution.[21] When baseline differences exist, those subjects farther away from the mean at their baseline value will show greater change, resulting in regression to the mean.[15] Thus, in observational studies where there may be large baseline differences, the baseline value as a covariate can bias the estimation and/or detection of treatment effects.[16]

3.5.4 Hierarchical linear modeling

Recently, another analysis technique was developed to address the issues of confounding and bias identified in the study design and statistical analysis of RCT and observational studies. Hierarchical linear modeling (HLM) is a newer type of analysis that is not constricted by the assumptions and rules imposed when using the classic analysis techniques.[14, 29] HLM can be used to determine individual change over time and be used to determine how a person changes independently from the group. A detailed description of the HLM technique[36] and the application of HLM in physical therapy has been described by Stratford(2003) and Resnik(2008).[27, 36] Briefly, HLM is based on two levels of regression equations, within-group (level-1) and between group(level-2).[35] The level-1 equation, answers questions about the change occurring within an individual, "How quickly has this person recovered?"[35] The level-2 equation answers the question about "how individual change differs from participant to participant."[35] The use of level data allows the characteristics of clusters, i.e., a patient, a clinician, a facility or geographic area, to be accounted for in the analysis. The main benefit of the HLM technique is many restrictions that apply to the previous analysis techniques (absolute difference, percentage change and baseline adjustment) are mitigated. The HLM technique is flexible in the application to time and inclusion of all a participant's information. Every data point is considered unique for each participant. Allowing each observation to have a unique time point accommodates measurements that were taken at varying time points. In HLM, the unique time point assignment reduces the possibility of selection bias due to missing data points. All data points remain in the analysis even if an observation related to that data point is missing. If a participant drops out of the study

early, his or her data points remain in the analysis and contribute even though he or she may not have completed the study. The application of the classic analysis techniques to outcome data collected where multiple visits are recorded at varying time points would result in a loss of valuable information and statistical power and may result in missed treatment effects.

In a recent observational study by Kennedy et al. (2008), repeated functional measurements from 84 participants with TKA were analyzed to describe the pattern of functional recovery 1 year after TKA. Participants differed in the number of assessments, ranging from two to six visits. Follow-up times were intentionally varied to provide a better indication of change after TKA. To accommodate the varied number of assessments and follow-up times, a HLM analysis, nonlinear mixed-effects, was used. Graphing of the predicted functional change identified the greatest improvement in the first 3 months after TKA. This was the first study with TKA participants to use this unique study design to model change.

3.6 Discussion

In this article, the RCT design and the observational study design along with their associated statistical techniques are used to evaluate treatment effects in the measurement of change are reviewed. Further, potential problems in study design and statistical analysis are outlined and new statistical analysis techniques to manage these problems are introduced. It is prudent to appreciate the methodological and statistical analysis options that can be applied to different study designs so that valid conclusions about treatment effects are established.

Historically, the RCT study design appears to be the most frequently used type of study design to identify treatment effectiveness in physical therapy. Recently, the use of clinically gathered outcomes data, patient registries and electronic medical records has introduced the observational study design as a tool to complement information provided by a RCT. The RCT design has strict conditions that allow causal conclusions based on straightforward statistical analysis. As a result of these strict conditions the application to clinical practice may be lost or unknown. In contrast, observational studies often use data originating from clinical practice (i.e., no restrictions). Using a heterogeneous population (i.e., clinical practice) can result in confounding requires advanced statistical analysis to ensure valid conclusions are being made.[13] Propensity score matching is an advanced method introduced and recommended for use in observational studies to reduce the differences that usually occur between groups.[26] Creating groups with similar characteristics can reduce the statistical analysis problems associated with baseline differences.

The classic statistical analysis techniques (absolute difference, percentage change and baseline adjustment) used in RCT and observational study designs have limitations. Their use is warranted under the specified conditions. HLM is a newer statistical analysis technique that can be used straightforwardly for both RCT and observational study designs.[36] The benefit of the HLM is that it is able to accommodate the many restrictions often noted with the classic statistical analysis techniques. Perhaps of particular interest to clinicians is the ability of the HLM to quantify what is observed within clinical practice by modeling the individual change over time and how a person changes independently from the group. In addition, modeling individual change using HLM can

allow for the individual characteristics of the clinic and the therapist to be included in the evaluation.

Attention to differences in study designs and statistical analysis is necessary to produce valid evidence that can be used to base decisions on treatment effectiveness. In the analysis of change these differences are highlighted and could potentially result in spurious conclusions. To guide and improve the rigor of the development and interpretation of studies using RCT and observational study designs, checklists have been developed.[2, 13, 18, 22-24, 26, 33, 37] The Consolidated Standards of Reporting Trials (CONSORT) was developed to identify features of the RCT that should be reported to determine the quality of the trial.[2, 22-23, 33] Similarly, the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) was produced for observation studies to improve the reporting quality.[37] Further, a series of three articles specifically targeting the critical appraisal of observational studies were recently published and provide guidance for the systematic review of observational studies.[13, 18, 26]

3.7 Conclusion

Observational and RCT are complementary study designs that add value to the effectiveness of physical therapy treatment. Awareness of the differences in these study designs, how these differences can lead to different study conclusions and how new techniques can be used to manage these differences may help to translate research into clinical practice and further the evidence on the effectiveness of physical therapy interventions.

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CHAPTER 4

SILENT MODIFIABLE FACTORS ASSOCIATED WITH PHYSICAL FUNCTION IN TOTAL HIP AND KNEE ARTHROPLASTY CANDIDATES

4.1 Abstract

4.1.1 Objective

To determine the association of five cardiometabolic risk factors (diabetes, hypertension, elevated triglycerides, low high density lipoproteins, obesity), and metabolic syndrome (MetS) with the level of physical function prior to surgery in patients undergoing total knee (TKA) and total hip arthroplasty (THA) surgery.

4.1.2 Methods

Patient physical function data were retrospectively extracted from a clinical orthopedic database between September of 2008 and November of 2010. Comorbidities were obtained by chart abstraction. Patients were ≥40 years old with a primary total hip or knee arthroplasty. Relationships between MetS and its individual components, and physical function were completed using the Lower Extremity Function Scale (LEFS) and SF-36 physical component score (PCS). Covariates were age, sex, comorbidities and physical activity.

4.1.3 Results

A total of 174 total knee and 112 total hip candidates were included in the study. For total knee candidates, mean LEFS scores were significantly ($p<0.001$) and clinically lower for patients with MetS (30.0 SD 14.2) than without MetS (39.9 SD 16.0). Adjusted analysis showed that MetS remained significantly associated with reduced lower-extremity physical function; additionally, female sex, chronic back pain and insomnia significantly reduced preoperative lower-extremity physical function. For total hip candidates, adjusted analysis found MetS and being female were significantly ($p<0.05$) associated with worse lower-extremity physical function. MetS was not significantly associated with preoperative physical health (PCS) in either the total knee or hip candidates.

4.1.4 Conclusions

Presurgical physical function impacts postoperative outcomes in total joint replacement. Identification of modifiable presurgical patient characteristics may alter the management of the total knee or hip arthroplasty candidate. This study provides evidence that MetS, back pain and insomnia are modifiable conditions that influence preoperative physical function. Additional research to better understand patient characteristics, long-term outcomes and optimal treatment options in the management of the total hip and knee arthroplasty population is warranted.

4.2 Introduction

Knee and hip replacement procedures are an effective treatment for osteoarthritis (OA) related pain and dysfunction.[1] Approximately 15-30% of the total hip and knee arthroplasty population does not have substantial improvement in their pain, functional status and overall health related quality of life.[2-6] During the course of the next 20 years, the number of TKA and THA procedures are predicted to increase 673% and 174%, respectively, resulting in 3.5 million TKA/THA procedures.[7] As a consequence, over half a million people undergoing TKA/THA surgery could have impaired function for activities such as walking and stair climbing. The healthcare resources needed to manage these limitations will result in a high economic burden to providers, patients and society.

Metabolic syndrome (MetS) is defined as the clustering of the following cardiovascular risk factors: abdominal obesity, hypertension, dyslipidemia (elevated TG and low high density lipoproteins) and elevated fasting glusose.[8] The prevalence of MetS in the U.S. has increased to approximately 34%.[9] MetS increases the risk of cardiovascular disease, stroke and dementia[10-11] and has a negative impact on quality of life.[12] Hypertension, hypercholesterolemia and elevated blood glucose are associated with OA independent of obesity.[13-14] TKA and THA candidates may have higher prevalence of MetS due to cardiovascular risk factors link with OA or simply due to inactivity that may accompany joint pain. Regardess of the cause, MetS has been linked to an increased risk of postoperative complications, deep vein thrombosis[15] and pulmonary embolus in the total hip and knee arthroplasty population.[16]

Individual components of MetS have been investigated in the total joint arthroplasty population with conflicting results. Population-based studies have

consistently shown a link between overweight or obesity and knee/hip OA,[17-18] although the impact of obesity on TKA and THA functional outcome is controversial.[19-20] Patients with diabetes reportedly achieve the same level of function as nondiabetic patients but take a longer duration of time to achieve similar results.[21-23] Recently, Gandhi et al. (2010) investigated the individual components of MetS and found hypertension and obesity to be predictive of poorer outcome following total hip arthroplasty.[24] There are limited data demonstrating the association of physical function outcomes with MetS in the total hip and knee arthroplasty population.[25]

The purpose of this study was to determine the association of each of five cardiometabolic risk factors (diabetes, hypertension, elevated triglycerides, low high density lipoproteins, obesity) and MetS (three or more risk factors present) with the level of physical function prior to surgery in patients with TKA and THA surgery. The main objectives of this study were to: (1) describe baseline (preoperative) characteristics (demographics, LEFS, SF36) between those with and without MetS and (2) explore associations between CMR factors on level of physical function adjusting for age, sex, physical activity and comorbidity.

4.3 Methods

4.3.1 Data source

All questionnaire data were collected as part of routine clinical practice from one academic total joint service (knee and hip), located in Salt Lake City from September 1, 2008 through November 30, 2010. The University of Utah-Total Joint Service maintains an electronic database that store data from all physician-patient encounters. The database

contains basic demographic information about each patient (age, gender, surgical date). Clinical outcomes, including a health status measure, region-specific disability score and a physical activity level measure, were collected at the beginning of each visit and entered into the electronic database. Medical record chart abstraction was completed to identify cardiovascular risk factors and comorbid conditions.

