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EVALUATION OF FUNCTION IN INDIVIDUALS WITH KNEE OSTEOARTHRITIS

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EVALUATION OF FUNCTION IN INDIVIDUALS WITH KNEE OSTEOARTHRITIS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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Education: the path from cocky ignorance to miserable uncertainty
- Mark Twain (possibly) -

ABSTRACT

Introduction: Osteoarthritis, the most common joint disease, results in joint pain and limited function. In clinical practice, the array of measurements used to evaluate function are generally restricted to patient-reported outcome measures and performance-based tests, as they do not require special equipment. What these measures are unable to answer is *how* a given activity is performed. Thus, there may be additional important aspects of function, including examination of movement patterns, which could provide complementary information in the evaluation of function. This thesis evaluates methods used to objectively assess function – e.g., gait patterns, movement strategies, and performance-based function – in individuals with knee osteoarthritis.

Methods: The studies include 40 individuals with primary knee osteoarthritis scheduled for total knee arthroplasty and a convenience sample of 25 healthy controls matched by age strata to individuals with osteoarthritis. All study participants completed a three-dimensional motion analysis session that rendered measurements of gait patterns and movement patterns used to perform a Sit-to-Stand test. Participants performed three performance-based tests including the Five Times Sit-to-Stand test, the Timed Up and Go test, and the Single Limb Mini Squat test. Participants completed one knee-specific questionnaire and one generic health-related quality of life questionnaire. Perceived pain was evaluated using a visual analogue scale. Individuals with osteoarthritis were evaluated within one month prior to total knee arthroplasty and one year after surgery. Controls were evaluated once.

Results: In **Study I**, the overall gait pattern, as represented by the Gait Deviation Index for kinematics and kinetics, was found to be affected on both the painful osteoarthritis limb and the contralateral limb compared to controls. In **Study II**, one year after surgery, measures of overall gait patterns and performance-based function were found to be improved although not restored to the level of healthy controls. In **Study III**, individuals reporting improvement in Knee-related Quality of Life displayed improved knee biomechanics during gait, whereas patients reporting small or no improvement in Knee-related Quality of Life remained unchanged one year after surgery despite similar reductions in pain. In **Study IV**, the body's Center of Mass was shown to be shifted anteriorly and towards the contralateral limb in individuals with osteoarthritis performing the Five Times Sit-to-Stand test. After surgery, when pain was substantially reduced, Center of Mass trajectories were comparable to those of healthy controls.

Conclusions: Alterations in joint loading were associated with both performance-based function and patient-reported outcomes whereas kinematic gait alterations were not associated to either, indicating that clinical outcome measures of function are not aligned with kinematic gait deviations. Based on post-operative changes in Five Times Sit-to-Stand test performance, individuals with considerable gait pattern improvements were identified. However, patient-reported measures of function could not detect differences between individuals improving in performance-based function and those who did not. Nevertheless, improvements in knee flexion-extension range during gait were related to large improvements in Knee-related Quality of Life. The body's Center of Mass trajectory during the Five Times Sit-to-Stand test was found to be a sensitive and responsive measure of functional compensations typical of knee osteoarthritis pathology.

POPULAR SCIENCE SUMMARY

Introduction: Osteoarthritis is the most common joint disease. Knee osteoarthritis causes joint pain and limits function. To establish which treatments have the best effect on improving function, appropriate evaluation measurements must be used. Today, function is typically evaluated using questionnaires, where individuals report their perceived function, or by having individuals perform specific tests, such as rising from a chair, or walking tests, and measuring the time taken to execute the test. However, questionnaires and performance tests are unable to answer *how* these movements are performed – i.e., the movement pattern. Greater knowledge of how persons with knee osteoarthritis move will help to identify how best to treat patients to improve function. This thesis evaluates methods used to assess function, including movement patterns and performance tests, in individuals with knee osteoarthritis.

Methods: The studies include 40 individuals with knee osteoarthritis scheduled for total knee replacement and 25 healthy controls. All study participants completed a three-dimensional motion analysis session, rendering biomechanical measures of walking (gait) patterns, and movement patterns used to perform a timed chair rising test (Sit-to-Stand test). Participants also completed questionnaires to report their knee function and general health and rated their perceived pain using a visual analogue scale.

Results: In **Study I**, knee osteoarthritis affected the way people walked by changing the movement of the painful leg with osteoarthritis as well as the other (contralateral) leg. In **Study II**, one year after surgery, function was found to improve, as measured by evaluation of gait pattern and performance on a Sit-to-Stand test. These improvements did however not reach the level of persons who were healthy and of the same age and gender. Results from the questionnaires could not differentiate between persons who improved on the Sit-to-Stand test and those who did not. In **Study III**, knee biomechanics during gait were evaluated among persons reporting a small or large improvement in Knee-related Quality of Life. Those reporting a large improvement in Knee-related Quality of Life displayed improved knee biomechanics, whereas patients reporting a small improvement remained unchanged one year after surgery despite similar reductions in pain. In **Study IV**, movement patterns used to perform a Sit-to-Stand test were found to be different among persons with osteoarthritis compared to controls.

Conclusions: In persons with knee osteoarthritis who were scheduled for knee replacement surgery, the disease affected the way they walked with both legs. One year after knee replacement surgery, function improved as measured by questionnaires, performance-based tests, and evaluation of how they walk and rise from a chair. However, the improvements found with surgery did not help these individuals reach the same level of performance as their age- and gender-matched healthy peers. Questionnaires have limited use in detecting the degree of changes in the way a person walks or how well they execute a timed chair rising test. Methods to examine movement patterns and the way a person walks may be used as complementary methods to objectively evaluate function.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original papers and manuscript. They will be referred to in the text by their Roman numerals as indicated below:

I. **Naili, J.E,** Esbjörnsson, AC, Iversen, M.D, Schwartz, M.H, Hedström, M, Häger, C.K, Broström, E.W. The impact of symptomatic knee osteoarthritis on overall gait pattern deviations and its association with performance-based measures and patient-reported outcomes. *Knee* (2017) 24:536-546.

II. **Naili, J.E,** Iversen, M.D, Esbjörnsson, AC, Hedström, M, Schwartz, M.H, Häger, C.K, Broström, E.W. Deficits in functional performance and gait one year after total knee arthroplasty despite improved self-reported function. *Knee Surg Sports Traumatol Arthrosc* (2016). DOI:10.1007/s00167-016-4234-7.

III. **Naili, J.E,** Wretenberg, P, Lindgren, V, Iversen, M.D, Hedström, M, Broström, E.W. Improved knee biomechanics among patients reporting a good outcome in knee-related quality of life one year after total knee arthroplasty. *BMC Musculoskelet Disord* (2017) 18:122.

IV. **Naili, J.E,** Broström, E.W, Gutierrez-Farewik, E, Schwartz, M.H. The centre of mass trajectory is a sensitive and responsive measure of functional compensations in individuals with knee osteoarthritis performing the Five Times Sit-to-Stand test. *Submitted manuscript.*

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LIST OF ABBREVIATIONS

3D	Three-Dimensional
5STS	Five Times Sit-to-Stand
ADL	Activities of Daily Living
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
CoM	Center of Mass
GDI	Gait Deviation Index
EQ5D	EuroQoL Five Dimensions
ICF	International Classification of Functioning, Disability and Health
KL	Kellgren and Lawrence Classification of Osteoarthritis
KOOS	Knee Injury and Osteoarthritis Outcome Score
MDC	Minimal Detectable Change
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PROM	Patient-Reported Outcome Measure
QoL	Quality of Life
RA	Rheumatoid Arthritis
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SLMS	Single Limb Mini Squat
TKA	Total Knee Arthroplasty
TUG	Timed Up and Go
VAS	Visual Analogue Scale
WHO	World Health Organization
WOMAC	Western Ontario McMasters Universities Osteoarthritis Index

THESIS AT A GLANCE

Study	Design and Aim	Methods	Results	Conclusions
I	Design: Cross-sectional observational study Aim: Evaluate the impact of knee OA on overall gait patterns in individuals scheduled for a TKA. Explore associations between the degree of gait pattern deviation, performance-based function, and patient-reported function.	Overall gait pattern deviations were examined using 3D motion analysis and the GDI and GDI-kinetic. The clinical outcome measures of function included the TUG, 5STS, and SLMS tests. Study participants completed the KOOS and EQ5D, as well as rated perceived pain using a VAS.	Individuals with knee OA demonstrated significantly lower GDI and GDI-kinetic scores on the OA and contralateral limbs compared to controls; with GDI-kinetic scores on the contralateral limb more impacted than the OA limb. GDI-kinetic scores were significantly associated with performance-based tests and patient-reported function, whereas kinematic GDI scores were not associated to either.	The overall gait pattern in individuals with symptomatic knee OA is affected both on the painful OA limb and the contralateral limb. Kinematic GDI scores provide different information regarding function that is not revealed by performance-based tests or PROM.
II	Design: Prospective cohort study Aim: Evaluate change in overall gait patterns, performance-based function, and patient-reported function one year after TKA, and explore how these aspects interrelate.	3D motion analysis rendered GDI and GDI-kinetic scores. Participants completed the 5STS test and the KOOS at baseline prior to surgery and one year after TKA. Perceived pain was monitored using a VAS.	Lower GDI-kinetic scores on both the operated and non-operated limb persisted in individuals with TKA at one year after surgery, while kinematic GDI scores were comparable to controls. Performance on the 5STS test and KOOS scores in individuals with knee OA improved significantly one year after surgery, but did not reach the level of controls.	Based on change in 5STS test performance, individuals with substantial gait pattern improvements were identified. Patient-reported measures of function could not detect differences between individuals improving in 5STS test performance and those who did not.
III	Design: Prospective cohort study Aim: Evaluate change in knee biomechanics during gait among individuals reporting a small or large improvement in Knee-related QoL. Secondly, to evaluate differences in perceived pain post-operatively.	Within one month prior to TKA and one year after surgery, individuals underwent 3D gait analysis, completed KOOS, and rated perceived pain using a VAS. A ‘Good’ outcome was defined as a change equal to or greater than the MDC in the KOOS subscale Knee-related QoL and a ‘Poor’ outcome was defined as change below the MDC.	Nineteen individuals were classified as having a ‘Good’ outcome, and they improved significantly in most knee gait biomechanical outcomes. Whereas, the only change at one year after surgery in knee biomechanics found for the nine individuals classified as having a ‘Poor’ outcome was a significant reduction in peak varus angle. Perceived pain during gait did not differ between groups post-operatively.	Smaller change in knee flexion-extension range and peak flexion moment had a good ability to predict a ‘Poor’ outcome after TKA. Individuals presenting with non-impacted knee biomechanics during gait prior to surgery may be at risk of rating the post-operative change in Knee-related QoL as small.
IV	Design: Prospective cohort study Aim: Evaluate whether the CoM trajectory is a sensitive and responsive measure of functional compensations in individuals with knee OA performing the 5STS test.	3D motion analysis data was collected while participants performed the 5STS test, one month prior to and one year after TKA. Perceived pain was evaluated using a VAS. The 5STS test was divided into four Sit-to-Stand-to-Sit cycles, and differences in the AUC in the medial-lateral and anterior-posterior directions were evaluated, respectively.	Pre-operatively, individuals with OA displayed a larger contralateral shift and forward displacement of the CoM than controls. Post-operatively, when pain was substantially reduced, CoM trajectories of OA individuals were not statistically different from controls. However, upon comparison of specific cycles, individuals with OA displayed a larger forward displacement towards the end of the test.	The increased contralateral shift of the CoM represents a strategy to reduce pain by unloading the affected knee. The forward displacement characterises a strategy to reduce muscular effort by reducing the required knee extension moment. The CoM trajectory appears to be a sensitive and responsive measure of functional compensations typical of knee OA pathology.

1 INTRODUCTION

Osteoarthritis (OA), the most common joint disease, affects an estimated 18% of women and 10% of men over 60 years of age (Woolf and Pfleger, 2003). While OA may affect any joint, the knee and hip joints are most often affected. The disease involves the entire joint including cartilage, subchondral bone, and synovium and lead to joint pain, stiffness, reduced range of movement, crepitus, varying degrees of local inflammation, and limited function (Woolf and Pfleger, 2003, Glyn-Jones et al., 2015). Osteoarthritis is chronic and currently no cure exists. The treatment of knee OA can be divided into first, second, and third line treatment (Roos and Juhl, 2012). First line treatment includes education, exercise, and weight control. Second line treatment includes pharmacologic management of pain, assistive devices, and treatment given by therapists and continued first line treatment. Third line treatment includes surgery, with total knee arthroplasty (TKA) being considered the treatment of choice for end-stage disease (Roos and Juhl, 2012).

In individuals with knee OA, TKA is generally considered a successful surgery. In the past, because these surgeries were performed on older patients with lower functional demands, functional improvement was not considered as important as pain relief. However, the number of patients receiving TKA is increasing (Nemes et al., 2015b, Kurtz et al., 2009), and research indicates that today's patients have higher expectations of post-operative function (Witjes et al., 2017). Many individuals receiving TKA want to maintain active lifestyles and increase their function to a level that allows them to resume their previous occupation and engage in physical activities (Mancuso et al., 2001, Witjes et al., 2017). These individuals are setting goals for improved function, such as walking without pain for longer distances (Mancuso et al., 2001). Most individuals with knee OA report decreased pain and improved function following TKA (Jones et al., 2000, Carr et al., 2012), yet studies indicate as many as 10-20% have persistent disabilities, limited function, reduced quality of life (QoL), diminished working capacity, and persistent gait pattern deviations (Wylde et al., 2007, Bourne et al., 2010, Milner, 2009). The percentage of dissatisfied patients is reported to be even higher when evaluating the ability to perform activities of daily living as compared to pain outcomes (Bourne et al., 2010).

Walking is the body's natural means of moving from one place to another (Perry, 2010). Gait, the manner of walking, has been the object of study in individuals with knee OA, but its response to treatment (i.e., TKA) has not been investigated as carefully or as in-depth as pain outcomes or other patient-reported outcomes. Individuals with knee OA walk nearly 30% fewer steps per day as compared to age-matched controls (Holsgaard-Larsen and Roos, 2012), and the level of actual physical activity among individuals with end-stage knee OA is lower to a significantly and clinically relevant degree compared to controls (de Groot et al., 2008). The current literature lacks sufficient information about the impact of knee OA on movement patterns, including gait, and the relationship between movement patterns and other commonly used outcome measures of function. In addition, the response of movement patterns to TKA is not clear.

1.1 OSTEOARTHRITIS

1.1.1 Definition of osteoarthritis

There are several definitions of OA. The Osteoarthritis Research Society International (OARSI) proposed a definition with the goal to achieve consensus on a globally recognized definition of the disease and worldwide standards for classifying the disease (Kraus et al., 2015). The OARSI anticipated that this definition would facilitate communication about OA among researchers, controlling agencies, funding organizations, third party payers, and patients (Kraus et al., 2015). The OARSI defines OA as

> [A] disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness (Kraus et al., 2015).

1.1.2 Radiologic classification and clinical criteria of osteoarthritis

Radiographic and symptomatic OA are the most commonly used case definitions. Just as with the definition of OA, there is more than one classification system to define the degree of radiographic severity of OA. The Kellgren and Lawrence (KL) classification of OA is a widely used radiographic classification system, wherein standard anterior-posterior radiographs are defined, ranging from mild (grade I) to severe (grade IV) radiographic OA (Kellgren and Lawrence, 1957). The Modified KL classification incorporates classification of the degree of joint space narrowing and bone attrition (Dieppe et al., 2009).

The criteria for symptomatic OA are based on findings from clinical examinations. These include knee pain and at least three of the following six findings: age >50 years, morning stiffness <30 minutes duration, crepitus on active motion, tenderness of the bony margins of the joint, bony enlargement noted on examination, and a lack of palpable warmth of the synovium (Altman et al., 1986).

1.1.3 Incidence and prevalence

Due to the difficulties related to defining OA and how to determine its onset, few data are available on the incidence (Woolf and Pfleger, 2003). Radiographic studies of US and European populations aged 45 years and older report rates for knee OA of 14.1% for men and 22.8% for women (Woolf and Pfleger, 2003). The prevalence of symptomatic knee OA in individuals aged 60 years or older is reported to be 8.8% for men and 15.7% for women (Pereira et al., 2011).

1.2 TREATMENT IN OSTEOARTHRITIS

First line treatment of knee OA includes education, exercise, and weight control (Figure 1). The OARSI (McAlindon et al., 2014), the American Academy of Orthopaedic Surgeons (Jevsevar, 2013), the American College of Rheumatology (Hochberg et al., 2012), and the European League Against Rheumatism (Fernandes et al., 2013) all recommend exercise and weight loss programs for overweight individuals with knee OA as first line treatment.

Exercise comprises several different methods, and it can be sub-grouped into land-based or water-based exercise and into strength training, neuromuscular training, and aerobic (cardiovascular) training (McAlindon et al., 2014). Comparisons of the different exercise interventions used in OA research are challenging due to heterogeneous data (Fransen et al., 2015). Nevertheless, exercise is proven effective for increasing patient-reported physical function and reducing pain in individuals with mild to moderate radiographic knee OA (Fransen and McConnell, 2009, Jamtvedt et al., 2008). The effect size of strength training on patient-reported physical function ranges between 0.3 and 0.6 (Fransen et al., 2015) and for neuromuscular exercise on patient-reported physical function between 0.4 and 0.5 (Fransen and McConnell, 2009, Fransen et al., 2015). The effects of exercise on pain reduction are small to moderate, yet significant (effect size 0.4) (Fransen et al., 2015).

The effects on pain and function from attending weight loss programs are overall small, but significant (effect size pain 0.2, physical function 0.2). Diet to promote weight loss has shown to be more effective for reducing compressive force than exercise alone and exercise and diet in combination (Messier et al., 2013).

Using magnetic resonance imaging, the Osteoarthritis Initiative evaluated the association of weight loss with progression of cartilage changes in overweight and obese individuals (Gersing et al., 2017). Over 48 months, participants who lost weight revealed significantly lower cartilage degeneration than participants in the weight-matched stable-weight reference group and that rates of progression were lower with greater weight loss (Gersing et al., 2017).

