Comorbidity in knee osteoarthritis

Development and evaluation of tailored exercise therapy

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Colofon

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Voor mijn ouders

Contents

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[1]. The prevalence of OA is roughly estimated at about 150 million people worldwide, of which approximately 1.2 million in the Netherlands[2]. It is well known that the prevalence of OA increases with age[3]. 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%[2]. 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[4]. Overall, women have up to a 50% higher risk of OA than men[5,6], 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[7]. 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

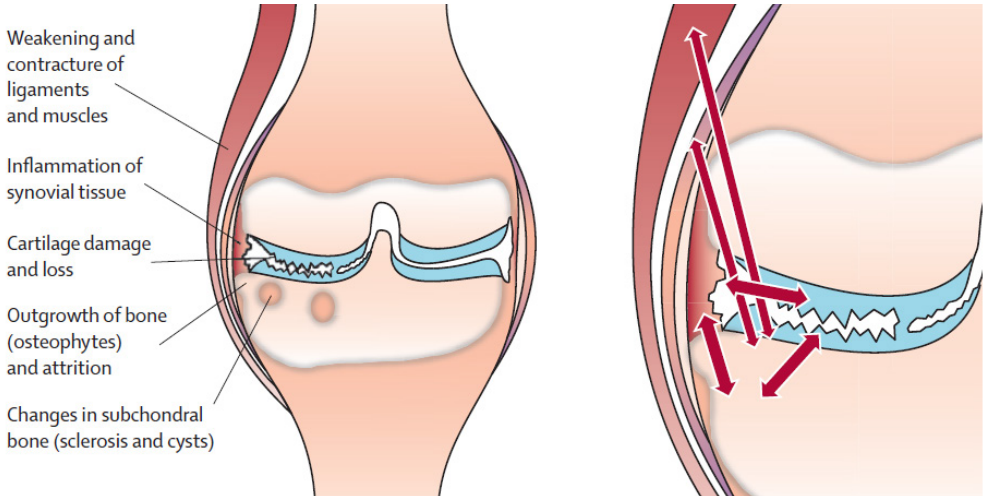

Figure 1. Schematic drawing of an osteoarthritic joint. Osteoarthritis is a disease of the whole joint, not just cartilage. The different tissues involved in clinical and structural changes of the disease are shown on the left (from Bijlsma et al.[1], printed with permission).

periarticular tissues like ligaments and muscles (see Figure 1)[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[9].

Pain is a predominant sign of OA for which patients seek care[10]. Other symptoms include joint stiffness, reduced range of joint motion, instability, synovitis and muscle weakness[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[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))[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[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[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[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[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.[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[19]. No evidence was found for predictors of deterioration of pain[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[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[20-23]. In these guidelines three treatment modalities are commonly distinguished: non-

Figure 2. Stepped care approach in the management of OA according to the BART strategy. (AJ Smink. Zorgwijzer Artrose©. Bone & Joint Decade NL 2010. Printed with permission).

pharmacological, pharmacological and surgical modalities. A stepped care approach is recommended in the management of patients with OA (see figure 2)[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[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[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[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)[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)[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[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[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[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'[34]. Studies have reported comorbidity rates of 68% to 85%[35-39]. A study of van Dijk et al.[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)[38]. 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)[40].

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[38]. In addition, the severity of these diseases is also associated with more pain[38]. 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[41]. Other studies have reported similar results[42-46]. 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[38]. 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[47,48].

In clinical practice, comorbidity is a frequent reason to exclude patients from exercise therapy[49]. 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[50,51]. 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[20-23]. 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[22]. 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[52-55], 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[56]. 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)[57,58]. 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.

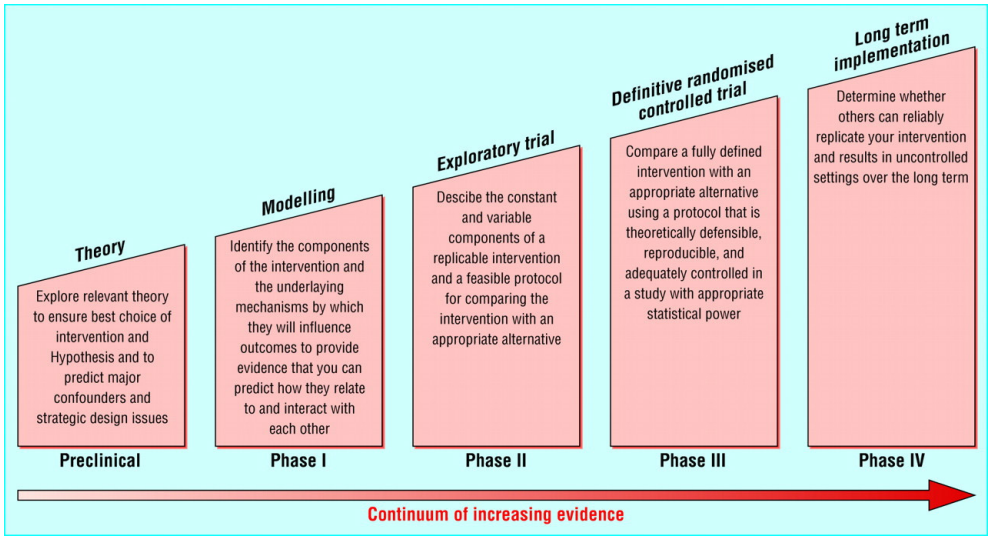

Figure 3. Sequential phases of developing randomized controlled trials of complex interventions. (Campbell M et al.57)

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1

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[1]. 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[2].

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[3–6]. 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.[7], 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[8]. No evidence was provided for predictors of deterioration in pain[7].

Since the previous systematic review, published in 2006[7], 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[9]. 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[10], or according to Kellgren and Lawrence grades[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)[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[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

rate), 2) study attrition (e.g., adequacy of the response rate, dropout rate, and loss to follow up), 3) measurement of prognostic factors (e.g., clarity of description of the independent variables measured, use of reliable measurement instruments, and proportion of the study sample that completed data for all independent variables), 4) outcome measurement (e.g., clarity of the definitions and descriptions of the variables measured and use of reliable and valid measurement instruments and cutoff points), 5) confounding, and 6) analysis (e.g., adequacy of the statistical analyses and presentation of the data, analyses, and results). We did not rate the risk of bias of confounding, because the aim of a prognostic model is to estimate the probability of a particular outcome and not to explore the causality of the association between a specific factor and the outcome. Thus we used a slightly modified Hayden score, by scoring 5 areas of potential bias, excluding confounding. The risk of bias of all 5 areas was rated as low, moderate, or high. As recommended by Hayden et al.[13], the studies were classified as high quality if in all 5 areas there was a low or a moderate risk of bias. Studies with a high risk for at least 1 area of bias were defined as low-quality studies. In case of disagreement between both reviewers, a third reviewer (JFMH) was consulted in order to achieve a final judgment.

Statistical analysis

Quantitative data analysis (meta-analyses) was performed if a minimum of 3 studies with eligible data were available. Data of the course were regarded as eligible for pooling if sufficient data (means ± SDs of the baseline and follow up measurement or change scores between baseline and follow up with SD) were presented in each individual study.

Table 1. Levels of evidence for predictors for pain and physical functioning outcome in persons with knee OA

Statistically significant	Level of evidence
Significant	
Strong	Consistent significant associations found in at least 2 high-quality studies
Moderate	Consistent significant associations found in 1 high-quality study and at least 1 low-quality study
Weak	Significant association found in 1 high-quality study or consistent significant associations found in at least 3 low-quality studies
Inconclusive	Significant association found in less than 3 low-quality studies
Inconsistent	Inconsistent significant findings irrespective of study quality
Nonsignificant	
Strong	Consistent non-significant associations found in at least 2 high-quality studies
Moderate	Consistent non-significant associations found in 1 high-quality study and at least in 1 low-quality study
Weak	Non-significant association found in 1 high-quality study or consistent non-significant associations found in at least 3 low-quality studies
Inconclusive	Non-significant associations found in less than 3 low-quality studies
Inconsistent	Inconsistent non-significant findings irrespective of study quality

Subsequently, these data were converted to standardized mean change (SMC) scores. Data of predictors were regarded as eligible for pooling if predictors were measured in a uniform way (i.e., using the same metric). To pool predictor effects for increase in pain and deterioration of physical functioning, estimates (and SEs) in individual studies were first converted to equal-effect sizes (and variance components). Log ORs were converted to log risk ratios using the prevalence, and regression coefficients were converted into standardized coefficients using the SD of the outcome and predictor variables. When univariable results were available, these were used for pooling; otherwise the multivariable estimates were used.

Pooling of effect sizes across studies was done using the SMC, log ORs, risk ratios, or standardized coefficients in a random effects model, weighted by the inverse variance[14]. Heterogeneity among studies was tested using the I^2 statistic[15]. The literature suggests 25% as low heterogeneity, 50% as moderate, and 75% as high[15].

In cases where studies were based on the same data (e.g., data from the progression cohort of the Osteoarthritis Initiative), we used results of the study of the highest quality and reported univariate instead of multivariate associations, with the longest follow up period, and with the largest sample size.

Sensitivity metaregression analyses of the course of pain and physical functioning were conducted using a random-effects model to examine the effects of follow up length (<3 years versus >3 years), study population (radiographically or clinically diagnosed knee OA versus knee pain population), and quality of studies (high versus moderate/low quality) on the outcome. Finally, data from included studies were entered into a funnel graph (a scatterplot of study effects against a measure of study sizes) to investigate the likelihood of publication bias[16]. In the absence of bias, the plot should resemble a symmetrical inverted funnel.

A qualitative data analysis (best-evidence synthesis) was performed for all studies reporting on predictors of deterioration in pain and physical functioning. Five levels of evidence (strong, moderate, weak, inconclusive, and inconsistent) were defined to summarize the available evidence for the course and the predictive value of identified predictors[17] (Table 1). In order to establish the level of evidence, we took into account the number of studies, the methodologic quality of the studies, and the consistency of a predictor for the outcome. Findings were deemed to be consistent if, in more than 75% of the studies reporting on a predictor, the direction of the association was the same[18]. In describing the results, a distinction was made between self-reported and performance-based outcome measurements.

Results

The combined knee and hip OA literature search resulted in a total of 16,066 hits (Figure 1). After duplicate removal, 9,702 hits were screened on title and abstract. This screening resulted in 209 full-text articles that were studied for eligibility, and 62 articles were considered for inclusion, of which 58 were included in the present study on knee OA.

Study characteristics

Fifty-seven of the 58 included studies were prospective cohort studies, and 1 study was a clinical trial that was analyzed as prospective cohort study[19]. Participants were recruited from community settings, general practices, rheumatology clinics, and orthopedic clinics. The mean follow up period ranged from 0.5 to 8 years, of which 12 studies had a follow up duration longer than 3 years. Twenty-seven studies included patients with radiographically and/or clinically diagnosed knee OA[8,19–44], and 31 studies included patients who were at high risk of developing knee OA[4–6,12,45–71]. Thirty-four studies reported results on pain[5,12,19–22,24–26,29–33,36,38,43–47,50–53,55–58,62,63,65,66,71], and 45 studies reported results on physical functioning[4–6,8,12,19,20,22,23,25,27–31,33–42,44,45,48–50,52,54–56,58–61,64–70]. (For details of the included studies, see Supplementary Table 2, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693/abstract).

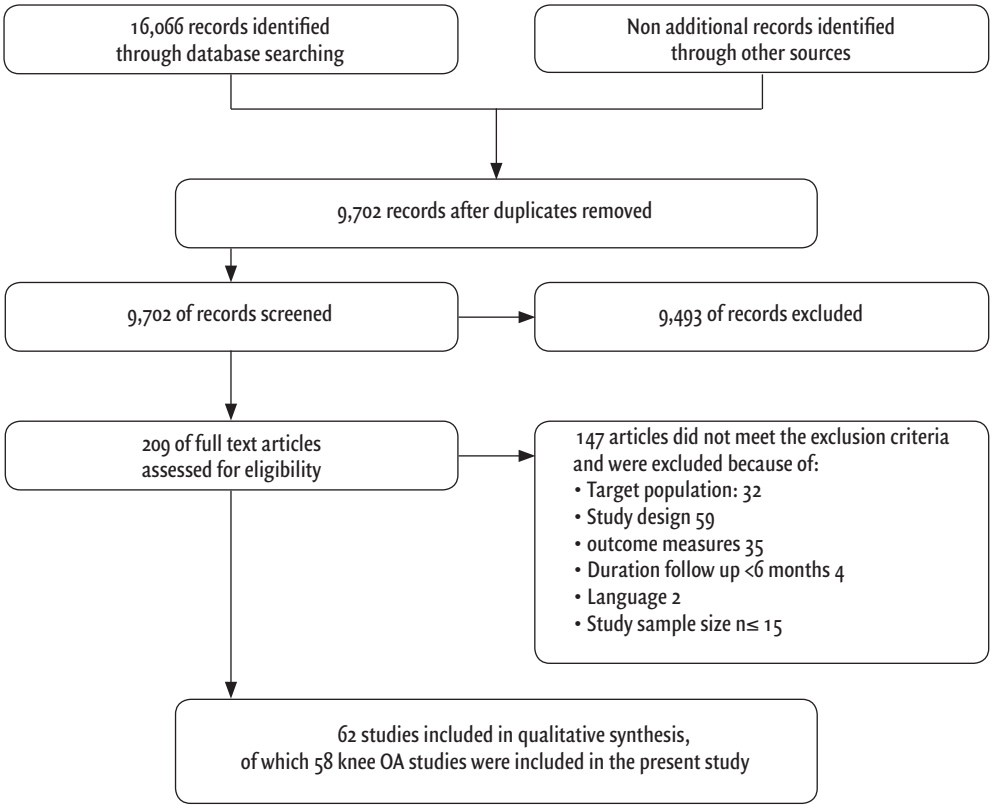

Figure 1. Screening for eligibility. OA = osteoarthritis

Methodologic quality scores

Overall agreement on methodologic quality scores between reviewers was 87.4%, while discussion was necessary in 12.6% of the cases to reach consensus. In 2 of 58 cases, the third reviewer made the final decision. Thirty-nine studies were of high quality (see Supplementary Table 3, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693/abstract).

Course of knee pain

Twenty-one studies reported on the course of pain[5,12,20,24,25,29,31,36,38,43–45,47,51,52,55,56,58,63,65,66]. Because of overlapping data from cohorts and inappropriateness of reported data, only 9 studies were included in the meta-analysis on the course of pain[12,25,31,36,38,44,47,52,58] (Figure 2). There was evidence of high statistical heterogeneity across studies (I^2 = 90.47%, P < 0.01). Sensitivity analysis showed that the course of OA did not depend on the effects of follow up length (<3 years versus >3 years), study population (radiographically or clinically diagnosed knee OA versus knee-pain population), or quality of studies (high versus moderate/low quality) (data not shown). Furthermore, large SDs of change scores were seen within studies. For example in the study of Riddle and Dumenci[38], the mean change ± SD of knee pain was 4.3 ± 16.59. If one neglects the heterogeneity, the results

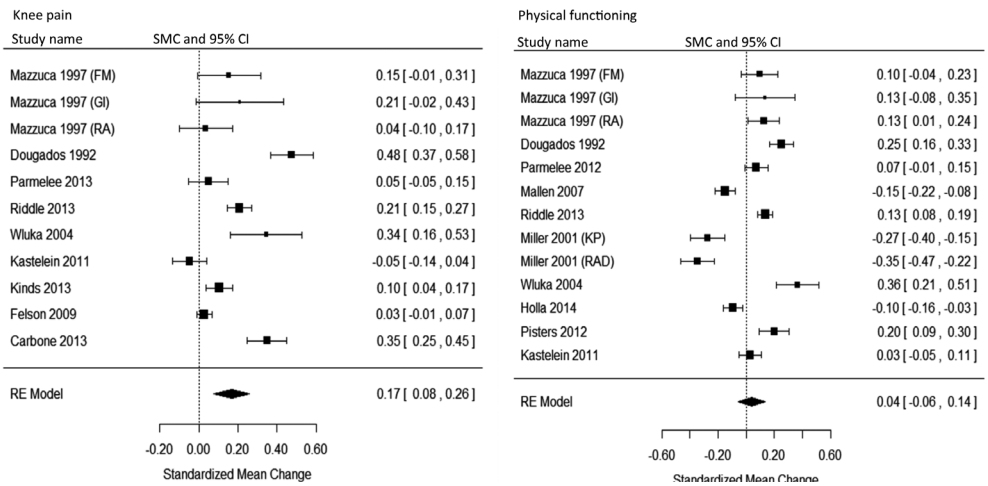

Figure 2. Standardized mean change (SMC) of the overall course of knee pain and physical functioning in patients with knee osteoarthritis. A positive mean change score indicates improvement in pain or physical functioning and a negative mean change score indicates deterioration in pain or physical functioning. Data from subgroup populations within a single study. 95% CI = 95% confidence interval; FM = referred from family medicine specialist; GI = referred from general internist; RA = referred from rheumatologist; KP = knee pain population; RAD = radiologic knee osteoarthritis; RE = random effects.

suggest a small, statistically significant improvement in pain over time (SMC = 0.17 [95% confidence interval (95% CI) 0.08, 0.26]). Egger's test provided evidence for no significant publication bias in the course of pain (data not shown).

Prognostic factors of deterioration in knee pain

Twenty-eight studies assessed a total of 80 prognostic factors of deterioration in pain[5,19–22,25,26,29–33,36,37,39,43–46,52,53,55,57,58,62,63,65,71]. A meta-analysis could be performed for only 2 prognostic factors (higher knee pain intensity at baseline and female sex). Of 6 studies evaluating baseline pain as a prognostic factor[19,33,37,46,58,63], 3 studies could be included in the meta-analysis[19,33,37]. The results indicate that a higher level of knee pain at baseline

Table 2. Summary of qualitative data analysis: studies describing prognostic factors of deterioration in pain in knee osteoarthritis for which strong evidence was found

Deterioration of knee pain predictors	Association*	Reference	Study quality
Predictors			
Clinical factors			
Higher knee pain intensity	Univariate	Blagojevic 2008[46]	High
	Univariate	Peat 2009[63]	Low
	Multivariate (?)	Kinds 2013[58]	High
	Multivariate (9)	Oak 2013[33]	High
	Multivariate (5)	Riddle 2013[37]	Low
	Multivariate (4)	Riddle 2013[38]	High
	Multivariate (5)	Steultjens 2001[19]	High
Bilateral knee symptoms	Univariate	Blagojevic 2008[46]	High
	Univariate	Jinks 2008[57]	High
Psycho social factors			
More depressive symptoms	Univariate	Blagojevic 2008[46]	High
	Univariate	Jinks 2008[57]	High
	Univariate, mulitvariate	Peat 2009[63]	Low
	Univariate, mulitvariate (15)	Riddle 2011[65]	High
	Multivariate (10)†	Parmelee 2013[36]	Low
Nonpredictors of deterioration knee pain			
Demographics			
Sex	Univariate†	Blagojevic 2008[46]	High
	Univariate†	Jinks 2008[57]	High
	Multivariate (?)†	Kinds 2013[58]	High
	Multivariate (?)†	Kinds 2013[58]	High
	Multivariate (4)†	Miranda 2002[62]	Low
	Multivariate (9)†	Oak 2013[33]	High
	Multivariate (10)†	Parmelee 2013[36]	Low
	Multivariate (5)†	Riddle 2013[37]	Low
	Multivariate (5)†	Steultjens 2001[19]	High

* Number of variables in multivariate model shown in parentheses. (?) = unkown.

