PREDICTIVE VALUE OF PERFORMANCE-BASED PHYSICAL FUNCTION MEASURES FOR OSTEOARTHRITIS-RELATED HEALTH OUTCOMES AND RESPONSE TO A PHYSICAL ACTIVITY INTERVENTION

by

Hiral S. Master

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

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PREFACE

At the time of preparing this dissertation document, one of the chapters has been accepted for publication or published and reused here with copyright permission of the journals. I want to take a moment to acknowledge my coauthors and clarify my contribution to these works.

Master, H., Thoma, L. M., Christiansen, M. B., Polakowski, E., Schmitt, L. A., & White, D. K. (2018). Minimum performance on clinical tests of physical function to predict walking 6,000 steps/day in knee osteoarthritis: an observational study. Arthritis care & research, 70(7), 1005-1011.

The conception and study design was a joint effort amongst coauthors. I was responsible for downloading, organizing, managing the data from the OAI website. I contributed to the statistical analysis with assistance from Daniel K White and interpretation of results with the assistance of Louise M Thoma and Daniel K White. I was the sole drafter of this manuscript, with editing assistance and manuscript review from the co-authors.

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ABSTRACT

Background: Over 14 million Americans have symptomatic knee osteoarthritis (OA), which has no cure. Knee OA is a leading cause of functional limitation such as difficulty walking and getting up from a chair, which can be addressed by rehabilitation. However, less than 14% of people with knee OA receive rehabilitation. One reason for low referrals may be the inability to identify those that are in need. Performance-based measures of physical function that identify functional limitation are a potential means to select such individuals. However, clinical assessment of performance-based measures is not part of the routine practice for knee OA. The purpose of this dissertation was to investigate the predictive value of selected clinically feasible performance-based measures with future health outcomes in order to better identify who may be possible candidates for rehabilitation.

Objective: The long-term goal of this work is to identify individuals with knee OA who may benefit from rehabilitation. The overall objective of this dissertation was to investigate if performance-based physical function measures predict OA-related health outcomes (Aims 1 to 3) in adults with knee OA and response to physical therapist led physical activity intervention in adults after total knee replacement (TKR) (Exploratory aim).

Methods: A publicly available large knee OA-related dataset, the Osteoarthritis Initiative (OAI) was used to answer research questions in Aims 1 to 3. The primary study exposures were physical function measures i.e., 1) walking speed measured using a 20-m walk test and 2) repeated chair stands measured using a five times sit-to-

stand test. The main study outcomes were 1) physical activity measured using accelerometers, 2) time to all-cause mortality, and 3) time to total knee replacement. For the exploratory aim, we used data from the on-going randomized clinical trial, where individuals post TKR who underwent physical therapy were recruited.

Results: Thresholds of physical function measures indicative of physical inability to walk at least 6000 steps/day were identified in Aim 1. These thresholds may indicate when people with knee OA need rehabilitation to address underlying functional limitation such as impaired endurance, to minimize the risk of future poor health and increase the ability to be physically active. The thresholds on the physical function measures may serve as a clinical target for health professionals. We found that physical function measures assessed at one time-point may be sufficient to gauge mortality risk rather than being measured repeatedly over time. The key finding from Aim 3 was that walking speed was a robust predictor for all-cause mortality in older as well as middle-aged adults with knee OA. Thus, walking speed may be a simple indicator of health in adults with knee OA. Health care professionals may use walking speed to assess expected health and tailor goals of care for knee OA population. Finally, findings from exploratory aim suggests there may be subgroups of patients post-TKR who experience greater benefit from physical therapist led physical activity intervention.

Conclusion: This dissertation provided preliminary evidence on the predictive value of physical function measures for OA-related health outcomes and response to a physical therapist led physical activity intervention. This evidence of the predictive value will provide healthcare professionals with meaningful clinical thresholds on the performance-based measures to assess functional limitation in adults with knee OA.

These thresholds will not only aid in clinical decision making by telling clinicians, which patients may need rehabilitation to address functional limitation but also identify candidates who are ready for a physical activity intervention vs. those who may need other interventions such as rehabilitation first to address functional limitation and/or weight management.

Chapter 1

INTRODUCTION

1.1 Dissertation overview

Over 14 million Americans have symptomatic knee osteoarthritis (OA) (1), and worldwide, over 250 million people have knee OA (2). Knee OA is a leading cause of functional limitation such as difficulty walking and getting up from a chair (3-6). These limitations in physical function have a detrimental effect on an individual's quality of life (4) and lead to disability (7, 8) and increase the risk of all-cause mortality (9-11). Assessing physical function in adults with knee OA is of utmost importance since it represents an individual’s ability to participate in daily activities such as bathing, dressing, fulfill social roles in contexts of work, community, and family (12, 13) and physiological well-being (14).

Further, performance-based measures used to assess walking speed and repeated chair stand quantify how much an individual can do rather than what an individual perceives to do (14). It is known that these assessments are excellent predictors of adverse health outcomes such as mortality (15) and falls (16) in well-functioning older adults. Therefore, performance-based physical function measure is considered a “functional vital sign” of the health in older adults (17).

To date, knee OA has no cure (1, 18) but the symptoms (e.g., knee pain) and functional limitation can be addressed by rehabilitation (19-21). However, less than 14% of people with knee OA receive rehabilitation (22, 23). One reason for low referrals may be the inability to identify those that are in need. Performance-based measures of physical function that identify functional limitation are a potential means to select such individuals. However, clinical assessment of performance-based physical function measures is not part of the routine practice for knee OA (24). Not assessing physical function in routine clinical practice may be one of the reasons that may explain low referral to rehabilitation (22, 23). We propose that health professionals could better refer people with knee OA to rehabilitation with the knowledge of meaningful thresholds of performance-based physical function measures for future health outcomes.

To elaborate on the above point, I would use the analogy of the use of body temperature as a vital sign of health. Body temperature is a vital sign, which can be assessed using a thermometer. The values of body temperature on a thermometer provide information regarding the current health status of the person such as mild versus moderate versus high fever. This degree of fever, may, in turn, guide the treatment, i.e., whether the patient would need medication or hospitalization.

Applying the same logic of body temperature as a vital sign of health to physical function as function vital sign, we know physical function can be assessed by valid and reliable performance-based measures. Clinicians may use performance-based measures to track the functional status of people with knee OA and identify if a patient has functional limitation severe enough that would warrant a referral to rehabilitation. However, meaningful clinical thresholds for the objective measures of

assessing functional limitation that may guide the care for knee OA is unclear. Investigating the predictive value of functional vital signs for OA-related health outcomes and response to rehabilitation is important because the functional vital signs may serve as a potent tool to identify people who need rehabilitation to address the existing functional limitation (20, 21) and reduce the risk of subsequent poor health outcomes.

The purpose of this dissertation is to investigate the predictive value of selected clinically feasible performance-based measures with future health outcomes that are relevant for knee OA to establish so-called 'functional vital signs' for this patient population.

1.2 Current and future health outcomes

Physical activity is an indicator of current and future health. More than half of people with knee OA are physically inactive (25), which is a critical problem mainly because of two reasons. First, people with knee OA who are inactive face a cascade of health problems such as cardiovascular disease, diabetes, and premature death (26-28). Worldwide over 5.3 million deaths occur due to physical inactivity (29). Second, tremendous growth is expected in this patient population. Currently, over 14 million Americans have symptomatic knee OA (1) and the lifetime risk of developing symptomatic knee OA is approximately 45% and this lifetime risk doubles in adults with knee OA who are obese compared to normal weight (30). Moreover, it is estimated that by 2050, over 130 million people worldwide will have knee OA, of which 40 million people will have a severe functional limitation due to knee OA (31). Therefore, we must understand why people with knee OA are physically inactive, which will contribute to the evidence-based planning of health interventions. The

effective intervention will have to target the factors known to cause physical inactivity.

Knee OA increases the risk of all-cause mortality. A population-based studies in England, China and showed that adults with symptomatic knee OA were 55% (10) and 90% (11) more likely for all-cause mortality respectively compared to the general population. A population-based study in the United States has shown that adults with radiographic knee OA also have increased mortality risk (32). Functional ability influences the individual's survival (15). Hawker and co-authors have shown that people with at least moderately severe symptomatic hip and/or knee OA who report walking difficulty i.e., use walking aid were 51% (adjusted HR 1.51, 95% CI [1.34, 1.70]) more likely to die over 13 years compared to those who do not report walking difficulty (9). However, little is known about what specific aspects of walking difficulty increase mortality risk. Walking speed is a strong predictor of mortality in older adults (15). We do not know whether functional vital signs, including walking speed and repeated chair stands, are equally strong predictors for all-cause mortality in the US population with knee OA. Investigating the predictive value of functional vital signs with mortality in adults with knee OA is important since a number of people with knee OA are projected to increase by 50% over the next 20 years (33). Further, if functional vital signs predict the mortality risk, it may lay a foundation for investigating and developing an intervention to target modifiable factors for health and survival.

Total knee replacement (TKR) is an important health outcome in adults with knee OA. TKR is the definitive treatment for end-stage knee OA, and more than 650,000 TKRs were done in America in 2008 that accounted for $10.4 billion (34).

Though cartilage loss and radiographic OA severity may predict the risk for future TKR (35), people with knee OA with mild radiographic severity may also undergo TKR due to severe knee pain and functional limitation (34). One reason for this inconsistencies in predicting TKR may be that structural impairment may not correlate with symptoms and functional limitation (36-42). No well-established approach predicts the need for TKR, which incorporates knee health and function. It is known that slow walking speed predicts incident knee OA (43) and worsening of depressive symptoms in adults with knee OA (44). However, it is unclear whether walking speed and repeated chair stands predict the risk of TKR. Investigating the predictive value of functional vital signs with TKR in adults with knee OA is important since the number of TKRs are projected to grow by 673% from 450,000 TKRs in 2005 to 3.48 million by 2030 (45).

1.3 Significance and implication

Physical function declines with age (46-49), and not all decline is uniform. Rather, there are different rates or trajectories of change in physical function, i.e., some decline quickly, while others' are stable or decline gradually. For instance, as people continue to age, walking speed declines (47), though these changes are not the same across all the individuals. White et al., have shown the older adults who had a fast decline in walking speed had a 90% greater risk for all-cause mortality compared to those who had a slow decline (50). However, individuals having similar walking speed in the present may have had different trajectories of decline, i.e., some may have experienced fast decline while others may remain relatively stable. It is unclear among those people who have similar walking speed in the present, the risk of all-cause mortality may be higher in those who experienced a fast decline over one year

compared to those who remained relatively stable over the past one year. In other words, it is unknown how well the predictive validity for a single assessment of walking speed at one time-point for future health outcomes, such as all-cause mortality, compares with repeated assessments over time.

On the one hand, the collection of physical function at the initial evaluation may be feasible since this evaluation is comprehensive in nature. On the other hand, most health professionals do not measure physical function in a standardized fashion as part of the routine clinical examination for knee OA. Barriers for repeated assessment include time, physical space, and equipment. Therefore, in this dissertation, we will investigate the predictive validity of one versus repeated assessments of physical function (functional vital signs) for mortality. This investigation is important, as it will clarify whether assessing prevalent physical function at one time is a reasonable substitute for repeated measures.

Previous studies show that walking speed is a strong predictor of all-cause mortality in well-functioning older adults (aged >65 years) (15, 51). Specifically, walking slower than 1.0 m/s increases the risk for all-cause mortality in older adults (15) while walking slower than 1.22 m/sec represents functional inability to be active (52) as well as difficulty crossing streets using timed signals (51). However, the specific cut point of walking speed predictive for OA-related health outcomes such as all-cause mortality and TKR in adults with knee OA is unclear. Identifying the specific level of walking speed predictive for OA-related health outcomes is important as it provides valuable information that can be applied clinically to identify the risk profile of the patients. Further, the cut-point may also provide a target for the interventions that promote physical functioning.

In this dissertation, we will use Maximum Likelihood Chi-Square approach to investigate the optimal thresholds of functional vital signs that best discriminate those who have versus those who do not have increased risk for poor health outcomes such as the time to death due to any cause, as the outcome of primary interest. As the time to death is a failure time outcome, we need to account for censoring since we do not have information whether the event occurred or not outside the study or in the subjects who were lost to follow-up. Accounting for time-to-event and accounting for censoring provides critical information about the time at risk, especially when the outcomes are measured at different time-points. Therefore, traditional analyses developed to identify optimal thresholds for uncensored binary outcomes such as receiver operating curves (ROC) would need to be modified. Sima and Gönen (53) consider several techniques modifying ROC-curve based methods and test-based methods for this purpose. Based on their simulation studies, they recommend the use of an approach maximizing the likelihood ratio test for selection of the optimal thresholds. Maximum Likelihood Chi-Square approach is sensitive compared to traditional ROC for identifying optimal thresholds, specifically when the time to all-cause mortality is important for the prognosis. Accounting for time to the event provides additional information, especially when the outcomes are measured at different time-points. The threshold for the walking speed at survival time longer than four years may be different from survival time longer than seven years. Identifying the survival time-related thresholds would yield an informative profile for investigating patient's prognosis and will also help evaluate the generalizability of single thresholds over different survival times. Previous studies have used visual inspection approach to identify the thresholds where they have calculated the event rates based on categories

of increasing walking speed (0.05 to 0.1 m/s) or percentile approach. This approach does not account for the model selection criteria and lack generalizability since the results are dependent on the population from which it is driven.

Lastly, I will focus on interventions to improve physical activity in adults after TKR. What is common in people with knee OA and people after TKR is that both groups are physically inactive (25, 54-56). There is a critical need to address physical inactivity after TKR to prevent consequences of health problems related to inactivity. People after TKR have less knee pain, yet their physical activity either remains the same or decreases compared to their physical activity pre-TKR (54-56). Therefore, there was a critical need to develop an intervention that targets physical activity, which was the foundation of our on-going clinical trial, i.e., physical therapist (PT)-led physical activity intervention after TKR at the University of Delaware. Preliminary results of the clinical trial showed that people who receive physical activity intervention were more active (i.e., walked more) compared to people who did not receive the intervention (57). However, quantifying clinical improvements in physical activity on a group level may not translate to clinical application. The improvements in physical activity following a PT-led physical activity intervention was variable. Over half of the people post TKR who received intervention did not have improvements in physical activity compared to the average improvement in the group since they remained at either the same or even lower physical activity post-intervention compared to the group average. We, therefore, seek to investigate whether functional vital signs may predict improvements in physical activity following a PT-led physical activity intervention in people after TKR. It is important to explore the predictors for meaningful improvements in physical activity following

the intervention as they may identify patients for whom the probability of treatment (i.e., PT-led physical activity intervention) success is low at the time of assessment. In turn, the predictors for achieving meaningful improvements in physical activity after TKR may lay a foundation for optimizing individually tailored rehabilitation programs as it may provide an insight into what to target in rehabilitation, i.e., exercise for addressing functional limitation, limited strength, and pain rather than physical inactivity.

In summary, the purpose of this dissertation was to study the predictive value of functional vital signs, i.e., walking speed and repeated chair stands for OA-related health outcomes and poor response to PT-led physical activity intervention. The findings from this proposal will drive forward both the scientific knowledge of and treatment strategies for knee OA. Specifically, it will provide clinicians with an objective tool to quantify functional ability. This tool, in turn, can serve as a measure for not only early referral to rehabilitation but also designing patient-specific rehabilitation program. Findings from Aims 1 to 3 will provide healthcare professionals with specific cut-points on 20-m walk test and five times sit to stand test. These thresholds may aid clinical decision making by telling clinicians which patients have functional ability to have good health and be physically active, and which need further rehabilitation services to address functional limitation to achieve better health outcomes. The exploratory aim will identify subgroups of people who may respond best to PT-led physical activity intervention using regression-tree based method without defining any hypotheses for subgroups. Future studies may test the hypothesis whether targeting individuals with the same characteristics as identified in

this study may respond better to treatment compared to those who do not meet the subgroup characteristics.

1.4 Overall Objective

My long-term goal is to identify individuals with knee OA who may benefit the most from rehabilitation. The overall objective of this dissertation is to investigate if functional vital signs predict OA-related health outcomes and response to rehabilitation in adults with knee OA. In this proposal, I will focus on interventions to increase physical activity (58, 59), since over half of the adults with knee OA are physically inactive (25) and subsequently face a cascade of health problems due to inactivity (26-28, 60). The response to a physical activity intervention is not uniformly positive. My central hypothesis is that walking speed and repeated chair stands can predict OA-related health outcomes and poor response to a physical activity intervention. I formulated this hypothesis based on the prior work where walking speed (61, 62) and repeated chair stands (16) predicted the risk for poor health outcomes in older adults.

1.5 Specific Aims and hypothesis

I used an existing large OA-related dataset, the Osteoarthritis Initiative (OAI) to answer my research questions in Aims 1 to 3. I prospectively collected, managed, and analyze the measures of physical activity from an ongoing physical activity intervention trial at the University of Delaware (UD) in adults after TKR for the exploratory aim. The primary study exposures will be functional vital signs, i.e., 1) walking speed measured using a 20-m walk test and 2) repeated chair stands measured using a five times sit-to-stand test 3) Timed Up and Go test (TUG). The main study

outcomes will be 1) physical activity measured using accelerometers, 2) time to all-cause mortality, 3) time to knee replacement (KR), and 4) response to a physical activity intervention. I will pursue the following aims to test my central hypothesis:

Aim 1: To determine the extent to which walking speed and repeated chair stands will be associated with risk for not participating in physical activity, i.e., walking less than 6,000 steps/day in adults with knee OA. We chose this threshold because White et al. found walking ≥ 6000 steps/day better discriminates between those who did versus those who did not develop functional limitation two years later people with or at high risk of knee OA more so than walking 10,000 steps/day or 3,000 steps/day (63).

(H1.1) I hypothesize that walking slowly on a 20-m walk test will be associated with increased risk for not participating in physical activity.

(H1.2) I hypothesize that taking more time to complete five times sit to stand test will be associated with increased risk for not participating in physical activity.

Aim 2: To determine the association of walking speed and repeated chair stands measured at one time-point and decline over one year with risk for all-cause mortality over 9 years.

(H2.1) I hypothesize that all the adults with knee OA who walk slower than 1.22 m/sec on a 20-m walk test will be associated with a higher risk for all-cause mortality regardless of the decline in walking speed over a year compared to those who walk at least 1.22 m/sec.

(H2.2) I hypothesize that of all the adults with knee OA who walked at least 1.22 m/sec on a 20-m walk test, those who had a meaningful decline in

walking speed over one year will have a higher risk for all-cause mortality compared to those who did not have meaningful decline over a year.