According to a recent report from the Swedish National Board of Health and Welfare (Socialstyrelsen), the proportion of individuals with OA receiving treatment from a physiotherapist directly (as first instance) has increased from 0% to around 4-5% between 2011 and 2015 (Socialstyrelsen, 2017). The increase may be related to increased availability of the Supported Osteoarthritis Self-Management Program (“Osteoarthritis School”) (BOA, 2017); however, the proportion of individuals who receive physiotherapy as first treatment is still small.

Second line treatment includes pharmacological treatment aimed at relieving pain together with other passive treatments such as load-modifying interventions (Roos and Juhl, 2012). Several pharmacological substances can be used for this purpose (e.g., acetaminophen, non-steroid anti-inflammatory drugs, and opioids). These treatments, however, will not be discussed further in this thesis.

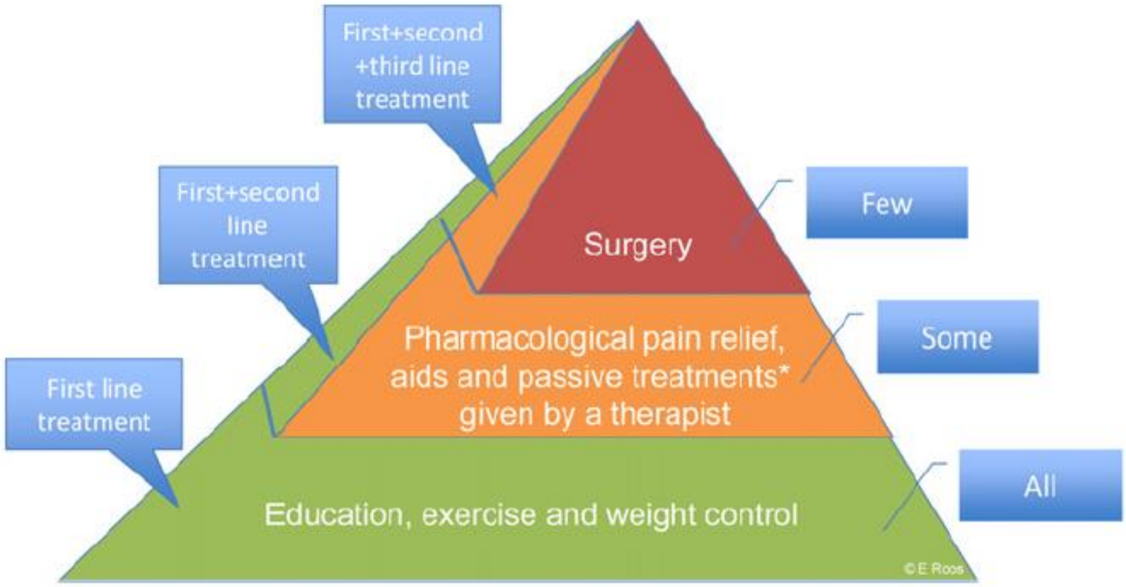


Figure 1. The osteoarthritis treatment pyramid. All individuals with osteoarthritis should be offered first line treatment, some will need second line treatment, and few will need third line treatment. *Passive treatments include manual therapy, acupuncture, and other treatments given by a therapist and not requiring an active lifestyle change by the individual. This figure was originally published by Roos and Juhl (2012) and reprinted with permission from the authors and the publisher.

1.2.1 Indication for total knee arthroplasty

There are no clear indications for the use of TKA (Dieppe et al., 2011). The rates for primary TKA surgery, the third line treatment, varies somewhat between regions (Judge et al., 2009, Ranstam and Robertsson, 2010), and unquestionably between countries (Kurtz et al., 2011). In Sweden, roughly 12,000 TKA (132 TKA/100,000 inhabitants) are performed yearly due to knee OA (SKAR, 2016). In the US, the corresponding numbers for TKA were 719,000 in 2010 (378 TKA/100,000 inhabitants) (CDC, 2010). In general, the indications for TKA surgery include pain, mainly during loading, which cannot be mitigated to an acceptable level with first and second line treatments.

The OARSI and Outcome Measures in Rheumatology aimed to define a cut point for pain and physical function in order to have a surrogate measure for “need for arthroplasty surgery” (Gossec et al., 2011). The most discriminatory cut point for joint arthroplasty was level of pain plus physical function adding up to >80 on a scale from 0-100, where 0 indicates “no problems” and 100 indicates “severe problems”. The authors concluded that the results did not support a specific level of pain or physical function that defines an indication for arthroplasty; nevertheless, the proposed cut point calls for further evaluation (Gossec et al., 2011).

1.3 DEFINITION OF FUNCTION

In everyday terms, function denotes "purpose for which something is designed, or the kind of action or activity proper to a person" (Simpson et al., 1989). The International Classification of Functioning, Disability and Health (ICF) uses *Body Functions* and *Body Structures* as one level in their taxonomy describing the interaction between health conditions and contextual factors (Figure 2) (WHO, 2001). In the ICF, the concept *Body Functions* includes physiological functions of body systems (i.e., muscle weakness) as well as psychological functions. *Body Structures* are anatomical parts of the body (i.e., joint space narrowing or knee malalignment). The execution of a task or action by an individual is categorized as an *Activity* (e.g., walking and rising from sitting to standing). The concept of *Participation* includes taking part in situations of life.

In this thesis, the concept of function is used with a broader and less specific meaning than the ICF definition of *Body Functions*. In relation to the ICF, the concept of function used within this thesis does not make any distinctions between *Body Functions*, *Body Structures*, and *Activity*. Throughout this work, the concept of function is used to describe body functions, body structures, and activities.

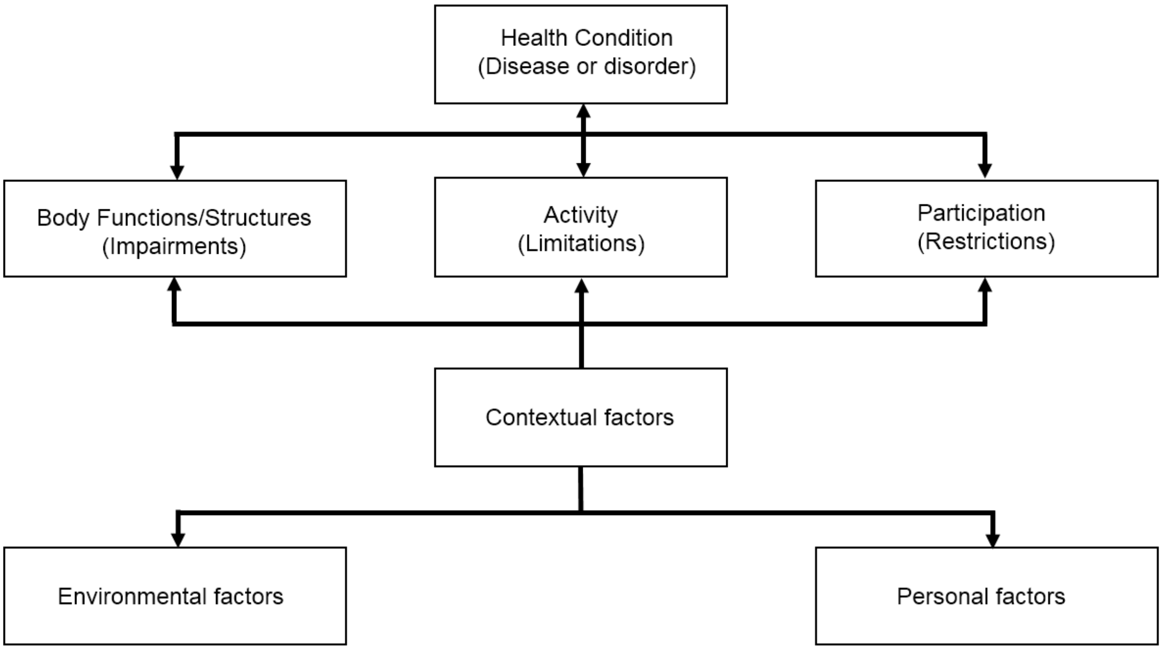


Figure 2. The International Classification of Functioning, Disability and Health model (WHO, 2001).

1.4 CLINICAL EVALUATION METHODS AND OUTCOME MEASURES OF FUNCTION

1.4.1 Patient-reported outcome measures

Perception of symptoms and function in individuals with knee OA are frequently evaluated using patient-reported outcome measures (PROM). These measures often constitute the primary outcome in trials involving individuals with OA. PROM can often be sub-divided into either disease-specific or generic outcome measures. In the OA research community, concerns have been raised regarding PROM being used beyond the scope for which they were intended (Hossain et al., 2015). In a systematic review of PROM, a variety of measures were evaluated and the data illustrated deficiencies in the capability of the measures to assess function with respect to leisure activities (Alviar et al., 2011).

1.4.1.1 Disease-specific outcome measures

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely-used disease-specific questionnaire (Bellamy et al., 1988) designed specifically for individuals with knee OA and recommended by the OARSI. The Knee Injury and Osteoarthritis Outcome Score (KOOS) is another commonly used disease-specific outcome measure, originally developed to be used for individuals who had an acute knee injury or post-traumatic knee OA (Roos et al., 1998). The KOOS expands the WOMAC by adding two subscales, physical function related to sport and recreational activities, and the impact the knee has on an individual’s QoL. This improves the questionnaire’s validity for physically active individuals, and individuals with a wider range of present or anticipated level of physical activity (Roos et al., 1998). It is possible to derive WOMAC scores from the KOOS.

The KOOS is divided into five separate subscales addressing Symptoms, Pain, Function in Activities of Daily Living (ADL), Function in Sport and Recreation, and Knee-related QoL (Table 1). Each subscale generates a final score ranging from 0 to 100, where 0 represents “worst” and 100 “best” (Roos et al., 1998). The KOOS is considered reliable for assessing baseline function and change over time in individuals with knee OA (Roos et al., 1998, Steinhoff and Bugbee, 2014) and following TKA (Gandek and Ware, 2017). All subscales of KOOS have demonstrated adequate test-retest reliability (intra class correlation range 0.85 – 0.90) (Collins et al., 2011).

1.4.1.2 Generic health-related quality of life measurements

Health-related QoL constitutes a multidimensional and subjective concept that includes the physical, psychological, and social functioning related to a health condition (Revicki, 1989). The health-related QoL measure reflects the impact of health status on an individual’s ability to function and a person’s perceived well-being in the physical, mental, and social domains of life (Moriarty et al., 2003). Both knee pain and knee OA are associated with substantial deterioration in health-related QoL (Kiadaliri et al., 2016, Farr Ii et al., 2013).

Several generic instruments exist for the assessment of health-related QoL, including the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (Kosinski et al., 1999) and the EuroQoL Five Dimensions (EQ5D) (Rabin and de Charro, 2001). Within this thesis, the EQ5D was used to assess health-related QoL among study participants.

The EQ5D consists of two parts: a visual analogue scale (VAS) and a self-administered questionnaire with five questions concerning five dimensions – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses are used to calculate an index score where -0.594 is the worst possible health and 1 is full health (Dolan and Roberts, 2002). The instrument includes a 20-centimeter VAS for the self-assessment of current overall health.

1.4.2 Performance-based outcome measures

Performance-based outcome measures aim to assess physical function. These tests are most frequently conducted by measuring the time taken to execute a task, the number of repetitions, or distance accomplished during the test (Johnson et al., 2007, Lord et al., 2002, Dobson et al., 2013). In contrast to PROM, which measures perceived performance, performance-based measures are intended to assess what an individual actually can do. Several studies report discrepancies between results from PROM of function and actual functional ability as these measures capture different aspects of function and are influenced by different underlying impairments (Stratford and Kennedy, 2006, Stevens-Lapsley et al., 2011, Mizner et al., 2011, Stratford et al., 2003). As a result, it is recommended to use both types of measurements in clinical trials (Stratford and Kennedy, 2006, Dobson et al., 2012, Pham et al., 2004).

In 2013, the OARSI presented a set of five performance-based tests of physical function selected by an advisory group (Dobson et al., 2013). The set included the 30-second chair stand test, the 40-meter fast-paced walk test, a stair-climb test, the Timed Up and Go (TUG) test, and the Six-minute walk test. The first three tests were recommended as a minimal basic set of tests to be used as performance-based outcome measures in OA research and clinical practice and are intended to be complementary to PROM (Dobson et al., 2013).

It is worth pointing out that the decision on which tests to include within the work of this thesis was made prior to the publication of the OARSI recommendation. Three performance-based tests were selected based on the different ways they challenge the participants: the Five Times Sit-to-Stand test (5STS) requires quadriceps strength and power, the TUG test uses self-selected speed and includes test of functional mobility and dynamic balance, and the Single Limb Mini Squat test (SLMS) requires unilateral muscle strength and the ability to quickly change between concentric and eccentric muscle work of the lower limbs (Table 1). The TUG test is the only test out of the three used within this thesis included in the OARSI recommended set (Dobson et al., 2013).

Table 1. Aspects of function intended to be assessed by the performance-based outcome measures and the patient-reported outcome measures of function included in the subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS).

Name of the measurement	What the measurement is supposed to assess
The Five Times Sit-to-Stand test	Lower extremity strength, dynamic balance, and functional mobility.
The Timed Up and Go Test	Functional mobility and dynamic balance (i.e., sit-to-stand, ambulatory transition, turning while walking, stand-to-sit).
The Single Limb Mini Squat test	Unilateral muscle strength, coupled eccentric-concentric muscle force over the knee joint, and coordination.
Function in Activities of Daily Living subscale of KOOS	Rising from sitting, standing, bending to floor, walking on flat surface, getting in/out of car, going shopping, putting on socks, rising from bed, taking off socks, lying in bed, getting in/out of bath, sitting, getting on/off toilet, light domestic duties, and heavy domestic duties
Function in Sports and Recreation subscale of KOOS	Squatting, running, jumping, twisting/pivoting, and kneeling.

1.4.2.1 The Five Times Sit-to-Stand test

The 5STS test is a valid performance-based test that is easy to use in clinical practice (Goldberg et al., 2012, Bohannon, 2006, Bohannon, 2011). The test shows excellent relative and absolute reliability in older adults (intra class correlation coefficient 0.95, standard error of measurement 0.9 seconds) (Goldberg et al., 2012). Performance on the 5STS test is associated with lower limb strength, especially quadriceps strength, and has been suggested as a surrogate measure for lower limb strength in older people with and without joint disease (Lord et al., 2002, Schenkman et al., 1996, Newcomer et al., 1993). However, studies also report that factors such as balance, age, weight, and sensorimotor measures play an important role in test performance (Lord et al., 2002, Schenkman et al., 1996).

Sit-to-stand performance has been evaluated beyond the time taken to complete the test (Turcot et al., 2012, Christiansen and Stevens-Lapsley, 2010, Alnahdi et al., 2016, Mizner and Snyder-Mackler, 2005, Anan et al., 2015). In a study by Christiansen et al., weight bearing asymmetry during the test was evaluated in individuals with knee OA (Christiansen and Stevens-Lapsley, 2010). The authors concluded that greater amounts of weight bearing asymmetry correlated with poorer functional performance up to six months after TKA and that weight bearing asymmetry also was associated with quadriceps strength asymmetry (Christiansen and Stevens-Lapsley, 2010). Similar results have been reported by Alnahdi et al., where individuals with TKA displayed unloading of the operated limb, shifting the load to the contralateral limb when performing a sit-to-stand test one year after surgery (Alnahdi et al., 2016).

1.4.2.2 The Timed Up and Go test

The TUG test is a common measure of functional mobility and fall risk in the elderly (Podsiadlo and Richardson, 1991, Bischoff et al., 2003). The test has shown good measurement properties in OA populations (Wright et al., 2011, Kennedy et al., 2005), is a predictor of six-minute walk performance after TKA (Bade et al., 2014), and a predictor of risk for disability (Makizako et al., 2017). Self-efficacy, quadriceps strength, and BMI are factors reported to have an influence on performance of the TUG test (Maly et al., 2005).

1.4.2.3 The Single Limb Mini Squat test

The SLMS test is a timed test that requires neuromuscular control and the ability to quickly change between concentric and eccentric muscle work of the hip and knee extensors (Bremander et al., 2007). The test has been demonstrated to be valid and reliable in individuals with knee OA (Bremander et al., 2007). The movement performed during the test is similar to that performed when walking in stairs.

In clinical practice, the array of measurements available for evaluating function is usually restricted to PROM and performance-based measures since they do not require special equipment. Previous research has demonstrated that there is a discrepancy between patient-reported function and function as evaluated by using performance-based measures. In addition, PROM are known to be largely influenced by pain. Performance-based measures are a valuable source for collecting information on *what* an individual can do, established by counting the number of repetitions performed, or the duration of time to execute a test. However, performance-based measures fail to answer *how* a given activity or task is performed. Thus, there may be additional important aspects of function including examination of movement patterns that could provide complementary information in the evaluation of function.

1.5 LABORATORY-BASED EVALUATION METHODS AND OUTCOME MEASURES OF FUNCTION

Three-dimensional (3D) motion analysis provides information about movement patterns that cannot be assessed through clinical observation. High speed motion analysis cameras and force plates provide detailed information regarding kinematics (i.e., motion of individual body segments and joint rotations) and kinetics (i.e., the forces and torques related to motions of segments) (Winter, 2004). Over the last decades, 3D motion analysis has been used to observe osteoarthritic gait patterns.

1.5.1 Gait deviations in individuals with knee osteoarthritis

Individuals with knee OA display decreased amplitude of the knee flexion moment, diminished range of knee motion (Zeni Jr and Higginson, 2009), and increased magnitude of the external knee adduction moment during stance (Deluzio and Astephen, 2007). These gait deviations appear to increase with disease severity (Astephen et al., 2008). Increased external knee adduction moment is associated to the presence, severity, and progression of medial knee OA (Sharma et al., 1998, Miyazaki et al., 2002) and to greater loss of cartilage volume (Bennell et al., 2011). Several specific kinematic variables at different point in the gait cycle are associated with a greater loss of medial cartilage thickness in individuals with medial compartment knee OA over a five-year follow-up period (Favre et al., 2016). In addition, increased magnitude of the overall external knee adduction moment together with altered sagittal plane movements are indicative of future TKA (Hatfield et al., 2015).

Kinematics and kinetics of the contralateral knee and joints other than the knee are altered in individuals with knee OA (Zeni Jr and Higginson, 2009, Metcalfe et al., 2013). Altered kinetics may exacerbate progression of OA (Felson, 2013, Shakoor et al., 2002).