† Nonsignificant

is a prognostic factor for higher levels of pain in the future (B = -0.48 [95% CI -0.52, -0.44]). Heterogeneity across studies was low to moderate (I^2 = 29.88%, P = 0.24) (see Supplementary Figure 1, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi /10.1002/acr.22693/abstract). Of 8 studies evaluating sex as a prognostic factor[19,33,36,38,46,57,58,62], 3 studies could be included in the meta-analysis[46,58,62]. The results indicate that female sex is a prognostic factor for higher levels of pain in the future (OR 0.76 [95% CI 0.63, 0.92]). Heterogeneity across studies was low (I^2 = 0.0%, P = 0.38) (Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693-/abstract).

In the qualitative data synthesis, strong evidence was found for the following prognostic factors as predictors for deterioration of pain: higher knee pain at baseline, presence of bilateral knee symptoms, and more depressive symptoms (Table 2). Sex was found to be a nonpredictor of deterioration of pain (strong evidence). For other variables, weak, inconclusive, or inconsistent evidence was found (see Supplementary Table 4, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693/abstract).

Course of physical functioning

Thirty-one studies reported on the course of self-reported physical functioning [4–6,8,12,20,25,27,28,31,35, 36,38,41,44,45,48–50,54–56,59,60,61,64–66,68–70]. Because of overlapping data from cohorts and inappropriateness of reported data, only 10 studies were included in the meta-analysis of the course of physical functioning[4,12,25,31,35,36,38,44,59,61] (Figure 2). There was evidence of high statistical heterogeneity across studies (I^2 = 92.93%, P < 0.01). Sensitivity analysis showed that the course of OA did not depend on the effects of follow up length (<3 years versus >3 years), study population (radiographically or clinically diagnosed knee OA versus knee pain population), or quality of studies (high versus moderate/low quality) (data not shown). Large standard deviations of change scores were seen within studies. For example, in the study of Holla et al.[54], the mean ± SD change of knee pain was -0.7 ± 9.8[54]. If one neglects the heterogeneity, the results suggest that the average course of physical functioning is stable over time (SMC = 0.04 [95% CI -0.06, 0.14]). Egger's test provided evidence for no significant publication bias in the course of physical functioning (data not shown).

Prognostic factors of deterioration of physical functioning

Thirty-eight studies assessed a total of 148 prognostic factors of deterioration in physical functioning[5,6,8,19,20,22,23,25,27–31,33–37,39–42,44,45,48,49,52,54,58–61,64,65,67–70]. A meta-analysis could be performed for only 2 prognostic factors. The results of the meta-analyses of 3 studies[54,67,69] indicate that the presence of bilateral knee pain is of predictive value for deterioration in physical functioning (risk ratio 0.79 [95% CI 0.63, 0.98]). Heterogeneity across studies was moderate (I^2 = 59.45%, P = 0.08) (see Supplementary Figure 2, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/ 10.1002/acr.22693/abstract). Of 5 studies evaluating knee pain intensity as a prognostic factor[8,

[35,48,54,59], 3 studies could be included in the meta-analysis[8,48,54]. The results suggest that higher knee pain at baseline is of prognostic value for deterioration in physical functioning (OR 0.90 [95% CI 0.83, 0.99]). Heterogeneity across studies was high (I^2 = 78.05%, P = 0.05) (Supplementary Figure 2, available at http://online-library.wiley.com/doi/10.1002/acr.22693/abstract).

In the qualitative data synthesis, strong evidence was found for the following prognostic factors for deterioration of self-reported physical functioning: worsening in radiographic OA, higher knee pain at baseline, worsening of knee pain, pain on patellofemoral joint compression, lower knee extension muscle strength, more disability, higher comorbidity count, poor general health, lower vitality, poor mental health, and more depressive symptoms. Lower walking speed at baseline and higher comorbidity count was found to be a prognostic factor for deterioration in physical functioning in performance-based outcome (strong evidence) (Table 3).

Sex, smoking, alcohol consumption, living with others, radiographic OA of the knee at baseline, decreased knee flexion, decreased hip internal/external rotation, and a specific coping strategy (retreating) were found to be non-predictors of self-reported physical functioning (strong evidence). For performance-based physical functioning, sex, radiographic OA of the knee at baseline, duration of knee symptoms, and specific coping strategies (reducing demands and transformation) were found to be nonpredictors of physical functioning (strong evidence) (Table 3).

Discussion

The aim of the present study was to describe the course of pain and physical functioning in patients with knee OA, and to identify prognostic factors for the course of OA through a systematic review of the literature. Quantitative and qualitative data analyses were used to summarize the results. A summary of predictors and nonpredictors of deterioration in pain and physical functioning for which strong evidence was found is presented in Table 4.

Because of high heterogeneity across studies, the course of pain and physical functioning in knee OA was found to be indistinct. Sensitivity analysis showed that these findings did not depend on the effects of follow up length (<3 years versus >3 years), study population (radiographically or clinically diagnosed knee OA versus knee pain population), or quality of studies (high versus moderate/low quality). However, within study populations, high heterogeneity was also present. Looking closely at the data, large SDs of change scores were seen, indicating that there are considerable within-patient differences in the course of pain and physical functioning; some patients deteriorate, some patients remain stable, and others improve. Calculating an average score neglects these between-patient differences. Our results strongly support current attempts to identify subgroups or phenotypes within OA populations. For example, in a 5-year follow up study, Holla et al.[4] identified 3 subgroups with distinct trajectories of

Table 3. Summary of qualitative data analysis: studies describing prognostic factors of deterioration in physical functioning in knee osteoarthritis for which strong evidence was found

Deterioration in physical functioning predictors	Outcome measurement	Association*	Reference	Study quality
Predictors				
Knee characteristics				
Worsening of ROA of the knee	Self-reported	Univariate	Wluka 2004[44]	High
	Self-reported	Multivariate (?)†	Ledingham 1995[29]	Low
	Self-reported	Multivariate (8)	Wesseling 2015[5]	High
	Self-reported	Multivariate (7)	White 2010[68]	High
Higher knee pain intensity at baseline	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate, multivariate (?)	Mallen 2007[59]	High
	Self-reported	Univariate, multivariate (10)†	Sharma 2003[8]	High
	Self-reported	Multivariate (19)	Colbert 2012[48]	High
	Self-reported	Multivariate (6)	Pisters 2012[35]	High
Worsening of knee pain	Self-reported	Univariate, multivariate (4)	van Dijk 2010[41]	High
	Self-reported	Univariate, multivariate (10)	Sharma 2003[8]	High
Pain on patella-femoral joint compression	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate	Thomas 2008[67]	High
Lower knee extension muscle strength	Self-reported	Univariate, multivariate (4)	Miller 2001[61]	High
	Self-reported	Univariate	Thomas 2008[67]	High
	Self-reported	Univariate†	van Dijk 2010[41]	High
	Self-reported	Multivariate (6)	Amin 2009[22]	High
	Self-reported	Multivariate (19)	Colbert 2012[48]	High
	Self-reported	Multivariate (6)†	Pisters 2012[35]	High
	Self-reported	Multivariate (4)	Rejeski 2001[64]	Low
Clinical Factors				
Lower walking speed	Performance-based	Univariate, multivariate (3)	van Dijk 2010[41]	High
	Performance-based	Multivariate (9)	Oak 2013[33]	High
More disability	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate, multivariate (4)	van Dijk 2010[41]	High
	Self-reported	Multivariate (?)†	Kinds 2013[58]	High
	Self-reported	Multivariate (9)	Oak 2013[33]	High
	Self-reported	Multivariate (4)	Riddle 2013[37]	Low
Higher comorbidity count	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate	Mallen 2007[59]	High
	Self-reported	Univariate, multivariate (4)	van Dijk 2010[41]	High
	Self-reported	Multivariate (19)	Colbert 2012[48]	High
	Self-reported	Multivariate (10)	Parmelee 2013[36]	Low
	Self-reported	Multivariate (6)	Pisters 2012[35]	High
	Self-reported	Multivariate (5)	Riddle 2013[37]	Low
Higher comorbidity count	Performance-based	Univariate, multivariate (3)	Van Dijk 2010[41]	High
	Performance-based	Multivariate (19)	Colbert 2013[49]	High
	Performance-based	Multivariate (5)†	Pisters 2012[35]	High
Poor general health	Self-reported	Univariate, multivariate (10)	Holla 2010[54]	High
	Self-reported	Univariate	Mallen 2007[59]	High
Psycho social factors				
Lower vitality	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate, multivariate (5)	van Dijk 2011[42]	High
Poor mental health	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate, multivariate (15)	Riddle 2011[65]	High
	Self-reported	Univariate, multivariate (10)	Sharma 2003[8]	High
	Self-reported	Univariate	van Dijk 2011[42]	High
More depressive symptoms	Self-reported	Univariate	Mallen 2007[59]	High
	Self-reported	Univariate, multivariate (10)	Parmelee 2013[36]	Low
	Self-reported	Univariate, multivariate (15)	Riddle 2011[65]	High
	Self-reported	Multivariate (19)	Colbert 2012[48]	High
	Self-reported	Multivariate (5)	Riddle 2013[37]	High

Table 3. (cont'd)

Deterioration in physical functioning predictors	Outcome measurement	Association	Reference	Study quality
Nonpredictors Demographics				
Sex				
	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Mallen 2007[59]	High
	Self-reported	Univariate, multivariate (10)†	Parmelee 2013[36]	Low
	Self-reported	Univariate†	van Dijk 2010[41]	High
	Self-reported	Multivariate (19)†	Colbert 2012[48]	High
	Self-reported	Multivariate (?)†	Kinds 2013[58]	High
	Self-reported	Multivariate (9) †	Oak 2013[33]	High
	Self-reported	Multivariate (6) †	Pisters 2012[35]	High
	Self-reported	Multivariate (5)	Riddle 2013[37]	Low
	Performance-based	Univariate†	van Dijk 2010[41]	High
	Performance-based	Multivariate (19)	Colbert 2012[48]	High
	Performance-based	Multivariate (19)†	Colbert 2012[48]	High
	Performance-based	Multivariate (9)†	Oak 2013[33]	High
	Performance-based	Multivariate (5)†	Pisters 2012[35]	High
	Performance-based	Multivariate (5) †	Steultjens 2001[19]	High
Other patient characteristics				
Smoking				
	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Mallen 2007[59]	High
Alcohol consumption	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Mallen 2007[59]	High
	Self-reported	Multivariate (19)†	Colbert 2012[48]	High
Living with others	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	van Dijk 2011[42]	High
Characteristics of the knee				
Radiographic OA of the knee at baseline	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Miller 2001[61]	High
	Self-reported	Univariate	Thomas 2008[67]	High
	Self-reported	Univariate†	van Dijk 2010[41]	High
	Self-reported	Univariate, multivariate (9)†	White 2010[68]	High
Radiographic OA of the knee at baseline	Performance-based	Univariate†	Miller 2001[61]	High
	Performance-based	Univariate†	Miller 2001[61]	High
	Performance-based	Univariate†	van Dijk 2010[41]	High
	Performance-based	Multivariate (5)†	Steultjens 2001[19]	High
Range of knee flexion at baseline	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Thomas 2008[67]	High
	Self-reported	Univariate†	Van Dijk 2010[41]	High
	Self-reported	Multivariate (6)†	Pisters 2012[35]	High
Duration of knee symptoms	Performance-based	Multivariate (5)†	Pisters 2012[35]	High
	Performance-based	Multivariate (5)†	Steultjens 2001[19]	High
Decreased Range of motion internal/external rotation hip	Self-reported	Univariate†	van Dijk 2010[41]	High
	Self-reported	Multivariate (6)†	Pisters 2012[35]	High
	Self-reported	Univariate†	Thomas 2008[67]	High
Psycho social factors				
Retreating	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	van Dijk 2011[42]	High
Reducing demands	Performance-based	Univariate†	Steultjens 2001[19]	High
	Performance-based	Univariate†	van Dijk 2011[42]	High
Transformation	Performance-based	Univariate†	Steultjens 2001[19]	High
	Performance-based	Univariate†	van Dijk 2011[42]	High

* Number of variables in multivariate model shown in paratheses. (?) unknown.† Nonsignificant
For other variables, weak, inconclusive, or inconsistent evidence was found (see Supplementary Table 5, available on the Arthritis Care & Research website at http://onlinelibrary-.wiley.com/doi/10.1002/acr. 22693/abstract).

functioning, patients with a good, moderate, or poor outcome of physical functioning. Moreover, recently, 5 homogeneous clinical phenotypes were identified (minimal joint disease phenotype, strong muscle strength phenotype, severe radiographic OA phenotype, obese phenotype, and depressive mood phenotype), based on 4 clinical characteristics in knee OA patients[72]. Future research of subgroups or phenotypes has high potential to advance our understanding of the disease and specifically to target treatment to these specific subgroups.

We identified a number of prognostic factors that predict the course of pain among patients with knee OA. The presence of higher knee pain intensity at baseline predicts deterioration of pain (as shown in the quantitative analysis). In addition, we found

Table 4. Summary of predictors and nonpredictors for deterioration in pain and physical functioning: strong evidence found in the quality synthesis*

	Deterioration of knee pain	Deterioration in physical functioning
Predictor		
Higher knee pain intensity at baseline	Yes	Yes
Presence of bilateral knee symptoms	Yes	_
More depressive symptoms	Yes	Yes
Worsening of radiographic OA in the knee	-	Yes
Worsening of knee pain	-	Yes
Pain on patella-femoral joint compression	-	Yes
Lower knee extension strength	-	Yes
Lower walking speed	-	Yes
More disability	-	Yes
Higher comorbidity count	-	Yes
Poor general health	-	Yes
Lower vitality	-	Yes
Poor mental health	-	Yes
More depressive symptoms	-	Yes
Nonpredictor		
Sex	Yes	Yes
Radiographic OA in the knee at baseline	-	Yes
Duration of knee symptoms	-	Yes
Decreased knee flexion	-	Yes
Decreased hip internal/external rotation	-	Yes
Smoking	-	Yes
Alcohol consumption	-	Yes
Living with others	-	Yes
Coping strategies (retreating, reducing demands and transformation)	-	Yes

* For all other variables studied in this review, weak, inconclusive, or inconsistent evidence was found (see Supplementary Tables 4 and 5, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693 / abstract). OA = osteoarthritis

strong evidence that the presence of bilateral knee symptoms and depressive symptoms predict deterioration of pain (qualitative analysis). From quantitative analysis, female sex was found to be a predictor of deterioration of pain. Remarkably, when applying a qualitative evidence synthesis, evidence was found for female sex to be a nonpredictor. These opposite conclusions could be due to differences in the number of included studies in the quantitative analysis compared to the qualitative analysis. Only a limited number of studies investigating sex as a risk factor could be included in the meta-analysis, due to inappropriateness of reported data for pooling and a lack of sex- specific effect estimates (as sex was often used as an adjustment factor rather than as a risk factor).

For all other factors identified in our review, the evidence was found to be limited, inconsistent, or inconclusive. Unexpectedly, we found inconsistent evidence that BMI predicts deterioration of pain (4 of 6 studies reported a positive association between BMI and deterioration of pain, while 2 studies did not find an association). This inconsistency might be explained by differences in how BMI was categorized or analyzed between studies.

With respect to prognostic factors that predict the course of physical functioning, we found strong evidence that knee characteristics (worsening of radiographic OA, worsening of knee pain, pain on patellofemoral joint compression, lower knee extension strength), clinical variables (lower walking speed at baseline, more disability, higher comorbidity count, poor general health), and psychosocial factors (lower vitality, poor mental health, more depressive symptoms) all predict deterioration (qualitative analysis). For all other factors identified in our review, the evidence was found to be limited, inconsistent, or inconclusive. Remarkably, we found inconsistent evidence that age predicts deterioration in physical functioning. Despite the fact that 11 studies reported on the association between age and physical functioning, we could not pool these data to calculate a precise effect estimate for the association between age and physical functioning, since variations in measurement scale and statistical analysis existed.

In comparison to a previous review on this topic[7], a large number of high-quality studies were included (39 compared with 1 in the previous review). These studies provided strong evidence for a large number of predictors of deterioration in pain and physical functioning. Contrary to the previous review[7], we distinguished between self-reported and performance-based outcomes of physical functioning and we presented an overview of nonpredictors of deterioration of pain or physical functioning.

Some of the identified prognostic factors are modifiable and could therefore be targeted during treatment. For example, in case of muscle weakness of the lower extremity, the course of pain and physical functioning would improve with specific strengthening exercises[73]. Also, as depressive symptoms predict deterioration in pain and physical functioning, early identification and treatment of depressive symptoms may have a positive impact on the course of knee OA. Finally, because pain predicted deterioration of physical functioning, prescription of effective pain medication may be indicated[74].

Some methodologic issues should be considered. First, we included a high number of eligible studies. Due to pragmatic reasons, we decided to include only studies with a sample size of ≥100 participants. This size selection may have resulted in selection bias of included studies. Second, patients may have received effective treatment, which may be a source of variance in the course of pain and physical functioning. Insufficient information is provided in the included studies as to whether or not patients received treatment during the study period. Third, to our knowledge, this is the first meta-analysis (quantitative analysis) on the course and prognostic factors. Despite the high number of included studies (which could be included in the qualitative analysis), only a small number of studies could be included in the meta-analyses because different measurement scales and metrics were used to assess the outcome and predictor variables. More uniformity in the selection of potential predictor variables and in instruments to measure these variables will facilitate future meta-analyses, leading to stronger conclusions. Finally, we preferably used univariable estimates, due to the considerable diversity in statistical techniques and choice of covariates used in individual multivariate models. Where univariable effect estimates were not available, we used multivariable effect estimates, which may have influenced our results, because risk factors, if adjusted for potential confounders, have different effect estimates compared to the univariable effect estimates.