(H2.3) I hypothesize that all the adults with knee OA who took >12 sec to complete five times sit to stand test will be associated with a higher risk for all-cause mortality regardless of the decline in repeated chair stands time over a year compared to those who took ≤12 sec to complete five times sit to stand test.

(H2.4) I hypothesize that of all the adults with knee OA who took ≤12 sec to complete five times sit to stand test, those who had a meaningful decline in repeated chair stands time over one year will have a higher risk for all-cause mortality compared to those who did not have meaningful decline over a year.

Aim 3: To determine the optimal threshold for walking speed and repeated chair stands that discriminate those who have risk compared to those who do not have a risk for A) all-cause mortality and B) KR over 9 years.

The threshold will be determined using the maximal likelihood chi-square approach. Specifically, we will run unadjusted and adjusted Cox models for different cut-points of the walking speed and then identified the model that will give the maximal chi-square value. This method is known to maximize the concordance, which is a metric used to evaluate the performance of the cut-points when there are censored endpoints. This metric is similar to maximizing the Youden index; criteria employed when using a Receiving Operating Curve (ROC) method.

Exploratory Aim: To investigate the association of physical function measures with the odds of achieving meaningful improvements in physical activity in adults after TKR who received PT-led physical activity intervention. The subgroups of people who may achieve meaningful improvements in physical activity following the intervention will be identified using regression-tree based method without defining any hypotheses for subgroups.

(H4.1) I hypothesize that limited performance on TUG will be associated to the odds of not achieving meaningful improvements in physical activity in participants who received PT-led physical activity intervention.

Chapter 2

MINIMIUM PERFORMANCE ON CLINICAL TESTS OF PHYSICAL FUNCTION TO PREDICT WALKING 6000 STEPS/DAY IN KNEE OSTEOARTHRITIS: AN OBSERVATIONAL STUDY

2.1 Introduction

Knee osteoarthritis (OA) is the 11th highest contributor to global disability (64) and the most common cause of functional limitation in older adults (65). People with knee OA often have low levels of physical activity (7). Physical activity is defined as any energy expenditure above a resting level (7, 66). This is a major problem since regular participation in physical activity lowers the risk of developing future comorbidities, such as cardiovascular disease, diabetes, and cancer (26, 27). Daily walking is the most common type of unstructured physical activity in older adults (67) and is recommended for people with knee OA (68). Evidence suggests that aerobic

walking program reduces knee pain and improve physical function for people with knee OA (69-71).

For people with knee OA, a potential barrier to daily walking is difficulty with physical function (72). For example, difficulty getting out of a chair or limited walking endurance may hinder how often one walks in the real world. However, it is not known whether reduced physical function is associated with less daily walking, i.e., taking fewer steps/day. If so, this would enable the investigation of minimum values of physical function that may be necessary in order walk at a meaningful level. Little is known regarding the minimum level of physical function predictive for an active lifestyle. In particular, we are interested in identifying levels of physical function predictive to walk ≥ 6000 steps/day. We chose this threshold because we previously found walking ≥ 6000 steps/day better discriminates between those who did versus those who did not develop functional limitation two years later people with or at high risk of knee OA more so than walking 10,000 steps/day or 3,000 steps/day (63). Identifying the minimal physical function predictive to walk ≥ 6,000 steps/day may help healthcare providers gauge when limitations in physical function may be a barrier to daily walking in the real world for people with or at high risk of knee OA.

The purpose of this study was to evaluate minimum performance thresholds on standardized clinical tests of physical function predictive of walking ≥ 6000 steps/day. We first evaluated the association of physical function with daily walking, then identified levels of physical function that have a high degree of specificity to predict walking ≥ 6,000 steps/day. We chose high specificity values to conservatively identify physical function levels that do not support walking ≥ 6,000 steps/day by

reducing the number of false positives, i.e., people who have poor physical function yet walk $\geq$ 6,000 steps/day.

2.2 Methods

2.2.1 Study participants

We used publicly available data from the Osteoarthritis Initiative (OAI), a large observational prospective cohort of people with or at risk of knee OA. The OAI examines the development and progression of OA in adults with or at high risk of knee OA. Study participants were recruited from clinical sites located in Maryland, Pennsylvania, Rhode Island and Ohio. Excluded were people with rheumatoid or inflammatory arthritis, a bilateral end-stage disease defined as severe joint space narrowing or total knee replacements in both knees, and those who used ambulatory aids other than a cane. Institutional review board approval was obtained from all OAI sites. The current analysis used accelerometer data collected on a sub-cohort of participants at the 48-month follow-up visit (63).

Figure 2.1 provides a summary of the number of accelerometer records at the 48-month follow-up visit and reasons for exclusion from our analytical sample. Of the 2,127 OAI participants who participated in the accelerometer study, 1,925 participants wore the accelerometer for $\geq$ 4 valid days and had steps/day data at the 48-month follow-up visit.

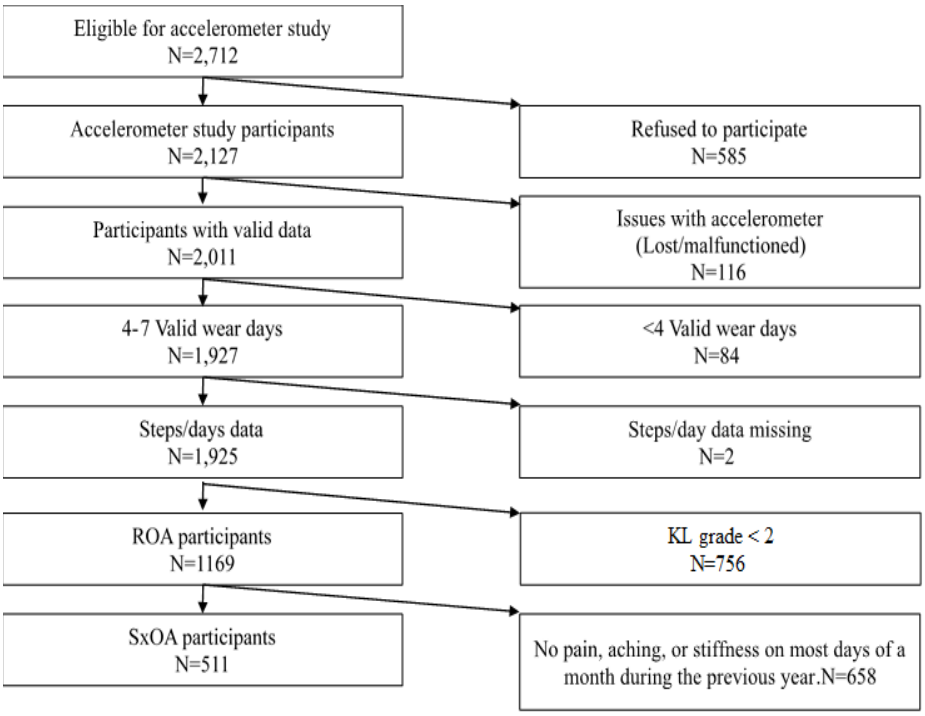


Figure 2.1: Data reduction from full OAI sample to the eligible sub-cohort of accelerometer study participants (n=2712) at 48-month follow-up.

Those who participated in the accelerometer study but were not included in the analytic dataset (n=202) had a higher BMI, were less educated, and had worse physical function compared to those included in the analytic dataset (n=1925) (Table 2.1).

Table 2.1: Characteristics of participants who were and were not included in the study analysis.

	Included (N=1925)	**Not included[a] (N=202)**	**p-value**
	Mean±sd or %(n)	Mean±sd or %(n)	
Age, years	65.1±9.1	64.1±9.5	0.14
Women	55 (1065)	59 (119)	0.25
Race, white	84 (1601)	66 (125)	0.0001*
Education, more than college	66 (1266)	57 (113)	0.012*
BMI (kg/m^2)	28.4±4.8	30.2±5.2	0.0001*
VAS pain			
Right	2.4±2.6	2.6±3.0	0.24
Left	2.3±2.6	2.4±3.0	0.76
Comorbidity	30 (566)	36 (71)	0.051
five times sit to stand test (sec)	10.5±2.9	11.1±3.5	0.009*
Walking speed (m/sec)	1.33±0.21	1.26±0.24	0.0001*
a - Not included – due to issues with valid days or had issues with accelerometer * - significant p-value <0.05 on independent t-test of means and proportions.			

2.2.2 Study Outcome

Daily walking was quantified as steps/day measured using a uniaxial accelerometer (Actigraph GT1M, Pensacola, FL, USA). The Actigraph GT1M is a valid device to quantify physical activity in free-living conditions (73, 74). Subjects were fitted with the accelerometer above the right hip (as shown in figure 2.2) and were instructed to wear the accelerometer during waking hours for 7 consecutive days.

(A) (B)

Figure 2.2 A-B:Actigraph GT1M (A) and participant wearing the monitor around the waist such that the accelerometer sits on right anterior superior iliac spine (B)

We employed previously published methods to determine valid physical activity records (75). Briefly, we defined a valid wear day as $\geq$ 10 hours of wear time and included participants with $\geq$ 4 valid wear days, as this is the minimum time predictive for a reliable estimate of physical activity behavior (76). Steps/day were averaged across the available valid days. We categorized people as walking < 6000 steps/day and $\geq$ 6000 steps/day (63).

2.2.3 Study Exposures

Physical function.

We used two performance-based clinical tests to measure physical function.

2.2.3.1 Walking speed

The 20-meter walk test was used to calculate self-selected walking speed. Participants were instructed to walk at their usual speed over a marked 20-meter course in an unobstructed and dedicated corridor. Timing with a digital stopwatch began at the initial movement from standing at the start and stopped when they crossed the 20-meter mark. Time to complete the walk (sec) was divided by distance (20 meters) to obtain walking speed in meters/second (meters/sec). The average of two trials was recorded, with slower walking speed indicating worse physical function (61). Measuring walking speed in a walkway has high test-retest reliability (intraclass correlation coefficients > 0.9) in older adults (62, 77).

2.2.3.2 Five times sit to stand test

Five times sit to stand test was used as a correlate for lower extremity functional strength. Participants were instructed to stand from a chair (straight back, flat, level firm seat and seat height of 45cm in front) and return to sitting five times as quickly as possible with arms folded across the chest. Total time (sec) was measured with a digital stopwatch, and started with initial movement to stand on the first repetition and ended after returning to sitting on the fifth repetition. The five times sit to stand was recorded as the average of two trials. Longer time to perform the test was indicative of worse physical function. The five times sit to stand test has high test-retest reliability (intraclass correlation coefficients > 0.9) in older adults with symptomatic hip or knee OA (78, 79).

2.2.4 Potential Confounders

We considered the following factors as potential confounders based on their association with daily walking and physical function (42, 80, 81) : age, sex (female versus male), race/ethnicity (white versus non-white), education (no college versus at least some college), body mass index (BMI, kg/m^2) computed from weight and height assessment, comorbidity using the modified Charlson comorbidity index (>1 versus none), and intensity of knee pain (0-10 on a visual analog scale (VAS) where the participant pointed to a whole number on the card that best describes the pain at its worst ranging from "0" meaning "No pain" and "10" meaning "Pain as bad as you can imagine."). These factors were ascertained at the 48-month visit by interview, questionnaire, and/or direct measurement, as appropriate.

2.2.5 Statistical Analysis

We described the study sample using means and standard deviations for continuous variables and percentages for categorical variables. To examine the association of steps/day with physical function, we calculated effect estimates using multiple linear regression adjusted for potential confounders, i.e., age, sex, BMI, race, education, knee pain intensity and comorbidity. Next, we calculated minimum performance thresholds on clinical tests of physical function corresponding to 80%, 85%, 90%, and 95% specificity values to predict walking ≥ 6000 steps/day (63). Specificity was defined as the proportion of participants whose test performance was above (better than) an identified threshold and walked ≥ 6000 steps/day divided by the entire analytic sample who walked ≥ 6000 steps/day (Table 2.2 and equation 2.1).

Table 2.2: Example 2 x 2 contingency table to illustrate how groups were identified to calculate specificity. The italicized qualifiers for poor and good physical function were changed iteratively to determine the specificity over a range of performance on the clinical tests of physical function.

	Inactive (< 6000 steps/day)	Active (≥ 6000 steps/day)
Poor physical function *(five times sit to stand test in > 10 sec)*	a	b
Good physical function *(five times sit to stand test in < 10 sec)*	c	d

Equation 2.1

$$\boldsymbol{Specificity = \frac{d}{b+d}} = \boldsymbol{\frac{Number\ of\ active\ indiviuals\ with\ good\ physical\ function}{Total\ number\ of\ active\ individuals}}$$

To illustrate this process, consider a test value of 10 sec to complete the five times sit to stand test. Since a slower time is indicative of worse physical function on this test, those who performed the five times sit to stand test in > 10 sec were identified as poor physical function. Likewise, those who performed the test in < 10 sec were identified as good physical function. We constructed a 2x2 contingency table (Table 2.3), and calculated specificity as shown in Equation 2.1. This process was repeated to determine the specificity over a range of possible performance on the clinical tests of physical function.

We chose high specificity cut points in order to minimize false-positives, i.e., minimize the number of people below minimum performance thresholds on clinical tests of physical function who walk $\geq$ 6,000 steps/day. Hence, we identified

inadequate performance on clinical tests of physical function that predicted the inability to walk > 6000 steps/day daily walking. Lastly, we repeated the analyses restricting our sample to people with radiographic OA (ROA) defined Kellgren–Lawrence (KL) grade ≥ 2 on x-ray in one or both knees, and people with symptomatic OA (SxOA) defined by the presence of ROA and pain, aching, or stiffness on most days of a month during the previous year. Our intention with these sub-analyses was to investigate the stability of our findings across samples of people with ROA and SxOA because the presence of knee OA and/or symptoms may affect the participation in daily walking and physical functioning (72)

2.3 Results

Table 2.3 displays the characteristics of the study participants that were included in the analytic study sample. The analytic study sample included 1925 people who were 65.1 ± 9.1 years of age (mean ± sd) with a BMI 28.4 ± 4.8 kg/m^2. Over half were women (55%), the majority (84%) were white, and 66% graduated from high school (Table 2.2). On average, the participants walked 6166 ± 2924 steps/day, with 54% of the study sample walking ≥ 6000 steps/day. Average performance on the clinical tests of physical function were 1.33 ± 0.21 meters/sec for walking speed over 20-meter walk test or 10.5 ± 2.9 sec on the five times sit to stand test.

Table 2.3: Characteristics of study participants

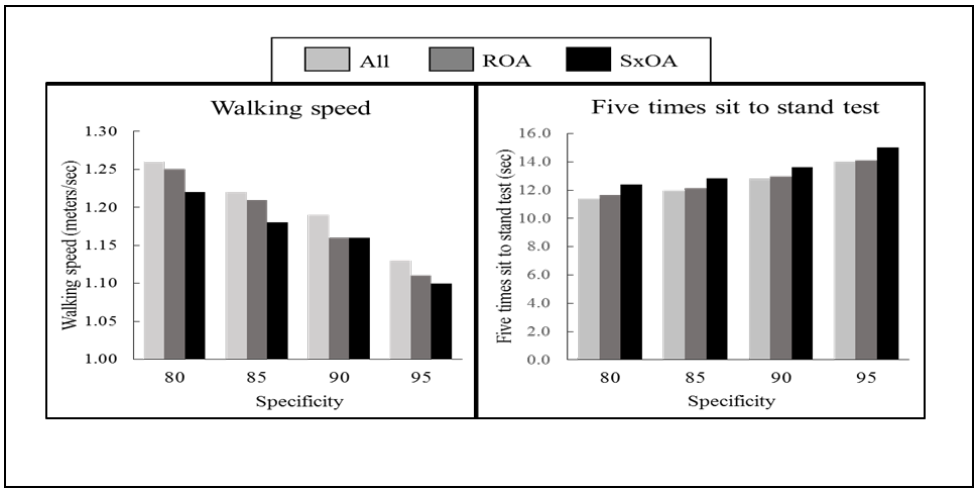
	All (N=1925) 100% of sample Mean±sd or % (n)	ROA (N=1169) 60.7% of sample Mean±sd or % (n)	SxOA (N=511) 26.5% of sample Mean±sd or % (n)
Age, years	65.1±9.1	66.1±9.1	65.6±8.9
Women	55 (1065)	55 (641)	54 (274)
Race, white	84 (1601)	81 (937)	78 (394)
Education, more than college	66 (1266)	64 (746)	62 (318)
BMI (kg/m2)	28.4±4.8	29.1±4.8 (1166)	29.7±4.7
VAS pain			
Right	2.4±2.6	2.7±2.7	3.9±2.9
Left	2.3±2.6	2.6±2.7	4.0±2.8
Comorbidity	30	31 (364)	35 (177)
Steps/day	6166±2924	5883±2821	5564±2778
Walked ≥ 6000 steps/day	45 (868)	42 (491)	40 (203)
Walking speed (m/sec)	1.33±0.21	1.31±0.21	1.28±0.21
Five times sit to stand test (sec)	10.5±2.9	10.8±3.0	11.4±3.4
ROA= radiographic OA SxOA= Symptomatic OA, BMI = body mass index, VAS = visual analog scale			

Worse performance on clinical tests of physical function was associated with taking fewer steps/day after adjustment for potential confounders (Table 2.4). Walking 0.1 meters/sec slower during the 20-meter walk test was associated with walking 342 fewer steps/day (95% CI [-276, -408]). Each additional 1 sec to complete the five sit to stand test was associated with walking 130 fewer steps/day (95% CI [-178, -83]).

Table 2.4: Unadjusted and *adjusted performance of physical function tests with steps/day using linear regression models.

Physical function	Steps/day (95% CI)	*Adjusted Steps/day (95%CI)
Walking speed (0.1 m/sec slower)	-569 (-510, -628)	-342 (-276, -408)
Five times sit to stand test (1 sec longer)	-261 (-307, -215)	-130 (-178, -83)
*Adjusted for age, sex, education, race, BMI, pain and Charlson comorbidity index.		

Performance on the clinical tests of physical function corresponding to 80% to 95% specificity to identify those who walked ≥ 6000 steps/day ranged from 1.13 to 1.26 meters/sec for walking speed, or 11.4 to 14.0 sec on the five times sit to stand (Figure 2.2). After restricting our study sample to participants with ROA, we observed that the thresholds for performance on the clinical tests of physical function to identify those who walked ≥ 6000 steps/day were almost identical to the full sample (Figure 2.2). When restricted to participants with SxOA, we observed that 80 to 95% specificity thresholds of performance on physical function tests ranged from 1.10 to 1.22 meters/sec for walking speed, or 12.4 to 15.0 sec on the five times sit to stand test (Figure 2.3).