4.3.2 Questionnaires

The health status measure, the Short Form-36 Medical Outcomes Study (SF-36) version 2.0 is a 36-question generic instrument for measuring quality of life.[26-27] Reliability and validity have been extensively evaluated in a variety of patient populations, including people with total hip and knee arthroplasty and community dwelling elderly.[26, 28] Reliability estimates for physical and mental summary scores usually exceed 0.90.[20] The range of scores vary from 0 to 100 with the lowest score 0, indicating the worst possible health and 100 the best health. The Physical Component Summary (PCS) score is based on 21 of the 36 questions.[26-27]

The Lower Extremity Functional Scale (LEFS)[29] is a region-specific disability questionnaire. It is a 20-item self-report measure designed to assess functional status for patients with a variety of conditions affecting the lower extremity. Each item of the LEFS is scored from 0-4, with the final score expressed as a sum out of 80 possible points. Higher scores are associated with higher functional status. Although the LEFS was designed for use with a variety of lower extremity conditions, high reliability estimates have been shown in the THA and TKA populations (internal consistency 0.93,

ICC 0.85-0.92 and minimally detectable change of 9 points).[29-30] The LEFS is easy for the patient to use and it is quick to administer and score.[29-30]

The Rapid Assessment of Physical Activity (RAPA) [31-32] is a self-administered questionnaire developed to assess levels of physical activity among adults older than 50 years. Items for the RAPA were developed based on Centers for Disease Control and Prevention (CDC) guidelines of 30 minutes or more of moderate physical activity on every or most days of the week. The final version is a nine-item questionnaire with a yes or no response option. The total score is from 1 to 7 points, with the respondent's score categorized into one of five levels of physical activity: 1=sedentary, 2=underactive, 3=regular underactive- light activities, 4= regular underactive and 5= regular active. Sensitivity, specificity and predictive value of the RAPA compare well with the Community Health Activities Model Program for Seniors (CHAMPS) physical activity questionnaire, sensitivity 81%, specificity 69% PPV 77% NPV 75%).[31-32]

4.3.3 Cardiometabolic risk

Cardiometabolic Risk (CMR) is defined using the National Cholesterol Education Program Adult Treatment Panel III (NCEP–ATP III) guidelines established for MetS and includes the following five risk factors: blood glucose, waist circumference, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), hypertension (HTN).[33] MetS is the clustering of any three of these five risk factors. The out of range values for each risk factor are as follows: fasting plasma glucose ≥126 mg/dL, body mass index >27 kg/m^2 , triglycerides ≥150 mg/dL, high density lipoprotein <40mg/dL (men) or <50mg/dL (women) and elevated blood pressure (Systolic ≥130 mm Hg or diastolic ≥85 mm Hg).[33]

Determination of the presence of each risk factor was completed using three different identification criteria (clinical, diagnostic, and treatment). *Clinical* criteria were based on laboratory test values, blood pressure, height and weight. Body mass index (BMI) was used as a proxy measure for waist circumference and calculated from the patients' height and weight measurements. Several studies have concluded that BMI and waist circumference are highly correlated.[34-36] *Diagnostic* criteria was based on patient self-report or preoperative report of elevated cholesterol, hypertriglyceridemia, hypertension (HTN), diabetes mellitus (DM), and obesity. *Treatment* criteria were based on the prescriptions recorded (patient self-report or preoperative report) indicating treatment for elevated cholesterol, hypertriglyceridemia, HTN, DM, and obesity. Patients identified using treatment criteria were those with a prescription for any one of the following drugs or drug classes: 1) weight loss agents (sibutramine hydrochloride, orlistat), 2) triglyceride lowering agents (fibrates, niacin), 3) antihypertensives (angiotensin converting enzyme-inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, thiazide diuretics, antihypertensive vasodilators, and combinations of these agents), and 4) drugs used for diabetes (sulfonylureas, metformin, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, and combinations of the preceding agents). Patients that had at least one of the three criteria of abnormality (clinical, treatment and diagnostic) for each of the five risk factors (blood glucose, BMI, HDL, TG, HTN) were classified as having elevated risk for that risk factor. Metabolic syndrome was defined as co-occurrence of an abnormality in three of the five (blood glucose, BMI, HDL, TG, HTN) risk factors.[33]

4.3.4 Demographics

Patient characteristics at baseline included age, sex, and comorbid conditions (arthritis, mental health, chronic back pain, cancer, insomnia, osteoporosis, gout, coronary artery disease and neuropathy) were collected from the hospital admission interview conducted on the day of surgery. Documentation on the admission form of any one of the following words was considered a positive indication of the comorbid condition: arthritis (arthritis, osteoarthritis, rheumatoid arthritis, fibromyalgia), mental health (depression, anxiety), cancer, insomnia, osteoporosis, gout, coronary artery disease (CAD) and neuropathy. This study qualified for exempt review from the Institutional Review Board at the University of Utah.

4.3.5 Subjects

Patients were included if they met all of the following criteria: age 40 years or older on the date of their surgery, and underwent a primary total knee or hip arthroplasty. Patients were excluded if they had another hip or knee arthroplasty surgery with a year from the index surgery, were missing LEFS or SF-36 scores or if they had a stroke, paralysis, or any major neurological disorder or medical condition that impaired ambulation.

A total of 415 and 287 people received a TKA and THA, respectively. Upon application of the inclusion criteria, 241 (58.1%) patients with TKA and 175 (61.0%) with THA were excluded Figure 4.1.

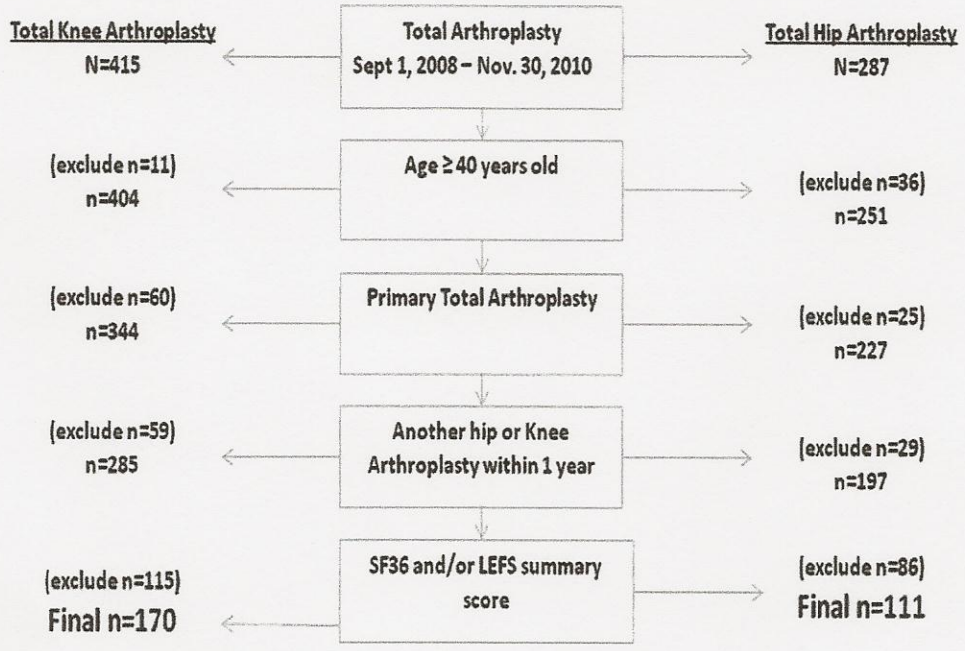

Figure 4.1 Study population flow chart

4.3.6 Analysis

The prevalence of CMR was established for each individual risk factor and for patients meeting none, one risk factor, two risk factors, and the MetS definition (three or more risk factors present) and expressed as a percentage of all subjects.

Comparisons were made between the study population and those not in the study using a t-test for continuous variables and chi-square test for dichotomous variables.

Univariate analysis was used to describe the demographics and physical function scores (LEFS, SF36) of the study cohort. Age, LEFS score, SF-36 Physical Component Score (PCS), and BMI (kg/m^2) were considered continuous variables and expressed with means with standard deviations. Dichotomous variables included the five cardiometabolic risk factors, MetS and the individual comorbidities and were expressed as the percentage of the population. The RAPA was treated as a categorical variable.

Unadjusted and adjusted models (age, sex, comorbid conditions, activity level) were used to evaluate the association of CMR factors with physical function. The LEFS and PCS scores were considered the dependent variables, and the five CMR factors, MetS, comorbid conditions and physical activity were the independent variables. Statistical analyses were performed using StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.

4.4 Results

There were 174 TKA study participants consisting of 110 women (63.2%), with a mean age (63.8 years, SD 10.2) and mean BMI (31.7 kg/m^2, SD 7.0). These individuals did not differ by age, BMI or sex from the 111 patients with TKA who were not selected (Table 4.1).

Table 4.1 Description between TKA and THA study population and nonparticipants

	Study population		Nonparticipants		p value
	(n=174)		(n=111)		
Total knee arthroplasty					
Female (n,%)	110	(63)	73	(67)	0.662
Age, years (mean,SD)	64	(10)	64	(11)	0.713
BMI, kg/m^2 (mean,SD)	32	(7)	32	(8)	0.856
Total hip arthroplasty	(n=112)		(n=85)		
Female (n,%)	64	57.14	50	58.82	0.162
Age, years (mean,SD)	61.29	11.91	60.25	11.71	0.787
BMI, kg/m^2 (mean,SD)	29.96	6.77	30.15	7.95	0.672

Patient characteristics (age, BMI, sex) of the 112 THA study participants were similar to the TKA population and also did not differ from those not included in the study. Arthritis, mental health, and chronic back pain were the most common comorbid conditions (Tables 4.2 and 4.3). The majority of the TKA (62.8%) and THA (57.6%) study populations were considered to have an underactive or sedentary level of physical activity.

4.4.1. Prevalence of individual cardiometabolic risk factors and MetS

The prevalence of diabetes, elevated BMI, hypertension, elevated cholesterol and MetS was higher in patients with a TKA compared to those with a THA (Figures 4.2 and 4.3). There was almost double the proportion of diabetes in the TKA population (20.1%) compared to THA population (11.7%). A small percentage, 5%, of the TKA study population and 13.4% of the THA population did not have any CMR factors (Figure 4.3). TKA and TKA patients classified with MetS were significantly ($p<0.05$) older, with a higher body mass index. In addition, patients with MetS and a TKA also had significantly ($p<0.05$) lower functional status (LEFS score) than those without MetS.