In 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 in pain and physical functioning. Treatment of modifiable factors such as knee pain, upper leg muscle strength, comorbidity, and depressive symptoms may reduce the risk of deterioration of knee pain and physical functioning.

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Chapter 3

Course and predictors of pain and physical functioning in patients with hip osteoarthritis: Systematic review and Meta-analysis

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Abstract

Objective. To systematically summarize the literature on: (i) the course of pain and physical functioning; and (ii) predictors of deterioration of pain and physical functioning in patients with osteoarthritis of the hip.

Methods. A literature search was conducted in PubMed, CINAHL, Embase, PsychINFO and SPORTDiscus up to July 2015. Meta-analyses and qualitative data syntheses were performed.

Results. Eleven of the 15 included studies were of high quality. With regard to the course of pain and physical functioning, high heterogeneity was found across studies (I^2 >71%) and within study populations (reflected by large standard deviations of change scores). Therefore, the course of pain and physical functioning was interpreted to be indistinct. Clinical characteristics (higher comorbidity count and presence of knee osteoarthritis), health behaviour factors (no supervised exercise and physical inactivity) and socio-demo- graphics (lower education) were found to predict deterioration of pain (weak evidence). Higher comorbidity count and lower vitality were found to predict deterioration of physical functioning (strong evidence). For several other predictive factors weak evidence was found (e.g., bilateral hip pain, increase in hip pain (change), bilateral knee pain, presence of knee osteoarthritis).

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. Several clinical characteristics, health behaviours and psychosocial factors prognosticate deterioration of pain and physical functioning. These findings may guide future research aimed at the identification of subgroups of patients with hip osteoarthritis.

Introduction

Pain and problems with daily functioning, such as walking, climbing stairs, sitting down and rising from a chair, are common in individuals with hip osteoarthritis (OA). The natural course of pain and physical functioning in OA is highly individual and variable; some patients remain stable, while others improve or gradually worsen[1,2]. Because of this variability, identification of predictors for deterioration in pain and physical functioning is important. Knowledge of predictors can be used to inform patients on the likely course of their condition and to adapt treatment according to the prognosis.

In a previous systematic review, published in 2006, 4 studies on the prognosis of pain and physical functioning in persons with OA of the hip were included[3]. Limited evidence (from 1 high-quality study) found that pain and physical functioning did not change from baseline to 3 years' follow-up, but deteriorated from baseline to 8 years' follow-up[4]. Due to a lack of high-quality studies, no predictive factors could be identified.

Since 2006 a number of longitudinal studies have been published on this topic. We systematically searched the literature and found no reviews on the course and prognosis of pain and physical functioning in persons with hip OA that were published since the previous systematic review in 2006[3]. Therefore, the aims of the present review were: (*i*) to systematically summarize the literature up to July 2015 on the course of pain and physical functioning in patients with OA of the hip; and (*ii*) to provide an overview of predictors of deterioration of pain and physical functioning in these patients.

Methods

Search methods for identification of studies

A protocol for conducting this review was developed with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[5] (protocol not published). The literature was systematically searched from inception up to 9 July 2015, using the following databases: PubMed, CINAHL, Embase, PsychINFO and SportDiscus. The search strategy was formulated in PubMed and, after consultation with an experienced medical librarian, adapted for use in other databases. The search terms were as follows: ((“Osteoarthritis, Hip”[Mesh] OR coxarthr*[tiab]) OR ((hip[tiab] OR hips[tiab] OR lower limb*[tiab] OR lower extremit*[tiab]) AND (osteoarthr*[tiab] OR degenerative arthr*[tiab] OR arthrosis[tiab] OR arthroses[tiab] OR arthralgi*[tiab]))) AND (“activity limitation*”[tiab] OR “functional status”[tiab] OR (activity[tiab] OR activities[tiab]) OR disabilit*[tiab] OR disabled[tiab] OR abilit*[tiab] OR limitation*[tiab] OR (function[tiab] OR functional[tiab] OR functioning[tiab] OR functions[tiab]) OR physical[tiab] OR physicalfitness[Mesh]

OR activities of daily living [Mesh] OR mobility limitations[Mesh] OR mobilit*[tiab] OR perform*[tiab] OR difficult*[tiab] OR pain[Mesh]) AND (cohort studies[Mesh] OR longitudinal studies[Mesh] OR prospective studies[Mesh] OR follow-up studies[Mesh] OR dis- ease progression[Mesh] OR follow-up[tiab] OR followup[tiab] OR prospective[tiab] OR cohort[tiab] OR progress*[tiab] OR prognos*[tiab] OR longitudinal[tiab] OR predict*[tiab] OR course[tiab] OR risk[tiab] OR determinant*[tiab]) Filters: Humans; Adult: 19+ years. The reference lists of all retrieved prognostic studies were also searched.

Criteria for considering studies for systematic review

Inclusion criteria for the present study were as follows: (*i*) the study population consisted of patients with: (a) radiographically and/or clinically diagnosed hip OA (as defined by the American College of Rheumatology (ACR) criteria[6], according to Kellgren & Lawrence (K&L) grades[7], or diagnosed by a physician; or (b) a high risk of having hip OA (i.e., having hip symptoms longer than 1 month)[8]; (*ii*) the study used at least 1 measure evaluating pain or physical functioning; (*iii*) the study addressed changes in pain or physical functioning over a period of 6 months or more; (*iv*) the study was a prospective cohort study (or analysed as a prospective cohort study when the data was obtained from a clinical trial); (*v*) separate analyses were presented for hip OA in case a mixed hip and knee OA population was included in the study; and (*vi*) the study was reported in the format of a full-text article. Review articles were excluded. If studies on the same cohort presented different information, or reported on different predictors, or presented results after different follow-up periods, all studies were included (see Methods: data analysis).

The studies were selected 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 (MR and ML) 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 and standard deviation (SD) or the percentage of change in pain and physical functioning (pre- and post- values), and predictive factors (univariate and multivariate associations (odds ratio (OR), relative risk (RR), beta coefficient)). The threshold level of significance of a predictor was set at $p \leq 0.05$. A non-significant association between a baseline characteristic and the outcome was regarded as an indication that this characteristic did not predict the outcome.

Methodological quality

The methodological quality of the selected studies was assessed in- dependently by 2 reviewers (MR and ML) using the Hayden criteria[9]. The Hayden criteria are appropriate to assess the methodological quality of studies on prognosis and predictive factors, and pertain to 6 areas of potential bias related to: (*i*) participation, (*ii*) study attrition, (*iii*) measurement of predictive factors, (*iv*) outcome measurement, (*v*) confounding,

and (*vi*) analysis. We did not rate the risk of bias of confounding, because the aim of a predictive model is to estimate the probability of a particular outcome and not to explore the causality of the association between a specific factor and the outcome. The risk of bias of all 5 areas was rated as low, moderate, or high. As recommended by Hayden et al.[9], the studies were classified as being of high quality if, in all 5 areas, there was a low or a moderate risk of bias. Studies with a high risk for at least one area of bias were defined as low-quality studies. In case of disagreement between both reviewers, a third reviewer (JH) was consulted in order to achieve a final judgement.

Data analysis

A *quantitative data analysis* (meta-analysis) was planned when homogeneity in study design, population, measured determinants and assessed outcome was assumed. Data of the course or predictors were regarded eligible for pooling if a minimum of 3 studies with eligible data were available and sufficient data (means and SDs of the baseline and follow-up measurement or change scores between baseline and follow-up with SD, or OR, RR or regression coefficients, respectively) were presented in each individual study. In case of predictors, when univariable results were available, these were used for pooling: otherwise the multivariable estimates were used.

Pooling of effect sizes across studies was done using the standardized mean change (SMC), log ORs, RRs, or standardized coefficients in a random effects model, weighted by the inverse variance[10]. The results were presented in a forest plot. Heterogeneity among studies was tested using the I^2 statistic[11]. The literature suggests 25% as low heterogeneity, 50% as moderate, and 75% as high[11].

In case of sufficient number of studies a sensitivity meta-regression analysis of the course of pain and physical functioning were planned using a random-effects model to examine the effects of: (*i*) follow-up length (shorter than 3 years vs longer than 3 years), (*ii*) study population (radiographically or clinically diagnosed hip OA vs hip pain population), and (*iii*) quality of studies (high vs moderate/low quality) on the outcome. Finally, data from included studies were entered into a funnel graph (a scatter-plot of study effects against a measure of study sizes) in order to investigate the likelihood of publication bias[12].

In case of absence of homogeneity or insufficient number of studies, a *qualitative data analysis* (best-evidence synthesis) was planned to summarize the data. Five levels of evidence (strong, moderate, weak, inconclusive, and inconsistent) were defined to summarize the available evidence for the predictive value of identified predictors[13,14] (Table I). In order to establish levels of evidence, the number of studies, the methodological quality of the studies, and the consistency of a predictor for the outcome were taken into account. Findings were deemed to be consistent if, in more than 75% of the studies reporting on a predictor, the direction of the association was the same[15]. In cases where studies were based on the same database we used the results of the study: (*i*) with the highest quality rating, (*ii*) that reported univariate instead of multivariate associations, or (*iii*) with the longest follow-up period. In describing the results, a distinction was made between self-report and performance-based outcome measurements.

Results

The literature search resulted in a total number of 8,748 hits. After duplicate removal, 5,072 hits were screened on title and abstract. This resulted in 56 full-text articles that were studied for eligibility, of which 15 articles were included in the present study (see Fig. 1).

Study characteristics

Thirteen[2,4,16–26] out of the 15 studies included patients diagnosed according to the ACR criteria or K&L grade (of which 2 studies included patients with severe hip OA)[21,22]. Two studies included patients who were at risk for having hip OA[8,27]. There was considerable variation across studies regarding sample size and length of follow-up. The sample size ranged from 20 to 745 subjects. The mean follow-up ranged from 0.5 to 8 years, of which 4 studies had a follow-up longer than 3 years[4,16,19,23]. All 15 included studies were analysed as prospective cohort studies. A detailed description of the included studies is presented in Table SI[1] available at: https://jrm/content/additional_content/2147SITab.pdf.

Methodological quality

Different categories of bias were rated. Overall agreement on methodological quality scores between reviewers was 93.7%. The disagreement mainly concerned the rating of participation and attrition of patients. No consultation of a third reviewer was necessary

Table 1. Levels of evidence for predictors of pain and physical functioning in persons with hip osteoarthritis (OA)

	Level of evidence
Statistically significant associations	
Strong	Consistent significant associations found in at least 2 high-quality studies
Moderate	Consistent significant associations found in 1 high-quality study and at least 1 low-quality study
Weak	Significant association found in 1 high-quality study or consistent significant associations found in at least 3 low-quality studies
Inconclusive	Significant association found in less than 3 low-quality studies
Inconsistent	Inconsistent significant findings irrespective of study quality
Statistically non-significant associations	
Strong	Consistent non-significant associations found in at least 2 high-quality studies
Moderate	Consistent non-significant associations found in 1 high-quality study and at least in 1 low-quality study
Weak	Non-significant association found in 1 high-quality study or consistent non-significant associations found in at least 3 low-quality studies
Inconclusive	Non-significant associations found in less than 3 low-quality studies
Inconsistent	Inconsistent non-significant findings irrespective of study quality

to resolve disagreement. Eleven studies were considered to be of high quality[2, 8, 16–18, 21, 23–27], and 4 were of low quality[4, 19, 20, 22] (see Table SII[1], available at https://jrm/ content/ additional_content/2147SIITab.pdf).

Course of hip pain and physical functioning

Four[17,21,22,27] out 6 studies[4,17,20–22,27] reporting on the course of hip pain were included in the meta-analysis (of which 3 were high-quality studies). There was evidence of high statistical heterogeneity across studies (I^2 = 71.16%, p = 0.02) (see Fig. 2). Also large SDs of change scores were seen within studies. For example, in the study of Botha-Scheepers et al., the mean change and SD of hip pain was 0.38 (SD 2.3)[27]. Six[8,17,19,21–23] out of 7 studies reporting on the course of physical functioning were included in the meta-analysis[8,17,19,21–23,25] (of which 4 were high-quality studies). Again, we found evidence of high statistical heterogeneity across studies (I^2 = 96.98%, p < 0.01) (see Fig. 2) and large SDs of change scores within studies[8]. Neglecting the heterogeneity, the results

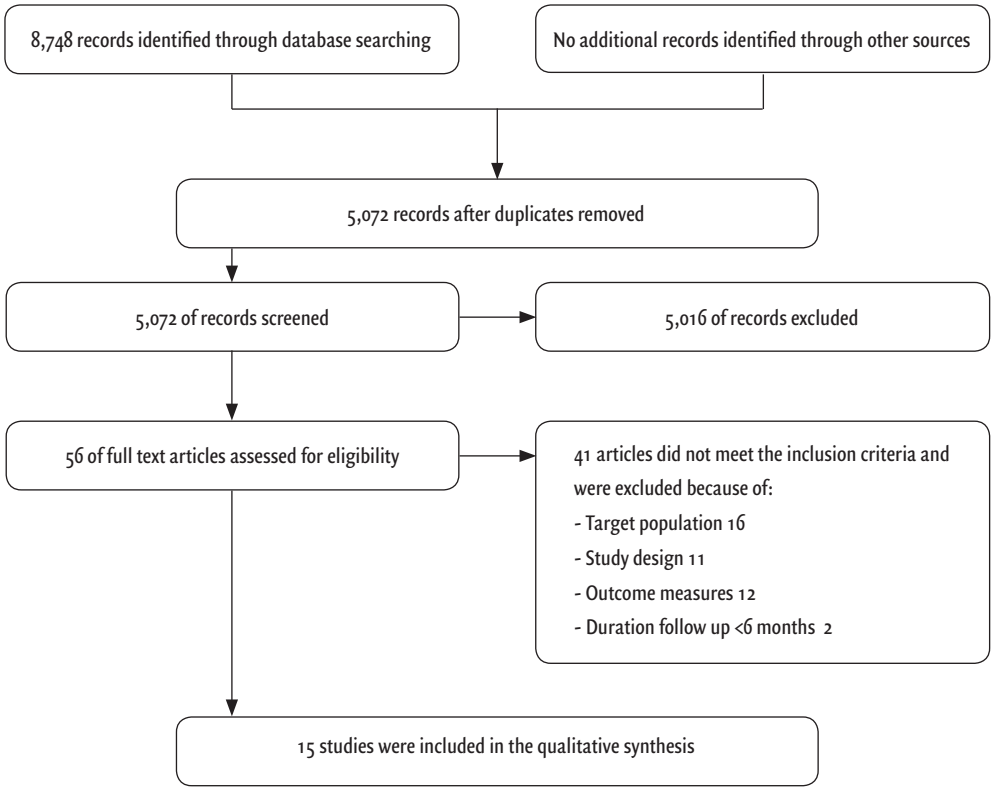

Figure 1. Screening for eligibility of studies

would suggest that the mean course of pain and physical functioning is stable over time: for hip pain SMC = 0.06; 95% confidence interval (95% CI) –0.13 to 0.26, for physical functioning SMC = –0.11; 95% CI –0.38 to 0.15 (see Fig. 2).

Sensitivity analyses on the course of hip pain and physical functioning

With regard to the course of pain, it was not possible to perform a meta-regression for sensitivity analysis due to a low number of available studies. With regard to the course of physical functioning, no factors (effects of follow-up length, study quality) were identified in the meta-regression that could account for the study heterogeneity. Sensitivity analysis based on study population (radiographically or clinically diagnosed hip OA vs hip pain population) was not possible because only one study included patients with hip pain.

Egger's test provided evidence for no publication bias in the course of physical functioning (data not shown).

Predictors for deterioration of pain

Two high-quality studies[18,24] assessed a total of 15 predictive factors for deterioration of hip pain. We considered a meta-analysis of predictors of deterioration of pain inappropriate because the predictors under study were measured in fewer than 3 studies, or there were differences in definitions of determinants under study or effect estimates, which hamper calculation of pooled effect estimates. We therefore performed a qualitative data synthesis (best-evidence synthesis). Weak evidence was found for the

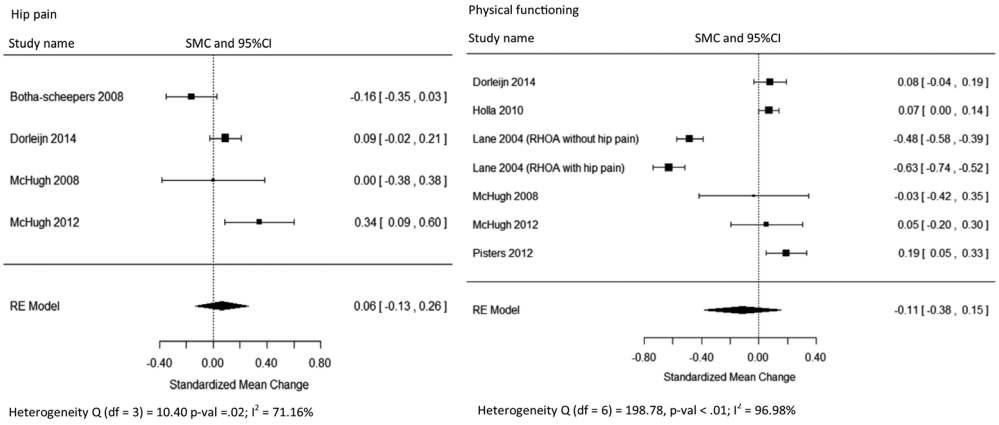

Figure 2. Standardized mean change (SMC) of the overall course of hip pain and physical functioning in patients with hip OA. A positive mean change score indicates improvement in pain or physical functioning and a negative mean change score indicates deterioration in pain or physical functioning.

following factors as predictors for deterioration of hip pain: additional knee OA, higher comorbidity count, no supervised exercise, lower level of physical activity and lower level of education (see Table 2).

Strong evidence was found that deterioration of pain is not predicted by sex, age, body mass index (BMI), duration of hip symptoms and radiological OA (K&L grade). For other variables weak or inconsistent evidence for being not predictive was found (Table SIII[1], available at: https: //jrm/content/additional_content/2147SIIITab.pdf).