***** Specificity was defined as the proportion of people who had less than threshold values of physical function and who walked ≥ 6000 steps/day divided by the proportion of people who walked ≥ 6000 steps/day.

Figure 2.3: Physical function measures that reflect 80, 85, 90 and 95% specificity* in all, ROA and SxOA participants

2.4 Discussion

In general, we identified preliminary performance thresholds on clinical tests of physical function predictive to walk ≥ 6,000 steps/day for people with or at high risk of knee OA. Specifically, walking more than 1.13 to 1.26 meters/sec, or completing the five times sit to stand test in less than 11.4 to 14 sec corresponds to 80-95% specificity values to predict walking ≥ 6,000 steps/day. Study subjects who are unable to meet any one of these thresholds may have an insufficient physical function to participate in walking more than 6,000 steps/day. We found these thresholds to be similar when analyses were restricted to those with ROA and SxOA. Previous work by White and his colleagues has found similar physical activity cut points across all, ROA and SxOA participants when predicting functional limitation (63). This indicates

that people with or at high risk of knee OA can be similarly screened for insufficient physical function to walk 6000 steps/day.

Walking speed is a well-established marker of health, a predictor of morbidity and mortality in older adults (15), and is feasible to test in the clinic (82). 80% specificity thresholds for the 20-meter walk test were 1.26, 1.25 and 1.22 meters/sec for all, ROA and SxOA participants respectively. There was the variability of approximately 0.04 meters/sec among all and SxOA participants, which is not a clinically meaningful difference (i.e. 0.08 meters/sec) (83). Therefore, walking slower than 1.22 meters/sec during 20-meter walk test, a general heuristic (i.e., guiding) value that can be used in clinical practice, may identify people without the capacity to walk ≥ 6,000 steps/day. This particular speed threshold is known to be important for community ambulation, as timed crosswalks are set to require a minimum speed of 1.22 meters/sec (51, 61). Hence, the inability to walk at this speed may represent the inability to walk in the community safely. Impairments in several body systems can slow walking speed (84), including vision, lower extremity strength (85, 86), aerobic capacity(87), postural control and proprioception (86), and can also restrict daily walking (15).

The five times sit to stand test is a practical objective assessment of functional lower extremity strength that is feasible for use by health professionals. The test requires a chair and stopwatch, can be done in a doctor's office, and has minimal risk of injury as patients simply stand from a chair. 80% specificity thresholds for the sit-to-stand test were 11.4, 11.6 and 12.4 sec for all, ROA and SxOA participants respectively. There was the variability of approximately 1 sec among all and SxOA participants, which is not a clinically meaningful difference (i.e. 2.3 sec) (88).

Therefore, taking longer than 12 sec to complete the five times sit to stand test, a general heuristic (i.e., guiding) value that can be used in clinical practice, may indicate inadequate physical function to walk ≥ 6000 steps/day. Similar thresholds have been reported in the literature in other populations (16, 78, 89-91). For instance, community-dwelling older adults who took more than 12 sec to complete the five times sit to stand test had double (OR = 2.0, 95%CI (1.3, 3.0)) the risk for multiple falls compared with those who took < 12 sec to complete the test (16). This test requires the use of lower body muscle groups, including knee and hip extensors, hip, knee and ankle range of motion and maintaining balance transitioning from sitting to stand (92). Poor performance, i.e., requiring greater time to complete the test, may reflect the presence of impairments including lower body pain, inadequate lower body muscle strength, poor balance or coordination deficits, which also can limit daily walking.

2.4.1 Limitations

Our study has several limitations. First, we employed only one definition of daily walking, i.e., 6000 steps/day, and did not examine thresholds of different intensities of physical activity, such as time spent in light, moderate or vigorous intensity activity. Future studies should consider intensity-based outcomes to confirm the extent to which our physical function thresholds also apply to time spent in moderate or vigorous intensity activity. Second, most of our sample was white, well educated, had a low BMI, and performed better on the physical function tests compared to those who participated in the accelerometer study but did not provide sufficient valid data (Table 2.1). Thus, caution should be taken when generalizing these results to other populations. Third, the cross-sectional design allowed us to

identify a relationship between physical function and physical activity, but not to draw conclusions about causation. Lastly, there is a possibility that study subjects chose to not participate in daily walking irrespective of their physical function ability possibly due to psychosocial barriers. Hence the physical function threshold values should be viewed as estimates that have some variability.

2.4.2 Strengths

Despite these limitations, our study has several strengths. First, we used a large analytic sample with objectively measured physical activity from a well-established cohort. Second, we selected thresholds of physical function that minimized false positives, i.e. people with knee OA who did not meet performance thresholds were highly unlikely to walk ≥ 6000 steps/day. Third, we established performance thresholds using clinically feasible measures of physical function that clinicians can employ in the real world.

2.4.3 Clinical Implication

One possible implication of our study is referral to rehabilitation, such as physical therapy, may be of benefit to those with or at risk of knee OA not meeting one or more of these physical function thresholds. Physical therapists assess underlying modifiable impairments that limit physical function, including pain, muscular strength, range of motion, limited cardiorespiratory fitness, and coordination, then use therapeutic exercise and manual techniques to target underlying impairments(93). These interventions that are employed by physical therapists are effective to improve physical function in people with knee OA (21, 94).

2.5 Conclusion

We identified preliminary thresholds for performance on clinical tests of physical function that may indicate inadequate physical ability to walk at least 6,000 steps/day, which is an important benchmark we previously found to be associated with protection against the development of future functional limitation. Clinicians may consider prioritizing referral to rehabilitation to improve physical function for people with knee OA that are unable to meet these minimum thresholds.

Chapter 3

THE RELATION OF PHYSICAL FUNCTION MEASURED AT ONE TIME-POINT VERSUS CHANGE OVER ONE YEAR TO ALL-CAUSE MORTALITY.

3.1 Introduction

Over 250 million people worldwide have knee osteoarthritis (OA) (2), which is a leading cause of pain and functional limitation (3, 4, 6), e.g., difficulty getting up from a chair or slow walking. Subsequently, people with knee OA are 55 to 90% more likely to die earlier compared to the general population (10, 11, 95). OA has no cure. Therefore, management strategies, such as rehabilitation, focus on reducing pain and functional limitation (19-21, 96). However, only one in four people with knee OA are referred to rehabilitation (22, 23, 97, 98). Determining who may be in need of referral to rehabilitation is an important area of investigation. Performance-based physical function measures such as walking speed (15, 51, 62, 77, 82, 99) and repeated chair stands (78, 79) are key measures of functional limitation, and by extension be employed to identify the need for rehabilitation for people with knee OA.

The collection of physical function at the initial evaluation may be feasible since this evaluation is comprehensive in nature. This kind of assessment has a limitation since physical function decline with age (46-49) and not all decline is uniform. Rather, there are different rates or trajectories of change in physical function, i.e., some decline quickly, while others' are stable or decline gradually. Moreover, we know that those with a fast decline in walking speed and repeated chair stands have

90% (50) and 27% (100) greater risk of all-cause mortality, respectively, compared with those who experienced a slow decline over time. Further worsening in physical functioning is known to increase the risk of cardiovascular diseases (101). Hence, capturing those with fast decline is important to identify people at risk for adverse health outcomes.

There are several caveats for repeated assessment of physical function over time. First, most health professionals do not measure physical function in a standardized fashion as part of the routine clinical examination for knee OA. Barriers for repeated assessment include time, physical space, and equipment. Second, individuals having similar physical functioning in the present may have had different histories of trajectories of decline, i.e., some may have experienced rapid decline while others may remain relatively stable. It is unclear whether testing the history of physical function decline is more informative in determining mortality risk, or if slow physical functioning at one time-point that portends mortality risk. In other words, we do not know how comparable the predictive validity of physical function measured at one time-point is to repeated measures over time for mortality risk.

Clarifying the predictive validity of one versus repeated assessments of a physical function for mortality is important as it will elucidate whether assessing prevalent physical function at one time is a reasonable substitute for repeated measures. Therefore, the purpose of this study was to investigate whether physical function measured at one time or change over time or both predict the risk for all-cause mortality over nine years in adults with knee OA.

3.2 Methods

3.2.1 Study Participants: the Osteoarthritis Initiative (OAI)

We used data from the Osteoarthritis Initiative, a large prospective observational cohort study of 4796 people with or at risk of knee OA. People were excluded from OAI study if they had rheumatoid or inflammatory arthritis, bilateral end-stage disease defined as severe joint space narrowing or total knee replacements in both knees, and those who used ambulatory aids other than a cane at baseline. Institutional review board approval was obtained from all OAI sites. The current analysis included data from participants who completed baseline and 12-month follow-up clinic visit conducted between 2004-2006 and 2005-2007 respectively.

3.2.2 Study Outcome

Time to all-cause mortality was quantified in months from the 12-month clinic visit to the date of death through the 108-month clinic visit, i.e., 9 years later. The date of death was confirmed through obituary or death certificates when available. We censored participants who lived past the study period or who were lost to follow-up during the 9-year study period.

3.2.3 Study exposure

3.2.3.1 Walking speed

The 20-meter (20-m) walk test was to calculate self-selected walking speed at baseline and 12-month follow-up clinic visit. During the 20-m walk test, the participants were instructed to walk at their usual speed over a marked 20-m course in an unobstructed and dedicated corridor. A digital stopwatch was used to record the timing to complete the test. The timing began at the initial movement from standing at

the start and stopped when they crossed the 20-m mark. Walking speed in meters/second was calculated by dividing the total distance (20 meters) by the total time to complete the 20-m walk (sec). Slower walking speed indicates worse physical function (61). The 20-m walk test has high test-retest reliability (intraclass correlation coefficients > 0.9) for measuring walking speed in older adults (62, 77).

We choose cut-point of < 1.22 m/sec at the 12-month follow-up to identify people with slow walking speed because it indicates difficulty crossing the streets using timed signals (51) and is predictive of inadequate physical function necessary to be physically active (52). The decline in walking speed was calculated by subtracting walking speed at the 12-month follow-up visit from baseline walking speed. Adults with knee OA were categorized as having a one-year decline in their walking speed if they declined $\geq$0.08 m/sec from baseline to one year, which represents a clinically meaningful decline (83, 102).

We classified study subjects into one of four combinations of 12-month follow-up walking speed and change in walking speed over one year. The first category was 'fast sustainers,' which include those whose walking speed was $\geq$ 1.22 m/sec, at 12-month follow-up visit and had < 0.08 m/s decline in walking speed over one year. The second category was 'slow sustainers,' which was defined as those whose walking speed was <1.22 m/sec and had <0.08 m/sec decline in walking speed over one year. Thus, slow sustainers had slower walking speed at 12-month follow-up but had a similar decline in walking speed over one year compared to fast sustainers. The third category was 'fast decliners,' which was defined as those whose walking speed was $\geq$ 1.22 m/sec at a 12-month follow-up visit and had $\geq$ 0.08 m/sec decline in walking speed over one year. Thus, fast decliners had similar walking speed at 12-

month follow-up visit but had more decline in walking speed over one year compared to fast sustainers. The fourth category was 'slow decliners,' which was defined as those whose walking speed at 12-month follow-up visit was < 1.22 m/sec and had $\geq$ 0.08 m/sec decline in walking speed over a year. Thus, slow decliners not only had a slower walking speed but also had more decline in walking speed over a year compared to fast sustainers.

3.2.3.2 Repeated chair stands time

The five times sit-to-stand test was to calculate repeated chair stands function at baseline and 12-month follow-up clinic visit. During five times sit to stand test, the participants were instructed to stand up from a seated position in a standard chair (chair with a straight back, flat, level firm seat and seat height of 45cm in front) and return to sitting five times as quickly as possible with arms folded across the chest. A digital stopwatch was used to record the total time (sec) to complete five times sit to stand test. The timing started with the initial movement to stand on the first repetition and ended after returning to sitting on the fifth repetition. Performance on the five times sit to stand test was recorded as the average of two trials. A longer time to complete five times sit to stand test was indicative of worse physical function (78). 5STS has high test-retest reliability (intraclass correlation coefficients > 0.9) for measuring repeated chair stand function in older adults with symptomatic hip and/or knee OA (79).

We choose cut-point of $\geq$ 12 sec at the 12-month follow-up to identify people with slow repeated chair stands time because it indicates risk for multiple falls in older adults(16) and inability to be physically active in knee OA (52). The one-year decline in repeated chair stands was calculated by subtracting time taken to complete five

times sit to stand test at 12-month follow-up visit from the baseline time. Adults with knee OA were categorized as having a one-year decline in repeated chair stands time if they declined > 2.3 sec from baseline to one year, which represents the clinically meaningful difference in repeated chair stands time (88).

We classified study subjects into one of four combinations of 12-month follow-up repeated chair stands and change in repeated chair stands time over one year. The first category was ‘fast sustainers,’ which include those whose repeated chair stands time was < 12 sec at 12-month follow-up and had $\leq$ 2.3 sec decline in repeated chair stands time over one year. The second category was ‘slow sustainers,’ which include those whose repeated chair stands time was $\geq$ 12 sec at 12-month follow-up and had $\leq$ 2.3 sec decline in repeated chair stands time over a year. Thus, slow sustainers took more time to complete five times sit to stand test but had a similar decline in repeated chair stands time compared to fast sustainers. The third category was ‘fast decliners,’ which include those whose repeated chair stands time was < 12 sec at a 12-month follow-up visit and had >2.3 sec decline in repeated chair stands time over one year. Thus, fast decliners took a similar time to complete five times sit to stand test at 12-month follow-up visit but had more decline in repeated chair stands over one year compared to fast sustainers. The fourth category was ‘slow decliners,’ which include those whose repeated chair stands time was > 12 sec at a 12-month follow-up visit and had a one-year decline in repeated chair stands time. Thus, slow decliners took more time to complete five times sit to stand test and had a more one-year decline in repeated chair stands time compared to fast sustainers.

3.2.4 Potential confounders

We considered the following factors as potential confounders based on their association with performance-based physical function measures and all-cause mortality(51, 103-107): Age, sex (female versus male), race/ethnicity (white versus non-white), education (less than college graduate versus at least college graduate), body mass index (BMI, kg/m^2) computed from weight and height assessment, comorbidities measured using the modified Charlson comorbidity index (108), depressive symptoms measured using the Center for Epidemiologic Studies Depression Scale (> versus <16) (109), symptomatic knee OA (SxOA), which was defined as presence of knee pain, aching or stiffness on most days in past month during the previous year in either right or left knee and the presence of radiographic knee OA, which was defined as Kellgren–Lawrence grade ≥ 2 on x-ray in one or both knees (present versus absent). These factors were ascertained at the study enrollment or 12-month visit by interview, questionnaire, and/or direct measurement, as appropriate.

3.2.5 Statistical Analysis

We described the study sample using means and standard deviations for continuous variables and percentages for categorical variables. We used the Kaplan-Meier survival curves to determine the mortality rate for each of the categories of the physical function measured at the one-time point and change over one year within exposure categories, i.e., fast sustainers, slow sustainers, fast decliners and slow decliners. To examine the association of walking speed and change in walking speed with all-cause mortality over 9 years, we calculated hazard ratios and 95% confidence intervals [HR (95%CI)] from Cox regression model adjusted for potential

confounders. To examine the association of repeated chair stands time and change in repeated chairs time with all-cause mortality over 9 years, we calculated hazard ratios and 95% confidence intervals [HR (95%CI)] from Cox regression model adjusted for potential confounders. All analyses were performed using SAS, version 9.4 (Cary, NC).

3.3 Results

3.3.1 Walking speed

Of 4796 participants recruited for the study, 4,229 participants have completed 20-m walk test at baseline and 12-month follow-up visit. Table 3.1 displays the subject characteristics who were included in the analytical sample.

Table 3.1: Characteristics of study participants who completed 20-m walk test at baseline and 12-month follow-up visit (N=4229)

Characteristics	Mean±sd or % (n)
Total sample	4229
Age, years	62.3±9.2(4229)
Women	57.6 (2437)
Race, white	81.3(3438)
Education, at least college grad	61.5(2600)
BMI (kg/m2)	28.5±4.8(4208)
Presence of knee pain, aching or stiffness: more than half the days of a month, past 12 months	
Right	29.7(1252)
Left	29.2(1229)
Index knee	39.8(1679)
Comorbidities	0.4±0.8(4185)
Depression	10.1(426)
ROA	56.6(2394)
SxOA	27.1(1146)
Baseline Walking speed (m/sec)	1.33±0.22(4229)
1-yr Walking speed (m/sec)	1.34±0.22(4229)
Time in the study, months	111.3±37.6(4229)
Number of deaths	6.4(270)

The average age was 62.3 ± 9.2 years (mean ± sd), BMI 28.5 ± 4.8 kg/m^2, over half were women (57.6%), the majority (81.3%) were white, and 61.5% were at least a college graduate. Over 6% of the analytic sample (270/4229) died over 9 years. The survival probability of 9-year follow-up was 95%, 85%, 96% and 85% for participants in fast sustainers, slow sustainers, fast decliners and slow decliners, respectively (Figure 3.1).

