Chapter 1

General introduction
Osteoarthritis of the knee or hip

Osteoarthritis (OA) is the most common rheumatic disease of the musculoskeletal system and frequently affects the knee, hip and hand joints. The prevalence of OA is roughly estimated at about 150 million people worldwide, of which approximately 1.2 million in the Netherlands. It is well known that the prevalence of OA increases with age. Based on demographic trends it is expected that between 2011 and 2030 the number of people with OA in The Netherlands will increase by almost 40%. In addition, with increasing prevalence of obesity (a major determinant of OA) and sedentary lifestyle, it is expected that the prevalence of OA will increase even further over the coming decades. Overall, women have up to a 50% higher risk of OA than men, especially after the age of 50. Compared to other global diseases, OA is counted as the sixth primary cause of moderate-to-severe disability and the eighth cause of disease burden in the European region. OA has become a major health-care and economic problem with a large demand on health services.

The pathogenesis of OA is not fully understood. OA has long been mainly characterized by changes initiated in the articular cartilage, while recent evidence also suggests involvement of the entire joint including subchondral bone, capsule, menisci and ligaments.
periarticular tissues like ligaments and muscles (see Figure 1)\textsuperscript{1,8}. Furthermore, knee or hip OA can be accompanied by a chronic patchy synovitis, causing clinical symptoms such as joint swelling and inflammatory pain\textsuperscript{9}.

Pain is a predominant sign of OA for which patients seek care\textsuperscript{10}. Other symptoms include joint stiffness, reduced range of joint motion, instability, synovitis and muscle weakness\textsuperscript{1}. These symptoms frequently lead to problems in performing daily activities, for example, walking, stairclimbing and sitting or rising up from a chair.

The diagnosis OA can be based on clinical and radiological features. In practice, the clinical diagnosis of OA is often used, which is based on symptoms and physical examination. Several standards have been proposed, but the diagnosis is mainly based on the American College of Rheumatology (ACR) criteria\textsuperscript{11}. According to these ACR criteria, knee OA is diagnosed if knee pain is present and three of the following six parameters hold true: age >50 years, morning stiffness <30 minutes, crepitus, bony tenderness, bony enlargement and no palpable warmth. Hip OA is diagnosed if hip pain is present and hip internal rotation <15˚ and erythrocyte Sedimentation Rate (ESR) ≤ 45 mm/hour (if ESR not available, substitute hip flexion ≤ 115˚) or hip pain is present and internal rotation ≥15˚, pain on hip internal rotation, morning stiffness of the hip ≤ 60 minutes and age > 50 years. Radiographs are widely used to diagnose OA and to assess the severity of the disease (e.g., formation of new bone at the joint margins (osteophytes) and narrowing of joint space and changes in the subchondral bone (sclerosis))\textsuperscript{8}. However, there can be a strong discrepancy between clinical symptoms and radiographic findings: for example, 60% of those with severe knee OA have symptoms and only 40% of patients with moderate radiographic knee OA experience symptoms\textsuperscript{12}.

There are several risk factors for the onset of knee or hip OA, which can be divided into personal factors and joint-level factors. Person-level factors for the onset of knee OA include age, gender, race/ethnicity, bone density, obesity, diet (e.g., vitamin D depletion) and genetic factors. Joint-level factors include injury and abnormal loading of the joints (certain intense or competitive sports, occupation), repetitive use of the joint and quadriceps weakness\textsuperscript{1,13-16}. Knee malalignment is the strongest predictor of progression of knee OA. Risk factors for the onset of hip OA slightly differ from those with knee OA. Person-level factors for the onset of hip OA include age, physical inactivity, body-mass index (including obesity) and genetic factors (including congenital deformities). Joint level factors include previous injury and intensive sport activities\textsuperscript{1}.