Predictors for deterioration of physical functioning

Eight studies (of which 1 was a low-quality study) assessed a total of 62 predictors for deterioration of physical functioning[8,16,18,19,23–26]. For the same reasons as above we considered a meta-analysis of predictors of deterioration of physical functioning inappropriate. We therefore performed a qualitative data synthesis (best-evidence synthesis). Strong evidence was found that self-reported deterioration of physical functioning is predicted by higher comorbidity count and low vitality. Furthermore, weak evidence was found that self-reported deterioration of physical functioning is predicted by having moderate or severe cardiac disease or eye-ear-nose throat disease, poor general health, the presence of bilateral hip pain, increase in hip pain (change), bilateral knee pain, additional knee OA, morning stiffness of the hip or knee, decrease in external hip rotation (ROM) (change), reduced knee extension (ROM) (at baseline), decrease in knee extension (ROM) (change), no supervised exercise, a lower level of physical activity, more avoidance of activities and having high bodily pain. For performance-based physical functioning, weak evidence for being predictive was found for more disability at baseline, lower walking speed, higher comorbidity count and having moderate or severe cardiac

Table 2. Results of the qualitative data analysis on studies describing predictors for deterioration of pain in patients with hip osteoarthritis (18)

Predictors for deterioration of hip pain	Level of evidence	Uni- and/or multivariable association (number of variables in multivariable model)
Other patient characteristics		
Lower level of education	Weak	Multi (11)
Clinical factors		
Higher comorbidity count	Weak	Multi (11)
Presence of additional knee osteoarthritis	Weak	Multi (11)
Health behavior factors		
No supervised exercise	Weak	Multi (11)
Lower level of physical activity	Weak	Multi (11)

Uni: univariable association; multivariable association. See Table SIII[1] for variables not predicting pain

disease or eye-ear-nose throat disease and reduced hip abduction muscle strength (Table 3). For other variables inconsistent evidence was found (see Table SIV[1], available at: https: //jrm/content/ additional_content/2147SIVTab.pdf).

Strong evidence for being not predictive for self-report physical functioning was found for age, sex, household composition > 1, employment status, duration of complaints, radiological hip OA (K&L grade), internal hip rotation (ROM), social support, mental health and specific coping strategies (distraction, retreating and worrying). For performance-based physical functioning, strong evidence for being not predictive was found for sex, BMI, duration of complaints, radiological hip OA (K&L grade), specific coping strategies (resting, transformation, reducing demands). For other variables weak or inconsistent evidence for being not predictive was found (see Table SIV[1], available at: https: //jrm/content/additional_content/2147SIVTab.pdf).

Discussion

The aim of this study was to describe the course of pain and physical functioning and to identify predictors of the course of hip OA through a systematic review of the literature. In all, 15 studies were included in this review, of which 11 were of high quality.

With regard to the course of pain and physical functioning we conclude that the course was found to be indistinct over time, because of high heterogeneity across studies and within study populations. Heterogeneity was not reduced by taking into account methodological issues, such as length of follow-up or quality of the study. Furthermore, it was found that individual patients show considerable variation in the course of physical functioning; some patients improve, while others remain stable or deteriorate. A statement on the mean course neglects these between-patient differences. Interestingly, similar conclusions were drawn in our study in patients with knee OA[28]. It has been hypothesized that the OA population actually consists of homogeneous subgroups or phenotypes[29]. This hypothesis is supported by Verkleij et al.[2], who identified subgroups based on the 2-year course of pain in patients with clinically and radiographically determined hip OA. They identified 5 subgroups consisting of patients with mild pain, moderate pain, continuous pain, regularly progressing pain, or highly progressing pain[2]. Our findings underline the importance of identifying predictors for deterioration of pain and physical functioning, and support the need for research aimed at the identification of subgroups or phenotypes in patients with hip OA.

Our results indicate that deterioration of hip pain is predicted by clinical characteristics (higher comorbidity count, additional presence of knee OA), health behaviour factors (no supervised exercise and a lower level of physical activity) and socio- demographics (lower level of education) (weak evidence). However, as these conclusions are derived from only 1 high-quality study they must be interpreted with caution. Deterioration in physical functioning has been investigated in 8 studies (of which 7 were high-quality studies) and

Table 3. Qualitative data analysis of studies describing predictors for deterioration of physical functioning in patients with hip osteoarthritis

Predictors for deterioration of physical functioning	Outcome measurement	Level of evidence	Uni- and/or multivariable association (number of variables in multivariable model)	Reference
Socio-demographics				
Older age	Performance-based outcome	Inconsistent	uni, multi (5) uni, multi (?) multi (5) ns	Pisters 2012[23] van Dijk 2010[25] Steultjens 2001[24]
Lower level education	Self-reported outcome	Inconsistent	uni ns multi (11) multi (6)	Holla 2010[8] Juhakoski 2013[18] Pisters 2012[23]
Clinical characteristics-other				
More disability	Self-reported outcome	Inconsistent	uni, multi (6) ns uni, multi (6)	Holla 2010[8] van Dijk 2010[25]
More disability	Performance-based outcome	Weak	multi (5)	Steultjens 2001[24]
BMI	Self-reported outcome	Inconsistent	uni uni ns multi (11) ns	Holla 2010[8] Pisters 2012[23] Juhakoski 2013[18]
High comorbidity count	Self-reported outcome	Strong	uni, multi (6) uni, multi (6) multi (11) multi (11) ns multi (6)	Holla 2010[8] van Dijk 2010[25] Juhakoski 2013[18] Juhakoski 2013[18] Pisters 2012[23]
High comorbidity count	Performance-based outcome	Weak	uni, multi (6) multi (5)	van Dijk 2010[25] Pisters 2012[23]
Having moderate or severe cardiac disease and eye-ear nose throat disease	Self-reported outcome/ performance-based	Weak	uni, multi (?)	van Dijk 2010[25]
Presence of CIRS 1, 6 (CIRS≥2)	Self-reported outcome	Weak	uni	van Dijk 2010[25]
Presence of CIRS 1,4,5,12,13 (CIRS≥2)	Performance-based outcome	Weak	Uni	van Dijk 2010[25]
Poor general health perception	Self-reported outcome	Weak	uni, multi (7)	Holla 2010[8]
Lower walking speed	Performance-based outcome	Weak	uni, multi (4)	van Dijk 2010[25]
Clinical characteristics-hip				
Increase in hip pain (change from to-t1)	Self-reported outcome	Weak	uni, multi (6)	van Dijk 2010[25]
Higher hip pain at baseline (VAS score)	Self-reported outcome	Inconsistent	uni ns uni ns multi (8) multi (6)	Holla 2010[8] van Dijk 2010[25] Lane 2004[19] Pisters 2012[23]

Table 3 (cont'd)

Predictors for deterioration of physical functioning	Outcome measurement	Level of evidence	Uni- and/or multivariable association (number of variables in multivariable model)	Reference
Morning stiffness hip ≤60 min	Self-reported outcome	Weak	uni	Holla 2010[8]
Bilateral hip pain with equal symptoms vs no pain	Self-reported outcome	Weak	uni, multi (6)	Holla 2010[8]
Decrease in hip external rotation (ROM) (change from to-t1)	Self-reported outcome	Weak	multi (6)	Pisters 2012[23]
Reduced muscle strength hip abduction	Performance based	Weak	uni, multi (3)	Pisters 2014[16]
Reduced hip flexion (ROM) at baseline	Self-reported outcome	Inconsistent	uni, multi (6)	Holla 2010[8]
			multi (6) ns	Pisters 2012[23]
Clinical characteristics-knee				
Presence of additional knee osteoarthritis	Self-reported outcome	Weak	multi (11)	Juhakoski 2013[18]
Bilateral knee pain with index knee vs no pain	Self-reported outcome	Weak	uni	Holla 2010[8]
Morning stiffness knee <30 min	Self-reported outcome	Weak	uni, multi (6)	Holla 2010[8]
Reduced knee extension (ROM) at baseline	Self-reported outcome	Weak	uni	van Dijk 2010[25]
			multi (6) ns	Pisters 2012[23]
Decrease in knee extension (ROM) (change from to-t1)	Self-reported outcome	Weak	uni	van Dijk 2010[25]
Health behavior factors				
No supervised exercise	Self-reported outcome	Weak	multi (11)	Juhakoski 2013[18]
Lower level of physical activity	Self-reported outcome	Weak	multi (11)	Juhakoski 2013[18]
Psycho-social factors				
Poorer cognitive functioning	Self-reported outcome	Inconsistent	uni, multi (6)	van Dijk 2010[25]
			multi (6) ns	Pisters 2012[23]
High bodily pain	Self-reported outcome	Weak	uni, multi (6)	Holla 2010[8]
Lower vitality (SF 36)	Self-reported outcome	Strong	uni	Holla 2010[8]
			uni	van Dijk 2011[26]
More avoidance of activity	Self-reported outcome	Weak	multi (6)	Pisters 2012[23]
			uni, multi (3)	Pisters 2014[16]
More avoidance of activity	Performance-based outcome	Inconsistent	uni ns	Steultjens 2001[24]
			multi (5)	Pisters 2012[23]
			uni, multi (3)	Pisters 2014[16]
Resting	Self-reported outcome	Inconsistent	uni	Holla 2010[8]
			uni ns	van Dijk 2011[26]
Transformation	Self-reported outcome	Inconsistent	uni	Holla 2010[8]
			uni ns	van Dijk 2011[26]

SF-36: Short-Form 36 Health Survey; VAS: visual analogue scale; BMI: Body Mass Index;. CIRS: Cumulative Illness Rating Scale; (?): Not known; ns: not significant; ROM: Range Of Motion; to-t1: change from baseline to follow up; Uni: univariable association; Multi: multivariable association. Predictor in bold represents strong level of evidence. See Table SIV for variables not predicting physical functioning.

is predicted by higher comorbidity count and lower vitality (strong evidence). We found weak evidence for prediction of deterioration in physical functioning for certain clinical characteristics of the hip (e.g., presence of bilateral hip pain, reduced hip flexion), clinical characteristics of the knee (e.g., bilateral knee pain, decrease in knee extension (ROM)), health behaviour factors (e.g., no supervised exercise), and psycho- social factors (i.e., more avoidance of activities). As consistent with knee OA, we found strong evidence that K&L grade did not predict deterioration in physical functioning[28]. This finding is in contrast with the review of Wright et al. who found strong evidence that K&L hip grade 3 is of predictive value of poorer outcome or progression of hip OA[30]. This discrepancy is probably related to the use of different outcome measures. We used deterioration in physical functioning as a main outcome measure, while Wright et al.[30] focused mainly on radiographic progression. In addition, it might be that sensitive methods (e.g., magnetic resonance imaging (MRI)), rather than K&L grade have a predictive value.

Some of the identified predictive factors have implications for treatment possibilities and planning. We found that per- forming no supervised exercise predicts deterioration in pain and in physical functioning. Indeed, land-based exercise has been proven to reduce pain and improve physical functioning in patients with hip OA[31]. Furthermore, we found that a higher comorbidity count predicts deterioration in pain and physical functioning. In OA the presence of comorbidity is highly prevalent[32]. Comorbidities have a significant influence on prognosis and may influence treatment outcome, therefore they should be closely monitored and managed. In addition, the presence of comorbidity may interfere with treatment possibilities, for example, exercise therapy. It may be necessary to adapt the OA exercise program to the comorbid disease in order to avoid serious adverse events[33,34]. Finally, low vitality predicts deterioration in physical functioning. The mechanism behind this can be 2-fold. First, low vitality is associated with avoidance of activities[35] and may reduce the level of physical activity, which in itself can result in decreased muscle strength and deconditioning. Secondly, low vitality is associated with depression[36,37], which is also related to a lower level of physical activity[38]. Both mechanisms can result in deterioration in physical functioning and pain. Behavioural interventions with or without exercise have been proven to positively affect these factors and thereby the course of hip OA[39–41].

Some limitations of the present study must be considered. First, shortcomings in the included studies may have influenced the outcome of this study. Four out of 15 studies were classified as low-quality studies. We found a high risk of bias particular in the description of the study population and study attrition. Improving the report on the selection of participants and reasons for drop-out or loss to follow-up will prevent bias and will allow stronger conclusions. Secondly, it was not possible to pool the data to quantify the strength of relationships between predictors and outcomes due to the small number of studies included, the variety of variables investigated and the different outcome measures that were used. The same limitation we found in analysing predictors of deterioration in pain and physical functioning in patients with knee OA[28]. Thirdly, we included studies that used longitudinal data analyses to predict future pain or

physical functioning. However, in some studies, using linear mixed models for repeated measurements, it appeared that the relationship between the determinant and the outcome was analysed cross-sectionally on different measurement points. In that case the determinant cannot be considered as a predictor of future pain or physical functioning. We there- fore excluded these studies[17,42]. Fourthly, the conclusions are preferably based on the results from univariable analyses, due to the considerable diversity in statistical techniques and choice of covariates used in individual multivariate models. Where univariable effect estimates were not available, we used multivariable effect estimates. This may have influenced the results, because risk factors (if adjusted for potential confounders) have different effect estimates compared with the univariable effect estimates. Fifthly, only 15 studies generated evidence for the course or predictors of deterioration in hip pain or physical functioning in patients with hip OA. To strengthen the evidence, more high-quality longitudinal studies are needed with more uniformity in investigated predictors, measurement outcomes and used definitions of determinants.

In 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. Several clinical characteristics, health behaviours and psychosocial factors predict deterioration of pain and physical functioning. These findings may guide future research aimed at the identification of prognostically homogeneous subgroups of patients with hip OA.

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Chapter 4

Osteoarthritis of the hip or knee: *which coexisting disorders are disabling?*

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Abstract

Objective. Exercise therapy is generally recommended in osteoarthritis (OA) of the hip or knee. However, coexisting disorders may bring additional impairments, which may necessitate adaptations to exercise for OA of the hip or knee. For the purpose of developing an adapted protocol for exercise therapy in OA patients with coexisting disorders, information is needed on which specific coexisting disorders in OA are associated with activity limitations and pain.

Methods. To describe the relationship between specific coexisting disorders, activity limitations, and pain in patients with OA of the hip or knee, a cross-sectional cohort study among 288 older adults (50–85 years of age) with OA of hip or knee was conducted. Subjects were recruited from three rehabilitation centers and two hospitals. Demographic data, clinical data, information about coexisting disorders (i.e., comorbidity and other disorders), activity limitations (WOMAC: physical functioning domain), and pain (visual analogue scale (VAS)) were collected by questionnaire. Statistical analysis included descriptive statistics and multivariate regression analysis.

Results. Coexisting disorders associated with activity limitations were chronic back pain or hernia, arthritis of the hand or feet, and other chronic rheumatic diseases (all musculoskeletal disorders); diabetes and chronic cystitis (non-musculoskeletal disorders); hearing impairments in a face-to-face conversation, vision impairments in long distances, and dizziness in combination with falling (all sensory impairments); and overweight and obesity. Coexistent disorders associated with pain were arthritis of the hand or feet, other chronic rheumatic diseases (musculoskeletal disorders), and diabetes (non- musculoskeletal disorder).

Conclusion. Specific disorders coexisting next to OA and associated with additional activity limitations and pain were identified. These coexisting disorders need to be addressed in exercise therapy and rehabilitation for patients with OA of the hip or knee.

Introduction

Osteoarthritis (OA) is one of the diseases with the highest rates of comorbidity[1]. Previous studies have reported comorbidity rates of 68% to 85%[2–5]. Diseases that frequently occur next to OA are diabetes, hypertension, and cardiovascular disorders; other disorders, including overweight and back pain, occur frequently as well[1,4,6]. Thus, coexisting disorders—defined as coexisting diseases and coexisting other disorders (e.g., overweight)—are highly prevalent in OA.

Exercise therapy is generally recommended in OA of the hip or knee: Exercise is effective in reducing activity limitations and pain in OA[7,8]. However, coexisting disorders may bring additional impairments, which necessitate adaptations to the exercise protocol for OA of the hip or knee. For the future purpose of developing such an adapted protocol, information is needed on which specific coexisting disorders in OA are disabling, i.e., which coexisting disorders are associated with activity limitations and pain. Coexisting disorders causing activity limitations and pain are likely to cause restrictions to exercise therapy as well, necessitating adaptations in the exercise protocol.

Previously, we have reported which coexisting disorders are associated with additional activity limitations and pain in OA of hip or knee[5,9]. In these studies, we used the Cumulative Illness Rating Scale (CIRS)[10–12] to assess coexisting disorders. The CIRS yields information on global categories of coexisting diseases, for example, ear, eye, nose, and throat diseases or endocrine and metabolic diseases. Although quite informative, more detailed information on which specific coexisting disorders are disabling is required in order to be able to develop the exercise therapy protocol with adaptations for coexisting disorders. The objective of the study was to describe the relationship between specific coexisting disorders, activity limitations, and pain in patients with hip or knee OA.

Methods

Design

The present study is a secondary analysis of previously reported data[5]. The design of this cross-sectional study is summarized below. The reader is referred to the original publication for a more detailed description of the design[5]. The study was approved by the Medical Ethical Committee of the VU University Medical Centre, Amsterdam, the Netherlands.

Study population

Participants were recruited from three rehabilitation centers and two hospitals (Departments of Orthopedics, Rheumatology, or Rehabilitation). Inclusion criteria were

(a) diagnosis of OA of the hip or knee by medical specialist according to radiological criteria or clinical criteria of the American College of Rheumatology[13,14], (b) 50 years of age or older, (c) referral to hospital or rehabilitation center less than a year before inclusion, (d) at least moderate functional problems (Lequesne algofunctional index score ≥5)[15], and (e) informed consent. Exclusion criteria were (a) 85 years of age or older, (b) insufficient understanding of the Dutch language, and (c) expected death due to fatal illness within 1 year after inclusion.

Measurements

Patients were invited to a test location. The data used in the present study were gathered by means of interview (demographic and clinical data) and questionnaires (activity limitations, pain, and coexistent disorders). X-rays were used to evaluate radiological impairment of the hip or knee.

Demographic and clinical data

Demographic and clinical data were collected for each patient including age, gender, height, weight, location of OA, duration of complaints, other joint complaints, level of education, and marital status. Body mass index (BMI) was calculated (weight/height^2). If available, X-rays of the hip and knee recorded in the year before inclusion were scored on joint space width and osteophytes, following a standardized procedure[16,17]. A 0–3 scale was used for rating the radiographs: 0 = normal; 1 = mild or 1–33% abnormal; 2 = moderate or 34–66% abnormal; 3 = severe or 67–100% abnormal. From these scores, Kellgren and Lawrence grades were calculated.

Activity limitations and pain

Activity limitations were measured using the physical functioning domain of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (range 0–100)[18,19]. WOMAC physical functioning score is a standardized score using the formula: ((68 – total score on the physical functioning domain) × 100)/68). A higher score on this standardized WOMAC stands for fewer activity limitations. Pain at the time of assessment was rated on a visual analogue scale (VAS) (range 0–10). A higher score on VAS reflects more pain.