1.5.2 Gait indices

Despite the fact that most studies examine specific gait parameters (measured at specific points in the gait cycle), there are several methods that evaluate the overall gait pattern throughout the entire gait cycle. In 2008, the Gait Deviation Index for kinematics (GDI) was published (Schwartz and Rozumalski, 2008) and in 2011 the Gait Deviation Index for kinetics (GDI-kinetic) (Rozumalski and Schwartz, 2011). The GDI and GDI-kinetic summarize gait patterns captured by 3D motion analysis and provide a single score describing the degree to which an individual's gait pattern deviates from a normal (pathology-free) gait pattern (Schwartz and Rozumalski, 2008, Rozumalski and Schwartz, 2011). The GDI and GDI-kinetic are linearly related to one another, however not strongly correlated (r^2=0.24), suggesting that they capture largely independent elements of human gait biomechanics (Rozumalski and Schwartz, 2011).

The GDI was developed in a context examining gait patterns in children with cerebral palsy and has mostly been used and evaluated amongst children and adults with cerebral palsy (Truong et al., 2011, Ries et al., 2015, Maanum et al., 2012). However, the GDI has been used to evaluate gait in individuals with other diseases such as Parkinson's disease (Galli et al., 2012), stroke (Speciali et al., 2014, Correa et al., 2017), rheumatoid athritis (RA) (Esbjornsson et al., 2014), and hip OA (Jensen et al., 2015, Rosenlund et al., 2016).

1.5.3 The Center of Mass

The Center of Mass (CoM) is a parameter that can be derived from 3D motion analysis. The CoM is a theoretical point and it can be calculated for individual body segments separately or for the entire body (Winter, 2004). The whole body CoM is the average position of the whole body mass. With an individual standing upright, equal weight distributed on both legs, and the weight and position of all other body segments equally distributed, the whole body CoM is approximately located in the pelvis, anterior to the second sacral vertebrae (Bojsen-Møller, 2000). When the body is not moving, the ground reaction force passes through the CoM, which is located above the center of pressure (the force vector). When each body segment is in motion, the whole body CoM is constantly changing. Therefore, knowledge of the trajectories of the CoM of each body segment is required to recalculate the whole body CoM after each interval of time (Winter, 2004).

The CoM has mainly been studied during level gait, where it has been observed to differ between individuals with knee and hip OA pathology compared to controls (Mandeville et al., 2008, Lugade et al., 2008). However, other types of movement (e.g., rising from a chair, walking up and down stairs, or activities more challenging than level gait) could display larger differences or more distinguishable movement patterns. The CoM can be used to analyze body posture and balance (Winter, 2004) and possibly to analyze strategies used to perform a Sit-to-Stand test in individuals with knee OA who are known to present with weight bearing asymmetries (Christiansen and Stevens-Lapsley, 2010, Turcot et al., 2012, Alnahdi et al., 2016).

By studying the CoM among individuals with knee OA, it is possible to generate information on *when* (what phase) and in *what way* (which direction) the movement pattern is deviating. Such information could be useful to establish what strategies are being used and to generate new hypotheses concerning which strategies are related to pain, muscle weakness, or other factors influencing movement patterns.

1.6 INTERPRETABILITY OF OUTCOME MEASURES

Outcome measures are crucial in healthcare as they constitute the foundation for evaluation of results of interventions (de Vet et al., 2011). When multiple methods and outcome measures exist, selecting the most appropriate ones are challenging (de Vet et al., 2011). Critical to all measurements used in healthcare is knowledge of their quality of measurement properties such as validity, reliability, and responsiveness to change (de Vet et al., 2011).

1.6.1 Responsiveness to change

Responsiveness to change relates to the ability of the measurement to detect changes when an individual's condition improves or declines (Fayers and Machin, 2007). There is limited use of a measurement for monitoring individuals unless it reflects changes in the individual's condition. A sensitive measurement is usually, but not necessarily, also responsive to changes; moreover, sensitive instruments can use smaller sample sizes to detect relevant differences (Fayers and Machin, 2007).

1.6.1.1 Effect size

Effect size is commonly calculated by using the mean change score in a group of individuals divided by the standard deviation (SD) of the baseline scores in this group (Cohen, 1988). Effect size is frequently used as a measure of the magnitude of the change scores and as a measure of responsiveness. Cohen suggested that effect sizes of 0.2 be interpreted as small, 0.5 as moderate, and 0.8 as large. However, the appropriateness of using effect size as a measure of responsiveness has been questioned (de Vet et al., 2011). The effect size is highly dependent of the SD of the baseline scores. Consequently, the effect size will be higher among homogenous groups (de Vet et al., 2011). According to de Vet et al., measures of effect size provide limited evidence of responsiveness of a measure without a comparison instrument (de Vet et al., 2011).

1.6.1.2 Minimal Detectable Change

The Minimal Detectable Change (MDC) (also referred to as the Smallest Detectable Change) is a statistical estimate that provides a threshold for interpretation of a measurement (Beaton et al., 2001). When a change score exceeds this threshold, there is reasonable certainty that it represents a true change and not a measurement error (Beaton et al., 2001). The MDC, however, is not an absolute value and should therefore be considered a guideline rather than an absolute truth (Beaton et al., 2001).

The MDC depends on the test-retest reliability of a measurement instrument. For a measurement instrument to have high test-retest reliability, it needs to yield stable, repeatable, and reproducible results in an individual with a stable condition. The more reliable an instrument is, the smaller the difference can be detected longitudinally (Fayers and Machin, 2007).

1.7 RATIONALE

To improve function in individuals with knee OA, patients must be provided the most effective treatment. However, to make this determination, appropriate evaluation methods and measures must be used. A combination of evaluation methods – e.g., PROM, performance-based measures, and measures derived from 3D motion analysis – could provide more detailed qualitative and quantitative aspects of function than PROM and performance-based measures alone. Such methods would most likely be more robust when evaluating interventions aimed at improving function, such as specific exercise programs, new surgical techniques, or implant designs. Deepened knowledge concerning alterations in movement patterns may help identify limitations and determine whether interventions aiming to improve function actually succeed.

2 AIMS OF THE THESIS

This thesis evaluates methods used to objectively assess function – including gait patterns, movement strategies, and performance-based function – in individuals with knee OA. To this end, this thesis explores associations between measures derived from 3D motion analysis and commonly used clinical outcome measures of function. The specific aims of the included studies are identified below.

Study I. Evaluate the impact of symptomatic knee OA on overall gait patterns in individuals scheduled for a TKA. Explore associations between the degree of gait pattern deviation, performance-based function, and patient-reported function.

Study II. Evaluate change in overall gait patterns, performance-based function, and patient-reported function one year after TKA, and explore how these aspects interrelate.

Study III. Evaluate change in knee biomechanics during gait among individuals reporting a small or large improvement in Knee-related QoL. Secondly, to evaluate differences in perceived pain post-operatively.

Study IV. Evaluate whether the body's CoM trajectory is a sensitive and responsive measure of functional compensations in individuals with knee OA performing the 5STS test.

3 RESEARCH APPROACH

3.1 ETHICAL APPROVAL

Ethical approval for this research was obtained from Stockholm's regional ethical review board (Dnr: 2010/1014-31/1). All study participants provided written informed consent to participate in accordance with the Declaration of Helsinki.

3.1.1 Ethical considerations

Individuals who were eligible to be included in the studies were asked about their willingness to participate by healthcare personnel who were not involved in their planned surgery. This interaction may have reduced the risk for individuals feeling pressured to accept participation to satisfy their surgeon.

Instrumented motion analysis requires participants to wear little clothing while performing the trials as the placement of reflective markers is less reliable if placed on clothing due to movement artifacts. All study participants received information prior to their participation on how motion analysis is conducted, including pictures of suggested garments to wear (shorts and tank top or sports bra).

The chosen performance-based tests resemble movements occurring in everyday life, such as sitting down and rising from a chair and walking up and down stairs. These tests provoked pain in the affected joints for some of the study participants with knee OA. During the test sessions, all participants were encouraged on several occasions to indicate their pain level. Participants rated their pain before and after each test; if needed the test was discontinued.

The benefits of participation included feedback on functional status and performance, an opportunity to discuss surgery and rehabilitation with a physiotherapist, and feedback on post-operative change at the one-year follow-up.

3.2 STUDY OUTLINE

Study I used a cross-sectional design to evaluate the impact of symptomatic knee OA on overall gait pattern deviations. In addition, the study examined associations between the degree of gait pattern deviation and commonly used clinical outcome measures of function. Forty individuals with knee OA and 25 age- and gender-matched healthy controls were included in this study. Overall gait patterns were examined using 3D motion analysis, GDI, and GDI-kinetic. The clinical outcome measures of function included the TUG, the 5STS, the SLMS tests, and the self-administered disease-specific questionnaire KOOS. Study participants also completed the EQ5D and rated their perceived pain using a VAS.

Study II used a prospective cohort design to evaluate change in overall gait pattern, performance-based function, and patient-reported function one year after TKA in individuals with symptomatic knee OA and to identify how these aspects of function interrelate. Out of the 40 individuals with knee OA included in Study I, 28 individuals completed the one-year follow-up and were included in this study. The control group from Study I was also included in Study II. Gait was evaluated using the GDI and GDI-kinetic, performance-based function was evaluated using the 5STS test, and patient-reported function was evaluated using KOOS.

Study III used a prospective cohort design to evaluate change in knee biomechanics during gait among individuals reporting small or a large improvement in Knee-related QoL. In addition, this study evaluated differences in perceived pain during gait after surgery. This study included the 28 individuals with knee OA and the 25 individuals in the control group included in Study I and II. Individuals with knee OA were dichotomized into two groups according to change in Knee-related QoL of KOOS one year after TKA surgery. In this sample, 19 (68%) individuals reported change equal to or greater than the MDC in Knee-related QoL at the one-year follow-up and were classified as having a 'Good' outcome. Nine (32%) individuals reported change in Knee-related QoL at a level less than the MDC and were classified as having a 'Poor' outcome. The 'Good' and 'Poor' outcome groups were analyzed separately, compared to each other, and compared to the control group.

Study IV used a prospective cohort design to evaluate whether the body's CoM trajectory is a sensitive and responsive measure of functional compensations among individuals with knee OA performing the 5STS test prior to and one year after TKA. Data from 21 individuals with knee OA and 21 controls (included in studies I-III) were included in this study. The CoM trajectory was calculated using a conventional biomechanical model (Plug-In-Gait). To quantify displacement of the CoM, the area under the curve (AUC) was calculated for each Sit-to-Stand-to-Sit cycle in the medial-lateral direction and the anterior-posterior direction. Individuals with knee OA were asked to rate their perceived pain after performing the 5STS test using a VAS.

3.3 SAMPLE SIZE AND STATISTICAL POWER

All power calculations were performed using the software program G*Power, version 3.1.9.9 (Universität Kiel, Germany) (Faul, 2007). For studies I and II, a priori power calculations were conducted using pilot data to determine the sample size needed to detect differences between individuals with knee OA and healthy controls. With regards to the GDI, the calculation was performed to detect a difference of five GDI scores between groups. For a statistical power of 0.8 and an α-value of 0.05, 24 individuals with knee OA were required. With regards to the 5STS test, the calculation was conducted to detect a difference of 2.5 seconds between groups. For a statistical power of 0.8 and an α-value of 0.05, 38 individuals with knee OA were required. In Study I, a post hoc power analysis was performed to determine the power of the sample of 40 participants to detect a moderate correlation (r-value of 0.4) between GDI/GDI-kinetic and clinical outcomes, and the power was found to be sufficient (>80%) (Faul, 2007). Due to the exploratory nature of Study IV, no power calculation was considered necessary prior to this study.

3.4 PARTICIPANTS

Forty individuals with symptomatic primary knee OA (25 women and 15 men) were recruited from two orthopedic departments in Stockholm County, Sweden (Ortho Center Löwenströmska Hospital, and Karolinska University Hospital) between 2010 and 2013 (Table 2). Criteria for inclusion were scheduled for a TKA within one month, ability to walk ten meters repeatedly without the use of a walking aid, and ability to understand verbal and written information in Swedish. Exclusion criteria were prior major orthopedic surgery in the lower extremities, rheumatoid arthritis, diabetes mellitus, BMI >40, neurologic disease, and other conditions affecting walking ability. A convenience sample of 25 healthy controls without any known musculoskeletal disease, lower extremity joint pain, or neurological disorder was recruited between 2013 and 2015. Controls were matched by gender distribution and age strata to individuals with knee OA (Table 2).

3.4.1 Excluded participants

Out of the 40 individuals with knee OA included at baseline, 12 (30%) were excluded from the one-year follow-up for several reasons (Figure 3). In Study IV, an additional seven individuals had to be excluded – six due to occluded upper limb markers needed to calculate the whole body's CoM and one who could not perform the 5STS test at baseline (Figure 3). The individuals who did not complete the one-year follow-up (n=12 Study II and III; n=19 Study IV) did not differ statistically from the studied OA group with respect to distribution of age, gender, weight, height, BMI, or duration of years with symptomatic knee OA, which was examined using independent sample t-tests or Mann Whitney U tests, depending on the distribution of data, and Fisher's exact test.

3.5 DATA COLLECTION

All data – including gait, performance-based tests, and PROM – were collected at the Motion Analysis Laboratory at Karolinska University Hospital, Solna, Sweden. Baseline assessments were performed within one month prior to surgery (mean 20 (SD 13) days) and post-operative assessments one year after surgery (mean 12 (SD 0.9) months). The control group was assessed once (Figure 3). Each test session began with a physical examination, followed by placement of reflective motion analysis markers. Thereafter, participants performed approximately 10-15 gait trials. After completing the gait trials, participants answered the self-administered questionnaires to allow for a rest period of approximately 20 minutes. The test session continued with the participants performing the performance-based tests in random order with reflective markers still on. Each test session lasted for 60 to 90 minutes.

3.5.1 Physical examination

A goniometer was used to record passive range of motion of the major lower extremity joints with the participant in a supine position for all measures, except hip extension and hip rotation, which were recorded with the participant in a prone position. Anthropometric measures were recorded using calibrated scales.

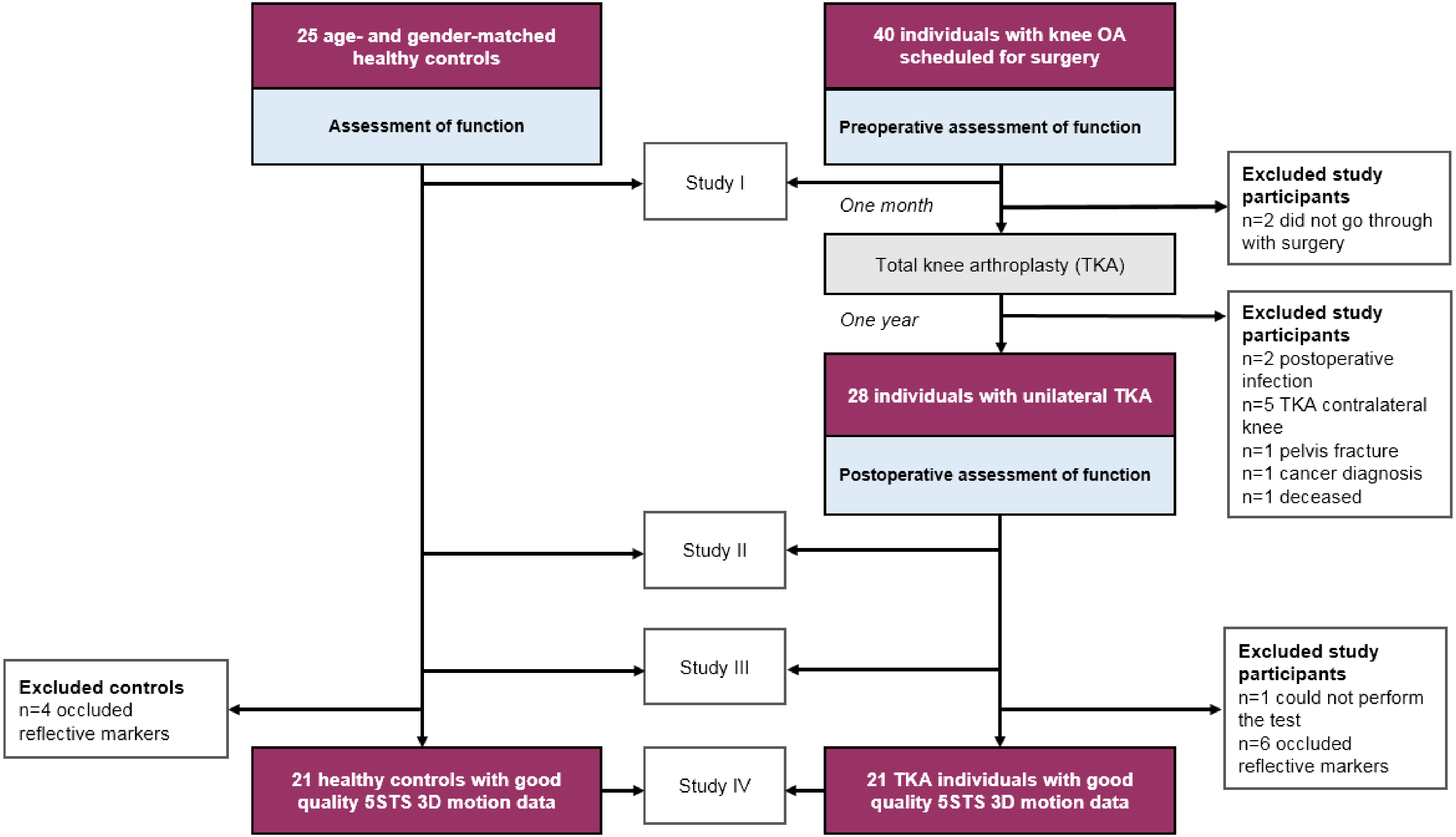


Figure 3. Flowchart of included and excluded study participants. OA, Osteoarthritis; 3D, Three-Dimensional; 5STS, Five Times Sit-to-Stand test.