**Course of pain and physical functioning in patients with knee or hip osteoarthritis**

The development of difficulties in performing daily activities is more progressive in middle aged and older persons with OA, than their contemporaries without this disease\textsuperscript{17}. However, the natural course of pain and physical functioning in patients with OA of the knee or hip is highly individual and variable. Some patients deteriorate, some patients remain stable, while others even improve. Because of this variability, identification of risk factors for deterioration in pain and physical functioning is important, as this knowledge can be used to inform patients of the likely course of their condition and to
adapt treatment according to the prognosis. The results of a previous systematic review by van Dijk et al.\textsuperscript{18}, indicate that pain and physical functioning deteriorate after three or more years of follow up in both patients with knee and hip OA. There is also limited evidence in knee OA that certain factors predict deterioration of physical functioning, i.e., older age, greater body mass index (BMI), greater knee pain intensity or increased knee pain, increased laxity and proprioceptive inaccuracy. However, the evidence for these conclusions was provided by only one high-quality cohort study with a follow up of three years\textsuperscript{19}. No evidence was found for predictors of deterioration of pain\textsuperscript{18}. Furthermore, a lack of high quality studies hampered the identification of prognostic factors in patients with hip OA. Since this previous systematic review, published in 2006\textsuperscript{18}, quite a number of longitudinal studies have been published on the course and prognosis of pain and physical functioning in persons with knee or hip OA. Therefore, we have updated the review on scientific evidence regarding the course and predictors of pain and physical functioning in patients with knee (Chapter 2) and hip OA (Chapter 3).

**Management of patients with knee or hip osteoarthritis**

Currently, no cure is available for patients with knee or hip OA. Several national and international guidelines describe the management of patients with knee or hip OA\textsuperscript{20-23}. In these guidelines three treatment modalities are commonly distinguished: non-
pharmacological, pharmacological and surgical modalities. A stepped care approach is recommended in the management of patients with OA (see figure 2)\textsuperscript{8,20,22,24}. The first treatment option in patients with knee or hip OA should consist of exercise therapy (strength training), weight management and education (about the disease and treatment modalities), possibly in combination with symptomatic pharmacological treatment (e.g., paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs)). However, the use of paracetamol has recently been questioned\textsuperscript{25}. It has been found that paracetamol does not seem to confer any demonstrable effect or benefit in osteoarthritis, at any dose, but the medical guideline has not been adapted yet. Finally, if non-pharmacological and pharmacological treatments are ineffective, referral for consideration of surgical treatment is indicated. In the Netherlands, a stepped care approach (Beating Osteoarthritis strategy (BART Strategy)) has been developed and implemented in order to improve the quality of the management for patients with knee and hip OA\textsuperscript{26}.

**Exercise therapy in knee osteoarthritis**

Exercise therapy is a core intervention in the non-pharmacological management of knee and hip OA in order to prevent or postpone knee joint replacement as long as possible. It is an effective intervention to reduce joint pain and improve physical functioning\textsuperscript{27}. Although the effect of exercise therapy in patients with knee OA has been proven, the effect of exercise therapy on pain and physical functioning in patients with knee OA has been found to be moderate (SMD =0.5) (immediate posttreatment) to small (SMD =0.15) (two to six months posttreatment)\textsuperscript{27}. The same applies to the effect of exercise therapy in patients with hip OA. The effect size is found to be small directly after treatment and after two to six months of follow up (SMD = 0.38)\textsuperscript{28}. Therefore, optimization of the effect of exercise therapy is required. Recently, research has focused on the identification of subgroups or phenotypes, because the knee and hip OA population is highly heterogeneous\textsuperscript{29-31}. It has been hypothesized that segregating patients into subgroups may help in finding the best targeted personalized care in knee OA. For example, Kitellson et al. found that psychological factors, joint sensitivity and comorbidity status, appear to be important in defining phenotypes of knee OA-related pain\textsuperscript{32}. As a result, interventions should be tailored to these specific subgroups to optimize overall effectiveness of exercise therapy. Exercise interventions tailored to comorbidity have not been described before.

**Comorbidity in patients with knee or hip osteoarthritis**

Comorbidity is highly prevalent in patients with knee and hip OA\textsuperscript{33}. Comorbidity can be defined as ‘any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease (i.e., osteoarthritis) under study’\textsuperscript{34}. Studies have reported comorbidity rates of 68% to 85%\textsuperscript{35-39}. A study of van Dijk et al.\textsuperscript{38} shows that almost all patients (98.6%) suffer from one or more coexistent diseases and 84.4% of the population suffers from one or more moderate or severe coexistent diseases.
Some comorbidities are more prevalent, i.e., cardiac diseases (54%), diseases of eye, ear, nose, throat and larynx (96.1%; mostly low vision), and endocrine and metabolic diseases (46%; mostly diabetes). Underlying mechanisms for this high prevalence are not clear yet. Apart from aging, overlap between chronic conditions due to shared pathophysiological mechanisms may play role (e.g., the mechanical impact of overweight on joints, chronic inflammation).