4.4.2 Association of individual cardiometabolic risk factors and MetS on physical function

4.4.2.1 Univariate associations

In Table 4.4, the unadjusted models of physical health (PCS), hypertension was the only risk factor significantly ($p=0.044$) associated with lower physical health in patients with a TKA; no risk factors were associated with physical health (PCS) for

Table 4.2. TKA study population description

Characteristics	Study Population N=174		No Metabolic Syndrome n=111		Metabolic Syndrome n=63		pvalue*
Demographics							
Female (n,%)	110	63.22	66	59.46	44	69.84	0.172
Age Mean years (SD)	63.80	10.18	62.46	10.43	66.16	9.34	0.021
BMI* Mean (SD)	31.73	6.97	30.49	6.61	33.92	7.12	0.002
Comorbid conditions (n,%)							
Arthritis	134	77.01	85	76.58	49	77.78	0.856
Mental health	68	39.08	41	36.94	27	42.86	0.442
Chronic back pain	52	29.89	28	25.23	24	38.10	0.075
Cancer	33	18.97	22	19.82	11	17.46	0.703
Insomnia	32	18.39	16	14.41	16	25.40	0.072
Osteoporosis	23	13.22	14	12.61	9	14.29	0.754
Gout	11	6.32	8	7.21	3	4.76	0.524
Coronary artery Disease	8	4.60	4	3.60	4	6.35	0.406
Neuropathy	4	2.30	2	1.80	2	3.17	0.561
Physical Function (mean, SD) SF-36 Score*							
PCS	34.13	8.88	34.98	8.91	32.69	8.72	0.104
LEFS*	36.50	16.06	39.88	16.00	30.02	14.19	0.001
Physical Activity (n,%)							
Sedentary	6	3.66	4	2.44	2	1.22	0.389
Underactive	13	7.93	11	10.48	2	3.39	
Underactive-light	39	23.78	23	21.90	16	27.12	
Underactive- regular	45	27.44	25	23.81	20	33.90	
Active	61	37.20	42	40.00	19	32.20	

**BMI: kg/m^2; Lower Extremity functional Scale, Short Form Physical Component Summary Score; test of significance are between no metabolic and metabolic syndrome*

Table 4.3. THA study population description

Characteristics	Study Population N=112		No Metabolic Syndrome n=81		Metabolic Syndrome n=31		pvalue *
Demographics							
Female (n,%)	64	57.14	49	60.49	15	48.39	0.247
Age Mean years (SD)	61.29	11.91	59.52	12.48	65.90	8.90	0.011
BMI* Mean (SD)	29.96	6.77	28.83	6.96	32.92	5.27	0.004
Comorbid conditions (n,%)							
Arthritis	86	76.79	61	75.31	25	80.65	0.550
Mental health	41	36.61	28	34.57	13	41.94	0.469
Chronic back pain	43	38.39	27	33.33	16	51.61	0.075
Cancer	13	11.61	8	9.88	5	16.13	0.355
Insomnia	14	12.50	8	9.88	6	19.35	0.175
Osteoporosis	21	18.75	14	17.28	7	22.58	0.521
Gout	0	0					
Coronary artery disease	1	0.89					
Neuropathy	1	0.89					
Physical Function (mean, SD)							
SF-36 Score*							
PCS	31.91	8.10	32.08	8.86	31.47	5.79	0.723
LEFS*	33.30	17.00	35.20	17.65	28.31	14.23	0.063
Physical Activity (n,%)							
Sedentary	5	4.72	3	3.95	2	6.67	0.357
Underactive	5	4.72	5	6.58	0	0	
Underactive	22	20.75	14	18.42	8	26.67	
Underactive- regular	29	27.36	19	25.00	10	33.33	
Active	45	42.45	35	46.05	10	33.33	

**BMI: kg/m^2; Lower Extremity functional Scale, Short Form Physical Component Summary Score; test of significance are between no metabolic and metabolic syndrome*

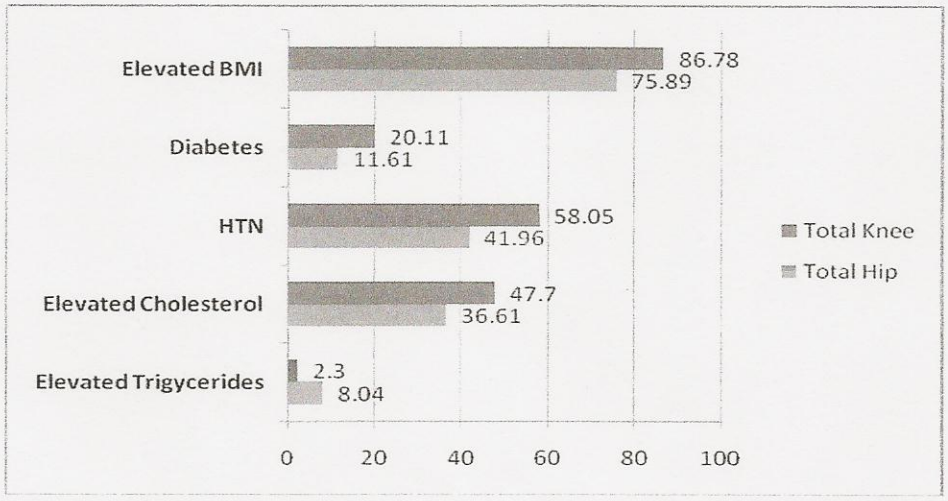

Figure 4.2 Prevalence of five cardiometabolic risk factors in those undergoing TKA and THA surgery

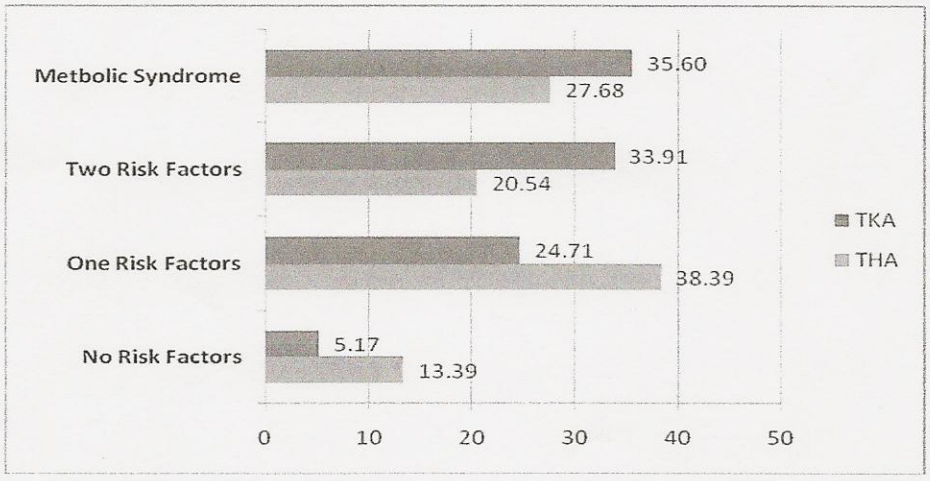

Figure 4.3 The frequency of cardiometabolic risk factors in those undergoing TKA and THA surgery

Table 4.4 Unadjusted associations of physical function with individual cardiometabolic risk factors and metabolic syndrome

	Total Hip Arthroplasty				Total Knee Arthroplasty			
	PCS		LEFS		PCS		LEFS	
	B (95% CI)	p value	B (95% CI)	p value	B (95% CI)	p value	B (95% CI)	p value
BMI	-1.56	0.388	-7.50	0.057	0.08	0.967	-4.28	0.237
	(-5.11 2.00)		(-15.23 0.23)		(-3.85 4.02)		(-11.41 2.85)	
Diabetes	1.15	0.633	-4.24	0.402	-2.16	0.206	-8.4	0.008
	(-3.61 5.91)		(-14.24 5.75)		(-5.50 1.20)		(-14.53 -2.26)	
HTN	0.64	0.684	-3.59	0.286	-2.78	0.044	-7.84	0.002
	(-2.46 3.73)		(-10.23 3.05)		(-5.48 -0.07)		(-12.73 -2.96)	
Cholesterol	0.7	0.662	-3.61	0.301	-0.74	0.590	-5.21	0.038
	(-2.47 3.87)		(-10.23 3.05)		(-3.42 1.95)		(-10.14 -0.28)	
TG*	-1.13	0.691	-8.35	0.211	1.36	0.762	0.26	0.975
	(-6.73 4.48)		(-21.50 4.79)		(-7.53 10.26)		(-15.85 16.37)	
Metabolic syndrome	-0.61	0.723	-6.89	0.063	-2.29	0.104	-9.86	0.000
	(-4.02 2.80)		(-14.15 0.38)		(-5.05 0.48)		(-14.87 -4.84)	

B-beta coefficient; TG-triglycerides,

patients with a THA. For those with a TKA, the unadjusted variables of diabetes ($p=0.008$), hypertension ($p=0.002$), elevated cholesterol ($p=0.034$), and MetS ($p<0.001$) had significant associations with lower-extremity physical function (LEFS). No individual CMR factors or MetS were significantly associated with lower-extremity physical function (LEFS) for those with a THA.

4.4.2.2 Multivariate models

Table 4.5 shows the multivariate regression for the association between the CMR factors and physical function (PCS and LEFS). Each analysis included the following covariates: demographic characteristics, comorbid conditions (arthritis, chronic back pain, mental health, cancer, insomnia and osteoporosis) and activity level.

Individual CMR factors (hypertension, elevated triglycerides, elevated cholesterol, elevated BMI and diabetes) were not significantly associated with physical function for either the TKA or THA population. For those with a THA, lower physical health was associated with female sex (β -4.68; 95% CI -8.15 to -1.21; $p=0.009$) and insomnia (β -6.58; 95% CI -11.06 to -2.11; $p=0.004$).

In the TKA population, a decrease in lower-extremity physical function was significantly ($p<0.05$) associated with female sex, chronic back pain and insomnia. Patients with a TKA and who were physically active had higher lower-extremity physical function scores (β 5.81; 95% CI 1.01 to 10.62; $p=0.018$) than those who were not active.

Table 4.6 shows the multivariate regression for the association between MetS and physical function (PCS and LEFS) adjusting for demographic characteristics, comorbid

Table 4.5. Multivariate regression results for cardiometabolic risk factors association with physical function in patients with hip or knee arthroplasty

	Total Hip Arthroplasty						Total Knee Arthroplasty					
	PCS			LEFS			PCS			LEFS		
	B coeff.	95% CI	p value	B coeff.	95% CI	p value	B coeff.	95% CI	p value	B coeff.	95% CI	p value
CMR Factors												
Hypertension	-1.16		0.510	-3.32		0.398	-2.22		0.154	-2.75		0.298
	(-4.66	2.34)		(-11.08	4.44)		(-5.28	0.84)		(-7.95	2.45)	
Elevated TG	-2.67		0.406	-5.33		0.477	2.88		0.507	6.77		0.363
	(-9.02	3.68)		(-20.16	9.50)		(-5.69	11.46)		(-7.89	21.44)	
Elevated Chol	0.39		0.829	0.96		0.815	0.08		0.954	-1.31		0.588
	(-3.20	3.99)		(-7.12	9.03)		(-2.73	2.89)		(-6.09	3.46)	
Elevated BMI	-1.15		0.554	-7.68		0.080	1.4		0.497	-3.59		0.305
	(-5.00	2.70)		(-16.27	0.92)		(-2.66	5.45)		(-10.48	3.30)	
Diabetes	0.7		0.783	-1.68		0.765	-0.59		0.747	-4.29		0.167
	(-4.31	5.71)		(-12.83	9.47)		(-4.20	3.02)		(-10.41	1.82)	
Demographics												
Female	-4.68		0.009	-7.05		0.070	-2.61		0.076	-5.47		0.030
	(-8.15	-1.21		(-14.69	0.59)		(-5.49	0.28)		(-10.41	-0.53)	
Age	0.17		0.030	0.04		0.808	-0.01		0.931	-0.12		0.349
	(0.02	0.33)		(-0.30	0.38)		(-0.16	0.15)		(-0.38	0.13)	

Table 4.5. (continued)

