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Chapter I

General introduction

Epidemiology of hip and knee osteoarthritis

Osteoarthritis (OA) is a whole joint disease that is characterized by local loss of cartilage, remodeling of adjacent bone and associated inflammation (1, 2). Currently, OA is among most common causes of disability in older adults worldwide (3, 4) and affects approximately 10-15% of all adults aged over 60 (5). Due to the aging population and the increasing number of people being overweight or obese, the numbers of persons suffering from OA are expected to rise (6, 7). Estimations for the year 2050 conclude that by then the amount of persons suffering from OA has increased to 130 million persons globally (8). Of those, the majority will suffer from OA in the knee, hand or hip (9). In the Netherlands, the expected numbers of people suffering from hip or knee OA by the year of 2040 are 560.000 and 800.000 persons, respectively (10).

Pathogenesis and risk factors of hip and knee OA

The aetiology and pathogenesis of OA are poorly understood. The occurrence of OA is considered to be multifactorial, with a number of risk factors. For both hip and knee OA, risk factors for their occurrence are ageing (11, 12), female sex (13), congenital or developmental deformities (such as hip dysplasia and knee malalignment) (6, 11, 12, 14, 15), previous joint injury (16), (repetitive) joint loading activities (mostly in the context of high-impact sports or employment) (2) and a genetic predisposition (17-20). Besides, additional risk factors for knee OA are obesity and increased joint laxity or instability (2, 21). The variation in risk factors suggests that OA is not a single joint disease, but a final common phenotype of different disorders (21).

Diagnosis of hip or knee OA

There are various sets of diagnostic criteria for the clinical diagnosis of either hip or knee OA (22-24). A confident diagnosis of OA is based on three symptoms and three signs by physical examination. Symptoms include joint pain (typically intermittent, worst during and after weight-bearing activities), brief stiffness (in the morning, after inactivity or particularly in the evening, generally resolving in minutes) and functional limitations (including limitations in daily activities such as stair climbing) (22-24). The three signs by physical examination are crepitus (a sensation of crunching or cracking), restricted active and passive movement and bony enlargement (from joint effusion and/or bony swelling). In addition, to abovementioned signs by physical examination, some guidelines include bone margin tenderness and the lack of palpable warmth of the joint (2, 22-24). Radiographic imaging or blood tests are not needed to confirm the diagnosis of OA (22, 23), but could help confirm the diagnosis of OA and/or make alternative or additional diagnosis when the presentation is atypical (25).

In the diagnostic process a holistic approach is recommended (2). As such, the initial assessment should include the effect of osteoarthritis on different domains of a person's life (i.e. function, quality of life, occupation, mood, relationships and leisure activities) as well as patients' preferences and beliefs towards certain treatment options (2). In addition, patient knowledge of disease and treatment options should be ascertained as well as previous medical experiences and expectations towards treatment modalities (2). All of this information should be used to develop an appropriately tailored management plan informed by patient expectations, preferences and goals, and existing evidence.

Imaging in hip and knee OA

OA is characterized by several structural changes of the joint. Loss of cartilage (i.e. joint space narrowing), osteophyte formation, subchondral sclerosis and bony deformity are important features recognizable on radiographic images and defining radiographic signs of OA (26). Radiographic imaging may be used to determine disease severity and progression (22, 23, 27). However, discordance is observed between disease severity as measured by radiographic imaging and the severity of OA symptoms. At the age of 70, the large majority of people has structural evidence of OA on radiographic images in at least one joint (11, 28). However, not all of them report symptoms of OA (28-30). According to a systematic review, 15-81% of the persons with radiographic knee OA reported OA-related knee pain (29). Conversely, of the persons with symptomatic OA, 15-76% had signs of radiographic knee OA (28, 29). This implicates that the experienced pain cannot solely be explained by structural damage of the joint. For this reason, it is not recommended to make the clinical diagnosis of hip or knee OA on radiographic imaging (31). As measured by magnetic resonance imaging (MRI), similar moderate associations were found between OA-related symptoms and structural evidence of OA (32).

Management of hip and knee osteoarthritis

Currently, there is no cure for OA. Therefore, treatment modalities are primarily aimed at reducing OA symptoms. Treatment of OA can be divided into conservative (which consists of non-pharmacological and pharmacological management) and surgical management. Conservative, non-pharmacological management includes education and self-management, weight loss, exercises to increase muscle strength and range of motion and the use of functional aids and mechanical assist devices (such as a walking aid or orthotics) (33, 34). Pharmacological management includes analgesics ant anti-inflammatory agents such as paracetamol, Non-Steroidal Anti-Inflammatory Drugs (NSAID's) and tramadol or tramadol plus paracetamol (33, 34). Opiates are mainly discouraged due to the small gains weighted against the side-effects and risk of addiction and overdosage (2). In addition, intra-articular corticosteroids are recommended and some guidelines consider duloxetine, a serotonin and norepinephrine reuptake inhibitor with antidepressant for pain reduction and improvement of function (2). International guidelines and expert-based opinions unanimously recommend a stepped care approach, combining conservative treatment modalities in the management of early OA (33). The evidence underpinning comprehensive management strategies is however scarce with few appropriately designed randomized controlled trials (RCTs) or well-designed studies including expert-based strategies (2, 33). Ultimately, when conservative treatments fail to provide adequate pain relief or functional improvement, surgical treatment could be considered (33). The most common surgical treatment option is total hip or knee arthroplasty (THA or TKA). Other surgical treatment options consist of arthroscopic debridement, subchondral bone stimulation, osteotomy (in case of malalignment), knee joint distraction (in case of knee OA) and unicompartmental joint arthroplasty (33). In addition, new treatment modalities for cartilage repair are developed such as nerve growth factor antibodies, injectable hydrogel and disease modifying

OA drugs (DMOADs), which are in development phase and not current practice yet (33, 35, 36).

Total Hip and Knee Arthroplasty: indications and outcomes

For hip and knee OA, over 30.000 THA and 25.000 TKA are performed in the Netherlands every year (37). In parallel with the rising prevalence of OA, the number of performed arthroplasties has increased over the past years and is expected to further expand (37). Still the indication criteria for THA and TKA are based on limited evidence and the diversity of disease severity at time of surgery is large (38-40). Recently, attempts have been made to define indication criteria to improve the timing of THA and TKA, but this research was not conclusive and more empirical research is needed (41). Selecting the right patient at the right time is of utmost importance to achieve optimal outcomes and to reduce health care cost. Until a few years ago, outcome of interventions were determined by the treating medical specialist, using surgeon-assessed outcomes and survival analyses of implants. According to these standards THA and TKA are considered very effective interventions (42-45). However, when judged by the patients, less optimistic results are seen (46-52). With the implementation of the concept of value-based-driven health care, where patient reported outcomes play a central part, the perspective of the patient has become more and more important in clinical practice.

Outcomes of THA and TKA: Patient perspective and the ICF model

To measure the perspective of patients in the clinical setting, several sets of patient-reported outcomes measures (PROMS) have been proposed for TKA and THA. A set that gained much attention is the set published by the Internal Consortium for Health Outcomes Measurements (ICHOM) on patient reported outcomes that should be included in joint registries (53). The set covers approximately all domains of the International Classification of Functioning, Disability and Health (ICF) model (54).The ICF model is recognized as an important framework and classification which contributes to a holistic approach and covers the typical spectrum of functional problems of patients with a specific health condition and environmental and personal factors that may have an impact on patient’s health. Hence, the Outcome Measures in Rheumatology Clinical Trials group (OMERACT) and the World Health Organization (WHO) recommend using various domains that are incorporated in the ICF model (54, 55). The ICF model assesses the functioning of the whole human being (physically, mentally and socially) on individual as well as society level including the interaction with contextual factors (i.e. environmental and personal factors) (figure 2). Body functions are physical functions of body systems (including psychological functions) at the level of the body or body parts. Body structures are anatomical parts of the body such as organs, limbs and their components. This domain contains all complaints and functional impairments directly derived from the body or body structure that is affected by the health condition (54). The activity domain comprises the physical activities people perform and the difficulties an individual may have in executing activities. Participation concerns involvement of people in all areas of life (functioning of a person as a member of society). An important component is occupational participation. Lastly, contextual factors include personal factors that influence how disability is experienced by the individual such as gender, age, lifestyle and the presence of comorbidities and environmental factors which comprise the physical, social and attitudinal environment in which people live and conduct their lives. This encompasses having a social network and the possibility of making social and occupational adaptions (54).

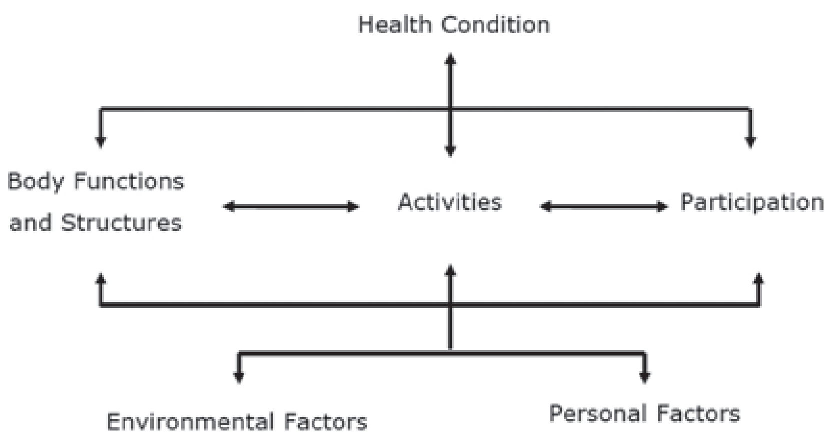

Figure 1. Bio-psycho-social model of the International Classification of Functioning, Disability and Health (ICF)

For OA, a specific ICF core set has been developed (56), which was modified for hip and knee OA by the Royal Dutch Society of Physical Therapy (57). With these core sets, the most important symptoms, health-associated problems and health-related domains of patients with hip and knee OA can be described. The current thesis focuses on a subset of factors within these domains namely pain, functional limitations and knee instability within the body functions and structures domain, and objectively measured physical activity within the activities domain and work participation within the participation domain. Thus, the focus of this thesis contributes to the holistic approach of patients with hip or knee OA undergoing total joint arthroplasty.

Body functions and structures

Pain and functional limitations

Pain and functional limitations are the most prominent and disabling symptoms of OA and among the main reasons for patients to undergo THA or TKA surgery (58). Yet, approximately 15-20% of the operated patients continues to experience persisting pain or functional limitations after surgery (46-52) resulting in 5300 THA and 4600 TKA patients with persisting pain, in the Netherlands alone (37). Persistent pain and associated disability have a substantial impact on quality of life as well as mortality, substantiating the urge to identify the patients with a risk of persistent postoperative pain, prior to surgery. Several studies focused on the preoperative prediction of postoperative pain and functional limitations after TKA and THA (59-62). These studies often included preoperative pain and radiographic OA severity as potential determinants, as they are important factors for orthopaedic surgeons to decide to perform surgery on (52, 63-65). Even though, no previous study investigated if radiographic OA severity modifies the effect of preoperative pain on postoperative outcome. Despite the previous attempts, it is currently still not possible to make reliable preoperative predictions on which patient is prone to have an unfavourable outcome. Therefore, the focus of research should probably shift towards the identification of patients with insufficient recovery shortly after surgery instead of prior to surgery, since these patients might still be influenced for the better. With early recognition of an unfavourable course, different treatment strategies can be applied in order to prevent development of chronic pain.

Knee instability

Knee instability is considered an important, yet relatively underexposed factor in patients with knee OA (66). Knee instability is the sensation of buckling, shifting or giving way of the knee and is reported by 60-80% of the patients suffering from knee OA (66-68). However, the origin of the sense of instability in patients with knee OA has not yet been elucidated. Two causal hypotheses regarding knee stability are based on the presence of structural damage to the joint: (i) osteophyte formation, fibrosis of joint ligaments and capsular thickening increase the tightness of the joint and restriction of movement, resulting in a stiff and stable knee or (ii) more pronounced joint space narrowing leads to reduced stress on the ligaments and capsule of the knee, resulting in a less stable knee joint (69-71). Besides, the sense of knee instability was found to be associated with pain and activity limitations in patients with knee OA (72). A previous randomized controlled trial including selected patients demonstrated that, six months after TKA, 32% of the patients retained self-reported knee instability (72). Retained self-reported knee instability was associated with pain and activity limitations (72). In the long run and in clinical care, it is unknown whether retained knee instability associates with persistent pain and activity limitations after TKA.

Activities

The impact of OA on patients' functioning is usually measured in terms of limitations in specific daily activities or performance-based methods such as the 6-minute walk test (73). Less is known on how OA affects the amount of actual everyday physical activity. Physical activity is important to maintain health and was suggested to have (at least short term) beneficial effects on pain and function in patients with hip and knee OA (74, 75). Physical exercise is therefore included in treatment recommendations for hip or knee OA (76-79). However, from a patient's perspective, pain could be perceived as activity-relate, leading to avoidance of physical activities (80). Indeed, several previous studies showed that perceived hip or knee related pain was associated with perceived physical activity (74, 81).

Whether this association also accounts for objectively measured physical activity, like accelerometers, in patients with an indication for THA or TKA (end-stage hip or knee OA) remains unknown. In addition, little is known on the association between patients' perception of quality of life (QoL) and the actual amount of objectively measured physical activity in this population.

Participation

Return to work

At time of THA or TKA, 15-45% of the patients is of working age (<65 years old) (82). These patients are dependent of their job to generate income, and thus consider return to work as one of the most important outcomes of surgery (83). The rates of patients who do not return to work postoperatively are substantial, and varying in the literature from 5-32%, (84). Overall, knowledge on determinants of partial or no return to work after total joint arthroplasties and potential differences between THA and TKA is scanty, especially information on prognostic factors after TKA (84, 85).

Outline of this thesis

In THA and TKA patients, knowledge of certain components of the ICF domains, specifically knee instability, physical activity and return to work and their association with pain and function prior to and after THA and TKA is limited. Therefore, the aims of this thesis are:

1. To investigate associations between radiographic OA severity, knee instability, pain and function prior to and after THA and/or TKA
3. To evaluate factors influencing physical activities in patients with end-stage hip or knee OA.
4. To identify determinants of return to work after THA or TKA.

In Chapters 2-5 the level of the body functions and structures domain of the ICF is addressed, with the main focus on pain and function. First, to gain more insight in the effect of radiographic evidence of OA and preoperative pain on postoperative pain and function, we investigated if radiographic OA severity modifies the effect of preoperative pain on postoperative pain and function (chapter 2). Second, to better predict postoperative outcome, it was investigated if preoperative pain and function and their initial clinical improvement predicted one-year pain and function (Chapter 3). Furthermore, Chapters 4 and 5 are focused on knee instability, by determining the prevalence of self-reported knee instability before and/or one year after TKA and its associations with radiographic features of OA, pain, function and QoL. Chapter 6, the focus is on activities domain, with an exploration of the cross-sectional association between preoperative pain, function and QoL with objectively measured physical activity. Lastly, regarding participation, particularly return to work, is addressed in Chapters 7 and 8, by identifying determinants of return to work, including physical activity and patients' beliefs and expectations.

LOAS

Most of the research described in this thesis was performed using data from the Longitudinal Leiden Orthopeadics Outcomes of Osteo-Arthritis study (LOAS), a multi-center, longitudinal prospective cohort study (Chapters 2-6, 8) (86). The LOAS study started in 2012 as, at that time, despite the availability of hip and knee registries and a considerable number of studies on the outcomes in terms of prosthesis survival, joint function and quality of life, knowledge on the impact of THA and TKA on societal participation (physical activity, sports, paid and unpaid work) and on health care usage, including rehabilitation was scarce. Moreover, at that time, available studies did not comprehensively include the role of personal factors on outcome. Therefore, the LOAS study was designed with the following aims: (1) to describe the midterm and long-term outcomes of THA and TKA in terms of health status as a whole, including the levels of body functions and structures, daily activities, participation in society and health care usage and (2) to determine which factors predict the outcomes of THA and TKA. Currently, the LOAS is still ongoing, with 7263 patients included by June 2019. Patients complete questionnaires preoperatively and 6, 12 and 24 months after surgery and every 2 years thereafter. Participating hospitals are the Leiden University Medical Centre, Leiden; Alrijne Hospital (former Diaconessenhuis and Rijnland Hospital), Leiden and Leiderdorp; Groene Hart Hospital, Gouda; Reinier de Graaf Hospital, Delft (participation from the start of the study up and until August 2013); LangeLand Hospital, Zoetermeer; Waterlandziekenhuis, Purmerend (participation from January 2015 up till December 2017). This thesis used data of patients recruited before June 2015.

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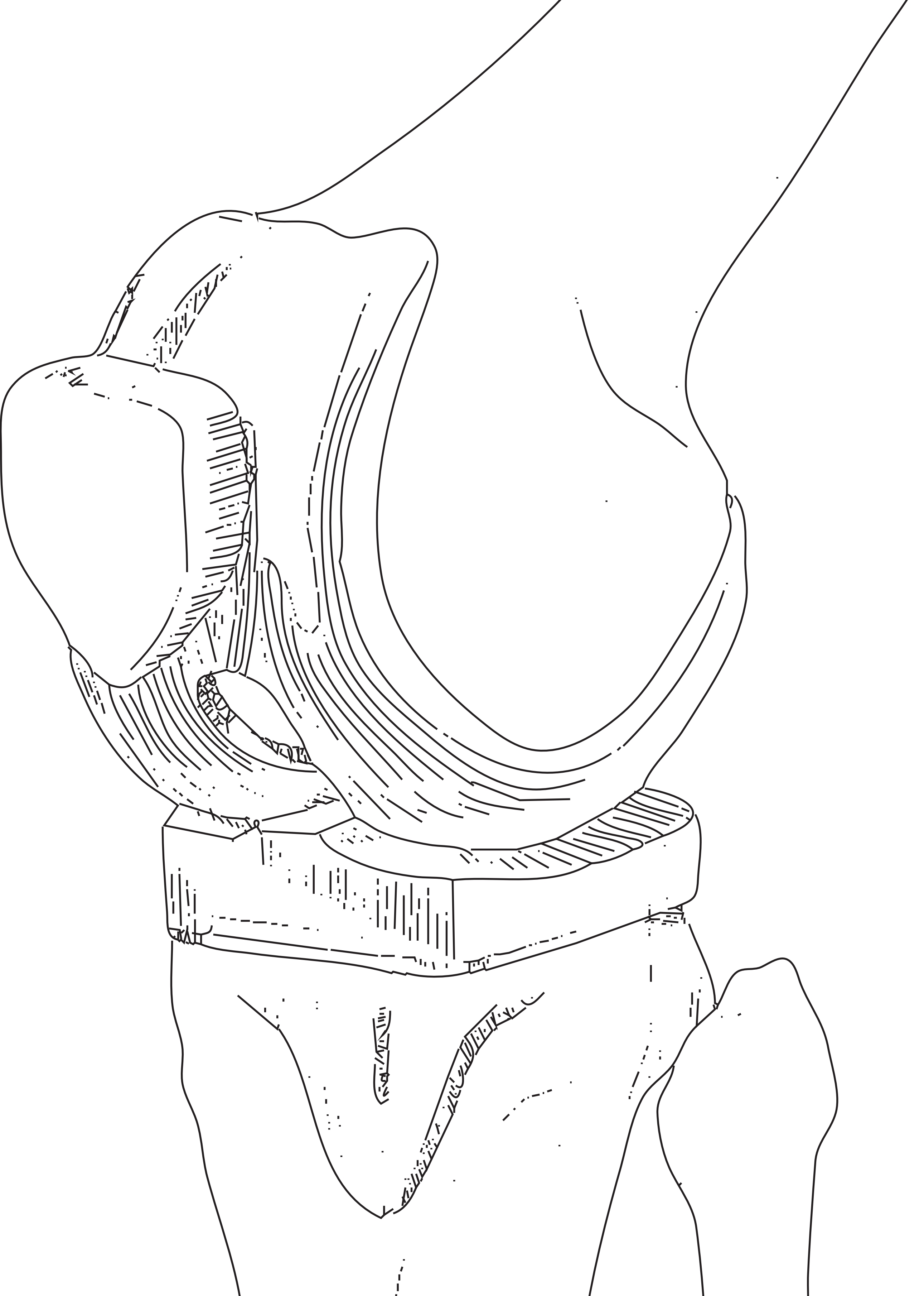

Chapter II

Preoperative radiographic osteoarthritis severity modifies the effect of preoperative pain on pain/function after total knee arthroplasty. Results at 1 and 2 years postoperatively.

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Abstract

Background: Osteoarthritis (OA) severity as demonstrated by preoperative radiographs and preoperative pain play an important role in the indication for total knee arthroplasty (TKA). We investigated whether preoperative radiographic evidence of OA severity modified the effect of preoperative self-reported pain on postoperative pain and function 1 and 2 years after TKA for OA.

Methods: Data from the Longitudinal Leiden Orthopaedics Outcomes of Osteoarthritis Study (LOAS), a multicenter cohort study on outcomes after TKA were used. OA severity was assessed radiographically with the Kellgren and Lawrence (KL) score (range, 0 to 4). Pain and function were evaluated with the Knee Injury and Osteoarthritis Outcome Score (KOOS). After adjustment for body mass index (BMI), age, sex, and Mental Component Summary Scores from the Short Form-12, multivariate linear regression analyses with an interaction term between the preoperative KL score and preoperative pain were performed.

Results: The study included 559 patients. The preoperative KL score was independently associated with 1-year postoperative pain (β = 5.4, 95% confidence interval [CI] = 1.4 to 9.4, and β = 7.7, 95% CI = 3.2 to 12.2, while preoperative pain was associated only with postoperative pain (β = 0.3, 95% CI = 0.1 to 0.6) and not with postoperative function (β = 0.2, 95% CI = -0.2 to 0.5). Comparable associations were found between 2-year postoperative pain and KL score (β = 8.0, 95% CI = 3.2 to 12.7) and preoperative pain (β = 0.5, 95% CI = 0.1 to 0.8) and between 2-year postoperative function and KL score (β = 7.7, 95% CI = 3.2 to 12.2. The study showed a trend toward the KL score modifying the effect of preoperative pain on 1-year postoperative pain (β = -0.1, 95% CI = -0.1 to 0.0) and 2-year postoperative pain (β = -0.1, 95% CI = -0.2 to 0.0) and on 1 and 2-year function (β = -0.1, 95% CI -0.2 to 0.0 for both), with the effect of preoperative pain on postoperative pain and function seeming to become less important when there was radiographic evidence of greater preoperative OA severity.

Conclusions: Patients with less pain and higher KL grades preoperatively had better function and pain outcomes 1 and 2 years after TKA. However, the effect of preoperative pain on the postoperative outcomes seems to become less important when the patient has radiographic evidence of more severe OA. We believe that analysis of the severity of preoperative pain is an important proxy for optimal postoperative patient outcome.

Level of Evidence: Prognostic Level II.

Introduction

Total knee arthroplasty (TKA), performed to treat end-stage symptomatic knee osteoarthritis (OA), results in improved physical function (1-7) and long-term pain alleviation in the majority of patients (8-10). Yet, approximately 20% of patients who have undergone TKA experience persisting pain and overall dissatisfaction (10) or are undecided or dissatisfied concerning their improvement in physical function (9). Therefore, efforts have been made to preoperatively define the subgroup of patients who will experience postoperative pain and/or impaired joint function (7, 8, 11-25).

Since OA severity seen on preoperative radiographs (7, 12-19) and self-reported pain (11, 14, 19-25) are important determinants of whether orthopaedic surgeons will perform TKA (26-28), several studies focused on the predictive value of these factors. In these studies, patients with radiographic evidence of severe OA preoperatively had greater improvements in physical function and greater relief of pain postoperatively (7, 13, 15-17). Furthermore, greater preoperative pain was associated with more improvement but also with more postoperative pain (12). However, none of these studies investigated the combined effect of OA severity seen on preoperative radiographs and preoperative pain on postoperative outcomes.

Preoperatively, a discordance is observed between OA severity seen radiographically and preoperative pain – i.e., more severe OA on radiographs is poorly associated with more preoperative pain. This illustrates that the experience of preoperative pain cannot be explained only by the structural damage of the knee in all patients with OA (12, 29, 30). Pain symptoms may originate from other sources such as central pain sensitization, peripheral knee lesions, or psychological factors (12, 31). Therefore, TKA outcomes in patients with relatively moderate damage seen on radiographs may differ between those with moderate pain and those with severe pain simply because all of the underlying causes for the severe pain may not be resolved by TKA.

The aim of the current study was to investigate whether OA severity seen on preoperative radiographs modified the effect of preoperative pain on postoperative pain and function 1 and 2 years after TKA for OA. We hypothesized that patients with less OA severity on preoperative radiographs and more preoperative pain would report poorer postoperative outcomes regarding pain and function. We believe that additional insight into the effects of radiographic evidence of OA severity and preoperative pain on postoperative pain and function will lead to a better understanding of the mechanisms influencing postoperative outcomes and to a better prediction of outcomes.

Materials and methods

Setting

This study is part of the Longitudinal Leiden Orthopaedics Outcomes of Osteoarthritis Study (LOAS; Trial ID NTR3348), an ongoing multicenter (7 hospital), longitudinal, prospective cohort study started in June 2012 that was designed to investigate long-term outcomes of total hip arthroplasty (THA) and TKA (32, 33). Ethical approval for the LOAS was granted by the Medical Ethics Committee of the Leiden University Medical Centre (LUMC; P12.047). All patients included in the LOAS provided written informed consent according to the Declaration of Helsinki.

General inclusion criteria for the LOAS included a diagnosis of OA, an age of 18 years or older, being listed for primary or revision THA or TKA, and sufficient Dutch language skills to complete the questionnaires. Included patients received questionnaires preoperatively; at 6, 12, 24 months postoperatively; and every consecutive 2 years until 10 years postoperatively. For the current study, we selected a subgroup of the LOAS cohort namely, all patients treated with primary TKA who had been included from June 2012 until June 2015 from the hospitals with, at the time of analysis, accessible radiographic images (LUMC Leiden, Alrijne Hospital Leiderdorp, LangeLand Hospital Zoetermeer, and Groene Hart Hospital Gouda) (n = 863). Patients with 12 months of postoperative data were eligible (n = 649). Excluded from the analysis were patients who had had a previous THA or TKA (either ipsilaterally or contralaterally), those who were treated with a hemiprosthesis and those for whom the severity of knee OA could not be determined properly from radiographs because of logistic or technical errors, for example. In total, 559 patients were included for this analysis (Fig. 1)

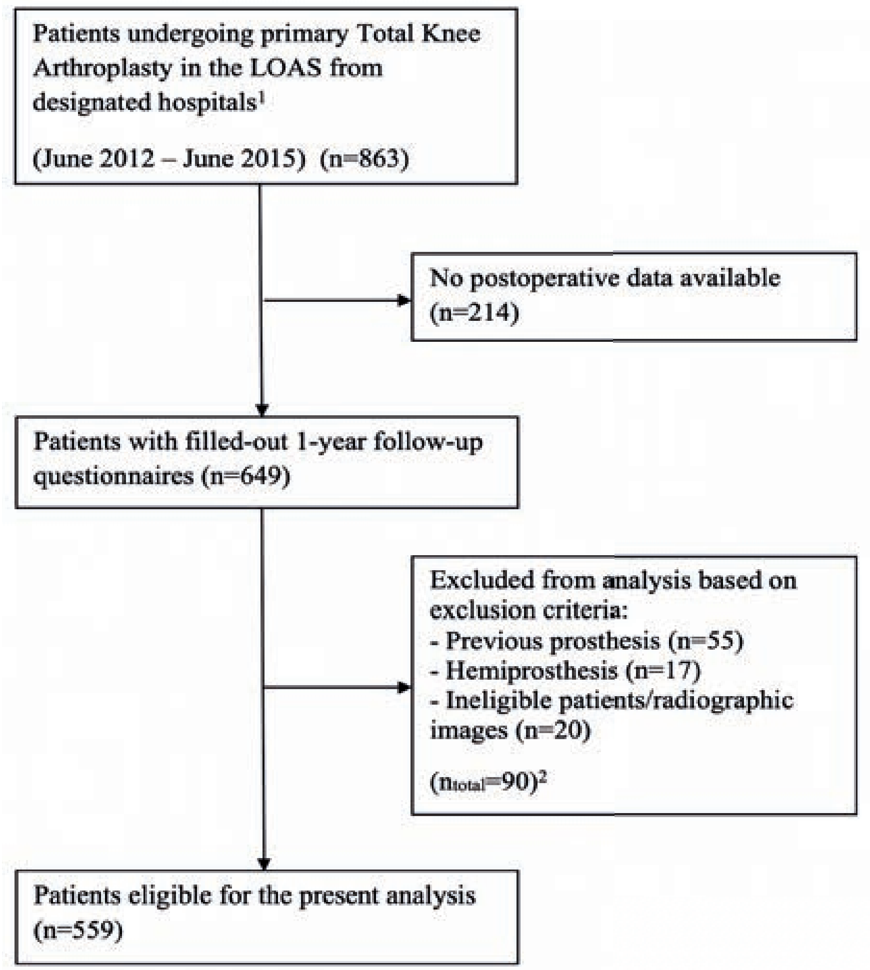


Figure 1. Flowchart of inclusion and exclusion of patients in the study.

[1]These hospitals included the LUMC, Alrijne Hospital Leiderdorp, LangeLand Hospital and Groene Hart Hospital. [2]The number of excluded patients per exclusion criterion does not add up to the total number of excluded patients due to patients complying with multiple exclusion criteria.'

Measurements

Patients' Baseline Characteristics

Sex, age at primary TKA, and height and weight to calculate the body mass index (BMI) were assessed at baseline. In addition, self-reported comorbidities were analyzed using the list of the Dutch Central Bureau of Statistics (34) and divided into 2 categories (33); non-musculoskeletal (chronic lung, cardiac or coronary disease; arteriosclerosis; hypertension; stroke; severe bowel disorder; diabetes mellitus; migraine; psoriasis; chronic eczema; cancer; incontinence; hearing or vision impairments; and dizziness in combination with falling) and musculoskeletal (severe elbow, wrist, hand or back pain and other rheumatic diseases).

Mental health was assessed with the Mental Component Summary Scale (MCS) on the Short Form-12 (SF-12) questionnaire. This questionnaire consists of 12 questions covering 8 different dimensions (General Health, Physical Functioning, Role Physical, Role Emotional, Bodily Pain, Vitality, Social Functioning and Mental Health). The MCS score ranges between 0 (lowest mental health) and 100 (highest mental health). Scores were standardized based on the basis of the average for the population of the United States at a mean of 50 and a standard deviation of 10.

Lastly, preoperative usage of medications was assessed. These included; paracetamol (paracetamol alone, Panadol, Finimal and Sinaspril), glucosamines, nonsteroidal anti-inflammatory drugs (NSAIDs; ibuprofen, diclofenac, diclofenac sodium/misoprostol, celecoxib and naproxen), tramadol (alone and tramadol hydrochloride/paracetamol), supplements (vitamin D, calcium, and bisphosphonates) and others (oxycontin; OxyNorm [oxycodone hydrochloride], MS Contin [morphine sulfate extended-release tablets], and buprenorphine).

Pain and Function

Pain was assessed preoperatively and at 12 and 24 months postoperatively using the validated Dutch version of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (35). The KOOS consists of 42 items subdivided into 5 subscales, including the pain subscale (9 items), which ranges from 0 (severe pain) to 100 (no pain). Preoperative and 12 and 24 month postoperative function was assessed with the KOOS functioning in daily living subscale (activities of daily living; 17 items). Function scores were determined on a scale from 0 (severe impairments in function) to 100 (no impairments in function).

OA Severity Seen on Preoperative Radiographs

Weight-bearing anteroposterior radiographs were obtained prior to surgery as part of routine care. Subsequently, the OA severity was assessed on these radiographs according to the Kellgren and Lawrence (KL) grading system by an experienced musculoskeletal radiologist (H.M.K.). Patients whose KL score was either 0 or 1 were analysed as a single group because the difference in severity between these scores was deemed negligible. As such, the patients were divided into groups ranging from ''no visible OA'' (grade 0 or 1) to ''severe OA'' (grade 4) (36). In addition, 10% of the images were randomly reclassified to assess intraobserver reliability, which was found to be 98% (95% confidence interval [CI] = 97% to 99%).

Statistical Analysis

To assess selection bias, baseline characteristics of the patients with knee OA who were included in the study were compared with those of the patients who were lost to follow-up (those with no 1-year postoperative data). The group that was lost to follow-up was also subjected to the set exclusion criteria prior to comparative analysis.

To correctly address partial or missing responses, multiple data imputation was performed on the data of patients who did not complete all items of the LOAS questionnaire or did not return the 2-year postoperative questionnaire. Predictive mean matching was used with the default SPSS (IBM) settings. Per individual, age, sex, BMI, SF-12 MCS score, and preoperative as well as 1- and 2-year postoperative pain and function were used to impute the missing values. Comparison of the original values (see Supplementary Tables 1 through 4) and the imputed values showed minimal differences.

To determine variances between the groups, 2-sample Student t-tests were used for continuous variables and Pearson chi-square test were used for categorical variables. Also, the baseline patient characteristics of the OA-severity groups were compared with each other using analysis of variance (ANOVA) for continuous data and Pearson chi-square test for discrete data. Five regression models were built to analyze the effects of the radiographic OA severity score (KL score) and preoperative pain on postoperative pain and function. In model 1, the effect of the KL score on postoperative pain and function was assessed with univariate linear regression analysis. Moreover, all regression models on postoperative function were adjusted for preoperative function. In model 2, the effect of preoperative pain on postoperative pain and function was evaluated. Model 3 included both KL score and preoperative pain. In model 4, the interaction between the KL score and preoperative pain was added to analyze whether effect modification was present in the unadjusted setting. Lastly, model 5 was generated to adjust model 4 for possible confounding factors—namely, BMI, age at primary TKA, sex and SF-12 MCS score. Analyses were free from normality assumptions because of sufficiently large sample sizes (37). In addition, figures were created to illustrate the effects of preoperative KL and pain on postoperative pain and function using Qplot (R, version R 3.2.3). The figures were based on the raw (non-imputed) dataset, and geom_smooth (lm) was used to estimate the colored lines. Significance was assumed at a p value of ≤0.05. All analyses were done using SPSS version 23.0.

Results

Study population

No significant differences were observed between the group in the study and the group lost to follow-up with the exception of the mean SF-12 MCS score, which was better for the study population (see Supplementary Table 5). Of the included patients, 66 had a KL score of 0 or 1; 85, a KL score of 2; 335, a KL score of 3; and 73, a KL score of 4 (Table 1). In all groups, the majority of patients were female; patients were on average 67 years of age at the time of surgery. The KL groups did not differ with regard to the mean preoperative KOOS pain (p = 0.681) or function (p = 0.171) score. In addition, no differences were found between BMI, self-reported comorbidities, usage of preoperative pain medication, or SF-12 MCS score (p > 0.05; Table 1).

Table 1: Baseline characteristics of patients with different KL grades.

	KL 0 or 1 (n=66)	KL 2 (n=85)	KL 3 (n=335)	KL 4 (n=73)	Total (n=559)	P value
Female (no (%))	52 (79)	56 (66)	216 (65)	54 (74)	378 (68)	0.081
Age at inclusion Mean* (yr)						0.059
No. (%)	64 ±10	67 ±9	67 ±8	67 ±10	67 ±9	
<50 yr						0.107
50-59 yr	6 (9)	1 (1)	11 (3)	3 (4)	21 (4)	
60-69 yr	13 (20)	14 (17)	47 (14)	14 (19)	88 (16)	
>70 yr	31 (47)	34 (40)	146 (44)	25 (34)	236 (42)	
	66 (24)	85 (42)	131 (39)	31 (43)	214 (38)	
BMI* (kg/m^2)	29 ±4	29 ±4	29 ±5	29 ±5	29 ±5	0.915
Comorbidities# (no (%))						
Musculoskeletal	19/38 (50)	29/50 (58)	99/199 (50)	22/46 (48)	169/333 (51)	0.730
Non-musculoskeletal	33/56 (59)	47/68 (69)	213/281 (76)	44/59 (75)	337/464 (73)	0.065
Preoperative pain medication use (no. (%))	61/65 (94)	71/82 (87)	293/319 (92)	67/72 (93)	492/538 (91)	0.353
Preoperative HOOS score (0-100)*						
Pain						
	38 ±18	37 ±19	40 ±17	39 ±19	39 ±18	0.681
Function	43 ±18	43 ±20	46 ±17	46 ±16	45 ±18	0.171
Preoperative SF-12 MCS score (0-100)*	56 ±9	57 ±8	56 ±9	56 ±10	56 ±9	0.849

BMI: Body-mass Index

KL: Kellgren & Lawrence

MCS: mental component summary scale

SF-12: Short Form 12

*The values are given as the mean and standard deviation. #The values to the right of the slash indicate the number of patients who answered the specific question.