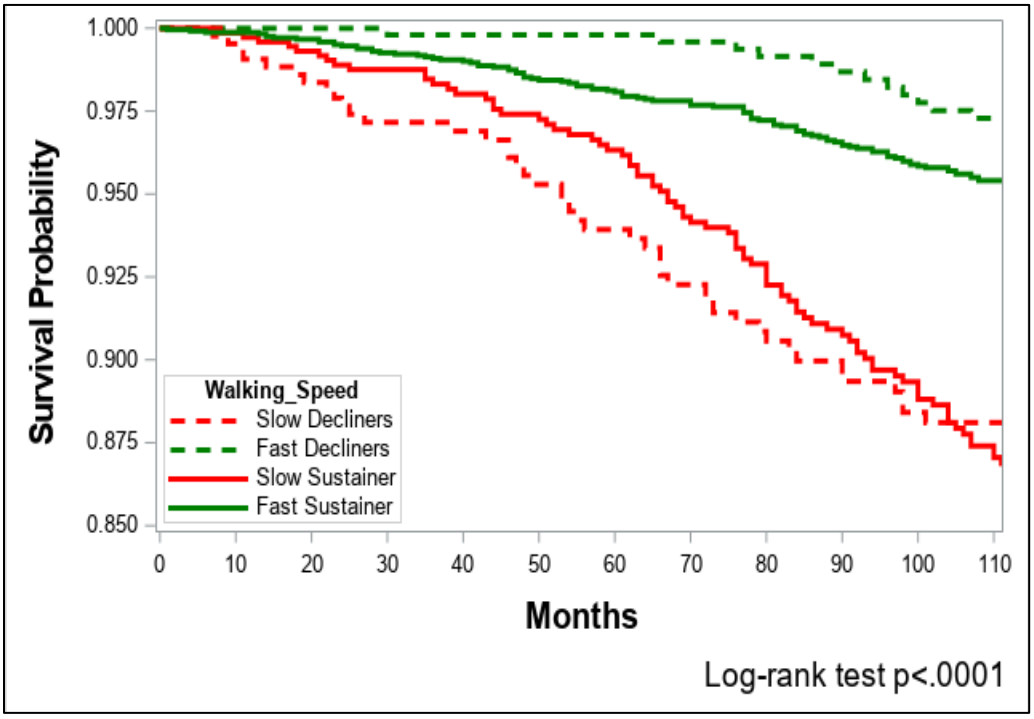


Figure 3.1: Kaplan-Meier survival curves for adults with knee OA who are defined as fast sustainers, slow sustainers, fast decliners and slow decliners using a 20-m walk test.

Slow sustainers had 96% more risk (adjusted HR 1.96 [1.44, 2.66]) and slow decliners had 108% more risk (adjusted HR 2.08 [1.46, 2.96]) for all-cause mortality compared with the fast sustainers (Table 3.2). Fast decliners had a lesser risk for all-cause mortality compared with the fast sustainers, which did not meet statistical significance (adjusted HR 0.57 [0.32, 1.01]).

Table 3.2: Association of walking speed and change in walking speed over a year to the risk of all-cause mortality over 9 years among all the study participants

	Baseline Walking speed Mean±SD	**12-month follow-up Walking speed Mean±SD**	**Deaths** %(n)	**Time in the study, months Mean±SD**	**Unadjusted HR (95% CI)**	***Adjusted HR (95% CI)**
Slow decliners (N=439)	1.24±0.15	1.06±0.15	11.6 (51)	102.2±43.2	**2.88 [2.07, 4.00]**	**2.08 [1.46, 2.96]**
Fast decliners (N=532)	1.56±0.16	1.41±0.14	2.8 (15)	113.8±36.5	0.61 [0.34, 1.05]	0.57 [0.32, 1.01]
Slow sustainers (N=751)	1.07±0.14	1.1±0.11	11.7 (88)	105.0±40.3	**2.79 [2.12, 3.69]**	**1.96 [1.44, 2.66]**
Fast sustainers (N=2507)	1.38±0.17	1.45±0.16	4.6 (116)	114.3±35.4	1.00 [Reference]	1.00 [Reference]

*Adjusted for baseline age, BMI, sex, race, education, comorbidities, the presence of depression (< vs. >16), and SxOA, i.e., ROA + pain

3.3.2 Repeated chair stands

Of 4796 participants recruited for the study, 3,754 participants have completed five times sit to stand test at baseline and 12-month follow-up visit. The average age was 61.9 ± 9.1 years (mean ± sd), BMI 28.4 ± 4.8 kg/m^2, over half were women (57.1%), the majority (82.1%) were white, and 62.3% were at least a college graduate. Over 6% of the analytic sample (223/3754) died over 9 years. (Table 3.3).

Table 3.3: Characteristics of study participants who completed five times sit to stand test walk test at baseline and 12-month follow-up visit (N=3754)

Characteristics	Mean±sd or % (n)
Total sample	
Age, years	61.9±9.1
Women	57.1
Race, white	82.1(3080)
Education, at least college grad	62.3(2339)
BMI (kg/m2)	28.4±4.8
Presence of knee pain, aching or stiffness: more than half the days of a month, past 12 months	
Right	28.0(1049)
Left	27.3(1021)
Index knee	37.6(1409)
Comorbidities	0.4±0.8
Depression	9.4(351)
ROA	55.1(2069)
SxOA	25.2(944)
Baseline Walking speed (m/sec)	11.15±3.36
1-yr Walking speed (m/sec)	10.89±3.3
Time in the study, months	112.0±36.88
Number of deaths	5.9(223)

The survival probability of 9-year follow-up was 94%, 89%, 95% and 89% for participants in fast sustainers, slow sustainers, fast decliners and slow decliners, respectively (Figure 3.2).

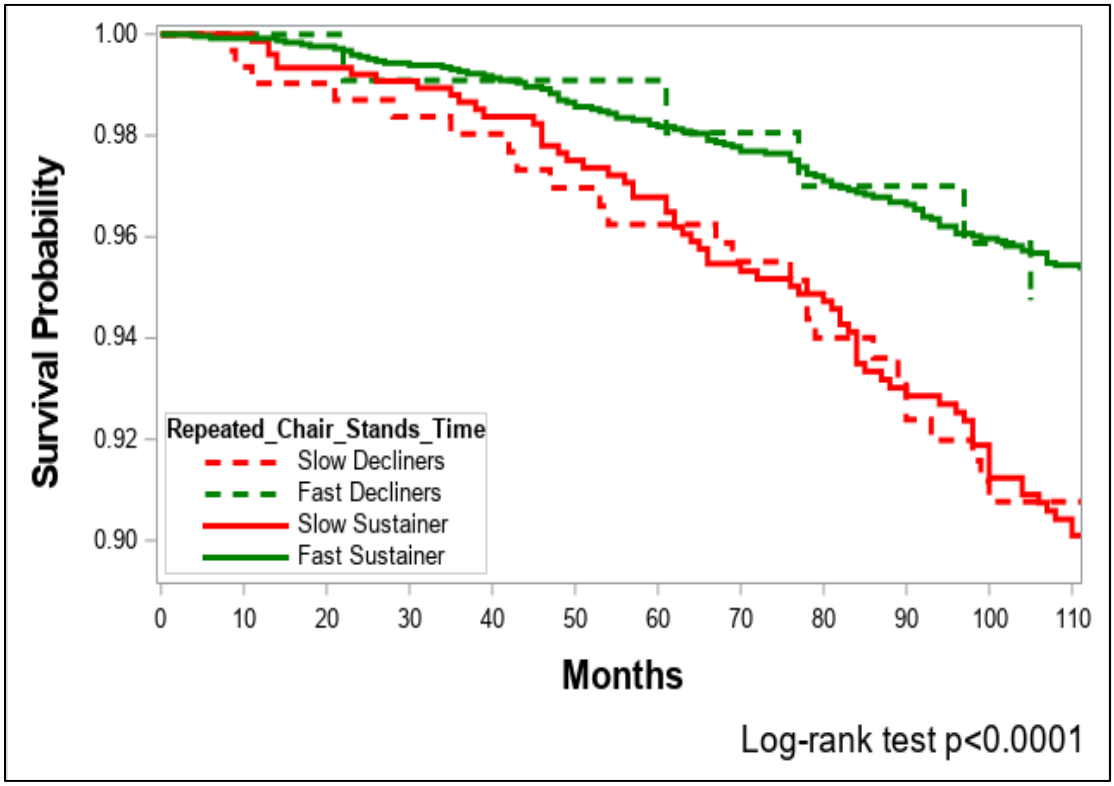


Figure 3.2: Kaplan-Meier survival curves for adults with knee OA who are defined as fast sustainers, slow sustainers, fast decliners and slow decliners using five times sit to stand test.

Slow sustainers had 94% more risk (unadjusted HR 1.94 [1.45, 2.60]) and slow decliners had 90% more risk (unadjusted HR 1.90 [1.25, 2.88]) for all-cause mortality compared with the fast sustainers. (Table 3.4). These effect estimates were attenuated and did not meet statistical significance when adjusted for potential confounders. Fast decliners had a lesser risk for all-cause mortality compared with the fast sustainers, which did not meet statistical significance (unadjusted HR 0.96 [0.39, 2.33]).

Table 3.4: Association of repeated chair stands time and change in repeated chair time over a prior year to the risk of all-cause mortality over 9 years among all the study participants

	Baseline Walking speed Mean±SD	**12-month follow-up Walking speed Mean±SD**	**Deaths** %(n)	**Time in the study, months Mean±SD**	**Unadjusted HR (95% CI)**	***Adjusted HR (95% CI)**
Slow decliners (N=322)	11.78±2.97	16.19±4.36	11.4 (40)	106.1±41.7	**1.89 [1.25, 2.88]**	1.32 [0.85, 2.07]
Fast decliners (N=111)	7.68±1.10	10.7±0.91	2.7 (13)	113.0±35.3	0.96 [0.39, 2.33]	0.90 [0.37, 2.20]
Slow sustainers (N=784)	14.88±3.59	14.05±2.31	11.0 (66)	108.6±39.2	**1.94 [1.45, 2.60]**	1.24 [0.90, 1.70]
Fast sustainers (N=2537)	10.06±2.34	9.25±1.62	4.5 (104)	113.7±35.4	1.00 [Reference]	1.00 [Reference]

*Adjusted for baseline age, BMI, sex, race, education, comorbidities, the presence of depression (< vs. >16), and SxOA, i.e., ROA + pain

3.4 Discussion

We found people with or at risk of knee OA who had a poor physical function at one time-point were at risk for all-cause mortality over 9 years irrespective of how much decline they had over previous year. These findings are robust as the results were consistent with both the definition of physical function measures. Our findings suggested that walking speed and repeated char stands time measured at one time-point may be more important than assessing a one-year decline for predicting the risk for all-cause mortality over 9 years in adults with knee OA. However, our findings for repeated chair stands time did not meet statistical significance.

Our findings highlighting the importance of physical function measures assessed at one time-point is consistent with previous literature. Walking speed is considered as a functional vital sign because it is a strong predictor for adverse health outcomes, i.e., mortality and prolonged hospitalization in older adults (15, 51, 82, 99) and poor response to rehabilitation in adults after stroke (82, 110). Slow walking speed reflects impairments in several body systems (84), i.e., vision, lower extremity strength (85, 86), aerobic capacity (87), postural control (86), and restrict daily walking (52).

One caveat for implementing walking speed in practice is that a clinic needs to maintain at least 5 to 10 meters dedicated straight path for valid walking speed assessment (111), which may limit feasibility in real-world clinics. Our study findings suggest that repeated chair stands time may be an acceptable alternative to walking speed for predicting all-cause mortality in adults with knee OA. Further, repeated chair stands time can be easily measured in the doctor's office using a valid objective test, i.e., five times sit to stand test (78, 79). However, it is important to note that this finding did not meet statistical significance when we adjusted for potential confounders. Our adjusted model indicates that baseline comorbidities and age primarily explained the joint association of repeated chair stands time measured at one time-point versus change over one year with the risk for all-cause mortality.

We found the people with or at risk of knee OA who were well-functioning in the present but had a meaningful decline in physical function over a year did not have a higher risk for all-cause mortality compared to those who did not have meaningful decline over a year. This finding is somewhat inconsistent with previous studies that showed people who had a fast decline in walking speed, and repeated chair stands time

had 90% (50) and 27% (100) greater risk for all-cause mortality compared to those who had a slow decline, respectively and increased risk for cardiovascular disease (101). It is important to note that White and co-authors found among all the older adults who walked at least 1.22 m/sec at baseline, those who experience fast, moderate and slow decline over 3 years walked slower than 1.2 m/sec, faster than 1.2 m/sec and faster than 1.4 m/sec at 3-year follow-up, respectively (50). Among these three categories, only those older adults who experienced a fast decline had increased risk for all-cause mortality compared to slow decline. Older adults with moderate decline did not have a significantly higher risk for all-cause mortality compared to slow decline. This finding suggests that older adults whose walking speed at 3-year follow-up were below the threshold predictive of poor health outcomes had a higher risk for all-cause mortality compared to those whose walking speed was above the threshold. This finding is consistent with our study. We observed among people with or at risk of knee OA who had a meaningful decline in physical function over a year but their present physical functioning was above the threshold predictive of poor health outcomes did not have a higher risk for all-cause mortality compared to those who did not experience a meaningful decline. On the other hand, people with knee OA did not have a meaningful decline in physical function over a year, but their current physical functioning was poor, i.e., below the threshold predictive of poor health outcomes had an increased risk for all-cause mortality. Our findings suggest that threshold effect at one time-point may be more portend compared to an absolute decline in walking speed over one year for mortality risk.

3.4.1 Strengths and limitations

The major strength of our study is that we used large dataset and 9-year follow-up, which provides a powerful means to study our primary research questions. However, our study had some limitations. First, there was a differential loss to follow-up, for example, people with knee OA whose walking speed was <1.22 m/sec experienced most loss to follow-up compared to those whose walking speed was ≥1.22 m/sec. Second, we caution generalizing the results of our study, since the majority of our sample was white and at least college graduates. Third, we did not account for intercurrent events such as hospitalization, knee replacement, which occurred during the follow-up. We believe understanding how such events alter the joint association of the physical function measured at one time-point and decline over a year with the risk of all-cause mortality is important and needed to study in future research. Lastly, walking speed was measured using a 20-m walk test. Therefore, we are not able to generalize the study findings to walking speeds taken over shorter or longer distances.

3.4.2 Clinical implications

Our study has several clinical implications. First, clinicians should consider measuring physical function at one time-point since it predicts risk for all-cause mortality. Further, performances on the physical function measured at one time-point may aid in clinical decision making by telling clinicians, which patients with knee OA may need rehabilitation to address functional limitation. Specifically, walking speed slower than 1.22 m/sec or taking more than 12 sec to complete five times sit to stand test may serve a threshold to refer to rehabilitation for patients with or at risk of knee OA. Second, when possible, health care professional should prefer assessing walking

speed in their clinic to identify adults with knee OA who have functional limitation severe enough that would warrant a referral to rehabilitation since it has stronger predictive validity compared to repeated chair stands.

3.5 Conclusion

In people with or at risk for knee OA, we found assessing performance-based physical function measure at a one-time point is predictive for all-cause mortality, irrespective of decline in the performance over one year. Specifically, we found walking speed to have stronger predictive validity compared to repeated chair stands time. Healthcare professionals should consider assessing walking speed in routine clinical practice. Walking slower than 1.22 m/sec on a 20-m walk test at a one-time point is sufficient to identify adults with knee OA who have an increased risk for all-cause mortality and may serve a threshold to refer to rehabilitation.

Chapter 4

OPTIMAL THRESHOLDS OF PHYSICAL FUNCTION MEASURE PREDICTIVE OF ALL-CAUSE MORTALITY AND KNEE REPLACEMENT IN KNEE OSTEOARTHRITIS: AN OBSERVATIONAL STUDY

4.1 Introduction

Over 250 million people worldwide have knee osteoarthritis (OA) (2), which has no cure. Knee OA is a leading cause of functional limitation such as difficulty walking and getting up from a chair (3-6), which can be addressed by rehabilitation(19-21). However, less than 14 to 60% of people with knee OA receive rehabilitation (22, 23, 97, 98). One reason for this low referral may be physicians are unsure when to refer people with knee OA to rehabilitation. One way to identify if people with knee OA have functional limitation severe enough that would warrant a referral to rehabilitation.people who need rehabilitation is to used performance-based physical function measures such as walking speed (62, 77) and repeated chair stands time(78, 79) since it can track the functional status of people with knee OA.

Presence of self-reported walking difficulty is strongly associated to increased risk for mortality in adults with knee OA (9-11). However, different individuals can perceive walking difficulty differently. One way to translate this concept clinically is to quantify the walking difficulty. Performance-based physical function measure such as walking speed can act as a marker for walking difficulty. Previous studies have reported that slow walking speed is a strong predictor of adverse health outcomes and all-cause mortality in well-functioning older adults (aged $\geq$65 years) (15, 51). Walking

slower than 1.0 m/sec increases the risk for all-cause mortality in well-functioning older adults (15) while walking at least 1.22 m/sec is the minimum speed needed to cross streets using timed signals(51). In addition, performance-based physical function measure such as limited repeated chair stands time is a well-established predictor of adverse health outcomes in well-functioning older adults (16, 103, 112, 113) and may be used as a surrogate marker for walking difficulty. Community-dwelling older adults who take more than 12 sec to complete five times sit-to-stand task have a higher risk for multiple falls (16) while those who take more than 17 sec for the same task are at a higher risk for mortality and persistent severe lower extremity limitation (103). At present, we do not know if similar thresholds can be applied to identify poor walking speed and limited repeated chair stands time that predicts the risk of OA-related health outcomes for the following reasons.

First, not all adults with knee OA are older adults, i.e., there are younger adults aged between 45 to 65 years who have knee OA. These younger adults with knee OA also report pain, functional limitation. Further, 38% of people who elected total knee replacement in the United States were younger, i.e., aged less than 65 years (114). The risk for all-cause mortality in younger adults with knee OA should not be discounted given they have a pre-existing functional limitation. Second, to the best of the knowledge, no studies to date, have investigated the predictive value of walking speed and repeated chair stands time for knee replacement (KR) risk. Third, people with knee OA are 55 to 90% more likely for early all-cause mortality compared to the general population (10, 11). 59 to 87% of people with OA have at least one other significant chronic condition such as cardiovascular disease, diabetes, and hypertension (115). Further, adults with knee OA have pain and pre-existing

functional limitation (116), which likely limits the ability to be active (52). Being inactive leads to poor fitness and cascade of health consequences (28) including increased risk for KR (117) and all-cause mortality (29).

Lastly, previous methods to identify walking speed thresholds predictive of all-cause mortality have treated death without considering censoring, i.e., we do not have information whether the event occurred or not outside the study period or in those who were lost to follow-up during the study period. Accounting for time-to-event and accounting for censoring provides critical information about the time at risk, especially when the outcomes are measured at different time-points. For example, the threshold for the walking speed at survival time longer than 4 years may be different from survival time longer than 7 years. Therefore, analyses developed to identify optimal thresholds for uncensored binary outcomes would need to be modified. Sima and Gönen (53) consider several techniques modifying receiver operating curves (ROC)-based methods and test-based methods for this purpose. Based on their simulation studies, they recommend the use of an approach maximizing the likelihood ratio test for selection of the optimal threshold. This approach is sensitive compared to traditional ROC for identifying an optimal threshold, specifically when the time to all-cause mortality and KR is important for the prognosis. Identifying a survival time-related threshold would yield an informative profile for investigating patient's prognosis and will also help evaluate the generalizability of a single threshold that takes into account time-to-event and censoring. Some studies have used visual inspection approach to identify the threshold where they have calculated the event rates based on categories of increasing walking speed (0.05 to 0.1 m /s) or percentile approach. These approaches do not account for the model selection criteria and lack

generalizability since the results are dependent on the population from which it is driven.