	Total Hip Arthroplasty						Total Knee Arthroplasty					
	PCS			LEFS			PCS			LEFS		
	B coeff.	95% CI	p value	B coeff.	95% CI	p value	B coeff.	95% CI	p value	B coeff.	95% CI	p value
Comorbid Conditions												
Arthritis	0.02	(-3.68 3.72)	0.992	0.71	(-7.40 8.83)	0.862	-0.61	(-4.06 2.84)	0.728	-0.95	(-6.90 4.99)	0.752
Chronic Back Pain	-2.00	(-5.20 1.20)	0.217	-3.54	(-10.56 3.47)	0.318	-3.94	(-6.94 -0.94)	0.010	-7.94	(-13.06 -2.82)	0.003
Mental Health	1.34	(-1.84 4.53)	0.405	-4.03	(-11.06 3.01)	0.258	0.12	(-2.87 3.11)	0.938	-4.16	(-9.27 0.96)	0.110
Cancer	2.63	(-2.15 7.40)	0.278	-0.17	(-10.86 10.52)	0.975	-1.63	(-5.06 1.81)	0.350	-0.69	(-6.56 5.17)	0.815
Insomnia	-6.58	(-11.06 -2.11	0.004	-5.96	(-15.72 3.81)	0.229	-4.14	(-7.58 -0.71)	0.018	-9.45	(-15.42 -3.48)	0.002
Osteoporosis	-4.48	(-9.18 0.22)	0.061	-5.77	(-16.26 4.72)	0.277	0.82	(-3.27 4.91)	0.693	1.4	(-5.48 8.27)	0.689
Physical Activity	-0.19	(-3.29 2.92)	0.905	-1.63	(-8.48 5.22)	0.637	2.59	(-0.23 5.40)	0.072	5.81	(1.01 10.62)	0.018

Table 4.6. Multivariate regression results for the association of metabolic syndrome with physical function in patients with hip or knee arthroplasty

	THA				TKA			
	PCS		LEFS		PCS		LEFS	
	β (95% CI)		β (95% CI		β (95% CI		β (95% CI	
Metabolic Syndrome	-2.10 (-5.50 1.30)	p=0.224	-7.98 (-15.62 -0.34)	p=0.041	-1.17 (-4.01 1.66)	p=0.415	-5.95 (-10.81 -1.09)	p=0.017
DEMOGRAPHICS						0. 077		
Female	-4.88 (-8.19 -1.56)	0.001	-7.72 (-15.11 -0.34)	0.041	-2.56 (-5.40 0.30		-4.99 (-9.84 -0.15)	0.044
Age	0.19 (0.05 0.33)	0.008	0.10 (-0.20 0.41)	0.504	-0.04 (-0.18 0.10)	0. 573	-0.11 (-0.35 0.13)	0.373
COMORBIDITIES								
Arthritis	-.29 (-3.86 3.27)	0.871	-0.78 (-8.66 7.10)	0.845	-0. 88 (-4.23 2.45)	0. 600	-1.43 (-7.13 4.28)	0.622
Chronic back pain	-1.82 (-4.88 -1.24)	0.242	-3.33 (-10.16 3.51)	0.336	-3.88 (-6.83 -0.94)	0. 010	-8.40 (-3.41 -3.39)	0.001
Mental health	130 (-1.77 4.37)	0.404	-3.79 (-10.63 3.05)	0.274	-0.06 (-2.74 2.88)	0. 961	-3.15 (-7.97 1.65)	0.196
Cancer	2.60 (-2.07 7.26)	0.272	-0.46 (-10.97 10.06)	0.931	1.56 (-4.95 1.83)	0. 365	-0.95 (-6.72 4.82)	0.745
Insomnia	-6.27 (-10.59 -1.96)	0.005	-5.54 (-15.06 -3.98)	0.251	-3.94 (-7.37 -0.51)	0. 025	-9.06 (-15.00 -3.11)	0.003
Osteoporosis	-4.20 (-8.66 0.26)	0.065	-3.44 (-13.42 6.54)	0.495	0.58 (-3.46 4.63)	0.776	1.27 (-5.52 8.06)	0.712
ACTIVITY LEVEL								
Physically Active	0.007 (2.91 3.04)	0.965	-0.90 (-7.53 5.73)	0.788	2.76 (-0.01 5.53)	0.050	6.34 (1.64 11.04)	0.009

β –beta coefficient; 95% CI- 95% confidence interval; p- p value

conditions (arthritis, chronic back pain, mental health, cancer, insomnia and osteoporosis) and activity level. For those with a THA, MetS (β -7.98; 95% CI -15.62 to -0.34, p=0.041) and female sex (β -7.72; 95% CI -15.11 to -0.34; p=0.041) were significantly associated with decreased lower-extremity physical function. For physical health (PCS), female sex (β -4.88 95% CI -8.19 to -1.15; p=0.001), and having insomnia (β -6.27; 95% CI -10.59 to -1.96; p=0.005) were significantly associated with decreased physical health (PCS). Physical activity was not associated with physical function (PCS and LEFS).

For patients with a TKA, MetS, female sex, chronic back pain and insomnia were shown to decrease preoperative lower-extremity physical function. Those with insomnia had the largest reduction (9 points on the LEFS) of preoperative lower-extremity physical function (β 9.06; 95% CI -15.00 to -3.11; p=0.003). For physical health (PCS), only chronic back pain was associated with reduced preoperative physical health (β -3.88; 95% CI -6.83 to -0.94; p=0.010). The patients with a TKA that were also physically active prior to surgery, had increased preoperative values ($p<0.05$) of physical health and lower-extremity physical function.

4.5 Discussion

This study provides preliminary evidence on the association of both individual CMR factors and MetS on the presurgical physical function score using two measures of physical function: lower-extremity physical function (LEFS) and physical health (SF-36). In our study, we found patients with total knee/hip arthroplasty and MetS had significantly worse preoperative levels of lower-extremity physical function than those without MetS; there was no significant difference found in preoperative physical health.

There is limited data in the total arthroplasty population demonstrating the health consequences of MetS.[24] It has been suggested that MetS could influence physical decline through increased inflammation,[37] sedentary behavior,[38] and low muscle strength.[39] Only one study has investigated the influence of risk factors of MetS on presurgical physical function in patients with a TKA or THA.[24] Risk factors were grouped together by the number of metabolic abnormalities and adjusted for age, sex and comorbidity. They found those with three risk factors (MetS) in the TKA population and four risk factors in the THA population had worse presurgical physical function.[24] Our study supports these findings, suggesting that MetS may affect preoperative physical function in those undergoing total hip or knee arthroplasty. [24]

A higher physical function score has indicated a better postoperative recovery physical function, in the total knee and hip arthroplasty population.[40-42] Little is known about patient characteristics that may influence the presurgical function. In addition to the association of MetS with preoperative lower extremity physical function in patients undergoing TKA and THA, we found patient sex (female), comorbidity (chronic back pain and insomnia) and physical activity, contributed significantly to physical function.

The presence of back pain, in the TKA population, has been identified as a preintervention predictor of worse outcome postarthroplasty.[40, 43] In our study, the patients with a TKA and concomitant chronic back pain also had worse preoperative physical function (lower-extremity and physical health). This effect was not seen in the THA population.

Good quality sleep is a critical for good health.[44] In the older population in general, sleep disturbances have been associated with a decrease health related quality of

life and physical function.[44] In the TKA/THA population, sleep disturbance has been shown to predict postoperative complications.[45-46] Our results indicate that insomnia is associated with worse preoperative physical health in both the THA and TKA populations. To our knowledge, this is the first report of sleep disturbance with functional outcomes prior to joint arthroplasty. Pain, backache and discomfort are proposed reasons for sleep disturbance in the total joint arthroplasty populations. It has been suggested that the treatment of the sleep symptoms may actually improve the patient's ability to function.[47] For those with osteoarthritis, pain control management is suggested.[48-50]

Our finding that women have worse presurgical physical function than men is supported in the total joint arthroplasty literature.[51-53] Women start the surgical process at a worse functional status than men, and do not attain the postoperative level of physical function that men achieve.[54-55] Further investigation is warranted to understand the sex related differences in preoperative physical function to target specific variables prior to surgery that may be unique to women.[51]

Regular physical activity can enhance musculoskeletal fitness, which is positively associated with functional mobility.[56] A significant improvement in lower-extremity physical function and physical health was found in patients with a TKA that were physically active however being physically active prior to surgery did not influence the physical function of the THA population. Preliminary evidence suggests hip and knee arthroplasty patients respond differently in the preoperative period.[57] It would seem that a preoperative exercise program may help to increase physical function; the data related to the direct effects of a prearthroplasty exercise intervention are inconclusive.[57-60]

Further research is needed to understand the potential role that physical activity plays in the preparation for surgery.

Our study has several limitations. This cohort was based from a single academic center orthopedic practice which may consist of patients with conditions that are more complicated than typically seen in the general total hip or knee arthroplasty population. Although when our study population's preoperative lower-extremity physical function scores, BMI and age are compared with published total knee and hip arthroplasty studies, they are similar.[54-55]

This study used physical function data gathered from routine clinical practice which resulted in a high number of patients that did not complete a preoperative measure of physical function. The individuals not included in this study were similar in age and body mass index compared to the individuals in the study but information on physical function and comorbidity prevalence was unknown and may have biased the results.

Due to the high reported prevalence of undiagnosed CMR factors, particularly the high rate of undiagnosed and/or untreated cardiometabolic risk in women, we may have underestimated the prevalence of MetS and its individual components.[61] Future research should incorporate current guidelines recommending a comprehensive assessment of CMR risk in both men and women.[62-64] The evaluation should include a complete a medical and family history to identify the presence of a known history of cardiometabolic disease, and a laboratory assessment (complete lipid panel and fasting glucose level).

4.6 Summary

Presurgical physical function impacts postoperative outcomes. MetS, back pain, and insomnia are modifiable conditions that influence preoperative physical function. Identification and management of modifiable presurgical factors that impact preoperative physical function may lead to improved postoperative outcomes. Future research is needed to evaluate whether these conditions influence postoperative outcomes.

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CHAPTER 5

ASSOCIATION OF CARDIOMETABOLIC RISK AND PHYSICAL FUNCTION AFTER TOTAL KNEE OR HIP ARTHROPLASTY

5.1 Abstract

5.1.1 Objective

To determine the association of five cardiometabolic risk (CMR) factors (diabetes, hypertension, elevated triglycerides, low high density lipoproteins, obesity), and metabolic syndrome (MetS), the presence of three of the five CMR factors, with physical function 6-weeks after surgery in patients with total knee (TKA) and total hip arthroplasty (THA) surgery adjusting for age, sex, physical activity, comorbidity and preoperative physical function.

5.1.2 Methods

Patient physical function data were retrospectively extracted from a clinical orthopedic database Sept 1, 2008 to November 30, 2010. Comorbidities were obtained by chart abstraction. Patients were ≥40 years old with a primary total hip or knee arthroplasty. Relationships between MetS and its' individual components, and physical function were completed using the Lower Extremity Function Scale (LEFS) and SF-36

physical component score (PCS). Covariates were age, sex, comorbidities, and physical activity.