Effects of Preoperative Pain and KL Score on Postoperative Pain

A positive association was found between the preoperative KL score and 1-year postoperative pain score (model 1) (β = 3.5, 95% CI = 1.7 to 5.2), suggesting better 1-year postoperative pain outcomes in patients with more severe OA seen on preoperative radiographs (Table 2).

Table 2: Preoperative prediction of 1-year postoperative pain*

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.5	1.7	5.2
Model 2	Preoperative pain	0.2	0.2	0.3
Model 3	KL score	3.3	1.6	5.0
	Preoperative pain	0.2	0.1	0.3
Model 4	KL score	5.5	1.6	9.5
	Preoperative pain	0.4	0.1	0.7
	KL score x preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	5.4	1.4	9.4
	Preoperative pain	0.3	0.1	0.6
	KL score x preoperative pain	-0.1	-0.1	0.0

*Multivariate linear regression models on the imputed dataset consisted of the following.
Model 1: KOOS pain outcome = β0 + β1*(KL score) + ε

Model 2: KOOS pain outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for BMI, age, gender and SF-12 MCS

Preoperative pain was also positively associated with 1-year postoperative pain (model 2) (β = 0.2, 95% CI = 0.2 to 0.3). This indicates that patients with higher preoperative pain levels can be expected to experience more pain after TKA. After combining models 1 and 2 (that is, including the KL score and pain [model 3]), the effects of the preoperative KL score and preoperative pain showed little change compared with the previous models (β = 3.3, 95% CI = 1.6 to 5.0 and β = 0.2, 95% CI = 0.1 to 0.3, respectively). Moreover, the interaction term between the KL score and preoperative pain showed a negative trend in model 4 (β = -0.1, 95% CI = 0.2 to 0.0) and in model 5 (after correction for confounding factors) (β = -0.1, 95% CI = -0.1 to 0.0). Comparable results were found for the association with 2-year postoperative pain outcomes (table 3).

Table 3: Preoperative prediction of 2-year postoperative pain*

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	4.3	2.2	6.5
Model 2	Preoperative pain	0.2	0.1	0.3
Model 3	KL score	4.2	2.0	6.3
	Preoperative pain	0.2	0.1	0.3
Model 4	KL score	8.1	3.3	12.8
	Preoperative pain	0.5	0.2	0.8
	KL score x preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	8.0	3.2	12.7
	Preoperative pain	0.5	0.1	0.8
	KL score x preoperative pain	-0.1	-0.2	0.0

*Multivariate linear regression models on imputed dataset consisted of the following.
Model 1: KOOS pain outcome = β0 + β1*(KL score) + ε

Model 2: KOOS pain outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for BMI, age, gender and SF-12 MCS

Effect of Preoperative Pain and KL Score on Postoperative Function

The preoperative radiographic KL score was found to have a positive association with 1 and 2-year postoperative function (Tables 4 and 5), suggesting that radiographic evidence of more severe damage is associated with better postoperative function (that is, higher KOOS scores). There was no association between preoperative pain and 1 and 2-year postoperative function. The interaction term between the KL score and preoperative pain again displayed a negative trend toward effect modification (β = -0.1, 95% CI = -0.2 to 0.0, for both 1 and 2-year postoperative function).

Table 4: Preoperative prediction of 1-year postoperative function*

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.6	1.9	5.2
Model 2	Preoperative pain	-0.1	-0.2	0.0
Model 3	KL score	3.2	1.2	5.2
	Preoperative pain	-0.2	-0.3	0.0
Model 4	KL score	7.3	2.8	11.8
	Preoperative pain	0.1	-0.2	0.5
	KL score x preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	7.7	3.2	12.2
	Preoperative pain	0.2	-0.2	0.5
	KL score x preoperative pain	-0.1	-0.2	0.0

*Multivariate linear regression models on imputed dataset consisted of the following.
All models were adjusted for preoperative function.
Model 1: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \varepsilon$

Model 2: KOOS function outcome = $\beta0 + \beta1*(\text{KOOS preoperative pain}) + \varepsilon$

Model 3: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \beta2*(\text{KOOS preoperative pain}) + \varepsilon$

Model 4: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \beta2*(\text{KOOS preoperative pain}) + \beta3*(\text{KL score*KOOS preoperative pain}) + \varepsilon$

Model 5: Model 4 adjusted for preoperative function, BMI, age, gender and SF-12 MCS

Table 5: Preoperative prediction of 2-year postoperative function*

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.3	1.2	5.3
Model 2	Preoperative pain	-0.2	-0.4	0.0
Model 3	KL score	3.2	1.2	5.2
	Preoperative pain	-0.2	-0.3	0.0
Model 4	KL score	7.3	2.8	11.8
	Preoperative pain	0.1	-0.2	0.5
	KL score x preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	7.7	3.2	12.2
	Preoperative pain	0.2	-0.2	0.5
	KL score x preoperative pain	-0.1	-0.2	0.0

*Multivariate linear regression models on imputed dataset consisted of the following.
All models were adjusted for preoperative function
Model 1: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \varepsilon$

Model 2: KOOS function outcome = $\beta0 + \beta1*(\text{KOOS preoperative pain}) + \varepsilon$

Model 3: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \beta2*(\text{KOOS preoperative pain}) + \varepsilon$

Model 4: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \beta2*(\text{KOOS preoperative pain}) + \beta3*(\text{KL score*KOOS preoperative pain}) + \varepsilon$

Model 5: Model 4 adjusted for preoperative function, BMI, age, gender and SF-12 MCS

Illustration of Effects of KL Score and Preoperative Pain on Postoperative Pain and Function

The associations of preoperative radiographic OA severity score and pain with 1 and 2-year postoperative pain and function levels in the raw (non-imputed) dataset are illustrated by figure 2-A through 2-D. Each figure consists of a graph with 4 lines illustrating the association between preoperative pain and 1 or 2-year postoperative pain or function in the different KL score subgroups. Patients with more severe OA seen on preoperative radiographs (higher KL grades) and less preoperative pain are expected to have good outcomes in terms of pain (Figs. 2-A and 2-C) and function (Figs. 2-B and 2-D) 1 and 2 years after TKA. The effect of preoperative pain on postoperative pain (that is, the steepness of the slope) seems smaller in patients with greater OA severity (that is, higher KL score) seen on preoperative radiographs than in patients with less severe OA seen on preoperative radiographs. This effect seems less evident with respect to postoperative function.

Fig. 2-A

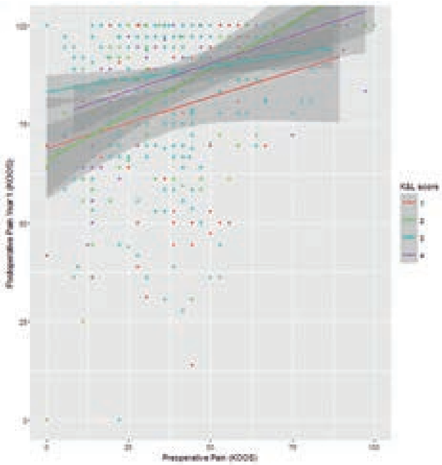


Fig. 2-B

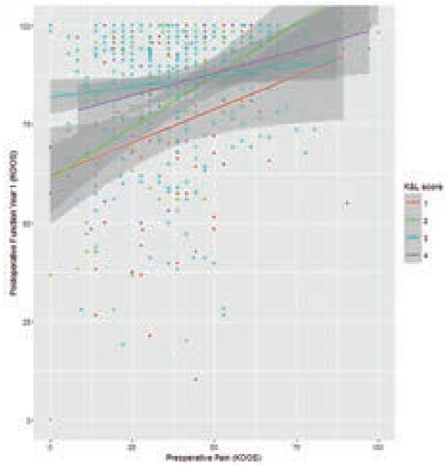


Fig. 2-C

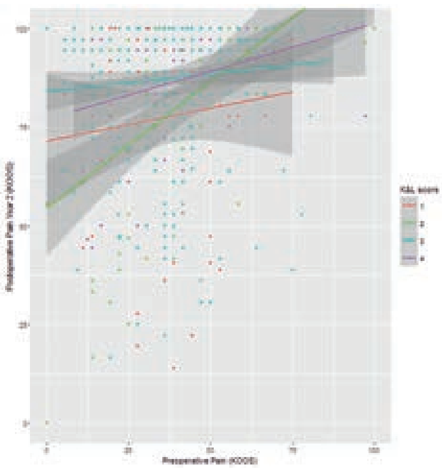
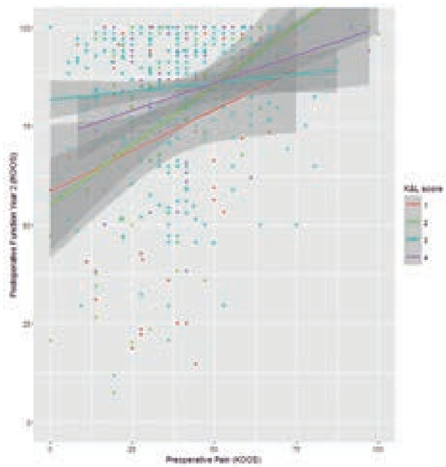


Fig. 2-D



Figures. 2-A through 2-D Graphs displaying the association between preoperative pain and postoperative outcomes in each KL group. The lines are plotted in the raw, non-imputed data. The associations are displayed divided by the KL score. **Fig. 2-A** Associations between preoperative pain (x axis) and 1-year postoperative pain (y axis). **Fig. 2-B** Fig. 2-B Associations between preoperative pain (x axis) and 1-year postoperative function (y axis). **Fig. 2-C** Fig. 2-C Associations between preoperative pain (x axis) and 2-year postoperative pain (y axis). **Fig. 2-D** Fig. 2-D Associations between preoperative pain (x axis) and 2-year postoperative function (y axis).'

Discussion

This is the first study of which we are aware that investigated the effect modification of radiographic evidence of OA severity on pain experienced by the patient preoperatively and their association with postoperative pain and knee function 1 and 2 years after TKA. Low OA severity seen on preoperative radiographs resulted in poorer scores for postoperative pain and function after TKA, whereas greater preoperative pain resulted in poorer postoperative pain scores (but not function). The reverse was also true; high OA severity seen on preoperative radiographs resulted in better postoperative pain and function levels, whereas low preoperative pain solely resulted in better postoperative pain (but not function). Furthermore, the effect of the preoperative pain level on postoperative outcomes seemed to become less important when more severe OA seen on preoperative radiographs was present.

Our finding that severe OA seen on preoperative radiographs was associated with better postoperative KOOS pain and function outcomes is in accordance with previous literature (7, 17, 38). However, some previous studies did not demonstrate these associations between OA severity and improvements in postoperative outcomes (39, 40). These divergent results may be due to variability in follow-up time, smaller study populations and variability in methods to assess pain and function in patients. Also, our finding that patients with more preoperative pain experienced more postoperative pain following TKA has been reported previously (12, 41-43). Nevertheless, none of these previous studies investigated whether radiographically demonstrated OA severity modified the effect of preoperative pain on postoperative pain and function after TKA. The effect of the interaction between widespread hyperalgesia (a reduced pain threshold at body sites distant to the painful joint) and the radiographic OA severity score on preoperative and postoperative pain was previously studied (44). The authors of that study found that patients with greater widespread hyperalgesia and limited OA severity seen on preoperative radiographs tended to have less improvement in pain after TKA than patients with less widespread hyperalgesia(44). That study included only patients with KL grades 3 and 4, limiting the variability in

OA severity. We expect that the effect modification of the radiographic grade of OA severity on widespread hyperalgesia would have been more pronounced if patients with KL grades lower than 3 had been included.

Our findings show that patients with lower radiographic OA severity scores are more likely to be managed with surgery because of pain rather than OA severity. This is underscored by the fact that the baseline pain levels were similar among all 4 different KL groups. The true source of pain that cannot be explained by structural damage of the knee joint remains a matter of debate. A possible explanation is central pain sensitization. In a study by Finan *et al.* (12) patients with low KL grades and high pain levels showed heightened central pain sensitization. When pain sensitization is apparent, the central nervous system is altered in such a way that patients experience higher levels of pain with less provocation. Consequently, patients with low KL grades and high pain levels derive less improvement from TKA compared with patients with high KL grades and high pain levels, as the true source of the pain is not from structural damage of the knee. This is also in accordance with the fact that preoperative anxiety and depression heighten preoperative pain and have adverse effects on postoperative outcomes (41). Comorbidities other than psychosocial conditions might have similar effects on the association between the preoperative and postoperative variables and may further explain the observed association. To our knowledge, however, no one has previously investigated these different possible underlying mechanisms in a single study. More research is necessary.

Our study had some strengths and limitations. Strengths included the large sample size, the multicenter longitudinal study design, and the consistent grading with the KL system as reflected by the high intra-rater reliability. One of the limitations was that we assessed pain and function with the KOOS questionnaire, which has been showed to be sensitive to ceiling effects (35, 45). In our cohort, 31.4% and 14.9% of the patients reported the maximum postoperative pain and function scores, respectively. The KOOS was chosen over other commonly used questionnaires such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, as its ceiling effects are known to be less prevalent (45). Also, some selection bias may have occurred in our study, as the patients who were loss to follow-up showed lower SF-12 MCS scores than our study group (see Supplementary Table 5). However, the mean difference was only 2 points on the 100 point scale, which we interpret as not clinically relevant (46-52).

Conclusion

We observed a trend that OA severity seen on preoperative radiographs modified the effect of preoperative pain on pain and function 1 and 2 years following TKA. As such, the effect of preoperative pain on postoperative pain and function seems to become less important when more severe OA is demonstrated by radiographs. We believe that the effect modification of the radiographic OA severity grade on the association of preoperative pain with postoperative outcomes after TKA should be taken into account when new prognostic models for outcomes after TKA are developed.

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Supplementary table 1: Preoperative prediction of 1-year postoperative pain; outcomes of original, not-imputed data

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.5	1.7	5.2
Model 2	Preoperative pain	0.2	0.2	0.3
Model 3	KL score	3.3	1.6	5.0
	Preoperative pain	0.2	0.1	0.3
Model 4	KL score	5.5	1.6	9.5
	Preoperative pain	0.4	0.1	0.7
	KL score * preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	6.1	1.7	10.5
	Preoperative pain	0.4	0.1	0.7
	KL score * preoperative pain	-0.1	-0.2	0.0

Multivariate linear regression models
Model 1: KOOS pain outcome = β0 + β1*(KL score) + ε

Model 2: KOOS pain outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for BMI, age, gender and SF12 MCS

Supplementary table 2: Preoperative prediction of 1-year postoperative function; outcomes of original, not-imputed data.

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.6	1.9	5.2
Model 2	Preoperative pain	-0.1	-0.2	0.0
Model 3	KL score	3.5	1.9	5.2
	Preoperative pain	-0.1	-0.2	0.0
Model 4	KL score	6.4	2.5	10.2
	Preoperative pain	0.1	-0.2	0.4
	KL score * preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	5.9	1.6	10.1
	Preoperative pain	0.0	-0.3	0.4
	KL score * preoperative pain	0.0	-0.1	0.1

Multivariate linear regression models
All models were adjusted for preoperative function.
Model 1: KOOS function outcome = β0 + β1*(KL score) + ε

Model 2: KOOS function outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS function outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS function outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for preoperative function, BMI, age, gender and SF12 MCS

Supplementary table 3: Preoperative prediction of 2-year postoperative pain; outcomes of original, not-imputed data

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.9	1.8	6.0
Model 2	Preoperative pain	0.2	0.1	0.3
Model 3	KL score	3.9	1.8	6.0
	Preoperative pain	0.2	0.1	0.3
Model 4	KL score	7.3	2.3	12.4
	Preoperative pain	0.5	0.1	0.8
	KL score * preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	7.5	2.2	12.9
	Preoperative pain	0.4	0.1	0.8
	KL score * preoperative pain	-0.1	-0.2	0.0

Multivariate linear regression models
Model 1: KOOS pain outcome = β0 + β1*(KL score) + ε

Model 2: KOOS pain outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for BMI, age, gender and SF12 MCS

Supplementary table 4: Preoperative prediction of 2-year postoperative function; outcomes of original, not-imputed data

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.4	1.4	5.4
Model 2	Preoperative pain	-0.2	-0.3	0.0
Model 3	KL score	3.3	1.3	5.3
	Preoperative pain	-0.2	-0.3	0.0
Model 4	KL score	7.3	2.4	12.2
	Preoperative pain	0.1	-0.2	0.5
	KL score * preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	7.4	2.2	12.5
	Preoperative pain	0.1	-0.3	0.5
	KL score * preoperative pain	-0.1	-0.2	0.0

Multivariate linear regression models
All models were adjusted for preoperative function.
Model 1: KOOS function outcome = β0 + β1*(KL score) + ε

Model 2: KOOS function outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS function outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS function outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for preoperative function, BMI, age, gender and SF12 MCS

Supplementary table 5: Comparative analysis of socio-demographic characteristics of the loss to follow-up patient population *versus* eligible patient population.

	Eligible patients (n=559)	Loss to follow-up patients (n=199)	Analysis of variance (p-value)
Female, n (%)	376 (68)	130 (66)	0.697
Age at inclusion, years	67 ±9	66 ±10	0.476
BMI, kg/m^2	25 ±4	25 ±4	0.431
Comorbidities, n (%)			
Muscular	184 (52)	59 (48)	0.544
Non-muscular	334 (72)	118 (78)	0.171
Preoperative painkilling medication usage, n (%)	492 (91)	170 (88)	0.170
Preoperative pain, 0-100 ±SD	39 ±18	37 ±20	0.124
Preoperative function, 0-100 ±SD	45 ±18	42 ±21	0.062
SF-12, 0-100			
Mean MCS	56 ±9	54 ±10	0.010

BMI: Body-mass Index

MCS: mental component summary scale

SF-12: Short Form 12

Chapter III

Recovery trajectories after total hip and knee arthroplasty and early postoperative identification of patients at risk for unfavourable one-year outcome

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Submitted

Abstract

Background and purpose: Aims were to (i)evaluate the initial clinical recovery in relation to one-year outcomes of primary total hip or knee arthroplasty (THA or TKA) by the use of four clinical recovery trajectories of pain and function and (ii)to investigate if one-year pain/function can be predicted by the initial clinical recovery of pain/function and their preoperative values.

Methods: A longitudinal multicentre cohort study of 972 THA and 892 TKA patients. Self-reported pain and function were assessed preoperatively, six and 12 months after surgery with the Pain and ADL subscales of the HOOS and KOOS. Cut-off for unfavourable pain and function were based on the 20th percentile of its one-year outcomes. The initial recovery was assessed at six months. Prediction of one-year outcome by the initial clinical recovery of pain/function and their preoperative values was assessed with multivariate logistic regression and Receiver Operating Curves.

Results: Approximately 7% THA and 9% TKA patients had an initial unfavourable, yet favourable one-year pain outcome,14% of THA/TKA patients had initial and one-year unfavourable pain outcome. Similar results were found for function. Of the patients with initial unfavourable outcome, 33-46% attained favourable one-year outcome. For both THA and TKA, more initial clinical recovery and better preoperative pain/function (ORs approximately 0.9) predicted unfavourable one-year outcomes. The AUC's of full prediction models were approximately 0.89.

Interpretation: In conclusion, of the patients with initial unfavourable outcome, approximately one-third attained favourable outcome at one-year. Patients at risk for one-year unfavourable outcome could be identified six months postoperatively by initial clinical recovery and preoperative values.

Introduction

Total hip and knee arthroplasties (THA/TKA) are performed to reduce pain and improve function in patients with disabling hip and knee osteoarthritis (OA). However, persistent pain occurs in 7-23% of patients after THA and 10-34% of patients after TKA, according to patient reported outcome scores (PROs) (1). As for function, 14-36% of THA patients (2) and 11-67% of TKA patients have persistent functional limitations one-year postoperatively (3-6).

Most of the recovery after THA or TKA seems to occur in the first months after surgery and beyond three months only small clinical changes are to be expected (7-10). However, these findings are based on group averages. Individual patients could still attain substantial clinical improvements after the first postoperative months. More information on individual recovery trajectories after THA or TKA is necessary to detect if and what proportion of patients with persistent pain or functional limitations attain substantial improvements on the longer term. Early identification of patients at risk for unfavourable outcome (i.e. persistent pain or functional limitations) may enhance the outcome by timely interventions. In depressive patients it was shown that the initial clinical recovery could be a valuable, strong predictor of outcome (11, 12). Moreover, in TKA patients acute pain in the first postoperative days was found to be a predictor for postoperative pain at three or six months (13-15). Whether the initial clinical recovery could also predict one-year outcomes and if this also accounts for functional outcome and in THA patients remains to be evaluated. If the initial clinical recovery has an important predictive value, it could provide an opportunity for orthopaedic surgeons to select which patients should be invited to the outpatient clinic for extra monitoring. Currently, there are no international guidelines for the timing of routine follow-up visits.

Therefore the current study aims to investigate if one-year pain/function outcomes can be predicted by the initial clinical recovery of pain/function and their preoperative values. In addition, to evaluate the initial clinical recovery in relation to the outcomes at one-year by four clinically relevant recovery trajectories of pain and function will be visualized.

Methods

Setting

This study is part of the Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis study (LOAS; Trial ID NTR3348), which started in June 2012 and is an ongoing multi-center, longitudinal prospective cohort study (Level of Evidence II) (16). Ethical approval was obtained by the Medial Ethics Committee of the Leiden University Medical Center (registration number P12.047). Eligible patients are OA patients undergoing primary THA/TKA, who are able to complete Dutch questionnaires and are >18 years. Excluded are patients who have a physical or mental status not allowing participation. Patients are included once written informed consent is obtained according to the Declaration of Helsinki.

For the current study we used the data of patients recruited before June 2015. In total, 1274 THA and 1220 TKA patients returned the preoperative questionnaire. Of those, 302 THA (24%) and 328 TKA (27%) patients were lost to follow-up, resulting in 972 THA and 892 TKA in the present study (Figure 1).

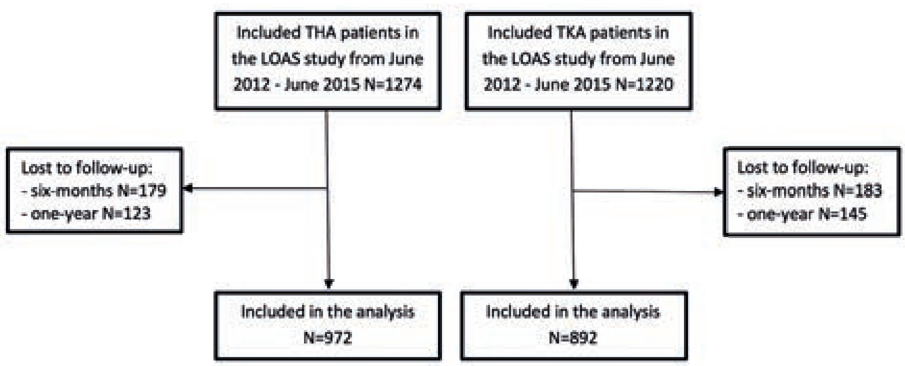


Figure 1. Flowchart of patients included in the Longitudinal Leiden Orthopaedics and Outcomes of Osteo-Arthritis Study (LOAS) from June 2012 up and until June 2015 undergoing Total Hip/ Knee Arthroplasty (THA/TKA). From a total of 1274 THA and 1220 TKA patients, 972 THA and 892 TKA patient were eligible for the present study. ‘

Assessments

Pain and Function

Preoperative, at six months and at one-year the Hip disability and Knee Injury Outcomes of Osteoarthritis Score (HOOS/KOOS) Pain and Activities in Daily Living (ADL) subscale scores were used to assess pain and function in THA and TKA patients, respectively (17-19). For each subscale a normalized score (100 representing the best outcome) was calculated. The initial clinical recovery of the HOOS and KOOS pain or function scores was assessed as the difference between six-month postoperative scores and preoperative scores.

Currently no validated cut-off values for favourable/unfavourable HOOS/KOOS outcome after arthroplasty are available. However, proportions of THA and TKA patients with unfavourable postoperative one-year outcome approximate 20% (1-6). Therefore, for the current study, we have chosen cut-off values based on the 20th percentile scores. Unfavourable outcome was defined as all scores below the 20th percentile of the one-year outcome after THA/TKA and favourable outcome was defined as all scores above the 20th percentile. For the HOOS the cut-off was 75.0 for pain and 70.3 for function. For the KOOS these cut-offs were 72.2 and 70.3, respectively. Based on the dichotomized outcome at six months and one year, four clinical recovery trajectories were identified: 1) Patients with favourable initial- and one-year outcome, 2) patients with favourable initial- and unfavourable one-year outcome, 3) patients with unfavourable initial- and favourable one-year outcome and 4) patients with unfavourable initial- and one-year outcome.

In addition, a sensitivity analysis was performed to test the robustness of the results. A cut-off defined by the FORCE-TJR in preoperative knee osteoarthritis patients was used (20). This cut-off (a KOOS score of 70) was also applied to the KOOS function and the HOOS pain and function scores.

Sociodemographic characteristics

Preoperatively self-reported age, gender and height and weight to calculate body mass index (BMI) were assessed.

Quality of Life

Quality of life (QoL) was measured using the QoL subscale of the HOOS and KOOS questionnaires. Similar to the pain and ADL subscale scores, for the QoL subscale a normalized score (100 representing the best outcome) was calculated.

Comorbidity

Preoperatively, comorbidities in the previous year were assessed according to the Dutch Central Bureau of Statistics (CBS) (21). These comorbidities were classified into two domains: musculoskeletal comorbidities (elbow, wrist or hand pain; back pain; other rheumatic diseases) and non-musculoskeletal comorbidities (chronic lung-; cardiac- or coronary diseases; arteriosclerosis; hypertension; stroke; bowel disorder; diabetes mellitus; migraine; psoriasis; eczema; cancer or a history of cancer; incontinence of urine; hearing or vision impairments; dizziness in combination with falling). Both domains were dichotomized (yes/no).

Mental Health

Preoperative mental health was assessed with the Mental Component Score (MCS) of the Short Form-12 Health Survey questionnaire (SF-12). The MCS ranges from 0 to 100, with 100 representing the best outcome (22).

Postoperative complications

At six months, postoperative complications were assessed by asking patients to report reoperations at the same joint, readmissions in relation to the joint arthroplasty surgery or visits to the first aid due to severe pain of the operated joint.

Statistical analyses

All analyses were done separately for THA and TKA and for pain and function outcomes. First, the prevalence of the four clinical recovery trajectories were assessed. Median pain/function outcomes and interquartile ranges of the clinical recovery trajectories were determined at six months and at one-year.

Secondly, descriptive statistics were calculated as means (SD) or medians (range) (depending on their distribution). Independent t-test (continuous data) and chi-square tests (categorical data) were used to compare demographic variables between (1) included and lost to follow-up patients and (2) patients with initial favourable and initial unfavourable pain/function outcomes. Third, univariate and multivariate logistic regression analyses were done with favourable/unfavourable one-year pain as dependent variable (favourable outcome = 0, unfavourable outcomes = 1) and the initial clinical recovery of pain and/or preoperative pain as continuous independent variable(s). Similar analyses were done for function. Fourth, Receiver Operating Curves (ROC) were calculated to assess the performance of the prediction based on solely initial clinical recovery or preoperative predictors versus predictions based on initial clinical recovery combined with preoperative predictors. Outcomes were expressed as Area Under the Curve (AUC). Based on the multivariate prediction models, different scenarios for unfavourable long-term pain or function outcome were sketched in patients with unfavourable initial pain or function outcome by filling in the prediction models with different values. Risks were calculated as follows: Linear predictor (LP) = $\alpha + \beta 1X1 + \beta 2X2$. The risk= exp(LP)/1+exp(LP).

Two sensitivity analyses were performed. First, the logistic regression models were repeated with the cut off of 70 as described by the FORCE-TJR. Secondly, univariate (including initial clinical recovery) and multivariate (including both initial clinical recovery and preoperative scores) linear regression analyses were done with the continuous one year pain/function outcome. All analyses were performed using IBM SPSS statistical package (version 23.0, SPSS, Chicago, Illinois).

Results

Study population

For both THA and TKA patients, the study group was older, had a lower BMI, better mental health and better preoperative function and QoL, as well as a better six-month QoL outcome as compared to the lost to follow-up (FU) group ($p<0.05$; supplementary table 1). Besides, the study group had reported less musculoskeletal comorbidities solely for THA and better six-month postoperative pain and function solely for TKA patients ($p<0.05$; supplementary table 1).

Table 1. Characteristics, preoperative score and initial clinical recovery of HOOS/KOOS scores of patients with favourable and unfavourable pain or function outcomes

	Initial favourable **pain** outcomes	Initial unfavourable **pain** outcomes	P-value	Initial favourable **function** outcome	Initial unfavourable **function** outcome	p-value
Total Hip	N=731	N=229		N=755	N=206	
Female; n (%)	440 (60%)	164 (72%)	0.002*	454 (60%)	151 (73%)	0.001*
Age; mean (SD)	68.2 (9.5)	68.0 (10.1)	0.816	68.1 (9.3)	68.4 (10.8)	0.709
BMI; mean (SD)	26.9 (4.3)	27.6 (4.3)	0.044*	26.8 (4.1)	28.1 (4.7)	0.000*
Comorbidity						
Musculoskeletal	254 (53%)	103 (71%)	0.000*	258 (52%)	100 (76%)	0.000*
Non-musculoskeletal	413 (68%)	145 (75%)	0.070	429 (68%)	131 (80%)	0.002*
Postoperative self-reported complications	65 (9%)	53 (23%)	0.000*	64 (9%)	54 (26%)	0.000*
SF12 MCS; mean (SD)	55.5 (9.2)	53.2 (10.1)	0.001*	55.5 (9.1)	53.1 (10.4)	0.002*
Preoperative HOOS; mean (SD)						
Function	42.4 (19.8)	34.1 (18.5)	0.000*	43.0 (19.4)	30.7 (18.2)	0.000*
Pain	40.1 (18.7)	31.8 (17.5)	0.000*	40.2 (18.6)	30.3 (17.3)	0.000*
QoL	29.8 (17.1)	24.4 (15.7)	0.000*	29.9 (17.0)	23.5 (15.5)	0.000*
6-month postoperative HOOS; mean (SD)						
Function	88.8 (10.8)	59.9 (17.6)	0.000*	89.6 (8.4)	53.6 (13.8)	0.000*
Pain	94.3 (6.4)	58.9 (14.4)	0.000*	92.3 (9.8)	62.2 (19.4)	0.000*
QoL	80.8 (17.1)	47.5 (17.1)	0.000*	79.8 (17.5)	47.2 (18.7)	0.000*
Initial clinical recovery HOOS; mean (SD)						
Function	46.6 (19.9)	26.5 (22.0)	0.000*	46.7 (19.9)	23.0 (20.5)	0.000*
Pain	54.3 (19.0)	27.3 (20.7)	0.000*	52.0 (19.9)	31.8 (24.7)	0.000*
QoL	51.1 (22.5)	23.3 (21.1)	0.000*	50.0 (22.8)	23.8 (22.3)	0.000*

Total Knee	N=646	N=233		N=682	N=200	
Female; n (%)	425 (66%)	172 (74%)	0.024*	453 (66%)	145 (73%)	0.106
Age; mean (SD)	68.2 (8.5)	66.2 (8.7)	0.002*	67.9 (8.4)	67.3 (9.1)	0.378
BMI; mean (SD)	29.0 (4.6)	29.5 (4.5)	0.128	28.9 (4.5)	29.8 (4.8)	0.013*
Comorbidity						
Musculoskeletal	196 (48%)	90 (65%)	0.001*	209 (49%)	78 (63%)	0.007*
Non-musculoskeletal	404 (75%)	138 (75%)	0.990	421 (74%)	121 (80%)	0.129
Postoperative self-reported complications	51 (8%)	77 (33%)	0.000*	60 (9%)	67 (34%)	0.000*
SF12 MCS; mean (SD)	56.1 (9.1)	54.2 (9.8)	0.010*	56.3 (9.0)	53.2 (10.0)	0.000*
Preoperative KOOS; mean (SD)						
Function	47.5 (18.0)	40.4 (17.3)	0.000*	47.8 (17.8)	38.1 (16.9)	0.000*
Pain	41.2 (18.3)	33.6 (16.2)	0.000*	40.6 (18.2)	34.3 (16.8)	0.000*
QoL	28.1 (15.9)	23.9 (13.8)	0.000*	28.2 (15.6)	23.1 (14.1)	0.000*
6-month postoperative KOOS; mean (SD)						
Function	88.2 (10.8)	59.5 (17.9)	0.000*	88.7 (8.7)	52.4 (13.7)	0.000*
Pain	91.3 (8.4)	54.1 (14.1)	0.000*	88.7 (11.9)	56.6 (19.2)	0.000*
QoL	70.4 (18.4)	41.7 (16.1)	0.000*	69.5 (18.2)	39.5 (16.7)	0.000*
Initial clinical recovery KOOS; mean (SD)						
Function	40.4 (18.2)	19.0 (21.0)	0.000*	40.7 (17.8)	14.3 (18.9)	0.000*
Pain	50.1 (19.6)	20.8 (20.0)	0.000*	47.9 (20.7)	22.6 (22.4)	0.000*
QoL	42.3 (22.4)	17.6 (17.8)	0.000*	41.3 (21.9)	16.4 (19.5)	0.000*

Baseline = 6 months after surgery
Favourable outcome = 1-year pain/function score above the 20^{th} percentile; unfavourable outcome = 1-year pain/function score below the 20^{th} percentile.
BMI = Body Mass Index
SF12 MCS = Short-Form 12 Mental Component Score
HOOS = Hip disability and Osteoarthritis Outcome Score
KOOS = Knee injury and Osteoarthritis Outcome Score
QoL = Quality of Life
* Significance level $p<0.05$

Initial clinical outcomes and trajectories

In THA, patients with an initial unfavourable outcome were more often female, had a higher BMI, more musculoskeletal comorbidities, more often self-reported postoperative complications, worse mental health as well as worse preoperative pain, function and QoL and initial clinical recovery scores compared to patients with initial favourable outcome (p<0.05) (Table 1). In TKA patients similar results were found (Table 1).

The recovery trajectories showed that most THA and TKA patients, approximately 70-74%, had favourable initial and one-year outcomes. (Table 2).

Table 2. The prevalence of different trajectories of clinical recovery of pain and function after THA or TKA

		1. Favourable initial – favourable one-year outcome	2. Favourable initial – unfavourable one-year outcome	3.Unfavourable initial – favourable one-year outcome	4. Unfavourable initial – unfavourable one-year outcome
THA N=972	**Pain** N=938	655 (70%)	61 (6%)	93 (10%)	129 (14%)
	Function N=943	694 (74%)	53 (6%)	65 (7%)	131 (14%)
TKA N=892	**Pain** N=860	598 (70%)	34 (4%)	104 (12%)	124 (14%)
	Function N=870	623 (72%)	49 (6%)	78 (9%)	120 (14%)

Initial outcome = outcome six months after surgery
THA/TKA = Total Hip Arthroplasty/Total Knee Arthroplasty

Moreover, approximately 7-12% of THA and TKA patients had an initial unfavourable pain/function outcome, yet a favourable one-year outcome (trajectory 3), whereas 14% of the THA and TKA patients remained an unfavourable outcome (trajectory 4) (Table 2). From these numbers can be derived that 42% of THA and 46% of TKA patients with initial unfavourable pain outcome eventually reached a favourable one-year outcome. For function, this were 33% THA and 39% TKA patients. The different pain and function trajectories are depicted in Figure 2a-d.