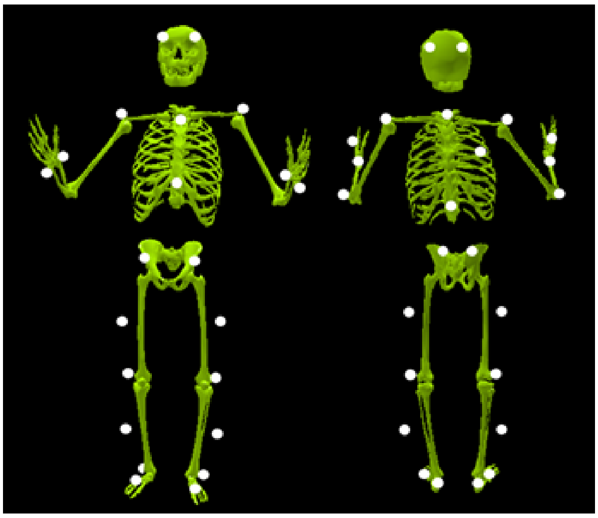
Table 2. Baseline characteristics and clinical features of included individuals with knee osteoarthritis scheduled for total knee arthroplasty and healthy controls.

	Knee OA (n=40)	Control group (n=25)
Characteristics		
Age (years), mean (SD)	65.7 (7.2)	65.7 (9.5)
40-49 years, n (%)	0	1 (4)
50-59 years, n (%)	9 (22.5)	5 (20)
60-69 years, n (%)	18 (45)	9 (36)
70-79 years, n (%)	12 (30)	9 (36)
80-89 years, n (%)	1 (2.5)	1 (4)
Female, n (%)	25 (62.5)	16 (64)
Body Mass Index (kg/m^2), mean (SD)	29.3 (4.4) *	24.9 (2.9)
Body weight (kg), mean (SD)	84.2 (12.9) *	72.8 (12.2)
Height (cm), mean SD	170 (9.3)	171 (8)
Symptom duration (years), mean (SD)	8 (7)	-
Previous minor orthopedic surgery, n (%)	19 (47.5)	-
Modified KL score (1-4b)		
1-2, n (%)	-	-
3a, n (%)	2 (5)	-
3b, n (%)	7 (17.5)	-
4a, n (%)	10 (25)	-
4b, n (%)	21 (52.5)	-
Use of analgesics		
Daily use, n (%)	18 (45)	-
If necessary (when needed), n (%)	11(27.5)	-
Never (Rarely), n (%)	10 (25)	-
Missing, n (%)	1 (2.5)	-
Pre-operative physiotherapy		
Yes, n (%)	10 (25)	-
No, n (%)	25 (62.5)	-
Missing, n (%)	5 (12.5)	-
EQ5D score (0-1) mean (SD)	0.61 (0.2) *	0.93 (0.1)
EQ5D VAS (0-100) median (range)	72 (19-98) *	90 (60-100)
Pain assessment with VAS (0-100)		
Prior to the test session, median (range)	15 (0-78)	-
After completed test session, median (range)	7 (0-75)	-

OA, Osteoarthritis; SD, Standard Deviation; n, Number; KL, Kellgren and Lawrence; EQ5D, EuroQoL Five Dimensions; VAS, Visual Analogue Scale. Minor orthopedic surgery refers to knee joint arthroscopy for all but two in the knee OA group, which instead refers to surgical treatment of hallux valgus. Parametric and non-parametric statistics and independent samples t-tests and Mann Whitney U test were used to calculate differences between the knee OA group and controls. Level of significance set to * $p<0.05$.

3.5.2 Three-dimensional motion analysis

After the initial physical examination, 35 retro-reflective markers were placed on anatomical landmarks (head, trunk, pelvis, and lower and upper extremities) (Figure 4) by one of two examiners according to the biomechanical model Plug-In-Gait (Davis et al., 1991). The Plug-In-Gait model computes joint motions as well as reaction forces, moments, and joint power. Kinetics were expressed by *internal* moments and total joint power.



Head
Left forehead
Right forehead
Left back of head
Right back of head

Upper body
Left shoulder
Right shoulder
Left elbow
Right elbow
Left wrist A
Right wrist A
Left wrist B
Right wrist B
Left finger
Right finger
Clavicle
Sternum
7th cervical vertebra
10th thoracic vertebra
Right back

Lower body
Left anterior superior iliac
Right anterior superior iliac
Left posterior superior iliac
Right posterior superior iliac
Left thigh
Right thigh
Left knee
Right knee
Left tibia
Right tibia
Left ankle
Right ankle
Left heel
Right heel
Left toe
Right toe

Figure 4. Marker placement during three-dimensional motion analysis according to the Plug-In-Gait model.

All study participants walked barefoot along a defined ten-meter pathway at a self-selected speed. Kinematic, kinetic, and spatiotemporal parameters (walking speed, stride length, and stance phase duration) were collected simultaneously using an eight-camera system (Vicon Motion Systems Ltd, Oxford, UK) and two force plates (Kistler, Winterthur, Switzerland).

3.5.2.1 Data reduction

For each participant, at each test session, approximately five gait trials with clean force plate strikes were analyzed for each participant. Gait trials were processed using the software program Vicon Nexus 1.8.5 (Vicon ® Motion Systems Ltd). Raw motion capture data were filtered in a Woltring Filter (Woltring, 1986) with a mean squared error setting of 15. The kinematic and kinetic gait data were then exported to the software program MATLAB®, R2014a (The MathWorks Inc., Natick, MA, USA) where minima, maxima, and the GDI for kinematics and kinetics were computed for the participants. Gait parameters from these five strides were averaged across trials to obtain one value for each parameter of interest for each participant at each test session.

3.5.2.2 Calculation of the Center of Mass

The position of the body's CoM was calculated based on the kinematics derived from the Plug-In-Gait model including 15 body segments: head, upper arms, under arms, hands, trunk, pelvis, thighs, shanks, and feet (Winter, 2004).

3.5.3 Radiologic classification of osteoarthritis

At each hospital, pre-operative standing anterior-posterior radiographs were collected according to standard procedures. Two experienced senior orthopedic surgeons assessed the radiographs together and provided the radiologic classification of knee OA according to the modified KL classification ranging from grade I-IV (Kellgren and Lawrence, 1957, Dieppe et al., 2009) (Table 2). Radiographs defined as KL scores of 3 to 4 were further sub-classified by incorporating scores of joint space narrowing (JSN) and bone attrition (Dieppe et al., 2009). Thus, a KL grade 3 radiograph with mild JSN was graded 3a, and radiographs with more severe JSN 3b. A KL grade 4 radiograph, demonstrating complete loss of joint space, was divided into 4a if there were no bone attrition and 4b if there were subchondral bone attrition. The intra-rater reliability of the modified KL classification has demonstrated substantial reproducibility, with intra-rater kappa values of 0.7 for the KL grade, 0.7 for medial JSN, and 0.8 for lateral JSN (Dowsey et al., 2012b).

3.6 OUTCOME MEASURES

An overview of the study design, study participants, and the outcome measures used in each study is provided below (Table 3).

Table 3. Overview of study design, participants, and outcome measures used in studies I-IV.

Study	Design	Participants	Outcome measures
I	Cross-sectional observational study	Total n=65 - 40 individuals with knee OA - 25 healthy controls	- GDI - GDI-kinetic - Trunk kinematics during gait - Time and distance parameters - 5STS time - SLMS repetitions/30 s - TUG time - KOOS - EQ5D - VAS Pain - Radiologic classification of OA
II	Prospective cohort study	Total n=53 - 28 individuals with knee OA - 25 healthy controls	- GDI - GDI-kinetic - Time and distance parameters - 5STS time - KOOS - EQ5D
III	Prospective cohort study	Total n=53 - 19 individuals with knee OA classified as having a 'Good' outcome - 9 individuals with knee OA classified as having a 'Poor' outcome - 25 healthy controls	- KOOS - Knee kinematics during gait - Knee kinetics during gait - Time and distance parameters - Passive range of knee motion - VAS Pain
IV	Prospective cohort study	Total n=42 - 21 individuals with knee OA - 21 healthy controls	- 5STS time - Area under the curve of CoM displacement in the medial-lateral direction - Area under the curve of CoM displacement in the anterior-posterior direction - VAS Pain

OA, Osteoarthritis; GDI, Gait Deviation Index; 5STS, Five Times Sit-to-Stand test; SLMS, Single Limb Mini Squat test; s, Seconds; TUG, Timed Up and Go test; KOOS, Knee Injury and Osteoarthritis Outcome Score; EQ5D, EuroQoL Five Dimensions; VAS, Visual Analogue Scale; CoM, Center of Mass.

3.6.1 Gait biomechanics

3.6.1.1 Gait parameters

In studies I-III, several gait parameters were evaluated. In Study I, the impact of symptomatic knee OA on gait was evaluated using both individual gait parameters and comprehensive measures of gait pattern deviations represented by the GDI and GDI-kinetic. In Study I, the individual gait parameters included range of trunk kinematics in the sagittal plane (anterior-posterior) and in the frontal plane (lateral displacement).

In Study III, the evaluated kinematic gait parameters included knee flexion-extension range during the entire gait cycle, peak knee flexion angle in swing phase, and peak knee varus angle during stance phase. The evaluated kinetic gait parameters during stance phase included peak knee flexion moment, peak knee extension moment, and peak knee valgus moment.

3.6.1.2 Time and distance parameters

Walking speed was evaluated in studies I-III, and in studies I and II walking speed was normalized (made non-dimensional) using gravity and leg length, as described by Hof (Hof, 1996). In addition, stride length and normalized stride length (stride length divided by leg length) (Hof, 1996) were evaluated in studies I and II. In studies I and III, the stance phase duration during gait (% of gait cycle) was evaluated.

3.6.1.3 The Gait Deviation Index

The GDI and GDI-kinetic allow comparison of kinematic or kinetic variables (respectively) from a participant's gait with those of a normal (pathology-free) reference group. To calculate the GDI and GDI-kinetic scores, the gait of the individuals in the knee OA group and in the control group were compared to the gait of those in a reference group. The reference group consisted of healthy individuals (n=59 for GDI, n=56 for GDI-kinetic) selected from the control database at the Motion Analysis Laboratory at Karolinska University Hospital. The reference group did not include the 25 individuals constituting the control group.

A GDI or GDI-kinetic score of ≥100 represents typical gait pattern, and each 10-point reduction below 100 represents one SD from typical gait. A GDI score of >100 indicates that an individual's gait is closer to the average normal than a randomly selected normal. The closer an individual gets to match the 'average normal gait pattern' on a point-by-point basis, the higher the GDI score (Schwartz and Rozumalski, 2008). The GDI is calculated from pelvis and hip kinematics in all three anatomical planes, the knee and ankle in the sagittal plane, and foot progression in the transversal plane (Figure 5A). The GDI-kinetic is calculated from the hip, knee, and ankle moments in the frontal and sagittal plane and total joint power in the hip, knee, and ankle (Figure 5B). Each limb is considered independently.

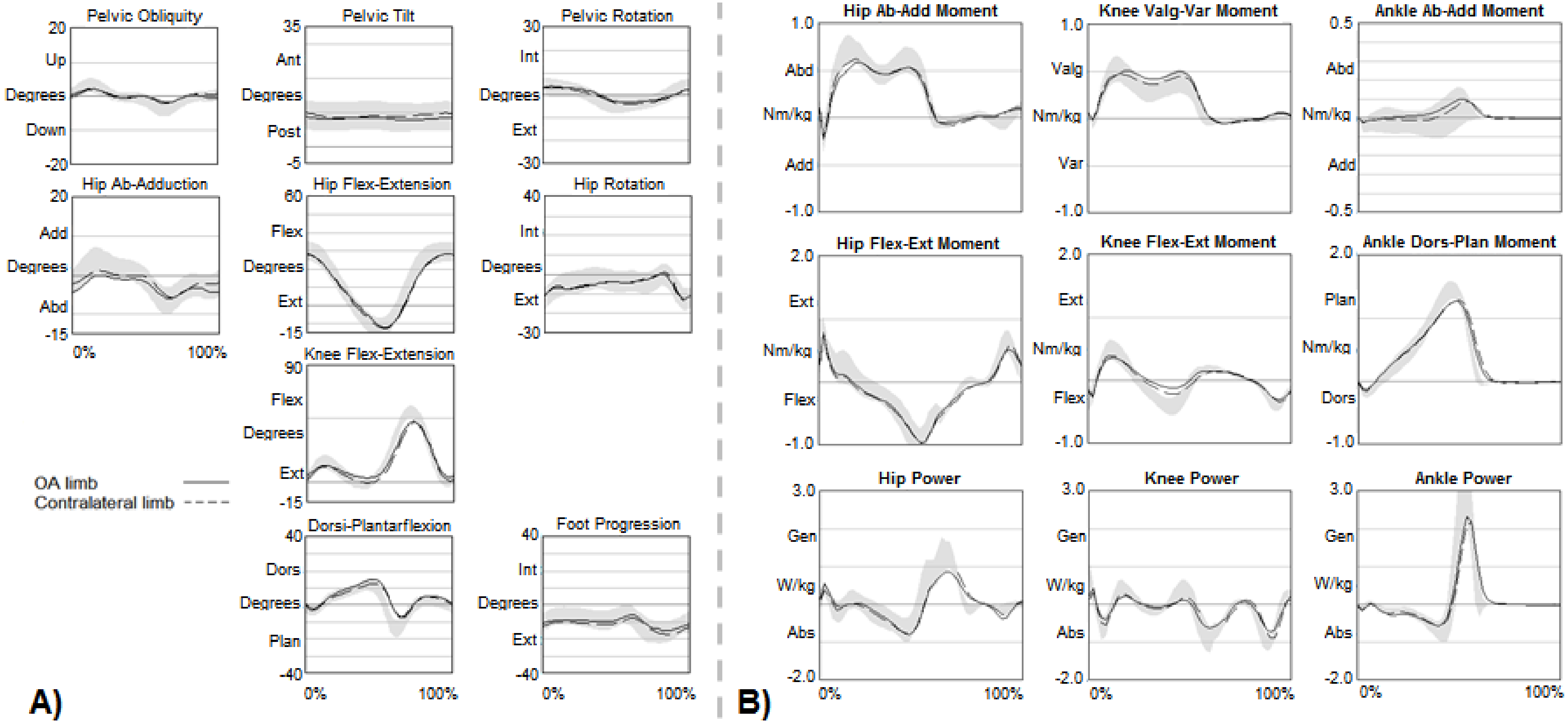


Figure 5. A) Joint kinematics of the pelvis, hip, knee, and ankle during gait, all of which are included in the Gait Deviation Index. B) Joint kinetics and total joint power of the hip, knee, and ankle during gait, all of which are included in the Gait Deviation Index-kinetic. The solid black line represents the group mean of the osteoarthritis (OA) limb and the dashed line the contralateral limb of the included individuals with symptomatic knee OA (n=40). The shaded area represents the mean ± 1 standard deviation of the control group (n=25). A gait cycle starts when one foot strikes the ground (0%) and ends when the same foot strikes the ground again (100%). During normal gait, foot-off occurs at approximately 60% of the gait cycle (Gage, 2009).

3.6.2 Performance-based outcome measures

3.6.2.1 The Five Times Sit-to-Stand test

The 5STS test was conducted by measuring the time taken for a participant to stand up from a seated position, with arms folded across the chest, five times as fast as possible. The test starts in a seated position and ends in standing (Lord et al., 2002). All participants used the same bench (seat height of 44.5 cm) according to the standard 5STS test protocol (Lord et al., 2002). The test was performed twice, timed to a hundredth of a second, and the best (lowest) value was used in the analysis. One practice repetition preceded the test.

To determine post-operative improvement in performance-based function in Study II, the 5STS test was used as this test is easily applicable in clinical practice. Individuals with knee OA were grouped and compared based on their 5STS test results according to the established MDC of 2.5 seconds in 5STS test performance (Goldberg et al., 2012). Individuals with a reduction in time equal to or greater than 2.5 seconds were considered to have a 'Good' 5STS outcome, and those with a reduction of less than 2.5 seconds or an increase in time were considered to have a 'Bad' 5STS outcome.

In Study IV, movement strategies used by individuals with knee OA to perform the 5STS test were evaluated using 3D motion analysis and compared to a control group. To explore movement strategies used to perform the 5STS test, the trajectory of the body's CoM in the anterior-posterior direction and in the medial-lateral direction was evaluated (Figure 6). The position of the body's CoM was calculated using the Plug-in-Gait model (Vicon ®, Oxford, UK).

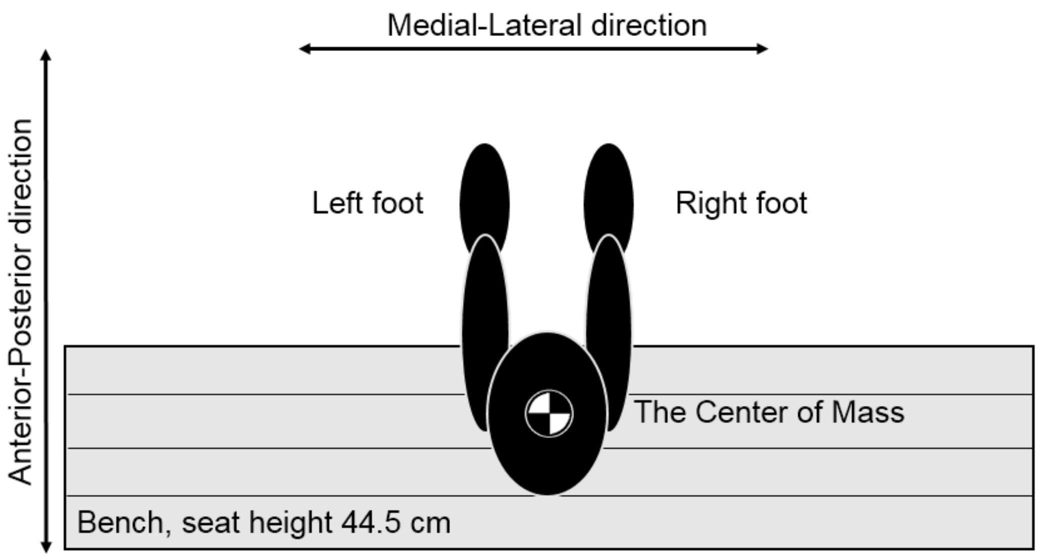


Figure 6. The evaluated directions of the Center of Mass displacement during the Five Times Sit-to-Stand test.