5.1.3 Results

A total of 170 and 111 patients with a total knee and total hip arthroplasty, respectively, were included in the study. For total knee patients, mean preoperative LEFS scores were significantly ($p<0.001$) and clinically lower for patients with MetS (29.8 SD 14.3) than without MetS (40.1 SD 16.0). Postoperatively, the adjusted analysis showed that of the CMR factors, only diabetes remained significantly associated with reduced lower-extremity physical function. Chronic back pain and presurgical physical function significantly reduced postoperative lower-extremity physical function. For total hip patients, adjusted analysis found being female, chronic back pain and presurgical physical function were significantly ($p<0.05$) associated with worse physical health. In the adjusted models, MetS was not significantly associated with postoperative physical function (PCS or LEFS) in the THA/TKA population.

5.1.4 Conclusions

Identification of modifiable patient characteristics may alter that management of the total knee or hip arthroplasty candidate. This study provides evidence that presurgical physical function, diabetes and back pain are modifiable conditions that influence postoperative physical function. It is known that presurgical physical function impacts postoperative outcomes. MetS, back pain and diabetes were found to influence preoperative physical function. Additional research to better understand whether

preoperative patient characteristics that influence physical function, such as chronic back pain, diabetes, insomnia and MetS can be mediated to increase prefunctional status and potentially increase long-term postoperative outcomes as the optimal treatment options in the management of total hip and knee arthroplasty population is warranted.

5.2 Introduction

The estimated total hospital cost per year for joint replacements (2004) was $30 billion.[1] The demand for hip and knee replacements is rising annually and growth is expected to be substantial with a doubling in the number of hip procedures and a five-fold increase in knee replacements compared to 2005.[2] As a result, there will be an exponential increase in the healthcare resources needed to manage the postoperative care of the total hip and knee arthroplasty population. To optimize resource utilization it will be important to identify the patients which would benefit from pre- and/or postarthroplasty medical and /or rehabilitation management.

There is evidence that the presence and number of comorbidities is related to disability and physical function outcomes in the total hip and knee populations.[3-5] There are no clear indications, however, of specific modifiable disease conditions in the arthroplasty population that may be adversely impacting the recovery of physical function. The majority of studies focus on a comorbidity count derived from a wide-ranging selection of conditions not necessarily related to total hip and knee population. Identifying the specific comorbidities that can be modified both pre- and postoperatively and determining how these changes are related to physical functioning should improve the management of postoperative recovery.

The clustering of five cardiometabolic risk factors, abdominal obesity, hypertension, dyslipidemia (elevated TG and low high density lipoproteins) and elevated fasting glucose, defines metabolic syndrome (MetS).[6] The prevalence of metabolic syndrome in the U.S. has increased to approximately 34%.[7] Metabolic syndrome increases the risk of cardiovascular disease, stroke and dementia[8-9] and has a negative impact on the quality of life.[10] In the TKA and THA population, MetS has been linked to risk of postoperative complications.[11-12] Complications have been shown to be much higher in those patients with risk factor component of metabolic system, obesity, diabetes and hypertension.[13-16] TKA and THA patients may also have a higher prevalence of metabolic syndrome due to the cardiometabolic risk factors link with individuals with OA.[17] Finally, the influence metabolic syndrome and its components may have on postoperative physical function is not well established.[18]

The purpose of this study was to determine the association of five cardiometabolic risk factors (diabetes, hypertension, elevated triglycerides, low high density lipoproteins, obesity) and MetS with physical function 6 weeks after surgery in patients with TKA and THA surgery adjusting for age, sex, physical activity, comorbidity and preoperative physical function.

5.3 Methods

5.3.1 Data source

All questionnaire data were collected as part of routine clinical practice from one academic Total Joint Service (knee and hip), located in the Salt Lake City region from September 1, 2008 through November 30, 2010. The University of Utah-Total Joint

Service maintains an electronic database that store data from all physician-patient encounters. The database contains basic demographic information about each patient (age, gender, surgical date). Clinical outcomes, including a health status measure, region-specific disability score and a physical activity level measure, are collected at the beginning of each visit and entered into the electronic database. Medical record chart abstraction was completed to identify cardiovascular risk factors and comorbid conditions.

5.3.2 Questionnaires

The health status measure, the Short Form-36 Medical Outcomes Study (SF-36) version 2.0, is a generic instrument for measuring quality of life and has been used extensively to evaluate people with total hip and knee arthroplasty.[19-21] Score values range from 0 (worst possible health) to 100 (best health). The Physical Component Summary (PCS) score is based on 21 of the 36 questions (reliability >0.90).[19-20, 22]

A region-specific disability questionnaire, the Lower Extremity Functional Scale (LEFS), is a short (20-item) measure designed to assess functional status for patients with a variety of conditions affecting the lower extremity.[23] Scores range from 0 (worst possible physical function) to 80 (best physical function), with high reliability estimates in the THA and TKA populations (internal consistency 0.93, ICC 0.85-0.92 and minimally detectable change of 9 points).[23-24] The LEFS is easy for the patient to use and it is quick to administer and score. [23-24]

The Rapid Assessment of Physical Activity (RAPA) is a self-administered questionnaire developed to assess levels of physical activity among adults older than 50

years.[25-26] The RAPA was developed based on Centers for Disease Control and Prevention (CDC) guidelines of 30 minutes or more of moderate physical activity on every or most days of the week(sensitivity 81%, specificity69% positive predictive value 77%, negative predictive value75%).[25-26] The total score is from 1 to 7 points, with the respondent's score categorized into one of five levels of physical activity: 1 (sedentary), 2 (underactive), 3 (regular underactive-light activities) 4 (regular underactive) and 5= regular active (sensitivity 81%, specificity69% positive predictive value 77%, negative predictive value75%).[25-26]

5.3.3 Cardiometabolic risk

Cardiometabolic Risk (CMR) is defined using the National Cholesterol Education Program Adult Treatment Panel III (NCEP–ATP III) guidelines established for metabolic syndrome and includes the following five risk factors: blood glucose, waist circumference, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), high blood pressure (HBP).[27] The out of range value for each risk factor are as follows: fasting plasma glucose ≥126 mg/dL, body mass index >27kg/m^2 , triglycerides ≥150 mg/dL, high density lipoprotein <40mg/dL (men) or <50mg/dL (women) and elevated blood pressure (Systolic ≥130 mm Hg or diastolic ≥85 mm Hg).[27] Determination of the presence of each risk factor was completed using three identification criteria (clinical, diagnostic and treatment). Clinical criteria were based on laboratory test values, blood pressure, height and weight. Body mass index (BMI) was used as a proxy measure for waist circumference and calculated from the patients' height and weight measurements. Several studies have concluded that BMI and waist circumference are highly

correlated.[28-30] Diagnostic criteria were based on patient self-report or preoperative report of elevated cholesterol, hypertriglyceridemia, hypertension(HTN), diabetes(DM) and obesity. Treatment criteria were based on the prescriptions recorded (patient self-report or preoperative report) indicating treatment for elevated cholesterol, hypertriglyceridemia, HTN, DM and obesity. Patients identified using treatment criteria were those with a prescription for any one of the following drugs or drug classes: 1) weight loss agents (sibutramine hydrochloride, orlistat), 2) triglyceride lowering agents (fibrates, niacin), 3) antihypertensives (angiotensin converting enzyme-inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, thiazide diuretics, antihypertensive vasodilators and combinations of these agents) and 4) drugs used for diabetes (sulfonylureas, metformin, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors and combinations of the preceding agents). Patients who had at least one of the three criteria of abnormality (clinical, treatment and diagnostic) for each of the five risk factors (blood glucose, BMI, HDL, TG, HTN) were classified as having elevated risk for that risk factor. Metabolic syndrome was defined as co-occurrence of an abnormality in three of the five (blood glucose, BMI, HDL, TG, HTN) risk factors. [27]

5.3.4 Demographics

Patient characteristics at baseline included age, sex and comorbid conditions (arthritis, mental health, chronic back pain, cancer, insomnia, osteoporosis, gout, coronary artery disease and neuropathy) were collected from the hospital admission interview which is routinely conducted on the day of surgery by a nurse. Documentation on the admission form of any one of the following words was considered a positive

indication of the comorbid condition: arthritis (arthritis, osteoarthritis, rheumatoid arthritis), mental health (depression, anxiety), chronic back pain, cancer, sleep disorder (sleep apnea, insomnia) osteoporosis, gout, coronary artery disease (CAD) and neuropathy. This study qualified for exempt review from the Institutional Review Board at the University of Utah.

5.3.5 Subjects

Patients were included if they met all of the following criteria: age 40 years or older on the date of their surgery and underwent a primary total knee or hip arthroplasty. Patients were excluded if they had another knee arthroplasty or hip surgery within a year from the index surgery, were missing LEFS or SF-36 scores and if they had a stroke, paralysis, or any major neurological disorder or medical condition that impairs ambulation.

A total of 415 and 287 people received a TKA and THA, respectively. Upon application of the inclusion criteria, 245(59%) patients with TKA and 176 (61%) with THA were excluded (Figure 5.1).

5.3.6 Statistical analysis

To describe the sample, means, standard deviations (SD), frequencies and percentages were used. Comparisons were made on and between the study population and those not in the study using a t-test for continuous variables (body mass index, [BMI], age) and chi-square test for dichotomous variables (sex). For all evaluations, separate analyses were completed for knee and hip patients.

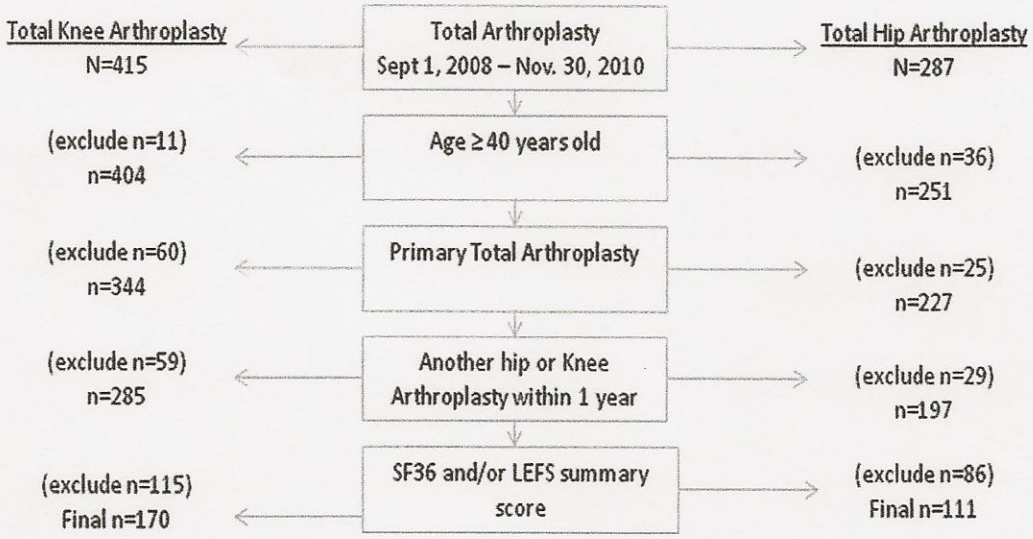

Figure 5.1 Total knee and hip arthroplasty study population flow chart

Due to the findings from previous research that indicate preoperative physical function influences postoperative physical function, we describe the physical function of the study populations preoperatively and 6 weeks after surgery. Additionally, in Chapter 4 of this dissertation, our findings indicate that worse preoperative physical function is associated with the presence of hypertension, diabetes, elevated cholesterol and MetS (identified in Chapter 4 of this dissertation); therefore we describe the physical function of the population preoperatively and 6 weeks after surgery by MetS and the individual CMR factors. Paired ttests (means,SD), mean differences and the associated p-values are reported.