Figure 2a. Self-reported pain trajectory from preoperative to one-year follow-up in THA patients

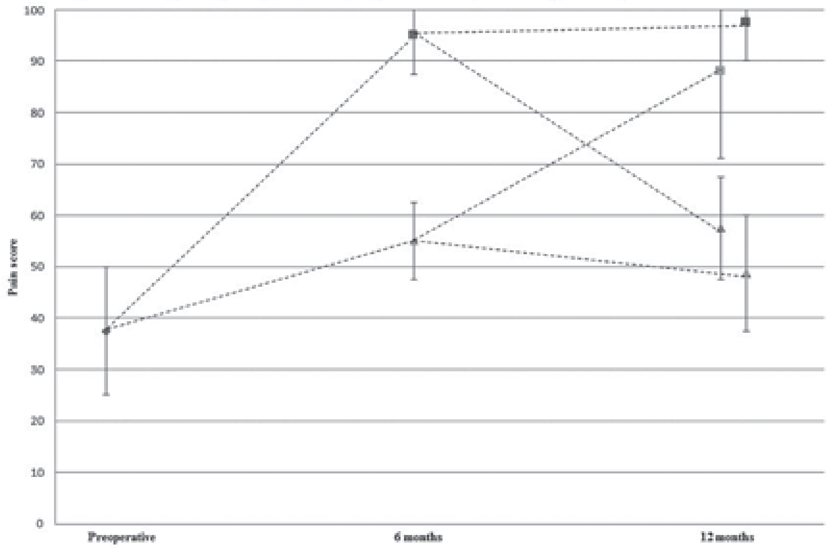


Figure is based on the median and interquartile range
■ = Favourable outcome (subscale score >75.0)
▲ = Unfavourable outcome (subscale score ≤75.0)

Figure 2b. Self-reported function trajectory from preoperative to one-year follow-up in THA patients

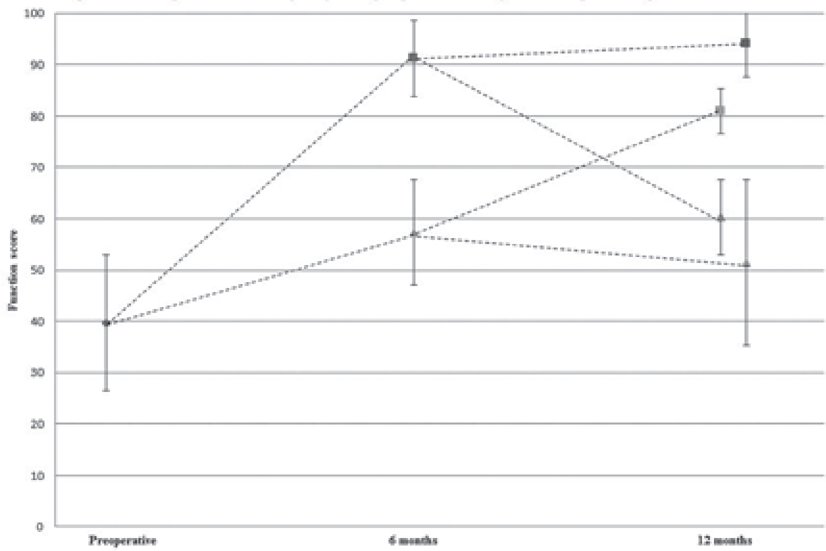
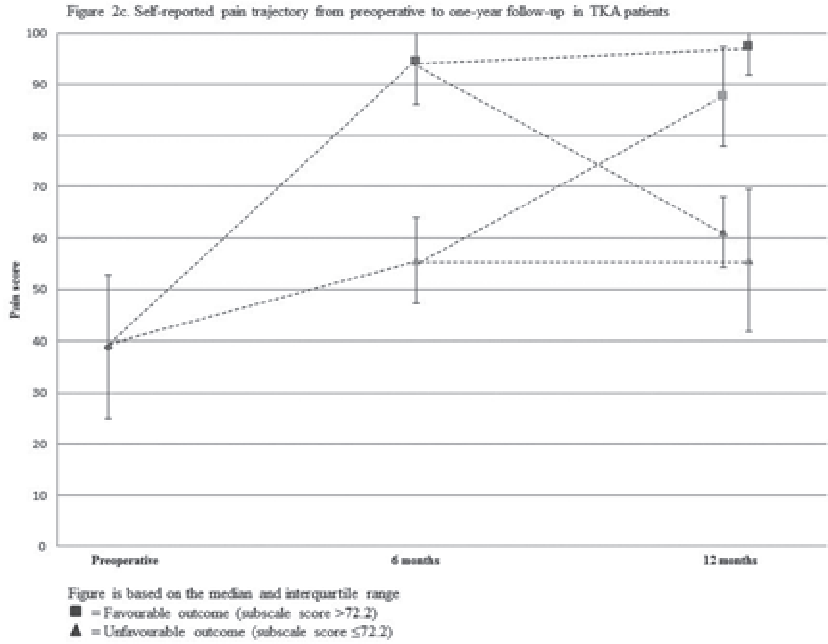


Figure is based on the median and interquartile range
■ = Favourable outcome (subscale score >70.3)
▲ = Unfavourable outcome (subscale score ≤70.3)



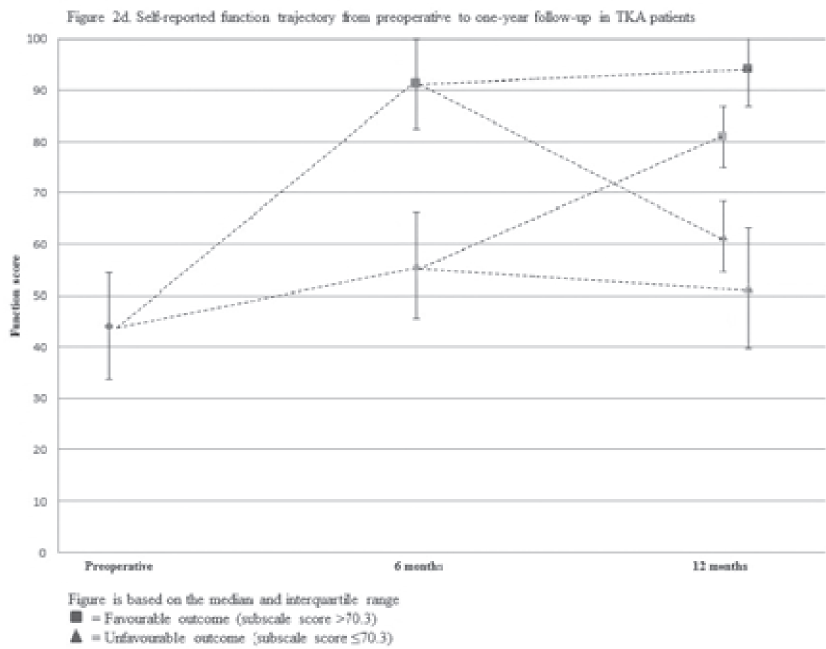


Figure 2. Self-reported pain/function trajectories from preoperative scores to one-year follow-up in patients undergoing Total Hip or Knee Arthroplasty (THA/TKA).'

Prediction of one-year pain

In both THA and TKA patients, higher initial clinical recovery and higher preoperative pain scores (e.g. less pain) were associated with a lower risk on an unfavourable one-year pain outcome (Table 3). A more accurate prediction of one-year outcome was determined based on the initial clinical recovery as compared to preoperative scores (AUC 0.69 versus 0.64 for THA and AUC 0.75 versus 0.63 for TKA), whereas the best prediction was based on the model including both variables (AUC 0.86 for THA and AUC 0.89 for TKA) (Table 3).

Table 3. Prediction of one-year unfavourable pain and function outcome

	Unfavourable one-year **pain or function** outcome					
Pain	**THA** N=938			**TKA** N=860		
	OR	95% CI	AUC	OR	95% CI	AUC
Model 1						
Initial clinical recovery	0.97	0.96-0.98	0.69	0.96	0.95-0.97	0.75
Model 2						
Preoperative pain#	0.97	0.96-0.98	0.64	0.97	0.96-0.98	0.63
Model 3						
Initial clinical recovery	0.92	0.91-0.94	0.86	0.92	0.91-0.93	0.89
Preoperative pain#	0.91	0.90-0.93		0.90	0.88-0.92	
Function	**THA** N=943			**TKA** N=870		
Model 1						
Initial clinical recovery	0.97	0.96-0.98	0.70	0.96	0.95-0.97	0.72
Model 2						
Preoperative function#	0.96	0.95-0.97	0.69	0.96	0.95-0.97	0.67
Model 3						
Initial clinical recovery	0.90	0.89-0.92	0.91	0.92	0.90-0.93	0.89
Preoperative function#	0.89	0.87-0.90		0.90	0.88-0.92	

#High pain scores indicate less pain
Unfavourable outcome = one-year pain/function score below the 20th percentile.
AUC = Area Under the Curve
Model 1 = Univariate analysis including initial clinical recovery
Model 2 = Univariate analysis including preoperative pain
Model 3 = Multivariate analysis including initial clinical recovery and preoperative scores
THA = Total Hip Arthroplasty
TKA = Total Knee Arthroplasty

To illustrate the importance of the initial clinical recovery and preoperative scores on the odds for the one-year outcome, different scenarios are described based on the 25th and 50th percentile of the initial clinical recovery and preoperative scores (Table 4). The odds for a THA patient with a poor profile (e.g. poor initial clinical recovery and high preoperative pain) on a unfavourable outcome was 1.5 as compared to 0.1 for a THA patient with a favourable profile (e.g. better initial clinical recovery and low preoperative pain). The risk on an unfavourable outcome for patients with a poor vs. favourable profile was 0.60 vs. 0.12, respectively. For TKA patients similar results were found with odds of 1.7 and 0.1 and risks of 0.63 and 0.09, respectively (Table 4).

<u>Prediction of one-year function</u>

With respect to function similar results were found in univariable and multivariable regression analyses (Table 3). Moreover, the one-year outcome was better predicted by both the initial clinical recovery and preoperative score, than on solely the initial clinical recovery or preoperative score. Furthermore, the importance of the initial clinical recovery and preoperative scores on the odds for one-year outcomes was described (Table 4). The risk on a one-year unfavourable outcome was 0.75 for a THA patient with a poor function profile and 0.09 for a THA patient with a favourable profile. For TKA patients, these risks were 0.59 and 0.12, respectively (Table 4).

Table 4. Different scenarios of the odds for unfavourable one-year pain or function outcome *in patients with unfavourable initial pain or function outcomes*

	Initial clinical recovery		Preoperative score		Odds for unfavourable one-year outcome		Risk on unfavourable one-year outcome	
Pain	**THA**	**TKA**	**THA**	**TKA**	**THA**	**TKA**	**THA**	**TKA**
Scenario 1	35	28	25	25	1.5	1.7	0.60	0.63
Scenario 2	50	44	25	25	0.5	0.4	0.31	0.30
Scenario 3	35	28	38	39	0.4	0.4	0.31	0.28
Scenario 4	50	44	38	39	0.1	0.1	0.12	0.09
Function								
Scenario 1	27	22	26	34	3.0	1.4	0.75	0.59
Scenario 2	43	35	26	34	0.6	0.4	0.36	0.31
Scenario 3	27	22	40	45	0.5	0.4	0.35	0.30
Scenario 4	43	35	40	45	0.1	0.1	0.09	0.12

Pain and function outcomes are based on the Hip Disability and Knee Injury and Osteoarthritis Outcome Scores (HOOS/KOOS) (range 0-100)
Scenarios are based on the 25th and 50th percentile of the initial clinical recovery and preoperative score.
Scenario 1 = low initial clinical recovery and preoperative score
Scenario 2 = good initial clinical recovery and low preoperative score
Scenario 3 = low initial clinical recovery and good preoperative score and
Scenario 4 = good initial clinical recovery and preoperative score
THA = Total Hip Arthroplasty
TKA = Total Knee Arthroplasty

Sensitivity analyses

The first sensitivity analysis showed comparable cut-offs, odds ratios and AUC outcomes to our initial analysis (supplementary table 2). In addition, the second sensitivity analyses showed comparable univariate and multivariate associations as compared to outcomes of the logistic regression analysis ($p<0.05$; supplementary table 3.

Discussion

This study evaluated outcomes after THA and TKA and showed that patients at risk for unfavourable outcome could be identified at six months postoperatively, which may provide opportunities for early interventions to improve long term outcome. First, we showed that of the patients with an unfavourable initial clinical recovery, 33-46% reported favourable outcomes at one-year. For both THA and TKA, patients at risk for unfavourable one-year outcome could be identified six months postoperatively by the initial clinical recovery of pain/function and the preoperative values. Patients with more preoperative pain and little initial clinical recovery have an increased likelihood of pain one-year after surgery. This also applies to function.

Previous studies suggested that patients could expect solely small clinical gains beyond three months (7-10), whereas we showed improvements between 20-35 points on the HOOS/KOOS subscale score beyond six months for a substantial amount of patients. A possible explanation for these differences is our focus on the clinical recovery in subgroups instead of the total group. Hence, we also did not find substantial recovery after six months when we averaged the recovery of the overall group (data not shown). This can be explained by the fact that patients with unfavourable initial outcomes that do further improve after six months represent a relatively small group of patients (here approximately 10%). The size of this group and the magnitude of their recovery beyond the initial six postoperative months are not sufficient to cause an improvement on group level. Nevertheless, this relatively small group of patients signifies yearly thousands of THA/TKA patients in the Western world (23, 24).

Besides, a recent study showed that three satisfaction trajectories could be distinguished in TKA patients: ‘early’, ‘persistent’, and ‘late’ dissatisfaction (25). This emphasises that recovery time differs between patients and that, when assessing recovery, an individual approach is needed.

Furthermore, the current study showed that, for both pain and function, recovery as well as preoperative scores predicted one-year outcomes. Our findings that more preoperative pain and worse preoperative function were related to lower outcomes, were in accordance with previous literature (26-29). Nevertheless, earlier studies concluded that, even though there was an association, the explained variance of solely preoperative pain and function on postoperative outcomes was not sufficient to adjust the decision making for THA or TKA (28), which was confirmed by our results (i.e. the AUC for solely preoperative pain or function was approximately 60-69). Moreover, we investigated if, in addition to the preoperative variables, the initial postoperative clinical recovery could be a predictor for one-year outcomes after THA or TKA as two other studies illustrated that initial postoperative outcomes could predict one-year outcomes (30, 31). In other medical specialties it is more common to use early treatment results as determinants for one-year outcomes, for example to evaluate psychiatric interventions (11, 12, 32). It is hypothesized that due to the impact of the intervention (e.g. THA/TKA), preoperative variables are no longer representative after surgery and are therefore less suitable to predict one-year outcomes (30, 31). Furthermore, early postoperative identification of patients at risk for one-year unfavourable outcomes provides the opportunity for early interventions (30, 31). By targeting these patients shortly after surgery, early postoperative interventions could result in shortened time to response, reduced distress for the patients and maximized cost-effectiveness (11). These interventions should include intensive rehabilitation programmes or postoperative non-surgical management strategies, aimed at their coping with persisting pain and functional disability (11). Besides, early postoperative identification of patients at risk for unfavourable long-term outcome could help orthopaedic surgeons to identify which patients should be invited at the outpatient clinic. Currently, orthopaedic surgeons invite all patients to the outpatient clinic for routine follow-up visits. These visits add substantial costs to the health care system and are time consuming for both patient and physician, whereas in only very few cases patient management is altered (33, 34). Our results emphasize that PROs, specifically the initial clinical recovery and preoperative scores, should be used for clinical decision-making and patient-centred care and not solely to measure and compare group-averages in the context of registries.

Several strengths and limitations of the present study should be acknowledged. Strengths of our study were that we used a large, unselected cohort of patients representing a common patient population in clinical care. Furthermore, our outcome measures are included in the international standard set of outcome measures for patients with hip or knee OA defined by the International Consortium for Health Outcomes Measurement (ICHOM)(35) and included in United States and European registries (23). As all patients included in these registries already complete the questionnaires, orthopaedic surgeons could implement our findings in clinical practice. Besides, we added two sensitivity analyses. Both showed comparable outcomes to our initial analysis (supplementary table 2 and 3). Our study also had some limitations. First, we used absolute cut off points to determine favourable and unfavourable outcome instead of change-scores such as the Minimal Clinical Important Difference (MCID) as the use of the MCID is accompanied by many pitfalls (36). Patients with good preoperative pain- and function are less likely to achieve the MCID. Moreover, patients with extremely low preoperative scores that do improve the MCID-threshold are considered to have favourable outcomes, whereas their absolute outcomes remain very low indicating severe complaints. Secondly, 24% of THA and 27% of TKA patients were lost to follow-up, which could have led to selection bias. Comparisons between included and lost to follow-up patients showed that lost to included patients reported fewer complaints compared to lost to follow-up patients (supplementary table 1). This reduces the generalizability of our results and could have influenced our results by over- or underestimating the amount of non-responding patients. Third, in line with the first postoperative data-measurement of TKA patients in the Dutch Arthroplasty Register, we measured the initial outcome six months after surgery. By then, a substantial part of the recovery already occurred. Whether targeted rehabilitation strategies at six months are capable of improving long-term outcome should be investigated in future studies. Lastly, patients at risk for unfavourable outcome could potentially be identified even sooner after surgery. The optimal time point to early postoperatively identify patients at risk for unfavourable outcome should be investigated in future studies.

In conclusion, most patients showed favourable initial postoperative pain and function outcomes after THA and TKA, and of the patients with unfavourable initial clinical recovery, one-third still improved up to one-year postoperatively. Patients at risk for unfavourable pain or function outcomes at one-year could be identified at six months after surgery by initial clinical recovery and their preoperative pain or function scores. The latter provides opportunities for timely postoperative interventions to optimize pain and function outcome.

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Supplementary table 1. Patient characteristics, preoperative score, six month outcome and initial clinical recovery of HOOS/KOOS scores of included patients and patients lost to follow-up

	Included	Lost to follow-up	P-value
Total Hip	(n=973)	(n=302)	
Female; n (%)	597 (63%)	188 (64%)	0.652
Age; mean (SD)	68.2 (9.6)	66.4 (10.9)	0.005*
BMI; mean (SD)	27.1 (4.3)	27.7 (5.1)	0.047*
Comorbidity			
Musculoskeletal	364 (57%)	137 (67%)	0.010*
Non-musculoskeletal	565 (70%)	172 (73%)	0.395
Postoperative complications	119 (12%)	16 (13%)	0.757
Mental health; mean (SD)	55.0 (9.4)	53.5 (11.0)	0.030*
Preoperative score; mean (SD)			
Function	40.4 (19.9)	37.3 (19.5)	0.021*
Pain	38.1 (18.8)	36.3 (19.4)	0.165
QoL	28.5 (16.9)	25.9 (16.8)	0.020*
Six-month outcome; mean (SD)	(n=962)	(n=118)	
Function	81.9 (17.8)	79.1 (20.5)	0.123
Pain	85.9 (17.6)	86.1 (18.2)	0.883
QoL	73.0 (22.2)	68.5 (22.1)	0.041*
Initial clinical recovery; mean (SD)	(n=962)	(n=118)	
Function	41.8 (22.2)	43.3 (23.0)	0.517
Pain	47.8 (22.6)	51.3 (23.5)	0.142
QoL	44.6 (25.1)	43.1 (26.2)	0.547
Total Knee	(n=892)	(n=328)	
Female; n (%)	592 (67%)	212 (65%)	0.504
Age; mean (SD)	67.8 (8.6)	66.1 (10.1)	0.005*
BMI; mean (SD)	29.1 (4.6)	29.8 (4.8)	0.013*
Comorbidity			
Musculoskeletal	287 (52%)	105 (51%)	0.850
Non-musculoskeletal	544 (75%)	194 (77%)	0.578
Postoperative complication	129 (15%)	20 (14%)	0.908
Mental health; mean (SD)	55.7 (9.3)	54.1 (10.3)	0.016*
Preoperative score; mean (SD)			
Function	45.5 (18.1)	41.6 (19.6)	0.002*
Pain	39.1 (18.1)	35.9 (18.5)	0.008*
QoL	27.1 (15.5)	23.7 (16.7)	0.002*
Six-month outcome; mean (SD)	(n=879)	(n=141)	
Function	80.4 (18.3)	73.9 (21.6)	0.000*
Pain	81.4 (19.4)	74.3 (23.0)	0.000*
QoL	62.7 (21.8)	57.8 (22.6)	0.014*
Initial clinical recovery; mean (SD)	(n=879)	(n=141)	
Function	34.5 (21.2)	31.5 (23.8)	0.133
Pain	42.1 (23.6)	38.1 (25.0)	0.079
QoL	35.7 (23.9)	34.6 (25.4)	0.619

Initial clinical recovery = clinical recovery at six months
HOOS/KOOS = Hip Disability or Knee Injury and Outcomes of Osteoarthritis Score
BMI = Body Mass Index
QoL = Quality of Life
* Significance level $p<0.05$

Supplementary table 2. Prediction of one-year unfavourable pain and function outcome based on a cut-off point according to the Function and Outcomes Research for Comparative Effectiveness in Total Joint Replacement (FORCE-TJR).

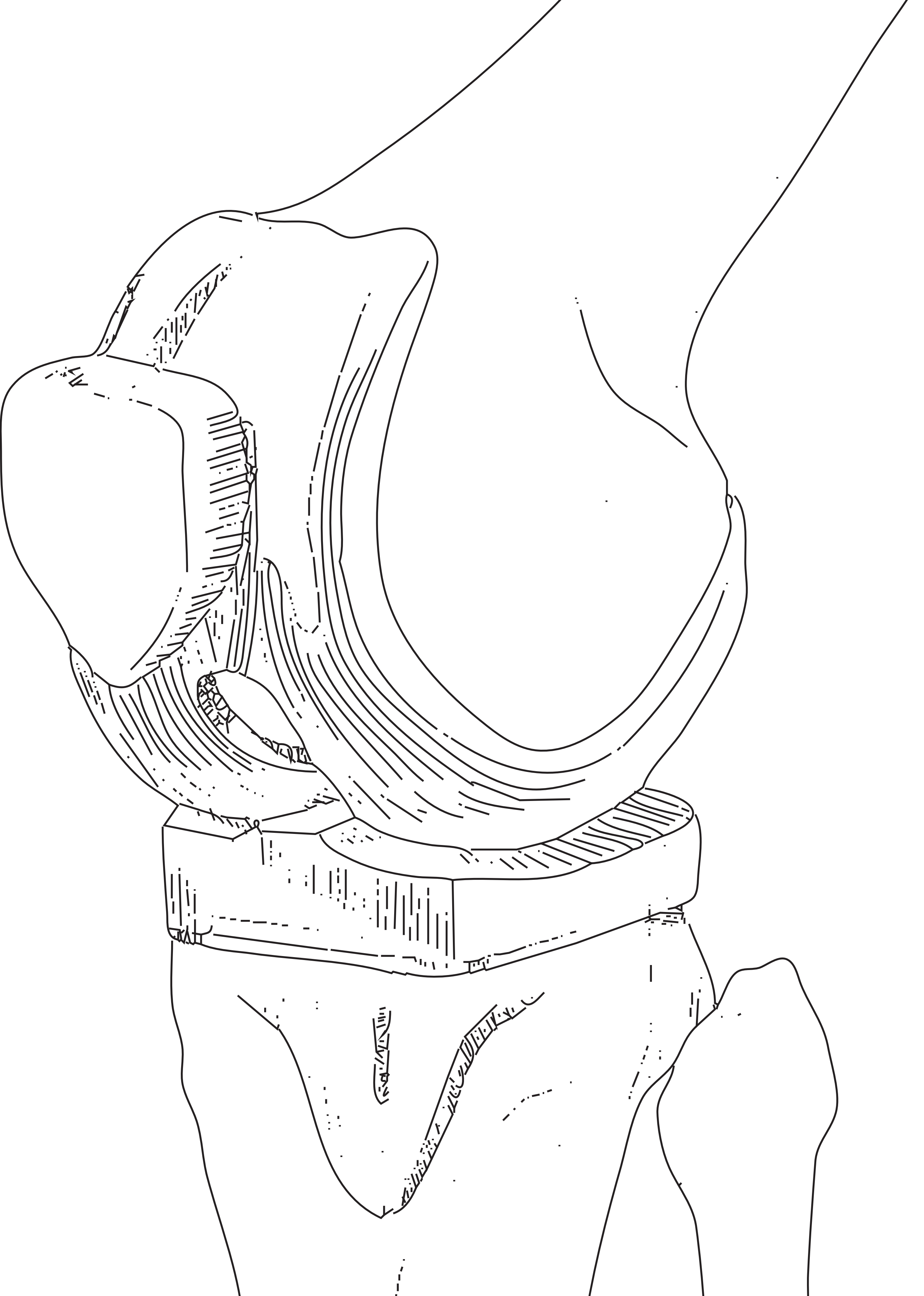
	Unfavourable one-year **pain or function** outcome					
Pain	**THA** N=938			**TKA** N=860		
	OR	95% CI	AUC	OR	95% CI	AUC
Model 1 Initial clinical recovery	0.97	0.96-0.98	0.70	0.96	0.95-0.97	0.76
Model 2 Preoperative pain#	0.96	0.95-0.97	0.69	0.97	0.96-0.98	0.63
Model 3 Initial clinical recovery	0.92	0.91-0.93	0.90	0.92	0.91-0.93	0.90
Preoperative pain#	0.90	0.88-0.91		0.90	0.88-0.92	
Function	**THA** N=943			**TKA** N=870		
Model 1 Initial clinical recovery	0.97	0.96-0.98	0.70	0.96	0.95-0.97	0.72
Model 2 Preoperative function#	0.96	0.95-0.97	0.69	0.96	0.95-0.97	0.67
Model 3 Initial clinical recovery	0.90	0.89-0.92	0.91	0.92	0.90-0.93	0.89
Preoperative function#	0.89	0.87-0.90		0.90	0.88-0.92	

#High pain scores indicate less pain
Unfavourable outcome = one-year pain/function score below the 20th percentile
AUC = Area Under the Curve
Model 1 = Univariate analysis including initial clinical recovery
Model 2 = Univariate analysis including preoperative pain
Model 3 = Multivariate analysis including initial clinical recovery and preoperative scores
THA = Total Hip Arthroplasty
TKA = Total Knee Arthroplasty

Supplementary table 3. Associations with one-year pain or function continuous outcome

	One-year unfavourable **pain or function** outcomes in all patients	
	B	95% CI
Pain; THA	N=955	
Model 1 Initial clinical recovery	0.26	0.21 – 0.31*
Model 2 Initial clinical recovery	0.67	0.62 – 0.72*
Preoperative pain#	0.75	0.69 – 0.81*
Pain; TKA	N=874	
Model 1 Initial clinical recovery	0.32	0.27 – 0.37*
Model 2 Initial clinical recovery	0.67	0.62 – 0.71*
Preoperative pain#	0.74	0.68 – 0.80*
Function; THA	N=951	
Model 1 Initial clinical recovery	0.28	0.22 – 0.33*
Model 2 Initial clinical recovery	0.78	0.73 – 0.83*
Preoperative function	0.86	0.80 – 0.91*
Function; TKA	N=880	
Model 1 Initial clinical recovery	0.32	0.27 – 0.38*
Model 2 Initial clinical recovery	0.72	0.68 – 0.77*
Preoperative function	0.82	0.77 – 0.88*

#High pain scores indicate less pain
Model 1 = Univariate analysis including initial clinical recovery
Model 2 = Multivariate analysis including initial clinical recovery and preoperative score
THA = Total Hip Arthroplasty
TKA = Total Knee Arthroplasty
ADL = Activity Daily Living
HOOS = Hip Disability and Outcomes of Osteoarthritis Score
KOOS = Knee injury and Outcomes of Osteoarthritis Score
* Statistical significance P<0.05



Chapter IV

No associations between self-reported knee joint instability and radiographic features in knee osteoarthritis patients prior to Total Knee Arthroplasty: a cross-sectional analysis of the Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis study (LOAS) data

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Abstract

Background: To describe the prevalence of self-reported knee joint instability in patients with pre-surgery knee osteoarthritis (OA) and to explore the associations between self-reported knee joint instability and radiological features.

Methods: A cross-sectional study including patients scheduled for primary Total Knee Arthroplasty (TKA). Self-reported knee instability was examined by questionnaire. Radiological features consisted of osteophyte formation and joint space narrowing (JSN), both scored on a 0 to three scale. Scores >1 are defined as substantial JSN or osteophyte formation. Regression analyses were provided to identify associations of radiological features with self-reported knee joint instability.

Results: Two hundred and sixty-five patients (mean age 69 years and 170 females) were included. Knee instability was reported by 192 patients (72%). Substantial osteophyte formation was present in 78 patients (41%) reporting and 33 patients (46%) not reporting knee joint instability. Substantial JSN was present in 137 (71%) and 53 patients (73%), respectively. Self-reported knee instability was not associated with JSN (relative to score 0, odds ratios (95%CI) of score 1, 2 and 3 were 0.87 (0.30-2.54), 0.98 (0.38-2.52), 0.68 (0.25-1.86), respectively) or osteophyte formation (relative to score 0, odds ratios (95%CI) of score 1, 2 and 3 were 0.77 (0.36-1.64), 0.69 (0.23-1.45), 0.89 (0.16-4.93), respectively). Stratified analysis for pain, age and BMI showed no associations between self-reported knee joint instability and radiological features.

Conclusion: Self-reported knee joint instability is not associated with JSN or osteophyte formation.

Introduction

Self-reported knee instability has been defined as a sensation of buckling, shifting, or giving way of the knee [1]. Knee joint stability has been studied in patients with mild to moderate knee osteoarthritis (OA), of which 60-80% of the patients reported this sensation [1-4]. The sensation itself or fear of the sensation may lead to limitations in daily life [3]. Besides, self-reported knee joint instability is associated with pain and muscle strength [1-3]. So far, knowledge on joint stability in patients with knee OA prior to Total Knee Arthroplasty (TKA) is scarce with only one study reporting a prevalence of 72% [5]. A clear cause for this sense of instability in patients with knee OA has not been elucidated yet. A possible mechanism underlining the presence of self-reported knee instability in severe knee OA is structural damage of the knee joint. No studies have so far addressed the relationship between self-reported knee instability in knee OA prior to TKA and structural damage of the knee presented by radiological features.

With respect to radiological features, two opposing hypotheses on knee joint instability have been described in patients with knee OA: (i) knee joint instability is low due to osteophyte formation and (ii) knee joint instability is high due to joint space narrowing [6,7]. The first hypothesis is based on the premise that osteophytes, fibrosis of joint ligaments and capsular thickening are responsible for an increased tightness of the joint and restriction of movement, resulting in a stiff and stable knee joint. The second hypothesis is based on the premise that more pronounced joint space narrowing leads to reduced stress on the ligaments and capsule of the knee, resulting in a less stable knee joint. In severe knee OA, osteophytes and joint space narrowing are well-known features, however in mild knee OA these features are less pronounced [8]. In mild to moderate knee OA no associations were found between radiographic features and knee joint stability, which might be explained by a reduced emphasis of these features [3]. It is to be expected that in patients with knee OA prior to TKA, osteophyte formation is more distinct and will result in a more stable knee joint. Whereas, in patients with a more distinct joint space narrowing instability will be more reported.

The aims of the study were to determine the prevalence of self-reported knee joint instability and to determine the association between radiographic features (i.e. joint space narrowing and osteophyte formation) with self-reported knee joint stability in patients with knee OA prior to TKA.

Materials and methods

Study design

The study participants were selected from the Longitudinal Leiden Orthopeadics Outcomes of Osteo-Arthritis study (LOAS), which is an ongoing multi-centre, longitudinal prospective cohort study designed to determine long-term outcomes of Total Hip Arthroplasty (THA) and TKA. The LOAS study (Trial ID NTR3348) started in June 2012 and included 2556 participants until December 2014, of which 1234 underwent TKA.

Study population

The present cross-sectional sub-study included all patients scheduled for primary TKA in the Alrijne (former Rijnland) Hospital Leiderdorp, the Netherlands. Patients who were able to complete questionnaires in Dutch and who were 18 years or older were included. Excluded were patients who did not provide informed consent, possessed insufficient Dutch language skills, had a physical or mental status not allowing participation, already underwent TKA or received a Unicompartmental Knee Arthroplasty (UKA) instead of a TKA after surgery. Eligible patients were informed about the study through written and oral information by their treating medical specialist at the outpatient clinic. Only patients who approved to be approached by the researcher received additional written information about the study by regular mail, as well as a questionnaire, a stamped return envelope and a consent form. Patients who did not return their preoperative questionnaire within one week were contacted by telephone. Patients were included once written informed consent was obtained according to the Declaration of Helsinki. For the purpose of the present analysis only data from patients who provided information about the presence of self-reported knee joint instability were included. Ethical approval was obtained by the Medial Ethics Committee of the Leiden University Medical Center (registration number P12.047) and funding was received from the Dutch Arthritis Foundation (LLP13).

The inclusion of patients is shown in Figure 1. During the first months of recruitment (June 2012 – December 2014) a sample of 349 participants with knee OA, scheduled for TKA was included at baseline in the Alrijne Hospital, Leiden, the Netherlands. Of these, 73 patients already possessed a TKA in the contralateral knee, three patients did not provide information on knee joint instability and eight patients received a UKA instead of TKA, resulting in 265 patients (76%) eligible for the present analysis.

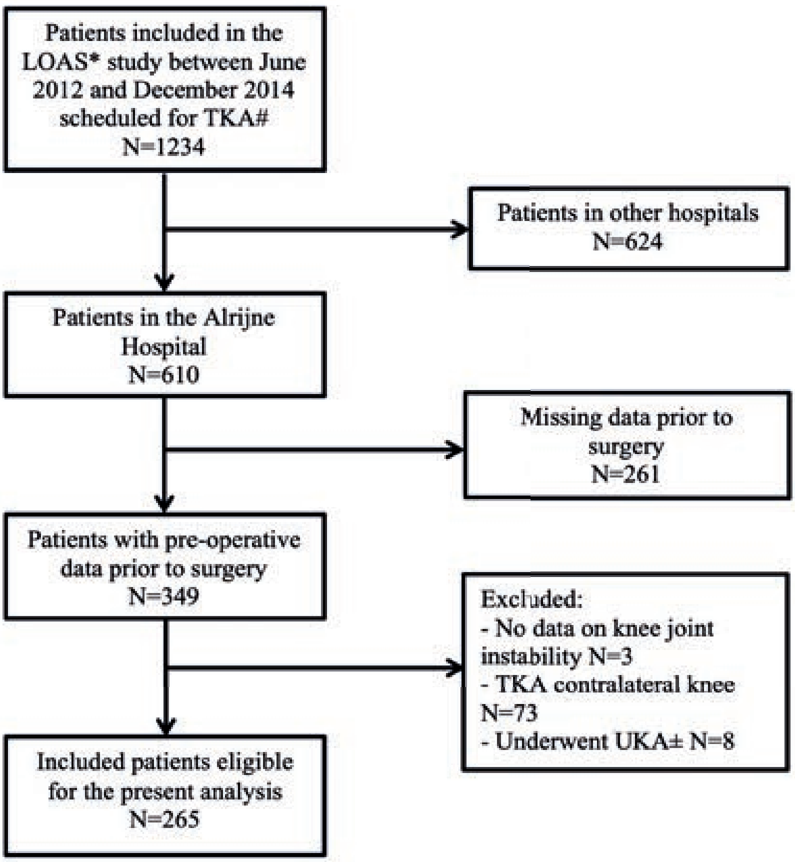

Figure 1. Flow-chart'

* LOAS = Longitudinal Leiden Orthopaedics and Outcomes of Osteo-Arthritis Study
# TKA = Total Knee Arthroplasty
± UKA = Unicompartmental Knee Arthroplasty

Assessments

Sociodemographic characteristics

Patient characteristics included: age, sex, weight (kg), height (m), Body Mass Index (BMI) and the duration of knee complaints (less than 1 year; between 1 – 5 years; between 5 – 10 years; more than 10 years).

Self-reported knee instability

Self-reported knee instability was assessed by means of a knee joint instability questionnaire, according to the questionnaire of Felson et al. [1]. The item on the presence of knee joint instability was formulated as follows: 'the sensation of buckling, shifting or giving way of the knee in the previous 3 months' with the following answering options: 1 never (0 episodes); 2 seldom (one or two episodes); 3 regular (three to five episodes); 4 very often (more than five episodes). These options were dichotomized into no episodes of knee joint instability (answering option 1) or one or more episodes of knee instability (answering options 2 to 4) [3].

Patients reporting knee instability were additionally asked if the sensation of buckling, shifting or giving way of the knee concerned the left, right or both knees and to what activities the sensation was perceived (walking; rising from chair; ascending stairs; twisting or turning; descending stairs; sitting down in chair).

Radiological damage

All radiographs were standardised according to the local protocol. This protocol included (1) standing, weight-bearing anteroposterior radiographs and (2) standing, weight-bearing lateral radiographs of the knee joint. All radiographs were assessed by an experienced musculoskeletal radiologist (HMK), who was blinded from patient characteristics. Ten percent of the radiographs were scored twice to establish inter-reader reliability (Intra-Class Correlation: 98% (95% CI 97-98%)). Discrepancies between the first and second readings were solved by consensus. The used scoring system [9,10] consisted of three items which were independently scored for the lateral and medial sides of the joint and separately for the left as well as the right knee. The scored items were (a) joint space narrowing (JSN) (b) osteophyte formation on the joint margins or tibial spines and (c) the Kellgren and Lawrence (K&L)

score. JSN and osteophyte formation were scored on a 0-3 scale ranging from 0 no JSN/osteophytes, 1 minute JSN/osteophytes, 2 definite JSN/osteophytes and 3 ankylosis JSN/large osteophytes. Substantial JSN or osteophyte formation is defined as a score greater than one. The K&L score was scored on a 0-4 scale (grade 0: indicating no OA; grade 1: doubtful OA; grade 2: minimal OA; grade 3: moderate OA and grade 4: indicating severe OA) [8].

For the present analysis the highest scores of osteophyte formation and joint space narrowing from the lateral or medial tibiofemoral compartment from the knee scheduled for surgery (the index knee) were used.