The trial performed with the best (shortest) time was used in the analysis. Six events were identified for each 5STS trial: the beginning of the test and the ends of each subsequent cycle, noting that cycle 5 ends in a standing position. Cycles 1-4 were considered full cycles and were used for further analysis. Each cycle was scaled to 100 data points (Figure 7). To quantify the displacement of the CoM, the AUC was calculated for each direction and each cycle as it captures both the magnitude and the duration of the compensation.

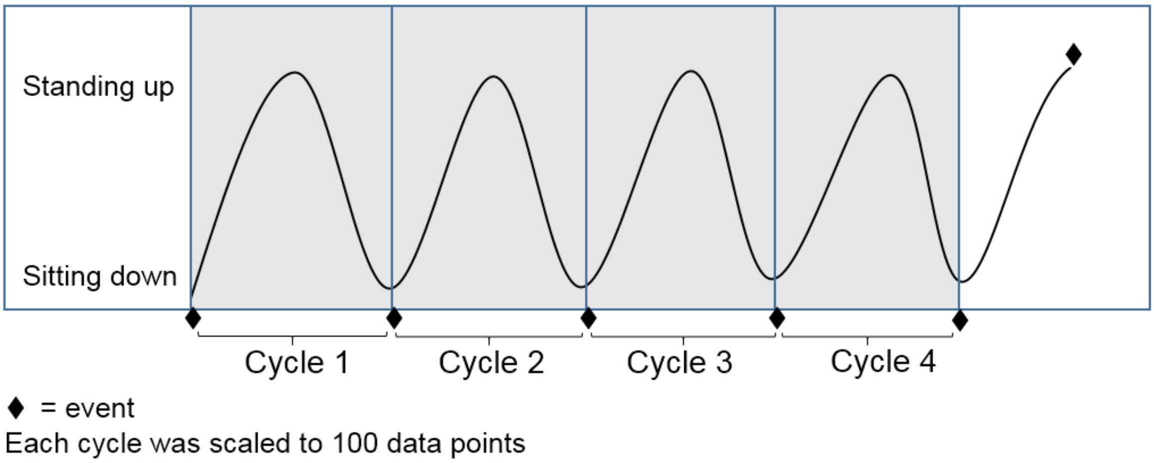


Figure 7. Schematic figure of the identified events of a Five Times Sit-to-Stand test trial.

3.6.2.2 The Timed Up and Go test

The TUG test was conducted by measuring time taken for a participant to rise from a chair (with arms passive, resting along the sides of the trunk), walk three meters, turn around, and return to seated position. The test was performed twice, one time clockwise and one time counter clockwise (Podsiadlo and Richardson, 1991). All participants used the same chair (seat height of 44 cm). The test was timed to a hundredth of a second, and the best (lowest) value was used in the analysis.

3.6.2.3 The Single Limb Mini Squat test

To perform the SLMS test, the participant stood on one leg on a well-defined area shaped like the letter “T” with the long axes of the foot on the stem and toes placed on the arm of the “T”. Fingertip support for balance was provided by a frame in front of the participant. The participant was instructed to flex the knee (on the standing leg) until toes were no longer visible and then fully extend the knee (Bremander et al., 2007). Approximately five practice squats preceded the test. The maximum number of mini squats in 30 seconds was recorded for each leg.

3.6.3 Patient-reported outcome measures

After completing the gait trials, study participants completed the self-administered questionnaires.

3.6.3.1 The Knee Injury and Osteoarthritis Outcome Score

The KOOS was used in studies I, II and III. In Study III, the MDC of the KOOS subscale Knee-related QoL was used as a cut-off to classify post-operative outcome as either a ‘Good’ outcome (change equal to or greater than the MDC) or as a ‘Poor’ outcome (change smaller than the MDC). One year after TKA, the MDC of KOOS Knee-related QoL is reported to be 21.1 points (Collins et al., 2011, Roos and Toksvig-Larsen, 2003).

3.6.3.2 The EuroQol Five Dimensions

In this thesis, the EQ5D version where each item has three response options (EQ5D 3L) was used and the United Kingdom (UK) EQ5D value set (tariff). The UK value set is based on modelled values to obtain a single index value for each of the 243 possible health states (Dolan and Roberts, 2002).

3.6.3.3 Visual analogue scale

A VAS, a valid and commonly used instrument for assessing pain, was used to evaluate perceived pain (Carlsson, 1983). The VAS consists of a ten-centimeter long line where the participant is asked to mark how much pain he or she is experiencing. It is measured in millimeters: 0 means “No pain at all” and 100 means “Worst imaginable pain”. Individuals with knee OA were asked to rate their perceived pain before and after completing gait trials, and after completing the 5STS test, the TUG test, and the SLMS test.

3.7 TOTAL KNEE ARTHROPLASTY

Seven senior orthopedic surgeons from two hospitals (Ortho Center Löwenströmska Hospital, and Karolinska University Hospital) performed the surgeries. All procedures were performed using a posterior cruciate ligament-retaining cemented TKA (PFC-Sigma, DePuy, Johnson & Johnson, Warsaw, Poland).

3.7.1 Post-operative rehabilitation

Post-operative regimes allowed full weight bearing, together with use of an appropriate walking aid, and unrestricted range of motion. Individuals with TKA completed post-operative rehabilitation according to the standard practice at each hospital. The rehabilitation program included in-patient physiotherapy (<1 week) and thereafter rehabilitation was provided in a primary care setting of the individual’s choice. The standard post-operative rehabilitation lasted for a median duration of three months (range: 1-6 months) following TKA.

3.8 STATISTICAL METHODS

All statistical analyzes were performed using IBM SPSS Statistics version 22 (Chicago, IL, USA) and the significance level was set at α = 0.05. An overview of the statistical methods used in studies I-IV is provided below (Table 4). With regards to data from the control group in studies I-III, a pathology-free and functionally symmetric group, the right leg was arbitrarily chosen in the statistical analysis in those cases where unilateral evaluations were performed.

Table 4. Statistical methods in alphabetical order used in studies I-IV.

Statistical method	Study I	Study II	Study III	Study IV
ANCOVA			x	
Bonferroni correction				x
Cohen's d effect size		x		
Descriptive statistics	x	x	x	x
Fishers exact test		x	x	x
Independent sample t-test	x	x	x	x
Interaction			x	x
Mann Whiney U test	x	x	x	
Multivariable linear regression	x			
Paired sample t-test	x	x		x
Receiver operating characteristic curve			x	
Spearman's rank correlation coefficients	x			
Two-way repeated measures ANOVA			x	x
Wilcoxon signed-rank test		x		x
95% Confidence interval		x	x	x

ANCOVA, Analysis of Covariance; ANOVA, Analysis of Variance.

3.8.1 Normal distribution of data

In studies I-IV, normal distribution of the data was assessed using Shapiro-Wilk's tests and Q-Q plots.

3.8.2 Differences between individuals with knee osteoarthritis and controls

In studies I, II and IV, differences between individuals with knee OA, and later individuals with TKA, and the control group were evaluated using independent sample t-tests and Mann Whitney U tests, depending on data distribution.

In Study IV, two separate two-way repeated measures ANOVA with a between-groups factor of Group (Knee OA pre/Knee OA post TKA vs. Control) and a within-groups factor Cycle (1-4) were performed to compare the AUC between individuals with knee OA and the control group. In addition, a Group × Cycle interaction was performed. The Group × Cycle interaction refers to the statistical test of whether the changes from cycle to cycle differed by group. In the case of a significant interaction, simple effects were tested; that is, effects of one factor were explored by holding the levels of the other factor fixed. The p-values where then adjusted according to the Bonferroni procedure.

3.8.3 Differences between pre- and post-operative assessments in individuals with knee osteoarthritis

In studies II, III, and IV, paired sample t-tests or Wilcoxon signed rank tests were used to evaluate change in outcome measures between pre- and post-operative assessments in individuals with knee OA, depending on the distribution of data. In Study II, the magnitude of change was evaluated using measures of effect size (Cohen's *d*) and 95% confidence intervals (CI) (Nakagawa and Cuthill, 2007):

$$d = t\text{paired}\sqrt{\frac{2(1-r12)}{\text{n}}},$$

where t_{paired} is the score from the paired t-test and $r12$ is the correlation coefficient between the two assessments (Nakagawa and Cuthill, 2007, Dunlap et al., 1996).

In Study IV, a two-way repeated measures ANOVA with within-groups factors of Time (pre-operative and post-operative) and Cycle (1-4) was performed to evaluate change in the AUC of the body's CoM trajectory pre-operatively to post-operatively. The interaction of Group × Cycle was also tested.

3.8.4 Differences between individuals classified as having a 'Good' or a 'Poor' outcome after total knee arthroplasty

In Study III, the MDC of the KOOS Knee-related QoL subscale was used to classify individuals' post-operative outcome as either a 'Good' outcome or a 'Poor' outcome. The 'Good' and 'Poor' outcome groups were analyzed separately and compared.

Differences in baseline data and change in VAS pain (raw scores) between the 'Good' and the 'Poor' outcome group were evaluated using independent sample t-tests and Mann Whitney U tests. Passive range of knee motion, knee gait biomechanics, and time and distance parameters were analyzed using a two-way repeated measures ANOVA with the within-groups factor Time (prior to TKA and one year after TKA) and the between-groups factor Group (the 'Good' outcome group and the 'Poor' outcome group) and the interaction Group × Time. The Group × Time interaction refers to the statistical test that determines whether the response profile for one group is the same as for the other group. In case of a significant interaction, simple effects were tested (i.e., effects of one factor holding the levels of the other factor fixed). To adjust for pre-operative differences between groups, an ANCOVA was performed. A Fisher's exact test was used to determine whether the proportion of patients differed between the groups with regards to the KL classification of radiographic severity of knee OA.

3.8.5 Associations between outcome measures

In Study I, associations between the primary outcomes (GDI and GDI-kinetic) and clinical outcomes (PROM and performance-based measures) were evaluated using Spearman's rank correlation coefficients. Correlations were interpreted according to Dancey and Reidy; an *r*-value of 1 is a perfect correlation, 0.7 - 0.9 strong, 0.4 - 0.6 moderate, 0.1- 0.3 weak, and 0 no correlation (Dancey and Reidy, 2007).

Characteristics of individuals with knee OA – including age, sex, BMI, radiologic classification, time and distance parameters, trunk motion during gait (kinematics in the sagittal and frontal plane), and VAS pain (raw scores) – were considered potential covariates to the associations between degree of gait pattern deviation and clinical outcomes in the regression models. Therefore, the relationships between these characteristics and dependent variables were also explored with Spearman's rank correlation coefficients and considered possible explanatory variables in the regression model (Rutz et al., 2013).

Separate multivariable linear regression models were created for each dependent variable: GDI OA limb, GDI contralateral limb, GDI-kinetic OA limb, and GDI-kinetic contralateral limb. Probability for entry in the backward regression was set at 0.05 and removal at 0.10. To enhance confidence in the final models, Cook's distance and residual plots were examined.

In Study III, receiver operating characteristic (ROC) curves were used to evaluate whether change in knee gait biomechanics could be used to correctly classify patients into either the 'Good' or the 'Poor' outcome group. The area under the ROC curve and 95% CI were calculated. An AUC of at least 0.7 was considered appropriate (de Vet et al., 2011).

In Study IV, the effect of BMI on the body's CoM trajectory was explored by adjusting for this variable in all models. Because BMI did not affect the AUC in either direction (medial-lateral and anterior-posterior), BMI was not included in the results of Study IV.

4 RESULTS AND DISCUSSION

This section summarizes and discusses the main findings of studies I-IV included in this thesis. Detailed results of each study are provided in the papers and manuscript.

4.1 OVERALL GAIT PATTERN DEVIATIONS

4.1.1 The Gait Deviation Index in individuals with knee osteoarthritis

Baseline GDI scores and change following TKA surgery for the study population included in this thesis and all subgroups featured in the included studies evaluating gait (studies I-III) are presented together for visual analysis purposes (Figure 8).

In Study I, the impact of symptomatic knee OA on overall gait pattern was evaluated using the GDI for kinematics and kinetics. These measures were deemed sensitive for identifying deviant gait kinematics and kinetics in individuals with knee OA compared to controls. Individuals with knee OA presented with significantly lower GDI and GDI-kinetic scores for the OA limb and the contralateral limb as compared to controls (Figure 8). GDI-kinetic scores were significantly lower for the contralateral limb than for the OA limb (Study I).

Visual analysis of the gait curves, from which the GDI scores are calculated, revealed that kinematic deviations of the OA limb were present in all three anatomical planes. Deviations were most evident in the sagittal plane, with lower ranges of joint rotations in all the major lower extremity joints (Figure 5A). Kinetic deviations were displayed in both the OA limb and the contralateral limb as represented by an increased internal knee valgus moment during mid and terminal stance, reduced moments in the hip, knee, and ankle in the sagittal plane, and reduced joint power in the hip, knee, and ankle (Figure 5B). The deviations exhibited in the studied OA group are in accordance with those described in previous knee OA research, including reduced range of knee flexion, reduced knee extension moments during loading response, reduced knee flexion moments during mid and terminal stance, increased knee valgus moments, and reduced hip abduction moments during stance phase (Zeni Jr and Higginson, 2009, Deluzio and Astephen, 2007, Astephen et al., 2008).

Kinematic gait deviations precede degenerative changes and are associated with the development of OA (Andriacchi and Mundermann, 2006). Furthermore, increased loading of the medial knee compartment during walking is associated with the rate of OA progression (Andriacchi and Mundermann, 2006). Study I reveals that symptomatic knee OA affects overall gait patterns on both the OA limb and the contralateral limb. In addition, GDI-kinetic scores were significantly lower for the contralateral limb than for the OA limb, suggesting joint loading alterations and greater deviations from normal for the contralateral limb than for the OA limb.

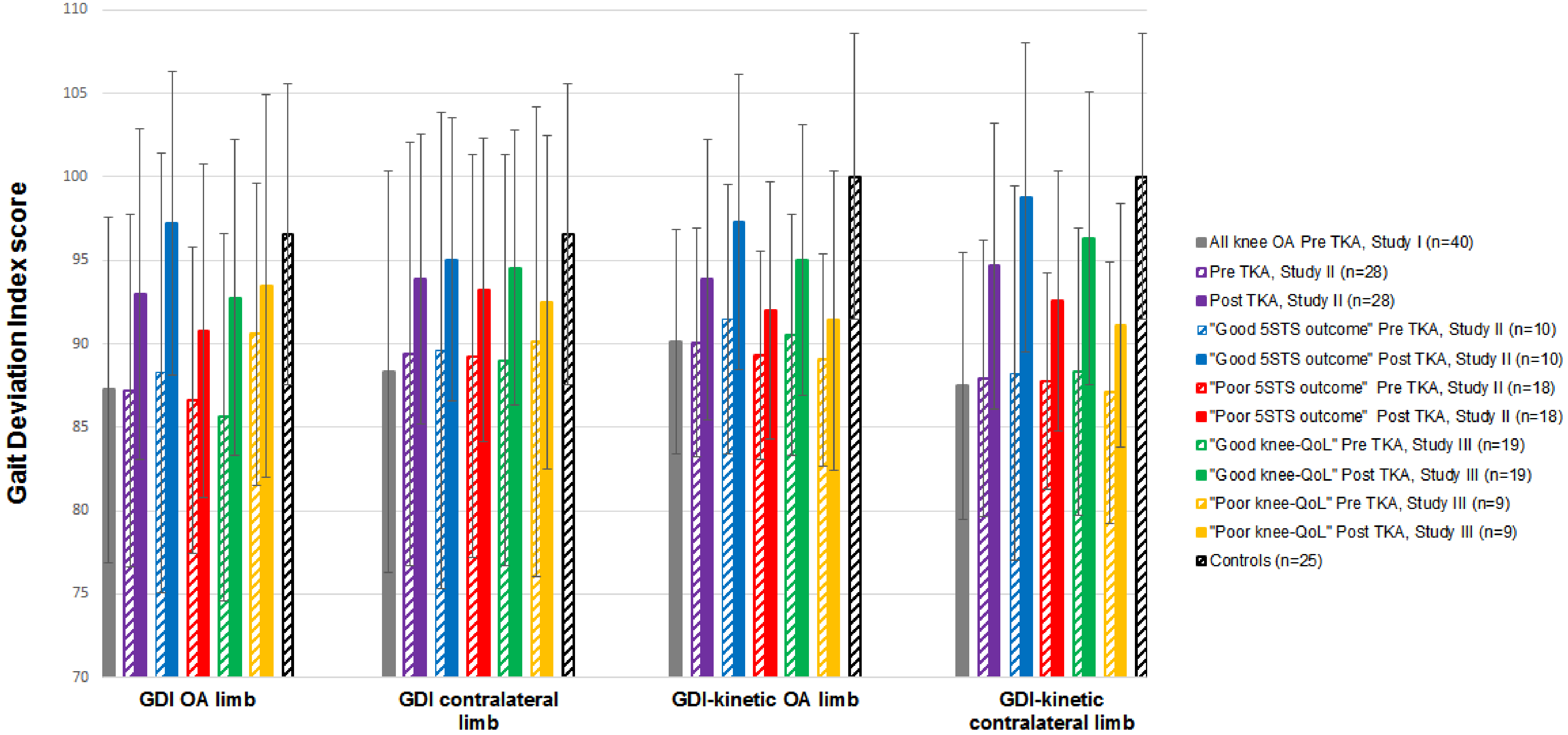


Figure 8. Mean (±1 standard deviation) kinematic and kinetic Gait Deviation Index (GDI) scores for the study population and subgroups included in this thesis. Pre-operative evaluations of individuals with knee osteoarthritis (OA) were performed within one month prior to total knee arthroplasty (TKA), and post-operative evaluations one year after surgery. 5STS, Five Times Sit-to-Stand test, QoL; Quality of Life.

4.1.1.1 Impact of total knee arthroplasty on overall gait pattern deviations

One year after TKA, improvements in overall gait patterns were found as indicated by increased GDI scores on the operated limb by 5.8 scores (effect size 0.4) and increased GDI-kinetic scores on the operated and the non-operated limb by 3.8 and 6.7 scores, respectively (effect size 0.5 and 0.9, respectively) (Study II). Compared to the control group, individuals with TKA demonstrated significantly lower GDI-kinetic scores, whereas kinematic GDI scores were comparable to the controls (Figure 8).