5.3.6.1 Postsurgical physical function

Univariate analysis using unadjusted linear regression was used to evaluate whether there was an association between cardiometabolic risk (MetS, the individual CMR factors) and the covariates (demographics, comorbid conditions and physical activity) with physical function (PCS and LEFS scores) at 6 weeks. This unadjusted analysis illustrates the association between variables without consideration for other potentially influential variables. The results are reported using β-coefficients, their 95% confidence intervals and p-values.

A multivariable analysis was used to evaluate if MetS and the individual CMR factors were associated with physical function (PCS and LEFS scores) at 6 weeks postoperatively, accounting for other influential variables. Two multiple linear regression models were used with MetS and the individual CMR factors as the independent variables while adjusting for the potential influence of the demographic characteristics, comorbid conditions, activity level and physical function scores prior to surgery. This adjusted model accounts for the known variables that may be influencing the 6-week postoperative physical function. The results are reported using β-coefficients, their 95% confidence intervals and associated P values.

5.4 Results

We had pre- and postoperative data on 170 patients with TKA and 111 patients with THA. There were no significant differences in age, BMI or sex between those included and not included in the study (Table 5.1).

Table 5.1 Description between TKA and THA study population and nonparticipants

	Study population		Non participants		p value
Total Knee Arthroplasty	**n=170**		**n=115**		
Female (n,%)	107	62.94	71	61.74	0.0930
Age, years (mean,SD)	64.17	10.10	62.95	10.44	0.3251
BMI, kg/m^2 (mean,SD)	31.81	6.93	33.11	8.52	0.1599
Total Hip Arthroplasty	**n=111**		**n=86**		
Female (n,%)	63	56.76	51	59.30	0.1288
Age, years (mean,SD)	61.15	11.89	60.51	11.81	0.7067
BMI, kg/m^2 (mean,SD)	29.99	6.79	30.30	8.05	0.7705

At baseline, the mean patient age of patients with a THA and TKA was 61.36 yrs (SD 11.94 yrs) and 63.66 yrs (SD 10.22 yrs); mean BMI was 31.69 kg/m^2 (SD 7.05) and 29.99 kg/m^2 (SD 6.79), respectively. The majority of the THA (n=64; 57.66%) and TKA (n=106; 62.35%) patients were women. The prevalence of metabolic syndrome (MetS) and the individual cardiometabolic risk factors for patients with a TKA or THA were MetS (61; 35.88% vs 31; 27.68%), diabetes (34; 20.00% vs 13; 11.71%), elevated cholesterol (81; 47.65% vs 41; 36.94%), elevated triglycerides (4; 2.35% vs 9; 8.11%) and elevated BMI (147; 86.47% vs 84, 75.68%). Patients with a TKA and metabolic syndrome were significantly older (65.9 yrs; SD 9.3 vs 62.4 years; SD 10.50; p=0.031) and had a higher BMI (34.00 kg/m^2; SD 7.20 vs 30.4 kg/m^2; SD 6.65; p=0.002) than those without metabolic syndrome. A similar pattern was seen in patients with a THA.

Tables 5.2 and 5.3 describe the pre- and postoperative physical function and the difference in physical function between the pre- and postsurgical time points, by the

Table 5.2 Presurgical and 6-week postoperative physical function scores (LEFS and PCS) by overall population and cardiometabolic risk for those with a total hip arthroplasty

		LEFS						PCS					
		Presurgery		6 week Post				Presurgery		6 week Post			
		Mean	sd	mean	sd	Diff	pvalue	mean	SD	mean	sd	Diff	pvalue
THA Cohort													
Overall		33.27	17.24	42.62	16.50	9.34	<0.001	31.91	8.10	37.41	9.33	5.50	<0.001
Cardiometabolic Risk													
MetS	yes	26.93	14.39	41.12	16.74	14.19	<0.001	31.47	5.79	36.78	9.82	5.31	0.002
	no	35.74	17.71	43.20	16.50	7.46	0.015	32.08	8.86	37.66	9.18	5.58	<0.001
DM	yes	27.73	15.01	40.18	12.95	12.45	<0.001	32.92	6.78	35.00	10.57	2.08	0.425
	no	34.02	17.46	42.94	16.96	8.93	<0.001	31.77	8.28	37.73	9.16	5.96	<0.001
HTN	yes	29.94	16.17	40.91	16.84	10.98	<0.001	32.28	7.10	37.27	9.30	5.00	<0.001
	no	35.79	17.73	43.91	16.29	8.11	0.002	31.64	8.81	37.51	9.42	5.88	<0.001
Chol	yes	29.79	15.04	43.49	16.95	13.69	<0.001	32.35	6.76	37.34	9.03	4.99	<0.001
	no	35.27	18.20	42.11	16.36	6.84	0.003	31.65	8.83	37.45	9.56	5.80	<0.001
BMI	yes	31.36	16.97	42.03	16.74	10.67	<0.001	31.53	8.09	37.48	9.47	5.95	<0.001
	no	39.45	17.00	44.53	15.93	5.07	0.137	33.09	8.18	37.19	9.03	4.11	0.013
TG	yes	22.83	14.66	37.00	14.13	14.12	0.145	30.87	5.36	33.22	8.18	2.35	0.505
	no	33.99	17.24	43.01	16.65	9.01	<0.001	32.00	8.31	37.78	9.36	5.78	<0.001

MetS-metabolic syndrome; DM-diabetes; HTN-hypertension; BMI-elevated body mass index; Chol-elevated cholesterol; TG-elevated trygycerides; diff-mean difference between pre and post values; p value-based on paired ttest; LEFS- lower extremity function score; PCS-physical component score

Table 5.3 Presurgical and 6-week postoperative physical function scores (LEFS and PCS) by overall population and cardiometabolic risk for those with a total knee arthroplasty

		LEFS						PCS					
		Presurgery		6-week Post				Presurgery		6-week Post			
		Mean	sd	mean	sd	Diff	pvalue	mean	SD	mean	sd	Diff	pvalue
TKA Cohort													
Overall		36.89	16.09	42.60	15.10	5.70	<0.001	34.35	8.77	35.81	8.56	1.46	0.046
Cardiometabolic Risk													
MetS	yes	30.25	14.30	39.72	15.77	9.47	<0.001	32.65	8.86	35.20	8.44	2.54	0.024
	no	40.25	15.97	44.06	14.62	3.81	0.025	35.33	8.62	36.17	8.66	0.84	0.379
DM	yes	30.59	16.32	36.12	15.73	5.75	0.126	32.32	9.20	35.34	7.43	3.03	0.041
	no	38.34	15.76	44.09	14.62	5.53	<0.001	34.81	8.62	35.91	8.84	1.08	0.198
HTN	yes	33.44	15.38	43.03	15.90	9.59	<0.001	32.98	8.35	36.26	8.91	3.27	<0.001
	no	41.43	16.00	42.04	14.09	0.60	0.766	36.34	9.05	35.17	8.06	1.17	0.312
Chol	yes	34.08	15.05	41.06	13.92	6.98	0.000	33.75	8.76	35.19	8.16	1.43	0.155
	no	39.33	16.66	43.94	16.03	4.61	0.019	34.90	8.79	36.39	8.93	1.49	0.161
BMI	yes	36.32	16.52	43.07	14.88	6.74	<0.001	34.40	9.21	35.92	8.77	1.52	0.053
	no	40.17	13.24	39.93	16.43	-0.23	0.951	34.07	5.36	35.14	7.23	1.07	0.598
TG	yes	36.75	11.06	42.00	6.48	5.25	0.152	35.47	5.73	37.18	3.15	1.71	0.724
	no	36.90	16.24	42.62	15.28	5.72	<0.001	34.33	8.84	35.78	8.66	1.46	0.050

MetS-metabolic syndrome; DM-diabetes; HTN-hypertension; BMI-elevated body mass index; Chol-elevated cholesterol; TG-elevated trygycerides; diff-mean difference between pre and post values; p value-based on paired ttest; LEFS- lower extremity function score; PCS-physical component score

overall population and cardiometabolic risk (MetS and the individual CMR factors). Overall by cohort, there were significant improvements in physical function from baseline to 6 weeks after surgery. In the TKA and THA cohorts, those with MetS or an individual CMR factor had lower preoperative physical function scores than those without cardiometabolic risk. Those patients with diabetes and MetS had the lowest pre- and postoperative LEFS scores.

5.4.1 Postoperative physical function

Univariate analysis was used to evaluate whether MetS and the individual CMR factors were associated with physical function at 6 weeks. The unadjusted analysis is reported in Table 5.4 for both the TKA and THA populations. For the THA cohort, worse 6-week postoperative physical function (LEFS and PCS) was significantly ($p<0.05$) associated with sex (female), chronic back pain and osteoporosis. An improved physical function was seen in those with a THA who were also physically active ($p=0.009$). For the TKA population, diabetes, MetS and chronic back pain were significantly ($p<0.05$) associated with 6-week postoperative lower-extremity physical function whereas only chronic back pain was significantly associated with physical health.