The number of comorbid diseases and the severity of these diseases are associated with additional limitations in daily activities, for example, walking, stair climbing, and rising up from of a chair. In addition, the severity of these diseases is also associated with more pain. Furthermore, according to a longitudinal study with a follow-up period of three years, a higher comorbidity count at baseline predicts deterioration in physical functioning and pain in patients with knee or hip OA. Other studies have reported similar results.

These findings indicate that health care providers must be aware of the relation between the presence of comorbidity and a decline in pain or physical functioning.

**Comorbidity and exercise therapy**

Regular exercise therapy for patients with knee or hip OA consists of muscle-strength training of the lower limb and aerobic training at a moderate to high training intensity. The presence of comorbidity may interfere with the application of regular exercise therapy, requiring adaptations to the exercise program for knee or hip OA.

Common comorbidities that may have an influence on exercise therapy in patients with knee or hip OA are for example, cardiovascular diseases, type 2 diabetes, chronic obstructive pulmonary disease (COPD) and obesity. Comorbidity limits exercise tolerance, depending on the type, number and severity of the comorbid disease(s). For example, comorbid heart failure or COPD may limit exercise capacity and may lead to exercise-induced adverse effects, such as decompensation in patients with heart failure, or desaturation in patients with COPD. The presence of comorbid conditions may also impose several, sometimes even contradictory requirements. An example is comorbid heart failure in patients with osteoarthritis of the knee. While the osteoarthritis guideline emphasizes the need for strength training, in patients with heart failure a rapid increase in the level of peripheral resistance should be avoided as this increases the afterload and risk of decompensation.

In clinical practice, comorbidity is a frequent reason to exclude patients from exercise therapy. If accepted into an exercise program, both therapists and patients tend to reduce exercise intensity to a level that is unlikely to be effective, because of fear of aggravating symptoms of the comorbid disease. Tailoring exercise therapy to the comorbid disease is complex and requires advanced clinical reasoning of the treating physical therapist. Guidelines on knee and hip OA do not provide guidance on tailoring exercise therapy to the presence of comorbidity. The OARSI guidelines for non-surgical management of knee OA is the first guideline that distinguishes recommendations in treatment modalities (e.g., NSAID) between knee OA patients with and without comorbidities. However, no guidance is provided in this OARSI
guideline on how to adapt or tailor exercise therapy to the presence of comorbidity.

The effect of exercise therapy in patients with knee or hip OA and severe comorbidity is not known. Patients with unstable medical conditions, precluding safe participation in an exercise program, are excluded from clinical trials because of the high risk of comorbidity induced adverse events. One study investigated the outcome of exercise therapy in a subgroup of patients with knee OA and comorbidity compared to patients without comorbidity. Beneficial effects of exercise therapy were found in both groups. However, patients with severe medical conditions such as congestive heart failure or insulin dependent diabetes mellitus were excluded. Therefore, we have developed and evaluated a comorbidity-adapted exercise protocol, which provides guidance in clinical reasoning with regards to diagnostics and treatment, enabling the therapist to tailor the exercise therapy to the comorbid disease in patients with knee or hip OA (see Chapter 4-8).

Aim and outline of this thesis
The aim of this thesis is twofold. The first aim is to describe the course of pain and physical functioning in patients with knee or hip OA and to provide an overview of prognostic factors of the course of pain and physical functioning. In Chapter 2, the scientific evidence is summarized in a systematic review and meta-analysis on the course of pain and physical functioning in patients with knee OA and an overview is presented of prognostic factors that predict deterioration in pain and physical functioning. Chapter 3 presents the results of a second systematic review and meta-analysis on the course of pain and physical functioning in patients with hip OA and prognostic factors that predict the course.