The largest gait pattern improvements were found in GDI-kinetic scores for the contralateral (non-operated) limb, implying correction of compensation strategies and demonstrating that TKA has a positive effect on gait patterns for both limbs. Compared to the control group, GDI-kinetic scores were still significantly lower in individuals with knee TKA one year after surgery (Study II). These results corroborate the findings of others who report that gait pattern recovery at the contralateral knee is variable and often incomplete (Metcalfe et al., 2013). However, one year to follow-up may be too short with regards to restoring joint loading patterns. That is, functional recovery may continue beyond one year and even up to two years after surgery (Kleijn et al., 2007).

4.1.1.2 Magnitude of change in overall gait pattern following total knee arthroplasty

Surgery, more specifically TKA, represents the treatment option of choice when other treatments to alleviate pain and improve physical function has failed. The procedure is well documented to reduce pain and improve patient-reported function (Carr et al., 2012, Skou et al., 2015); however, its effect on other aspects of functions is not as well understood.

In Study II, the magnitude of change in gait pattern following TKA was evaluated using effect size, and improvements in overall gait pattern achieved one year after surgery ranged between 0.3 and 0.9 for the GDI and GDI-kinetic, respectively. The corresponding effect size for improvement in the KOOS subscale Function in ADL was 0.8. The smallest change was found in (kinematic) GDI scores of the contralateral limb with an effect size of 0.3 (Study II).

The mean GDI scores were relatively high among individuals awaiting TKA: GDI OA limb mean 87 (SD 11) and GDI-kinetic OA limb mean 90 (SD 7). Thus, the room for improvement was fairly limited (Figure 8). With gait patterns close to normal, the measurement used to detect changes in gait must be responsive to distinguish improvements following interventions. Results from studies I and II demonstrate that the GDI and GDI-kinetic are sensitive measures, responsive to detect change in the overall gait pattern following TKA, and can be used to evaluate gait deviations in individuals with knee OA prior to and following TKA. However, specific gait parameters, such as knee flexion-extension range or peak knee varus angle, is likely even more discriminative within this population.

How large of a change is needed to regard the gait pattern improved? This question is highly relevant and at the very same time a great challenge to answer. The awareness of one's gait pattern will differ between individuals. Therefore, merely asking individuals of their perceived change in gait pattern and relate this to change in GDI scores will most likely render a cut-off that will vary between individuals and across populations.

Within this thesis, the MDC of 5.4 GDI scores, previously established among adults with RA (Esbjornsson et al., 2014), was used as a cut-off for classifying individuals into functional improvement. The MDC is not an absolute truth, but purely a statistical estimate that provides a threshold for interpretation (Beaton et al., 2001). Interestingly, there was little variation between trials (inter-sessional) among individuals with knee OA. Therefore, it is probable that a MDC calculated within this study sample (Standard error of measurement*1.96√2) may have generated an even lower MDC value (Beckerman et al., 2001). In children with cerebral palsy, who walk with large gait pattern variations, the MDC of the GDI has been reported to be 10.8 (Rasmussen et al., 2015).

4.1.1.3 Strengths of the Gait Deviation Index

The strengths of the GDI are that it summarizes the gait pattern of each limb, including all major lower extremity joints, in addition to taking the entire gait cycle into account. In doing so, the limitation of merely choosing a few specific gait variables at a specific point in the gait cycle is avoided. Because the GDI provides an index score of overall gait pattern deviations from normal, it may be useful in evaluating treatment. It may also be more convenient for a clinician, patient, or non-expert to appraise an index score, describing the overall gait pattern expressed as the degree of deviation from normal gait, than extensive reports generated from a single gait analysis.

4.1.1.4 Weaknesses of the Gait Deviation Index

The GDI and GDI-kinetic do not explicitly identify the underlying deficits, and the measures have no direction specificity (i.e., five degrees excess flexion is indistinguishable from five degrees excess extension). Consequently, there is still a need for interpretation of the underlying gait deviations. To calculate the GDI, normative data is needed, and preferably this should be lab-specific. A marker set including the pelvis, hip, knee, and ankle joints is needed, so the practical advantages over other specific gait variables are not tangible. In addition, all limitations that are associated with 3D motion analysis, including errors related to marker placement and movement artefacts due to soft tissue, are also limitations that apply to the GDI. The GDI is speed-dependent (Schwartz et al., 2008), which may be regarded as a weakness. This can be handled by using a speed-matched reference set; however, for individuals walking at a very slow walking speed, it may be difficult to find healthy reference subjects. Furthermore, the GDI has displayed modest reliability and responsiveness to change among individuals with cerebral palsy (Rasmussen et al., 2015). In individuals with large gait pattern variations between trials, it should be noted that relatively large changes in GDI scores are needed at an individual level to accurately claim that a true change in the overall gait pattern has occurred.

4.1.2 Associations between the degree of overall gait pattern deviation and clinical outcome measures of function

In Study I, the aim was also to explore associations between the degree of gait pattern deviation and commonly used clinical outcome measures of function. Weak associations between PROM and GDI scores were hypothesized, since previous research has reported a discrepancy between patient-reported function and actual functional ability (Stratford et al., 2003, Stratford and Kennedy, 2006, Stevens-Lapsley et al., 2011, Mizner et al., 2011). The KOOS subscale Function in ADL is the only subscale that includes questions concerning walking, so that subscale was hypothesized to show a weak-to-moderate association to the GDI scores. No significant correlations were found between the kinematic GDI and any of the clinical outcome measures evaluated (Table 5). Neither perceived pain assessed with a VAS nor radiographic severity of knee OA according to the modified KL classification was found to be associated to the GDI or GDI-kinetic. A probable explanation for the lack of association between GDI scores and perceived pain may be that adaptive gait deviations effectively reduce pain during gait for some individuals, compensations that result in variable ratings of perceived pain. Results of Study I demonstrate that the kinematic GDI captures different aspects of function that cannot be identified by performance-based tests or PROM.

Joint loading deviations, as measured by the GDI-kinetic, were found to be negatively associated to a moderate-to-strong degree with all the evaluated performance-based tests (Table 5). Furthermore, lower GDI-kinetic scores were moderately associated to the KOOS subscales Function in ADL and Knee-related QoL. Performance on the TUG test was negatively associated with GDI-kinetic, indicating that increased time to complete the TUG is associated with increased joint loading deviations during gait (lower GDI-kinetic scores). This information is useful to clinicians evaluating individuals with knee OA in clinical practice. Performance on the TUG test could guide treatment towards rehabilitation exercises promoting normalized loading (i.e., strengthening the quadriceps muscles to tolerate an increased loading response, strengthening hip abductors to allow for increased hip abduction moments, and increase knee joint range of motion to allow for full extension during stance phase).

Multivariable linear regressions revealed that walking speed and lateral trunk sway explained 43% of the total variance in GDI-kinetic scores of the contralateral limb. Walking speed and age explained 22% of the total variance in kinematic GDI scores of the OA limb (Study I). Thus, it may be concluded that age does not limit the usefulness of the GDI and GDI-kinetic. Performance on the SLMS test was the only explanatory variable among the clinical outcomes remaining in the regression models of GDI and GDI-kinetic. No other clinical outcome remained significant in either of the regression models.

Table 5. Correlations between overall gait patterns summarized using the Gait Deviation Index, performance-based function, and patient-reported function in individuals with knee osteoarthritis scheduled for total knee arthroplasty.

Knee OA n=40	GDI OA	GDI contralateral	GDI-kinetic OA	GDI-kinetic contralateral	TUG	5STS	SLMS
GDI contralateral	**0.527 ᴥ**						
GDI-kinetic OA	**0.467 ᴥ**	**0.474 ᴥ**					
GDI-kinetic contralateral	**0.502 ᴥ**	**0.596 ᴥ**	**0.675 ᴥ**				
TUG	-0.219	-0.301	**-0.684 ᴥ**	**-0.419 ᴥ**			
5STS	-0.167	-0.017	**-0.381***	**-0.328 ***	**0.583 ᴥ**		
SLMS	0.044	0.088	**0.373***	0.186	**-0.394 ***	-0.294	
KOOS ADL	-0.072	0.010	**0.354 ***	0.160	-0.281	**-0.509 ᴥ**	0.258
KOOS Sport/Rec	-0.047	0.086	-0.075	-0.036	-0.041	-0.068	-0.057
KOOS QoL	0.020	0.117	**0.349 ***	0.196	-0.231	-0.158	0.109

OA, Osteoarthritis; GDI, Gait Deviation Index; TUG, Timed Up and Go test; 5STS, Five Times Sit-to-Stand test; SMLS; Single Limb Mini Squat test; ADL, Function in Activities of Daily Living; Sport/Rec, Function in Sport and Recreation; QoL, Knee-related Quality of Life. Spearman's rank order correlations were used to examine the correlations. Level of significance set to * $p<0.05$, ᴥ $p<0.01$.

4.1.2.1 Impact of walking speed on the Gait Deviation Index

Walking speed is often a subject for debate within gait analysis circles. The question is whether to control for speed. Proponents of controlling for walking speed often refer to the fact that gait mechanics depend on the velocity and to compare results between individuals and groups speed must be adjusted. All gait analyzes included in this thesis were performed with the participants walking at a self-selected speed. Slow walking speed is known to cause lower GDI scores (Esbjornsson et al., 2014, Schwartz et al., 2008), as previously discussed. To account for walking speed, an alternative approach could have been to ask the control group to walk at different speeds and use walking speed as an additional feature to match. However, there was an interest in evaluating the effect of walking speed on GDI scores in a knee OA population, and therefore walking speed was one of the patient characteristics included in the regression models.

In adults with RA, the GDI was found to be partially influenced by walking speed; however, disease-related pathology was a greater contributor to gait deviation (Esbjornsson et al., 2014). In individuals with severe hip OA, stronger hip flexor and hip abductor muscles were found to be associated with higher GDI scores, and higher patient-reported physical function and QoL-scores were associated with higher GDI scores (Rosenlund et al., 2016). However, adjusting the analysis for walking speed did not influence the associations.

4.1.3 Interrelationship between change in overall gait pattern deviations and clinical outcome measures of function

Study II examined interrelated changes of function one year following TKA. Individuals with knee OA were dichotomized into two groups based on change in performance on the 5STS test. The MDC of 2.5 seconds was used as a cut-off to classify individuals' post-operative outcome as either a 'Good' 5STS outcome (change equal to or greater than the MDC) or a 'Bad' 5STS outcome (change smaller than the MDC). Ten individuals (36%) were classified as having a 'Good' 5STS outcome, and 18 (64%) as having a 'Bad' 5STS outcome (Study II).

Change in GDI and GDI-kinetic scores were evaluated for the 'Good' and 'Bad' 5STS outcome groups separately. The 'Good' 5STS outcome group demonstrated significant improvements in GDI scores on the operated limb and GDI-kinetic scores on both the operated and non-operated limb. In the 'Bad' 5STS outcome group, no significant changes were found in GDI scores, whereas GDI-kinetic scores on non-operated limb increased significantly (Figure 8). The improvements leading to a better performance on the 5STS test may be related to pain reduction, increased quadriceps strength, and improved balance. All these improvements seem to also generate improvements in GDI and GDI-kinetic scores. However, upon evaluation of differences in patient-reported function between groups, no differences in either of the KOOS subscales were found, suggesting that neither patient-reported pain nor perceived function differed between the groups (Figure 10).

In summary, individuals improving their performance on the 5STS test beyond the MDC exhibited substantial improvements in their overall gait pattern as represented by increased GDI and GDI-kinetic scores. The ability of the KOOS to differentiate between individuals improving in performance-based function was insufficient. These findings are in accordance with findings of others, highlighting that PROM and performance-based outcome measures capture different aspects of function and should be used as complementary measures (Mizner et al., 2011, Stratford and Kennedy, 2006, Stevens-Lapsley et al., 2011). Furthermore, Study II findings also advocate for the use of the 5STS test in clinical practice as improvements on this test are accompanied by overall gait pattern improvements.

4.2 PERFORMANCE-BASED FUNCTION

In Study I, performance on the TUG, 5STS, and SLMS tests in individuals with knee OA were compared to controls. Results demonstrated significantly longer time to complete the TUG and the 5STS tests, and fewer SLMS repetitions performed in individuals with knee OA as compared to controls. One year after surgery, performance on the 5STS test improved significantly (a reduction in time of 1.6 seconds; effect size 0.6) although test performance in individuals with TKA were still significantly slower than the control group (Study II).

4.2.1 The Five Times Sit-to-Stand test

The 5STS test was introduced as a performance test reflecting lower limb strength. Research has shown that the test is a good predictor of quadriceps strength (Bohannon, 1998, Lord et al., 2002), and that it is a valid test of dynamic balance (Whitney et al., 2005). The sit-to-stand movement is an important movement occurring many times each day. A recent literature review suggested it is reasonable to expect older community-dwelling individuals to perform at least 45 sit-to-stand transitions per day (Bohannon, 2015).

4.2.1.1 Responsiveness to change of time to complete the Five Times Sit-to-Stand test

In Study II, it was hypothesized that performance on the 5STS test would improve one year after surgery but would not reach the level of healthy controls. Individuals with knee OA significantly improved their performance after surgery by reducing the time taken to complete the test (Study II). However, only 10 (36%) individuals with TKA reduced their time to perform the 5STS test by 2.5 seconds or more.

The MDC of 2.5 seconds on the 5STS test was used in Study II (Goldberg et al., 2012). This MDC is based on a sample of 29 females, with a mean age of 74 years, who could walk at least ten meters and stand at least ten minutes without an assistive device, and had no neurological disease, diabetes, visual deficits, or amputated extremities (Goldberg et al., 2012). Caution should be taken not to overestimate the importance of this value, since the two studied groups (ours and Goldberg's) might differ substantially.

The MDC of the 5STS test has been evaluated among individuals with severe knee or hip OA (Villadsen et al., 2012). Twenty individuals with a mean age of 69 years with severe knee or hip OA were assessed for test-retest reliability and agreement on two occasions one week apart. In this sample, the MDC of the 5STS test was 2.7 seconds. Had the 2.7 seconds MDC been used as the cut-off in Study II, the results would have remained the same as all ten individuals classified as having a 'Good' 5STS outcome reduced their time by at least 3.1 seconds. The similar MDC's found by Goldberg et al. and Villadsen et al. together with the results of Study II strengthens the use of the MDC when evaluating 5STS test performance in clinical practice among individuals with knee OA.

4.2.1.2 Movement strategies used to perform the Five Times Sit-to-Stand test

In Study IV, strategies used to perform the 5STS test were evaluated using 3D motion analysis. Specifically, the trajectory of the body's CoM when performing the test was estimated and compared between individuals with knee OA and healthy controls. It was hypothesized that an increased shift away from the painful OA limb would be observed in individuals with knee OA in the medial-lateral direction as a strategy to unload the painful osteoarthritic limb. In addition, it was hypothesized that individuals with knee OA would display an increased forward (anterior) displacement of the CoM to reduce muscular effort by reducing the knee extension moment (Figure 6).

In Study IV, 21 of the 40 originally included individuals with knee OA had complete pre- and post-operative assessments with good quality 3D motion analysis data and were included in the study. Prior to surgery, individuals with knee OA displayed a larger contralateral shift and a larger forward displacement of the CoM than controls. Upon evaluating the cycles separately, results showed that during the first cycle there were no differences between trajectories in the knee OA group pre-operatively and controls (Figure 9). During the following cycles, the AUC in the anterior-posterior direction was reduced in the control group, indicating the controls adapted their movement after the first cycle and could perform it more efficiently with less displacement of the CoM (Figure 9). One year after surgery the CoM trajectory in the medial-lateral direction was comparable to the controls. The CoM trajectory in the anterior-posterior direction was not statistically different from the controls. However, upon comparison among specific cycles, individuals with TKA regressed towards pre-operative levels during the last cycle and displayed a larger forward displacement compared to the control group.

4.2.1.3 Responsiveness to change of the Center of Mass trajectory

In this sub-set of 21 study participants, no significant differences were found in time to complete the 5STS test between individuals with knee OA and the control group, neither pre-operatively nor post-operatively. However, significantly larger CoM displacements towards the contralateral limb and anteriorly were found among individuals with knee OA compared to the controls. After surgery, when pain was reduced, the CoM displacement in the medial-lateral direction was no longer different to that of the control group. In the anterior-posterior direction, the AUC decreased after surgery in cycles 2 and 3, but not in cycle 4 (Figure 9). This finding may reflect residual quadriceps weakness that only becomes evident towards the end of the test. Although the data collected in Study IV cannot support this statement directly, previous research has shown reduced maximal and explosive quadriceps strength six months after TKA (Vahtrik et al., 2012). At long term follow-ups (six to 13 years after TKA), the hamstring-to-quadriceps ratio is increased, suggesting weakness of the quadriceps and compensations by the hamstrings (Huang et al., 1996).

4.2.1.4 Strengths of the Five Times Sit-to-Stand test

Using a study sample of 40 individuals with knee OA awaiting TKA and a control group of 25 individuals, time to complete the 5STS demonstrated good selective ability (Study I). Furthermore, the 5STS test was responsive to change in performance when re-evaluated one year after surgery, demonstrating an effect size of 0.6 (95% CI 0.2-1.0) (Study II). When evaluating the CoM trajectory during the 5STS test, good selective ability was observed among individuals with knee OA and healthy controls and this using an even smaller study sample (21 individuals in each group) (Study IV). Quantification of the CoM trajectory appears to be a sensitive and responsive measure of functional compensations among individuals with knee OA. By observing how the sit-to-stand movement is performed in addition to time taken to complete the test, valuable information on what may be the cause of compensation could be obtained.

4.2.1.5 Weaknesses of the Five Times Sit-to-Stand test

At the baseline assessment, one individual in our study sample of 40 individuals with knee OA was unable to perform the 5STS test without using arms to push off the seat. Although the group of individuals with knee OA were scheduled for TKA, they had no other comorbidities, and they all ambulated without the use of a walking aid. Therefore, the 5STS test may be too difficult to perform for individuals with advanced OA and additional comorbidities.