Identifying the specific level of walking speed and repeated chair stands time predictive for KR and all-cause mortality in both older and younger adults with knee OA is important as it provides valuable information that can be applied clinically to identify the risk profile of the patients. Further, the threshold may not only serve as an indicator to refer patients with or at risk for knee OA to rehabilitation but also provide a target for the interventions that promote physical functioning and general well-being. Therefore, the purpose of this study was to examine the association of walking speed, and repeated chair stands time with KR and all-cause mortality in adults with or high risk of knee OA. We also investigated this association separately in older and younger adults with or at high risk of knee OA to test the generalizability of the findings given the age adults with knee OA could range from as young as 45 years to older than 65 years, which could confound the association. We will also examine the specific threshold of the walking speed, and repeated chair stands time that will discriminate people who have versus who do not have a risk for KR and all-cause mortality.

4.2 Methods

4.2.1 Study Participants: the Osteoarthritis Initiative (OAI)

We used data from the Osteoarthritis Initiative, a large prospective observational cohort study of 4,796 people with or at risk of knee OA. OAI excluded people with rheumatoid or inflammatory arthritis, bilateral end-stage disease defined as severe joint space narrowing or total knee replacements in both knees, and those who used ambulatory aids other than a cane at baseline. Institutional review board

approval was obtained from all OAI sites. The current analysis included data from participants who completed the baseline assessment of performance-based physical function measures conducted between 2004-2006.

4.2.2 Study Outcome

4.2.2.1 All-cause mortality

Time to all-cause mortality was quantified in months from baseline visit to the date of death through the 108-month clinic visit. The date for death was confirmed through from adjudicated obituary or death certificates when available. We censored participants who survived at the 108-month visit or who were lost to follow-up during the 9-year study period.

4.2.2.2 KR.

Time to KR was quantified in months from the baseline visit to the date of KR through the 108-month clinic visit. The date for KR was confirmed through adjudicated medical records when available. We censored participants without KR at the 108-month visit, or who were lost to follow-up, or died during the 9-year study period.

4.2.3 Study exposure

4.2.3.1 Walking speed

The 20-m walk test was to calculate the self-selected walking speed at the baseline visit. During the 20-m walk test, the participants were instructed to walk at their usual speed over a marked 20-m course in an unobstructed and dedicated corridor. A digital stopwatch was used to record the timing to complete the test. The

timing began at the initial movement from standing at the start and stopped when they crossed the 20-m mark. Walking speed in meters/second was calculated by dividing the total distance (20 meters) by the total time to complete the 20-m walk (sec). Slower walking speed indicates worse physical function (61). 20-m walk test has high test-retest reliability (intraclass correlation coefficients > 0.9) for measuring walking speed in older adults (62, 77).

4.2.3.2 Repeated chair stands time

The five times sit-to-stand test was to calculate repeated chair stands function at baseline. During five times sit to stand test, the participants were instructed to stand up from a seated position in a standard chair (chair with a straight back, flat, level firm seat and seat height of 45cm in front) and return to sitting five times as quickly as possible with arms folded across the chest. A digital stopwatch was used to record the total time (sec) to complete five times sit to stand test. The timing started with the initial movement to stand on the first repetition and ended after returning to sitting on the fifth repetition. Performance on the five times sit to stand test was recorded as the average of two trials. A longer time to complete five times sit to stand test was indicative of worse physical function (78). five times sit to stand test has high test-retest reliability (intraclass correlation coefficients > 0.9) for measuring repeated chair stand function in older adults with symptomatic hip and/or knee OA (79).

4.2.4 Potential confounders

We considered the following factors as potential confounders based on their association with walking speed, repeated chair stands time, all-cause mortality and KR(34, 51, 103-107, 118): age, sex (female versus male), race/ethnicity (white versus

non-white), education (less than college graduate versus at least college graduate), body mass index (BMI, kg/m^2) computed from weight and height assessment, comorbidity measured using the modified Charlson comorbidity index(108), depressive symptoms measured using the Center for Epidemiologic Studies Depression Scale (> versus <16) (109), symptomatic knee OA (SxOA), which was defined as presence of knee pain, aching or stiffness on most days in past month during the previous year in either right or left knee and presence of radiographic knee OA, which was defined as Kellgren–Lawrence grade ≥ 2 on x-ray in one or both knees (present versus absent). These factors were ascertained at the study enrollment by interview, questionnaire, and/or direct measurement, as appropriate.

4.2.5 Statistical Analysis

We described the study sample using means and standard deviations for continuous variables and percentages for categorical variables. To examine the association of walking speed with all-cause mortality and KR over 9 years, we calculated hazard ratios (HR) and 95% confidence intervals (95%CI) from separate Cox regression model for each outcome, which was adjusted for potential confounders. To examine the association of repeated chair stands time with all-cause mortality and KR over 9 years, we calculated hazard ratios and 95% confidence intervals [HR (95%CI)] from separate Cox regression model for each outcome, which was adjusted for potential confounders.

We used Maximal Likelihood Ratio Chi-square Approach to identify the optimal threshold of walking speed and repeated chair stands that predicted the risk of all-cause mortality and KR (53). Specifically, we ran unadjusted and adjusted Cox models for different thresholds of the walking speed iteratively. We then identify the

threshold corresponding to the model that gave the maximal Chi-Square value. This method is known to maximize the concordance with the observed follow-up times between walking speed and all-cause mortality risk. Maximizing the concordance is a metric that is used to evaluate the performance of the thresholds when there is censored endpoints and is similar to maximizing the Youden index; criteria employed when using a ROC method.

Finally, we repeated analyses restricting our sample by age groups, i.e., older (≥65 years) and younger (<65 years) adults. Our intention with these sub-analyses was to investigate the stability of our findings across samples of people with different age groups because age may influence an individual's risk for all-cause mortality(10) and KR(34) as well as walking speed(46, 119) and repeated chair stands time(46, 48).

4.3 Results

4.3.1 Walking speed

Of 4796 participants recruited for the study, 4,775 participants have completed the 20-m walk test at the baseline visit. Table 4.1a displays characteristics of the participants who were included in the analytical sample. The average age was 61.14 ± 9.18years (mean ± sd), BMI 28.62 ± 4.84kg/m^2, over half were women (59.39%), the majority (79.18%) were white, and 59.20% were at least a college graduate. Over 6.5% and 9.2% of the analytic sample died or had KR over 9 years, respectively. (Table 4.1)

Table 4.1: Characteristics of study participants who completed 20-m walk test at baseline (N=4775)

Characteristics	Overall Sample Mean±sd or % (n)	Younger adults Mean±sd or % (n)	Older adults Mean±sd or % (n)
Total sample	4775	2966	1809
Age, years	61.14±9.18	55.07±5.35	71.1±4
Women	58.39(2788)	41.71(1237)	41.46(750)
Race, white	79.18(3781)	75.69(2245)	84.91(1536)
Education, at least college graduate	59.2(2827)	62.02(1752)	55.81(927)
BMI (kg/m2)	28.62±4.84	28.94±5.13	28.1±4.28
Knee pain severity in past 30 days, rated on scale of 0-10			
Right	2.67±2.73	2.81±2.76	2.44±2.67
Left	2.63±2.80	2.82±2.83	2.32±2.71
Index knee	3.56±2.87	3.73±2.86	3.28±2.85
Comorbidities	0.32±0.77	0.32±0.77	0.51±0.95
Depression	9.93(474)	12.07(358)	6.41(116)
ROA	53.55(2557)	48.15(1428)	62.41(1129)
SxOA	28.98(1384)	28.56(847)	29.68(537)
Walking speed (m/sec)	1.33±0.22	1.36±0.22	1.27±0.21
Number of deaths	6.53(312)	2.97(88)	12.38(224)
Number of KR	9.15(437)	7.59(225)	11.72(212)
Time to deaths	121.09±39.96	92.14±27.57	117.87±41.02
Time to KR	89.93±28.73	71.1±40	86.32±30.19

Walking 0.1 meters/sec slower during the 20-meter walk test was associated with a 16% greater risk of all-cause mortality over 9 years (Table 4.2). We found similar results when we stratified the analysis based on younger and older adults with or at risk of knee OA.

Table 4.2: Association of walking speed and risk of all-cause mortality over 9 years in adults with knee OA

	Overall	Younger adults	Older adults
Unadjusted HR (95%CI) (0.1 m/sec slower)	**1.25 (1.19, 1.32)**	**1.20 (1.10, 1.33)**	**1.19 (1.11, 1.27)**
*Adjusted HR (95%CI) (0.1 m/sec slower)	**1.16 (1.09, 1.23)**	**1.14 (1.02, 1.28)**	**1.14 (1.02, 1.28)**
*Adjusted for sex, race, education, baseline age, BMI, comorbidities, the presence of depression and SxOA			

Walking slower than 1.2 m/sec was found to be optimal thresholds to discriminate people who are at higher risk for all-cause mortality since it yielded maximal chi-square value in unadjusted as well as in adjusted Cox model (Table 4.3). We found similar thresholds when we re-ran the analysis for older and younger adults with or at high risk of knee OA (Table 4.4 and 4.5).

Table 4.3: Maximal Likelihood Ratio Chi-square Approach^ to identify the optimal threshold of walking speed that predicted the risk of all-cause mortality in overall sample (N=4775)

Threshold	# deaths/total people		Adjusted HR	Maximal Likelihood Chi-Square value obtained from Cox model	
	Walk slower	Walk faster		unadjusted	*adjusted
0.8 m/s	7/53 (13.2%)	305/4722 (6.5%)	1.58 (0.69, 3.62)	5.48	272.45
0.9 m/s	20/118 (16.9%)	292/4657 (6.3%)	**2.43 (1.49, 3.98)**	20.24	281.57
1.0 m/s	48/317 (15.1%)	264/4458 (5.9%)	**2.02 (1.44, 2.83)**	39.52	286.26
1.1 m/s	88/686 (12.8%)	224/4089 (5.5%)	**1.97 (1.49, 2.60)**	54.95	292.86
1.2 m/s	146/1355 (10.8%)	166/3420 (4.9%)	**1.81 (1.41, 2.31)**	61.63	293.2
1.3 m/s	200/2185 (9.2%)	112/2590 (4.3%)	**1.62 (1.26, 2.09)**	54.07	285.82
1.4 m/s	246/3089 (8%)	66/1686 (3.9)	**1.48 (1.11, 1.99)**	37.29	278.82

*Adjusted for baseline age, BMI, sex, race, education, comorbidities, the presence of depression (< vs. >16), and symptomatic knee OA (yes or no), defined as presence of Kellgren–Lawrence grade ≥ 2 on x-ray in one or both knees, and pain, aching, or stiffness on most days of a month during the previous year. ^higher chi-square values represent greater concordance between the threshold and all-cause mortality.

Table 4.4: Maximal Likelihood Ratio Chi-square Approach^ to identify the optimal threshold of walking speed that predicted the risk of all-cause mortality in younger adults with knee OA (N=2966)

Threshold	# deaths/total people		Adjusted HR	Maximal Likelihood Chi-Square value obtained from Cox model	
	Walk slower	Walk faster		unadjusted	*adjusted
0.8 m/s	2/26 (7.7%)	86/2940 (2.9%)	1.59 (0.22, 11.66)	2.34	33.54
0.9 m/s	5/61 (8.2%)	83/2905 (2.9%)	2.30 (0.78, 6.74)	5.34	35.24
1.0 m/s	7/147 (4.8%)	81/2819 (2.9%)	1.13 (0.47, 2.72)	2.28	33.43
1.1 m/s	19/334 (5.7%)	69/2632 (2.6%)	**1.89 (1.06, 3.37)**	10.14	37.87
1.2 m/s	33/678 (4.9%)	55/2288 (2.4%)	**1.92 (1.19, 3.11)**	11.92	40.06
1.3 m/s	48/1171 (4.1%)	40/1795 (2.2%)	**1.64 (1.03, 2.61)**	10.17	37.7
1.4 m/s	63/1734 (3.6%)	25/1232 (2.0%)	1.54 (0.93, 2.54)	8.04	36.34

*Adjusted for baseline age, BMI, sex, race, education, comorbidities, the presence of depression (< vs. >16), and symptomatic knee OA (yes or no), defined as presence of Kellgren–Lawrence grade ≥ 2 on x-ray in one or both knees, and pain, aching, or stiffness on most days of a month during the previous year. ^higher chi-square values represent greater concordance between the threshold and all-cause mortality.

Table 4.5: Maximal Likelihood Ratio Chi-square Approach^ to identify the optimal threshold of walking speed that predicted the risk of all-cause mortality in older adults with knee OA (N=1809)

Threshold	# deaths/total people		Adjusted HR	Maximal Likelihood Chi-Square value obtained from Cox model	
	Walk slower	Walk faster		unadjusted	*adjusted
0.8 m/s	5/27 (18.5%)	219/1782 (12.3%)	1.73 (0.69, 4.33)	1.91	99.05
0.9 m/s	15/57 (26.3%)	209/1752 (11.9%)	**2.53 (1.45, 4.45)**	11.39	106.46
1.0 m/s	41/170 (24.1%)	183/1639 (11.2%)	**2.19 (1.51, 3.17)**	25.77	113.08
1.1 m/s	69/352 (19.6%)	155/1457 (10.6%)	**1.91 (1.39, 2.62)**	27.08	112.68
1.2 m/s	113/677 (16.7%)	111/1132 (9.8%)	**1.73 (1.30, 2.31)**	24.73	111.84
1.3 m/s	152/1014 (15.0%)	72/795 (9.1%)	**1.56 (1.15, 2.10)**	20.08	106.35
1.4 m/s	183/1355 (13.5%)	41/454 (9.0%)	1.40 (0.98, 2.00)	9.37	101.44

*Adjusted for baseline age, BMI, sex, race, education, comorbidities, the presence of depression (< vs. >16), and symptomatic knee OA (yes or no), defined as presence of Kellgren–Lawrence grade ≥ 2 on x-ray in one or both knees, and pain, aching, or stiffness on most days of a month during the previous year. ^higher chi-square values represent greater concordance between the threshold and all-cause mortality.

Walking 0.1 meters/sec slower during the 20-meter walk test was associated with 9% greater risk of KR over 9 years in older adults with or at risk of knee OA. However, these effects were attenuated and did not meet statistical significance in the overall sample and younger adults with or at risk of knee OA. (Table 4.6).

Table 4.6: Association of walking speed and risk of KR over 9 years in adults with knee OA

	Overall	Younger adults	Older adults
Unadjusted HR (95%CI) (0.1 m/sec slower)	**1.14 (1.09, 1.19)**	1.11 (1.04, 1.18)	**1.12 (1.05, 1.20)**
*Adjusted HR (95%CI) (0.1 m/sec slower)	1.03 (0.98, 1.09)	1.00 (0.94, 1.07)	**1.09 (1.01, 1.18)**

*Adjusted for sex, race, education, baseline age, BMI, comorbidities, the presence of depression and SxOA

Walking slower than 1.4 m/sec was found to be an optimal threshold to discriminate older adults only who are at higher risk for KR. (Table 4.7). We did not investigate the thresholds of the walking speed for discriminating people who are at KR risk since we did not find an association between walking speed and KR in the overall sample and younger adults with or at risk of knee OA.

Table 4.7: Maximal Likelihood Ratio Chi-square Approach^ to identify the optimal threshold of walking speed that predicted the risk of KR in older adults with knee OA (N=1809)

Threshold	# deaths/total people		Adjusted HR	Maximal Likelihood Chi-Square value obtained from Cox model	
	Walk slower	Walk faster		unadjusted	*adjusted
0.8 m/s	2/27 (7.4%)	210/1782 (11.8)	0.61 (0.15, 2.55)	0.15	122.77
0.9 m/s	5/57 (8.8%)	207/1752 (11.8%)	0.65 (0.25, 1.73)	0.06	121.18
1.0 m/s	24/170 (14.1%)	188/1639 (11.5%)	1.19 (0.75, 1.89)	2.68	122.72
1.1 m/s	44/352 (12.5%)	168/1457 (11.5%)	1.00 (0.70, 1.43)	1.45	121.3
1.2 m/s	85/677 (12.6%)	127/1132 (11.2%)	1.08 (0.81, 1.45)	2.18	122.11
1.3 m/s	135/1014 (13.3%)	77/795 (9.7%)	1.34 (1.00, 1.79)	7.58	125.44
1.4 m/s	177/1355 (13.1%)	35/454 (7.7%)	1.66 (1.14, 2.42)	10.8	128.09

*Adjusted for baseline age, BMI, sex, race, education, comorbidities, the presence of depression (< vs. >16), and symptomatic knee OA (yes or no), defined as presence of Kellgren–Lawrence grade ≥ 2 on x-ray in one or both knees, and pain, aching, or stiffness on most days of a month during the previous year. ^higher chi-square values represent greater concordance between the threshold and all-cause mortality.

4.3.2 Repeated chair stands time

Of 4796 participants recruited for the study, 4,486 participants have completed five times sit to stand test at the baseline visit. Table 4.1b displays characteristics of the participants who were included in the analytical sample. The average age was 60.96±9.16 years (mean ± sd), BMI 28.58±4.84 kg/m^2, over half were women (59.72%), the majority (79.78%) were white, and 59.72% were at least a college

graduate. Over 6.29% and 8.72% of the analytic sample died or had KR over 9 years, respectively. (Table 4.8).

Table 4.8: Characteristics of study participants who completed five times sit to stand test at baseline (N=4486)

Characteristics	Overall Sample Mean±sd or % (n)	Younger adults Mean±sd or % (n)	Older adults Mean±sd or % (n)
Total sample	4486	2825	1661
Age, years	60.96±9.16	55.02±5.35	71.04±4.02
Women	58.09(2606)	42.09(1189)	41.6(691)
Race, white	79.78(3579)	76.71(2167)	85.01(1412)
Education, at least college graduate	59.72(2679)	45.56(200)	69.92(372)
BMI (kg/m2)	28.58±4.84	28.88±5.11	28.08±4.29
Knee pain severity in past 30 days, rated on scale of 0-10			
Right	2.59±2.69	2.73±2.71	2.37±2.64
Left	2.58±2.77	2.76±2.79	2.29±2.71
Index knee	3.49±2.84	3.65±2.83	3.22±2.84
Comorbidities	0.31±0.74	0.31±0.74	0.5±0.92
Depression	9.61(431)	11.65(329)	6.14(102)
ROA	53.03(2379)	47.72(1348)	62.07(1031)
SxOA	28.15(1263)	27.79(785)	28.78(478)
five times sit to stand test (m/sec)	11.46±3.81	11.05±3.79	12.17±3.74
Number of deaths	6.53(312)	2.8(79)	12.22(203)
Number of KR	9.15(437)	7.19(203)	11.32(188)
Time to deaths	121.09±39.96	92.54±27.25	118.19±40.69
Time to KR	89.93±28.73	71.04±4.02	86.91±29.85

Each additional 1 sec needed to complete five times sit to stand test was not associated with risk of either all-cause mortality or KR over 9 years. We found similar

non-significant results when we stratified the analysis based on younger and older adults with or at risk of knee OA. (Table 4.9 and 4.10).