The second aim is to develop and evaluate tailored exercise therapy in patients with knee OA and comorbidity. The development of the intervention was conducted by following the Medical Research Council’s (MRC) framework on complex intervention design (see figure 3). The MRC framework addresses strategies for developing and evaluating complex interventions and proposes a phased approach that consists of five phases:

- Phase 0, the preclinical or theoretical phase;
- Phase I, the modeling phase;
- Phase II, the exploratory trial;
- Phase III, definitive randomized controlled trial; and,
- Phase IV, the implementation phase.

In phase 0, the theoretical basis for the intervention is reviewed and potentially active ingredients are identified. In phase I, the intervention is developed based on the information gathered of the previous phase. In phase II, the optimum intervention is developed, based on the information gathered during the previous phases. Furthermore, the explanatory trial study design for the evaluation of the intervention is developed. In the exploratory trial, the consistency with which the intervention is delivered is explored, the ways to measure the optimal outcome are selected and a preliminary estimate of the effect size of the outcome is obtained. In phase III, the definitive protocol is evaluated
in a randomized controlled trial. In the final phase of the MRC framework a long-term implementation of the intervention is studied. In this thesis the first four phases of the MRC framework are described. The long-term implementation is not part of the study presented in this thesis.

In Chapter 4, highly prevalent comorbidities are described, that have impact on pain and physical functioning in patients with knee or hip OA. This knowledge contributes to the preclinical phase of the MRC framework. Chapter 5 describes the theoretical foundations of the developed protocols by summarizing the literature on contraindications and restrictions for exercise therapy for common comorbidities in patients with knee or hip OA by using a narrative approach. This knowledge also contributes to preclinical phase of the MRC framework. In Chapter 6, the development of a tailored exercise therapy protocol for patients with knee OA and comorbidity is described. The first part of this chapter describes the development of the protocol based on the results of chapter 4 and 5, contributing to the modeling phase of the MRC framework. The second part of this chapter describes the feasibility of the protocol and evaluation of treatment outcome in a pilot study, which contributes to the exploratory phase of the MRC framework. Chapter 7, presents the results of a randomized clinical trial of the efficacy of tailored exercise therapy in patients with knee OA and comorbidity. This knowledge contributes to the randomized control trial phase of the MRC framework. In Chapter 8, a general strategy is described to develop comorbidity-related adaptations to exercise therapy.

Finally, in Chapter 9, the results of this thesis are summarized and discussed.

Figure 3. Sequential phases of developing randomized controlled trials of complex interventions. (Campbell M et al.57)
References

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Chapter 2

Prognosis of Pain and Physical Functioning in Patients With Knee Osteoarthritis: A Systematic Review and Meta-Analysis

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Abstract

Objective. To systematically summarize the literature on the course of pain in patients with knee osteoarthritis (OA), prognostic factors that predict deterioration of pain, the course of physical functioning, and prognostic factors that predict deterioration of physical functioning in persons with knee OA.

Methods. A search was conducted in PubMed, CINAHL, Embase, Psych-INFO, and SPORTDiscus up to January 2014. A meta-analysis and a qualitative data synthesis were performed.

Results. Of the 58 studies included, 39 were of high quality. High heterogeneity across studies ($I^2 >90\%$) and within study populations (reflected by large SDs of change scores) was found. Therefore, the course of pain and physical functioning was interpreted to be indistinct. We found strong evidence for a number of prognostic factors predicting deterioration in pain (e.g., higher knee pain at baseline, bilateral knee symptoms, and depressive symptoms). We also found strong evidence for a number of prognostic factors predicting deterioration in physical functioning (e.g., worsening in radiographic OA, worsening of knee pain, lower knee extension muscle strength, lower walking speed, and higher comorbidity count).

Conclusion. Because of high heterogeneity across studies and within study populations, no conclusions can be drawn with regard to the course of pain and physical functioning. These findings support current research efforts to define subgroups or phenotypes within knee OA populations. Strong evidence was found for knee characteristics, clinical factors, and psychosocial factors as prognostics of deterioration of pain and physical functioning.
Introduction

Osteoarthritis (OA) of the knee is a major cause of joint pain and problems in daily functioning, such as difficulty with walking, climbing stairs, and sitting and rising from a chair. In Europe, OA is among the 10 most disabling conditions. The development of difficulties in performing daily activities is more progressive in persons with OA than in persons without this disease. Persons with OA at middle age are more likely to develop persistent problems in daily functioning during the following 10 years.