Comorbidity

Information on comorbidities was gathered to measure musculoskeletal and non-musculoskeletal comorbidities that potentially could influence to the sensation of instability. A comorbidity questionnaire developed by the Dutch Central Bureau of Statistics (CBS) [11] was used in which the presence or absence of comorbidities in the previous year was asked. These comorbidities were classified in two domains: musculoskeletal comorbidities (severe elbow, wrist or hand pain; back pain; other rheumatic diseases) and non-musculoskeletal comorbidities (chronic lung diseases; cardiac disorder or coronary disease; arteriosclerosis; hypertension; (consequences of) stroke; severe bowel disorder; diabetes mellitus; migraine; psoriasis; chronic eczema; cancer; incontinence of urine; hearing or vision impairments; dizziness in combination with falling) [12].

Pain and function in daily living

Pain and function in daily living were assessed using two of the subscales from the self-reported Dutch version of the Knee Injury and Osteoarthritis Outcome Score (KOOS) [13]. The KOOS is a knee-specific instrument, developed to assess the opinion of patients about their knee and associated problems. The KOOS holds 42 items divided over five separately scored subscales: Pain (nine items); Activities of daily living (ADL) (17 items); Symptoms (seven items); Sport and Recreation Function (Sport) (five items); and Knee Related Quality of Life (QoL) (four items). Standardised answer options are given on a five-point Likert scale resulting in a score from 0 to four. A normalized score (100 representing the best outcome and 0 indicating the worst outcome) is calculated for each subscale. In 2007 Groot et al. translated and validated the KOOS into a Dutch version [14].

Statistical analyses

Firstly, descriptive statistics for patient characteristics were calculated in the total group, as well as for persons reporting knee instability and persons reporting no knee instability. Chi-square tests and independent T-tests were used to identify significant differences in demographic variables between patients reporting knee joint instability and patients reporting no knee joint instability. Secondly, logistic regression analyses were provided to identify associations of JSN and osteophyte formation (independent variables) with self-reported knee joint instability (dependent). In addition, stratified logistic regression analyses were performed for sex, comorbidities and, based on the median, for BMI, pain and limitations in daily activities. Statistical significance was accepted at p values less than 0.05. All data were analysed using the SPSS statistical package (version 20.0, SPSS, Chicago, Illinois).

Results

Characteristics of all patients

The characteristics of the participants are described in Table 1. Two hundred and sixty-five patients with a mean age of 68.9 years (standard deviation (SD) 8.4) and a mean BMI of 28.6 (SD 4.3) were included. A total of 244 patients (93%) reported knee complaints for more than a year; 126 patients (48%) even for more than five years. Furthermore, comorbidities were observed in 188 patients (72%) of which 89 patients reported a musculoskeletal comorbidity. In addition, 55 patients (29%) reported comorbidities in more than one category and six patients (three percent) reported comorbidities in all the three categories.

The mean (SD) KOOS subscale scores were 39.3 (17.8) for pain, 46.1 (18.3) for ADL, 44.3 (13.4) for symptoms, 10.5 (14.4) for sport and 26.5 (15.6) for QoL in the total group.

Table 1. Patient characteristics, self-reported knee instability and radiological features of the study population

	Total group (n=265)	Knee-instability (n=192)	Knee-stability (n=73)	p-value
Age, mean (SD)	68.9 (8.4)	68.1 (8.0)	70.7 (9.0)	0.028
Sex, Female; n (%)	170 (64%)	121 (63%)	49 (67%)	0.567
Body Mass Index, mean (SD)	28.6 (4.3)	28.4 (4.4)	29.1 (3.9)	0.203
Comorbidity, n (%)				
Musculoskeletal	(n=172) 89 (52%)	72 (61%)	17 (32%)	0.001*
Non-musculoskeletal	(n=259) 157 (61%)	113 (61%)	44 (60%)	0.943
Duration of knee complaints, years				
< 1	17 (7%)	13 (7%)	4 (6%)	0.184
1 – 5	118 (45%)	79 (42%)	39 (55%)	
5 – 10	47 (18%)	34 (18%)	13 (18%)	
> 10	79 (30%)	64 (34%)	15 (21%)	
Knee joint instability Activities performed when instability was experienced				
Walking		(n=162) 140 (86%)		
Ascending stairs		(n=135) 63 (47%)		
Descending stairs		(n=125) 59 (47%)		
Twisting or turning		(n=146) 92 (63%)		
Sitting down in chair		(n=124) 17 (14%)		
Rising from chair		(n=145) 65 (45%)		
Radiology indexknee				
K&L indexknee				
0-1	43 (16%)	31 (16%)	12 (16%)	0.141
2	49 (19%)	34 (18%)	15 (21%)	
3-4	173 (65%)	127 (66%)	46 (63%)	
Osteophyte formation				
No	57 (21%)	44 (23%)	13 (17%)	0.814
Minute	97 (37%)	70 (36%)	27 (37%)	
Definite	103 (39%)	72 (38%)	31 (43%)	
Large	8 (3%)	6 (3%)	2 (3%)	
Joint Space Narrowing				
No	28 (11%)	21 (11%)	7 (10%)	0.744
Minute	47 (18%)	34 (18%)	13 (17%)	
Definite	126 (47%)	94 (49%)	32 (44%)	
Ankylosis	64 (24%)	43 (22%)	21 (29%)	
Health-related Quality of Life				
KOOS, mean (SD)	39.3 (17.8)	36.7 (16.2)	45.7 (20.0)	0.001*
Pain	46.1 (18.3)	43.6 (17.8)	52.1 (18.3)	0.001*
ADL	44.3 (13.4)	41.5 (12.3)	51.3 (13.7)	0.000*
Symptoms	10.5 (14.4)	8.6 (11.8)	15.4 (18.8)	0.001*
Sport	26.5 (15.6)	24.6 (14.8)	31.4 (16.7)	0.001*
Quality of Life				

SD = standard deviation
n = number of patients
K&L = Kellgren & Lawrence score
KOOS = Knee injury and Osteoarthritis Outcome Score
ADL = Activity limitations Daily Living
*Comparison of patients with knee stability and patients with knee instability by means of Chi Square or Independent tests where appropriate. Significance level < 0.05

Self-reported knee joint instability

Self-reported knee instability in the previous three months was present in 192 patients (72%), of which 170 patients (89%) also reported knee joint instability in the previous six weeks. Most patients (91%) reported instability in one of the knees, whereas nine percent of the patients in both knees. In addition, in 98% of the patients, the knee scheduled for surgery was reported as (one of the) instable. Furthermore, an episode of knee joint instability occurred most in the majority (86%) of patients during walking, followed by twisting or turning movements (reported by 63% of the patients).

Moreover, the proportions of patients with a younger age ($p = 0.028$), reporting more often musculoskeletal comorbidities ($p = 0.001$) as well as the proportions of patients with worse KOOS Pain ($p = 0.001$), ADL ($p = 0.001$), Symptoms ($p = 0.000$), Sport ($p = 0.001$) and Quality of Life ($p = 0.001$) subscale scores were somewhat higher in patients reporting knee joint instability compared to patients reporting no knee joint instability.

Radiographic severity

Both patients reporting knee joint instability as well as patients reporting no knee joint instability 84% (158 and 61 patients, respectively) had a K&L score >1. In the 43 patients with K&L <2, the decision for surgery was based on symptomatology (pain and function) (17 patients), information from arthroscopy (three patients) or information from Magnetic Resonance Imaging (MRI)/Computed Tomography (CT) (22 patients). Osteophyte formation was substantial in 78 patients reporting knee joint instability (46%) along with 33 patients reporting no knee joint instability (46%). Besides, 137 patients reporting knee joint instability (71%) and 53 patients reporting no knee joint instability (73%) had substantial JSN. Osteophyte formation and JSN were not significantly different between patients reporting knee instability and patients reporting no knee instability ($p = 0.814$ and $p = 0.744$, respectively).

Associations of self-reported knee joint instability and radiographic severity

In univariate regression analyses no significant associations were found between self-reported knee instability and JSN (relative to score 0, the outcomes of score 1, 2 and 3 were odds ratio (OR) 0.87; 95% CI 0.30-2.54, OR 0.98; 95% CI 0.38-2.52, OR 0.68; 95% CI 0.25-1.86, respectively) or osteophyte formation (relative to score 0, the outcomes of score 1, 2 and 3 were OR 0.77; 95% CI 0.36-1.64, OR 0.69; 95% CI 0.23-1.45, OR 0.89; 95% CI 0.16-4.93, respectively) (shown in Table 2). Additional stratified analyses were provided for sex, BMI, limitations in daily living, pain and comorbidities. Analysis in men and females separately showed no association between OA and self-reported knee joint instability. Furthermore, separate analyses of patients with a BMI > 27.9 versus patients with a BMI < 27.9 or patients with severe limitations in daily activities versus patients with minor limitations in daily activities (ADL median subscale score of 44.1) showed no associations between self-reported knee instability and JSN or osteophyte formation. In addition, stratified analyses for patients with severe pain versus minor pain (pain median subscale score of 39.3) showed no associations. Finally, stratified analyses for the presence/absence of comorbidities were done in the two dichotomized groups separately; 1) musculoskeletal comorbidities present/absent; and 2) non-musculoskeletal comorbidities present/absent. There were no significantly different associations between self-reported knee joint instability and radiographic features between patients with comorbidities or not in any of the groups.

Table 2. Associations of self-reported knee joint instability with radiological features

	B	P-value	OR	95% CI
Osteophyte formation score, relative to score 0 (no				
osteophyte formation)	0.166	0.631	1.2	0.6-2.3
1 (minute osteophyte formation)	0.045	0.898	1.0	0.5-2.1
2 (definite osteophyte formation)	0.171	0.832	1.2	0.2-5.8
3 (large osteophyte formation)				
JSN score, relative to score 0 (no JSN)				
1 (minute JSN)	-0.112	0.821	0.9	0.3-2.4
2 (definite JSN)	-0.123	0.778	1.2	0.4-2.1
3 (ankylosis)	0.187	0.702	1.3	0.5-3.1

*B = regression coefficient; OR = odds ratio; 95% CI = 95% confidence interval

Discussion

This cross-sectional cohort study focused on the presence of self-reported knee joint instability in 265 patients with knee OA awaiting TKA surgery. Furthermore, the associations between self-reported knee joint instability and radiological features were evaluated. The majority of patients (72%) with knee OA prior to TKA reported knee joint instability. Though we hypothesised that self-reported knee joint instability would be associated with radiographic features, no associations were found with either JSN or osteophyte formation. This suggests that structural damage of the knee joint prior to TKA might not be related to the sense of knee instability. The high prevalence of self-reported knee instability in patients awaiting knee surgery indicates that it is an important issue in patients with knee OA, warranting the need to identify factors responsible for the sense of instability in this patient group.

It was our aim to identify an association between radiographic osteoarthritic features and self-reported knee joint instability. This aim was based on the assumption that osteophytes stabilise the knee joint as first described by Pottenger et al. [15] and widely accepted by physicians as well as cited in multiple articles and books [1,6,16,17]. It has been hypothesised that structural features compose the underlying mechanism for knee instability in patients with knee OA. Narrowing of the joint could contribute to a higher prevalence of knee joint instability in patients with knee OA [15], but results supporting this statement were lacking, as narrowing of the joint was not measured [15]. In addition, the authors suggested that osteophyte formation prevented progression of instability in OA knees [15]. Contradictory, our data do not support these suggestions. Two possible explanations for the differences in results were the used definition of stability and the different types of osteophytes. The difference in definition is based on previous studies where the varus-valgus laxity of the tibiofemoral joint was assessed, which is a different concept of knee stability as compared to self-reported knee stability [18]. The difference in definition of knee joint instability (self-reported versus laxity) could explain the difference in results. Knee joint instability measured with other techniques could still be associated with radiographic features. The second possible explanation for the different results lies in the grouping of different types of osteophytes, which was beyond the scope of this study. A study of Nagaosa et al. [10] characterised the size and direction of osteophytes in knee OA and suggested that only small, predominantly outward extending osteophytes create stability. Thus, not only the size of osteophytes, but also the location in the tibiofemoral joint (e.g. central versus the edge of the joint) could be taken into account when performing the analysis. Future studies will be necessary to evaluate the effect of different types and locations of osteophytes on self-reported knee joint instability.

Muscle weakness was associated with self-reported knee joint instability in patients with knee OA [3]. It can be speculated that muscle weakness is associated with the perception of knee joint instability in situations when the joint is loaded, for example during walking. Muscles of the knee joint are delayed to respond to external forces, which can result in the perception of not controlling the knee. This is supported by our data, where a majority of the patients (86%) reported knee joint instability during walking. The perception of not controlling the knee during daily activities is closely related to the notion of confidence of the knee. In our study, uncertainty regarding knee control was highly prevalent and strongly associated with self-reported knee instability (data not shown), which is in agreement with previous studies [19,20]. In addition, effusion of the knee joint is common in patients with knee OA [21] and hypothesised to influence the perception of knee joint instability. Unfortunately, we had no data on knee effusion in our patients. Moreover, our study found age, pain and limitations in daily living to be associated with self-reported knee joint instability, which is in accordance with previous literature [1-3]. This illustrates that we used a representative approach to measure associations with self-reported knee joint instability. Besides, stratified analyses were performed, aiming to validate the results, showing no differences in associations between self-reported knee instability and radiological features. This supports the hypothesis that structural damage of the knee joint is not related to the perception of knee instability.

Several limitations of the study should be mentioned. First, this study was of a cross-sectional design, therefore, no causal conclusions are allowed. Second, since the assessment of the sensation of knee joint instability could be biased by subjective bias it is important to assess objectified knee instability. Future studies are needed to assess objectified knee joint instability. Third, muscle strength was not assessed before surgery. This is a serious limitation since it is known that muscle strength is identified as one of the main factors associated with self-reported knee joint instability [3]. Fourthly, other clinical characteristics of the knee were not assessed, such as local inflammation of the knee joint. It is to be expected that swelling of the joint by effusion and synovitis could increase the perception of knee instability. Hence, future studies would benefit from including inflammatory characteristics. Fifthly, self-reported knee instability has been included as outcome in an intervention study [22], showing an improvement in self-reported knee instability by exercises. Reliability of this measure of instability is unknown. Sixthly, 43 patients with K&L score 0-1 were included. It has been reported that decisions for TKA should be based on symptomatology rather than radiographic features alone [23]. Therefore, the decision for surgery in these patients was based on symptomatology or information from arthroscopy or MRI. Moreover, several strengths of the study should be acknowledged. First, assessment of knee joint instability was done according to several previous studies and our prevalence rates are in accordance with previous literature. Secondly, we used unselected patients and thirdly, solely patients prior to TKA were included resulting in an appropriate population to test our hypothesis.

Conclusion

In conclusion, self-reported knee joint instability is not associated with either JSN or osteophyte formation. If further studies aim to focus on the relationship between self-reported knee joint instability and radiographic features, the effect of different types, locations and directions of osteophytes should be taken into account.

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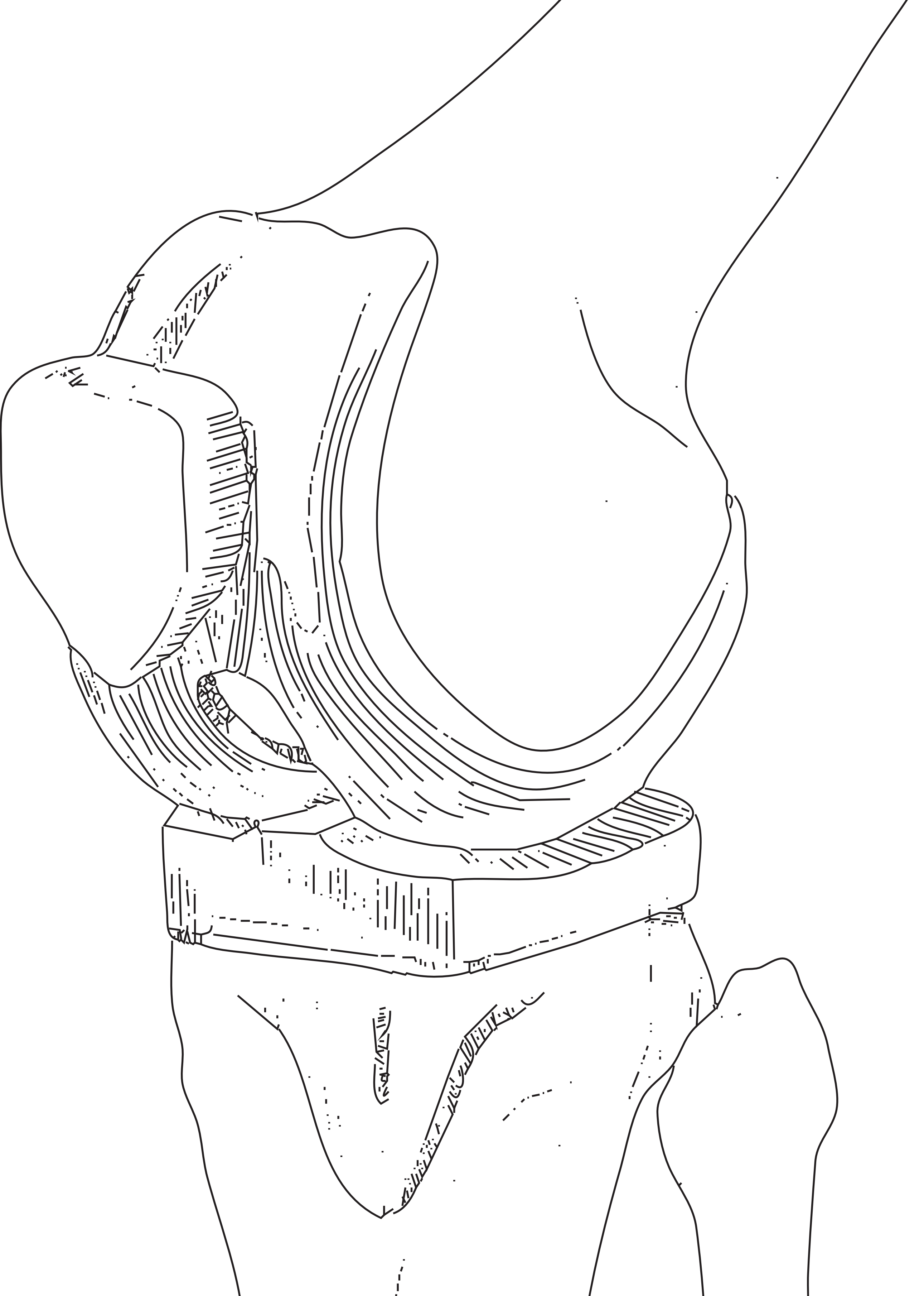

Chapter V.

Self-reported knee instability associated with pain, activity limitations, and poorer quality of life before and 1 year after total knee arthroplasty in patients with knee osteoarthritis.

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Abstract

Information on the association of self-reported knee instability with clinical outcomes after Total Knee Arthroplasty (TKA) and one year follow-up is scarce. The aims were to determine (i) the course and prevalence of self-reported knee instability before and one year after TKA and (ii) the associations of preoperative, postoperative, and retained self-reported knee instability with pain, activity limitations, and quality of life (QoL) in patients with knee osteoarthritis. Patients undergoing primary TKA, selected from the Longitudinal Leiden Orthopaedics and Outcomes of OsteoArthritis Study, had their knee instability measured using a questionnaire. The Knee injury and Osteoarthritis Outcome Score pain, activity limitations, and QoL subscales were administered before and one year after surgery. Multivariable regression analyses were performed to examine associations between knee instability, pain, activity limitations, and QoL, adjusted for covariates (age, gender, comorbidities, and radiographic severity). Of the 908 included patients, 649 (71%) and 187 (21%) reported knee instability before and following TKA, respectively. Of the patients with preoperative knee instability, this perception was retained in 165 (25%) cases. Knee instability was preoperatively associated with pain (B -9.6; 95%CI: -12.4 to -6.7), activity limitations (B -7.5; 95%CI: -10.2 to -4.8), and QoL (B -4.7; 95%CI: -7.0 to -2.4) and postoperatively with pain (B -15.0; 95%CI: -18.5 to -11.6), activity limitations (B -15.1; 95%CI: -18.4 to -11.8), and QoL (B -18.7; 95%CI: -22.3 to -15.3). Retained knee instability was associated with postoperative pain (B -15.1; 95%CI: -18.9 to -11.2), activity limitations (B -14.1; 95%CI: -17.8 to -10.4), and QoL (B -18.0; 95%CI: -21.7 to -14.3). In conclusion, in clinical care, self-reported knee instability is retained postoperatively in 25% of the patients. Retained knee instability is associated with more pain, activity limitations, and poorer QoL postoperatively.

Introduction

Total knee arthroplasty (TKA) is carried out to reduce pain and limitations in daily activities in patients with severe knee osteoarthritis (OA). Overall, TKA is a highly effective treatment (1, 2). Nevertheless, persisting pain and activity limitations 6-36 months after surgery are reported by 10-30% of the patients (3-7). Older age, female gender, overweight, comorbidities, and radiographic severity have been suggested to be associated with persisting pain and activity limitations (8-11). Recently, an association was reported between, on the one hand, postoperative pain and activity limitations and, on the other hand, postoperative knee instability (12).

Previous research concluded that the majority (60-80%) of patients with knee OA report knee instability (12-16). Self-reported knee instability is the sensation of buckling, shifting, or giving way of the knee (13), and is associated with pain and activity limitations prior to TKA (14-16). It is to be expected that after TKA, self-reported knee instability reduces due to the decrease in postoperative pain, and due to the damaged, uneven articulated joint surface of the tibia and femur having been replaced by a smooth implant surface. Nevertheless, a previous randomized controlled trial demonstrated that, six months after TKA, a third of the included patients (32%) retained self-reported knee instability (12). Moreover, retained self-reported knee instability was associated with pain and activity limitations six-month postoperatively in a randomized controlled study (12).

In the long run and in clinical care it is unknown whether patients with retained knee instability represent a population with poor clinical outcomes (i.e., persistent pain and activity limitations) after TKA. It is to be expected that retained postoperative knee instability patients can be characterized by having worse pain, more activity limitations, and accordingly, poor quality of life (QoL) compared with patients who postoperatively no longer report knee instability.

The aims of the study were to determine (i) the prevalence of self-reported knee instability before and at one year after TKA. Along with, the clinical course of knee instability within individual patients; and (ii) the associations of preoperative, postoperative, and retained self-reported knee instability with pain, activity limitations, and QoL.

Methods

Study Design

The present study analyzed a subset of data from the Longitudinal Leiden Orthopeadics Outcomes of Osteo-Arthritis study (LOAS), which is an ongoing, multi-center, longitudinal prospective cohort study designed to determine long-term outcomes of Total Hip Arthroplasty (THA) and TKA (Level of Evidence II). The LOAS study (Trial ID NTR3348) started in June 2012 and has preoperative and postoperative data until June 2015 on 1220 patients undergoing TKA.

Study Population

The patients involved underwent primary TKA in one of the six participating hospitals (Leiden University Medical Center, Leiden; Alrijne Hospital [former Diaconessenhuis and Rijnland Hospital], Leiden and Leiderdorp; Groene Hart Hospital, Gouda; Reinier de Graaf Hospital, Delft; LangeLand Hospital, Zoetermeer; Waterland Hospital, Purmerend). The inclusion criteria of the LOAS study were being enlisted to undergo THA or TKA, being able to complete questionnaires in Dutch and being aged 18 years or older. Excluded were patients who did not provide informed consent or who had a physical or mental status not allowing participation. Recruitment of patients in the LOAS has previously been described (17). Eligible patients were informed about the study through written and oral information by their treating medical specialist. Additional written information about the study was provided by regular mail, as well as a consent form, a questionnaire, and a stamped return envelope. Patients were included once written informed consent was obtained according to the Declaration of Helsinki. Postoperative questionnaires were sent by regular mail 6, 12, and 24 months after surgery, and every

2 years thereafter. Solely the preoperative and 12-month postoperative questionnaires included a questionnaire on self-reported knee instability.

Only data from patients undergoing primary TKA who reported on knee instability both preoperatively as well as one year postoperatively were analysed. Ethical approval was obtained by the Medial Ethics Committee of the Leiden University Medical Center (registration number P12.047) and funding was received from the Dutch Arthritis Foundation (LLP13).

Assessments

Self-Reported Knee Instability

Self-reported knee instability was assessed by means of a Dutch version of the knee instability questionnaires used in previous studies (13, 18). The item on the presence of knee instability can be translated into English as follows: “the sensation of buckling, shifting, or giving way of the knee in the previous 3 months”, with the following answering options: 1 never (0 episodes); 2 seldom (1-2 episodes); 3 regularly (3-5 episodes); 4 very often (more than five episodes). These options were dichotomized into “no episodes of knee instability” or “one or more episodes of knee instability”.

Pain, Activity Limitations, and QoL

Pain, activity limitations, and QoL were assessed using three of the subscales from the Knee Injury and Osteoarthritis Outcome Score (KOOS). The KOOS comprises 42 items in five subscales, including the subscales Pain (9 items), Activity in Daily Living (17 items), and Knee Related QoL (4 items). The Activity in Daily Living subscale was used to assess activity limitations. Standardized answer options are given on a 5-point Likert scale resulting in a score from 0 to 4. A normalized score (100 representing the best outcome and 0 indicating the worst outcome) is calculated for each subscale (19, 20).

Patient Characteristics and Comorbidities

Patient characteristics included age, gender, mass (kg), and height (m) to calculate Body Mass Index (BMI).

Information on comorbidities was gathered using a questionnaire developed by the Dutch Central Bureau of Statistics (CBS) (21), in which the presence or absence of comorbidities in the previous year was determined. These comorbidities were classified in two domains: Musculoskeletal comorbidities (severe elbow, wrist, hand or back pain; other rheumatic diseases) and non-musculoskeletal comorbidities (chronic lung, cardiac, or coronary disease; arteriosclerosis; hypertension; [consequences of] stroke; severe bowel disorder; diabetes mellitus; migraine; psoriasis; chronic eczema; cancer; urine incontinence; hearing or vision impairments; dizziness in combination with falling). In analysis, comorbidities were categorized into absent, musculoskeletal, non-musculoskeletal, or both musculoskeletal and non-musculoskeletal.

Preoperative Radiographic Severity of OA

Preoperative weight bearing anteroposterior and lateral radiographs of the knees were assessed by an experienced musculoskeletal radiologist (HMK), who was shielded for patient characteristics. The Kellgren and Lawrence (KL) grading system was used to classify the severity of OA (22). In addition, 10% of the radiographs were scored twice to establish intra-reader reliability (Intra-Class Correlation 98% [95% CI: 97-99%]). Discrepancies between the first and second readings were solved by consensus.

Statistical Analysis

Patients' characteristics, pain, activity limitations, and QoL were calculated as means (SD) or medians (range). For categorical or nominal level variables (self-reported knee instability, gender, comorbidities, radiographic severity of OA) frequencies and percentages were calculated. Differences in age, gender, BMI, comorbidities, radiographic severity, and outcome variables between patients reporting knee instability and patients reporting no knee instability pre- or postoperatively were analyzed by means of Chi Square, Independent T-test, or Mann-Whitney U test, as appropriate. In patients reporting instability prior to TKA, the course of instability over a one-year period was determined. Additionally, among patients reporting no instability prior to TKA, the incidence of instability was determined. Subsequently, differences in age, gender, BMI, comorbidities, radiographic severity, and outcome variables between patients with retained knee instability and patients with resolved knee instability were analyzed by means of Chi Square, Independent T-test, or Mann-Whitney U test, as appropriate. Linear regression analyses were used to calculate the associations between self-reported knee instability (independent variable), pain, activity limitations, and QoL (dependent variables), controlled for age, gender, BMI, comorbidities, and radiographic severity first prior to TKA and then one year after TKA. Finally, linear regression analyses were performed to study the associations between retained knee instability, pain, activity limitations, and QoL, adjusted for baseline scores, age, gender, BMI, comorbidities, and radiographic severity. All analyses were performed using SPSS software, version 23.0 (Chicago, IL).

Results

Of the 1220 patients undergoing TKA between June 2012 and July 2015 who completed the preoperative assessment, 261 (26%) patients were lost to follow-up and 51 patients did not report any information regarding their perception of knee instability in one of the questionnaires, resulting in 908 (74%) patients included in the present study (Fig. 1).

Prevalence of Self-Reported Knee Instability Before and one Year After TKA

Of the 908 patients, 649 (72%) reported preoperative knee instability and 187 (21%) reported knee instability one year after surgery (Table 1). In patients reporting preoperative knee instability, preoperative pain, activity limitations, and QoL scores were worse than corresponding outcomes for patients reporting no preoperative knee instability ($p<0.001$). Patients reporting preoperative knee instability were also more often female ($p<0.05$). Postoperative pain, activity limitations, and QoL subscale scores were lower (i.e., more pain and activity limitations, and poorer QoL) in patients reporting postoperative knee instability compared with patients reporting no postoperative knee instability ($p<0.001$). In addition, reporting postoperative knee instability was associated with a younger age ($p=0.012$).

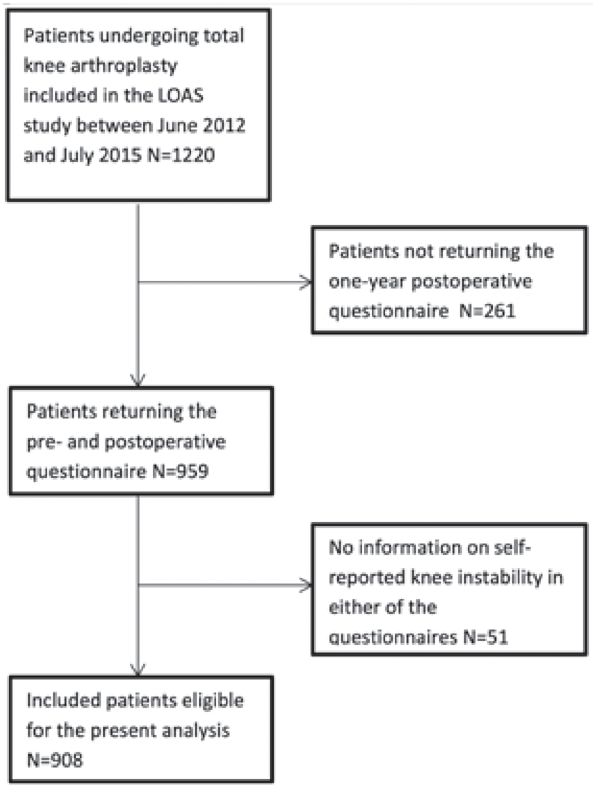

Figure 1. Flowchart of patients included in the Longitudinal Leiden Orthopaedics and Outcomes of Osteo-Arthritis Study (LOAS) between June 2012 and July 2015 undergoing Total Knee Arthroplasty. From a total of 1200 patients, 908 patients were eligible for the present study.

Association of Knee Instability with Pain, Activity Limitations and QoL before and one year after TKA

Cross-sectional analyses adjusted for covariates showed that preoperative knee instability was statistically significantly associated with pain (B -9.6; 95% CI: -12.4 to -6.7), activity limitations (B 7.5; 95% CI: -10.2 to -4.8), and QoL (B -4.7; 95% CI: -7.0 to -2.4). Postoperative knee instability was also associated with more postoperative pain (B -15.0; 95% CI: -18.5 to -11.6), activity limitations (B -15.1; 95% CI: -18.4 to -11.8), and poorer QoL (B -18.8; 95% CI: 22.3 to - 15.3) (Table 2).

Table 1. Patients characteristics, Self-Reported Knee Instability and Self-Reported Pain, Function and Quality of Life of the study population preoperatively (T0) and one year postoperatively (T1) separated into patients with and without self-reported knee joint instability.

	Knee-instability T0 N=649 (72%)	No knee-instability T0 N=259 (28%)	P-value	Knee-instability T1 N=187 (21%)	No knee-instability T1 N=721 (79%)	P-value
Age, mean (SD)	67.3 (8.6)	68.3 (8.5)	0.117	67.2 (9.2)	69.0 (8.4)	0.012*
Female, n (%)	453 (70%)	154 (60%)	0.003*	131 (70%)	476 (66%)	0.338
Body Mass Index, mean (SD)	(n=640) 29.1 (4.7)	(n=255) 29.1 (4.5)	0.928	(n=183) 29.7 (4.5)	(n=712) 29.0 (4.6)	0.051
Comorbidity, n (%)	(n=589)	(n=238)				
None	114 (19%)	51 (21%)	0.082	-	-	-
Musculoskeletal	80 (14%)	27 (11%)		-	-	-
Non-musculoskeletal	247 (42%)	117 (49%)				
Both	148 (25%)	43 (18%)				
Kellgren&Lawrence grade	(n=500)	(n=197)	0.227			
indexknee, n (%)	62 (12%)	22 (11%)		-	-	-
0-1	90 (18%)	25 (13%)		-	-	
2	280 (56%)	126 (64%)		-	-	
3	68 (14%)	24 (12%)				
4						
KOOS Pain, median (range)	(n=578) 36.2 (0-91)	(n=230) 44.4 (0-100)	0.000*	(n=186) 78.2 (0-100)	(n=705) 94.4 (17-100)	0.000*
KOOS Function, median (range)	(n=582) 42.6 (0-99)	(n=236) 50.0 (4-100)	0.000*	(n=185) 76.5 (0-100)	(n=713) 92.6 (6-100)	0.000*
KOOS Quality of Life, median (range)	(n=642) 31.3 (0-81)	(n=257) 31.3 (6-88)	0.989	(n=186) 43.8 (6-81)	(n=674) 57.8 (17-68)	0.000*

*Comparison of patients with knee stability and patients without knee instability by means of Chi Square, Independent T-test or Mann-Whitney U test where appropriate. Significance level <0.05
SD = Standard Deviation
n = number of patients
KOOS = Knee injury and Osteoarthritis Outcome Score

V

Table 2. Uni- and Multivariable Regression Analyses of Knee Instability on Pain, Activity Limitations and Quality of Life Preoperatively and one Year After Total Knee Arthroplasty, Adjusted for Covariates

	Preoperative pain				**Preoperative activity limitations**				**Preoperative quality of life**			
	Beta	SE	P-value	95% CI	Beta	SE	P-value	95% CI	Beta	SE	P-value	95% CI
Knee Joint Instability T0	-9.6	1.4	0.000	-12.4 - -6.7	-7.5	1.4	0.000	-10.2 - -4.8	-0.43	0.84	0.610	-2.1 – 1.2
Age	-9.1	1.4	0.000	-11.9 - -6.3	-7.3	1.4	0.000	-10.0 - -4.5	-0.28	0.83	0.734	-1.9 – 1.4
Gender	-8.8	1.4	0.000	-11.6 - -6.0	-6.8	1.4	0.000	-9.5 - -4.2	-0.18	0.82	0.831	-1.8 – 1.4
BMI	-9.4	1.4	0.000	-12.2 - -6.6	-7.4	1.4	0.000	-10.1 - -4.7	-0.46	0.84	0.581	-2.1 – 0.3
Comorbidities	-9.5	1.5	0.000	-12.4 - -6.6	-6.5	1.4	0.000	-9.4 - -3.7	-0.09	0.85	0.912	-1.8 – 1.6
Radiographic Severity	-9.8	2.1	0.000	-13.8 - -5.8	-6.5	2.0	0.001	-10.3 - -2.6	0.91	1.1	0.410	-1.3 – 3.1
	Postoperative pain				**Postoperative activity limitations**				**Postoperative quality of life**			
	Beta	SE	P-value	95% CI	Beta	SE	P-value	95% CI	Beta	T	P-value	95% CI
Knee Joint Instability T1	-15.0	1.8	0.000	-18.5 - -11.6	-15.1	1.7	0.000	-18.4 - -11.8	-11.0	1.3	0.000	-13.4 - -8.5
Age	-14.7	1.7	0.000	-18.1 - -11.3	-15.1	1.7	0.000	-18.4 - -11.9	-10.3	1.3	0.000	-12.8 - -7.9
Gender	-14.9	1.8	0.000	-18.4 - -11.5	-14.9	1.7	0.000	-18.2 - -11.6	-10.7	1.3	0.000	-13.2 - -8.2
BMI	-15.3	1.8	0.000	-18.8 - -11.7	-15.1	1.7	0.000	-18.5 - -11.7	-10.9	1.3	0.000	-13.4 - -8.5
Comorbidities	-14.8	1.9	0.000	-18.4 - -11.2	-14.6	1.7	0.000	-18.0 - -11.2	-10.8	1.3	0.000	-13.3 - -8.2

T0 = Preoperatively, T1 = one year postoperatively
SE = Standard Error

Course of Instability over one Year

Among the 649 patients with preoperative self-reported knee instability, 165 patients (25%) retained knee instability whereas 484 patients' knee instability resolved (75%). The patients with retained knee instability were younger and had more preoperative pain and more activity limitations compared with the patients with resolved knee instability ($p<0.05$) (Table 3). Moreover, the median of one-year postoperative pain, activity limitations, and QoL outcomes was 77.8 (Interquartile Range [IQR] 35.4), 76.5 (IQR 32.4) and 50.0 (IQR 25.0) for patients with retained instability and 94.4 (IQR 16.7), 92.2 (IQR 16.2) and 75.0 (IQR 31.3) for patients with resolved instability, respectively. All outcomes were statistically significantly worse for patients with retained instability as compared with those with resolved instability ($p<0.001$).