Table 4.9: Association of repeated chair stands time and risk of all-cause mortality over 9 years in adults with knee OA

	Overall	Younger adults	Older adults
Unadjusted HR (95%CI) (1 sec longer)	**1.07 (1.04, 1.09)**	**1.06 (1.00, 1.11)**	**1.04 (1.00, 1.07)**
*Adjusted HR (95%CI) (1 sec longer)	1.02 (0.98, 1.05)	1.03 (0.97, 1.10)	1.01 (0.97, 1.05)
*Adjusted for sex, race, education, baseline age, BMI, comorbidities, the presence of depression and SxOA			

Table 4.10: Association of repeated chair stands time and risk of KR over 9 years in adults with knee OA

	Overall	Younger adults	Older adults
Unadjusted HR (95%CI) (1 sec longer)	1.01 (1.00, 1.01)	1.01 (1.02, 1.01)	1.01 (1.00, 1.01)
*Adjusted HR (95%CI) (1 sec longer)	1.00 (0.99, 1.00)	0.98 (0.95, 1.02)	1.00 (1.00, 1.01)
*Adjusted for sex, race, education, baseline age, BMI, comorbidities, the presence of depression and SxOA			

We did not investigate the thresholds of the repeated chair stands time for discriminating people who are at risk of either all-cause mortality or KR since we did not find an association between the performance on five times sit to stand test and OA-

related health outcomes (all-cause mortality and KR) in the overall sample, older and younger adults with or at risk of knee OA.

4.4 Discussion

We found walking speed was associated with risk of all-cause mortality over 9 years, after adjusting for potential confounders in adults with or at risk of knee OA. Walking slower than 1.2 m/s on a 20-m walk test was found to be optimal threshold given it yielded higher chi-square values and walking slower than these thresholds significantly increased the risk of all-cause mortality in overall, older as well as younger adults with knee OA. Walking speed was associated with risk of KR over 9 years in older adults with or at risk of knee OA only. However, these findings were not consistent in younger adults with or risk of knee OA. Walking slower than 1.4 m/sec increased the risk of KR over 9 years by 66% in older adults with knee OA. Lastly, repeated chair stands time was not associated with all-cause mortality and KR in adults with or at risk of knee OA.

We found slow walking speed was strongly associated with all-cause mortality in adults with knee OA. This finding is consistent with previous research that shows walking speed was a strong predictor for all-cause mortality in community-dwelling older adults (15, 51). Specifically, it is a strong predictor for adverse health outcomes, i.e., mortality and prolonged hospitalization in older adults (15, 51, 82, 99) and poor response to rehabilitation in adults after stroke (82, 110).

Plausible mechanism why slow walking speed is such as strong predictor in knee OA is that it reflects impairments in several body systems (84), i.e., vision, lower extremity strength (85, 86), aerobic capacity (87), postural control (86), and restrict daily walking (52). Due to the strong predictive validity of walking speed with

adverse health outcomes, it is considered as a functional vital sign (99) in older adults. This, concept can be translated in knee OA population too given walking speed is a strong predictor for all-cause mortality.

Walking speed can be used as a marker to quantify walking difficulty. Our study findings are consistent with previous findings, where people with knee OA who report walking difficulty via self-report measure have a higher risk for all-cause mortality compared to those who do not report walking difficulty (9-11). Hawker and co-authors have shown that people with at least moderately severe symptomatic hip and/or knee OA who report walking difficulty i.e., use walking aid were 51% [adjusted HR 1.51, 95% CI (1.34, 1.70)] more likely to die over 13 years compared to those who do not report walking difficulty. We found that walking speed predicted the risk for all-cause mortality in younger as well as older adults with knee OA. Therefore, walking speed is a robust predictor for all-cause mortality since association exists even in a sample where few people died, e.g., younger adults in the OAI.

Walking speed is a robust predictor for all-cause mortality given the association was consistent in older and younger adults with knee OA. The threshold of the walking speed required in younger and older adults to predict all-cause mortality was similar. Specifically, walking slower than 1.2 m/sec may identify younger as well as older adults with knee OA with functional limitation severe enough to warrant for rehabilitation since walking slower than this threshold increases the risk for all-cause mortality. These thresholds are consistent with previous literature in well-functioning older adults and knee OA. Walking slower than 1.0 m/sec increases the risk for all-cause mortality in well-functioning older adults (15) while walking at least 1.22 m/sec is the minimum speed needed to cross streets using timed signals (51). Walking slower

than 1.22 m/s is predictive of inadequate physical function necessary to be physically active (52) in knee OA.

We found walking speed was not associated with risk of KR in the overall sample and in younger adults with knee OA. There are various possible explanations for these non-significant findings. First, the expectations for electing KR differs in older and younger adults. Younger adults elect for KR to better perform activities on a demanding level (120) as opposed to older adults with knee OA. A second possible explanation for walking speed not able to predict the risk of KR in the overall sample as well as in younger adults is that association may be confounded by other factors such as age, depression, comorbidities or knee OA severity. Our study attempted to account for these potential confounders, which could explain the mechanism underlying the association between walking speed and KR. Our adjusted model indicates that the predictive value of walking speed time and KR was explained by the presence of SxOA at baseline in the overall sample as well as in younger adults with knee OA.

Repeated chair stands time was not associated with all-cause mortality and KR in adults with or at risk of knee OA. These findings were consistent with previous studies where they found five times sit to stand test independently could not predict the risk of all-cause mortality in community-dwelling older French women (121) and the risk of hospitalization in acute care unit within the first year of follow-up in well-functioning older adults (103). One possible explanation for our study finding is that the association between repeated chair stands time and OA-related health outcomes, i.e., all-cause mortality and KR may be confounded by other factors such as age, depression, comorbidities or knee OA severity. Our study attempted to account for

these potential confounders, which could explain the mechanism underlying the association between repeated chair stands time and OA-related health outcomes. Our adjusted model indicates that the predictive value of repeated chair stands time and all-cause mortality was explained by baseline comorbidities, while the predictive value of repeated chair stands time and KR was explained by the presence of SxOA at baseline. Another possible explanation for not finding an association between repeated chair stands time and KR is that our study follow-up of 9 years only, which may be truncated for the overall sample and younger adults with knee OA given the average amount of time people with knee OA spend in nonsurgical regimens is 13 years before electing KR (114).

4.4.1 Strengths and Limitations

The major strength of our study is that we used a large dataset and 9-year follow-up, so they provide a means to effectively describe the people with different performance on performance-based measures including walking speed, and repeated chair stands time. However, our study had some limitations. First, we caution generalizing the results of our study to all individuals, since the majority of our sample was white and overweight. Second, we did not account for intercurrent events such as hospitalization, knee replacement, which occurred during the follow-up when we investigated the association of walking speed with all-cause mortality. We believe understanding how such events alter the association of walking speed with all-cause mortality is important and needed to study in future research. Lastly, walking speed was measured using a 20-m walk test. Therefore, there should be caution while generalizing the study findings to walking speeds taken over shorter or longer distances. However, this limitation is not fatal because 5 to 10 meters dedicated

straight path for valid walking speed assessment (111) and in our study we had a 20-m path, so the measurement of walking speed was valid.

4.4.2 Clinical Implication

Given our study findings, we recommend, health care professionals should assess walking speed in routine clinical practice. Walking speed appears to be a simple, reliable, and valid screening tool to predict all-cause mortality in younger as well as older adults with knee OA. Assessing walking speed alone may aid in clinical decision-making by telling clinicians, which patients with knee OA may need rehabilitation to address functional limitation. Specifically, walking slower than 1.2 m/sec on a 20-m walk test may serve as a threshold to refer to rehabilitation for older as well as younger patients with or at risk of knee OA. These thresholds are similar to previous study reporting minimum levels of physical function needed for being physically active (defined as walking at least 6000 steps/day) (52).

4.5 Conclusion

Slow walking speed and not limited repeated chair stands time may signify a higher risk of all-cause mortality over 9 years in adults with or at risk of knee OA, and a higher risk of TKR in older adults aged >65 years. Therefore, walking speed can be considered as a robust predictor for all-cause mortality in knee OA. Health professionals may consider referring patients with or at high risk of knee OA who walk slower than 1.2 m/sec on a 20-m walk test for further examination targeting potential modifiable factors for health and survival. In addition, clinicians may consider slow walking as a means to identify older adults at high risk of KR, and who may benefit from rehabilitation to address functional limitations that may precipitate

the need for KR. Thus, health care professionals may use walking speed to assess the patient's expected health and tailor goal of care accordingly.

Chapter 5

IDENTIFYING SUBGROUPS WITH DIFFERENTIAL IMPROVEMENT IN PHYSICAL ACTIVITY FOLLOWING PHYSICAL THERAPIST-LED PHYSICAL ACTIVITY INTERVENTION IN ADULTS AFTER TOTAL KNEE REPLACEMENT: AN EXPLORATORY STUDY

5.1 Introduction

Worldwide over 250 million adults have knee osteoarthritis (OA) (2), which is a leading cause of pain and functional limitation (4). More than 60% of people with knee OA are physically inactive (25). Though total knee replacement (TKR) is a definitive treatment for knee OA and is known to decrease pain and functional limitation, physical activity either remains same or decreased compared to the pre-operative level (54-56). Being physically inactive increases the risk of adverse health outcomes such as cardiovascular disease, diabetes, cancer, and all-cause mortality (26-29, 60, 122).

Improving physical activity in people after TKR was a primary goal of the "physical therapist (PT)-led physical activity intervention randomized control trial" study at the University of Delaware Physical Therapy Clinic (UDPT) (123). The preliminary findings of this study were that people who received PT-led physical activity intervention, on average, walked 1798 more steps per day as well as spent 73.4 minutes more time per week in moderate-to-vigorous physical activity (MVPA) compared to the control group (124). However, quantifying clinical improvements in physical activity on a group level may not translate to clinical application (125) because these improvements following an intervention may not be uniformly positive.

This non-uniformity in the response means not all the people who received PT-led physical activity intervention showed improvements in their physical activity level at discharge at the same level compared to the average improvement. At present, it is unclear why some people may not achieve improvement in physical activity in a similar fashion as compared to average improvements in the group.

One factor that may explain the variability in the improvements in physical activity following the intervention is the variability in the participant's baseline characteristics. These characteristics in a clinical trial differ considerably regardless of how strict the inclusion/exclusion criteria are set. The variability may exist in the baseline characteristics such as age, body mass index (BMI), sex, education, and performance on physical function tests, which in turn may influence the effectiveness of the intervention and may jeopardize the generalizability of the findings. One way to overcome this limitation is to identify the subgroup (125) of the participants for whom the intervention is more effective compared to those who are in the control group (don't receive the intervention). The subgroups may identify specific characteristics of the patients for whom the probability of treatment, i.e., a physical activity intervention success is low at the time of assessment. This investigation of the subgroups was important because it may lay a foundation for optimizing individually tailored rehabilitation programs. Future studies may test the hypothesis whether targeting individuals with the same characteristics as identified in this study may respond better to treatment compared to those who do not meet the subgroup characteristics.

There are various ways of identifying subgroups. Subgroups may be identified using a biological rationale without pre-defined statistical method (126) or mining the data post-hoc in an undefined or uncontrolled fashion. However, these approaches

may be subjected to individual bias, either lack a statistical approach or may lead to false positives (127). There is a need to identify a subgroup using a pre-defined statistical approach, which is reproducible as well as has clinical implication. Several statistical approaches have been developed within the machine learning communities to identify the subgroup of patients with an enhanced intervention effect if it truly exists. In this dissertation, we used an approach developed by Foster and colleagues, i.e., Virtual Twins, to identify the subgroups (128). In this approach, subgroup identification was based on predicting the response probabilities for intervention and control twins for each subject (128). We used this approach because we know based on our preliminary findings that PT-led physical activity intervention is more effective to increase physical activity than the control, i.e., standard physical therapy (124).

This study was exploratory in nature since the subgroups of people who may achieve meaningful improvements in physical activity following the intervention were identified using regression-tree based method without defining any hypotheses for subgroups. Therefore, the purpose of this study was to explore the subgroup of the patients after TKR who experience greater benefit from a PT-led physical activity intervention compared to the control group. We also investigated the association of this subgroup with the likelihood of achieving improvements in physical activity in people who only received a PT-led physical activity intervention.

5.2 Method

5.2.1 Study participants

We used the data from the ongoing single-blinded randomized control clinical trial. People receiving physical therapy for a unilateral TKR at the UDPT clinic were

recruited in the trial. Specifically, patients who were over 45 years of age and, had an interest in increasing physical activity were included in the trial. Participants were excluded from the trial if they had any additional comorbidities that would prevent them from participating in a physical activity intervention, e.g., unstable angina. They were excluded from the study if they had another lower extremity surgery in the previous 6 months and/or had another lower extremity surgery planned for 6 months after enrolling in the study.

The participants were randomized to either the physical activity intervention group or a control group.

A PT-led physical activity intervention group (123) received the following (see figure 5.1)**:**

- **Standard physical therapy** was provided by a licensed PT using the UD's Rehabilitation Guidelines for Unilateral TKR. The therapy was provided on an individual basis and supervised by a licensed PT. Exercises focus on pain management, restoring range of motion, lower extremity strengthening, and functional activities. Some examples of intervention include sit-to-stand training, stair training, and walking program. The supervising PT also prescribed home exercise once they feel confident that the patient can perform them safely and effectively. Lastly, the participant received a home exercise log, which was discussed with the treating PT on a weekly basis.
- **Activity monitor:** Participants were provided a Fitbit Zip within one week of enrolling in the study. Participants were given written and face-to-face instructions on how to set up, use, and sync the Fitbit Zip to their smartphone, tablet, or home computer using the app or program provided by Fitbit. They

were instructed to wear the Fitbit Zip around their waist at their right anterior-superior iliac crest daily during waking hours and were asked to monitor their steps/day using with the Fitbit Zip. Extra batteries and instructions on how to install the batteries were provided as needed.

1. **Steps/Day Goal Setting:** Treating PT and patient jointly set weekly steps/day goals. For the first three weeks after surgery for TKR (i.e., weeks 0, 1, and 2), patient's were encouraged to continue their normal activities as tolerated. This goal for physical activity was set to prevent exacerbation of pain response and delay from recovery from surgery. After three weeks after surgery for TKR, a 10% to 20% increase in average steps/day was recommended towards a 6,000 steps/day goal. This increase was based on clinical observations made by treating PT at UDPT during treatment. The discharge goal was set to 6,000 steps/day or more since this threshold was found to better discriminate between those who did versus those who did not develop functional limitation two years later people with or at high risk of knee OA (122) and risk of all-cause mortality in older women (129).

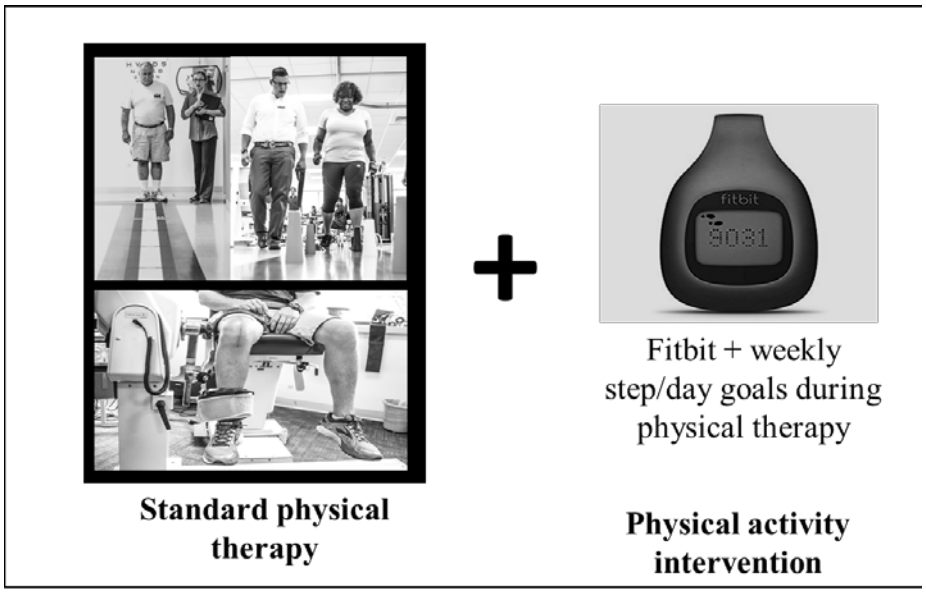


Figure 5.1: Physical therapist-led physical activity intervention

Control group received only standard physical therapy. More details on the study protocol can found in our protocol paper, which is already published(123).

5.2.2 Study outcome

Improvements in physical activity

Physical activity was quantified as steps/day measured using a triaxial accelerometer (Actigraph GT3X, Pensacola, FL, USA) at two time-points, i.e., baseline and discharge from the randomized control trial. The Actigraph GT3X is a valid device to quantify physical activity in free-living conditions (73, 74) (See Figure 5.2A-B). Subjects were fitted with the accelerometer above the right hip and were instructed to wear the accelerometer during waking hours for seven consecutive days (Figure 5.2C).