The natural course of pain and physical functioning in OA of the knee is highly individual and variable. Some patients have been found to remain stable, while others will worsen or even improve. Because of this variability, identification of risk factors for functional decline is important. Knowledge of risk factors can be used to inform patients of the likely course of their condition and to adapt treatment according to the prognosis.

In a previous systematic review by van Dijk et al., the course of pain and physical functioning in knee OA during the first 3 years of follow up was found to be variable between studies; limited evidence was found for worsening of pain and physical functioning after 3 years of followup. A number of prognostic factors were identified: increased laxity, proprioceptive inaccuracy, age, a higher body mass index (BMI), knee pain intensity, and increased knee pain were found to predict a deterioration in physical functioning. However, the evidence for these conclusions was provided by only 1 high-quality cohort study with a follow up of 3 years. No evidence was provided for predictors of deterioration in pain.

Since the previous systematic review, published in 2006, quite a number of longitudinal studies have been published on the course and prognosis of pain and physical functioning in persons with knee OA. The purpose of the present review is 4-fold. We systematically summarize the literature on the course of pain in patients with knee OA, prognostic factors that predict deterioration of pain, the course of physical functioning, and prognostic factors that predict deterioration of physical functioning in persons with knee OA.

Materials and Methods

A protocol for conducting this review was developed with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The literature was systematically searched from inception up to January 7, 2014, using the following databases: PubMed, CINAHL, Embase, Psych-INFO, and SPORTDiscus. The search strategy was formulated in PubMed and, after consultation with an experienced medical librarian, adapted for use in other databases. We also included hip OA patients in the search strategy, but due to the large number of studies (see Results), we only present
the results for knee OA in the present study. Details on the Medline search strategy are presented in Supplementary Table 1 (available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693/abstract). The reference lists of all retrieved prognostic studies were also searched.

Inclusion criteria for the present study were the following: 1) the study population consisted of patients with radiographically and/or clinically diagnosed knee OA as defined by the American College of Rheumatology criteria\textsuperscript{10}, or according to Kellgren and Lawrence grades\textsuperscript{11}, or as diagnosed by a physician, or of patients who had knee pain for more than 1 month and were at high risk for developing knee OA (ages <35 years and/or with a high BMI and/or a history of knee injury)\textsuperscript{12}; 2) the study used at least 1 measure evaluating pain or physical functioning; 3) the study was a prospective cohort study (or was analyzed as a prospective cohort study when the data were obtained from a clinical trial); 4) the study addressed changes in pain or physical functioning outcome over a period of more than 6 months; 5) the study sample consisted of at least 100 participants; 6) separate analyses were presented for knee OA in cases where a knee and hip OA population was included in the study; 7) the study was reported in the format of a full-text article; and 8) the study was published in English, Dutch, or German.

Review articles were excluded. If studies on the same cohort presented different information, or reported on different prognostic factors, or presented results after different follow up periods, all studies were included (see Data analysis below). The selection was performed independently by 2 reviewers (MR and ML), using the criteria described above. If agreement was not achieved, a third reviewer (JH) was consulted, who made the final decision.

Data extraction
Two reviewers (MdR and MvdL) systematically extracted the following information from the included studies: authors, year of publication, setting, study population, study design, timing of outcome assessment, outcome measures, mean ± SD or the percentage of change in pain and physical functioning (pre and post values), and prognostic factors (univariate and multivariate associations, odds ratio [OR], risk ratio, and B coefficient) with outcome. The threshold level of significance of a predictor was set at \( P \leq 0.05 \). A nonsignificant association between a baseline characteristic and the outcome was regarded as an indication that this characteristic did not predict the outcome.

Methodologic quality
The methodologic quality of the selected articles was assessed independently by 2 reviewers (MdR and MvdL). A standard checklist of predefined criteria was used to assess the quality of the included studies, based on the Hayden criteria\textsuperscript{13} (available from the corresponding author). The Hayden criteria are appropriate to assess the methodologic quality of studies on prognosis and prognostic factors and pertain to 6 areas of potential bias related to 1) participation (e.g., adequacy of the description of the target population, sampling frame, recruitment, inclusion and exclusion criteria, baseline study sample, and participation