Among the 259 patients with no preoperative self-reported knee instability, 22 patients (8%) reported knee instability one year after surgery. The analysis of the 22 patients who developed knee instability showed, compared to the patients with no, retained or resolved instability, no significant differences on preoperative pain, activity limitations or QoL (p-value's 0.063, 0.265 and 0.309, respectively), or on postoperative pain or activity limitations (p-value's 0.268 and 0.077, respectively), only on postoperative QoL (p-value 0.014).

Association of Retained Knee Instability with Pain, Activity Limitations, and QoL

Statistically significant associations were found between retained knee instability and postoperative pain (B -15.1; 95%CI: -18.9 to -11.2), activity limitations (B -14.1; 95% CI: -17.8 to -10.4), and QoL (B-18.0; 95%CI: -21.7 to -14.3), adjusted for baseline scores and covariates. Patients with retained self-reported knee instability had worse postoperative pain, more activity limitations, and poorer QoL compared with the patients with no instability and those whose instability resolved.

Table 3. Patients Characteristics and Self-Reported Preoperative Pain, Activity Limitations and Quality of Life of patients with a retained versus resolved perception of knee instability

	Retained knee instability N=165	Resolved knee instability N=484	P-value
Age, mean (SD)	66 (9.3)	68 (8.4)	0.039*
Female, n (%)	117 (71%)	336 (69%)	0.179
Body Mass Index, mean (SD)	30 (4.7)	29 (4.7)	0.101
Comorbidity, n (%)	(n=148)	(n=441)	
None	30 (20%)	84 (19%)	0.748
Non-musculoskeletal	23 (15%)	57 (13%)	
Musculoskeletal	57 (39%)	190 (43%)	
Both	38 (26%)	110 (25%)	
Kellgren&Lawrence grade indexknee, n (%)			
0-1	18 (22%)	28 (12%)	0.245
2	15 (18%)	40 (18%)	
3	40 (49%)	132 (58%)	
4	9 (11%)	28 (12%)	
KOOS Pain, median (range)	33 (16.4)	37 (17.0)	0.005*
KOOS Function, median (range)	39 (16.6)	45 (18.0)	0.000*
KOOS Quality of life, median (range)	33 (9.0)	34 (10.2)	0.410

*Comparison of patients with knee stability and patients with knee instability by means of Chi Square, Independent T-test or Mann-Whitney U test where appropriate. Significance level <0.05
SD = Standard Deviation
n = number of patients
KOOS = Knee injury and Osteoarthritis Outcome Score

Discussion

Before and one year after TKA, respectively 72% and 21% of the patients reported knee instability. Twenty-five percent of the patients with preoperative knee instability retained this one year after TKA. Patients with retained knee instability reported clinically significant more pain, more activity limitations, and poorer QoL than patients with no perception of knee instability or with resolved knee instability. These results suggest that a substantial number of the patients who undergo TKA retain knee instability and that these patients suffer from more pain, more activity limitations, and poorer QoL compared to patients who no longer reported knee instability.

The percentages of patients reporting knee joint instability pre- and postoperatively, as well as the percentage of patients with retained knee instability were in accordance with previous studies (12-14, 16). Preoperatively, patients with knee instability had more pain and more activity limitations as compared with those with no instability, which corresponds to previous studies (12-14, 16). Our study found similar results for patients reporting knee instability one year postoperatively. The differences in postoperative pain and activity limitations between those with and without knee joint instability exceeded the minimal clinically important difference (range between 8 and 10 for both subscales) and are therefore clinically significant (19, 23). These results are in line with the study of Fleeton et al., a randomized controlled trial where a selected patient population was used that excluded the worst patients (e.g., patients aged 75 and over, those who had previously undergone lower limb surgery, or those with severe comorbidities) (12). In addition, one group of patients received an intensive postoperative exercise programme that potentially influenced the perception of knee joint instability (12, 24). This is different from our study, in which both young and old patients could have undergone uncontrolled interventions: A situation typical of clinical care. Our results emphasize that associations found earlier between self-reported knee instability and pain and activity limitations are also present in clinical care and persist up to one year after surgery. Moreover, patients with retained knee joint instability reported more preoperative pain and worse preoperative function compared with patients who no longer reported knee instability. Future research in clinical care should identify whether preoperative pain and function predict retained instability.

In addition to patients' perspectives on pain and activity limitations, QoL was assessed to include aspects of psychosocial function and emotional-social dimensions (25, 26). QoL as a generic outcome plays an important and complementary role in evaluating outcomes of lower limb arthroplasty surgery (7). Our results demonstrated that patients with self-reported knee instability reported worse pre- and postoperative QoL. A possible explanation for poor QoL is the combination of pain and a decline in physical function resulting in loss of functionality. Variables influenced by emotions, such as depression and the perception of knee instability can be seen as indicators of poor QoL. Studies are needed to understand the underlying mechanisms of poor QoL in patients with retained knee instability.

For the associations found between self-reported instability, pain, activity limitations, and QoL, no causal conclusions can be drawn despite the longitudinal study design. However, one can speculate about possible underlying mechanisms that might explain or clarify the results found. Potential underlying mechanisms include muscle strength and pain catastrophizing (15, 27-29). Muscle weakness may thus contribute to a delayed response of muscles to sudden forces that results in excessive movements of the knee joint and the perception of knee joint instability (15). In addition, knee pain itself was found to impair quadriceps control, likely provoking knee instability (27). This suggests that improving muscle strength, and in particular quadriceps strength, could be a target for intervention. A previous study showed that the perception of knee instability could be improved through exercise therapy and additional knee stabilization training (24). Future studies should determine if patients with retained knee joint instability benefit from exercise therapy and/or knee stabilization training. Furthermore, pain catastrophizing appeared to be related to experienced pain and activity limitations (28, 30). Pain catastrophizing is a method of cognitively coping with pain, characterized by negative self-statements and overly negative thoughts and ideas about the future (29, 31). Knee instability is also a perception and could therefore be closely related to pain catastrophizing. Future studies should determine the associations between pain catastrophizing and self-reported knee instability.

From a clinical perspective, knee instability might help orthopaedic surgeons to evaluate outcome after TKA. Differences between orthopaedic surgeon derived outcome scores and patient reported outcomes have been shown (32-34). In estimating outcomes, surgeons focus on pain, range of motion, alignment, joint laxity, and walkability, whereas patients focus on pain and limitations in daily activities (32-34). This discrepancy in scoring outcome (i.e., physician based and patient based) contributes to a disparity in postoperative results with possible overestimation of positive results by orthopaedic surgeons (26, 27). Due to the associations with clinical outcomes, retained knee joint instability could be an easily identifiable alarm symptom for poor clinical outcomes. When retained knee joint instability is present, orthopaedic surgeons could be aware of a higher risk for poor clinical outcomes. This implies that retained knee joint instability could be acknowledged as an important surrogate outcome. A surrogate outcome is defined as ''a laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives'' (35). Although there are disadvantages to the use of surrogate outcomes, surrogate outcomes have been accepted as proxy measures of patient-important outcomes, being often easier and quicker to measure, making surrogate outcomes suitable for usage in clinical care (35). It is therefore recommendable to use simple questions on self-reported knee instability in clinical care, for example as new patient reported outcome measure (PROM). Currently, PROMs are not only used for the measurement of surgery outcomes from the patients' perspective, but also included in national joint registries worldwide and considered as important quality marker after surgery (36).

Several strengths and limitations of the study should be acknowledged. Strengths of our study included the use of a large, unselected clinical cohort of patients of different ages, and postoperative analyses that contained one-year postoperative measurements. However, our study equally demonstrated some limitations. First, the measurement of objective instability was not included due to the clinical character of the study. Measuring objective dynamic instability requires an advanced measuring system that is currently only available with highly qualified gait analysis laboratories. Second, 26% of the patients did not return the postoperative questionnaire or did not complete information regarding knee instability, which resulted in substantial missing data and a potential risk of selection bias. We determined the distribution of gender and age and found no differences between the patients included in the analysis and the patients not included in the analysis (data not shown). Therefore, we believe that our patient population represents a general patient population in clinical care.

In conclusion, in 25% of the patients self-reported knee joint instability is prevalent preoperatively and retained at one year. The retained knee instability by patients is associated with more pain, activity limitations, and poor QoL postoperatively.

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Chapter VI

Are pain, functional limitations and quality of life associated with objectively measured physical activity in patients with end-stage osteoarthritis of the hip or knee?

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Submitted

Abstract

Study Design: Cross-sectional cohort study.

Background: Physical activity is promoted in patients with hip or knee osteoarthritis (OA), yet little is known about its relationship with symptoms, functional limitations and Quality of Life (QoL).

Objectives: To examine if OA-associated pain, functional limitations and QoL are associated with objectively measured physical activity in end-stage hip/knee OA.

Methods: Patients scheduled for primary total hip/knee arthroplasty were included. Patients wore an accelerometer (Activ8) with physical activity assessed over waking hours, and expressed as number of activity daily counts (ADC) per hour, %time spent on physical activity i.e. walking, cycling or running (%PA), and %time spent sedentary (%SB). Pain, functional limitations and joint-specific and general QoL were assessed with the Hip disability/Knee Injury and Osteoarthritis Outcome Score (HOOS/KOOS) and the Short Form (SF)-12. Multivariate linear regression models with the three to Z-scores transformed parameters of physical activity as dependent variables and adjusted for confounding, were conducted.

Results: 49 hip and 48 knee OA patients were included. In hip and knee OA patients the mean number of ADC, %PA and %SB were 18.79±7.25 and 21.19±6.16, 14±6.4 and 15±5.0, and 66±10.5 and 68±8.7, respectively. In hip OA, better joint-specific and general QoL were associated with more ADC, (β0.028; 95%CI:0.007–0.048, β0.041; 95%CI:0.010–0.071). Also, better general QoL was associated with the %PA (β 0.040, 95%CI:0.007–0.073). No other associations were found.

Conclusion: Whereas QoL was associated with physical activity in hip OA, pain and functional limitations were not related to objectively measured physical activity in patients with end-stage hip or knee OA.

Introduction

Osteoarthritis (OA) of the hip or knee joint is among the most common musculoskeletal conditions in adults worldwide, in particular in the elderly. Given the associated pain and functional limitations in daily life, it is a major health problem for individuals as well as society (1). The impact of OA on patients' functioning is usually measured in terms of limitations in specific daily activities such as taking a shower, dressing oneself, or preparing meals or performance-based methods such as the 6-minute walk test (2), whereas less is known on how OA affects the amount of actual everyday physical activity. Physical activity is an important factor to maintain health and function as it contributes to the prevention of disease and has beneficial effects on bones, joints and muscles (3, 4)

Previously, it was suggested that patients with lower limb OA avoid physical activities due to the associated pain and pain cognitions (5, 6). Pain and pain cognitions were suggested to serve as an obstacle to engage in physical activity, even though such activities are important in managing pain and disability (6). Indeed, several previous studies showed that perceived hip and knee related pain was associated with perceived physical activity (7, 8). However, perceived physical activity may not correspond with objectively measured physical activity levels (9, 10). This was illustrated by a study in hip or knee OA patients, showing that perceived physical activity as measured by PASIPD (Physical Activity Scale for Individuals with Physical Disabilities), increased over 200% after surgery, whereas only minor improvements were seen with objectively measured physical activity (9). Whether perceived hip or knee related pain and physical functioning are associated with objectively measured physical activity has been investigated in a number of studies (11-21). These studies had contradictive outcomes, presumably due to the heterogeneity in study populations and the used physical activity outcome measures. Moreover, none of the studies investigated whether patients' perception of QoL was related to the actual amount of objectively measured physical activity. This is important, as in the general population, perceived QoL was found to be a facilitator and motivator for the perceived amount of physical activity (22-24). As such, QoL is a potential target for interventions to maintain or improve physical activity in patients with severe hip or knee osteoarthritis.

Given the scarcity of knowledge and contradictive results, the aim of the present study was to examine to what extent OA-associated pain, functional limitations and joint-specific and general QoL are associated with objectively measured physical activity in end-stage hip/knee OA.

Methods

Study Design

The present cross-sectional analysis of data from a cohort study included a subgroup of participants of the Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis Study (LOAS) (Trial ID NTR3348). For the present analysis, only preoperative data were used. The LOAS started in 2012 and is an ongoing multicentre (7 hospitals) study on the long-term outcomes of Total Hip or Knee Arthroplasty (THA or TKA). The current study included study participants from the Leiden University Medical Center (LUMC), Leiden; the Alrijne Ziekenhuis, Leiderdorp; and the Albert Schweitzer Hospital, Dordrecht. Approval from the Medical Ethics Committee of the LUMC (ID 12.047) and all local research review boards was obtained for this physical activity study as part of the larger study. All patients provided written informed consent, both for the larger study and the physical activity study separately. Funding was received from the Dutch Arthritis Foundation (LLP13).

Patients

All patients scheduled for primary THA or TKA, who were physically and mentally able to complete questionnaires in Dutch and were 18 years or older, were eligible to participate in the LOAS study. Eligible patients were informed about the study by their treating medical specialist and, if they agreed, approached by the study coordinator. Between October 2013 and October 2014, all patients who (i) provided written informed consent for the LOAS study, (ii) were treated in one of the designated hospitals and (iii) were at least 2 weeks prior to surgery, were subsequently approached for the physical activity study. Patients who agreed to participate and provided written informed consent for the physical activity study were sent an activity monitor (accelerometer, Activ8) together with material for attachment and instructions, an information leaflet, physical activity diary and a pre-stamped return envelope. Excluded were patients (1) who refused participation after receiving the activity monitor, (2) of whom the accelerometer data were unavailable due to measurement errors or empty batteries and (3) of whom the surgery was cancelled, mostly because of improvement of pain or being accidentally placed on the surgical list.

Assessments

Physical activity

Physical activity was measured using the Activ8 Professional accelerometer, Remedy Distribution Ltd, Valkenswaard, the Netherlands, which is a recently validated, three-axis accelerometer, able to register 6 different activity categories (lying down, sitting, standing, walking, cycling and running) and the levels of physical activity in activity counts (in total and per activity category) (Horemans et al, The Activ8 Activity Monitor: validation of posture and movement classification, submitted). Data are stored in 5-minute epochs showing the duration of time spent on each activity category (seconds), as well as the levels of physical activity per activity category expressed in activity counts. Patients were instructed to (a) place the device (20 gram, 30x30x10 mm) halfway the front side of the upper leg between the hip and the knee (fixated with Tegaderm waterproof transparent dressing), (b) wear the monitor 24 hours a day and (c) wear the monitor at least 5 and at most 7 consecutive days including two weekend days. In addition, patients were asked to complete an activity diary in which predefined activity categories (i.e. lying down, standing, sitting, walking, running, cycling) had to be filled in hourly for as long as they wore the activity monitor. The activity diary was used to determine sleeping periods to easily exclude data measured during night-time. Patients with insufficient data due to measurement errors, empty batteries, less than 5 measurement days or incomplete physical activity diaries were excluded from the analysis.

Data from the accelerometer were summarized into three outcome parameters, calculated over wake time periods:

1) Mean levels of physical activity per hour, defined as the mean amount of hourly activity daily counts (ADC)
2) Percentage time spent on physical activity, defined as the time spent in the categories walking, cycling or running (%PA).
3) Percentage time spent on sedentary behaviour, defined as the time spent lying down or sitting (%SB).

Patient characteristics, comorbidities and clinical characteristics
Patient characteristics, comorbidities and clinical characteristics were collected by means of questionnaires.

Patient characteristics
Patient characteristics included: age, sex, length and weight to calculate Body Mass Index (BMI) and use of pain medication (yes/no).

Comorbidities
Information on the presence of comorbidities in the previous year was gathered by a comorbidity questionnaire developed by the Dutch Central Bureau of Statistics (CBS) (25). These comorbidities were classified in two domains: musculoskeletal comorbidities (severe elbow, wrist or hand pain; back pain; other rheumatic diseases) and non-musculoskeletal comorbidities (chronic lung diseases; cardiac disorder or coronary disease; arteriosclerosis; hypertension; (consequences of) stroke; severe bowel disorder; diabetes mellitus; migraine; psoriasis; chronic eczema; cancer; incontinence of urine; hearing or vision impairments; dizziness in combination with falling) (25).

Pain, functional limitations and joint specific Quality of Life
The Hip disability and Osteoarthritis Outcome Score (HOOS) and Knee injury and Osteoarthritis Outcome Score (KOOS) are joint specific questionnaires (26, 27). 12A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) was calculated for each subscale (28). The pain, ADL and joint specific QoL subscales were used to assess pain, functional limitations and joint-specific quality of life.

Health related Quality of Life (QoL)

Quality of life (HrQoL) was assessed with the Short Form-12 (SF12) Physical Component Score (PCS) and Mental Component Score MCS) (29, 30).

Statistical Analysis

All analyses were done for patients with hip and knee OA separately. First, student's unpaired T-tests (continuous, normally distributed data), Mann-Whitney-U-tests (continuous, not normally distributed data) and Chi-squared tests (categorical data) were used to compare the patient characteristics, pain, functional limitations and QoL of included and non-included patients.

Univariate and multivariate (adjustment for age, gender, BMI, the presence of comorbidities) linear regression analyses were performed to examine the associations between pain, function, QoL and physical activity outcomes. The three physical activity outcomes (mean levels of physical activity (ADC), percentage of time spent on physical activity (%PA), percentage of time spent on sedentary behaviour (%SB) were standardized into z-scores to improve comparisons of outcomes. A z-score is a number representing the amount of standard deviations below or above the population mean. Z-scores range from -3 up to +3 standard deviations. The z-score formula is $z = (x - \mu) / \sigma$.

Results

Patients

Of the 408 patients who were eligible and invited for the physical activity study (192 Hip OA patients (47%) and 216 Knee OA patients (53%)), 121 patients (58 hip (30%) and 63 knee (29%)) were willing and able to participate. Due to measurement errors, empty batteries, subsequent refusal of participation or cancelled surgery, data from 97 patients (49 hip and 48 knee patients) were available (Figure 1).

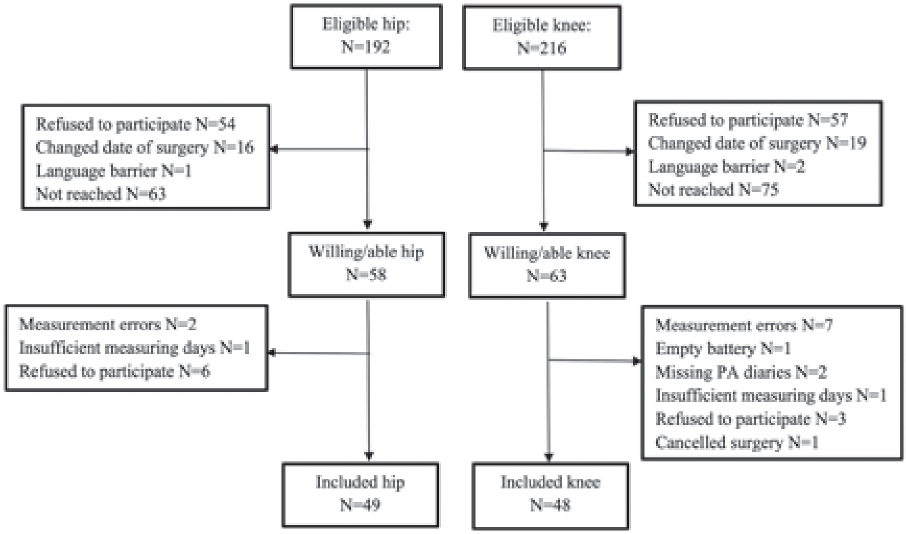

Figure 1. Flow chart of patient enrolment

Comparison of patient characteristics of eligible patients with participating patients showed no differences except that non-participating patients with hip OA reported more pain as compared to participating patients with hip OA (supplementary table).

The characteristics of the patients with hip and knee OA are described in Table 1. Hip and knee OA patients had a mean age of 66 (SD 9.1) and 68 (SD 7.3) years and most patients were female (approximately 63%).

<u>Physical activity</u>

Physical activity outcomes are shown in Table 2. For the total group (patients with hip and knee OA) the median number of days the accelerometer was worn was 6 (range 5-7). Hip and knee OA patients spent on average 14% (SD 6.4) and 15% (SD 5.0) of their time during waking hours on physical activity, respectively. Moreover, on average 66% (SD 10.5) and 68% (SD 8.7) of their time during waking hours was spent on sedentary behaviour, respectively. The remaining time during waking hours (approximately 20%) was spent on standing.

In patients with hip OA, HrQoL (SF12 PCS) was positively associated with levels of physical activity and percentage time spent on physical activity (table 3). In addition, joint specific QoL (KOOS QoL) was positively associated with levels of physical activity. These effects remained after adjusting for age, sex, BMI and comorbidities in multivariate analysis. Pain and functional limitations were not associated with levels of physical activity, percentage time spent on physical activity nor with sedentary behaviour.

Table 1. Patient characteristics, hip and knee pain, functional limitations and quality of life (QoL) of all included patients and patients with hip and knee OA separately

	All patients (n=97)	Hip OA (n=49)	Knee OA (n=48)
Age, years; mean (SD)	67 (8.3)	66 (9.1)	68 (7.3)
Gender (n=94), male; n (%)	35 (37)	18 (38)	17 (37)
Body Mass Index (n=95); mean (SD)	29 (5.3)	28 (4.7)	30 (5.8)
Non-musculoskeletal comorbidities†; n (%)	80 (83)	39 (80)	41 (85)
Musculoskeletal comorbidities† (n=95); n (%)	53 (55)	19 (49)	34 (58)
Pain medication (n=95), n (%)	71 (73)	39 (81)	32 (68)
HOOS or KOOS; mean (SD)			
Pain (n=79)	38 (18.0)	33 (17.8)	43 (14.5)
Symptoms (n=80)	41 (16.9)	35 (16.0)	48 (14.9)
Functional limitations (n=86)	46 (22.2)	44 (24.8)	50 (18.0)
Sport/Recreation (n=90)	14 (15.2)	15 (16.9)	12 (13.2)
QoL (n=93)	26 (13.6)	25 (14.3)	28 (12.8)
SF12 Physical Component Score (n=90); mean (SD)	35 (9.7)	32 (9.3)	35 (10.0)
SF12 Mental Component Score (n=90); mean (SD)	56 (10.1)	56 (10.5)	56 (9.9)

† Presence of one or more co-morbidities as determined by a questionnaire including 22 comorbidities.
HOOS/KOOS = Hip disability and Osteoarthritis Outcome Score/Knee injury and Osteoarthritis Outcome Score
SF12 = Short-Form 12

Table 2. Physical activity of all patients and patients with hip and knee OA separately

	All patients (n=97)	Hip OA (n=49)	Knee OA (n=48)
Activity Monitor			
Hours that patients were awake/day; mean (SD)	15 (1.1)	15 (1.1)	15 (1.1)
Levels of physical activity/hours; mean (SD)	19978 (6807)	18787 (7247)	21193 (6164)
Percentage time spent on physical activity/ hours awake; mean% (SD)	15 (6.8)	14 (6.4)	15 (5.0)
Percentage time spent on sedentary behaviour/hours awake; mean% (SD)	67 (9.6)	66 (10.5)	68 (8.7)

OA = Osteoarthritis

In patients with knee OA, after adjusting for confounding factors no associations were found for pain, joint specific QoL or HrQOL with physical activity outcomes (table 3).

Table 3. Standardised[@] accelerometer levels of activity and self-reported joint pain, functional limitations and QoL in end stage hip and knee OA patients.

	Levels physical activity; β (95% CI)		**Percentage time spent on physical activity ; β (95% CI)**		**Percentage time spent on sedentary behaviour; β (95% CI)**	
Hip OA	Univariate analyses	Multivariate analyses#	Univariate analyses	Multivariate analyses#	Univariate analyses	Multivariate analyses#
HOOS						
Pain	0.012 (-0.001 – 0.032)	0.016 (-0.003 – 0.036)	0.013 (-0.008 – 0.033)	0.018 (-0.003 – 0.039)	<0.0001 (-0.20 – 0.20)	-0.005 (-0.025 – 0.016)
Symptoms	0.009 (-0.012 – 0.031)	0.016 (-0.003 – 0.036)	0.009 (-0.013 – 0.032)	0.016 (-0.005 – 0.037)	-0.004 (-0.026 – 0.018)	-0.009 (-0.030 – 0.011)
Functional limitations	0.005 (-0.007 – 0.018)	0.008 (-0.004 – 0.021)	0.004 (-0.009 – 0.017)	0.007 (-0.007 – 0.020)	0.000 (-0.013 – 0.013)	-0.003 (-0.016 – 0.011)
Sport	0.001 (-0.018 – 0.021)	0.003 (-0.017 – 0.024)	0.001 (-0.019 – 0.021)	0.003 (-0.019 – 0.025)	-0.001 (-0.021 – 0.018)	-0.003 (-0.024 – 0.018)
QoL	0.023 (0.002 – 0.044)*	0.028 (0.007 – 0.048)*	0.014 (-0.009 – 0.037)	0.018 (-0.005 – 0.041)	-0.006 (-0.029 – 0.017)	-0.006 (-0.029 – 0.017)
SF-12 PCS	0.041 (0.009 – 0.073)*	0.041 (0.010 – 0.071)*	0.040 (0.007 – 0.073)*	0.040 (0.007 – 0.073)*	-0.029 (-0.064 – 0.005)	-0.032 (-0.065 – 0.000)
SF-12 MCS	0.012 (-0.018 – 0.043)	0.013 (-0.016 – 0.042)	0.023 (-0.008 – 0.053)	0.023 (-0.007 – 0.053)	-0.003 (-0.035 – 0.028)	-0.003 (-0.033 – 0.027)
Knee OA						
KOOS						
Pain	0.014 (-0.007 – 0.036)	-0.001 (-0.022 – 0.020)	0.007 (-0.014 – 0.028)	-0.007 (-0.029 – 0.014)	0.001 (-0.020 – 0.022)	0.009 (-0.013 – 0.032)
Symptoms	0.014 (-0.007 – 0.034)	0.001 (-0.020 – 0.021)	0.018 (-0.002 – 0.038)	0.008 (-0.013 – 0.028)	-0.004 (-0.024 – 0.017)	0.004 (-0.018 – 0.026)
Functional limitations	0.021 (0.005 – 0.037)*	0.004 (-0.016 – 0.023)	0.017 (0.001 – 0.033)*	0.002 (-0.018 – 0.022)	-0.006 (-0.023 – 0.011)	0.006 (-0.015 – 0.027)
Sport	0.018 (-0.003 – 0.039)	0.012 (-0.009 – 0.034)	0.010 (-0.011 – 0.031)	0.004 (-0.017 – 0.026)	-0.003 (-0.024 – 0.018)	-0.003 (-0.025 – 0.020)
QoL	0.017 (-0.004 – 0.038)	0.005 (-0.017 – 0.026)	0.013 (-0.008 – 0.033)	0.002 (-0.020 – 0.024)	-0.002 (-0.023 – 0.020)	0.006 (-0.016 – 0.028)
SF-12 PCS	0.027 (-0.001 – 0.054)	0.018 (-0.008 – 0.044)	0.018 (-0.009 – 0.045)	0.010 (-0.017 – 0.036)	-0.010 (-0.038 – 0.018)	-0.004 (-0.031 – 0.023)
SF-12 MCS	0.002 (-0.027 – 0.031)	-0.010 (-0.037 – 0.017)	0.003 (-0.025 – 0.031)	-0.008 (-0.035 – 0.020)	0.000 (-0.029 – 0.029)	0.011 (-0.017 – 0.039)

HOOS/KOOS = Hip disability and Osteoarthritis Outcome Score/Knee injury and Osteoarthritis Outcome Score
Levels physical activity = Mean amount of hourly activity counts during the hours patients were awake
Percentage time spent on physical activity = Time spent in the categories walking, cycling or running as a percentage of total wear time
Percentage time spent on sedentary behaviour = Time spent lying down or sitting as a percentage of total wear time
SF-12 = Short-Form 12; SF-12 PCS = Physical Component Score of the Short-Form 12; SF12-MCS = Mental Component Score of the Short-Form 12.
OA = Osteoarthritis
QoL = Quality of Life
@; Activity counts and percentages are standardised to z-scores ($z = (x - \mu) / \sigma$)
* = $P < 0.05$; # Adjusted for age, sex, BMI and comorbidities

Discussion

In this cross-sectional analysis of patients with end-stage hip and knee OA scheduled for THA or TKA, joint pain and functional limitations did not show any association with objectively measured physical activity; QoL was associated with accelerometer-measured parameters of physical activity only in hip OA patients.

The finding that joint-specific pain or functional limitations were not associated with physical activity as measured with an accelerometer in end-stage OA is in accordance with three previous studies (12, 16, 20), but is contradictory to one other study (31). The study that showed that patient-reported "more pain" was associated with reduced physical activity levels in patients with end-stage lower limb OA included selected patients (solely women with moderate pain who were highly educated) limiting the generalizability of conclusions (31). However, comparison with these previous studies is hampered due to different types of accelerometers used, varying accelerometer outcome measures and variation in the number of measured-days.

The absence of an association between joint pain or joint-related functional limitations with objectively measured physical activity may be related to physical activity being more related to a general lifestyle and overall health than to specific health problems. Indeed, previous studies in TKA patients as well as the general population showed that physical activity was associated with lifestyle, socioeconomic status, general health and health-related utility, the latter being closely related to QoL (12, 32, 33). Indeed, in our study physical activity was associated with QoL in THA patients, but not in TKA patients, although the association in the latter group pointed into the same direction.

Moreover, the absence of a relationship between pain or functional limitations and objectively measured physical activity could also be related to intentionally retained physical activity levels. Activities which are part of regular human behaviour like washing oneself, cleaning, cooking or shopping may still need to be performed despite symptoms

(20). In addition, international evidence-based guidelines for hip and knee OA recommend conservative treatment including physiotherapy, for hip and knee OA in general, or specifically prior to surgery, in order to improve functional recovery. Therefore, some patients with perceived severe pain and functional disability could have retained their physical activity levels in order to reduce their symptoms or improve their overall health to be optimally prepared for a surgical treatment (20, 34). This is supported by the time spent on sedentary behaviour in our population (on average 66-68% of waking hours/day), which is comparable with subjects of the same age in the general United States population (i.e. 60%), suggesting that in patients with end-stage OA time spent on sedentary behaviours is not increased (35). Besides, the observed variation in physical activity levels could be a result of the differences in physical activity due to a natural variation in daily physical behaviour. In the general population the amount of physical activity varies largely among individuals, due to several determinants and variation in daily physical behaviour (36). Lastly, the absence of an association may be caused by inaccurate outcome measures. The distribution of activities over the day, the momentary duration of activities or other activity-related measures such as step count and step length could be more affected by perceived pain and functional limitations than the total amount of physical activity or the percentages time spent on physical activity/sedentary behaviour. As such, patients with high perceived pain and functional limitations could have spent the same time on physical activity, yet accomplished fewer results as measured by step count or step length due to the pain and functional limitations.

The present study has several strengths and limitations. Strengths of our study are, that we differentiated between levels of physical activity and time spent on certain activities such as sedentary behaviour as outcome measures (16). Furthermore, we used a relatively small accelerometer with assumable little discomfort for the patients, measured physical activity 24 hours during a minimum of five days and included at least two weekend days which made our data representative for everyday life activities (37).

Limitations include the relatively small sample sizes of hip and knee OA patients, although the participating and non-participating patients were comparable with respect to baseline characteristics (supplementary table). Secondly, the used accelerometer expresses energy expenditure as ADC-counts, whereas a Metabolic Equivalent Task (MET) was more often used in previous studies, which makes our results more difficult to interpret (38, 39). In addition, differences in physical activity over time could not be identified due the cross-sectional design of the current study. Yet, over time, pain and functional limitations could still be associated with physical activity. Besides, objectively measured physical activity was found to increase less than expected after THA or TKA (9, 40, 41). Pain is among the most important reasons for patients to undergo surgery. As pain is not associated with physical activity levels, it is unlikely that the amount of physical activity increases after surgery. This is important to address in the preoperative consultation to improve expectations of postoperative physical activity levels (9).

Conclusion

In conclusion, joint pain and functional limitations were not associated with physical activity as measured with an accelerometer measured in neither hip nor knee OA patients. In hip OA patients QoL was associated with objectively measured physical activity. Our results emphasize that, as they appear to be different constructs, actual physical activity could be encouraged despite perceived pain or functional limitations. For that matter, our conclusions are important to address in the preoperative consultation. As pain and objective physical activity are not associated, it is not to be expected that physical activity levels increase after total hip or knee arthroplasty.

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Supplementary table. Patient characteristics, hip and knee pain, functional limitations and quality of life of all included patients and patients with hip and knee OA separately

	Included hip OA (N=49)	Non-participant hip OA (N=73)	p-value	Included knee OA (N=48)	Non-participant knee OA (N=75)	p-value
Age, years; mean (SD)	66 (9.1)	68 (10.4)	0.30	68 (7.3)	68 (8.6)	0.88
Gender, male; n (%)	18 (38)	32 (45)	0.39	17 (37)	31 (41)	0.42
Body Mass Index; mean (SD)	28 (4.7)	26 (3.4)	0.09	30 (5.8)	29 (4.5)	0.25
Non-musculoskeletal comorbidities; n (%)	39 (80)	41 (63)	0.21	41 (85)	31 (78)	0.87
Musculoskeletal comorbidities; n (%)	19 (49)	38 (60)	0.29	34 (58)	18 (49)	0.34
HOOS or KOOS; mean (SD)						
Pain	33 (17.8)	41 (18.0)	0.03*	43 (14.5)	40 (20.3)	0.51
Symptoms	35 (16.0)	41 (19.4)	0.10	48 (14.9)	51 (22.4)	0.30
Functional limitations	44 (24.8)	43 (20.8)	0.97	50 (18.0)	47 (21.1)	0.49
Sport/Rec	15 (16.9)	20 (22.0)	0.20	12 (13.2)	12 (18.1)	0.84
QoL	25 (14.3)	27 (15.5)	0.45	28 (12.8)	28 (16.4)	0.88
SF12 Physical Component Score; mean (SD)	32 (9.3)	32 (8.9)	0.79	35 (10.0)	34 (9.5)	0.74
SF12 Mental Component Score; mean (SD)	56 (10.5)	55 (10.1)	0.65	56 (9.9)	56 (8.9)	0.98

P-value is based on the difference between hip OA and knee OA
* Significance level < 0.1
HOOS/KOOS = Hip disability and Osteoarthritis Outcome Score/Knee injury and Osteoarthritis Outcome Score, range 0-100 points
SF 12 = Short-Form 12, range 0-100 points.

Chapter VII

Determinants of return to work 12 months after total hip and knee arthroplasty.

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Abstract

Introduction: A substantial number of patients undergoing total hip or knee arthroplasty (THA or TKA) do not or only partially return to work. This study aimed to identify differences in determinants of return to work in THA and TKA.

Methods: We conducted a prospective, observational study of working patients aged <65 years undergoing THA or TKA for osteoarthritis. The primary outcome was full versus partial or no return to work 12 months postoperatively. Factors analysed included preoperative sociodemographic and work characteristics, alongside the Hip Disability and Osteoarthritis Outcome Score (HOOS)/ Knee Injury and Osteoarthritis Outcome Score (KOOS), and Oxford Hip and Knee Scores.

Results: Of 67 THA and 56 TKA patients, 9 (13%) and 10 (19%), respectively, returned partially and 5 (7%) and 6 (11%), respectively, did not return to work 1 year postoperatively. Preoperative factors associated with partial or no return to work in THA patients were self-employment, absence from work and a better HOOS Activities of Daily Living (ADL) subscale score, whereas only work absence was relevant in TKA patients. Type of surgery modified the impact of ADL scores on return to work.

Conclusion: In both THA and TKA, absence from work affected return to work, whereas self-employment and better preoperative ADL subscale scores were also associated in THA patients. The impact of ADL scores on return to work was modified by type of surgery. These results suggest that strategies aiming to influence modifiable factors should consider THA and TKA separately.

Introduction

Total hip and knee arthroplasty (THA and TKA) are effective procedures to reduce pain and improve function in patients with hip or knee osteoarthritis[1,2]. A substantial proportion (15%–45%) of patients are of working age (<65 years old) at the time of surgery[3,4]. While the majority of patients return to work postoperatively (68%–95% following THA; 71%–83% after TKA)[5], the absolute number of patients who do not return to work is substantial. Research into potentially modifiable factors for return to work after total joint replacements is therefore warranted.

The determinants of return to work after THA or TKA have been addressed in two systematic reviews[5,6]. The authors, based on a limited number of studies (five THA, one TKA and one mixed study), concluded that sociodemographic (age, sex, educational level), work (self-employment, physical demands, preoperative work disability, accessibility of the workplace, receiving workers' compensation), joint function and surgical-(complications) and rehabilitation-related factors (surgical approach) are associated with postoperative work status. Clinical studies of both THA and TKA published after these reviews also identified one or more of these determinants[7,8].