The 5STS test is suggested to be a surrogate measure of lower limb strength, yet several other factors (e.g., balance, age, weight, and sensorimotor measures) influence test performance (Lord et al., 2002, Schenkman et al., 1996). The seat height used during the test is an additional factor that will affect performance. A decision should be made whether to adjust the seat height according to the height of the participant or to standardize the test and use the same settings for all. Within this project, the same bench, with a seat height of 44.5 cm, was used for all participants. A taller person will have to produce a larger knee extension moment due to longer lever arms to rise from a seated to a standing position compared to a shorter person. It may, however, be argued that using the same seat height for all is the most functional choice as it represents real life. Moreover, if individuals are tested repeatedly, it is recommended to use a chair of constant height (Bohannon, 1995).

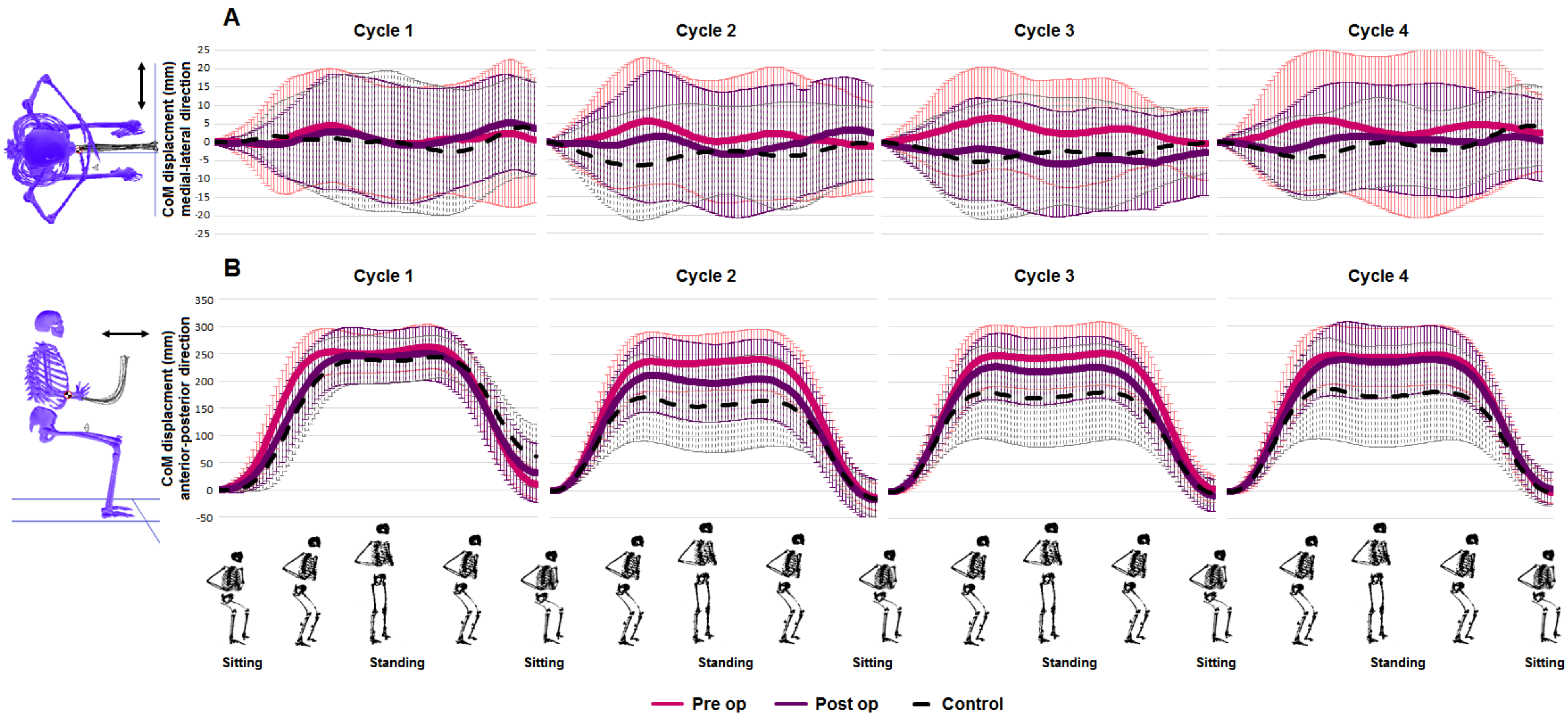


Figure 9. The mean (±1 standard deviation) Center of Mass (CoM) trajectory during the Five Times Sit-to-Stand test in individuals with symptomatic knee osteoarthritis within one month prior to total knee arthroplasty (n=21), one year post-operatively, and in a healthy control group (n=21). The test starts in a seated position and ends in a standing position. Cycles 1-4 were considered full cycles and were used for further analysis; cycle 5 ends in a standing position. A) The contralateral shift of the CoM is observed in the medial-lateral direction and B) the forward displacement of the CoM in the anterior-posterior direction.

4.3 PATIENT-REPORTED FUNCTION

4.3.1 The Knee Injury and Osteoarthritis Outcome Score

For visual analysis purposes, mean KOOS scores for the study population included in this thesis and for all subgroups included in the studies using KOOS (studies I-III) are presented together (Figure 10).

Prior to surgery, the lowest (worst) patient-reported KOOS scores were found in the subscales Sport and Recreation and Knee-related QoL (Study I). One year after TKA, significant improvements were found in all KOOS subscales with the largest improvements in subscales Pain (73%, effect size 1.5), Symptoms (85%, effect size 1.5), and Knee-related QoL (121%, effect size 1.4) (Study II). Compared to the control group, significantly lower scores remained in all subscales one year after surgery (Figure 10).

4.3.2 Change in Knee-related Quality of Life and knee biomechanics

In Study III, changes in specific knee biomechanics parameters were evaluated. In this study, individuals with knee OA were grouped according to their self-reported change in the KOOS subscale Knee-related QoL, rendering a 'Good' outcome group and a 'Poor' outcome group. The 'Good' and 'Poor' outcome groups were evaluated separately and compared.

4.3.2.1 Changes in the 'Good' Knee-related Quality of Life outcome group

The 'Good' outcome group displayed significant improvements in the majority of the evaluated knee biomechanics parameters. During gait, peak knee flexion angle increased by five degrees, flexion-extension range increased by eight degrees, peak varus angle was reduced by five degrees, peak flexion moment increased by 0.08 Nm/kg, and peak valgus moment was reduced by 0.16 Nm/kg.

4.3.2.2 Changes in the 'Poor' Knee-related Quality of Life outcome group

The 'Poor' outcome group displayed a significant reduction in peak varus angle during stance phase by 2.9 degrees. No other knee gait biomechanics parameters or passive knee joint range of motion showed any significant change one year after surgery.

4.3.2.3 Pre-operative differences between groups

Pre-operatively, the 'Good' outcome group presented with significantly less knee flexion-extension range (five degrees) during gait compared to the 'Poor' outcome group. The 'Poor' outcome group reported significantly lower scores in the KOOS subscale Function in ADL pre-operatively, one of few parameters found to differ among the groups prior to surgery (Figure 10).

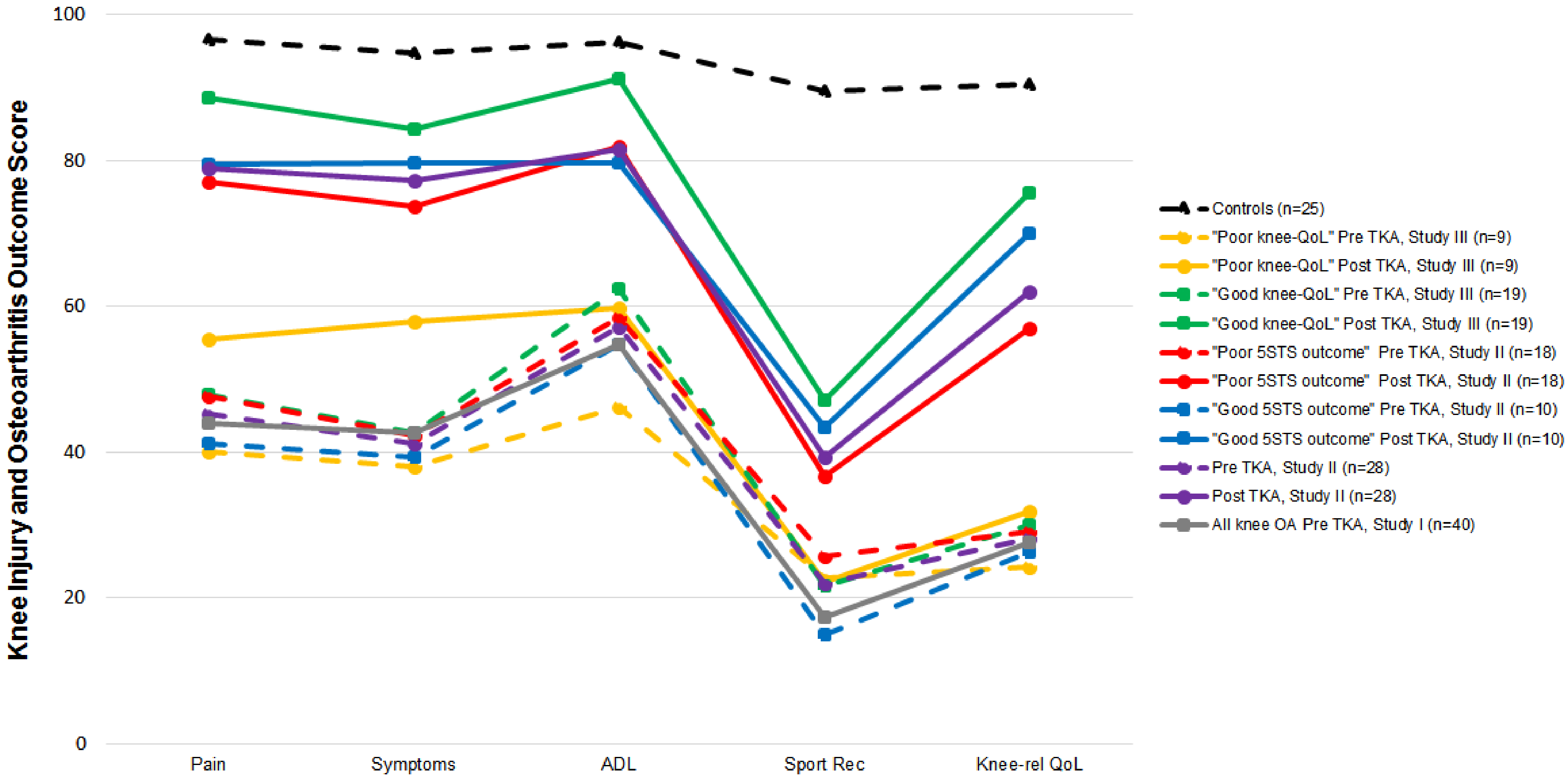


Figure 10. Mean Knee Injury and Osteoarthritis Outcome Scores (KOOS) for the study population included in this thesis and subgroups featured in the included studies (studies I-III) presented together for visual analysis purposes. The typical KOOS profile prior to surgery reveals that the lowest scores are found in subscales Function in Sport and Recreation (Sport Rec), followed by Knee-related Quality of Life (QoL). One year after total knee arthroplasty (TKA) the profile shape is still intact although improvements are evident in all subscales. 5STS, Five Times Sit-to-Stand test.

Previous research has shown that younger patients with less radiographic OA report lower patient-reported outcome scores and tend to be less satisfied with the outcome following TKA than older patients (between 65 and 75 years old) (Haynes et al., 2016). In our sample, there was no difference in age between the 'Good' and 'Poor' outcome groups. Nevertheless, the 'Poor' outcome group reported less improvement following TKA (Study III). With regards to radiographic severity, there was not a statistical difference between groups when divided across modified KL scores (3a, 3b, 4a, and 4b). However, the proportion of individuals with a KL score of three or less was significantly higher in the 'Poor' outcome group (p=0.006). These results are in accordance with findings of Dowsey et al. who reported that individuals with more severe radiographic knee damage at the time of surgery were the ones to have the largest improvements in terms of both pain relief and improved function following TKA (Dowsey et al., 2012b). However, when exploring pre-operative function and radiographic severity, no associations were found (Dowsey et al., 2012a). The associations between radiographic severity and its impact on clinical presentation have been explored in several studies (Leichtenberg et al., 2017, Dowsey et al., 2012a, Tilbury et al., 2016, Pereira et al., 2016), but results are somewhat conflicting. Tilbury et al. found a positive association between pre-operative radiographic severity of hip OA and reduction in pain, and improvements in function following hip arthroplasty. The association, however, was not evident among individuals with knee OA (Tilbury et al., 2016).

4.3.2.4 Clinical phenotypes of osteoarthritis

Individuals with knee OA constitute a heterogeneous population. Five clinical phenotypes of knee OA have been identified based on clinically relevant patient characteristics (Knoop et al., 2011). The clinical phenotypes include the 'Minimal joint disease phenotype,' the 'Strong muscle phenotype,' the 'Non-obese and weak muscle phenotype,' the 'Obese and weak muscle phenotype,' and the 'Depressive phenotype.' The 'Depressive phenotype' and 'Obese and weak muscle' phenotype have demonstrated different clinical outcomes, with higher pain levels and more severe self-reported activity limitations than the other three phenotypes (Knoop et al., 2011). Based on differences in structural degradations and symptoms, four clinical subtypes of knee OA have been identified (Waarsing et al., 2015). These subtypes also differed in risk factors, suggesting that different causes lead to different types of knee OA.

In 2016, a systematic review aimed to synthesize the current evidence for the existence of distinct sets of variables that may suggest the presence of clinical phenotypes of knee OA (Dell'Isola et al., 2016). Six main groups of variables were identified, which suggests the presence of different underlying disease mechanisms in the knee OA population (Dell'Isola et al., 2016).

Due to the small sample in Study III, it is not meaningful to try to classify patients according to clinical phenotypes, although if one were to speculate, it is possible that some individuals in the 'Poor' outcome group fit the description of the phenotype called 'Minimal joint disease'

(Knoop et al., 2011). These individuals may not have had severe joint damage but had pain. Thus, beyond pain relief, they did not view the surgery as affecting their Knee-related QoL.

4.3.2.5 Clinical relevance of changes in knee biomechanics

The magnitude of improvements found in knee biomechanics during gait are difficult to appraise with regards to their clinical relevance. As previously discussed, in relation to clinically relevant changes in GDI scores, it is a great challenge to establish thresholds for what constitutes a clinically relevant change in specific gait parameters, as this threshold likely will differ among individuals. The increase in knee flexion-extension range by eight degrees in the ‘Good’ outcome group, likely mirrored in the increased KOOS Knee-related QoL scores, is beyond the measurement error, which is reported to be less than four degrees in the sagittal plane (McGinley et al., 2009).

4.3.2.6 Predictive value of change in knee biomechanics

ROC curves were used to evaluate the ability of change in knee gait biomechanics to correctly classify patients into either the ‘Good’ outcome group or the ‘Poor’ outcome group. The results of the ROC curves showed that smaller change in knee flexion-extension range and peak flexion moment had a good ability to predict a ‘Poor’ outcome after TKA. The AUC was 0.83 for change in flexion-extension range (95% CI 0.67 - 0.98) and 0.77 for change in peak flexion moment (95% CI 0.59 - 0.94). The ability to predict a ‘Poor’ outcome in Knee-related QoL for the other evaluated knee gait biomechanics parameters were low.

4.3.2.7 Strengths of the Knee Injury and Osteoarthritis Outcome Score

The KOOS is a user friendly and easily administered questionnaire completed by the participant in less than 15 minutes. The questions included in the KOOS are relevant to most individuals with knee OA, especially those who are physically active or have a desire to be physically active. Results of Study III demonstrated that change in KOOS Knee-related QoL was accompanied by change in knee biomechanics during gait. This specific subscale is the most responsive KOOS subscale when outcomes are measured at six and 12 months after TKA (Roos and Lohmander, 2003) and performs particularly well in capturing combined knee-specific outcomes as it broadly conceptualizes the impact of knee problems, including their functional, emotional, cognitive, and overall consequences (Gandek and Ware, 2017). In addition, 90% of individuals with TKA consider this subscale to be extremely or very important (Roos and Toksvig-Larsen, 2003).

4.3.2.8 Weaknesses of the Knee Injury and Osteoarthritis Outcome Score

Although the questions of the KOOS are found to be relevant for individuals with knee OA, some questions are difficult to answer following TKA surgery. In the subscale Function in Sport and Recreation, individuals rate the degree of difficulty they experienced during the last week, due to their knee, in activities such as squatting, running, jumping, twisting, and kneeling. Some individuals find these questions difficult to answer as they do not run, jump, or kneel as part of their daily life. Some individuals were told by their surgeon not to engage in jumping or running after surgery. Hence, some individuals report that they have not experienced any difficulties due to their knee, although they never perform these activities, and others guessed their degree of difficulty.

Among individuals with knee OA awaiting TKA, floor effects were observed for the subscale Function in Sport and Recreation, where 12 (30%) out of 40 reported the worst possible score (0) in this subscale. One individual reported the worst possible score in the subscale Knee-related QoL. In comparison, one individual was not able to perform the 5STS test prior to surgery, and seven were not able to perform the SLMS test on their OA limb. This observed floor effect means that further deterioration cannot be demonstrated due to this limitation of the measurement instrument.

The control group used in studies I-IV consisted of healthy individuals without known musculoskeletal disease. However, the mean control group KOOS scores were below 100 (best) in all subscales, and the lowest scores were found in the subscale Function in Sport and Recreation, followed by Knee-related QoL (Figure 10). Other studies including control or reference groups consisting of individuals without joint symptoms report KOOS scores below 100 (Ageberg et al., 2010, Thorlund et al., 2010, Ilich et al., 2013). The mean KOOS scores of the control group included in this thesis did not reach the maximum score in any KOOS subscale, while at the same time reporting no pain (VAS 0) during the performance-based tests which may be considered equally or more intense activities than what is asked in KOOS. This raises questions whether a KOOS score of 100 is impossible to reach for individuals with a mean age of 66 years. In comparison, the mean number of mini squats performed during the SLMS test was 29. This could be interpreted in relation to previous research reporting mean number of mini squats of 23 in a group of 43 reference individuals with a mean age of 69 years (Ageberg et al., 2013) and group mean number of 30 mini squats in a group of 89 non-symptomatic meniscectomized individuals with a mean age of 54 years (Bremander et al., 2007). Thus, the performance-based function of the control group within this thesis must be considered as good.