Coexisting disorders

Patients indicated the presence or absence of coexisting disorders in the year prior to the interview, using the list of the Dutch Bureau of Statistics (CBS). This list describes the most common chronic diseases and disorders in the Netherland[20]. Based on expert consultation, impairments in vision and hearing were added to this list. Overweight was defined as 25 kg/m^2 ≤ BMI <30 kg/m^2; obesity was defined as BMI≥30 kg/m^2. Coexisting disorders were categorized as musculoskeletal disorders, non-musculoskeletal disorders, sensory impairments, and overweight and obesity.

Statistical analyses

The presence of coexisting disorders, activity limitations, and pain was analyzed using descriptive statistics. Subsequent analyses were limited to those disorders that affected ≥5% of the study population. The association between coexisting disorders (present or absent) and activity limitations was evaluated in multivariate regression analyses, correcting for age and gender. Similar analyses were done for the association between coexisting disorders and pain, correcting for age and gender. An association was termed significant if the p value was <0.05. For all analyses, the SPSS (version 14.0) was used[21].

Results

Study population

Initially, 775 patients with osteoarthritis of the hip or knee that visited the department in the year prior to inclusion were contacted by mail and were asked to participate in the study. Of those patients that volunteered (n = 364), 288 were included. Seventy-six patients were excluded because they did not meet the inclusion criteria. Reasons of

Table 1. Baseline characteristics (N=288)

Gender: male, n (%)	83 (28.8%)
Age, mean (sd)	66 (8.7)
Body mass index, mean (sd), kg/m²	27.8 (4.5)
Location OA	
Knee OA, *n* (%)	139 (48.4%)
Hip OA, *n* (%)	72 (25.1%)
Both, *n* (%)	76 (26.5%)
Duration of complains (years), mean (sd)	9.9 (10.7)
Physical functioning (WOMAC), mean (sd)	56.51 (19.85)
Pain (VAS), mean (sd)	4.81 (2.56)
Radiological impairment knee[a]	
K&L grade ≥ 2; *n* (%)	118 (95.2)
Radiological impairment hip[b]	
K&L grade ≥ 2; *n* (%)	83 (97.6)

N, *n* number, *sd* standard deviation, *OA*: osteoarthritis, *WOMAC*, Western Ontario and McMasters Universities Osteoarthritis Index; *VAS*, Visual Analogue Scale

[a] N = 138 (from only a part of the included patients X-rays were available)

[b] N = 90 (from only part of the included patients X-rays were available)

Table 2. Presence of coexisting disorders

	Present n (%)
Musculoskeletal disorders	
Chronic back pain (> 3 month) or hernia	*85 (29.5)*
Arthritis of the hands or feet	*53 (18.4)*
Other chronic rheumatic diseases (> 3 month)	*29 (10.1)*
Non-musculoskeletal disorders	
Asthma or COPD	*45 (15.6)*
Sinusitis	*35 (12.2)*
Severe cardiac disorder or coronary disease	*23 (8)*
Hypertension	*92 (31.9)*
(Consequences of) a stroke	6 (2.1)
Peptic ulcer or duodenal ulcer disease	10 (3.5)
Severe bowel disorder (> 3 month)	*19 (6.6)*
Gallstones or inflammation of the gall bladder	6 (2.1)
Liver disorder or cirrhosis of the liver	0 (0)
Kidney stones (calculus renalis)	7 (2.4)
Severe kidney disorder	2 (0.7)
Chronic cystitis	16 (5.6)
Prolapse (only females, N=205)	*17 (8.3)*
Diabetes	*28 (9.7)*
Thyroid disorders	*25 (8.7)*
Epilepsy	2 (0.7)
Migraine	*19 (6.6)*
Severe skin disease	4 (1.4)
Cancer and malignant diseases	7 (2.4)
Sensory impairments	
Hearing impairments in a group conversation (N=286)	*90 (31,5)*
Hearing impairments in a face-to-face conversation (N=287)	*22 (7.7)*
Vision impairments in short distances (N=287)	*77 (26.8)*
Vision impairments in long distances (N=287)	*33 (11.5)*
Dizziness in combination with falling	*24 (8.3)*
Overweight and obesity (N=285**)**	
Overweight (25≤BMI <30)	149 (51.7)
Obesity (BMI ≥ 30)	68 (23.9)

N = 288, unless otherwise stated.
Data in italics are present in >5%

exclusion were age (n = 2), language (n = 4), less than moderate functional problems (n = 48), and referral longer than 1 year before inclusion (n = 22). Analyses showed that there were no differences between the group of patients that were initially contacted (N = 775) and the patients that were included in the study (N = 288) with regard to age and gender. Some differences were found in the location of OA. Compared to our study population, patients that were initially contacted suffered less frequently from both hip and knee OA (6.2%) and more frequently from knee OA (59.5%) and hip OA (34.3%)[5].

Table 1 shows baseline characteristics of the study population. The majority of the study population was female (71,2%), the mean age was 66 (SD = 8,7) years. The largest part of the subjects (48.4%) suffered from knee OA, 25.1% suffered from hip OA, and 26.5% had both hip and knee OA. The mean physical functioning score on the WOMAC was 56.5 (SD = 19.6), and the mean pain score on the VAS was 4.8 (SD = 2.6). Most patients (80%) were recruited from the departments of orthopedics; the other 20% originated from departments of rheumatology and departments of rehabilitation.

Coexisting disorders

The presence of coexisting disorders in the study population is presented in Table 2. Eighteen coexisting disorders occurred in >5% of the sample (see Table 2). In the category of musculoskeletal disorders, coexisting conditions occurring in > 5% of the patients included chronic back pain or hernia, 29.5%; arthritis of the hand or feet, 18.4%; and other chronic rheumatic diseases, 10.1%. In the category of non-musculoskeletal disorders, coexisting conditions occurring in > 5% of the patients included hypertension, 31.9%; asthma or COPD, 15.6%; sinusitis, 12.2%; diabetes, 9.7%; thyroid disorders, 8.7%; severe cardiac disorder or coronary disease, 8%; severe bowel disorder, 6.6%; migraine, 6.6%; chronic cystitis, 5.6%; and prolapse in 8.3% of the female patients. In the category of sensory impairments, coexisting conditions occurring in > 5% of the patients were hearing impairments in a group conversation, 31.5%; vision impairments in short distances and long distances, 26.8% and 11.5%, respectively; and dizziness in combination with falling, 8.3%. Overweight and obesity occurred in 51.7% and 23.9%, respectively.

Association between coexisting disorders and activity limitations

Table 3 shows the relationship between specific coexisting disorders and activity limitations. Significantly more activity limitations were found in OA patients with chronic back pain or hernia ($p < 0.05$), arthritis of the hand or feet ($p < 0.05$), and other chronic rheumatic diseases ($p < 0.05$) (all in the category of musculoskeletal disorders); with diabetes ($p < 0.05$) and chronic cystitis ($p < 0.05$) (category of non-musculoskeletal disorders); with hearing impairments in a face-to-face conversation ($p < 0.05$), vision impairments in long distances ($p < 0.05$), and dizziness in combination with falling ($p < 0.05$) (category of sensory impairments); and with overweight ($p < 0.01$) and obesity ($p < 0.05$).

Table 3. Association between coexisting disorders, activity limitations, and pain

	Activity limitations (WOMAC)	Pain (VAS)
Musculoskeletal disorders		
Chronic back pain (> 3 month) or hernia		
Present (mean (sd))[a]	51.7 (18.2)	5.0 (2.5)
Absent (mean (sd))[a]	58.5 (20.2)	4.7 (2.5)
B (95%CI)[b]	-6.4 (-11.5 ; -1.4)*	0.3 (-0.4 ; 1.0)
R^2	0.033	0.008
Arthritis of hands or feet		
Present (mean (sd))[a]	50.1 (20.3)	5.8 (2.5)
Absent (mean (sd))[a]	57.9 (19.5)	4.6 (2.5)
B (95%CI)[b]	-7.4 (-13.4 ; -1.5)*	1.2 (0.4 ; 1.9)**
R^2	0.032	0.037
Other chronic rheumatic diseases (> 3 month)		
Present (mean (sd))[a]	47.3 (18.3)	5.9 (2.6)
Absent (mean (sd))[a]	57.5 (19.8)	4.7 (2.5)
B (95%CI)[b]	-10.0 (-17.6 ; -2.4)*	1.1 (0.1 ; 2.1)*
R^2	0.035	0.023
Non-musculoskeletal disorders		
Asthma or COPD		
Present (mean (sd))[a]	55.2 (19.1)	4.8 (2.6)
Absent (mean (sd))[a]	56.7 (20.0)	4.8 (2.6)
B (95%CI)[b]	-1.7 (-8.0 ; 4.7)	0.0 (-0.8 ; 0.9)
R^2	0.012	0.005
Sinusitis		
Present (mean (sd))[a]	54.5 (15.8)	4.9 (2.6)
Absent (mean (sd))[a]	56.8 (20.4)	4.8 (2.6)
B (95%CI)[b]	-2.0 (-9.1 ; 5.1)	0.1 (-0.8 ; 1.0)
R^2	0.012	0.006
Severe cardiac disorder or coronary disease		
Present (mean (sd))[a]	51.2 (20.6)	5.1 (2.8)
Absent (mean (sd))[a]	57.0 (19.8)	4.8 (2.6)
B (95%CI)[b]	-5.5 (-14.1 ; 3.1)	0.4 (-0.7 ; 1.6)
R^2	0.012	0.008
Hypertension		
Present (mean (sd))[a]	55.8 (21.9)	4.9 (2.5)
Absent (mean (sd))[a]	56.8 (18.8)	4.8 (2.6)
B (95%CI)[b]	-0.6 (-5.6 ; 4.5)	0.3 (-0.4 ; 0.9)
R^2	0.012	0.007
Severe bowel disorder (> 3 month)		
Present (mean (sd))[a]	54.3 (20.3)	4.5 (3.2)
Absent (mean (sd))[a]	56.7 (19.9)	4.8 (2.5)
B (95%CI)[b]	-2.0 (-11.3 ; 7.2)	-0.4 (-1.6 ; 0.8)
R^2	0.012	0.007

Table 3. (cont'd)

	Activity limitations (WOMAC)	Pain (VAS)
Chronic cystitis		
Present (mean (sd)) [a]	45.2 (17.6)	5.4 (2.9)
Absent (mean (sd)) [a]	57.2 (19.8)	4.8 (2.5)
B (95%CI) [b]	-10.8 (-20.9 ; -0.7) †	0.7 (-0.6 ; 2.1)
R^2	0.027	0.01
Prolapse (females only)		
Present (mean (sd)) [a]	47.0 (22.0)	5.2 (2.9)
Absent (mean (sd)) [a]	56.4 (19.7)	4.8 (2.6)
B (95%CI) [b]	-9.0 (-18.9 ; 0.9)***	0.4 (-0.9 ; 1.7)
R^2	0.03	0.005
Diabetes		
Present (mean (sd)) [a]	49.5 (18.2)	5.9 (2.2)
Absent (mean (sd)) [a]	57.3 (19.9)*	4.7 (2.6)
B (95%CI) [b]	-8.2 (-15.9 ; -0.4)*	1.2 (0.2 ; 2.2)*
R^2	0.026	0.024
Thyroid disorders		
Present (mean (sd)) [a]	51.4 (22.6)	5.6 (2.8)
Absent (mean (sd)) [a]	57.0 (19.6)	4.7 (2.5)
B (95%CI) [b]	-5.8 (-14.2 ; 2.6)	1.1 (0.0 ; 2.1)***
R^2	0.018	0.018
Migraine		
Present (mean (sd)) [a]	56.6 (20.8)	4.5 (2.6)
Absent (mean (sd)) [a]	56.5 (19.8)	4.8 (2.6)
B (95%CI) [b]	0.1 (-9.2 ; 9.5)	-0.4 (-1.6 ; 0.8)
R^2	0.012	0.007
Sensory impairments		
Hearing impairments in a group conversation		
Present (mean (sd)) [a]	55.4 (19.1)	4.6 (2.7)
Absent (mean (sd)) [a]	57.0 (20.2)	4.9 (2.5)
B (95%CI)**	-0.9 (-6.0 ; 4.2)	-0.3 (-0.9 ; 0.4)
R^2	0.011	0.004
Hearing impairments in a face-to-face conversation		
Present (mean (sd)) [a]	46.7 (19.9)	5.6 (2.8)
Absent (mean (sd)) [a]	57.2 (19.7)	4.8 (2.5)
B (95%CI) [b]	-9.6 (-18.4 ; -0.8)*	1.0 (-0.1 ; 2.2)***
R^2	0.027	0.016
Vision impairments in short distances		
Present (mean (sd)) [a]	54.1 (19.8)	5.0 (2.6)
Absent (mean (sd)) [a]	57.3 (19.8)	4.8 (2.6)
B (95%CI) [b]	-2.9 (-9.1 ; 2.3)	0.3 (-0.4 ; 1.0)
R^2	0.016	0.007

Table 3. (cont'd)

	Activity limitations (WOMAC)	Pain (VAS)
Vision impairments in long distances		
Present (mean (sd)) [a]	47.6 (19.1)	5.2 (2.5)
Absent (mean (sd)) [a]	57.6 (19.7)	4.8 (2.6)
B (95%CI) [b]	-9.0 (-16.3 ; -1.6)*	0.6 (-0.4 ; 1.6)
R^2	0.031	0.01
Dizziness in combination with falling		
Present (mean (sd)) [a]	45.4 (23.4)	5.7 (2.9)
Absent (mean (sd)) [a]	57.5 (19.2)	4.7 (2.5)
B (95%CI) [b]	-11.2 (-19.6 ; -2.8)**	1.1 (0.0 ; 2.2)***
R^2	0.035	0.019
Weight		
Overweight (25 ≤ BMI < 30)		
Present (mean (sd)) [a]	54.7 (19.1)	4.9 (2.6)
Absent (mean (sd)) [a]	62.7 (19.0)	4.4 (2.6)
B (95%CI) [b]	-8.0 (-13.7 ; -2.4)**	0.5 (-0.3 ; 1.2)
Obesity (BMI ≥ 30)		
Present (mean (sd)) [a]	54.1 (21.4)	5.0 (2.6)
Absent (mean (sd)) [a]	62.7 (19.0)	4.4 (2.6)
B (95%CI) [b]	-8.6 (-15.3 ; -1.9)*	0.6 (-0.3 ; 1.5)
R^2	0.041	0.014

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, *VAS* Visual Analogue Scale, B regression coefficient; 95% CI: 95% Confidence interval

* p < 0.05; ** p < 0,01;***p-value < 0,1

[a] observed value; [b] adjusted value for age and sex

Association between coexisting disorders and pain

Table 3 also shows the relationship between coexisting disorders and pain. Arthritis of the hand or feet (p < 0.01) and other chronic rheumatic diseases (p < 0.05) (category of musculoskeletal disorders) and diabetes (p < 0.05) (category of non-musculoskeletal disorders) were found to be significantly associated with more pain.

Discussion

The aim of this study was to describe the relationship between specific coexisting disorders, activity limitations, and pain in patients with OA of the hip or knee. We have previously reported that "symptoms of other musculoskeletal disorders" occur frequently in OA[5]: We have now found chronic back pain or hernia, arthritis of the hands or feet,

and other chronic rheumatic diseases to be associated with activity limitations. In our previous study, we found "endocrine and metabolic diseases" to be associated with activity limitations: We now discovered that this applies to diabetes. We also found "other urogenital diseases" to be associated with activity limitations[5]: We now discovered that this applies in particular to chronic cystitis. Previously, we found "ear, eye, nose, and throat diseases" to be associated with activity limitations[5]: We have now observed that this applies in particular to hearing impairments in a face-to-face conversation and vision impairments in long distances. We also found dizziness in combination with falling to be associated with activity limitations. Finally, overweight and obesity were found to be related to activity limitations.

Regarding coexistent disorders and pain, we have now found arthritis of the hands or feet and other chronic rheumatic diseases to be associated with pain. Previously we did not find a relationship between endocrine and metabolic diseases and pain[5]; however, we now found an association between diabetes and pain.

Coexisting disorders may bring additional impairments, which necessitate adaptations to exercise for patients with OA of the hip or knee. For the future purpose of developing a protocol for exercise in OA patients with coexisting disorders, information is needed on which specific coexisting disorders in OA are associated with activity limitations and pain. The present study brings highly relevant new information in this respect. To our knowledge, this is the first study suggesting that hearing impairments, vision impairments, dizziness, and chronic cystitis need to be addressed in order to optimize functioning of patients with OA. Only Peters et al. have previously reported on the (near significant) relationship between eye diseases and future disability in patients with knee OA[22]. The present results shows that coexisting sensory impairments in hearing, vision, and balance, as well as motor impairments in bladder control (in the case of cystitis), have impact on functioning of patients with OA of the hip or knee: Apparently, these impairments need to be addressed in the rehabilitation of OA patients.

It is well known that OA is associated with other musculoskeletal disorders[23]. In contrast, very little information is available on the impact of coexisting musculoskeletal disorders on activity limitations and pain. Cimmino et al. describe greater pain in patients with generalized OA than in patients with hip or knee OA alone[24]. The present study found an association between arthritis of the hand or feet, "other" chronic rheumatic diseases, chronic back pain or hernia, and activity limitations. We also found a relationship between arthritis of the hand or feet, other chronic rheumatic diseases, and pain.

The present study confirms earlier observations on the impact of diabetes, overweight, and obesity on activity limitations in OA. Diabetes causes physiological restrictions to exercise therapy[25], whereas overweight and obesity introduce behavioral restrictions to exercise[26]. Combining exercise therapy with a weight loss program has been shown to result in moderately improved outcome, compared to exercise therapy alone[27]. Further work on adaptations to exercise therapy for OA patients with diabetes, overweight, and obesity is urgently required, because of the high prevalence and the functional impact of these coexisting disorders.

In our previous study, we found 54% of the study population to have cardiac diseases, and a significant relationship with activity limitations was found[5]. Caporali et al. found cardiac diseases (myocardial infarction and/or angina pectoris) to influence pain, quality of life, and joint function in OA patients[4]. Ettinger et al. also describe a higher likelihood of disabilities in OA patients with heart diseases[28]. In the present study, no significant relationship was found between cardiac diseases and activity limitations or pain. A likely explanation is that subjects rated the presence of "severe heart diseases or coronary diseases." This item might have implicated a too serious stage of disease, causing us to miss patients with mild or moderate heart disease. Despite our present results, adaptations for cardiac disease in exercise therapy for OA patients seem to be required.

The number of coexisting disorders associated with activity limitations (n = 10) was larger than the number of coexisting disorders associated with pain (n = 3). It seems that coexisting disorders easily impact on activity limitations, while the impact on pain is less strong. Future research is needed to elucidate the mechanisms of how coexisting disorders have an impact on activity limitations and pain. This research may also clarify the differential impact of coexisting disorders on activity limitations and pain.