Overall, data on the determinants of partial or no return to work after total joint arthroplasty, and potential differences between THA and TKA, is scarce, particularly as, in the aforementioned systematic reviews, no synthesis of the individual studies could be made due to their limited number and large methodological variations. Moreover, the majority of studies included only THA patients, meaning that the factors related to return to work after TKA remain largely unknown. Finally, few studies considered reductions in working hours, which indicates productivity loss as an outcome.

Given the lack of knowledge, we aimed to identify, prospectively, differences in determinants of partial or no return to work 1 year after surgery in patients undergoing THA or TKA for osteoarthritis.

Methods

This study was part of a 1-year observational study of THA and TKA outcomes, which aimed to include all consecutive patients undergoing primary THA or TKA for osteoarthritis in the Alrijne Hospital, Leiderdorp, the Netherlands, between October 2010 and September 2012. All patients were required to have a physical and mental status that allowed the completion of questionnaires, and the ability to read and understand Dutch. The study protocol was reviewed and approved by the local hospital review board (registration number 10/07), which is associated with the Medical Research Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

All potentially eligible patients were identified from the surgical planning list. Patients with rheumatoid arthritis, a tumor, (hemi)paresis or amputation of the (lower)leg, and patients undergoing a hemi-arthroplasty or revision THA or TKA were excluded. One day preoperatively, the treating orthopedic surgeon provided oral and written information about the study to all eligible patients, as well as a questionnaire and a consent form. Patients who returned the set of questionnaires and informed consent form when admitted to the hospital for surgery were posted the postoperative questionnaire 12 months after surgery. Patients who did not return the questionnaire were contacted by telephone 4 weeks later.

Of the 845 total joint arthroplasty patients who were interested in taking part in the study, 343 THA (80%) and 322 TKA (77%) patients completed the postoperative questionnaire. Of those, 67 THA patients and 56 TKA patients were aged under 65 years and working preoperatively, provided information on their number of working hours postoperatively and did not retire after surgery. They were therefore included in the current analysis (Figure 1).

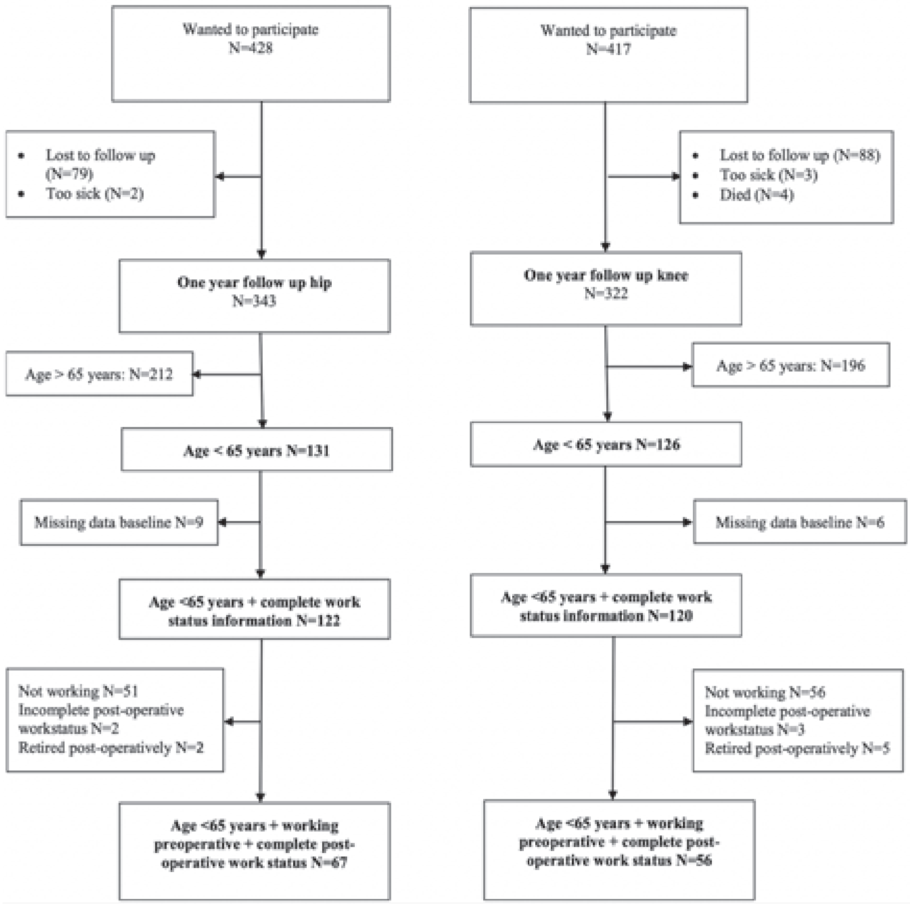

Figure 1. Flow Diagram

Assessments

The primary outcome measure was the presence of full versus partial or no return to work 12 months after THA or TKA. Preoperative factors found to be related to work outcomes were classified as patient and work characteristics, joint functioning and health status. In case of incomplete or unclear provision of data on working hours or postoperative work status, an additional questionnaire was sent and/or a telephone interview was performed by the primary investigator (CL).

Patient characteristics included: age (years); sex; body mass index (BMI); educational attainment, which was defined as low (primary school or lower vocational education), medium (lower general secondary school or intermediate vocational education) or high (higher general secondary school, higher vocational education or university); and living status, which was defined as independent, assisted living or in a nursing home.

Preoperatively, all patients were asked to indicate whether they had a paid job (yes/no). If no, they were asked whether they were a pensioner, housewife/houseman or unemployed. The following aspects of the patients' working situation were recorded: amount of hours currently worked per week; self-employed or salaried; absenteeism from work due to hip or knee complaints (yes/no); and the presence of work adaptations (yes/no), with yes including at least one of the following: change of tasks; performing fewer tasks; changes in working hours; other work-related adaptions or devices. Job title was recorded and classified as light, medium or heavy, in terms of its physical demands on the hip or knee, by two occupational physicians who independently scored the job based on work activity risk factors. The scoring system was derived from the evidence-based exposure criteria for the work relatedness of hip and knee osteoarthritis developed by the Netherlands Center for Occupational Diseases[9]. Disagreements in coding were resolved by consensus.

The patients' preoperative expectations to return to work were examined using one item of the Hospital for Special surgery Hip Replacement and Knee Replacement Expectations Surveys[10], formulated as: ''the expectation regarding being able to have a paid job''. The 5-point Likert scale was dichotomized into 'back to normal' or 'less than back to normal'.

Postoperatively, all patients were asked whether they were currently working (yes/no). If yes: they were asked to report their current number of working hours per week. Based on the difference in pre- and postoperative working hours, return to work was classified as: complete return (no difference in, or higher postoperative working hours); partial return (working fewer hours postoperatively); or no return to work (complete work disability pension, full-time sick leave or out of work). For the present analysis, partial return and no return to work were combined.

Hip and knee functioning and health status

The Hip disability and Osteoarthritis Outcome Score (HOOS) and Knee injury and Osteoarthritis Outcome Score (KOOS) consist of 40 and 42 items respectively, divided over 5 subscales: Pain (10 items); Symptoms, including stiffness and range of motion (5 items); Activities of Daily Living (ADL) (17 items); Sport and Recreation Function (4 items); and Quality of Life (4 items)[11, 12]. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale[13]. The Oxford Hip Score (OHS) and the Oxford Knee Score (OKS) are 12-item questionnaires, with each item scored from 1 to 5, and the total ranging from 12 to 60 (lower scores representing fewer symptoms)[14, 15].

Statistical analyses

Descriptive analyses were performed for the preoperative and postoperative sociodemographic characteristics, working situation, joint function and health status. Mean changes in scores between preoperative and postoperative clinical variables (HOOS/KOOS, OHS/OKS) and the 95% confidence interval (CI) were calculated using a paired t-test. Mann-Whitney U or Chi-squared tests were used to compare the preoperative characteristics of patients undergoing THA or TKA and the change in HOOS/KOOS and OHS/OKS scores between patients who fully returned to work and those who returned partially or not at all at 12 months. The analyses were performed for THA and TKA separately and then combined.

To explore the relative importance of preoperative factors associated with return to work on univariate analyses ($p<0.15$) and those known from the literature, exploratory stepwise logistic regression analyses were carried out within the THA, TKA and combined groups. All factors associated with return to work were entered into ordinary logistic regression analysis for the combined group. This included interaction terms related to the type of surgery (hip or knee) to identify the possibility of effect modification, such as the impact of THA or TKA on return to work being dependent on a third variable. All data were analysed using SPSS Statistics version 20.0 (IBM, Armonk, NY, USA).

Results

Sixty-seven THA And 56 TKA patients, with a mean age of 56 years (standard deviation 6.6 and 5.7, respectively) were included in the analysis (Table 1.)

The preoperative mean number of working hours was 32±12.5 hours/week (median 32 hours/week, range 4-70) in THA patients and 31±12.3 hours/week (median 32 hours/week, range 10-70) in TKA patients. Patients who underwent THA had, compared with TKA patients, a significantly lower BMI (p=0.0001), and were significantly less likely to have light physically demanding work (p=0.008). THA patients were also less likely to have adaptations at work, although the difference was not significant (p=0.180). The only significant baseline difference in function was that patients who underwent THA had significantly lower Symptoms subscale scores on the HOOS/KOOS versus TKA patients (p=0.001).

There were significant differences between the pre- and postoperative HOOS/KOOS subscale, as well as OHS and OKS scores, with all improvements on the HOOS subscales and on the OHS being greater than the corresponding improvements of the KOOS subscales and the OKS. The only exceptions were for improvements on the HOOS and KOOS Quality of Life scores, which were not significantly different between pre- and postoperative measures.

Fifty-three (79%) THA patients and 40 (71%) TKA patients who were working preoperatively fully returned to work 1-year postoperatively. Nine (15%) patients in the THA group and 10 (18%) in the TKA group worked fewer hours than preoperatively, while five (7%) THA patients and six (11%) TKA patients did not return to work at all.

Among the 19 patients who partially returned to work, the mean decrease in working time was 17±11.5 hours/week (range 5-35) in the THA group, 14±13.0 hours/week (range 2-38) in the TKA group and 15±12.0 hours/week in the total group. Table 2 shows the factors associated with partial or full return to work 1 year after THA or TKA in patients of working age.

Table 1. Preoperative general and working characteristics of working patients < 65 years of age undergoing total joint arthroplasty

	THA patients (N=67)	TKA patients (N=56)	p value
Sex, female	33 (49)	31 (55)	0.587
Mean age, years (SD)			0.612
Age groups	56 (6.6)	56 (5.7)	
18-45	8 (12)	4 (7)	
46-55	16 (24)	15 (27)	
56-65	43 (64)	37 (66)	
Body Mass Index, mean (SD)	28 (6.0)	30 (4.4)	0.000*
Education level	(N=66)		0.781
Low	19 (29)	16 (29)	
Medium	26 (39)	25 (45)	
High	21 (32)	15 (27)	
Living status, Living independently	(N=64) 64 (100)	(N=55) 55 (100)	0.380
Employment status, self-employed	(N=59) 11 (18)	(N=54) 8 (15)	0.624
Hours working preoperatively, mean (SD)	32 (12.5)	31 (12.3)	0.460
Physical demands of work	(N=59)	(N=54)	0.008*
Light work	41 (70)	47 (87)	
Medium work	14 (24)	2 (4)	
Heavy work	4 (7)	5 (9)	
Preoperative sick leave from work due to hip/knee complaints	(N=59) 19 (32)	(N=50) 16 (32)	1.000
Preoperative work adaptations	(N=46) 11 (24)	(N=46) 16 (35)	0.180
Preoperative workers' compensation	(N=59) 5 (8)	(N=54) 6 (11)	0.437
Expectation over return to work	(N=48)	(N=46)	1.000
Back to normal	43 (90)	41 (89)	
Baseline HOOS or KOOS, mean (SD)			
ADL	(N=62) 42 (18)	(N=51) 44 (16)	0.421
Pain	(N=64) 38 (21)	(N=54) 36 (15)	0.596
Quality of life	(N=65) 34 (9)	(N=53) 31 (9)	0.135
Sport	(N=64) 15 (18)	(N=53) 8.8 (11)	0.079*
Symptoms	(N=65) 31 (19)	(N=54) 42 (15)	0.001*
Change in HOOS or KOOS, mean			
(95% CI)	(N=50) 49 (44-55)	(N=44) 35 (29-41)	0.001*
ADL	(N=53) 53 (47-58)	(N=47) 42 (35-48)	0.009*
Pain	(N=54) 20 (15-25)	(N=45) 14 (9-20)	0.052
Quality of life	(N=52) 52 (44-59)	(N=45) 32 (23-40)	0.000*
Sport	(N=55) 52 (45-58)	(N=47) 7 (2-11)	0.000*
Symptoms			
Oxford Knee/Hip Score baseline, mean (SD)	(N=60) 23 (7)	(N=54) 24 (15)	0.525
Oxford Knee/Hip change Score, mean (95% CI)	(N=53) 20 (18-22)	(N=48) 15 (12-17)	0.009*

*Comparison of THA and TKA patient by means of Chi Square or Mann-Whitney U tests where appropriate. Significance level: $p < 0.05$.
All values n (%) unless otherwise stated.
ADL = Activity limitations Daily Living; HOOS/KOOS = Hip disability and Osteoarthritis Outcome Score/Knee injury and Osteoarthritis Outcome Score; SD = standard deviation; THA = Total Hip Arthroplasty; TKA = Total Knee Arthroplasty

Table 2. Factors associated with return to work in working patients < 65 years of age undergoing total joint arthroplasty

	THA patients working preoperatively				**TKA patients working preoperatively**			
	Full return to work (N=53)	No or partial return to work (N=14)	p value**	Odds Ratio (95% CI)***	Full return to work (N=40)	No or partial return to work (N=16)	p value**	Odds Ratio (95% CI)***
Sex, female	28 (53)	5 (36)	0.369		24 (60)	7 (44)	0.374	
Mean age, years (SD)#	55.1 (6.5)	58.7 (6.6)	0.012*		55.3 (5.7)	57.0 (5.7)	0.317	
18-45	7 (13)	1 (7)			3 (8)	1 (6)		
46-55	15 (28)	1 (7)			13 (33)	2 (13)		
56-65	31 (59)	12 (86)			24 (60)	13 (81)		
Body Mass Index, mean (SD)	(N=52) 28.0 (6.2)	26.1 (4.8)	0.153		(N=39) 29.7 (4.3)	30.9 (4.7)	0.344	
Education level#	(N=52)		0.006*				1.000	
Low	10 (19)	9 (64)			11 (28)	5 (31)		
Medium	24 (46)	2 (14)			18 (45)	7 (44)		
High	18 (35)	3 (21)			11 (28)	4 (25)		
Self employed #	(N=46) 5 (11)	(N=13) 6 (46)	0.009*	7.63 (1.5-39.8)	(N=39) 5 (13)	(N=15) 3 (20)	0.390	2.69 (0.5-15.8)
Preoperative working hours, mean (SD)	30.8 (11.9)	36.1 (14.2)	0.230		29.8 (11.4)	34.4 (14.1)	0.207	
Type of work	(N=46)	(N=13)	0.672		(N=39)	(N=15)	0.270	
Light work	33 (72)	8 (62)			33 (85)	14 (93)		
Medium work	10 (22)	4 (31)			1 (3)	1 (7)		
Heavy work	3 (7)	1 (8)			5 (13)	0 (0)		
Preoperative absence from work due to hip or knee complaints#	(N=46) 10 (22)	(N=13) 9 (69)	0.002*	8.62 (1.9-39.0)	(N=36) 9 (25)	(N=14) 7 (50)	0.105	4.18 (1.0-17.1)
Preoperative adaptions at work#	(N=35) 6 (17)	(N=11) 5 (45)	0.100		(N=33) 13 (39)	(N=13) 3 (23)	0.493	
Preoperative workers' compensation	(N=46) 3 (7)	(N=13) 2 (15)	0.302		(N=39) 4 (10)	(N=15) 2 (13)	1.000	
Expectation over return to work, Back to normal	(N=40) 36 (90)	(N=8) 7 (88)	1.000		(N=36) 33 (92)	(N=10) 8 (80)	0.201	

Baseline HOOS or KOOS,								
mean (SD)	(N=49) 39 (16)	(N=13) 53 (18)	0.018*	1.03 (1.0-1.1)	(N=36) 46 (15)	(N=15) 40 (18)	0.331	0.99 (0.9-1.0)
ADL#	(N=51) 36 (19)	50 (24.2)	0.058		(N=38) 36 (14)	34 (17)	0.711	
Pain#	(N=52) 33 (9)	35 (11)	0.913		(N=37) 32 (10)	28 (6)	0.114	
Quality of life#	(N=51) 13 (16)	24 (22)	0.096		(N=37) 10 (11)	7 (11)	0.188	
Sport#	(N=52) 32 (18)	29 (25)	0.439		(N=37) 43 (15)	41 (14)	0.642	
Symptoms#								
Change in HOOS or KOOS, mean (95% CI)								
ADL	(N=39) 53 (47-58)	(N=11) 38 (27-50)	0.016*		(N=31) 37 (31-44)	(N=14) 29 (14-44)	0.166	
Pain	(N=42) 54 (48-60)	(N=11) 49 (35-63)	0.546		(N=33) 44 (38-51)	(N=15) 36 (21-50)	0.278	
Quality of life	(N=43) 19 (14-24)	(N=11) 20 (8-32)	0.786		(N=33) 16 (9-23)	(N=13) 10 (2-17)	0.299	
Sport	(N=42) 52 (43-60)	(N=10) 51 (35-67)	0.798		(N=32) 37 (27-47)	(N=14) 19 (6-32)	0.039*	
Symptoms	(N=44) 49 (42-56)	(N=11) 65 (48-82)	0.075		(N=33) 9 (4-14)	(N=15) 0.7 (-7-9)	0.072	
Oxford Knee/Hip Score, mean (SD)	(N=48) 23 (7)	(N=12) 25 (8)	0.244		(N=38) 24 (7)	24 (7)	0.962	
Oxford Knee/Hip change score, mean (95% CI)	(N=42) 20 (1-18)	(N=11) 18 (14-23)	0.356		(N=34) 16 (14-19)	(N=15) 12 (5-18)	0.086	

*Comparison of full return to work versus partial or no return to work patients by means of Chi Square or Mann-Whitney U tests, where appropriate.
** Univariate analysis
***Multivariable stepwise regression model
#Variable entered into model. Significance level $p<0.05$. All values n (%) unless otherwise stated.
ADL = Activity limitations Daily Living; HOOS/KOOS = Hip disability and Osteoarthritis Outcome Score/Knee injury and Osteoarthritis Outcome Score; SD = standard deviation; THA = Total Hip Arthroplasty; TKA = Total Knee Arthroplasty

Univariate analyses indicated that, for THA patients, age (p=0.012), level of educational level (p=0.006), self-employment (p=0.009), preoperative absence from work (p=0.002) and HOOS ADL baseline score (p=0.018) were significantly different between those who did not return to work or returned only partially and those who returned to work fully. A multivariable stepwise logistic regression model including age, educational level, preoperative work adaptations and baseline HOOS Pain, QoL and Sport subscale scores, showed that being self-employed (odds ratio [OR] 7.63, 95% CI 1.5-39.8), preoperative absence from work (OR 8.62, 95% CI 1.9-39.0) and a higher preoperative HOOS ADL score (OR 1.03, 95% CI 1.0-1.1) were statistically significantly associated with partial or no return to work.

In TKA patients, the only variable associated with a full return to work was change in KOOS Sport subscale score from baseline (p=0.039). In a multivariable exploratory logistic regression model that included the same preoperative variables as the THA model, only preoperative absence from work (OR 4.18, 95% CI 1.0-17.1) was associated with partial or no return to work.

Table 3 shows that, on univariate analysis, patients who did not or only partially returned to work were significantly more likely to be older (p=0.010), have a lower level of education (p=0.043), be self-employed (p=0.019) and have preoperative absence from work (p=0.001), In contrast, the type of surgery (hip or knee) and other factors were not significantly associated with return to work.

Exploratory multivariable stepwise logistic regression taking into account prosthesis, sex, age, educational level, self-employment, preoperative working hours, type of job, absence from work, work adaptations, receipt of workers' compensation and all baseline HOOS/KOOS subscale and OHS/OKS scores indicated that self-employment, preoperative absence from work and baseline HOOS/KOOS ADL subscale scores were associated with return to work.

Table 3. Comparison of characteristics of 123 patients undergoing Total Hip Arthroplasty (THA, n=67) or Total Knee Arthroplasty (TKA, n=56) who returned to work either completely or incompletely or not one year after surgery

	Full return to work N=93	Partial or no return to work N=30	p value*	Odds Ratio (95% CI)**
Type of prosthesis, THA#	53 (79)	14 (21)	0.400	
Sex, female#	52 (56)	12 (40)	0.146	
Mean age, years (SD) #	55 (6.1)	58 (6.1)	0.010*	
18-45	10 (11)	2 (7)		
46-55	28 (30)	3(10)		
56-65	55 (59)	25 (83)		
Body Mass Index, mean (SD)	(N=92) 29 (5.9)	29 (5.3)	0.929	
Education level#	(N=92)			
Low	21 (23)	14 (47)	0.043*	
Medium	42 (46)	9 (30)		
High	29 (32)	7 (23)		
Self employed#	(N=85) 10 (12)	(N=28) 9 (32)	0.019*	**6.68 (1.9-23.4)**
Preoperative hours worked, mean (SD) #	31 (11.6)	35 (13.9)	0.119	
Type of work#	(N=85)	(N=28)	0.627	
Light work	66 (78)	22 (79)		
Medium work	11 (13)	5 (18)		
Heavy work	8 (9)	1 (4)		
Preoperative absence from work due to hip or knee complaints#	(N=82) 19 (23)	(N=27) 16 (59)	0.001*	**7.22 (2.4-21.5)**
Preoperative work adaptations#	(N=68) 19 (28)	(N=24) 8 (33)	0.795	
Preoperative workers' compensation#	(N=85) 7 (8)	(N=28) 4 (14)	0.461	
Expectation over return to work	(N=76)	(N=18)	0.397	
Back to normal	69 (91)	15 (83)		
Baseline HOOS or KOOS, mean (SD) #				
ADL	(N=85) 42 (16.1)	(N=28) 46 (18.9)	0.272	**1.03 (1.0-1.1)**
Pain	(N=89) 36 (16.9)	(N=29) 41 (21.5)	0.308	
Quality of life	(N=89) 33 (9.5)	(N=29) 31 (9.1)	0.187	
Sport	(N=88) 11 (13.9)	(N=29) 15 (18.5)	0.875	
Symptoms	(N=90) 37 (17.5)	(N=29) 36 (20.3)	0.840	
Change in HOOS or KOOS, mean (95% CI)				
ADL	(N=69) 46 (18.4)	(N=25) 33 (22.3)	0.008*	
Pain	(N=74) 50 (19.8)	(N=26) 41 (25.0)	0.169	
Quality of life	(N=75) 18 (18.0)	(N=24) 14 (16.0)	0.475	
Sport	(N=73) 45 (28.8)	(N=24) 33 (27.2)	0.055*	
Symptoms	(N=76) 32 (27.9	(N=26) 28 (37.8)	0.341	
Oxford Knee/Hip Score, mean (SD)	(N=86) 24 (7.0)	(N=28) 24 (7.6)	0.341	
Oxford Knee/Hip change score, mean (95% CI)	(N=75) 18.7 (7.9)	(N=26) 14 (10.1)	0.063	

*Comparison of full return to work versus partial or no return to work patients using Chi Squared or Mann-Whitney U test, where appropriate. Stepwise logistic regression analysis used to correct for type of prosthesis, including all significant associations. Significance level < 0.05.
** Univariate analysis
*** Multivariable stepwise regression model
ADL = Activity limitations Daily Living; HOOS/KOOS = Hip disability and Osteoarthritis Outcome Score/Knee injury and Osteoarthritis Outcome Score; SD = standard deviation; THA = Total Hip Arthroplasty; TKA = Total Knee Arthroplasty

VII

Following logistic regression analysis, only the interaction between prosthesis and the baseline HOOS/KOOS ADL subscale scores was found to be associated with return to work (p=0.023). A higher preoperative HOOS ADL subscale score was associated with partial or no return to work in THA patients (p=0.018), whereas in TKA patients the reverse association was seen, although this did not reach statistical significance (p=0.331).

Discussion

This prospective study showed that there are differences in the determinants of no or partial return to work 1 year after primary THA and TKA surgery. In THA patients, self-employment, preoperative absence from work and a better preoperative HOOS ADL subscale score were associated with partial or no return to work versus only preoperative absence from work in TKA patients. We also found that type of surgery (hip or knee) modifies the impact of preoperative HOOS/KOOS ADL subscale scores on return to work.

Few studies on the determinants of return to work following THA or TKA are available for comparison. Moreover, comparisons are hampered by the use of different definitions of work outcomes (number of hours before and after intervention, return to work yes/no, etc). Our finding that older age, lower educational level and preoperative absenteeism from work were associated with partial or no return to work appear to be in accordance with previous studies [5,7]. In our analysis, self-employment was found to be associated with partial or no return to work whereas it was associated with a faster return to work in previous research [16]. It should be noted, however, that in that study the speed of return to work was the outcome, regardless the number of working hours. Our finding may be related to the observation that self-employed patients in all likelihood work more hours than wage earners and above the average for full-time workers (approximately 36-40 hours per week),[17] yielding a larger potential for productivity loss. The observation that self-employed persons reported working hours exceeding the national average warrants the need to develop valid instruments to measure productivity.

In contrast with previous studies, we did not find female gender, physical work and receiving workers' compensation[5,6,8] to be associated with worse work outcomes, which is most likely, again, due to differences in work outcome measurements.

Our study was unique in that we compared the determinants of partial or n return to work between THA and TKA, showing that preoperative absence from work was a factor in both groups. This can be identified easily in patients, allowing the provision of extra postoperative guidance to at-risk patients.

In the overall group, the preoperative HOOS/KOOS ADL score was found to be related to return to work. This was based on a better HOOS ADL score being significantly associated with partial or no return to work, whereas for the KOOS ADL score the reverse, yet non-significant, association was seen. Although not statistically significant, the direction of the association seen in TKA is in line with the literature[8]. We have, however, no plausible explanation for the relationship seen in patients who underwent THA, other than that the average improvement in patients partially or not returning to work was relatively small compared to those who fully return to work.

One of the main strengths of our study is that, in contrast with previous research, we included patients prospectively and provided multivariable analyses. Moreover, we included both patients with THA and TKA, and analyzed the results separately. We also looked at full return to work versus partial or no return to work. We showed that 13% of THA patients and 19% of TKA patients returned to work with a substantially reduction in working hours. It remains to be established the extent to which the reduction in working hours was related to THA or TKA, or can be explained by other factors. Limitations of our study are that data was gathered by telephone interviews in the case of incomplete data on working hours or postoperative work status. Consequently, part of the information was gathered retrospectively, making it prone to recall bias. Second, only THA and TKA patients from one hospital in The Netherlands were included, while a multicenter study would have been preferable. However, given the patients' baseline characteristics and their mean improvement in patient-reported outcomes, they appear to be a representative group of osteoarthritis patients undergoing THA or TKA [18-20]. Third, we included a relative small sample size, as the majority of arthroplasty patients are not of working age at the time of surgery. Comparisons between full and no or partial return to work were therefore hampered by a lack of power.

Conclusions

Our study showed that, although the majority of patients return to work after THA or TKA, a considerable proportion of those work fewer hours postoperatively. Furthermore, preoperative absence from work is an important and modifiable determinant of partial or no return to work in both THA and TKA. Self-employment plays a role in return to work following THA, whereas activities of daily living had the opposite effect in both THA and TKA. This latter finding implies that there are differences in the determinants of return to work following THA and TKA, warranting further research.

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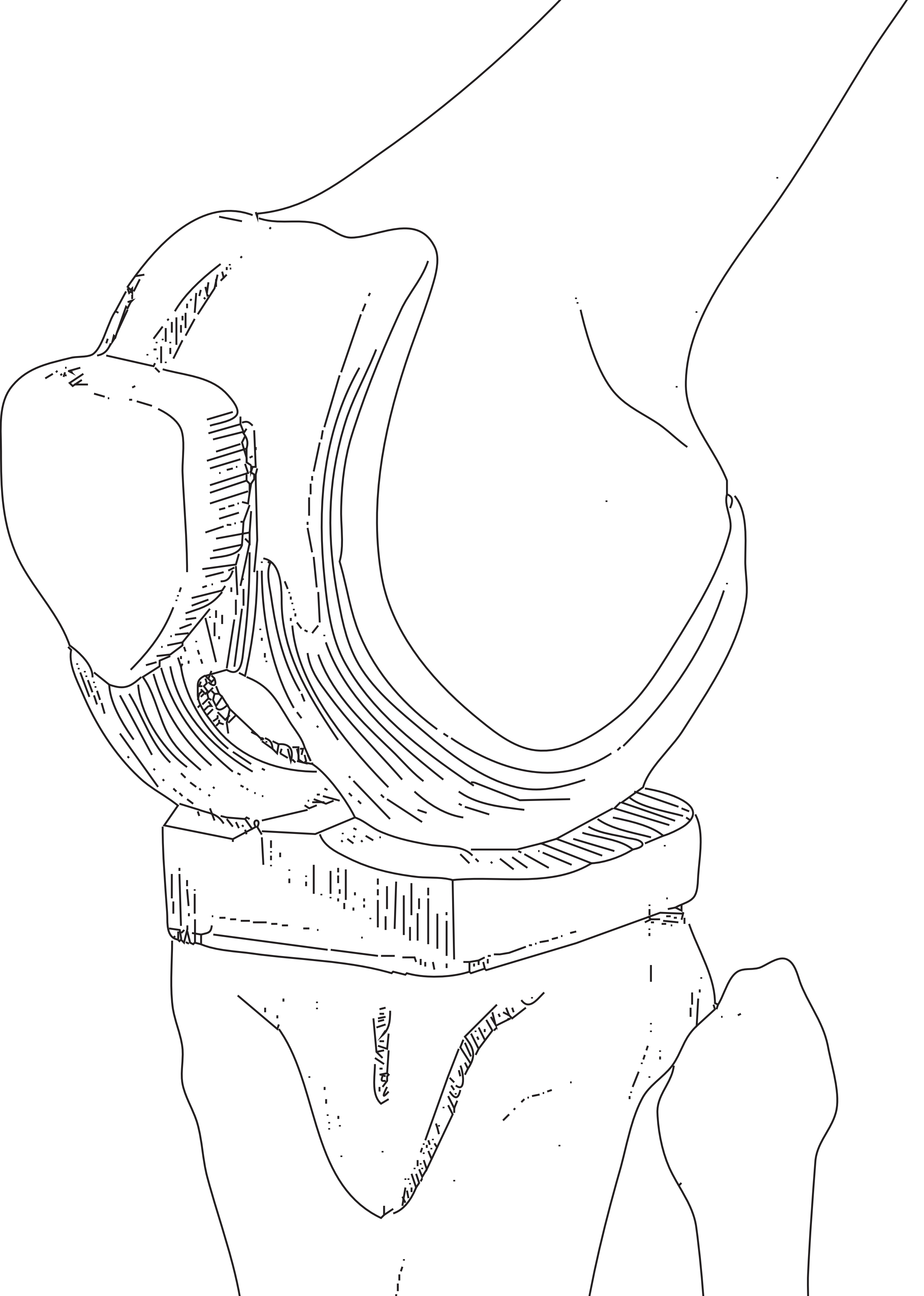

Chapter VIII

Not physical activity, but patient beliefs and expectations are associated with return to work after knee arthroplasty.

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Abstract

Background: After total knee arthroplasty (TKA), 17%-60% of the patients do not or only partially return to work (RTW). Reasons for no or partial RTW remain unclear, warranting further research. Physical activity (PA) has proven beneficial effects on work participation. Therefore, we hypothesized that preoperative PA is associated with RTW after TKA.

Methods: Working TKA patients participating in an ongoing prospective cohort study were included. Preoperatively and 1 year postoperatively, patients were asked to define their work status and PA level according to the Dutch Recommendation for Health-Enhancing PA and the Fitnorm. Multivariate logistic regression analysis was performed to assess the effect of PA on RTW, taking into account established prognostic factors for RTW among TKA patients.

Results: Of 283 eligible patients, 266 (93%) completed the questionnaires sufficiently. Preoperatively, 141 patients (54%) performed moderate PA for ≥5 d/wk and 42 (16%) performed intense PA for ≥3 d/wk. Concerning RTW, 178 patients (67%) reported full RTW, 59 patients (22%) partial RTW, and 29 patients (11%) no RTW. Preoperative PA was not associated with RTW. Patients who reported that their knee symptoms were not or only partially work-related had lower odds of no RTW (odds ratio 0.37, 95% confidence interval 0.17-0.81). Also, for each additional week patients expected to be absent from work, the likelihood of no RTW increased (odds ratio 1.11, 95% confidence interval 1.03-1.18).

Conclusion: No association between preoperative PA and RTW after TKA was found. Patient beliefs and preoperative expectations did influence RTW and should be addressed to further improve RTW after TKA.

Introduction

In the Netherlands, an expected 57,900 patients will undergo total knee arthroplasty (TKA) in 2030 [1]. The greatest increase in TKA is seen in patients who are of working age. Already, the number of TKA patients below 65 years of age tripled between 1995 and 2003 in the Netherlands, and this number is expected to rise further [1]. Similar trends of increasing numbers of TKA patients below 65 years of age have been identified in the United States and the United Kingdom [2,3]. For the United States, it is estimated that by 2030, up to 62% of TKAs will be performed in patients below 65 years of age [2], and for the United Kingdom, this estimation is 50% by 2035 [3].

This growing TKA population of working age is dependent on their job to generate income, and thus considers return to their own work as one of the most important outcomes of surgery [4]. Although many patients do successfully return to work (RTW), a reported 17%-60% of patients do not or only partially RTW after TKA [5-7]. To improve RTW rates, analysis of factors influencing RTW after TKA is essential. However, the remarkable conclusion of a systematic review by Kuijer et al in 2009 [8] was that there was an almost complete lack of literature on prognostic factors for RTW after TKA. A second systematic review in 2014 identified only 3 studies that reported on determinants of work status after TKA [9]. Factors associated with a faster RTW included female sex, age <50 years, self-employment, better mental and physical health scores, less comorbidity, and a handicap accessible workplace [7,9,10]. A slower RTW was found in patients with lower preoperative pain levels, with more physically demanding jobs and in those receiving workers' compensation [9,10]. More recently, these determinants were confirmed in several clinical studies [5,11-13], as well as a systematic review which identified 11 studies investigating 33 beneficial and limiting factors for RTW after TKA [14].

Although the abovementioned studies have identified several factors that influence RTW after TKA, these factors only partially explain why patients do not RTW after TKA, with a maximum explained variance of 50%, warranting further research [5]. None of the previous studies investigated the influence of preoperative physical activity (PA) on RTW. Evidence from a prospective cohort study, including 1228 workers, and a recent systematic review suggested that PA reduced sickness absence [15,16]. Workers with higher levels of PA were generally less likely to be absent from work because of sickness [15,17]. Also, Bernaards et al [18] found that strenuous leisure time PA might prevent long-term absenteeism in a working population. These findings seem to indicate that PA has a beneficial influence on work participation.

Based on the abovementioned findings, we formulated the hypothesis that preoperative PA is associated with RTW after knee arthroplasty. If, apart from current knee function and sociodemographic and work characteristics, preoperative PA is indeed an independent determinant of RTW, health care professionals could try to improve PA before and after surgery to further optimize RTW after TKA.

Methods

Study Design and Patient Selection

This study is based on TKA patients of working age participating in an on-going prospective longitudinal cohort study, the Longitudinal Leiden Orthopaedics Outcomes of Osteoarthritis Study (LOAS, Trial ID NTR3348), which aims to include all patients undergoing TKA at 6 regional hospitals and 1 university hospital in the Netherlands. Recruitment of patients in the LOAS has previously been described [19]. Patients were required to have a mental status allowing them to complete questionnaires, and had to understand the Dutch language. Patients with rheumatoid arthritis, a tumor, (hemi)paresis, or amputation of the leg, and patients undergoing a hemiarthroplasty or revision THA or TKA were excluded. All patients provided written informed consent. For the present study, a selection was made from this prospective cohort. Eligible patients were below 70 years of age and provided information on their work status and levels of PA preoperatively and 1 year postoperatively.

In case of incomplete or unclear provision of data on working hours or postoperative work status, the primary investigator (AH) performed a telephone interview between January and March 2017. Of the 1211 TKA patients who completed both questionnaires, 928 patients (76%) did not work preoperatively, and 283 patients (24%) were working preoperatively and provided information on their RTW postoperatively. These patients were included in the present analysis (Figure. 1). The study protocol was reviewed and approved by the local hospital review board (registration number P.12.047), associated with the regional Medical Research Ethics Committee.