4.3.3 The EuroQol Five Dimensions

The EQ5D was used in studies I and II to evaluate health-related QoL. In individuals with knee OA awaiting TKA, health-related QoL was lower compared to controls (Table 2). One year after surgery individuals with TKA reported improvements in their health-related QoL (19%, effect size 0.5), but their scores were nonetheless still lower as compared to the control group. The EQ5D values reported in studies I and II were calculated based on the modelled UK values (Dolan and Roberts, 2002). In 2014, Swedish experience-based EQ5D health state values were published (Burstrom et al., 2014). In a study with a sample of more than 56,000 individuals with total hip arthroplasty, correlations between the Swedish experience-based values and VAS value sets were evaluated along with correlations between the modelled UK values and VAS value sets (Nemes et al., 2015a). The results demonstrated the Swedish value sets to be more accurate in terms of representation of the Swedish hip arthroplasty individuals than the currently used UK value set (Nemes et al., 2015a). It is likely that the experience-based EQ5D values are more appropriate to use in studies of individuals with knee OA. Therefore, with regards to the EQ5D, future research could use experience-based EQ5D values instead of modelled ones.

4.3.4 Perceived pain

In studies I, III, and IV, perceived pain was evaluated using a VAS. Participants were asked to rate their perceived pain before and after gait trials and after completing each of the performance-based tests. In the total group of 40 individuals awaiting TKA, the level of perceived pain during gait trials was median 39 (range 4-90) and median 20 (range 0-95) when performing the 5STS test (Study I). The highest level of perceived pain was rated when performing the SLMS test, with a median VAS score of 50 (range 0-95) (Study I).

One year after surgery, the level of pain during gait reduced to median 0 (range 0-50) for the 28 individuals evaluated post-operatively. In Study III, there were no differences in perceived pain during gait between the ‘Good’ and ‘Poor’ outcome groups. At baseline, the ‘Good’ outcome group reported a median VAS score of 35 (range 4-79) and the ‘Poor’ outcome group reported a median VAS score of 45 (range 4-74). At the one-year follow-up, both groups reported reduced pain during gait, indicated by a median VAS score of 0 (range 0-18) for the ‘Good’ outcome group and a median VAS score of 1 (range 0-50) for the ‘Poor’ outcome group (Study III). The sub-set sample of 21 individuals with knee OA, included in Study IV, rated their perceived pain to be median VAS 15 (range 0-84) prior to surgery. One year after surgery, pain was significantly reduced, with a median VAS score of 0 (range 0-28) (Study IV).

4.4 METHODOLOGICAL CONSIDERATIONS

4.4.1 External validity

4.4.1.1 Study design

Study I used a cross-sectional design, which is useful for examining factors that are associated with specific characteristics (Kazdin, 2003). The aim of Study I was to examine whether the amount of gait pattern deviation was associated with performance-based and patient-reported function in individuals with symptomatic knee OA. While this type of design is useful for generating new hypotheses and theories, the design does not lend itself to determinations of cause and effect (Kazdin, 2003).

Studies II-IV used a prospective cohort design, which has several advantages. Prospective designs allow researchers to assess factors at pre-test that may influence study results (Kazdin, 2003). Specifically, a prospective cohort design allows researchers to examine who changed and what proportion of individuals changed in a certain way. Prospective designs have limitations. For example, it may take substantial time to complete a prospective study, which can be expensive in terms of resources and personnel. In addition, loss of subjects over time may bias study results. The outcome of interest (i.e., who does not improve in function after TKA) may have a relatively low base rate, leading to issues related to sample size and statistical power (Kazdin, 2003).

Within this thesis, we also used a case-control design, matching healthy control subjects by age strata and gender distribution to individuals with OA. Matching within the study design precludes analysis of those factors matched to subjects (Kazdin, 2003). Gender was not expected to influence GDI scores, but with regards to the 5STS and SLMS tests, gender was considered to possibly affect the results.

4.4.1.2 Study sample

The recruitment of the studied sample of individuals with knee OA was not carried out consecutively, and the number of eligible individuals declining participation has not been controlled throughout this project. This must be viewed as a threat to the external validity, limiting the conclusions that can be drawn from the results (Kazdin, 2003). The control group participants consisted of a convenience sample of individuals recruited through friends and acquaintances.

The results from the four studies included in this thesis are based on a single cohort of 40 individuals with knee OA and 25 healthy controls. In most research contexts, this sample size may be considered small. In studies using 3D motion analysis, this sample size may be regarded as sufficient with regards to the number of participants needed to detect a difference in a specific variable of interest.

To evaluate gait kinetics, we restricted our study sample to participants who were able to ambulate without the use of a walking aid. This specific inclusion criteria, along with the other inclusion and exclusion criteria (i.e., comorbidities such as diabetes mellitus), limits the external validity of the results, so the results cannot be generalized to all individuals with knee OA.

Our study sample of individuals with knee OA are highly comparable to individuals with knee OA eligible for a TKA in Sweden (SKAR 2016) with respect to age, gender distribution (where there is a slight overweight of women to men), and pre-operative KOOS scores. Not surprisingly, the included individuals with OA presented with significantly higher weight and BMI as compared to the control group. However, values for weight and BMI of the studied knee OA sample is in accordance with that of many other study populations consisting of individuals with knee OA awaiting TKA (Bennell et al., 2014, Al-Khlaifat et al., 2016, Metcalfe et al., 2013, Debbi et al., 2015, Huber et al., 2015, W-Dahl et al., 2014). The higher weight and BMI may have influenced both gait patterns and performance-based function.

4.4.1.3 Sample size and statistical validity

The most common threat to statistical validity is relatively weak power of detecting a difference if one truly exists. When power is weak, the probability that the researchers will conclude that there are no differences between groups is increased (Kazdin, 2003). In Study III, the sample size of the ‘Poor’ outcome group was too small to yield sufficient statistical power (>0.8) for several parameters. Thus, the results may have been predisposed towards type II errors. Dividing populations into subgroups is quite intriguing, although it is not always a scientifically sound approach. The risk for type II errors increases with small samples, which greatly limits the conclusions that can be drawn from such results. On the other hand, small studies, possibly underpowered studies, still contribute information and are therefore not entirely useless (Campbell, 2007). Data can be pooled in a meta-analysis, providing results that are more generalizable than one large study.

The repeated use of one cohort in several studies, and multiple statistical comparisons also threaten statistical validity (Kazdin, 2003). The more statistical tests that are performed, the more likely a chance difference will be found even if no true differences exist. Consequently, multiple comparisons increase the risk for type I error, where it is falsely concluded that there are differences between groups (Kazdin, 2003). Furthermore, a debate exists regarding the need to use a statistical correction (e.g., Bonferroni correction) to account for multiple testing when interpreting data and drawing conclusions about the results (Armstrong, 2014).

4.4.2 Internal validity

Improvement over time can be related to several factors. In the included studies of this thesis, all change is assumed to be associated to the TKA and post-operative rehabilitation. The use of a control group in experimental study designs is one way to address threats to internal and construct validity and therefore adds accuracy to the conclusions that can be drawn. An alternative approach to evaluate change could have been to evaluate the control group twice with a year between assessments to see the effect of time, how stable the different measurements are, and to control for effects of testing and regression (Kazdin, 2003). Such an approach would have increased the internal validity of the prospective studies included in this thesis.

As previously mentioned, there are several known limitations to the biomechanical models used for 3D motion analysis, including errors related to marker placement and to movement artefacts due to soft tissue. The Plug-In-Gait model, used in the included studies, is a commonly used biomechanical model; however, the model is not free of faults (Baker and Rodda, 2003). Perhaps the most discussed limitation of the Plug-In-Gait model is the definition of the hip joint center. The calculation is based on the width of the pelvis (to define the medial-lateral position of the hip joint center) and the distance between the anterior superior iliac and the greater trochanter (Davis et al., 1991). However, difficulties arise when the markers cannot be placed directly on the anterior superior iliac due to soft tissue. In addition, the greater trochanter can assume many positions in relation to the hip joint center depending on hip rotation and femoral anteversion (Baker and Rodda, 2003). There are uncertainties with all biomechanical models as they rely on certain assumptions, and the Plug-In-Gait model is no exception. Still, this model is widely used, and as for data comparison purposes it is probably the best model to use.

Reliability studies of the Plug-In-Gait model demonstrates an inter-sessional standard error of two degrees for global kinematic data in healthy adults (Eve L et al., 2006) and good intra-sessional repeatability (Ferrari et al., 2008). However, these numbers cannot merely be translated to other labs as these numbers depend on the examiner placing the markers and lab settings. During the data collection in the included studies, marker placement was carried out by one of two examiners. Efforts were made to reduce differences between examiners, such as careful training of placing the markers, frequent discussions, exploring the effect of modifying marker placement, and evaluating inter-examiner reliability. Efforts were also made to standardize measurement procedures and test conditions.

4.5 LIMITATIONS

Out of the 40 individuals with knee OA included at baseline, 12 (30%) were excluded from the one-year follow-up due to different reasons (Figure 3). In Study IV, an additional seven individuals had to be excluded – six due to occluded upper limb markers and one unable to perform the test. The number of individuals excluded due to occluded markers could have been reduced if observation of the reflective markers while collecting data had been even more careful. There is a risk for bias when individuals from a cohort are excluded or lost to follow-up as these individuals may display a specific characteristic (i.e., age or gender), which consequently may alter the results. The individuals excluded within this thesis did not differ statistically from the studied OA group with respect to distribution of age, gender, weight, height, BMI, or duration of years with symptomatic knee OA.

In the included studies of this thesis, the post-operative rehabilitation was not standardized nor was it monitored other than that the duration of it was recorded, and this should be regarded as a limitation. Consequently, it has not been possible to control for the impact of rehabilitation on function. Moreover, there is always a risk for recall bias when information, such as the length of the post-operative rehabilitation, is collected afterwards. No data on muscle strength were collected within this project, such as strength testing using a dynamometer or muscle activity measured with electromyography. This too should be considered a limitation since the conclusions regarding muscle strength are not validated although logically inferred. This should also be viewed in the light of what is practical and reasonable in relation to the time the study participants spent in the motion analysis lab.

The individuals with knee OA were never asked about their perception of their gait patterns nor were they asked whether they experienced any changes in their gait pattern at the one-year follow-up. Had they been asked, it would have been possible to comment on whether the magnitude of change in GDI scores was related to any self-perceived changes by the study participants. As this was not done, we can only speculate how large the change in GDI scores must be for the individual to recognize a difference. However, gait patterns and gait asymmetries are difficult to self-assess as it is also difficult for an observer to assess multiple joints just by observing. Of course, this is one of the major implications for the use of instrumented 3D motion analysis to be able to capture what the eyes fail to see. Furthermore, the search for the minimally clinically relevant change will go on forever for all measurements, as this value will differ within populations and within the context it is measured. Just as with PROM, where some individuals may overestimate their functional ability and some will underestimate their ability, this will likely occur when participants are asked about their perception of their gait pattern.

4.6 CLINICAL IMPLICATIONS

Increased time to complete the TUG test is associated with increased joint loading deviations during gait (lower GDI-kinetic scores). This knowledge is useful to clinicians when evaluating individuals with knee OA in clinical practice, where performance on the TUG test could guide treatment towards rehabilitation exercises promoting normalized loading.

Based on change in 5STS test performance, individuals with substantial gait pattern improvements were identified, whereas patient-reported measures of function could not detect differences between individuals who improved and those who did not in 5STS test performance. These findings highlight the use of the 5STS test in clinical practice since improvement, beyond the MDC of 2.5 seconds, on this test appears to be accompanied by significant reductions in kinematic and kinetic gait pattern deviations.

The selective ability of time to complete the 5STS test to discriminate between individuals with knee OA and controls may be insufficient if groups are too small. However, quantification of CoM trajectories in the medial-lateral and anterior-posterior directions demonstrates good selective ability. These findings are of importance to clinicians using the 5STS test in clinical practice as time to complete the test does not necessarily reflect the underlying movement pattern.

Patient-reported measures of function have limited use in detecting change in performance-based function. This has implications for pre-operative patient education. Individuals undergoing TKA should be informed that this surgery is an effective treatment for alleviating pain and symptoms of the affected joint, but activities of daily living and more strenuous activities requiring strength, power, and balance may not become fully restored after surgery.

Smaller change in flexion-extension range and change in peak flexion moment during gait had a good ability to predict a ‘Poor’ outcome in Knee-related QoL after TKA. Therefore, individuals presenting with non-impacted knee biomechanics during gait prior to surgery may be at risk of rating the post-operative change in Knee-related QoL as small, whereas individuals presenting with impacted knee biomechanics during gait prior to surgery have a larger potential to improve in knee biomechanics and in their Knee-related QoL.

4.7 FUTURE RESEARCH

Results of this thesis demonstrate that knee OA impacts the overall gait pattern on both the osteoarthritic and the contralateral limb, and even though gait improves after surgery, deviations persist compared to age- and gender-matched controls one year after TKA. Few long-term (i.e., five years or more) follow-up studies investigating the course of gait pattern changes following TKA exist (Ullrich et al., 2015, McClelland et al., 2007). This raises questions whether the gait pattern following surgery continues to improve beyond the one-year follow-up or if a steady state is reached. In the same context, but further down the road, one may wonder if and when the gait pattern in individuals with TKA will deteriorate. Could specific signs of gait pattern changes precede implant failure? If such signs were possible to detect, could any intervention postpone failure of the implant?

Results of Study IV revealed that there is an effect of number of cycles on CoM displacement. Consequently, it would be of interest to evaluate additional repetitions and its effect on CoM displacement. It is likely that the 30-second chair stand test would be superior to the 5STS test. To determine more conclusively the cause of compensation, future studies should evaluate the effect of consecutive cycles on CoM displacement using additional repetitions or a longer duration and by measuring muscle strength directly.

There are many challenges when conducting exercise intervention studies where the primary hindrance is often compliance with exercise regimes. With that in mind, it would still be of great interest to evaluate the impact of different specific exercise programs on restoring normal movement strategies used during functional performance tests. It would also be valuable to examine whether more extensive post-operative rehabilitation (i.e., higher volume, increased frequency, and longer duration) could lead to greater reductions in deviating movement strategies used during performance-based tests. That is, future studies should examine to what extent exercise impacts the movement strategy used and how much exercise would be needed.

Hypothetically, increased strength of the quadriceps could reduce the forward displacement of the CoM during a sit-to-stand movement. Perhaps neuromuscular exercises would be the type of training to best promote symmetrical loading and thereby reduce the contralateral shift of the CoM during the 5STS test and possibly also increase GDI-kinetic scores. Perhaps traditional strength training with a focus on increasing maximal strength and volume of the quadriceps muscles would best impact the increased forward displacement of the CoM.

The different clinical phenotypes among individuals with knee OA identified by several researchers offers another very intriguing approach to sub-classify individuals and explore function (Knoop et al., 2011, Waarsing et al., 2015, Dell'Isola et al., 2016), as interventions may need to be adapted to these clinical phenotypes (Knoop et al., 2011). Consequently, future studies should explore whether the biomechanical response to TKA or specific exercise programs is different across different clinical phenotypes. This will require a relatively large sample size in terms of typical 3D motion analysis studies, but could possibly generate valuable information to help understand why a fifth of all individuals receiving a TKA are dissatisfied with their outcome. Subgrouping individuals with knee OA according to clinical phenotype or other subtype classification could also provide further insights to exercise response. Because these phenotypes present with different muscular profiles, it would be of great interest to assess muscle strength pre- and post-intervention as well as to closely monitor compliance to post-operative rehabilitation across these clinical phenotypes.

Another interesting idea would be to incorporate aspects of OA subtype in the joint arthroplasty registries and possibly aspects of function other than patient-reported measures to follow functional status longitudinally. There is still a knowledge gap to fill with regards to establishing which classification of phenotype or subtype of OA to rely on. With regards to the different aspects of function, the OARSI recommended set of performance-based measures have been available since 2013. Although not all these tests may be practical to conduct and add to the registry, adding just one test would be a beneficial start. If a test were to be added to the registry, it should also be coordinated with the evaluation measurements used within the registry Better Management of Patients with Osteoarthritis (Bättre omhändertagande av patienter med artros, BOA). Since 2008, the BOA registry evaluates the impact of the Supported Osteoarthritis Self-Management Program (education, weight control, and exercise for individuals with OA) in terms of its effect on pain and patient-reported physical activity (BOA, 2017).

Prevention of OA is of great importance and should therefore be a priority of future research, as the number of individuals with OA is increasing and is predicted to increase even more rapidly in the future (Nemes et al., 2015b, Kurtz et al., 2009). Previous research has demonstrated that kinematic gait deviations precede degenerative changes and these changes are associated with the development of OA (Andriacchi and Mundermann, 2006). Obviously, not all individuals at risk of developing knee OA can be sent to a motion analysis lab to be screened for kinematic changes; however, measurement instruments to screen for increased risk for the disease is the key to prevention. It is possible that a comprehensive test battery evaluating several aspects of function (i.e., muscle strength, neuromuscular control, and dynamic balance) in addition to classifying individuals according to clinical subtype could serve as a prognostic measure. Finding individuals at risk for developing OA early offers a wider time span to prevent the disease and possibly slow down its progression.

5 CONCLUSIONS

- Altered overall gait patterns, as represented by kinematic and kinetic GDI scores, were found in the osteoarthritic and contralateral limbs in individuals with symptomatic knee OA awaiting TKA. GDI-kinetic scores were significantly lower for the contralateral limb than for the OA limb, demonstrating that joint loading alterations and deviations from normal are more pronounced in the contralateral limb.

- Kinetic GDI scores were found to be associated to both performance-based outcome measures and PROM, whereas kinematic GDI scores were not associated to either, indicating that commonly used clinical outcome measures of function are not aligned with kinematic gait deviations.

- Measures of overall gait patterns, the 5STS test, and PROM revealed improvements in function one year after TKA, but these improvements were not restored to the level of healthy controls. Based on change in 5STS test performance, individuals with substantial gait pattern improvements were identified. Patient-reported measures of function could not detect differences between individuals improving in 5STS test performance and those who did not.

- Individuals reporting a large improvement in Knee-related QoL one year after surgery displayed improved knee biomechanics during gait, while individuals reporting small improvement in Knee-related QoL displayed unchanged knee biomechanics during gait despite similar reduction in pain.

- Quantification of the body's CoM trajectory during the 5STS test appears to be a sensitive and responsive measure of functional compensations typical of knee OA pathology.

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