Some limitations of the present study need to be discussed. Firstly, we relied on self-report to assess coexisting disorders, instead of medical record review. However, self-reported coexisting disorders tend to correspond rather well with coexisting disorders derived from medical record review (29): The percentage of agreement exceeded 90% for all coexisting disorders except for tumors; the kappa statistic ranged from 0.35 to 0.85, reflecting fair to substantial agreement. Fair agreement (kappa <0.40) was found for ulcer disease, end organ damage resulting from diabetes, and connective tissue disease (not assessed in the present study); substantial agreement (kappa >0.60) was found for myocardial infarction, stroke, and renal disease. Thus, self-report on coexisting disorders seems to be valid, with some exceptions noted above. Secondly, in assessing coexistent disorders, we used the list of the Dutch Bureau of Statistics (CBS). Unfortunately, this list did not include psychiatric disorders. From previous studies, it is known that depression plays an important role in developing activity limitations[30,31]. Thirdly, patients included in this study were recruited from hospitals and rehabilitation centers; these patients may have received some form of rehabilitation. Thus, the results of the present study cannot be generalized to the general population suffering from OA. Nevertheless, the results are applicable to the group of patients consulting in hospitals and rehabilitation centers: This is a highly relevant group. Fourthly, the study focused on patients with OA of the hip or knee. We did not have information on a reference group of subjects without OA or subjects with another index disease. In subjects without OA and subjects with another index disease, comorbidity is likely to be associated with activity limitations and pain as well. In future studies, it would be interesting to compare impact of comorbidity in OA patients and other subjects. Finally, we did not adjust the analysis for multiple comparisons: This could easily result in false-negative errors (type II errors) because of the limited number of subjects with a specific coexisting disorder. It is acknowledged that this may have introduced some risk of false-positive errors (type I errors).

In conclusion, specific disorders coexisting next to OA and associated with additional activity limitations and pain were identified. These coexisting disorders need to be addressed in exercise therapy and rehabilitation for patients with OA of the hip or knee.

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Chapter 5

Narrative Review Restrictions and contra-indications for exercise therapy in patients with hip and knee osteoarthritis and comorbidity

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Abstract

Background. Osteoarthritis (OA) has a very high rate of comorbidity. Exercise therapy is recommended in current guidelines on the management of OA of the hip and knee. Unfortunately, current protocols and guidelines for exercise therapy in OA of the hip and knee do not offer advice concerning comorbidity- associated adaptations for exercise therapy in OA patients. Because of the high prevalence of comorbidity in OA, it is important to establish when exercise therapy for OA of the hip and knee should be adapted when patients have one or more comorbidities.

Objective. To identify restrictions and contraindications for exercise therapy for common comorbidities (cardiac diseases, hypertension, type 2 diabetes, obesity, chronic obstructive pulmonary disease (COPD), depression, chronic pain, low back pain (LBP), visual or hearing impairments, and chronic cystitis) in hip and knee OA patients.

Major findings. Cardiac diseases, hypertension, type 2 diabetes, COPD, and chronic cystitis are associated with restrictions resulting from physiological impairments. Conversely, LBP, chronic pain syndromes, and depression are associated with psychological and behavioural restrictions to exercise therapy. Visual and hearing impairments result predominantly in environmental restrictions to exercise. Obesity is associated with restrictions resulting from physiological and psychological impairments and behavioural barriers. Several absolute contraindications exist and patient safety cannot be guaranteed when these are not taken into account during exercise therapy.

Conclusion. Restrictions and contraindications for exercise in patients with OA of the hip and knee and comorbidity have been identified. This overview is helpful in decisions on the treatment of patients and will be instrumental in the development of a protocol for comorbidity related adaptations in exercise therapy for OA patients.

Introduction

Osteoarthritis (OA) is the most prevalent joint disease and one of the most common chronic diseases in Western Society. Moreover, OA has a very high rate of comorbidity[1]: rates between 68 to 85% have been reported[2-5]. Such high rates of comorbidity are also found in the older population in general[1]. Feinstein defined comorbidity 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 (OA) under study'[6]. Common comorbidities in hip and knee OA are cardiac diseases, hypertension, type 2 diabetes, obesity, chronic obstructive pulmonary diseases (COPD), OA of the foot and hand, depression, chronic pain, low back pain, visual or hearing impairments, chronic cystitis, stroke, and severe bowel disorders (>3 month)[7,8]. In patients with OA of the hip and knee comorbidity is associated with greater limitations in daily activities, more pain and a poor functional prognosis[5,9].

Exercise therapy is an effective intervention to relieve pain and to improve daily functioning of patients with OA of the knee[10,11] and most likely also for hip OA[12]. Furthermore, exercise therapy is recommended in current guidelines on the management of OA of the hip and knee[13-18]. Exercise therapy consists of exercise for lower–limb muscle strengthening, aerobic capacity, range of joint motion (ROM), joint stability, hydrotherapy, graded activity, and training of daily activities like walking, stair climbing, and transfers (e.g., rising from a chair, getting into and out of a car)[16-22].

When comorbidity is present, adaptations of exercise therapy protocols for patients with OA of the hip and/or knee may be required. For example, in chronic heart failure (HF), breathlessness and fatigue disproportional to the level of exertion should be avoided because of the risk of cardiac decompensation[23]. Also, in COPD, endurance training is limited due to dyspnoea. Examples of psychological obstacles to standard exercise therapy include avoidance of exercise in chronic pain patients[24] and low adherence to exercise regimes in overweight or obese patients[25]. In some cases, comorbidity and the ensuing impairments might constitute an absolute contraindication for exercise therapy, for example, not healing foot ulcers in diabetic patients which may cause serious health problems to the patient[26,27].

Unfortunately, current protocols and guidelines for exercise therapy in OA of the hip and knee do not offer advice concerning comorbidity-associated adaptations for exercise therapy in OA patients[13-18]. Current clinical decision making tends to ignore comorbidity and adaptations to exercises are often based on intuition and clinical experience. Because of the high prevalence of comorbidity in OA of the hip and knee, it is important to establish how exercise therapy for OA of the hip and knee should be adapted when patients have one or more comorbidities. A protocol on comorbidity-related adaptations for exercise therapy in OA of the hip and knee is therefore required.

The goal of the present study was to make an inventory of restrictions and contraindications for exercise therapy in patients with OA of the hip and knee with comorbidity. This overview is helpful in decisions on the treatment of patients. It also functions as a first step in the development of a protocol for comorbidity-related adaptations in exercise therapy.

Methods

Selection of comorbid diseases

Based on previous research, we selected comorbidities in OA which were: (1) common (present >5%) and (2) have impact on pain and/or affect daily functioning. The following comorbidities were selected: cardiac diseases, hypertension, type 2 diabetes, obesity, COPD, OA of the foot and hand, low back pain, chronic pain, depression, visual or hearing impairments and cystitis[8].

Review of the literature about exercise therapy in comorbidities

A literature search in the PubMed (1966–2009) database was conducted. Studies on exercise therapy in cardiac diseases, type 2 diabetes, obesity, COPD, depression, chronic pain, low back pain, visual or hearing impairments, and chronic cystitis were included. The full search strategy can be found in Appendix 1. References of included studies were checked for additional papers. Retrieved papers were reviewed for information on restrictions and contraindications for exercise therapy.

Analysis

First, a distinction was made between restrictions to exercise therapy and absolute contraindications. Restrictions limit the application of exercise therapy, necessitating adaptations to the therapeutic protocol. However, if a contraindication is present, exercise therapy is not an option and the patient should be excluded from exercise therapy.

Second, for each comorbidity, the information on exercise restrictions obtained from the literature was categorized according to the International Classification of Functioning (ICF)[28]. The ICF is a classification of health and health-related domains. According to the ICF, exercise restrictions were categorized as relating to body structure and function, activities, participation, personal factors or environmental factors.

Results

Outcome of the literature search

Our literature search has enabled us to make an overview of restrictions and contraindications for exercise therapy in patients with OA of the hip or knee and comorbidity (Table 1). It was found that cardiac diseases (coronary heart diseases and HF), hypertension, type 2 diabetes, COPD and chronic cystitis are mostly associated with restrictions resulting from impairments in body structure and function. Conversely, low back pain, chronic pain syndromes and depression are mostly associated with psychological and behavioural restrictions to exercise therapy. Visual and hearing impairments result predominantly in environmental restrictions to exercise. Obesity is associated with restrictions resulting from physiological and psychological impairments and behavioural barriers. Several absolute contraindications exist; patient safety during exercise therapy cannot be guaranteed when these are not taken into account during exercise therapy, for example, pain in the chest before or during exercise in a patient with coronary heart disease. In the following paragraphs, we will elaborate on restrictions and contraindications associated with each comorbidity.

(Table 1 on next page)

Table 1. Inventory of restrictions and contraindications for exercise therapy for common comorbidities in patients with OA of the hip and knee

	Exercise restrictions	Contraindications
Coronary heart disease	Body structure and function • pain in the chest during exercise • cardiac arrhythmias during exercise (high heart rate frequency disproportional to the level of exertion, irregular heart rate frequency, changes in known heart arrhythmias, increase in number of ventricular extra systolen) • abnormal changes in blood pressure during exercise • common malaise like fainting, nausea, paling, dizziness during exercise • level 3 NYHA (New York Heart Association classification) Personal factors • fear of exertion • insufficient knowledge of the disease and exercise options • inactive lifestyle	• acute myocardial infarction within the last three months, • present unstable angina e.g., pain in the chest at rest or pain that does not react to specific medication • pain in the chest before exercise • changes in known or new cardiac arrhythmias • present inflammation (pericarditis, myocarditis, endocarditis) • present symptomatic aortic stenosis • patients with level 4 NYHA • present dyspnea at rest • within 10 days after a period of fever or present fever
Heart failure	Body structure and function • pain in the chest during exercise • cardiac arrhythmias (high heart rate frequency disproportional to the level of exertion, irregular heart rate frequency, changes in known heart arrhythmias, increase in number of ventricular extra systolen) • known left ventricular ejection fraction of <30% • abnormal changes in blood pressure during exercise • common malaise like faint, nausea, pale, dizziness • level 3 NYHA • reduced maximum heart rate due to the use of beta-blockers • breathlessness disproportional to the level of exertion • fatigue disproportional to the level of exertion • reduced recovery capacity Personal factors • fear of exertion • insufficient knowledge of the disease and options to exercise • inactive lifestyle	• acute myocardial infarction within the last three months • present unstable angina for example pain in the chest at rest or pain that does not react to specific medication • pain in the chest before exercise • changes in known or new cardiac arrhythmias • present inflammation (pericarditis, myocarditis, endocarditis) • present symptomatic aortic stenosis • patients with level 4 NYHA • present dyspnoea at rest • increase in bodyweight more than 2kg in the last two days • within 10 days after a period of fever or, present fever
Hypertension	Body structure and function • increased risk of high blood pressure, especially in case of left side hypertrophy • ≥ 1stage hypertension • reduced aerobic capacity due to the use of betablockers • inactive lifestyle	• resting systolic blood pressure of >200mgHG or diastolic blood pressure of >115mmHG

Table 1. (cont'd)

	Exercise restrictions	Contraindications
Type 2 diabetes	Body structure and function *Glucose related factors* • blood glucose > 16 mmol/L or < 5 mmol/L • occurrence of induced hypoglycemia during exercise and up to 48 hours afterwards or 72 hours after intense strength training • poorly regulated diabetes characterized by a high (>7%) HbA1c and/or highly variable blood sugar levels (high or low) and frequent hypoglycemia Vascular or neuropathy related factors • delayed recovery when injured • incipient foot ulcers on weight bearing activities • autonomic neuropathy with impaired cardiovascular response to exercise, response to dehydration thermoregulation, postural hypotension, and/or decreased maximum aerobic activity • loss of sensibility of the feet • increased eye pressure during exercise due to proliferative retinopathy Personal factors • insufficient knowledge of the disease, medication and exertion • fear of exertion • inactive lifestyle • inefficient monitoring of blood glucose levels	• foot ulcer
Obesity	Body structure and function • increased stress, pressure and pain in weight bearing joints • shortness of breath • poor thermoregulation during exertion Personal factors • inactive lifestyle • fear of movement • lack of motivation for weight reduction	
COPD	Body structure and function • peripheral muscle atrophy and weakness • poor nutritional status • reduction of respiratory muscle function • insufficient control of respiration and cough techniques • blood oxygen saturation <90% • present exacerbation of the disease • severe COPD (Gold stadium 3/4) • severe dyspnea Personal factors • fear of exertion / fear of breathlessness • insufficient knowledge of the use of medication combined with exertion • inactive lifestyle Environmental factor • instrument required to measure saturation in GOLD stadium 3/4	• pneumonia • exceptional loss of bodyweight (10% in the past half year or > 5% in the past month)

Table 1. (cont'd)

	Exercise restrictions	Contraindications
Osteoarthritis of the hand and feet	Body structure and function • increase in pain during exercise Personal factor • limited use of a walking aid	
Low back pain	Body structure and function • severe low back pain before exercise • increase of low back pain during or after exercise • signs of neuropathy, radiculopathy before exercise Personal factors • fear of exertion, movement and pain avoidance • inadequate pain coping styles and cognitions • inactive lifestyle	• specific spinal pathology
Chronic pain	Body structure and function • pain may limit the exercise tolerance • increase in pain during exercise • fatigue before or during exercise Personal factors • increase in pain not directly related to impaired body structures and functions • fear of exertion, movement and pain avoidance • inadequate pain coping styles and cognitions • inactive lifestyle	
Depression	Body structure and function • generalized fatigue may limit exercise Personal factors • lack of therapy compliance • fear of exertion • inadequate cognitions • inactive lifestyle • lack of initiative or motivation	• serious psychiatric disorders • major depression
Vision/ hearing impairments	Body structure and function • orientation difficulties due to impaired vision and hearing • reduced capacity for processing images and text Personal factors • fear of falling • inactive lifestyle Environmental factors • furniture and exercise equipment in exercise hall • lighting and dark/light contrast in exercise hall • inadequate environment for home exercises	
Chronic cystitis	Body structure and function • urine incontinence • increase in abdominal pressures during physical exertion Personal factor • fear of leakage of urine • inactive lifestyle	

Coronary heart disease

Coronary heart disease is a common term for cardiac diseases caused by myocardial ischemia due to inadequate regional blood supply relative to myocardial oxygen requirements. The most common cause for this problem is arteriosclerosis of the coronary blood vessels. When symptoms like pain in the chest, cardiac arrhythmias, and irregular changes in blood pressure occur during exercise, exercise should be aborted[29]. A left ventricular ejection fraction of less than 30% may give restrictions in undertaking strength training[30]. Personal factors like avoidance of exercise resulting from fear of myocardial infarction can play a role[31]. When patients have insufficient knowledge of the disease and exercise options, they can be at risk of under- or overloading during exercise. Also, changing to an active lifestyle can be hindered by sedentary behavior[29,32]. Patients with a New York Heart Association classification (NYHA) 3 (i.e., patients who are comfortable at rest; less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain) can only perform light exercises aimed at improvement of coordination, balance or range of motion[33]. Patients with an NYHA classification level 4 (i.e., cardiac disease resulting in inability to carry out any physical activity without discomfort) are contraindicated for exercise therapy[33]. Other absolute contraindications for exercise therapy include acute myocardial infarction within the last 3 weeks, present unstable angina, pain in the chest before exercise, changes in known or new cardiac arrhythmias and the presence of inflammation of the heart, symptomatic aortic stenosis, dyspnea at rest, severe hypertension and doing exercise within 10 days after a period of fever or present fever[29].

Heart failure

HF is defined as the inability of the heart to maintain or increase cardiac output at a rate commensurate with systematic aerobic requirements, resulting in fatigue or dyspnea on exertion progressing to dyspnea at rest. In addition to the exercise restrictions applying to coronary heart disease, physiological impairments such as reduced maximum heart rate due to the use of beta-blockers and symptoms of breathlessness and fatigue disproportional to the level of exertion, are of relevance to HF patients[34]. All patients with HF should have their clinical status carefully reviewed by the cardiologist before starting an exercise program[33]. Cardiac decompensation (defined as a worsening of the symptoms, typically shortness of breath (dyspnea), edema and fatigue, in a patient with existing heart disease)[35] should be avoided[23]. Personal factors limiting exercise options are similar to those named for coronary heart disease (see above). An additional contraindication to those named for coronary heart disease (see above) is an increase in bodyweight of more than 2kg in the preceding two days, which is a sign of decompensation cordis[36].

Hypertension

Hypertension is classified as Grade 1: systolic blood pressure 140–159 mmHg and/or diastolic blood pressure 90–99 mmHg, Grade 2: systolic blood pressure 160–179 mmHg and/or diastolic blood pressure 100– 109 mmHg, Grade 3: systolic blood pressure

≥180 mmHg and/or diastolic blood pressure ≥110 mmHg[37]. Treatment-demanding hypertension is defined as a systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg[37,39]. High intensity training can result in high blood pressure. Medication to lower blood pressure like Beta-blockers can limit exercise tolerance in persons without myocardial ischemia[37,39]. The guidelines of the American College of Sports Medicine (ACSM) recommend caution when performing intensive dynamic exercise or strength conditioning with heavy weights[23,40,41]. A contraindication for exercise therapy is a resting systolic blood pressure of ≥200 mmHg or ≥ diastolic blood pressure of ≥115 mmHg[37].

Type 2 diabetes

Type 2 diabetes is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels[42]. Type 2 diabetic patients frequently suffer from severe exercise intolerance as a result of low oxidative capacity[43], neuropathy related muscle weakness[44-46], sarcopenia[47] and micro- and macrovascular diseases[43]. This leads to a number of exercise restrictions and contraindications, including problems in regulating blood-glucose levels and problems related to neuropathic and/or vascular factors.

If blood glucose is >15 or <5 mmol/l, exercise should be postponed[27,48]. Hypoglycaemia may occur up to 48–72 hours after intense aerobic exercises and strength training in patients using exogenous insulin[49-50]. A restriction for exercise could be poorly controlled diabetes characterized by a high stick of glucose to haemoglobin A1c (HbA1c >7%) and/or variable blood sugar levels and frequent hypoglycaemia[27].