To evaluate if other variables were contributing to physical function at 6 weeks postsurgery, a multivariable analysis was completed with all the univariate variables remaining in the model with the addition of preoperative physical function. The multivariable analysis for the association of the individual cardiometabolic risk factors (elevated BMI, diabetes, elevated cholesterol, elevated triglycerides and hypertension)

Table 5.4 Unadjusted association of cardiometabolic risk factors, demographic, comorbid conditions and physical activity with physical health (PCS) and lower extremity physical function (LEFS) for patients 6 weeks after THA or TKA surgery

	THA				TKA			
	PCS		LEFS		PCS		LEFS	
	β (95%CI)	p value	β(95%CI)	p	β (95%CI)	p	β (95%CI)	p
CARDIOMETABOLIC RISK FACTORS								
Diabetes	-2.73 (-8.2 2.7)	0.323	-2.22 (-12.66 8.22)	0.674	-0.36 (-3.59 2.87)	0.826	-7.7 (-13.57 1.83)	0.010
Elevated BMI	0.29 (-3.8 4.4)	0.889	-2.73 (-10.27 4.81)	0.473	0.87 (-2.90 4.65)	0.648	2.95 (-3.88 9.77)	0.395
Hypertension	-0.24 (-3.8 3.3)	0.893	-3.31 (-9.92 3.30)	0.323	0.87 (-1.75 3.49)	0.513	0.77 (-4.03 5.57)	0.752
Cholesterol	-0.11 (-3.8 3.5)	0.954	0.43 (-6.32 7.18)	0.900	-1.29 (-3.87 1.29)	0.326	-3.44 (-8.15 1.27)	0.151
Elevated TG	-4.56 (-10.96 1.8)	0.161	-8.33 (-20.26 3.60)	0.169	1.31 (-7.22 9.84)	0.761	-0.48 (-15.88 14.91)	0.951
MetS	-0.88 (-4.80 3.1)	0.658	-2.86 (-10.13 4.41)	0.437	-1.09 (-3.78 1.61)	0.427	-4.83 (-9.72 0.05)	0.052
DEMOGRAPHIC								
Female	-3.70 (-7.20 -0.20)	0.038	-10.93 (-17.16 -4.70)	0.001	0.12 (-2.55 2.78)	0.932	-3.20 (-8.10 1.69)	0.198
Age	0.04 (-0.11 0.19)	0.608	-0.02 (-0.29 0.25)	0.907	-0.01 (-0.13 0.12)	0.907	-0.14 (-0.37 0.09)	0.234
COMORBID CONDITIONS								
Arthritis	-0.49 (-4.65 3.67)	0.815	1.34 (-6.55 9.24)	0.737	-2.58 (-5.61 0.44)	0.094	-1.5 (-7.07 4.07)	0.595
Mental Health	-1.00 (-4.66 2.67)	0.592	-7.94 (-14.72 -1.16)	0.022	-1.53 (-4.17 1.10)	0.253	-4.13 (-8.93 0.68)	0.092
Chronic back pain	-5.40 (-8.87 1.93)	0.003	-7.83 (-14.40 1.27)	0.020	-4.78 (-7.51 -2.06)	0.001	-10.89 (-15.79 5.98)	0.000
Cancer	-0.40 (-5.88 5.08)	0.885	-0.6 (-10.67 9.46)	0.905	-1.21 (-4.48 2.05)	0.464	-1.31 (-7.37 4.75)	0.669
Insomnia	-4.39 (-9.63 0.85)	0.100	-4.09 (-13.48 5.30)	0.389	0.86 (-2.45 4.16)	0.609	0.22 (-5.85 6.28)	0.944
Osteoporosis	-4.54 (-8.96 0.12)	0.044	-8.27 (-16.44 -0.10)	0.047	1.68 (-2.17 5.52)	0.390	1.61 (-5.35 8.57)	0.649
Physically active	3.33 (-0.32 6.97)	0.073	8.86 (2.27 15.45)	0.009	1.74 (-0.94 4.43)	0.202	3.37 (-1.63 8.36)	0.185

β-Beta coefficients; 95%CI-95% confidence interval; PCS-physical component score; LEFS- lower extremity functional score; BMI-body mass index; TG-triglycerides

and covariates (demographic characteristics, comorbid conditions and activity level) with physical function for the TKA and THA populations are shown separately on Table 5.5. The multivariable analysis for the association of MetS with physical function adjusting for covariates is shown in Table 5.6.

For the knee cohort, worse lower-extremity function (LEFS) at 6-weeks postsurgery was significantly associated with diabetes (β -7.43 CI -13.13 to -1.74, p=0.011) and chronic back pain (β -6.97, CI -11.79 to -2.15, p=0.005). Those with hypertension had significantly lower preoperative scores of physical function and significantly increased postoperative scores of physical function (PCS: β2.93; 95% CI 0.09 to 5.77, p=0.043) and lower-extremity function (LEFS: β 6.67, CI 1.94 to 11.40, p=0.006); no significant difference was found in unadjusted postoperative physical function between those with and without hypertension. These results indicate that those with and without hypertension achieved similar levels of physical function recovery at 6 weeks, but those with hypertension had increased physical function since baseline because they started lower (Table 5.5). In the MetS multivariable model, only chronic back pain remained significantly associated with lower-extremity physical function (β -7.53 95% CI: -12.46 to -2.60) (Table 5.6).

For the hip cohort, neither MetS nor the individual cardiometabolic risk factors were associated with physical function after controlling for demographics, comorbidities, preoperative physical function and physical activity. Two covariates, chronic back pain and the preintervention physical function score, were significantly associated with physical health and lower extremity function at 6 weeks postsurgery (Table 5.5). Those

Table 5.5 Adjusted association of cardiometabolic risk factors, demographic, comorbid conditions and physical activity with physical health (PCS) and lower extremity physical function (LEFS) for patients 6 weeks after THA or TKA surgery

	THA				TKA			
	PCS		LEFS		PCS		LEFS	
	β 95%CI	p value	β 95%CI	pvalue	β 95%CI	p value	β 95%CI	p value
CARDIOMETABOLIC RISK FACTORS								
Elevated	2.20	0.291	0.83	0.826	0.84	0.656	3.31	0.293
BMI	-1.92 6.33		-6.65 8.31		-2.88 4.57		-2.89 9.51	
Diabetes	-2.59	0.339	0.90	0.859	-0.97	0.568	-7.43	0.011
	-7.95 2.77		-9.19 11		-4.33 2.39		-13.1 -1.7	
Hypertension	0.59	0.756	-1.16	0.739	2.93	0.043	6.67	0.006
	-3.16 4.34		-8.04 5.73		0.09 5.77		1.94 11.4	
Cholesterol	-0.38	0.846	3.44	0.322	-0.70	0.592	0.11	0.960
	-4.22 3.47		-3.43 10.3		-3.29 1.89		-4.23 4.45	
Elevated TG	-1.76	0.608	-0.05	0.994	0.94	0.813	1.20	0.857
	-8.58 5.05		-12.6 12.5		-6.93 8.81		-11.9 14.3	
DEMOGRAPHICS								
Female	-0.86	0.657	-7.86	0.023	1.26	0.356	0.36	0.876
	-4.72 2.99		-14.6 -1.1		-1.43 3.94		-4.23 4.96	
Age	0.12	0.165	0.20	0.192	-0.02	0.829	-0.11	0.344
	-0.05 0.29		-0.1 0.5		-0.16 0.12		-0.34 0.12	
COMORBID CONDITIONS								
Arthritis	0.19	0.923	0.21	0.956	-2.78	0.085	-3.52	0.202
	-3.77 4.15		-7.3 7.72		-5.96 0.39		-8.95 1.91	
Chronic back	-5.02	0.005	-8.72	0.007	-2.61	0.07	-6.97	0.005
pain	-8.47 -1.6		-14.9 -2.5		-5.43 0.21		-11.8 -2.2	
Mental	0.83	0.630	-0.32	0.923	-1.83	0.194	-3.79	0.116
health	-2.59 4.26		-6.84 6.2		-4.6 0.94		-8.54 0.95	
Cancer	-2.49	0.339	-3.08	0.494	-1.35	0.403	-1.92	0.487
	-7.63 2.66		-12 5.84		-4.52 1.82		-7.36 3.52	
Insomnia	-0.90	0.723	-0.16	0.970	1.90	0.246	3.58	0.208
	-5.9 4.11		-8.43 8.12		-1.32 5.12		-2.02 9.18	
Osteoporosis	-1.70	0.512	-0.03	0.995	3.09	0.11	5.70	0.073
	-6.82 3.42		-9.28 9.22		-0.71 6.89		-0.53 11.9	
Physically	3.51	0.038	7.57	0.013	0.70	0.597	-1.22	0.593
Active	0.19 6.83		1.61 13.5		-1.92 3.32		-5.72 3.28	
Pre-surgical								
PCS	0.51	0.000	0.43	0.000	0.38	0.000	0.37	0.000

5.6 Adjusted multivariable regression of metabolic syndrome, demographic, comorbid conditions and physical activity with physical health (PCS) and lower extremity physical function (LEFS) for patients 6 weeks after THA or TKA surgery

	THA						TKA					
	PCS			LEFS			PCS			LEFS		
	β	95% CI	pvalue	β	95% CI	pvalue	β	95% CI	pvalue	β	95% CI	pvalue
Metabolic	1.17		0.533	3.32		0.330	0.10		0.939	0.13		0.956
syndrome	-2.53	4.87		-3.42	10.06		-2.54	2.75		-4.59	4.85	
DEMOGRAPHICS												
Female	-0.86		0.650	-7.45		0.024	1.16		0.387	-0.54		0.820
	-4.60	2.88		-13.92	-0.98		-1.49	3.81		-5.21	4.13	
Age	0.09		0.248	0.20		0.129	0.02		0.819	-0.06		0.590
	-0.06	0.24		-0.06	0.47		-0.12	0.15		-0.28	0.16	
COMORBID CONDITIONS												
Arthritis	-0.02		0.994	0.35		0.920	-2.05		0.193	-1.47		0.593
	-3.87	3.84		-6.66	7.36		-5.14	1.05		-6.87	3.94	
Chronic back												
pain	-5.31		0.002	-9.23		0.003	-2.73		0.055	-7.53		0.003
	-8.64	-1.98		-15.16	-3.31		-5.53	0.06		-12.46	-2.60	
Mental health	0.49		0.772	-0.25		0.935	-1.81		0.174	-2.82		0.227
	-2.84	3.82		-6.42	5.91		-4.42	0.81		-7.41	1.77	
Cancer	-2.77		0.282	-2.81		0.522	-1.73		0.279	-2.31		0.413
	-7.84	2.31		-11.49	5.88		-4.88	1.42		-7.88	3.25	
Insomnia	-0.52		0.832	-0.33		0.934	1.89		0.250	3.64		0.215
	-5.38	4.34		-8.20	7.54		-1.34	5.11		-2.14	9.42	
Osteoporosis	-1.72		0.488	-0.09		0.984	2.99		0.120	5.12		0.116
	-6.62	3.18		-8.84	8.67		-0.79	6.77		-1.28	11.53	
Physically	3.22		0.050	7.74		0.009	0.36		0.785	-1.75		0.453
Active	0.01	6.43		2.02	13.46		-2.24	2.95		-6.35	2.85	
Pre-intervention	0.52		0.000	0.44		0.000	0.36		0.000	0.36		0.000
Score	0.30	0.74		0.26	0.62		0.21	0.51		0.20	0.51	

with chronic back pain had lower 6-week postoperative PCS scores by 5.0 points (95%CI -8.47 to -1.57, p=0.005) and LEFS score by 8.7 points (95% CI -14.93 to -2.50, p=0.007) also indicating clinically significant differences. Unique to the THA cohort, physical activity and sex were found to be associated with postsurgical physical function. Physical activity increased both physical health (β 3.51, CI 0.19 to 6.83, p=0.038) and lower extremity function (β 7.57, CI 1.61 to 13.53, p=0.013) 6 weeks postoperatively. Women were found to have reduced lower-extremity function 6 weeks after surgery compared to men (β -7.86, CI -14.62 to-1.09, p=0.023).

MetS was not significantly associated with physical function at 6 weeks after surgery for either the TKA or THA group after controlling for covariates (Table 5.6).