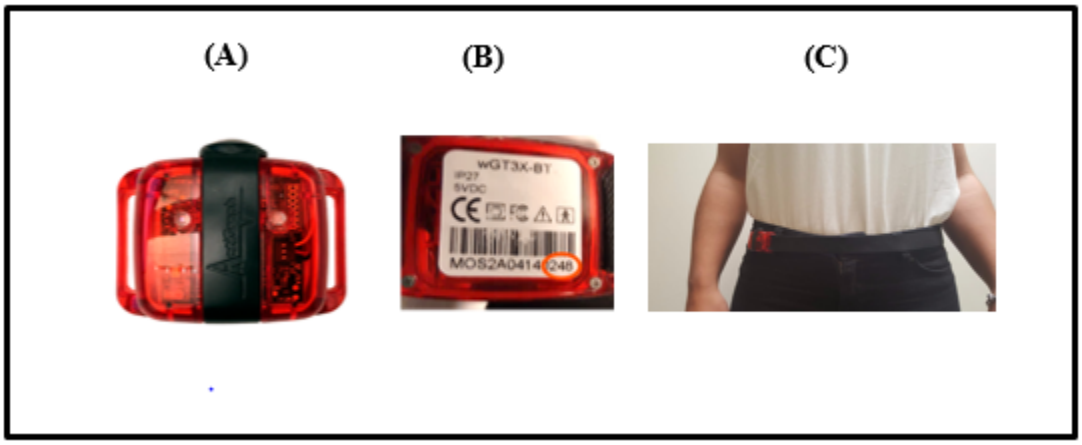


Figure 5.2 A-C: Actigraph GT3X monitor (A and B) and participant wearing the monitor around the waist such that accelerometer sits on the right anterior superior iliac spine (C).

We employed previously published methods to determine valid physical activity records (75). Briefly, we defined a valid wear day as at least 10 hours of wear time and included participants with ≥ 1 valid wear day. Steps/day were averaged across the available valid days. Currently, there are not established values for meaningful clinical difference (MCID) for physical activity (i.e., steps/day). Therefore, we used three approaches to define people who had a meaningful improvement in their steps/day at discharge compared to their baseline steps/day.

Approach 1: Participants who met the discharge goal, i.e., walked at least 6,000 steps/day at discharge were classified as having meaningful improvements in physical activity. If the participants did not meet the 6,000 steps/day threshold at discharge, they were classified as not having meaningful improvements in physical activity.

Approach 2: Participants whose absolute change in steps/day from baseline to discharge (Steps/day at discharge – Steps/day at baseline) is above the average change

(i.e., absolute change ≥2500 steps/day) were classified as a having meaningful improvements in physical activity. Other participants whose absolute change in steps/day were less than the average change in steps/day were classified as not having meaningful improvements in physical activity.

Approach 3: Participants who had at least a 100% increase in the steps/day from baseline to discharge and met 6,000 steps/day at discharge were as having meaningful improvements in physical activity. Other participants were classified as not having meaningful improvements in physical activity.

5.2.3 Study exposures

Following baseline characteristics will be included as exposure to identify the subgroups.

1. Demographic characteristics such as age, BMI (kg/m^2) computed from height and weight assessment, sex (female versus male), race (white versus non-white), education (less than college graduate versus at least college graduate).
2. We used a performance-based physical function test, i.e., Timed Up and Go test (TUG) to evaluate baseline physical functioning (130). TUG measures the time it takes to rise from a chair walk 3-meters and return to sit. The patient was instructed to rise from a chair without the use of the armrests and move as quickly and safely as possible to a mark on the ground designating 3 meters. After crossing the mark, they returned to the chair and sat as quickly as they felt safe and comfortable. The timing started when the researcher or treating PT said “Go” and stopped when the patient’s touched the back of the chair. Two trials were performed and recorded in seconds, and the average of the two trials was reported. Longer time to perform the TUG test was indicative of

worse physical function. TUG has a high test-retest reliability (intraclass correlation coefficients > 0.7) in adults with peripheral arthritis(131) and mild to moderate knee OA(132).

5.2.4 Statistical Analysis

We described the study sample using means and standard deviations for continuous variables and percentages for categorical variables. Participants with any missing baseline characteristics were excluded from the analysis.

We used Virtual Twins (VT; aVirtualTwins R package), a regression tree-based method that searches for cutpoints of exposure variables where the differential treatment effect exceeds a pre-specified threshold. In VT, we used quantile distribution i.e., 50^{th}, 60^{th}, 70^{th} and 80^{th} percentile, recommended by the VT package to set the thresholds for the difference in the rate of improvement between PT-led physical activity intervention and control groups for subgroup identification, maximum depth of trees to 3. We also ran second VT where we modified the threshold to 10% difference in the rate of improvement between PT-led physical activity intervention and control groups for subgroup identification, keeping the maximum depth of trees to 3. We used to VT method to identify the rate of improvement in physical activity defined by approach 1 only since walking 6000 steps/day at discharge is clinically meaningful given previous studies have shown that walking at least 6000 steps/day reduce the risk of functional limitation over 2 years in knee OA (122) and risk of all-cause mortality in older women (129). We used the following baseline characteristics for potential subgroup identification: age, sex, BMI, performance on TUG, baseline steps/day, race, and education status. We used these factors based on their association with physical activity (42, 80, 81). We ran VT using

different thresholds of improvement rate to investigate the stability of the study findings. Specifically, we only selected the baseline variables that were consistently identified using VT methods across different thresholds to define the rate of improvement between PT-led physical activity intervention and control groups.

Once the thresholds for exposure variables were identified, we tested the association of identified exposures with the odds of achieving meaningful improvements in physical activity using logistic regression by calculating the odds ratio and 95% confidence interval in participants who received a PT-led physical activity intervention only. This analysis was conducted to test the association of thresholds of the predictors identified using VT methods to improvement in physical activity, given the exploratory nature of regression tree-based methods. Next, we tested this association between the thresholds identified using VT methods and achieving the improvement in physical activity using separate logistic regression model for the other two approaches used to define improvements in physical activity. This investigation was carried out to evaluate the stability of the findings since there is no well-established MCID value for physical activity, i.e., steps/day.

5.3 Results

Table 5.1 shows the characteristics of the participant who received PT-led physical activity intervention and who were in the control group.

Table 5.1: Characteristics of the participants who were in the control group (N=31) and who received PT-led physical activity intervention (N=36).

	Control	Intervention
N	31	36
	mean±SD or %(n)	
Age	67.5±6.1	68±7.2
BMI	31.7±6	31.3±6.2
days since TKR	15±31	13.5±27.9
TUG baseline	15.4±7.1	14.9±6.3
Sex (Females)	52(16)	42(15)
Race (white)	94(29)	98(35)
Education (at least college grad)	52(16)	56(20)
Steps/day		
baseline	2715±1306	2460±1355
discharge	4912±1817	5387±3090
Received PA intervention	100(31)	0(0)

36 participants received a PT-led physical activity intervention with the average age was 68.7 ± 7.2 years (mean ± sd), BMI 31.3±6.2 kg/m^2, 15 were women (42%), and the majority were white (98%) and had graduated from college (56%). 31 participants were in control group with the average age was 67.5±6.1 years (mean ± sd), BMI 31.7±60 kg/m^2, 16 were women (57%), and the majority were white (94%) and had graduated from college (52%).

Table 5.2 shows how many people achieved improvements in physical activity defined using 3 different approaches.

Table 5.2: Participant characteristics stratified by those who achieved (Yes) versus those who did not achieve (No) improvements in physical activity defined using 3 different approaches.

	Approach 1*		Approach 2**		Approach 3***	
	Yes	No	Yes	No	Yes	No
N	23(34.33)	44(65.67)	30(44.78)	37(55.22)	14(20.9)	53(79.1)
Age	65.2±7.2	69.1±6.1	67±7.2	68.4±6.3	65.5±8.6	68.4±6.1
BMI	30.6±6.5	31.9±5.8	30.8±6.2	32±6	30.9±6.4	31.6±6
days since TKR	16.3±33.8	13±27	9.6±6.6	18±39	7.4±4.8	16±33
TUG baseline	13.8±6.8	15.8±6.6	13.9±6	16.2±7.1	16.1±7.9	14.9±6.4
Sex (Females)	31(7)	55(24)	34(10)	57(21)	29(4)	51(27)
Race (white)	100(23)	94(41)	97(29)	95(35)	100(14)	95(50)
At least college graduate	44(10)	60(26)	44(13)	63(23)	43(6)	57(30)
Steps/day						
baseline	3216±1438	2245±1149	2717±1382	2465±1291	2421±1191	2619±1370
discharge	8007±1945	3682±1287	7191±2267	3525±1346	8367±2323	4321±1889
Received PA intervention	57(13)	53(23)	60(18)	49(18)	72(10)	50(26)

*Approach 1 states that participants achieved meaningful improvement in physical activity if they walked at least 6000 steps/day at discharge from the physical therapy.
**Approach 2 states that participants achieved meaningful improvement in physical activity if an absolute change in steps/day (steps/day at discharge – steps/day at baseline) is above the average change in steps/day.
***Approach 3 states that participants achieved meaningful improvement in physical activity if the percentage change in steps/day is more than 100% and if they walked at least 6000 steps/day at discharge from the physical therapy.

Of the total 67 participants with complete data, 23 (24%), 30 (45%) and 14 (21%) participants had improvements in a physical activity described using approaches 1, 2, and 3 respectively.

Table 5.3 shows subgroups who walked at least 6000 steps/day at discharge were identified using the VT method when the quantile distribution was used to set the threshold for the difference in the rate of improvement between PT-led physical activity intervention and control groups.

Table 5.3: Subgroups identified using VT method when quantile distribution i.e., 50th, 60th, 70th and 80th percentile was used to set the thresholds for the difference in the rate of improvement between PT-led physical activity intervention and control groups

	Subgroup	Sub-group size	Treat-ement event rate	Control event rate	Treat-ment sample size	Control sample size	*RR (95% CI)
Tree1	BMI $\geq$ 28.8 & Age < 73 & Age $\geq$ 63.5	20	0.33	0.25	12	8	1.33 (0.31, 5.64)
Tree2	**BMI < 28.5 & TUG < 13.5**	**18**	**0.63**	**0.40**	**8**	**10**	**1.56 (0.62, 3.96)**
Tree3	BMI $\geq$ 28.5 & Age < 73 & Age $\geq$ 66.5	15	0.30	0.20	10	5	1.50 (0.20, 11.00)
Tree4	**BMI < 28.5 & TUG < 13.5**	**17**	**0.63**	**0.44**	**8**	**9**	**1.41 (0.57, 3.49)**
Tree5	BMI < 28.5 & TUG < 12.7	16	0.57	0.44	7	9	1.29 (0.46, 3.40)
Tree6	BMI < 28.5 & Age < 68.5	0	0.80	0.40		5	2.00 (0.63, 6.38)
*Risk ratio (95 % Confidence Interval)							

In each of the trees, at least 43% of people receive a PT-led physical activity intervention. Baseline age, BMI, and performance on TUG were found to important predictors in identifying a subgroup of the people who walked at least 6,000 steps/day at discharge.

Table 5.4 shows subgroups who walked at least 6000 steps/day at discharge were identified using the VT method when 10% threshold was used to set a threshold for the difference in the rate of improvement between PT-led physical activity intervention and control groups. In each of the trees, at least 47% of people receive a PT-led physical activity intervention. Baseline age, BMI, and performance on TUG were found to important predictors in identifying a subgroup of the people who walked at least 6,000 steps/day at discharge.

Table 5.4: Subgroups identified using VT method when the threshold was set to 10% difference in the rate of improvement between PT-led physical activity intervention and control group

	Subgroup	Sub-group size	Treatment event rate	Control event rate	Treatment sample size	Control sample size	*RR (95% CI)
Tree1	BMI ≥ 28.5 & Age < 73 & Age ≥ 65.5	17	0.30	0.14	10	7	2.10 (0.27, 16.22)
Tree2	**BMI < 28.5 & TUG < 13.5**	**17**	**0.63**	**0.44**	**8**	**9**	**1.41 (0.57, 3.49)**
*Risk ratio (95 % Confidence Interval)							

However, the thresholds for baseline BMI and performance on TUG were consistently identified across 2 VT methods that used a different threshold for the rate of improvement between PT-led physical activity intervention and control groups. Specifically following thresholds for each predictor variables were found - BMI less than 28.5 kg/m^2 and completing TUG within 13.5 seconds (Table 5.3 and 5.4).

Given exploratory nature of the analysis, we further investigated the association of meeting each of the threshold identified by VT method to the likelihood of achieving improvements in physical activity defined using 3 approaches in the logistic regression in adults who received PT-led physical activity intervention only. Specifically, we tested the following criteria formulated based on predictors and threshold identified by the VT method:

(i) BMI and TUG criteria – People met the criteria if their BMI was less than 28.5 kg/m2 and completed the TUG within 13.5 seconds at baseline.

(ii) BMI only criteria – People met this criterion if their BMI was less than 28.5 kg/m^2 at baseline

(iii)TUG only criteria – People met this criterion if they completed the TUG within 13.5 seconds at baseline.

We found of all the people post-TKR who received PT-led physical activity intervention, 10, 12, and 18 people met BMI and TUG, BMI only and TUG only criteria, respectively.

Table 5.5: Association of predictor variables identified using a VT method to the odds of achieving the improvements in physical activity defined using 3 different approaches in people after TKR who received PT-led physical activity intervention only (N=36).

	Met Approach 1* (N=13)		Met Approach 2** (N=18)		Met Approach 3*** (N=10)	
Criteria	% (n˅)	OR [95% CI]	% (n˅)	OR [95% CI]	% (n˅)	OR [95% CI]
BMI and TUG^						
Met the criteria (N=10)	40 (4)	1.25 [0.28, 5.65]	70 (7)	3.18 [0.67, 15.15]	40 (4)	2.22 [0.47, 10.57]
Did not meet the criteria (N=26)	35 (9)	1.00 [Reference]	42 (11)	1.00 [Reference]	23 (6)	1.00 [Reference]
BMI only^^						
Met the criteria (N=12)	58 (7)	4.22 [0.96, 18.32]	58 (7)	1.66 [0.41, 6.71]	33 (4)	1.50 [0.33, 6.82]
Did not meet the criteria (N=24)	25 (6)	1.00 [Reference]	45 (11)	1.00 [Reference]	25 (6)	1.00 [Reference]
TUG only^^^						
Met the criteria (N=18)	50 (9)	3.50 [0.55, 14.85]	61 (11)	2.47 [0.65, 9.43]	33 (6)	1.75 [0.40, 7.70]
Did not meet the criteria (N=18)	22 (4)	1.00 [Reference]	39 (7)	1.00 [Reference]	22 (4)	1.00 [Reference]

˅number of participants with meaningful improvement in physical activity
Approach 1 states that participants achieved meaningful improvement in physical activity if they walked at least 6000 steps/day at discharge from physical therapy.
**Approach 2 states that participants achieved meaningful improvement in physical activity if an absolute change in steps/day (steps/day at discharge – steps/day at baseline) is above the average change in steps/day.
***Approach 3 states that participants achieved meaningful improvement in physical activity if the percentage change in steps/day is more than 100% and if they walked at least 6000 steps/day at discharge from the physical therapy.

^participants had BMI less than 28.5 kg/m2 and completed TUG within 13.5 seconds.
^^participants had BMI less than 28.5 kg/m2.
^^^participants had BMI completed TUG within 13.5 seconds.

People who met BMI and TUG criteria had 25% [OR: 1.25, 95%CI (0.28, 5.65)], 218% [OR: 3.18, 95%CI (0.67, 15.15)], 122% [OR: 2.22, 95%CI (0.47, 10.57)] higher odds of achieving improvements in physical activity defined using approaches 1, 2 and 3, respectively. None of the effects met statistical significance given the small sample size. We found similar higher odds of achieving improvements in physical activity when we used BMI only and TUG only criteria (Table 5.5). However, none of these effects reached statistical significance.

5.4 Discussion

In this exploratory analysis, we applied a regression tree-based method to identify a subgroup of patients post-TKR who have improvements in physical activity following a randomized control clinical trial. We found of all the people post TKR who received a PT-led physical activity intervention, those who had BMI less than 28.5 kg/m^2 and completed TUG within 13.5 seconds at baseline were more likely to achieve improvement in physical activity defined using different approaches, i.e., they responded best to PT-led physical activity intervention. However, our results did not meet statistical significance given the small sample size and exploratory nature of the analysis.

This exploratory study suggests people who have BMI less than 28.5 kg/m^2 and who complete TUG within 13.5 seconds at baseline may have a higher likelihood to benefit from a PT-led physical activity intervention following a TKR. This finding suggests that if people post-surgery have poor physical functioning at baseline, i.e.,

take more time to complete TUG may need intervention targeting their physical functioning to increase their physical ability to engage in physical activity. Further people who have higher BMI, treatment for weight reduction may also be needed in addition to improving the physical activity. Our study challenges the notion "one-size-fits-all" approach in rehabilitation care for people post-TKR. Understanding the effects of heterogeneity in patient characteristics post-TKR is important and may influence an individual's ability to respond to a particular intervention.

To the best of our knowledge, this is the first time that regression-tree based methods have been used to identify patient profile who may best respond to PT-led physical activity intervention. We found BMI and physical function, may be used to develop a patient profile. Previous studies have reported that higher BMI and worse physical function may be associated with poor health outcomes in TKR population. Specifically, people with higher BMI have a higher surgical-related complication (e.g., hematoma, neuromas) rate (133), lower prosthetic survival (134), lower activity scores measured using self-report questionnaires (133). People pre-TKR who have marked difficulty with physical have the worst outcomes post-operatively (135).

This study can be considered as preliminary evidence for tailoring the rehabilitation to achieve meaningful improvement in physical activity for patients post TKR. People post-TKR who have lower BMI (less than 28.5 kg/m^2) and good physical functioning (completes TUG within 13.5 seconds) may be an ideal candidate for receiving physical activity intervention. On the other hand. If a person has BMI over 28.5 kg/m^2, then along with standard physical therapy and physical activity intervention, weight management may be needed for patients to improve their physical activity. Also, if the patient had a poor physical function, i.e., takes more than 13.5

seconds to complete TUG, then may there is need for additional rehabilitation to improve their physical ability before implementing physical activity intervention.

Our study has several limitations. First, we do not have control over the qualitative treatment-subgroup interaction, i.e., for one subgroup PT-led physical activity intervention is better than control, and for another subgroup is vice versa. Such kind of qualitative interaction may have an impact on clinical practice since some subgroups of patients should be treated differently than others. Recently, a new tree-based method, called Qualitative INteraction Trees, was developed, which accounts for qualitative interaction (136). However, we did not use this method since it was out of the scope of this study. Future studies should test this method and investigate if the results are consistent. Second, we did not have a standardized definition for categorizing people who achieve improvements in physical activity following the intervention. However, this limitation is not fatal since we used 3 different approaches to define the improvement and investigated the stability of the study findings. Third, there should be caution when generalizing the study findings given the exploratory nature of the analysis, as well as the majority of the study sample, was White. Lastly, there is a possibility that psychosocial factors may play a role in identifying the subgroups who may respond best to PT-led physical activity intervention. Hence, the subgroups identified in this study should be viewed as estimates that have some variability.