Vascular and/or neuropathic factors restricting exercise are: delayed recovery following injury, increased risk of wounds and greater risk of incipient foot ulcers with weight bearing activities[51,52]. Nephropathy usually reduces the capacity for physical exertion. The exertion is often adjusted by the patient. Low to moderately intense exercise is recommended[53]. Also, autonomic neuropathy may result in decreased cardiovascular response to exercise, impaired response to dehydration, impaired thermoregulation due to impaired skin blood flow and sweating, postural hypotension, and/or decreased maximum aerobic capacity[52]. Loss of sensibility of the feet can lead to restrictions in training aimed at stability and daily activities like walking[52]. Increased eye pressure during exercise should be avoided in case of proliferative retinopathy[54]. Personal factors leading to exercise restrictions include: insufficient knowledge of the disease, medication and exertion, fear of exertion and inefficient monitoring of blood glucose levels. Changing to an active lifestyle can be limited by sedentary behavior[55]. Furthermore a contraindication for exercise therapy in patients with diabetes is foot ulcer[26,27,51,52].

Overweight

Overweight is a condition in which an abnormally large proportion of body mass consists of fat. Overweight is defined by a body mass index (BMI) 25–29.9 kg/m^2; obesity is defined as a BMI ≥30 kg/m^2 [56]. Obesity is not only a risk factor for developing OA, but also for developing diabetes, hypertension and cardiovascular diseases. It is known that obesity affects the knee in a biomechanical way[57,58] and causes increasing pain[59], systemic inflammation[60] and functional disability[61,62]. Overweight and obesity lead to increased stress and pressure on and pain of the joints[63] and may restrict weight-bearing exercises. Another physiological restriction in these patients may be shortness of breath as a result of de-conditioning and poor thermoregulation during exertion and warm climatic conditions[64]. Often there are also psychological restrictions to exercise in overweight or obese patients, for example joint pain may trigger fear of movement and activity avoidance[65] leading to low adherence to an exercise regime[25]. Over time, discontinuation of physical activity will result in weight increase.

COPD

COPD is characterized by airflow limitation that is not fully reversible. A diagnosis of COPD is established if the post-dilatory ratio of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) is <0.70[66]. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases[67]. In an advanced stage, COPD is characterized by a protracted and agonizing course of gradually worsening and eventually debilitating dyspnoea. An important consequence of exertional dyspnoea is activity limitation[68]. Symptoms of COPD include a change in muscle fibre type[69-71], reduction of respiratory muscle function[70,71], insufficient control of respiration and cough techniques, blood oxygen saturation <90%[72,73], and cardiovascular problems, each of which may lead to exercise restrictions. Present exacerbation of the disease and severe COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or 4 can also lead to restrictions to exercises. GOLD stage 3 is defined as FEV1% 30–50% and GOLD stage 4 is defined as FEV1% <30%[66]. There are personal factors that lead to restrictions to exercise like fear of exertion and breathlessness and insufficient knowledge of the use of medication combined with exertion and an inactive lifestyle[74]. Environmental factors can cause restrictions, for example, the need for equipment measuring oxygen saturation in severe COPD patients[72,75]. Contraindications for exercise therapy include having pneumonia and exceptional loss of bodyweight: >10% in the past half year or >5% in the past month[72].

OA of the hand and feet

OA of the hand and feet is characterized by cartilage degeneration in one or more joints according to the criteria of the American College of Rheumatology (ACR)[76]. Criteria are hand pain, aching or stiffness for most days of the prior month plus 3 of the following 4 criteria: hard tissue enlargement of ≥2 of 10 selected hand joints, metacarpophalangeal

joint swelling in ≤2 joints, hard tissue enlargement of ≥2 distal interphalangeal joints, deformity of ≥1 of 10 selected hand joints. OA of the hand can cause pain, ROM and grip strength limitations, giving problems for grasping and holding, for example, walking aids or exercise equipment. The ACR has formulated no specific criteria for diagnosis of foot OA, but foot OA is characterized by degeneration in the tarsometaphalangeal joint and the talonavicular joint[77]. OA of the feet can lead to restrictions in weight-bearing exercise and training of daily activities like walking.

Low back pain

Low back pain is characterized by pain between the twelfth rib and the inferior gluteal folds, with or without leg pain[78,79]. Most cases are non-specific, but in about 10% of the cases a specific cause is identified, for example, a herniated intervertebral disc[78,79]. Restriction in movements and worsening of low back pain or signs of neuropathy can contribute to exercise intolerance[80,81]. Personal factors, including fear of exertion and movement, pain avoidance, inadequate pain coping styles and cognitions, and an inactive lifestyle can play a large role in restricting exercise [80,82,83]. Contraindications for exercise therapy include red flags like presence of specific spinal pathology (e.g., a tumor)[82,84].

Chronic pain

Chronic pain is defined by the ACR as pain present in at least two contralateral body quadrants and the axial skeleton, which has persisted for at least 3 months[85]. It is frequently associated with a number of other physical and affective symptoms such as fatigue, psychological distress and somatic symptoms[85]. Pain and fatigue may limit exercise tolerance. Personal factors such as inadequate pain coping styles and cognitions, fear of movement and pain avoidance and an inactive lifestyle[24] can play a large role in restricting exercise.

Depression

Depression is defined by the World Health Organization (WHO) as a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration[86]. It is known that depression plays an important role in developing activity limitations[7,87] and will restrict the level of physical activity and exercise. Restrictions for exercise therapy may be secondary symptoms of depression such as fatigue and pain. Personal factors like lack of therapy compliance, initiative or motivation, an inactive lifestyle and inadequate pain cognitions can play a role in restricting exercise[88]. Contraindications for exercise therapy include serious psychiatric disorders or a major depression which hampers the compliance to exercise therapy.

Low vision and hearing

Low vision is defined by the WHO as the best corrected visual acuity in the better eye <0.3, but >0.05, and/or visual field <20° around the fixation point[86]. Hearing impairment is defined by the WHO as the loss of hearing in one or both ears. There are different levels of hearing impairments. The level of impairment can be mild, moderate and severe or profound[86]. We will describe restrictions and contraindications for exercise for the mild or moderate impaired hearing group only. Associated poor balance may restrict performing exercise in patients with vision or hearing impairments. Orientation difficulties due to impaired vision and hearing may be a restriction to exercise[89]. Reduced capacity for processing images and text may also restrict the prescription of exercises, for example restriction in reading instructions on a home exercise regimen or the use of nonverbal communication. Personal factors like fear of falling[90], an inactive lifestyle[91], and environmental factors such as equipment, conditions (e.g., lighting) and location can all have restricting influence on exercising[92].

Chronic cystitis

Chronic cystitis refers to any inflammatory condition of the bladder. If the condition occurs more than twice in 6 months, it is considered recurrent. Recurrent urinary tract infections in women are strongly associated with incontinence[93]. Leakage of urine or fear of leakage of urine could inhibit exercising and could result in an inactive lifestyle[94].

Discussion

In the present study restrictions and contraindications for exercise therapy were identified for common comorbidities in patients with OA of the hip and knee. Although a high prevalence of comorbidity in patients with OA of the hip and knee has been reported[2-5] and exercise therapy is among the dominant interventions in OA[14-18], this is the first study describing restrictions and contraindications for exercise in OA patients with comorbidities.

We identified three types of restrictions for exercise therapy caused by comorbidities which may limit the application of exercise therapy, namely restrictions resulting from impairments in: (1) body structure and function, (2) psychological or behavioural impairments and (3) environmental impairments.

Cardiac diseases, hypertension, type 2 diabetes, COPD, and chronic cystitis mostly caused restrictions for exercise therapy resulting from impairments in body structure and function. Although these restrictions limit the therapeutic options for exercise, it is likely that appropriate adaptations ensure patient safety and will prevent adverse events. Some of the comorbidities studied provide absolute contraindications for exercise therapy and patient safety cannot be guaranteed, for example, pain in the chest before or during exercise in a patient with coronary heart disease[32].

Chronic low back pain, other chronic pain syndromes and depression mostly caused restrictions for exercise therapy resulting from impairments in psychological or behavioural factors. We found fewer absolute contraindications for exercise therapy in the literature for these comorbidities. It might be that this group of comorbidities has a lower risk of adverse events and the restrictions to exercise are more related to psychological or behavioural barriers.

Visual and hearing impairments mostly caused restrictions for exercise therapy resulting from environmental factors. The prevalence of visual and hearing impairments is often under-estimated. In the study of van Reeuwijk et al.[8], 26.8 and 11.5% of the study population had vision impairments in short distances and long respectively; 31.5% had hearing impairments in a group conversation. These comorbid diseases were also related to activity limitations in patients with OA of the hip or knee[8]. In our study, we found several restrictions for exercise therapy, indicating that these impairments need to be addressed in the rehabilitation of OA patients.

Obesity caused restrictions for exercise therapy resulting from impairments in body structure and function, as well as psychological and behavioural impairments. Combining exercise therapy with a weight loss program has been shown to result in moderately improved outcome, compared to exercise therapy alone[95]. To lose bodyweight, patients need to be more active and need to reduce their calorie intake. However, more activity may lead to more pain, exertion and fatigue, which may discourage patients to be physically active. To change this vicious circle, therapists need to adapt treatment to the restrictions resulting from impairments in body structure and psychological and behavioural impairments.

We have made a distinction between restrictions and contraindications for exercise therapy. A continuous process of clinical decision making is required to differentiate between restrictions and contraindications for exercise therapy. During exercise therapy, a restriction may change into a contraindication, for example, when in a poorly regulated diabetic patient (normally listed as a restriction) blood sugar levels frequently become lower than 5 mmol, exercise therapy is contraindicated because of hypoglycemia. The distinction between restrictions and contra- indications depends on factors such as context, severity of the comorbidity and time of occurrence.

Some limitations of the present study need to be discussed. Firstly, information on restrictions and contraindications for exercise therapy is scattered over the literature and it is not easy to identify relevant information. We cannot exclude the possibility that we have missed relevant information. Secondly, documentation on restrictions and contraindications was found only in relation to the comorbid disease itself (e.g., contraindication to exercise in diabetes). There is no information on restrictions and contraindications specifically related to OA and the comorbid disease. Thirdly, we have classified our inventory of restrictions and contraindications to the 'primary' comorbid disease (e.g., diabetes). However, OA patients frequently suffer from more than one comorbidity[4] and often these comorbid diseases interfere with each other; for example, OA patients with diabetes often have a cardiac disease as well[96]. This implies that the

presence of more than one comorbidity may require several, sometimes contradictory, adaptations of exercise. In case of multi-morbidity, implementation in clinical practice will require clinical reasoning and decision making by the therapist.

Further work is necessary to investigate how OA exercise should be adapted in the presence of comorbidity. A suggestion would be to combine the specific recommendations of exercise for OA of the hip or knee[14,16-18] with the specific exercise recommendations/ guidelines of the comorbid disease.

In conclusion, restrictions and contraindications for exercise in patients with OA of the hip and knee and comorbidity have been identified. This overview is helpful in decisions on the treatment of patients and will be instrumental in the development of a protocol for comorbidity related adaptations in exercise therapy for OA patients.

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Appendix 1. Full search strategy in PubMed for restrictions and contraindications for exercise therapy for common comorbidities in patients with hip and knee OA.

heart diseases OR heart failure OR cardiovascular diseases OR hypertension OR diabetes OR obesity OR chronic obstructive pulmonary diseases OR depression OR chronic cystitis OR urinary tract infection OR chronic pain OR wide spread pain OR low back pain	AND	exercise therapy OR resistance training OR strength training OR aerobic exercise OR endurance training OR exercise therapy OR behavioural therapy OR graded activity	AND	complication OR intolerance OR limitation OR contraindication OR restriction OR risk factors

Chapter 6

Development of comorbidity-adapted exercise protocols for patients with knee osteoarthritis

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Abstract

Background. Exercise therapy is generally recommended for patients with osteoarthritis (OA) of the knee. Comorbidity, which is highly prevalent in OA, may interfere with exercise therapy. To date, there is no evidence-based protocol for the treatment of patients with knee OA and comorbidity. Special protocols adapted to the comorbidity may facilitate the application of exercise therapy in patients with knee OA and one or more comorbidities.

Purpose. The purpose of this study was to develop comorbidity-adapted exercise protocols for patients with knee OA and comorbidity.

Method. Several steps were undertaken to develop comorbidity-adapted protocols: selection of highly prevalent comorbidities in OA, a literature search to identify restrictions and contraindications for exercise therapy for the various comorbid diseases, consultation of experts on each comorbid disease, and field testing of the protocol in eleven patients with knee OA and comorbidity.

Results. Based on literature and expert opinion, comorbidity-adapted protocols were developed for highly prevalent comorbidities in OA. Field testing showed that the protocols provided guidance in clinical decision making in both the diagnostic and the treatment phase. Because of overlap, the number of exercise protocols could be reduced to three: one for physiological adaptations (coronary disease, heart failure, hypertension, diabetes type 2, chronic obstructive pulmonary diseases, obesity), one for behavioral adaptations (chronic a-specific pain, nonspecific low back pain, depression), and one for environmental adaptations (visual or hearing impairments). Evaluation of patient outcome after treatment showed significant ($P < 0.05$) and clinically relevant improvements in activity limitations and pain.

Conclusion. Comorbidity-adapted exercise protocols for patients with knee OA were developed, providing guidance in clinical reasoning with regard to diagnostics and treatment. To evaluate the effectiveness of treatment in line with our protocols, a randomized clinical trial should be performed.

Introduction

Osteoarthritis (OA) is among the diseases with the highest rates of comorbidity[1,2]. 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 under study"[3]. Common comorbidities in OA include cardiovascular diseases, diabetes, obesity, chronic obstructive pulmonary disease (COPD), chronic pain, depression, and visual and hearing impairments[4]. Comorbidity in older adults with OA is associated with more pain, greater limitations in daily activities, and a worse prognosis with respect to these limitations[5,6].

Performing exercises is one of the key recommendations in current guidelines for the management of knee OA[7,8]; this has been found to relieve pain and to reduce activity limitations[9]. Comorbidity may interfere with the application of exercise therapy in OA, however[10]; for example, in persons with heart failure, only moderate-intensity resistance training is recommended, and the last repetitions should not be straining[11]. Furthermore, the warming-up and cooling-down sessions should be prolonged; perceived exertion and/or dyspnea scales should take precedence over heart rate and work rate targets; and isometric exercises should be avoided[12].

Because comorbidities have a significant influence on prognosis[6] and may influence treatment, they should be routinely taken into account[13]. Unfortunately, there is no evidence-based protocol available for the treatment of patients with knee OA and comorbidity[14]. Current OA guidelines do not offer specific recommendations concerning comorbidity-associated exercise adaptations[7,8,15]. It is often not feasible to combine different disease-specific treatment guidelines, since one treatment might interact negatively with another treatment or affect the natural course of a coexisting disease[16]. Furthermore, in clinical practice, older adults with knee OA and (severe) comorbidity are seldom referred for exercise therapy; often drop out at an early stage of the treatment; or may be treated inadequately (e.g., therapists may reduce the intensity of treatment to an ineffective level).

When dealing with comorbidity, a patient-centered rather than a disease-oriented approach, in which the process of decision making should be based on clinical reasoning, is preferred[16]. The Hypothesis-Oriented Algorithm for Clinicians (HOAC) II[17] describes a framework for clinical decision making in physical therapy; it addresses examination, evaluation, diagnosis, prognosis, and intervention in a specific patient. Although the HOAC II gives general direction in clinical reasoning, specific advice concerning comorbidity-adapted OA exercise therapy and comorbidity is not available in the literature.

Therefore, there is a need for comorbidity-adapted protocols for exercise therapy in older adults with knee OA and comorbidity. These protocols are expected to improve

the application of OA-specific exercise therapy, may help to avoid adverse events, and may improve the outcome of exercise therapy. The evaluation of complex interventions requires a phased approach, because of specific difficulties in developing, identifying, documenting, and reproducing the intervention. To design a complex intervention, we used the Medical Research Council (MRC) framework, which was developed to help researchers to define clearly where they are in the research process[18]. The framework describes four phases in the design and evaluation of complex interventions: the preclinical or theoretical phase; Phase I, or the modeling phase; Phase II, or the exploratory trial; and Phase III, or definitive randomized controlled trial. In the preclinical or theoretical phase, the evidence that the intervention might have the desired effect is identified. The theoretical basis for the intervention is reviewed and potentially active ingredients are identified. In Phase I, or the modeling phase, the components of the intervention are defined and tested, using qualitative techniques (e.g., case studies). In Phase II, or the exploratory trial, the optimum intervention is developed, based on the information gathered in Phase I. Phase III consists of the definitive randomized controlled trial, and Phase IV the long-term implementation of the intervention[18].

In a previous study, restrictions and contraindications for exercise therapy for patients with knee OA and comorbidity (theoretical phase) were identified in the literature[10]. The purpose of the present study was to develop comorbidity- adapted exercise protocols for older adults with knee OA and comorbidity (Phase I, modeling phase).

Methods

Development of comorbidity- adapted protocols

Five steps were undertaken to develop comorbidity adapted protocols. First, based on previous work[4], we selected comorbidities in OA that 1) are common (present >5%), and 2) have impact on pain and/or affect daily functioning. The following comorbidities were selected: cardiac dis- eases; hypertension; type 2 diabetes; obesity; COPD; low back pain; chronic pain; depression; and visual or hearing impairments[4]. Second, a literature search in the PubMed (publication date range 1966–2009) database was conducted to make an inventory of restrictions and contraindications for exercise therapy in patients with OA of the knee and highly prevalent comorbidities. The method and the results of this search have been reported previously[10]. Third, a preliminary version of the protocols was developed. Based on the results of the first two steps, comorbidity-related adaptations to the diagnosis and treatment of OA were described. Guidelines on exercise therapy in each comorbidity (e.g., cardiac disease, diabetes, COPD, and nonspecific low back pain) were consulted[19-23]. If there was no exercise therapy guideline available for a specific comorbidity, an available medical guideline was used (e.g., guidelines for depression or hypertension)[24,25]. The principles described in these guidelines were incorporated into the adapted protocols for exercise therapy in OA of the knee. Fourth,

the preliminary versions of the protocols were discussed with clinical experts in the fields of each comorbid disease and, subsequently, based on their feedback, further improved. The experts had extensive experience in the fields of cardiac rehabilitation, diabetes, COPD rehabilitation, chronic nonspecific pain, and visual and hearing impairments. Advice was sought on the treatment of each comorbidity and on how the principles of exercise therapy and training of the comorbid diseases should be incorporated into the exercise regimen for OA of the knee. After optimizing the protocols, the clinical experts were consulted again for the collection of feedback and to gain final consensus on the protocols.

Fifth, the draft protocols were field-tested in a pilot study in patients with knee OA and the target comorbidities. Thereafter, the protocols were further improved, based on the feedback from therapists and patients, leading to a final version of the protocols. The method for field-testing of the protocols in this pilot study is further described below.