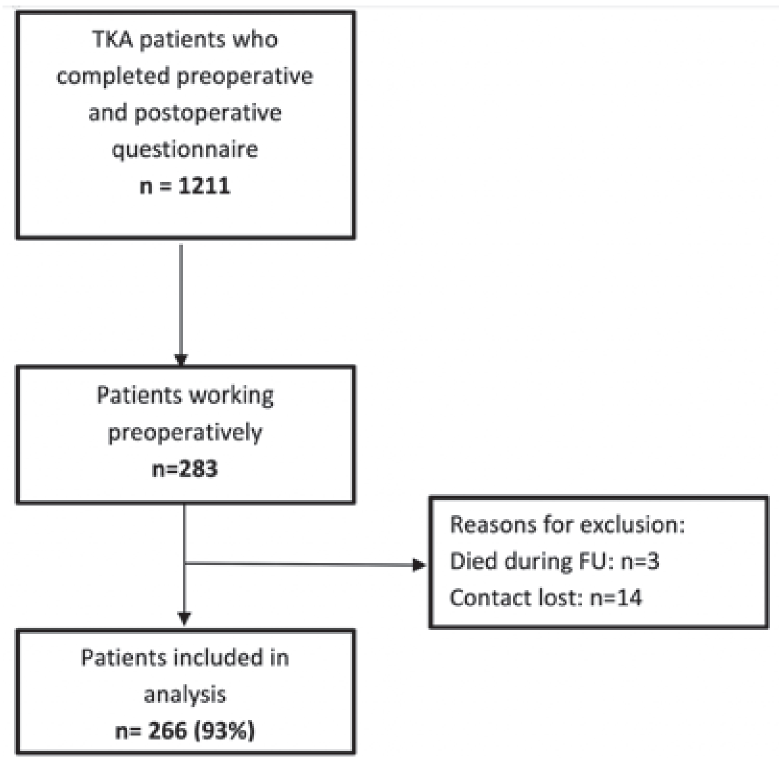

Figure 1 Flowchart for patient in- and exclusion. FU, follow-up; TKA, total knee arthroplasty.

Assessments

General Patient Characteristics

The following patient characteristics were collected: sex, age (years), and body mass index (BMI; kg/m2). The presence of musculoskeletal and/or non-musculoskeletal comorbidities was asked.

Work Status

Preoperatively, all patients were asked to indicate whether they had a paid job (yes/no). The following aspects of the patients' preoperative working situation were recorded: number of hours worked per week; self-employed or salaried; absenteeism from work because of knee complaints (yes/no); and the presence of work adaptions (yes/no), with yes including at least one of the following: change of tasks; performing fewer tasks; changes in working hours; other work-related adaptations or devices. Job title was recorded and classified as light, medium, or heavy, in terms of its physical demands on the knee, by 2 occupational experts who independently scored all jobs based on work-related physical demands. The scoring system was derived from the evidence-based exposure criteria for the work relatedness of hip and knee osteoarthritis developed by the Netherlands Center for Occupational Diseases [20].

Postoperatively, all patients were asked whether they were currently working (yes/no). If yes, they were asked to report their current number of working hours per week. Based on the difference in preoperative and postoperative working hours, RTW was classified as: full return (no difference in, or higher postoperative working hours); partial return (working fewer hours postoperatively); or no RTW (complete work disability pension, full-time sick leave, or out of work). The patients' preoperative expectations on RTW were examined using one item of the Hospital for Special Surgery Hip Replacement and Knee Replacement Expectations Surveys [21], formulated as: "the expectation regarding being able to have a paid job." The 5-point Likert scale was dichotomized into "back to normal" or "less than back to normal." Also, the expected number of postoperative working hours and expected timing of RTW (weeks) were asked.

Physical Activity

Preoperatively and at follow-up, all patients were asked to define their level of PA, using the Dutch Recommendation for Health-Enhancing PA (NNGB), which is based on recommendations by the American College of Sports Medicine [22]. For adults (aged 18-54 years), the recommendation is: at least half an hour of moderately intensive PA (4-6.5 metabolic equivalent of task, walking [5 km/h] or cycling [16 km/h] briskly), on at least 5 days a week. For persons over 55 years of age, the recommendation is: at least half an hour of moderately intensive PA (3-5 metabolic equivalent of task, walking [4 km/h], or cycling [10 km/h]) on at least 5 days a week. Patients were asked if they met the NNGB (yes/no). Also, patients were asked if they met the Fitnorm: at least 20 minutes of heavy intensive PA at least 3 times a week (yes/no) [22]. In addition, the self-reported number of hours patients participated in sport and leisure time activities were also taken into account.

Knee Function

To assess knee function, the Knee injury and Osteoarthritis Outcome Score (KOOS) was administered preoperatively and 1 year postoperatively. The KOOS includes subscales on symptoms, pain, activities of daily living, quality of life, and a subscale on sports activities (ie, squatting, running, jumping, twisting/pivoting, kneeling) [23].

Statistical Analysis

Patient demographics, preoperative and postoperative working status, overall health status, and joint function were analyzed with descriptive statistics for 3 separate groups: full RTW, partial RTW, and no RTW (Table 1). For each of the KOOS subscales, mean changes in scores between preoperative and 1 year postoperative were calculated, including the 95% confidence interval (CI). Because of the expected low number of patients not returning to work, RTW was divided into 2 categories: full RTW and partial/no RTW. First, associations between preoperative PA and postoperative work status were analyzed with univariate regression analyses. Also, the association between preoperative sick leave and KOOS scores, and their association with preoperative PA, were analyzed with univariate regression analysis. Next, logistic regression was performed to ascertain the effects of preoperative PA and other prognostic factors on the likelihood that patients did not fully RTW at 12 months. Three logistic regression models were created. Model 1 analyzed the effect of PA on RTW, including the NNGB, the Fitnorm, and the number of hours participated in sport and leisure time activities. Model 2 analyzed the effect of known prognostic factors for no RTW among TKA patients, based on literature and the univariate analysis. Model 3 analyzed the combined effect of PA and known risk factors on RTW. Age, sex, and BMI were included as covariates in all the 3 models. A P value <.05 was considered significant and 95% CIs were calculated. All statistical analyses were performed with SPSS for Windows (version 24.0; IBM Corp, Armonk, NY).

Results

Patients

Of 283 patients working preoperatively, 3 patients died during follow-up (not related to TKA) and 14 patients did not complete the questionnaire sufficiently and could not be reached by telephone. Thus, 266 patients with a mean age of 58.3 years (SD ± 6.0) could be included in the analysis (response rate 93%). Table 1 presents the baseline characteristics for all included patients.

Associations Between Preoperative PA and Baseline Characteristics

Preoperatively,141 patients (54%) met the NNGB and 42 patients (16%) met the Fitnorm (Table 1). Patients performed sport or leisure activities for a median of 3 hours per week (range 0-6). Patients' age and BMI were not associated with meeting the NNGB or the Fitnorm. Furthermore, none of the preoperative KOOS subscales were associated with meeting the NNGB or Fitnorm. Finally, complying to the NNGB preoperatively was not associated with preoperative sick leave. However, patients complying to the Fitnorm preoperatively were less likely to report preoperative sick leave (P = .02).

Table 1. Preoperative patient and work characteristics of working patients undergoing total knee arthroplasty (total group) and specified per RTW category (yes/partial/no)

	Total group (n = 266)	Full RTW (n = 178)	Partial RTW (n = 59)	No RTW (n = 29)
Sex, female (%)	149 (56%)	98 (55%)	30 (51%)	21 (72%)
Mean age, years (SD)	58.3 (6.0)	58.0 (6.1)	59.1 (5.5)	58.3 (6.6)
18 – 45 (n (%))	5 (2%)	3 (2%)	1 (2%)	1 (3%)
46 – 55 (n (%))	71 (27%)	48 (27%)	15 (25%)	8 (28%)
>55 (n (%))	190 (71%)	127 (71%)	43 (73%)	20 (69%)
BMI, kg/m^2 (SD)	29.6 (4.2)	29.5 (4.1)	29.1 (4.4)	30.9 (4.5)
Musculoskeletal comorbidities, yes	86 (48%)	62 (47%)	17 (50%)	7 (47%)
Nonmusculoskeletal comorbidities, yes	161 (61%)	104 (65%)	35 (70%)	22 (79%)
Physical workload				
Light work	140 (54%)	97 (56%)	31 (52%)	12 (43%)
Medium work	71 (27%)	45 (26%)	14 (24%)	12 (43%)
Heavy work	48 (19%)	30 (17%)	14 (24%)	4 (14%)
Working hours (median (IQR))	30 (20 – 40)	30 (20 – 40)	36 (21 – 40)	24 (19 – 35)
Sick leave, yes	74 (28%)	38 (22%)	24 (41%)	12 (44%)
Work adaptations, yes	83 (33%)	54 (32%)	21 (40%)	8 (30%)
Work status, %				
Employed	228 (87%)	152 (87%)	50 (85%)	26 (90%)
Self-employed	34 (13%)	22 (13%)	9 (15%)	3 (10%)
Self-reported work-relatedness of symptoms				
Not related	11 (5%)	9 (5%)	1 (2%)	1 (4%)
Partially related	108 (45%)	86 (52%)	17 (34%)	5 (23%)
Strongly related	119 (50%)	71 (43%)	32 (64%)	16 (73%)
Expected working hours postoperatively, hours (median (IQR))	30 (20 – 40)	30 (20 – 40)	32 (20 – 40)	25 (18 – 40)
Expected timing of RTW, weeks (median (IQR))	8 (6 – 12)	8 (5 – 10)	12 (7 – 15)	10 (8 – 12)
Expectations concerning working ability, back to pre-symptomatic state	172 (69%)	117 (70%)	41 (72%)	14 (52%)
Meeting preoperative NNGB, yes (%)	141 (54%)	91 (53%)	32 (55%)	18 (62%)
Meeting preoperative Fitnorm, yes (%)	42 (16%)	28 (16%)	10 (17%)	4 (14%)
Leisure/sport activities, hours/wk (median (IQR))	3 (0 – 6)	4 (2 – 6)	2 (0 – 5)	4 (0 – 9)
Expectations concerning sports ability, back to pre-symptomatic state	89 (35%)	57 (33%)	23 (40%)	9 (32%)
KOOS scores, mean (SD)				
Symptoms	42 (13)	43 (13)	41 (12)	35 (13)
Pain	35 (17)	35 (18)	36 (17)	28 (15)
ADL	42 (18)	43 (18)	43 (16)	35 (15)
Sport	9 (12)	10 (13)	7 (10)	3 (8)
Quality of life	34 (10)	34 (9)	34 (11)	32 (10)

All values are n (%) unless stated otherwise. Numbers of patients and percentages may vary slightly because of missing data points.
ADL, activities of daily living; BMI, body mass index; IQR, interquartile range; KOOS, Knee Injury and Osteoarthritis Outcome Score; NNGB, Dutch Recommendation for Health-Enhancing Physical Activity; RTW, return to work; SD, standard deviation.

<u>Return to Work</u>

One year after TKA, of 266 patients, 178 patients (67%) had fully returned to work, 59 patients (22%) had partially returned to work, and 29 patients (11%) had not returned to work. Patients returned to work (fully or partially) at a median of 3 months (interquartile range [IQR] 2-5). Patients who were self-employed (n = 34) returned to work significantly faster (2 months, IQR 1-3) than employed patients (3 months, IQR 2-5, P < .001). For the patients who partially returned to work (n = 59), the median decrease in working hours was 8 h/wk (range 1-50). Table 2 presents the results of univariate analysis of variables associated with RTW. Preoperative sick leave was a significant predictor of no RTW (odds ratio [OR] 2.63, 95% CI 1.51-4.61). Also, patients who believed that their knee symptoms were not related to their work were more likely to RTW (OR 0.38, 95% CI 0.21-0.69). Patients who did RTW expected to be absent from work significantly shorter than the patients who did not RTW (median 8 vs 12 weeks, OR 1.12, 95% CI 1.06-1.18). Finally, a trend was present for the number of hours that patients participated in sports and leisure time activities (P = .067).

Table 2. Univariate analysis of factors associated with RTW (full vs. partial/no RTW) after total knee arthroplasty, including odds ratios with 95% CI

	TKA patients working preoperatively (n=266)			
	Full RTW (n=178)	**Partial or no RTW (n=88)**	**P-value***	**OR (95% CI)****
Sex, female (%)	98 (55%)	51 (58%)	0.65	1.13 (0.67 – 1.89)
Mean age, years (SD)	58.0 (6.1)	58.8 (5.9)	0.31	1.02 (0.98 – 1.07)
18-45, n (%)	3 (2%)	2 (2%)		
46-55, n (%)	48 (27%)	23 (26%)		
>55, n (%)	127 (71%)	63 (72%)		
BMI, categories, n (%)			0.99	
18.5 – 25 (normal)	20 (11%)	10 (11%)		1
25.1 – 30 (overweight)	84 (47%)	41 (47%)		0.98 (0.42 – 2.28)
>30 (obese)	74 (42%)	37 (42%)		1.00 (0.43 – 2.35)
Musculoskeletal comorbidities, yes (%)	62 (47%)	24 (49%)	0.81	1.08 (0.56 – 2.09)
Non-musculoskeletal comorbidities, yes (%)	104 (65%)	57 (73%)	0.19	1.49 (0.82 – 2.70)
Physical workload			0.57	
Light work	97 (56%)	43 (49%)		1
Medium work	45 (26%)	26 (30%)		1.30 (0.71 – 2.38)
Heavy work	30 (17%)	18 (21%)		1.35 (0.68 – 2.69)

Table 2. continued

	TKA patients working preoperatively (n=266)			
	Full RTW (n=178)	**Partial or no RTW (n=88)**	**P-value***	**OR (95% CI)****
Preoperative sick leave, yes	38 (22%)	36 (42%)	**<0.005**	**2.63 (1.51 – 4.61)**
Preoperative work adaptations, yes	54 (32%)	29 (36%)	0.50	1.21 (0.69 – 2.12)
Work status, %			0.82	1.09 (0.51 – 2.32)
Employed	152 (87%)	76 (85%)		
Self-employed	22 (13%)	12 (14%)		
Self-reported work-relatedness of symptoms			**<0.01**	
Not related	9 (5%)	2 (3%)		**0.38 (0.21 – 0.69)**
Partially related	86 (52%)	22 (30%)		0.33 (0.07 – 1.59)
Strongly related	71 (43%)	48 (67%)		1
Expected working hours postoperatively, hours (median (IQR))	30 (20 – 40)	32 (20 – 40)	0.89	1.00 (0.98 – 1.02)
Expected timing of RTW, weeks (median (IQR))	8 (5 – 10)	12 (8 – 15)	**<0.001**	**1.12 (1.06 – 1.18)**
Expectations concerning working ability, back to pre-symptomatic state	117 (70%)	55 (66%)	0.46	1.23 (0.71 – 2.16)
Meeting preoperative NNGB, yes (%)	91 (53%)	50 (58%)	0.46	0.82 (0.49 – 1.38)
Meeting preoperative Fitnorm, yes (%)	28 (16%)	14 (16%)	0.99	1.01 (0.50 – 2.03)
Preoperative sport/leisure participation, hours (median (IQR))	4 (2 – 6)	2 (0 – 6)	0.89	1.00 (0.94 – 1.05)
Expectations concerning sports ability, back to pre-symptomatic state	57 (33%)	32 (38%)	0.48	0.82 (0.48 – 1.41)
KOOS change scores, mean (95% CI)				
Symptoms	11 (8 – 14)	15 (11 – 18)	0.22	-
Pain	48 (44 – 52)	50 (45 – 55)	0.78	-
ADL	40 (36 – 43)	41 (37 – 46)	0.69	-
Sport	37 (33 – 42)	37 (30 – 44)	0.59	-
Quality of life	18 (15 – 21)	17 (13 – 21)	0.61	-

Numbers of patients and percentages may vary slightly because of missing data points. The significance of the bold values is mentioned in the table (<0.005; <0.01; <0.001).
ADL, activities of daily living; BMI, body mass index; CL, confidence interval; IQR, interquartile range; KOOS, Knee Injury and Osteoarthritis Outcome Score; NNGB, Dutch Recommendation for Health-Enhancing Physical Activity; OR, odds ratio; RTW, return to work; SD, standard deviation; TKA, total knee arthroplasty.
* Univariate analysis, significance was assumed at p <0.05 (bold).
** Odds ratios (with 95% confidence intervals) for partial or no RTW are presented. In cases of more than 2 options, the reference category is presented as 1.

Table 3 presents the results of the 3 multivariate logistic regression models analyzing the effect of PA, known risk factors for no RTW, and a combination of these 2, respectively, on the likelihood of no RTW. Model 1 was statistically significant ($P < .01$), explained 1% (Nagelkerke R2) of the variance in RTW and correctly classified 71% of cases. Lower levels of preoperative PA did not result in higher odds for no RTW (Table 3). Model 2 was statistically significant ($P < .01$), explained 16% (Nagelkerke R2) of the variance in RTW and correctly classified 71% of cases. Odds for no RTW were significantly lower for patients who reported partial work relatedness of their knee symptoms (OR 0.35 95% CI 0.16-0.75). Also, for each additional week patients expected to be absent from work, the likelihood of no RTW increased (OR 1.10, 95% CI 1.03-1.17; Table 3). Model 3 was statistically significant ($P < .01$), explained 17% (Nagelkerke R2) of the variance in RTW and correctly classified 71% of cases. Model 3 confirmed that preoperative PA had no effect on RTW (Table 3). Odds for no full RTW were significantly lower for patients who reported partial work-relatedness of their knee symptoms (OR 0.37 95% CI 0.17-0.81). Also, for each additional week patients expected to be absent from work, the likelihood of no RTW increased (OR 1.11, 95% CI 1.03-1.18).

Table 3. The effect of PA (model 1), known prognostic factors (model 2) and the combination of PA and known prognostic factors (model 3), on the odds for no full RTW in total knee arthroplasty patients

Model #	Predictors for no RTW	Reference	OR	95% CI
Model 1	Age (years)	-	1.01	0.96 – 1.07
	BMI (kg/m^2)	-	1.00	0.93 – 1.09
	Sex, female	Male	1.25	0.64 – 2.45
	Meeting preoperative NNGB, no	Yes	0.78	0.40 – 1.50
	Meeting preoperative Fitnorm, no	Yes	1.23	0.50 – 3.02
	Preoperative sport/leisure participation	-	1.00	0.94 – 1.06
Model 2	Age (years)	-	0.64	0.26 – 1.53
	BMI (kg/m^2)	-	1.04	0.97 – 1.11
	Sex, female	Male	1.32	0.64 – 2.73
	Preoperative sick leave, yes	No	1.22	0.51 – 2.90
	Self-reported work-relatedness of knee symptoms	Highly related	1	
		Partially related	**0.35**	**0.16 – 0.75**
		Not related	0.48	0.09 – 2.72*
	Physical workload	Light	1	
		Medium	0.75	0.33 – 1.69
		High	0.51	0.17 – 1.53
	Expected timing of RTW (weeks)	-	**1.10**	**1.03 – 1.17**

Table 3. continued

Model #	Predictors for no RTW	Reference	OR	95% CI
Model 3	Age (years)	-	1.04	0.97 – 1.11
	BMI (kg/m^2)	-	0.97	0.89 – 1.06
	Sex, female	Male	1.37	0.65 – 2.87
	Meeting preoperative NNGB, no	Yes	0.80	0.39 – 1.66
	Meeting preoperative Fitnorm, no	Yes	0.69	0.28 – 1.70
	Preoperative sick leave, yes	No	1.18	0.49 – 2.83
	Self-reported work-relatedness of knee symptoms	Highly related	1	
		Partially related	**0.37**	**0.17 – 0.81**
		Not related	0.62	0.11 – 3.58*
	Physical workload	Light	1	
		Medium	0.74	0.32 – 1.71
		High	0.47	0.15 – 1.43
	Expected timing of RTW (weeks)	-	**1.11**	**1.03 – 1.18**

Odds ratios with 95% CIs for partial or no RTW are presented. Values in bold are significant ($p < 0.05$).
- = No reference category for continuous variables in the model.
BMI, body mass index; CI, confidence interval; NNGB, Dutch Recommendation for Health-Enhancing Physical Activity; OR, odds ratio, PA, physical activity; RTW, return to work.
* Not enough power to detect a significant difference because of small sample size (n=11)

VIII

Discussion

The aim of the present prospective cohort study was to investigate if preoperative PA is associated with RTW after TKA. Our most important finding is that preoperative PA was not associated with full RTW in our TKA population within 1 year postoperatively. Two other modifiable factors, namely self-reported work-relatedness of knee symptoms and the expected timing of RTW, were associated with RTW. Thus, our hypothesis that preoperative PA levels would be associated with RTW after TKA could not be confirmed.

No previous studies have investigated the association between preoperative PA and RTW among TKA patients, complicating the comparison between our results and existing literature. Yet, several studies have investigated the effect of PA on comparable outcomes, such as sickness absence and employment status. In a representative sample of the Dutch working population, vigorous PA for at least 3 times a week had a positive effect on sick leave [24]. More recently, a systematic review on the impact of PA on sickness absence found several studies that suggest that PA interventions reduce sickness absence [16]. In addition, insufficient PA was associated with sick leave in a Dutch working population (OR 1.12, 95% CI 1.03-1.21) [25]. Finally, in a systematic review and meta-analysis, workers with lack of PA were found to be at an increased risk of disability pension and unemployment [26]. Yet, in our TKA population, meeting the NNGB preoperatively was not associated with preoperative sick leave nor full RTW. In contrast, meeting the Fitnorm was associated with less preoperative sick leave, but not with full RTW. It is possible that patients on sick leave are still able to meet the NNGB because of the relatively low PA requirements, but cannot participate in strenuous PA and therefore do not meet the Fitnorm. In addition, our study is the first to prospectively investigate the association between PA and work participation in TKA patients after surgery. This hampers the comparison with the abovementioned reviews, which included mostly observational studies and did not investigate the effect of a clinical intervention such as TKA. Finally, the NNGB and Fitnorm were self-reported by our patients. It is likely that this resulted in an overestimation of the actual PA, particularly in patients who are not physically active [27]. Thus, it is possible that we could not detect an association between PA and RTW because patients who did not or only partially RTW overestimated their PA. Another explanation might be that we combined patients who partially returned to work and patients who did not RTW, whereas the other studies only investigated complete absence from work (because of sick leave or unemployment). It is possible that PA differs between partial and no RTW, but our sample size was insufficient to study these groups separately.

Concerning other factors that predict RTW after TKA, prospective studies including multivariate analysis to identify TKA-specific prognostic factors associated with RTW are limited [5,7,10,12,13]. The present study includes the largest prospective cohort investigating RTW after TKA. Univariate analysis did show that preoperative sick leave was a strong predictor of no RTW, which is in line with previous studies [5,11,13]. Interestingly, sick leave was no significant predictor in the multivariate models. A possible explanation is that significant prognostic factors such as work-relatedness of knee symptoms and expected timing of RTW are also associated with sick leave. Self-reported work-relatedness of knee symptoms was associated with no full RTW in our population, indicating that patients who reported that their knee complaints were caused by their work are less likely to RTW. This is in line with the study by Kuijer et al [5], who found an OR for no RTW of 5.3(90% CI 2.0-14.1).

In addition, we found that patients who did not or partially RTW already expected to be absent from work longer than patients who did RTW (12 vs 8 weeks, P < .001). The regression model showed an OR of 1.11 (95% CI 1.03-1.18) for no full RTW for each additional week patients expected to be absent from work. This is in line with data from a recent systematic review, which identified “a sense of urgency about RTW” as an acceleration factor for RTW [14]. These findings confirm that patient beliefs about the work-related cause of their knee complaints and preoperative expectations regarding timely RTW play an important role in the process of fully returning to work after TKA [10]. Timely referral to an occupational physician for an independent evaluation of the work-relatedness of knee symptoms and for timely work-directed care may improve RTW of these patients [5].

The association between physical workload and RTW remains disputable. Physical workload was not associated with RTW in our study. Other studies have reported conflicting findings, with some authors finding an association between medium or heavy physical workload and faster RTW [7,12,28], and others reporting high physical workload as a limiting factor for RTW [5,11]. As stated by Pahlplatz et al [14], part of the explanation for this discrepancy lies in the definitions of physical workload that were used. In the studies by Leichtenberg et al, Kuijer et al [20], and the present study, the same methodology was used to classify physical workload. Leichtenberg et al found no association, but their study sample was very small (n = 56) [13]. Kuijer et al (n = 167) found that patients with a medium physical workload were at risk for no RTW compared with patients with a light physical workload (OR 3.3, 90%CI 1.2-8.9) [5]. However, in the present study (n = 263), we could not confirm this association. Workload appears to influence RTW after TKA, but having a high physically demanding job does not necessarily result in lower RTW. Thus, patients with high physical job demands should not be discouraged to RTW after TKA.

The present study describes RTW in the largest prospective cohort of working TKA patients. However, a limitation of the present study, as well as of previous studies on TKA-specific factors associated with RTW, is the low absolute number of patients not returning to work after TKA. In previous studies with cohorts of 56-261 patients, no RTW percentages ranged from 11%-60% [5,7,10,12,13] and partial RTW percentages ranged from 7%-19% [5,13]. In the present study with 266 patients, no RTW was 11% and partial RTW was 22%. A small sample size may limit the statistical power of a multivariate model. To address this, we combined the group of patients who reported a partial RTW with the group who reported no RTW (cf. Leichtenberg et al) [13]. However, for future studies, it would be preferable to include more patients to analyze the groups of full RTW, partial RTW, and no RTW separately. Another limitation is the fact that our questionnaire did not enable us to investigate the exact reasons for no RTW. It is possible that some patients deliberately did not RTW, for example, because they decided to retire after surgery. Yet, patients' intention to RTW was reflected by the expected number of postoperative working hours. The median expected number of 30 hours with an IQR of 20-40 hours showed that 75% of patients expected to work for at least 20 hours postoperatively. In a comparable study, Kuijer et al did report reasons for no RTW and found that of 46 patients not returning, 17% did not RTW because of their TKA, 15% because of other physical complaints, and 57% reported that they had "retired" (not further specified) [5]. To further clarify exact reasons for no RTW after TKA, future studies should explicitly ask patients for their reasons for no RTW. Also, future studies should aim to collect more reliable measures of PA to avoid bias because of an overestimation in self-reported PA. Finally, in cases of incomplete RTW data, telephone interviews were performed, collecting data retrospectively. Thus, a small part of our data may be prone to recall bias.

Finally, even though our hypothesis could not be proven, TKA patients should not be discouraged to be physically active before surgery. Evidence that PA is effective in primary and secondary prevention of chronic diseases (eg, cardiovascular disease, diabetes, obesity, osteoporosis) and premature death is irrefutable [29]. Also, exercise therapy is one of the proven effective conservative treatment modalities for knee osteoarthritis [30]. Thus, patients of working age might be able to postpone their TKA while improving their work ability. Still, in TKA patients, other modifiable factors appear to be stronger predictors of RTW, such as patient beliefs and expectations.

Conclusion

The present study is the first to investigate the effect of preoperative PA on full RTW after TKA. Our results did not show an association between PA and full RTW, whereas self-reported work-relatedness of knee symptoms and the expected timing of RTW were associated with no full RTW. Nevertheless, PA should never be discouraged in patients with knee osteoarthritis, given the many positive effects of PA on general health.

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Chapter IX

Summary

Aims of this thesis

Osteoarthritis (OA) is among one of the most common causes of disability in older adults worldwide, with the most prevalent forms being knee, hip, hand and cervical spine OA (1, 2). Total hip and knee arthroplasties (THA and TKA) are, according to clinical outcomes (pain relief and functional improvement) and survival analyses of implants, very effective interventions for patients with hip or knee OA (3-6). Apart from the technical result, the patient's perception of outcome is extremely relevant (7-13). Since the last decades, a holistic approach and the perspective of the patient has become more and more important in health care in general, in particular in outcomes research. The International Classification of Functioning, Disability and Health (ICF) is a comprehensive framework to describe health status, as well as external and personal factors that may have an impact on a person's health (14). In accordance with the ICF, disease specific core sets, including the aspects of health most relevant for patients with a specific condition and their physicians were developed, including an ICF core set for OA (15). The current thesis focuses on a subset of aspects described in the ICF core set for OA that are currently insufficiently researched.

In THA and TKA patients, knowledge of certain components of the ICF domains, specifically knee instability, physical activity and return to work and their association with pain and function prior to and after THA and TKA is limited. Therefore, the aims of this thesis were:

1. To investigate associations between radiographic OA severity, knee instability, pain and function prior to and after THA and/or TKA
2. To evaluate factors influencing physical activities in patients with end-stage hip or knee OA.
3. To identify determinants of return to work after THA or TKA.

The studies described in Chapters 2-6 and 8 were based on the multicentre Longitudinal Leiden Orthopeadics Outcomes of Osteo-Arthritis study (LOAS), a multi-center, longitudinal prospective cohort study. The analyses in this thesis were done with the data from patients enrolled before June 2015. The study described in Chapter 7 was based on data from a one-year observational cohort study including consecutive patients undergoing primary THA or TKA for osteoarthritis in the Alrijne Hospital, Leiderdorp, the Netherlands, between October 2010 and September 2012.

Part 1. Preoperative (and early postoperative) pain and function, radiographic OA severity and knee instability and their association with postoperative pain and function outcome.

<u>Effect modification of radiographic OA severity on the effect of preoperative pain on postoperative pain and function</u>

The study described in Chapter 2 investigated whether preoperative radiographic OA severity modified the effect of preoperative self-reported pain on postoperative pain and function 1 and 2 years after TKA. Data were derived from the multicentre observational LOAS study. OA severity was assessed radiographically with the Kellgren and Lawrence (KL) score. Pain and function were evaluated with subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS). After adjustment for Body Mass Index (BMI), age, sex, and the Mental Health Component scores from the Short Form-12, multivariate linear regression analyses with an interaction term between the preoperative KL score and preoperative pain were performed.

This analysis included 559 TKA patients. The results showed that a worse preoperative radiological OA severity score was associated with higher one- and two-year postoperative pain and worse one- and two-year postoperative function, while more preoperative pain only associated with more postoperative pain, not with a worse postoperative function. Moreover, a trend was found toward the preoperative OA severity score modifying the effect of preoperative pain on one-year postoperative pain (β −0.1; 95% Confidence Interval (CI) −0.1-0.0) and two-year postoperative pain (β −0.1; 95% CI −0.2-0.0), with the effect of preoperative pain on postoperative pain seeming to become less important when the preoperative OA severity score worsened. Similar results were found for the effect modification of preoperative OA severity on the association between preoperative pain and one- and two-year postoperative function (β −0.1; 95% CI −0.2-0.0 for both). In conclusion, patients with less pain and worse OA severity preoperatively had better pain and function outcomes one and two years after TKA. However, the effect of preoperative pain on the postoperative outcomes seems to become less important when there was more severe radiographic evidence of OA. These results suggest that it is recommended to consider this effect modification of radiographic OA severity and preoperative pain on postoperative outcomes when new prognostic models for outcomes after TKA are developed.

Recovery trajectories after THA and TKA and early postoperative identification of patients at risk for unfavourable one-year outcome

The study presented in Chapter 3 evaluated the initial clinical recovery after primary THA or TKA up and until one year. In order to do so, four clinically relevant recovery trajectories of pain and function were used. Moreover, it was investigated if one-year pain/function could be predicted by the initial clinical recovery of pain/function and their preoperative values. Self-reported pain and function were assessed preoperatively, six and 12 months after surgery with the Pain and Activity Daily Living (ADL) subscales of the Hip Injury and Osteoarthritis Outcome Score (HOOS) and KOOS. Cut-off for unfavourable pain and function were based on the 20th percentile of its one-year outcomes. The six months assessments were taken to evaluate the initial clinical recovery. Prediction of one-year outcome by the initial clinical recovery of pain/function and their preoperative values was assessed with multivariate logistic regression analyses and Receiver Operating Curves.

This analyses included 972 THA and 892 TKP patients. Most patients, 70% of both THA and TKA patients, had a favourable outcome at 6 months and one-year. Ten percent THA and 12% TKA patients had an initial unfavourable outcome at 6 months, whereas 14% of THA/TKA patients had initial and one-year unfavourable pain outcomes. Similar results were found for function. Hence, of the patients with initial unfavourable outcome, 33-46% attained favourable one-year outcome. For both THA and TKA, more initial clinical recovery and worse preoperative pain/function predicted unfavourable one-year outcomes (all ORs 0.96-0.97), whereas a prediction model including both variables attained the best prediction (AUCs of full models were approximately 0.89). Thus, patients with more preoperative pain/worse preoperative function and little initial clinical improvement had an increased risk of more pain or worse function one-year after surgery. In conclusion, of the patients with initial unfavourable outcome, approximately one-third attained favourable outcome at one-year. Patients at risk for one-year unfavourable outcome could be identified six months postoperatively by initial clinical recovery and preoperative values. These results may help orthopaedic surgeons to identify which patients should be invited at the outpatient clinic for an altered rehabilitation strategy, potentially reducing the risk on poor outcome.

Knee instability and its associations with radiographic features, pain, function and QoL

Chapter 4 described the prevalence of self-reported knee instability in patients with pre-surgery knee OA and explored associations between self-reported knee instability and radiological features. Radiological features consisted of joint space narrowing (JSN) and osteophyte formation on a 0-3 scale. Scores >1 were defined as substantial JSN or osteophyte formation. Logistic regression analyses were provided to identify associations of radiological features with self-reported knee instability.

This analysis included 265 patients with knee OA. Knee instability was reported by the majority (72%) of patients. Self-reported knee instability was not associated with JSN or osteophyte formation (relative to score 0, odds ratios of score 1-3 ranged 0.68-0.98 and 0.69-0.89, respectively). A stratified analysis for pain, age and BMI showed no associations between self-reported knee joint instability and radiological OA features. From these results it was concluded that self-reported knee instability was not associated with JSN or osteophyte formation.

In Chapter 5 the course and prevalence of self-reported knee instability before and one year after TKA was evaluated. Furthermore, the associations of preoperative, postoperative, and retained self-reported knee instability with pain, activity limitations, and QoL in patients with knee OA were explored. Pain, activity limitations, and QoL were evaluated

with the KOOS subscales. Multivariable linear regression analyses were performed adjusted for covariates (age, gender, comorbidities, and radiographic severity).
In this study data of 908 patients with an indication for TKA were included. Following TKA, knee instability was reported by 21% of all included patients and 25% of the 649 patients who reported preoperative knee instability. In line with previous studies, associations were found between preoperative knee instability and preoperative pain, activity limitations, and QoL. Moreover, our results showed that associations were even stronger between postoperative and retained knee instability with postoperative pain, activity limitations, and QoL. In conclusion, in clinical care, self-reported knee instability is retained postoperatively in about 25% of TKA patients. Retained knee instability is associated with more postoperative pain, activity limitations, and poorer QoL. As such, perceived retained knee instability could be an easily identifiable alarm symptom for poor clinical outcome after TKA, which could be used by orthopaedic surgeons.

Part 2. Factors influencing physical activity in patients with end-stage hip or knee OA

In Chapter 6 it was investigated if OA-associated pain, functional limitations and QoL were associated with objective measurements of physical activity in patients with end-stage hip/knee OA. Included patients wore an accelerometer (Activ8) for 5-7 days with physical activity expressed as number of activity daily counts (ADC) per hour, percentage time spent on physical activity and percentage time spent sedentary. The HOOS/KOOS and Short Form (SF)-12 were used to assess pain, functional limitations and joint-specific and general QoL. Multivariate linear regression models with the three to Z-scores transformed parameters of physical activity as dependent variables and adjusted for confounding, were used for analysis.

This analysis included 49 hip OA and 48 knee OA patients. The results showed that in hip OA patients, better joint-specific and general QoL were associated with more ADC, (β 0.028 (95% CI 0.007–0.048), β 0.041 (95% CI 0.010–0.071), respectively). Also, better general QoL was associated with a higher percentage time spent on physical activity (β 0.040 (95%CI 0.007–0.073)). No other associations were found for either hip or knee OA patients. To conclude, whereas QoL was associated with objective measurements of physical activity in hip OA, pain and functional limitations were not related to objective measurements of physical activity in patients with end-stage hip or knee OA. Our conclusions are important to address in the preoperative consultation when outcome expectations are discussed.

Part 3. Determinants for return to work after THA or TKA

The studies in Chapters 7 and 8 aimed to identify determinants of return to work after THA or TKA. In Chapter 7 determinants of return to work were compared after THA and TKA. Patients with a paid job and aged <65 years were included. The outcome measure was the presence of full versus partial (working less hours) or no return to work 12 months postoperatively. Potential determinants were preoperative sociodemographic and work characteristics and joint function.

In this analysis 67 THA and 56 TKA patients were included. Of the included THA patients, 13% returned as part-time workers and 7% did not return to work one year postoperative. For TKA patients these numbers were 19% and 11%, respectively. In THA patients, preoperative factors associated with partial or no return to work were: self-employment, absence from work and a better function score. Whereas in TKA patients only absence from work was associated with partial or no return to work. Type of surgery (THA/TKA) modified the effect of the function score on return to work. In conclusion, both in THA and TKA patients, preoperative absence from work was associated with return to work, whereas only in THA patients self-employment and better preoperative function were. Moreover, the impact of preoperative function on return to work was modified by type of surgery. These results suggest that strategies aiming to influence potentially modifiable factors in the postoperative course of THA and TKA need to evaluate THA and TKA separately.