5.5 Discussion

This aim of this study was to evaluate whether cardiometabolic factors are associated with postoperative TKA/THA physical functional recovery. This study confirms previous knowledge of improvement in physical function postoperatively.[31] In the THA and TKA populations, MetS was not associated with 6-week postoperative physical function. In patients with a TKA, we found diabetes was significantly associated with worse lower-extremity physical function at 6-weeks. Concomitant pre-intervention variables (sex, chronic back pain, physical activity and presurgical level of physical function) had significant impact on postsurgical physical function. Specifically, chronic back pain and level of physical function prior to surgery had a significant impact on postsurgical TKA lower-extremity physical function and being female, chronic back

pain, being physically active prior to surgery and presurgical level of physical function had significant impact on postsurgical THA lower extremity physical function.

5.5.1 Cardiometabolic risk

There are limited data in the total arthroplasty population demonstrating the health consequences of MetS.[18] Previous research has documented that the individual components of MetS and MetS are risk factors for osteoarthritis.[32-34] It has been suggested that MetS can influence physical decline through increased inflammation,[35] sedentary behavior,[36] and low muscle strength.[37] In this study, the only association with MetS and postoperative physical function was found in the univariate analysis with TKA patients. No associations with MetS and physical function were found with the THA population. However, the TKA MetS-postoperative physical function relationship did not remain when the covariates were added into the model, suggesting that the covariates, chronic back pain and presurgical level of physical function are stronger indicators than MetS of low postoperative physical function.

Of the individual CMR factors, only diabetes was predictive of poorer physical function following TKA surgery. None of the individual CMR factors were predictive of physical function after THA. Our results contradict the findings reported by Gandhi et al.(2010). They found worse outcome was associated with hypertension and obesity in the THA population while only obesity was predictive of poor outcome in the TKA population. Our study and the study by Gandhi et al.(2010)[18] are the first two studies to evaluate the association of MetS and the individual components on physical function.

Further studies are required to establish if the presence of MetS and the individual CMR factors are predictive preoperative variables that impact postoperative outcomes.

5.5.2 Preoperative physical function and chronic back pain

Our study supports previous findings that have identified the importance of preoperative level of physical function as an indication of postoperative TKA recovery.[4, 38-39] We investigated the relationship between preoperative physical function and MetS and the individual CMR factors. Our findings indicate that the presence of cardiometabolic risk (MetS and the individual CMR factors) is associated with worse preoperative level of physical function. Future research should focus on identifying what influences preoperative physical function and strategies to improve the preoperative level of physical function from a broad prospective. To date, previous research aimed at improving preoperative physical function has focused on improving the strength and endurance around the hip or knee and the results of these physical exercise programs are inconclusive.[40-46] Preoperative management should include risk-factor recognition and subsequent modifications designed to treat the components of MetS prior to surgery. Targeting those with MetS and the individual components may lead to improved physical function before surgery thereby impacting physical function after surgery

Previous studies have identified the presence of back pain as a preintervention predictor of worse outcome post THA[47-48] and TKA.[4, 49] Our study supports this finding, preoperative chronic back pain was significantly associated with worse postoperative physical health and lower-extremity physical function in the TKA/THA populations. Possible explanations for the relationship between the hip and back pain have included

degenerative joint disease in both the hip and spine resulting in difficulty differentiating between symptoms caused by a spine disorder or a hip disorder,[47, 50] poor spinal sagittal alignment,[51] leg length discrepancy that disrupts gait,[52] and the presence of preexisting dormant back pain that may be exacerbated during the perioperative recovery.[53] There has been less attention placed on the relationship between back pain and knee dysfunction. Recent studies have established a link between decreased physical function and the presence of back pain in the total knee and total knee revision populations.[4, 49, 54] Explanations for this association have been limited to the biomechanical aspect reporting patients that have a loss of extension in their knee have decreased lumbar lordosis and this may affect their posture and result in pain.[55] Based on the previous findings, chronic back pain can be used to identify a subgroup of people who may have reduced physical function after their TKA/THA. Further research is required to evaluate if the impact of chronic back pain on TKA/THA recovery can be modified.

5.5.3 Limitations

Our study has several limitations. This cohort was based from a single academic center orthopedic practice that may consist of patients with conditions that are more complicated than typically seen in the general total hip or knee arthroplasty population. Although when our study population's preoperative lower-extremity physical function scores, BMI and age were compared with published total knee and hip arthroplasty studies, they were similar.[56-57]

This study used physical function data gathered from routine clinical practice, which resulted in a high number of patients who did not complete a preoperative measure

of physical function. The individuals not included in this study were similar in age and body mass index compared to the individuals in the study but information on physical function and comorbidity prevalence was unknown and may have biased the results.

Although we accounted for known confounders, there may be unknown confounders that were not identified that could impact the relationship between MetS and physical function. Specifically, we were unable to measure the amount and type of physical therapy the patient received after surgery and this may have influenced the level of physical function postoperatively.

Due to the high reported prevalence of undiagnosed cardiometabolic risk factors, particularly the high rate of undiagnosed and/or untreated cardiometabolic risk in women, we may have underestimated the prevalence of MetS and the individual components.[58] Future research should incorporate current guidelines recommending a comprehensive assessment of cardiovascular risk in both men and women.[59-61] The evaluation should include a complete a medical and family history to identify the presence of a known history of cardiometabolic disease and a laboratory assessment (complete lipid panel and fasting glucose level).

5.6 Conclusion

In our study, diabetes was the only CMR factor to be associated with worse postoperative physical function in the population with a TKA. MetS was not associated with postoperative physical function in either the TKA or THA cohort. Back pain and preoperative physical function were covariates that were found to significantly influence postoperative physical function. Our results suggest that attention to those with chronic

back pain and diabetes, modifiable conditions, may improve postoperative physical function. Although it is well known that presurgical physical function impacts postoperative outcomes, further research is needed to understand how to improve presurgical physical function and if this improvement leads to improved postsurgical physical function. Only two studies have investigated the association of cardiometabolic risk with physical function. Future research is needed to reach a consensus whether these conditions influence TKA/THA postoperative outcomes.

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CHAPTER 6

DISCUSSION AND LIMITATIONS

6.1 Overall study

Due to the predicted increase hip and knee replacements in the next 20 years[1] and the large (15-30%) proportion of those with TKA/THA who report lack of improvement in their pain, functional status, and overall health related quality of life[2-4] evidence is warranted to provide guidance on the specific patient characteristics that affect TKA/THA outcomes.

The overall purpose of this research topic was to identify patient characteristics and comorbidities that may influence the physical function of those undergoing TKA/THA surgery. A greater number of comorbidities indicate worse postoperative outcomes. The specificity of which comorbidity may be important to physical function is lacking. The choice of CMR factors was based on the high prevalence of these conditions in the osteoarthritis (OA) population, the recent finding that MetS and OA may share similar etiology related to the inflammatory state and that CMR factors are modifiable.

This research project provides a preliminary exploration into the effect that CMR factors, and comorbid conditions may have on physical function in the TKA/THA population. This study supports established reports that presurgical physical function

impacts postoperative outcomes. A new finding from this study is that modifiable conditions, MetS, back pain, diabetes and insomnia, influence preoperative physical function. This is important because treatment practice may alter preoperative physical function through the management of CMR factors and comorbid conditions, an area not yet addressed in the TKA/THA population. The possibility of changing postoperative outcomes through the mediation of preoperative physical function is an area in need of future research.

In the TKA population, diabetes was the only CMR factor to be associated with worse postoperative lower-extremity physical function recovery after adjusting for age, sex, and comorbid conditions. There were no CMR factors associated with physical function in the THA population. This may be a reflection of the differences between these two populations. We found the prevalence of CMR factors in the THA population is much lower than the TKA population and those with a THA appeared to be a healthier population (13% THA had no risk factors vs 5% TKA).

There are limitations to this study. First, the data used were from a real-world clinical practice setting and inclusive of diverse characteristics of those undergoing TKA/THA surgery. The data are only as good as what is documented by the patient and in their patient record. Although no differences were found between the patients included in the study and those that were not, there is still a chance that those that were not included in the study are different than the study sample. Second, only one clinical practice, in an academic setting was used to evaluate the CMR factors in the TKA/THA population; therefore, the results may not be applicable to the general TKA/THA population. Third, although physical function scores were adjusted for some identified

comorbidities, there may be unknown confounders that were not identified that could impact the relationship between MetS and physical function. Fourth, it was not possible to achieve the study objective to evaluate the association of MetS with physical performance measures (PPM) in the TKA/THA population. The implementation of the preoperative PPMs included only those patients that attended *Joint Camp* prior to their surgery. Approximately 30% of the TKA/THA population attended Joint *Camp* preoperatively resulting in a severely limited the dataset that did not represent the study population. Thus this subgroup was not analyzed in the final dissertation. Finally, I had proposed tracking patients longitudinally over 6-12 months. The verbal instructions from the orthopedic surgeon to the patient indicated a required follow-up visit would be scheduled postoperatively at 6 months or at 1 year (or both). Although the orthopedic surgeon identified these follow-up appointments as an important part of the postoperative recovery condition, we found less than 50% of the patients returned for their postoperative visit. Therefore, I did not include the 6-month time point in the analysis because of the severe loss of patient follow-up.

6.2 HOAP project

The HOAP project was an immensely rewarding experience. I was very fortunate to work with an incredible team of people that are dedicated to improving patient satisfaction and outcomes. The HOAP project successfully adopted patient reported measures seamlessly into a very busy clinical practice. The data collection process has continued for 2 ½ years and continues to function. In the future, an evaluation of the initial processes should be conducted with a goal to facilitate an increased response rate

from those undergoing surgery. For example, one of the main goals of the HOAP project was to minimize the time required from patients to complete the measures. To accomplish this we were required to the collect patient related outcomes prior to knowing who will go for surgery. This provided the benefit of potentially evaluating those who and who do not undergo surgery but this process made tracking the surgical patient difficult.

Presently the UOC is undergoing immense changes in the evaluation of outcomes. It would be my HOAP that our experience developing, implementing and analyzing this clinical data will provide a platform to discuss needs and wants for future outcomes research initiatives.

6.3 Future research

In the evaluation of MetS with physical functional outcome, the future work should include preoperative measurements of the individual components of MetS that meet the standard definitions of MetS (i.e., serum cholesterol and triglyceride levels). This would allow systematic comparisons to be made in the TKA/THA population. In addition, it would be interesting to take postoperative measurements to investigate whether MetS is changed because of the ability to mobilize is increased due to the TKA/THA surgery. Second, future research is needed to ascertain if the trends we identified in this study continue over a longer duration in the recovery process.

In the management of patients with TKA/THA surgery, there is a need to preoperatively target a subgroup of people that have low preoperative physical function. This research could be a clinical trial to evaluate the effect of a comprehensive wellness

model, which would include CMR factor education, treatment along with physical conditioning, on pre- and postoperative physical function. Additionally we identified chronic back pain as an important contributor to worse physical function outcome post-operatively. Further research may include using specific chronic back pain measures to quantify and identify if back pain management strategies need to be incorporated into the TKA/THA population postoperatively.

6.4 References

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