5.5 Conclusion

Multidimensional subgroups defined by baseline demographics and physical functioning predicted improvements in physical activity among patients post-TKR. These exploratory analyses suggest that a “profile” of patients who may respond best

to PT-led physical activity intervention may have BMI less than 28.5 kg/m^2 and/or completes TUG within 13.5 seconds at baseline. These results are exploratory, but this study may be considered as the first step towards identifying subgroups. It suggests that there may be subgroups of patients post-TKR who experience greater benefit from PT-led physical activity intervention. Further research in this area may help to guide targeted dissemination of PT-led physical activity intervention.

Chapter 6

SUMMARY

To date, knee OA has no cure, and management strategies focus on managing symptoms. Knee OA is a leading cause of functional limitation such as difficulty walking and getting up from a chair (3-6), which can be addressed by rehabilitation (19-21). However, less than 14% of people with knee OA receive rehabilitation (22, 23). One reason for low referrals may be the inability to identify those that are in need. Performance-based measures of physical function that identify functional limitation are a potential means to select such individuals. However, clinical assessment of performance-based measures is not part of the routine practice for knee OA (22, 23). We propose that referral to rehabilitation can better be guided with the identification of specific thresholds that hold clinical meaning on performance-based measures. The purpose of this study was to investigate the predictive value of selected clinically feasible performance-based measures with future health outcomes that are relevant for knee OA to establish so-called 'functional vital signs' for this patient population.

My long-term goal is to identify individuals with knee OA who may benefit the most from rehabilitation. The overall objective of this dissertation was to investigate if functional vital signs predict OA-related health outcomes and response to rehabilitation in adults with knee OA. In this proposal, I focused on interventions to increase physical activity (58, 59), since over half of the adults with knee OA are physically inactive (25) and subsequently face a cascade of health problems due to inactivity (26-28, 60). The response to a PT-led physical activity intervention was not

uniformly positive. My central hypothesis is that walking speed and repeated chair stands can predict OA-related health outcomes and poor response to a PA intervention. I formulated this hypothesis based on the prior work where walking speed (61, 62) and repeated chair stands(16) predicted the risk for poor health outcomes in older adults. I pursued the following aims to test my central hypothesis:

Aim 1: To determine the extent to which walking speed and repeated chair stands will be associated with risk for not participating in physical activity, i.e., walking less than 6,000 steps/day in adults with knee OA. We chose this threshold because White et al. found walking ≥ 6000 steps/day better discriminates between those who did versus those who did not develop functional limitation two years later people with or at high risk of knee OA more so than walking 10,000 steps/day or 3,000 steps/day (63).

- *(H1.1) I hypothesize that walking slowly on a 20-m walk test will be associated with increased risk for not participating in physical activity.*

We found walking 0.1 meters/sec slower during the 20-meter walk test was associated with walking 342 fewer steps/day (95% CI [-276, -408]) in adults with knee OA. Performance on the 20-m walk test corresponding to 80% to 95% specificity to identify those who walked ≥ 6000 steps/day ranged from 1.13 to 1.26 meters/sec. We found similar findings when we restricted the analytical sample to adults with ROA only and SxOA only. Slow walking speed reflects impairments in several body systems (84), including vision, lower extremity strength (85, 86), aerobic capacity(87), postural control and proprioception (86), and can also restrict daily walking (15).

- *(H1.2) I hypothesize that taking more time to complete five times sit to stand test will be associated with increased risk for not participating in physical activity.*

We found each additional 1 sec to complete the five sit to stand test was associated with walking 130 fewer steps/day (95% CI [-178, -83]). Performance on the five times sit to stand test corresponding to 80% to 95% specificity to identify those who walked ≥ 6000 steps/day ranged from 11.4 to 14.0 sec. We found similar findings when we restricted the analytical sample to adults with ROA only and SxOA only. Poor performance, i.e., requiring greater time to complete the test, may reflect the presence of impairments including lower body pain, inadequate lower body muscle strength, poor balance or coordination deficits, which also can limit daily walking.

Aim 2: To determine the association of walking speed and repeated chair stands measured at one time-point and decline over one year with risk for all-cause mortality over 9 years.

- *(H2.1) I hypothesize that all the adults with knee OA who walk slower than 1.22 m/sec on a 20-m walk test will be associated with a higher risk for all-cause mortality regardless of the decline in walking speed over a year compared to those who walk at least 1.22 m/sec.*

Groups with walking speed < 1.22 m/s over a 20-m walk test at one time-point were at higher risk of mortality irrespective of history of decline in walking speed compared with those walking >1.22 m/s without meaningful decline over the previous year. Those walking <1..22 m/s with and without decline had 108% and 96% more

risk of mortality compared with those walking >1.22 m/s without meaningful decline over the previous year.

- *(H2.2) I hypothesize that of all the adults with knee OA who walked at least 1.22 m/sec on a 20-m walk test, those who had a meaningful decline in walking speed over one year will have a higher risk for all-cause mortality compared to those who did not have meaningful decline over a year.*

Our findings did not support this hypothesis. Of all the adults with knee OA who walked at least 1.22 m/s, those with a meaningful decline, in fact, had a lower risk for all-cause mortality compared to those without meaningful decline over the previous year. One plausible explanation of this study findings is that adults who walked at least 1.22 m/s in the present but had a meaningful decline over a previous year, started off walking at a much higher speed. Their current walking speed was well above the threshold predicting of poor health outcomes. These findings suggest that threshold effect at one time-point may be more portend compared to an absolute decline in walking speed for mortality risk in adults with knee OA.

- *(H2.3) I hypothesize that all the adults with knee OA who took >12 sec to complete five times sit to stand test will be associated with a higher risk for all-cause mortality regardless of the decline in repeated chair stands time over a year compared to those who took ≤12 sec to complete five times sit to stand test.*

Our hypothesis was partially supported. Groups with >12 sec to complete five times sit to stand test at one time-point were at higher risk of mortality irrespective of

history of decline compared with those who took ≤12 sec to complete five times sit to stand test without meaningful decline over the previous year. Those taking >12 sec to complete five times sit to stand test at one time-point with and without decline had 32% and 24% more risk of mortality compared with those ≤12 sec to complete five times sit to stand test without meaningful decline over the previous year. However, the effect estimates did not reach statistical significance. However, we could see the trend in the findings.

- *(H2.4) I hypothesize that of all the adults with knee OA who took ≤12 sec to complete five times sit to stand test, those who had a meaningful decline in repeated chair stands time over one year will have a higher risk for all-cause mortality compared to those who did not have meaningful decline over a year.*

Our findings did not support this hypothesis. Of all the adults with knee OA who took ≤12 sec to complete five times sit to stand test, those with a meaningful decline, in fact, had a similar risk for all-cause mortality compared to those without meaningful decline over the previous year.

Aim 3: To determine the optimal threshold for walking speed and repeated chair stands that discriminate those who have risk compared to those who do not have a risk for A) all-cause mortality and B) knee replacement (KR) over 9 years.

- *The threshold will be determined using the maximal likelihood chi-square approach. Specifically, we will run unadjusted and adjusted Cox models for different cut-points of the walking*

speed and then identified the model that will give the maximal chi-square value. This method is known to maximize the concordance, which is a metric used to evaluate the performance of the cut-points when there are censored endpoints. This metric is similar to maximizing the Youden index; criteria employed when using a Receiving Operating Curve (ROC) method.

Walking 0.1 meters/sec slower during the 20-meter walk test was associated with a 16% greater risk of all-cause mortality over 9 years. We found similar results when we stratified the analysis based on younger and older adults with or at risk of knee OA. Walking slower than 1.2 m/sec were found to be optimal cut-points to discriminate people who are at higher risk for all-cause mortality since it yielded maximal chi-square value in unadjusted as well as in adjusted Cox model. We found similar cut-points when we re-ran the analysis for older and younger adults with or at high risk of knee OA.

Walking 0.1 meters/sec slower during the 20-meter walk test was associated with 9% greater risk of KR over 9 years in older adults with or at risk of knee OA. However, these effects were attenuated and did not meet statistical significance in the overall sample and younger adults with or at risk of knee OA. Walking slower than 1.4 m/sec was found to be an optimal cut-point to discriminate older adults only who are at higher risk for KR. We did not investigate the cut-points of the walking speed for discriminating people who are at KR risk since we did not find an association between walking speed and KR in the overall sample and younger adults with or at risk of knee OA.

Each additional 1 sec needed to complete five times sit to stand test was not associated with risk of either all-cause mortality or KR over 9 years. We found similar non-significant results when we stratified the analysis based on younger and older adults with or at risk of knee OA. We did not investigate the cut-points of the repeated chair stands time for discriminating people who are at risk of either all-cause mortality or KR since we did not find an association between the performance on five times sit to stand test and OA-related health outcomes (all-cause mortality and KR) in the overall sample, older and younger adults with or at risk of knee OA.

Exploratory Aim: To investigate the association of physical function measures with the odds of achieving meaningful improvements in physical activity in adults after TKR who received PT-led physical activity intervention.

- *(H4.1) I hypothesize that limited performance on TUG will be associated with not achieving meaningful improvements in physical activity.*

This aim was considered exploratory in nature since the subgroups of people who may respond best to PT-led physical activity intervention were identified using regression-tree based method without defining any hypotheses for subgroups. These exploratory analyses suggest that a "profile" of patients who may respond best to PT-led physical activity intervention may have BMI less than 28.5 kg/m^2 and/or completes TUG within 13.5 seconds at baseline. I investigated the association of performance on TUG with odds of achieving meaningful improvement in physical activity in patients post-TKR who received PT-led physical activity intervention only. Of all the people post TKR who received a PT-led physical activity intervention, those completed TUG within 13.5 seconds (good TUG performance) had higher odds of achieving

meaningful improvement in physical activity compared to those with limited TUG performance (took at least 13.5 seconds). However, our results were not statistically significant, given small sample size and should be viewed conservatively. Future research is needed to test these study findings.

6.1 Limitations and Future Directions

Our work, however, did not support all the hypothesis regarding the predictive value of functional vital signs. Walking speed seem to have higher predictive value for OA-related health outcomes compared to repeated chair stands time. There are several limitations with regard to the sample with prevent generalizing the study findings given the majority of our sample was white and at least college graduates. Second, we did not account for intercurrent events such as hospitalization, knee replacement, which occurred during the follow-up when we investigated the association of walking speed with all-cause mortality. We believe understanding how such events alter the association of functional vital signs with OA-related health outcomes are important and needed to study in future research. Future studies are needed to investigate the predictive value of functional vital signs for OA-related health outcomes in population-based studies because it will validate the predictive value of functional vital signs for OA-related health outcomes and establish their generalizability - an important pre-requisite before recommending the functional vital signs for widespread use for knee OA(137, 138). There is a possibility that study subjects may choose to not participate in physical activity (i.e., walk <6000 steps/day) or may have increased risk for all-cause mortality or KR, irrespective of their physical function ability possibly due to psychosocial barriers, hence the physical function threshold values should be viewed as estimates that have some variability. Future studies are needed to

investigate whether psychosocial factors mediate or moderate the relationship between physical function and OA-related health outcomes.

6.2 Conclusion and Clinical Significance

This dissertation provided direct evidence on the predictive value of functional vital signs for OA-related health outcomes and response to rehabilitation. In chapters 2-5, we investigated the predictive value of functional vital signs for OA-related health outcomes in patients with knee OA and the ability to achieve meaningful improvement following a PA intervention in adults post-TKR. This direct evidence of the predictive value may provide healthcare professional with objective tests to measure functional limitation in adults with knee OA. Further, the thresholds identified for the functional vital signs may indicate when people with knee OA need rehabilitation to address underlying functional limitation such as impaired endurance, to minimize the risk of future poor health and increase the ability to be physically active. The thresholds on the functional vital signs may serve as a clinical target for health professionals. Recommending PA to a patient post TKR without adequate physical functioning to do so will simply set them up for failure. If patients meet these thresholds, then they will be appropriate for a PA intervention. Thus, this dissertation provided empirical support to develop the evidence-based planning of the interventions to improve PA. As an effective intervention will target the factors known to cause physical inactivity.

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Appendix A

IRB APPROVAL LETTER: TO USE PUBLICLY AVAILABLE DATA – OSTEOARTHITITS INITATIVE (OAI)

UNIVERSITY OF DELAWARE
RESEARCH OFFICE
210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	September 26, 2017
TO:	Daniel White, PT, ScD, MSc
FROM:	University of Delaware IRB
STUDY TITLE:	[1125357-1] Physical activity, physical function, demographics and psychological factors in people with or without knee osteoarthritis using large data sets.
SUBMISSION TYPE:	New Project
ACTION:	DETERMINATION OF EXEMPT STATUS
DECISION DATE:	September 26, 2017
REVIEW CATEGORY:	Exemption category # *(4)*

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has determined this project is EXEMPT FROM IRB REVIEW according to federal regulations.

We will put a copy of this correspondence on file in our office. Please remember to notify us if you make any substantial changes to the project.

If you have any questions, please contact Nicole Farnese-McFarlane at (302) 831-1119 or nicolefm@udel.edu. Please include your study title and reference number in all correspondence with this office.

Appendix B

IRB APPROVAL LETTER FOR RANDOMIZED CONTROL CLINICAL TRIAL - PHYSICAL THERAPIST-LED PHYSICAL ACTIVITY INTERVENTION AFTER TKR

UNIVERSITY OF DELAWARE
RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: September 28, 2018

TO: Daniel White, PT, ScD, MSc
FROM: University of Delaware IRB

STUDY TITLE: [946165-26] A novel physical therapy administered physical activity intervention after TKR

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: APPROVED
APPROVAL DATE: September 20, 2018
EFFECTIVE DATE: September 28, 2018

EXPIRATION DATE: September 20, 2019
REVIEW TYPE: Full Committee Review

REVIEW CATEGORY: Full Board Review

Revised consent to contact form for sceening purposes approved. However request for waiver of documentation of informed consent not granted as the request does not meet the requirements as outlined per 45 CFR 46. 117(c).

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

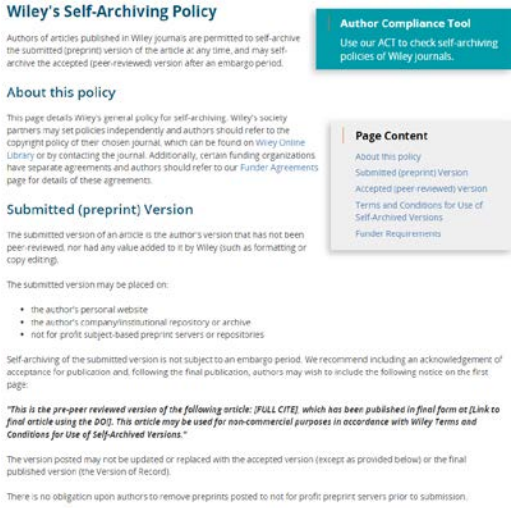
Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Appendix C

PERMISSION TO USE PAPER PUBLISHED IN ARTHITIS CARE & RESEARCH JOURNAL

Chapter 2 is the pre-peer reviewed version of the following article: Master, H., Thoma, L. M., Christiansen, M. B., Polakowski, E., Schmitt, L. A., & White, D. K. (2018). Minimum performance on clinical tests of physical function to predict walking 6,000 steps/day in knee osteoarthritis: an observational study. Arthritis care & research, 70(7), 1005-1011, which has been published in final form **https://doi.org/10.1002/acr.23448**. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.



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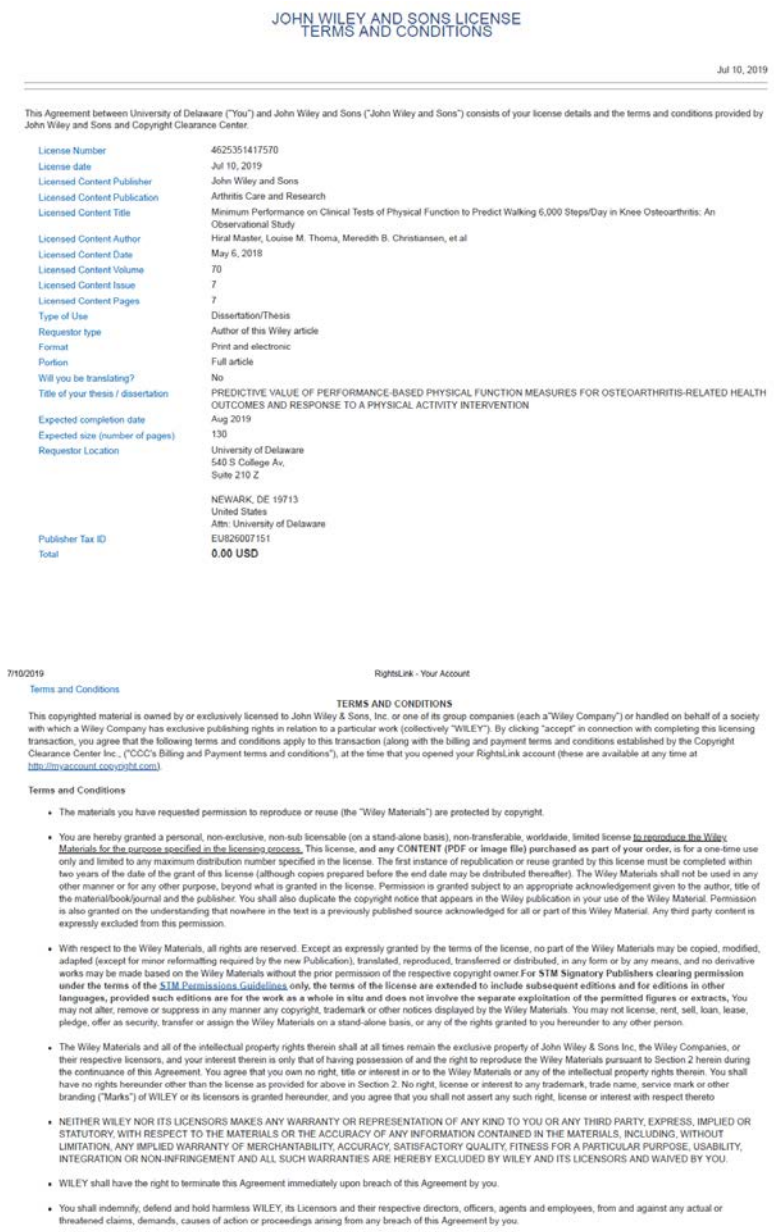

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