In Chapter 8 we hypothesized that preoperative physical activity (PA) would be associated with return to work after TKA. Work status and

PA level according to the Dutch Recommendation for health-enhancing PA (NNGB) and the Fitnorm were assessed preoperative and 1 year postoperative. A multivariate logistic regression analysis was used to evaluate the effect of PA on return to work, adjusting for prognostic factors for return to work among TKA patients.

The analysis included 266 working patients undergoing TKA, with a mean age of 58 years old. Preoperative, 54% of patients performed moderate PA for ≥5 days/week and 16% performed intense PA for ≥3 days/week. Concerning return to work, 67% of patients reported full return to work, 22% partial return to work and 11% no return to work. Preoperative PA was not associated with return to work. Patients who reported that their knee symptoms were not or only partially work-related had lower odds for not returning to work (OR 0.37, 95% CI 0.17 – 0.81). Also, for each additional week patients expected to be absent from work, the likelihood of not returning to work increased (OR 1.11, 95% CI 1.03 – 1.18). In conclusion, no association between preoperative PA and return to work after TKA was found. Instead, patient beliefs and preoperative expectations did influence return to work and should be addressed to further improve return to work after TKA.

In conclusion, the research in this thesis showed that the combination of preoperative radiographic OA severity and pain perception of the patient are important predictors for the expected postoperative pain/function outcome due to effect modification. Furthermore, the initial clinical recovery after arthroplasty surgery and preoperative scores can be used during the postoperative recovery period to identify patients at risk for an unfavourable one-year outcome. Besides, it showed that knee-instability could be considered as an easy identifiable surrogate outcome for poor pain relief and poor function. Furthermore, pain and functional limitations were not associated with an objective technical measurement of physical activity in patients with end-stage hip or knee OA. Finally, we found that preoperative occupational information (more specifically preoperative absence from work) and work-related expectations are important predictors for return to work after THA or TKA.

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Chapter X.

General Discussion

This thesis focused on patient-reported pain, function and participation in patients with hip or knee OA prior to and after total hip or knee arthroplasty (THA and TKA). Based on the ICF-model, a comprehensive model for health status, specifically the ICF core set for OA (1-3), three study aims were formulated in the introduction:

1. To investigate associations between radiographic OA severity, knee instability, pain and function prior to and after THA and/or TKA
2. To evaluate factors influencing physical activities in patients with end-stage hip or knee OA.
3. To identify determinants of return to work after THA or TKA.

The current chapter discusses the results and clinical implications of the abovementioned aims consecutively.

Part 1. Associations between radiographic OA severity, knee instability, pain and function prior to and after THA and/or TKA.

<u>Effect modification of radiographic OA severity on the effect of preoperative pain on postoperative pain and function (Chapter 2)</u>

The results of the study described in Chapter 2 showed that, in line with the literature, less radiographic OA severity and more preoperative pain were associated with worse postoperative pain (Chapter 2) (4-8). Function was solely affected by radiographic OA severity (4, 5). To our knowledge, no previous study investigated the combined effect of OA severity and preoperative pain on postoperative outcomes. We found that the effect of preoperative pain on the postoperative outcomes seemed to become less important when patients had more severe OA. We believe that this effect modification of radiographic OA severity on the association of preoperative pain with postoperative outcomes should be taken into account, when new prognostic models for outcomes after TKA are developed. Another interesting finding was that a substantial part of the included patients (12%) had only mild radiographic OA according to the KL score. In these patients, pain or functional disability were probably the main indications for surgery rather than their OA severity. Accordingly, the finding may also indicate that, in these patients, structural damage of the knee may not have been the major driver of perceived pain. It may indeed be more plausible that other mechanisms, such as central pain

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sensitization, may underlie pain levels (7). When pain sensitization is apparent, the central nervous system is altered in such a way that patients experience more pain than one should expect with a certain provocation (7). A previous study showed that increased central pain sensitization was apparent in OA patients who perceived much pain but who had little radiographic OA severity (7). Consequently, if the main source of the pain is not structural damage of the knee, patients with low radiographic OA severity and much perceived pain will gain less improvement from TKA compared to patients with high radiographic OA severity who experience the same levels of pain. More research on the source of pain in knee OA patients with mild structural damage of the knee joint is necessary.

Recovery trajectories after total hip and knee arthroplasty and early postoperative identification of patients at risk for unfavourable one-year outcome (Chapter 3)

In this thesis we showed that patients at risk for an unfavourable pain or function outcome at one-year could be identified six months postoperatively by preoperative pain and function scores as well as clinical change in the first six months (Chapter 3). Early postoperative identification of patients at risk for one-year unfavourable outcomes provides the opportunity to start early interventions for optimising clinical outcome (9, 10). These early postoperative interventions could probably result in shortened time to recovery, reduced distress to patients and maximized cost-effectiveness for the healthcare system as such (11). Besides, early postoperative identification of patients at risk for unfavourable long-term outcome, could help orthopaedic surgeons to identify which patients should be invited for follow-up visits at the outpatient clinic. Currently, many orthopaedic surgeons invite all patients for routine follow-up visits during the first postoperative year. This imposes substantial costs to the health care system, whereas in only very few cases patient management is altered (12, 13). Although the latter is true from a managerial perspective, the patient perspective on subjective well-being and reassurance on outcome has to be taken into account as well in future studies. Further research should identify the generalizability of our findings in other cohorts and focus on rehabilitation strategies improving outcomes in patients with unfavourable initial recovery.

Knee instability and its associations with radiographic features, pain, function and QoL (Chapters 4 and 5)

The majority of patients (72%) with knee OA reported knee instability prior to TKA. Although we hypothesised that self-reported knee instability would be associated with radiographic features, no associations were found. This suggests that structural damage of the knee prior to TKA might not be related to the sense of knee instability, whereas previous studies suggested that either osteophyte formation prevented the progression of instability or joint space narrowing contributed to a higher prevalence of instability in OA knees (14-16). Possible explanations for the discrepancy could be related to the definition of stability (varus-valgus laxity versus self-reported knee stability) and the different types of osteophytes (17, 18). A recent radiographic study on the size and direction of osteophytes in knee OA suggested that only small, predominantly outward extending osteophytes (i.e. increasing the surface area of the joint) create stability (18). Thus, future studies should not only include size, but also the location of osteophytes when analysing the association with instability.

In another analysis it was found that one year following TKA, the proportion of patients with perceived instability was much lower than before surgery, with 21% of the patients reporting a sense of knee instability. Of the patients with preoperative knee instability, this perception was retained in 25%. Pre-, postoperative and retained knee instability were associated with more perceived pain, activity limitations, and poorer QoL. Potential underlying mechanisms for these associations include muscle weakness and fear of movement, closely related to pain catastrophizing (19-22). Muscle weakness, a factor associated with complaints of OA, may contribute to a delayed response of muscles to sudden forces on the knee, which results in excessive moments of the knee joint and the perception of knee joint instability (19). This suggests that improving muscle strength could be a target for intervention. Furthermore, the associations between knee instability and perceived pain, activity limitations and (to a lesser extent) QoL could be related to the previous found association between knee stability and fear of movement (23, 24). Fear of movement results, according to the fear-avoidance model, in decreased physical activity, which worsens pain perception, increases pain catastrophizing and alters joint proprioception. Proprioception is one of the main factors affecting the sense of joint instability (23). Fear of movement could thereby increase the sense of joint instability, which leads to more avoidance of activities and increased pain catastrophising (23, 24). Future studies should identify if improving fear-avoidance and encouraging performance can improve proprioception and thus the sense of knee instability. From a clinical perspective, knee instability might help orthopaedic surgeons to evaluate outcome after TKA. Due to the associations with clinical outcomes, retained knee joint instability could be an easily identifiable alarm symptom for poor clinical outcomes. When retained knee joint instability is present, orthopaedic surgeons should be aware of a higher risk for poor clinical outcomes.

Part 2. Factors influencing physical activity in patients with end-stage hip or knee OA

In Chapter 6 we showed that joint pain and functional limitations were not associated with physical activity as measured with an accelerometer in neither hip nor knee OA patients scheduled for joint replacement. However, in hip OA patients QoL was associated with objectively measured physical activity. The observation that pain and functional limitations do not influence objective physical activity levels are in line with previous studies, that concluded that patients with OA are equally active as compared to the general population (25) and that physical activity levels do not increase after interventions such as THA or TKA (26, 27). If OA-related complaints are not associated with objectively measured physical activity, no difference is to be expected in physical activity levels between OA patients compared to the general population, or after interventions for hip or knee OA such as THA or TKA. There are several potential explanations for the absence of an association between pain or functional limitations with objectively measured physical activity. First, physical activity may be more related to a general lifestyle and overall health than to specific health problems, which is supported by previous studies as well as emphasized by our own result regarding QoL (28, 29). Second, patients could have retained activities despite symptoms, because some activities simply have to be performed (like washing oneself, cleaning or cooking) (30). Third, as recommended by international guidelines, patients with severe pain and functional disability could have retained their physical activity levels in order to reduce their symptoms or improve their overall health to be optimal prepared for a surgical treatment (30-33). Our research showed that incorporation of an accelerometer-study within the logistics of a large, multicentre cohort study, such as the LOAS, involved substantial efforts and difficulties. Especially the collection and processing of accelerometer-data was time-consuming and several technical problems occurred, such as software errors or loss of data due to damaged or lost devices. It is expected that research with wearable technology such as accelerometers may become more feasible in the future when personal devices such as watches and personal phones become more widely available and accessible for research purposes (34). Our conclusions are important to address in the preoperative consultation when outcome expectations are discussed.

Part 3. Determinants for return to work after THA or TKA

Chapter 7 focused on identification of determinants of return to work in both THA and TKA patients 12 months postoperative as well as differences between these two patient groups. In THA patients, self-employment, preoperative absence from work and less preoperative functional limitations were associated with partial or no return to work one year after surgery. Yet, in patients undergoing TKA only preoperative absence from work was associated with partial or no return to work. Besides, type of surgery (hip or knee) modified the effect of preoperative functional limitations on return to work. Thus, in patients undergoing THA, less preoperative functional limitations were associated with partial or no return to work, whereas in patients undergoing TKA a trend was seen of worse preoperative functional limitations being associated with no or partial return to work. The latter is in accordance with previous literature, whereas the first is more difficult to explain (35). However the improvement in functional limitations was better in patients who returned partially or not as compared to patients who fully returned to work. This resulted in similar postoperative scores regarding functional limitations, questioning the clinical relevance of the preoperative difference. Besides, we showed that a substantial number of patients returned to work, yet with reduced working hours. Future research should identify to what extent the reduction in working hours was related to the THA or TKA, or can be explained by other factors such as planned partial retirement or worsening of the economic tide. These results suggest that strategies aiming to influence modifiable factors need to consider THA and TKA separately.

In addition, in Chapter 8 we hypothesized that preoperative physical activity was associated with return to work after TKA. However, no association between preoperative physical activity and full return to work after TKA was found. Instead, patient beliefs and preoperative expectations (self-reported work-relatedness of knee symptoms and the expected timing of return to work) did influence return to work. A potential explanation for the absence of an association between physical activity and return to work, is that we measured self-reported physical activity. It is likely that this resulted in an overestimation of the actual physical activity, particularly in patients that are not physically active (36). Another explanation might be that we combined patients that partially returned to work and patients that did not return to work (37). It is still possible that physical activity differs between partial and no return to work. In addition, we found that certain beliefs and expectations regarding return to work influenced the actual return to work. The latter confirms that patient beliefs about the work-related cause of their knee complaints and preoperative expectations regarding timely return to work play an important role in the overall process of patients before they return to full-time work after TKA (38). This is in line with previous studies regarding overall expectations after TKA. Preoperative expectations towards TKA outcome were consistently associated with the actual postoperative outcome (39). Therefore, when planning surgical treatment, orthopaedic surgeons should take patients' expectations towards surgery and return to work into account. With respect to return to work, providing adequate and sufficient preoperative information regarding return to work and/or referring to an occupational physician for an evaluation of the work-relatedness of knee symptoms and for timely work-directed care may improve return to work of these patients (40).

Overall, this thesis contributed to knowledge on preoperative factors associated with outcome after total joint arthroplasty of the lower extremity. The research from this thesis yielded several findings related to various levels of outcomes: (1) the combination of preoperative radiographic OA severity and pain appeared to be important for the expected postoperative pain/function outcome, as preoperative radiographic OA severity was found to modify the effect of preoperative pain on postoperative pain/function; (2) PROs, specifically those reflecting the initial clinical recovery and preoperative scores of pain and function, could be used for the early postoperative identification of patients at risk for unfavorable outcome at six months postoperatively. PROs that are administered relatively early after surgery may help orthopaedic surgeons to identify which patients should be eligible for an enhanced rehabilitation strategy, potentially reducing the risk on poor outcome; (3) knee-instability could be considered as an easy identifiable surrogate outcome for more pain, and worse function and QoL; and (4) gathering information on patients' work status preoperatively (specifically absence from work) and expectations about return to work and the rehabilitation trajectory could be important to improve the speed of return to work after THA or TKA. More research in these areas is needed to identify the consistency of the results and to eventually adjust clinical decision making preoperatively as well as postoperatively. Moreover, future studies should identify which early postoperative interventions for patients at risk for unfavourable outcomes would be (cost)effective as well as the optimal timing for early postoperative screening.

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Chapter XI

Summary in Dutch
(Nederlandse samenvatting)

Doelstellingen proefschrift

Artrose behoort wereldwijd tot een van de meest voorkomende invaliderende aandoeningen in de oudere populatie. De gewrichten van de knie, heup, hand en cervicale wervelkolom, zijn het meest frequent aangedaan.

Ten aanzien van artrose van heup of knie zijn totale heup- of knieprothese operaties (THP en TKP), wanneer er gekeken wordt naar klinische uitkomsten en de levensduur van de prothese, zeer effectieve interventies voor patiënten met artrose in het eindstadium. In Nederland worden jaarlijks meer dan 30.000 THP en 25.000 TKP operaties uitgevoerd en deze aantallen stijgen door de vergrijzing en de toename van het aantal mensen met overgewicht.

In de laatste decennia is, in de gezondheidszorg en in het bijzonder bij het evalueren van interventies, een holistische benadering vanuit het perspectief van de patiënt steeds belangrijker geworden. Naast het technische resultaat is de perceptie van de patiënt over de uitkomst van groot belang. De ‘International Classification of Functioning, Disability and Health’ (ICF) is een holistisch raamwerk om de gezondheidstoestand te beschrijven. Daarin worden, naast het functioneren zelf, ook externe en persoonlijke factoren die daarop van invloed kunnen meegenomen. Op basis van de ICF zijn voor verschillende aandoeningen waaronder artrose, ziekte-specifieke, de zogenaamde Core Sets, beschreven. Deze Core Sets bevatten díe aspecten van de gezondheid die door patiënten met een specifieke aandoening en hun behandelaar als meest relevant worden beschouwd. Dit proefschrift richt zich op enkele aspecten van de gezondheidstoestand van mensen met een THP of TKP in verband met heup of knie artrose, waarnaar nog relatief weinig onderzoek is verricht:

1. De relatie tussen radiologische afwijkingen, een instabiel gevoel van de knie, pijn- en functieklachten voor en na een totale heup- en/of knieprothese (THP/TKP) operatie;
2. Fysieke activiteit van patiënten met eindstadium heup of knie artrose en factoren die daarop van invloed zijn.
3. Het identificeren van determinanten voor terugkeer naar werk na THP of TKP.

De studies beschreven in hoofdstuk 2-6 en 8 waren gebaseerd op het LOAS onderzoek (Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis), een multicenter, longitudinaal prospectief cohortonderzoek waarin patiënten met een indicatie voor een primaire THP of TKP operatie geïncludeerd werden. De analyses in dit proefschrift werden uitgevoerd met data van patiënten die werden geïncludeerd tussen Juni 2012 en Juni 2015. De studie beschreven in hoofdstuk 7 was gebaseerd op gegevens van een éénjarig, observationeel cohortonderzoek dat tussen oktober 2010 en september 2012 werd uitgevoerd met patiënten uit één centrum, het Alrijne Ziekenhuis, Leiderdorp, Nederland.

Deel 1. Preoperatieve (en vroeg postoperatieve) pijn en functie, radiologische ernst van artrose en knie instabiliteit en hun associaties met postoperatieve uitkomsten van pijn en functie.

<u>Effectmodificatie van de radiologische ernst van knieartrose op de associatie tussen preoperatieve pijn en postoperatieve pijn en functie.</u>
Zowel de radiologische ernst van artrose en preoperatieve pijn spelen een belangrijke rol bij de indicatiestelling van een TKP. Eerdere studies lieten slechts een zwakke associatie zien tussen de preoperatieve radiologische ernst van knieartrose en de hoeveelheid preoperatieve pijn. Dit suggereert dat de preoperatieve pijn niet bij alle patiënten verklaard kan worden door structurele schade van de knie. Als de structurele schade niet de enige oorzaak is van de pijn, is het te verwachten dat een TKP maar een deel van de pijn zal wegnemen. De studie beschreven in Hoofdstuk 2 onderzocht daarom of er sprake was van effect modificatie van de preoperatieve radiologische ernst van artrose op de associatie tussen preoperatieve pijn en postoperatieve pijn en functie één en twee jaar na TKP. De ernst van artrose werd radiologisch bepaald met de Kellren and Lawrence (KL) score. Pijn en functie werden gemeten middels de gelijknamige subschalen van de Knee Injury and Osteoarthritis Outcome Score (KOOS). Er werden multivariate lineaire regressieanalyses, gecorrigeerd voor Body Mass Index (BMI), leeftijd, geslacht en de Mental Health Component Score (MCS) van de Short Form-12 verricht, waarbij een interactieterm tussen de preoperatieve KL score en preoperatieve pijn werd opgenomen in het model.

In de analyse werden 559 patiënten die een TKP ondergingen betrokken. De resultaten lieten zien dat een slechtere preoperatieve radiologische artrose score geassocieerd was met minder postoperatieve pijn en een betere postoperatieve functie één en twee jaar na TKP, terwijl meer preoperatieve pijn enkel geassocieerd was met meer postoperatieve pijn en niet met een slechtere postoperatieve functie. Tevens werd er een trend gevonden waarbij de preoperatieve radiologische artrose score het effect van preoperatieve pijn op één en twee jaar postoperatieve pijn modificeerde. De effect grootten hadden een β van −0.1 (95% betrouwbaarheidsintervallen -BI- waren respectievelijk -0.1 tot 0.0 en -0.2 tot 0.0). Dit betekent dat bij een slechtere preoperatieve radiologische artrose score het effect van preoperatieve pijn op postoperatieve pijn steeds minder belangrijk werd. Vergelijkbare resultaten werden gevonden voor het effect van de radiologische ernst van artrose op de associatie tussen preoperatieve en één en tweejaar postoperatieve functie (β −0.1; 95% BI −0.2-0.0 voor beide). Concluderend hadden patiënten die preoperatief minder pijn hadden en een slechtere radiologische artrose score betere pijn- en functie uitkomsten één en twee jaar na TKP. Echter, het effect van preoperatieve pijn op de postoperatieve uitkomsten leek minder uitgesproken te zijn bij radiologisch ernstigere artrose. Deze bevindingen suggereren dat het aan te bevelen is om de effect modificatie tussen de radiologische ernst van artrose en preoperatieve pijn op postoperatieve pijn en functie mee te nemen bij het ontwikkelen van nieuwe prognostische modellen voor uitkomsten na TKP.

Hersteltrajecten na THP en TKP en vroege postoperatieve identificatie van risicopatiënten voor een ongunstige uitkomst na één jaar.

Het onderzoek dat beschreven wordt in hoofdstuk 3 evalueerde het initiële klinische herstel (6 maanden) en het herstel tot en met één jaar na een primaire THP of TKP en de relatie hiertussen. Zelf gerapporteerde pijn en functie werden preoperatief, zes maanden en één jaar na de operatie geëvalueerd middels de Pijn en Activity Daily Living (ADL) subschalen van de HOOS en de KOOS. Er werden vier klinisch relevante hersteltrajecten van pijn en functie gedefinieerd, namelijk (1) een gunstige initiële en één jaar uitkomst, (2) een gunstige initiële en ongunstige één jaar uitkomst, (3) een ongunstige initiële en gunstige één jaar uitkomst en (4) een ongunstige initiële en één jaar uitkomst.

Het 20[ste] percentiel van de pijn of functie uitkomst na één jaar werd gebruikt als afkappunt voor een gunstige dan wel ongunstige 6-maanden en één jaar uitkomst. Door middel van multivariate logistische regressie analyses en receiver operating curves (ROC) werd beoordeeld in welke mate, naast de preoperatieve pijn en functie, het initiële herstel in de eerste 6 maanden de pijn en functie uitkomst na één jaar konden voorspellen.

In deze analyse werden 972 THP en 892 TKP patiënten betrokken. Het grootste deel van de patiënten, 70% voor zowel THP als TKP patiënten, had een gunstige pijnuitkomst zowel na zes maanden als na één jaar (traject 1), terwijl 6% van de THP en 4% van de TKP patiënten een gunstige zes maanden echter ongunstige één jaar uitkomst had (traject 2). Tien% van de THP en 12% TKP patiënten hadden initieel een ongunstige pijnuitkomst, die veranderde naar een gunstige uitkomst na één jaar (traject 3), terwijl 14% van zowel THP als TKP patiënten een ongunstige initiële en één jaar pijnuitkomst hadden (traject 4). Vergelijkbare resultaten werden gevonden voor functie. Daaruit kon worden afgeleid dat van de patiënten met een initieel ongunstige pijn of functie uitkomst, 33-46% een gunstige uitkomst na één jaar behaalde. Voor zowel THP als TKP patiënten waren meer pijn of een slechtere functie en een lager initiële klinisch herstel voorspellend voor een slechtere uitkomst na een jaar (alle odds ratios (ORs) 0.96-0.97), terwijl een voorspelmodel met beide variabelen de beste voorspelling behaalde (AUCs voor volledige modellen waren 0.86-0.91). Dit betekent dat patiënten met meer preoperatieve pijn of een slechtere preoperatieve functie en een kleinere initiële klinische verbetering een verhoogd risico op meer pijn of een slechtere functie één jaar na de operatie hadden. Samenvattend, had 70% van de mensen na zowel een THP als een TKP een gunstige initiële en een-jaar uitkomst. Circa een derde van de patiënten met een initieel ongunstige uitkomst had een gunstige uitkomst na één jaar. Het klinische herstel in de eerste zes maanden is samen met de preoperatieve pijn- of functiescore geassocieerd met de uitkomst één jaar na THP of TKP. De uitkomst na zes maanden kan daarom bijdragen aan de voorspelling van de uitkomst na één jaar. Vervolgonderzoek moet uitwijzen of we deze risicopatiënten nog eerder in het herstelproces, bijvoorbeeld na 6 weken kunnen identificeren. Tevens moet worden onderzocht of vroege revalidatiestrategieën in deze patiëntengroep de uiteindelijke uitkomst kunnen verbeteren.

Knie instabiliteit en de associaties met radiologische kenmerken, pijn, functie en kwaliteit van leven (KvL).

Hoofdstuk 4 beschrijft de prevalentie van zelf-gerapporteerde knie instabiliteit bij patiënten met eindstadium knieartrose en onderzocht de associatie tussen zelf-gerapporteerde knie instabiliteit en radiologische kenmerken. Knie instabiliteit werd gemeten middels een knie-instabiliteit vragenlijst waarbij gevraagd wordt naar het doorzakken, wegschuiven, wiebelen of wankelen van de knie in de voorgaande 3 maanden. Radiologische kenmerken waren gewrichtsspleetversmalling en osteofytvorming, welke geduid werden op een 0-3 schaal. Scores >1 werden gedefinieerd als substantiële gewrichtsspleetversmalling/osteofytvorming. Logistische regressieanalyses werden verricht om associaties tussen radiologische kenmerken en zelf gerapporteerde knie instabiliteit te identificeren. In deze analyse werden 265 patiënten met knieartrose betrokken. Knie instabiliteit werd geapporteerd door de meerderheid (72%) van de patiënten. Zelf gerapporteerde knie instabiliteit was niet geassocieerd met gewrichtsspleetversmalling (de ORs van score 1-3 ten opzichte van score 0 hadden een reikwijdte van 0.68-0.98) of osteofytvorming (de ORs van score 1-3 ten opzichte van score 0 hadden een reikwijdte van 0.69-0.89). Ook gestratificeerde analyses voor pijn, leeftijd en BMI lieten geen associaties zien tussen zelf-gerapporteerde knie instabiliteit en radiologische kenmerken voor artrose in subgroepen. Op basis van deze resultaten werd geconcludeerd dat zelf-gerapporteerde knie instabiliteit niet geassocieerd was met gewrichtsspleetversmalling of osteofytvorming.

XI

In hoofdstuk 5 wordt een studie naar het beloop en de prevalentie van zelf-gerapporteerde knie instabiliteit over één jaar na TKP beschreven. Ook werden associaties tussen preoperatieve, postoperatieve en persisterende zelf-gerapporteerde knie instabiliteit enerzijds en pijn, functie en KvL anderzijds bij patiënten met knieartrose onderzocht. Pijn, functie en KvL werden geëvalueerd met de gelijknamige KOOS subschalen. Multivariate lineaire regressieanalyses werden verricht en gecorrigeerd voor covariaten (leeftijd, geslacht, comorbiditeit en radiologische ernst van artrose). In dit onderzoek werden data van 908 patiënten met een indicatie voor een TKP betrokken. Na TKP werd knie instabiliteit gerapporteerd door 21% van de totale studiepopulatie en door 25% van de 649 patiënten die ook preoperatieve knie instabiliteit rapporteerden. In overeenstemming met voorgaande studies werden associaties gevonden tussen preoperatieve knie instabiliteit en preoperatieve pijn, functie en KvL. Daarnaast lieten de resultaten zien dat postoperatieve en persisterende knie instabiliteit geassocieerd waren met postoperatieve pijn, activiteiten beperkingen en KvL. Voor persisterende knie instabiliteit waren de effect groottes respectievelijk β -15.1 (95% CI -18.9 tot -11.2), β -14.1 (95% CI -17.8 tot -10.4) en β -18.0 (95% CI -21.7 tot -14.3). Concluderend persisteert het gevoel van knie instabiliteit na de operatie in circa 25% van de patiënten die een TKP operatie ondergaan. Gezien de gevonden cross-sectionele associaties tussen postoperatieve knie instabiliteit en pijn, activiteiten beperkingen en KvL kunnen orthopedische chirurgen een persisterend gevoel van knie instabiliteit na TKP als een alarmsymptoom voor slechte klinische uitkomsten beschouwen.

Deel 2. Factoren die van invloed zijn op fysieke activiteit in patiënten met eindstadium heup- of knieartrose.

In hoofdstuk 6 werd onderzocht of pijn, functionele beperkingen en KvL geassocieerd waren met objectieve metingen van fysieke activiteit in patiënten met eindstadium heup- of knieartrose. Geïncludeerde patiënten droegen gedurende 5-7 dagen een accelerometer (Activ8). Fysieke activiteit werd uitgedrukt als (1) aantal ‘activity daily counts’ (ADC) per uur, (2) percentage van de tijd besteed aan fysieke activiteit en (3) percentage van de tijd besteed aan sedentair gedrag (zitten/liggen). De HOOS/KOOS en Short-form 12 werden gebruikt om pijn, functionele beperkingen en KvL te beoordelen. Multivariate lineaire regressieanalyses werden verricht met de drie tot Z-scores getransformeerde parameters van fysieke activiteit als afhankelijke variabele, gecorrigeerd voor confounders.

In deze analyse werden 49 patiënten met heupartrose en 48 patiënten met knieartrose betrokken. De resultaten lieten zien dat bij heupartrose patiënten betere gewrichtspecifieke en algehele KvL geassocieerd waren met meer ADC (β 0.028 (95% CI 0.007–0.048), β 0.041 (95% CI 0.010–0.071, respectievelijk). Daarnaast was betere algehele KvL geassocieerd met een hoger percentage van de tijd besteed aan fysieke activiteit (β 0.040 (95%CI 0.007–0.073)). Er werden geen andere associaties gevonden voor zowel heup- als knieartrose patiënten. Concluderend kan gesteld worden dat KvL geassocieerd is met objectieve metingen van fysieke activiteit bij patiënten met eindstadium heupartrose, terwijl pijn en functionele beperkingen niet geassocieerd zijn met objectieve metingen van fysieke activiteit bij patiënten met eindstadium heup- of knieartrose. Deze conclusies zijn belangrijk om te bespreken tijdens het preoperatieve consult wanneer verwachtingen omtrent uitkomsten van totale heup- of knieprothese operaties worden besproken.

Deel 3. Determinanten voor terugkeer naar werk na THP of TKP

De onderzoeken die worden beschreven in hoofdstukken 7 en 8 beoogden determinanten voor terugkeer naar werk na THP of TKP te identificeren. In hoofdstuk 7 werden determinanten voor terugkeer naar werk onderzocht en vergeleken tussen THP en TKP. In deze analyses werden patiënten met een betaalde baan en een leeftijd <65 jaar geïncludeerd. De uitkomstmaat was het volledig versus gedeeltelijk of niet terugkeren naar werk 12 maanden na de operatie. Potentiële determinanten waren preoperatieve sociaal-demografische karakteristieken, werkkarakteristieken en lichamelijk functioneren.

In deze analyse werden 67 THP en 56 TKP patiënten betrokken. Een jaar na de operatie was 13% van de werkende THP patiënten parttime en 7% niet teruggekeerd naar werk. Voor TKP patiënten waren deze getallen respectievelijk 19% en 11%. Bij THP patiënten waren het niet in loondienst zijn, preoperatief ziekteverzuim en een betere preoperatieve lichamelijke functie geassocieerd met gedeeltelijk of helemaal niet terugkeren naar werk. Bij TKP patiënten was enkel preoperatief ziekteverzuim geassocieerd met gedeeltelijk of helemaal niet terugkeren naar werk. In tegenstelling tot THP patiënten, werd bij TKP patiënten een

trend tot een relatie tussen een slechtere preoperatieve functie en het gedeeltelijk of niet terugkeren naar werk gezien.
Concluderend, preoperatief ziekteverzuim was zowel in THP als TKP patiënten geassocieerd met terugkeer naar werk, terwijl het niet in loondienst zijn en een betere preoperatieve functie enkel in THP patiënten geassocieerd was met terugkeer naar werk. Deze resultaten suggereren dat er bij onderzoek naar terugkeer naar betaald werk onderscheid gemaakt moet worden tussen patiënten die een THP of TKP operatie ondergaan.

In hoofdstuk 8 wordt een studie beschreven die onderzocht of preoperatieve fysieke activiteit, naast sociaalgeografische- en werkkarakteristieken waaronder werkgerelateerde verwachtingen en de perceptie of de knieklachten geassocieerd zijn met werk, geassocieerd was met terugkeer naar werk één jaar na TKP. Werkstatus en fysieke activiteit werden preoperatief en één jaar postoperatief gemeten met behulp van de Nederlandse Norm Gezond Bewegen (NNGB) en Fitnorm. Om, naast bekende prognostische factoren, het effect van fysieke activiteit op terugkeer naar werk (ja/nee) bij TKP patiënten te evalueren werd multivariate logistische regressie toegepast. De analyses werden uitgevoerd met de gegevens van 266 TKP patiënten, die gemiddeld 58 jaar oud waren en preoperatief betaald werk hadden. Preoperatief was 54% van de patiënten op ≥5 dagen/week matig intensief lichamelijk actief en 16% op ≥3 dagen/week zwaar intensief lichamelijk actief. In dit cohort was één jaar na de operatie 67% van de patiënten volledig aan het werk, 22% gedeeltelijk en 11% niet. Preoperatieve lichamelijke activiteit was niet geassocieerd met het terugkeren naar werk. De perceptie dat knie symptomen niet of slechts gedeeltelijk werkgerelateerd waren was wel geassocieerd met het terugkeren naar werk (OR 0.37, 95% CI 0.17 – 0.81). Daarnaast was er een relatie tussen het niet terugkeren naar werk en de verwachting meer weken postoperatief te verzuimen (OR 1.11, 95% CI 1.03 – 1.18). Concluderend werden er geen associaties gevonden tussen preoperatieve fysieke activiteit en terugkeer naar werk na een TKP. Wel bleken preoperatieve ideeën en verwachtingen van patiënten geassocieerd te zijn met het terugkeren naar werk. Deze moeten daarom meegenomen worden om terugkeer naar werk in TKP patiënten te verbeteren.

Concluderend, het onderzoek in dit proefschrift richtte zich op enkele aspecten van de gezondheidstoestand van mensen met een THP of TKP in verband met heup of knie artrose aan de hand van het ICF-model:

1. De relatie tussen radiologische afwijkingen, een instabiel gevoel van de knie en pijnklachten voor en na een totale heup- en/of knieprothese (THP/TKP) operatie;
De combinatie van de preoperatieve radiologische ernst van artrose en preoperatieve pijn is belangrijk voor de te verwachten postoperatieve pijn/functie door effectmodificatie van de radiologische ernst van artrose op de associatie tussen preoperatieve pijn en postoperatieve pijn/functie. Daarnaast kan het initiële klinische herstel bijdragen aan het vroegtijdig identificeren van risicopatiënten voor een ongunstige één jaar uitkomst. Vervolgonderzoek moet laten zien of vroegtijdige revalidatiestrategieën in deze specifieke patiëntengroep de uiteindelijke uitkomst kunnen verbeteren. Ook liet dit proefschrift zien dat knie instabiliteit niet geassocieerd is met radiologische afwijkingen, maar wel gebruikt kan worden als surrogaat uitkomst voor een slechte pijn- en functie-uitkomst.

2. Fysieke activiteit van patiënten met eindstadium heup of knie artrose en factoren die daarop van invloed zijn.
Preoperatief bleken pijn en functie niet geassocieerd met objectieve metingen van fysieke activiteit in patiënten met eindstadium heup- of knieartrose.

3. Het identificeren van determinanten voor terugkeer naar werk na een THP of TKP operatie.
Tot slot werd gevonden dat preoperatieve werk-gerelateerde informatie waaronder ziekteverzuim en verwachtingen na de operatie geassocieerd zijn met het terugkeren naar werk na THP of TKP operaties.

Chapter XII

Publications

List of publications

Peer reviewed publications

van de Water RB, Leichtenberg CS, Nelissen RGHH, Kroon HM, Kaptijn HH, Onstenk R, Verdegaal SHM, Vliet Vlieland TPM, Gademan MGJ. Preoperative radiographic osteoarthritis severity modifies the effect of preoperative pain on pain/function after total knee arthroplasty: results at 1 and 2 years postoperatively. J Bone Joint Surg Am 2019;101(10): 879-887.

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Curriculum Vitæ

Claudia Susanne Leichtenberg werd op 21 augustus 1993 geboren in Amstelveen en is opgegroeid in Almere. In 2011 behaalde zij haar VWO diploma aan het Baken Park Lyceum in Almere en in datzelfde jaar startte zij met de studie Geneeskunde aan de Universiteit van Amsterdam. Gedurende haar studie was zij lid van verschillende commissies van het Zonshofje, een woongroep voor studenten, en Stichting Signaalkampen, een stichting die zeilkampen voor kinderen organiseert.

Haar interesse voor de wetenschap werd al vroeg in haar medische carrière gewekt. In 2013 startte zij als student-onderzoeker op de afdeling Orthopaedie van het Leids Universitair Medisch Centrum. Zij leverde een bijdrage aan verschillende wetenschappelijke onderzoeken en schreef haar bachelor scriptie over een studie die zij verrichte naar determinanten voor terugkeer naar werk na een totale heup- of knieprothese. In 2014 startte zij als promovenda bij de afdeling Orthopaedie van het Leids Universitair Medisch Centrum onder begeleiding van prof.dr. T.P.M. Vliet Vlieland, prof.dr R.G.H.H. Nelissen en dr. M.G.J. Gademan. Van 2014-2017 was zij fulltime als onderzoeker aan de afdeling Orthopaedie verbonden. De resultaten van het onderzoek voor haar bachelor scriptie en het onderzoek verricht tijdens haar promotietraject staan beschreven in dit proefschrift. Zij presenteerde de onderzoeksresultaten op diverse nationale en internationale congressen. In 2015 kreeg zij een congresreis subsidie toegekend door het Reumafonds (nu: ReumaNederland).

In 2017 ging zij verder met haar master aan de Universiteit van Amsterdam. Daarnaast zette zij zich in 2018 in voor Stichting Dream4Kids, een organisatie die droomdagen organiseert voor kinderen die een ernstige traumatische ervaring hebben meegemaakt. In 2020 zal zij als laatste coschap een tropencoschap in Tanzania volgen en in mei 2020 verwacht zij af te studeren als basisarts.