Field-testing

Procedure. Participants were referred to our rehabilitation center by their general practitioner because of persistent knee problems. Participants' eligibility was assessed by physical examination by a rheumatologist and a rehabilitation physician. Physical measurements were carried out by a research assistant and questionnaires were filled out by the participants. The questionnaires and physical tests were administered at baseline and directly after treatment. The study was approved by the Medical Ethical Review Board of the Slotervaart Hospital and Reade, Amsterdam, the Netherlands. All participants gave written informed consent and the study was conducted in accordance with the Handbook for Good Clinical Research Practice of the World Health Organization and Declaration of Helsinki principles[26].

Participants. Fourteen participants were recruited. Inclusion criteria were: 1) diagnosis of knee OA according to the clinical American College of Rheumatology criteria[27]; 2) presence of at least one of the target comorbidities, i.e., coronary disease, heart failure, hypertension, type 2 diabetes, obesity, COPD, chronic pain, nonspecific low back pain, depression, and vision and/or hearing impairment (diagnosed by a medical specialist); 3) severity score ≥2 of the comorbidity on the Cumulative Illness Rating Scale[28], indicating that the comorbidity has an impact on daily activities; and 4) the primary treatment goal should be OA related (instead of comorbidity related). Exclusion criteria were: 1) indication for total knee replacement; 2) inability to participate in treatment, e.g., due to transport problems; 3) insufficient capacity in the Dutch language.

Therapists. The protocols were applied and evaluated by three qualified physical therapists with extensive experience (3, 8, and 12 years) in knee/hip rehabilitation OA treatment. In addition, two of the three therapists were members of the Committee for Hip and Knee OA Guideline Development for the Royal Dutch Society of Physical Therapy.

Measurements. To evaluate the treatment process, the therapists completed a weekly registration form, providing information about the duration of the treatment period, content of the treatment, adaptations in the treatment due to the comorbidity, and any problems encountered in applying the protocols. Adverse events, defined as any undesirable experience occurring in a subject during the study (regardless of whether or not this was related to the treatment), were registered. To evaluate the feasibility of the protocols, semi-structured interviews were held by the first author (MdR) along with therapists and participants. Topic lists were used to structure the interview (see Table 1). To evaluate patient outcome after treatment, performance-based tests were performed and self-reported questionnaires were filled in by participants at baseline and directly after treatment.

Functional ability was assessed with self-reported questionnaires and performance-based measurements. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a disease-specific, self-administered questionnaire, developed to study patients with hip and knee OA[29,30]. The WOMAC consists of 24 questions grouped into three subscales (pain: five questions; stiffness: two questions; and physical function: 17 questions) and scaled in a 5-point Likert (LK) scale. The maximum score in the LK scale is 20 points for pain, 8 points for stiffness, and 68 points for physical function. Higher scores indicate more pain, stiffness, or limitations. The WOMAC is widely used in clinical research, and has been shown to be reliable, valid, and responsive for use in patients with OA[29-32]. The Patient-Specific Functioning Scale was used to evaluate limitations in activities of the individual patient[32]. Patients were asked, "Which activities do you perceive as important and were hampered by knee pain during the last week?" A list of activity suggestions was offered to support recall, and patients were allowed to provide other limited activities that were not on the list. Of these activities, the patient selected three main activities and ranked them in order of importance. The difficulty of performance of the main activities were scored by self-assessment on a numeric rating scale ([NRS from 0-10] 0= no problems to perform the activity; 10= impossible to perform the activity). Patient-Specific Functional Scale is an efficient and valid measure for assessing limitations in activities and change in limitations in persons with knee dysfunction[32]. The Get Up and Go test[33,34] was performed with subjects seated on a high standard chair (seat height 49 cm). The subjects were instructed to stand up without the help of the arms on the command "go" and walk 15 m along an unobstructed corridor as fast as possible without running. The chronometer was stopped when they reached the 15 m mark on the floor. All subjects wore walking shoes. Patients who normally used walking devices were allowed to use them during the test. A longer time taken to perform the test was considered a higher activity limitation. The 6-minute walk test was completed by patients on a 30 m walkway. Patients were instructed to walk their maximum distance in a 6-minute period. The total distance covered in meters during 6 minutes of walking was scored[35,36].

Quality of life was assessed with the 36-Item Short-Form Health Survey (SF-36)[37]. The SF-36 is a widely applied generic instrument for measuring health status and consists

of eight dimensions: physical functioning, social functioning, physical role, emotional role, mental health, energy, pain and general health perception. The SF-36 gives scores on a 0–100 scale, with higher scores indicating better health. The reliability (median reliability coefficient 0.85 for all subscales) for the SF-36 has been established[38-40], and its validity has been shown in an elderly population, in which the instrument distinguished between those with and without poor health[41].

Psychological functioning was assessed with the Hospital Anxiety and Depression Scale (HADS)[42]. The HADS is a self-report rating scale of 14 items on a 4-point LK scale (range: 0–3). It is designed to measure anxiety and depression (seven items for each subscale). The total score is the sum of the 14 items, and, for each subscale, the score is the sum of the respective seven items (ranging from 0–21). The HADS is widely used in clinical research and has been shown to be reliable, valid, and responsive for use as a screening tool in patients with OA[43].

Pain was assessed with a subscale of the WOMAC. Muscle strength was assessed for flexion and extension of the knee using an isokinetic dynamometer (EnKnee; Enraf-Nonius B.V., Rotterdam, the Netherlands)[44]. Quadriceps and hamstring strength were measured isokinetically at 60°/second. Patients performed a maximum of three test repetitions to measure the strength of the quadriceps and hamstrings for each knee. Mean muscle strength per leg was calculated to obtain a measure of overall leg muscle strength (in Nm). Subsequently, mean muscle strength was divided by the patient's weight to control for the correlation between muscle strength and weight. This measure (in Nm/kg) was used for the analyses. Excellent intra-rater reliability (intraclass correlation coefficient 0.93) has been reported for this measure in knee OA patients[45].

At the end of the treatment, patients were asked to rate global perceived effect (GPE) of the treatment[46] on a scale of 1–9, with a score of 1 meaning much better, 5 meaning no change, and 9 meaning much worse. Patient satisfaction with the kind of treatment was measured by the NRS (0–10), with higher scores indicating greater satisfaction.

Additional data recorded were age, sex, and duration of complaints. The weight (kg) and height (m) were measured in standing position. Body mass index was calculated using the standard formula (kg/m^2). Comorbidity was scored with the Cumulative Illness Rating Scale[28]. Radiographs of the knee were scored using the grading scales proposed by Kellgren and Lawrence (K&L)[47].

Table 1 Brief summary of specific adaptations to osteoarthritis exercise therapy due to comorbid disease

Hypertension	• Contra indications for participation in the training program include: resting systolic blood pressure of >200 mmHG or diastolic blood pressure of >115 mmHG. • Check blood pressure lowering medication with physician. If adequate but still hypertensive, low-to-moderate intensity strength training should be performed instead of high-intensity strength training. • Be aware that medication to lower blood pressure, like beta blockers, can limit exercise tolerance in persons without myocardial ischemia.
Coronary disease/ heart failure	• Contraindications for participation in the training program include: progressive increase in heart failure symptoms; severe ischemia of the cardiac muscle upon exertion; dyspnea while speaking; respiratory frequency of more than 30 breaths per minute; heart rate at rest > 110 bpm; VO_2 max < 10 mL/kg/minute; ventricular tachycardia upon increasing exertion; fever; acute systemic diseases; recent pulmonary embolism (< 3 months ago) causing severe hemodynamic strain; thrombophlebitis; acute pericarditis or myocarditis; hemodynamically serious aortic stenosis or mitral valve stenosis; presence of unstable angina, for example, pain in the chest at rest or pain that does not react to specific medication; NYHA functional classification class 4, myocardial infarction less than 3 months before the start of the training program; atrial fibrillation with rapid ventricular response at rest (> 100 bpm); weight gain of > 2 kg within a few days, whether or not accompanied by increased dyspnea at rest is related to weight gain. • Use the results of a maximum or symptom-limited exercise test to calculate the individual aerobic exercise intensity in patients with cardiac problems. (If the patient is using beta blockers, the exercises should be based on the results of the maximum or symptom-limited exercise test with beta blocker use). The optimized exercise zone can be calculated using the Karvonen formula, which calculates the exercise heart rate as a percentage of the heart rate reserve (the difference between the maximum heart rate and the heart rate at rest), added to the resting heart rate. Patients should start with 2 weeks of exercise at 40–50% of their VO_2 max then gradually raise the training intensity from 50% to 80% of their VO_2 max or VO_2 reserve. • Base the exercise intensity on a percentage of the maximum capacity expressed in watts or METs, and/or a Borg RPE scale50 (6–20)[50] if the patient's heart rate does not rise sufficiently during the maximum or symptom-limited exercise test • Prolong the warming-up and cooling down sessions to decrease the risk of cardiac decompensation. • Reduce the training intensity in warm climatic conditions • Terminate the exercise session in patients with coronary heart disease if any of the following signs of strain upon exertion apply: angina; impaired pump function (shortness of breath disproportionate to exertion; abnormal fatigue disproportionate to exertion; increased peripheral/central edema); arrhythmias (high heart rate not in proportion to exertion, irregular heartbeat, changes in known arrhythmias); abnormal increase or decrease of blood pressure; fainting; dizziness; vegetative reactions (e.g., excessive perspiring, pallor). • Terminate the exercise session in patients with heart failure if any of the following reasons for excessive strain apply: severe fatigue or dyspnea out of proportion to the level of exertion; increase in breathing rate out of proportion to the level of exertion; low pulse pressure (< 10 mmHg); reduction of systolic blood pressure during exercise (> 10 mmHg); increasing ventricular or supraventricular arrhythmias; angina; vegetative reactions such as dizziness or nausea. • Avoid a rapid increase in the peripheral resistance training in patients with heart failure, as this increases the afterload strongly and the risk of decompensation. For improving muscle strength, start with 2 weeks on 30-40% of 1RM and then gradually increase the resistance from 50% to 70-80% of 1RM. • Perform interval training for patients in poor physical condition instead of aerobic training.
Type 2 diabetes	• In the case of insulin-dependent diabetes patients monitor blood glucose levels before and after the training and in the evening. • Postpone exercise training in case of blood glucose values ≤ 5 and ≥ 15 mmol/L. • Avoid intensive resistance training in type 2 diabetes patients with retinopathy grade ≥3. • Check patients with type 2 diabetes regularly for wounds and sensory defects (monofilaments). • Be aware of autonomic neuropathy. This may result in decreased cardiovascular response to exercise, impaired response to dehydration, impaired thermoregulation due to impaired skin blood flow and sweating, postural hypotension, and/or decreased maximum aerobic capacity. The patient's heart rate may not rise or abate sufficiently during or after the training.

Table 1 Continued

COPD	• Contraindications for participation in the training program include pneumonia and exceptional loss of bodyweight (10% in the past half year or >5% in the past month). • Start with interval training in patients with COPD with ventilator limitation or disturbed oxygen transport in the lungs (hypoxemic [saturation <90%]/hypocapnic [Pa CO_2 >55 mmHg] during exercising). Start endurance training if walking on 70% of maximum watts level for at least ten minutes is possible. • Check saturation level: patients with pulmonary problems should not desaturate; this usually means that O_2 saturation (SaO_2) should remain ≥ 90% during exercising (and should not fall by ≥ 4%). • Give advice and exercises targeting body position and breathing if hyperinflation is present. • Be aware of a poor nutritional status. • Coach the patient when there is presence of fear of exercise due to breathlessness.
Obesity	• Stimulate weight reduction due to overweight or obesity and/or refer to a dietician. • Reduce weight–bearing exercises because of increase in knee joint pain . • Reduce the training intensity in warm climatic conditions.
Chronic nonspecific pain/ nonspecific low back pain/ depression	• Contraindications for participation in the training program include serious psychiatric disorders, a major depression or specific spinal pathology. Provide a graded activity program[49] • Educational message: not pain relief, but improvement of functioning is the primary goal of the treatment. Exercise and physical activity are recommended. The performance of physical activity should not depend on the amount of pain. • With patients, select problematic activities (maximum of three) from an activity list. • Set short-term and long-term goals for each activity and record them in a treatment agreement form. • Determine baseline values of the patient by performing the selected activities until (pain) tolerance over 1 week and record these activities in a diary. • Determine the duration of the treatment program. An individually-based scheme is made on a time-contingent basis for each activity and exercise, starting slightly under baseline values and increasing gradually towards the preset short-term goal. Patients should neither underperform nor overperform on this gradually increasing scheme. The exercise quotas are preset and not subject to change during the course of the intervention, regardless of level of pain. • Use performance charts to record and visualize the performance of activities and exercises. • Give positive reinforcement toward healthy and active behaviour; pain behaviour is ignored to extinguish the pain behaviour. • Coach patients on coping with stress and fear of movement. • Interrupt the gradual increase of activities when an active inflammatory process is suspected or diagnosed (e.g., redness of the knee, increase in knee effusion, or comparable symptoms). Hereafter, the increase of activities starts at a lower level. In case of recurrent inflammatory processes, the treatment goal needs to be changed and the rate of increasing activities needs to be decelerated. • Adapt the starting position of exercises, reduce the training intensity, and advise the patient to stay active in case of acute/subacute low back pain (< 3 months). • Give the patient time to discuss feelings due to depression and avoid appointments early in the morning.
Hearing and or visual impairments	• Change the way in which patients are handled and use more manual guidance in case of visual impairments. • Check whether or not the patient has understood the information in case of hearing impairments. • Change the training environment when possible, e.g., take into account the lighting or background noise in the exercise hall, line-of-sight communication, or poor auditory impressions. • Add balance training in case of poor balance in patients with hearing or visual impairments. • Coach patients in order to reduce fear of falling. • Use a sign-language interpreter if normally used by the patient. • Be aware of orientation difficulties due to hearing or visual impairments. • Adapt the font or size of the font to prescribed exercise instructions for those with impaired vision.

Abbreviations: 1RM, one-repetition maximum; bpm; beats per minute; COPD; chronic obstructive pulmonary disease; MET; metabolic equivalent; NYHA; New York Heart Association; $PaCO_2$, partial pressure of oxygen in the blood; SaO_2, saturation level of oxygen in haemoglobin; VO_2 max, maximal oxygen uptake.

Analysis. In order to evaluate the treatment process, a descriptive analysis of the treatment registration forms was performed. The feasibility of the protocols was evaluated by analyzing the notes that were taken during the interviews with the therapists and participants. A faithful depiction of the experiences of the participants and therapists was achieved by verifying with the participant or therapist whether the remarks were interpreted in a correct way by giving a summary at the end of the interview. To analyze the patient outcomes after treatment, change scores were determined by subtracting the baseline scores from the posttreatment scores. Because the data were not normally distributed, pre- and posttreatment scores were analyzed with a nonparametric Wilcoxon signed-rank test (*P*-value ≤0.05).

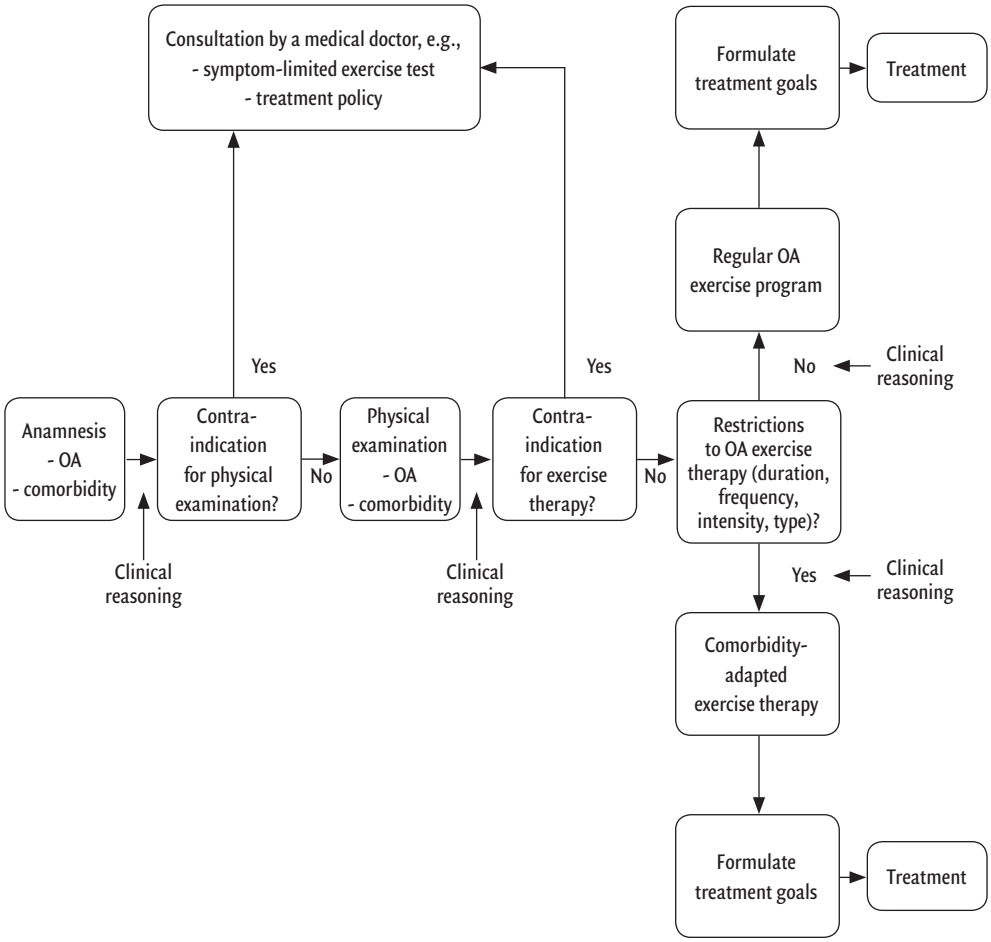

Figure 1. Flow chart of physical therapy intake

Results

Results of the development of the protocols

Eleven draft protocols for exercise therapy in persons with knee OA and comorbidity were developed based on our literature search and consultation with experts. Regular OA exercise therapy as recommended in OA guidelines[7,8,15] was the basis of the protocols. In the protocols, it was made explicit 1) how comorbidity compromises the regular application of exercise therapy in OA of the knee, and 2) how the therapist should consider the whole system, consisting of integrated body structures/functions and activities instead of separate organs, for all phases of treatment (examination, evaluation, diagnosis, prognosis, and intervention). The HOAC II framework was used to incorporate principles of clinical reasoning into the protocols[17].

The protocols on exercise therapy in persons with knee OA and comorbidities consist of a diagnostic phase and an intervention phase. Each step in the protocols encourages clinical reasoning in order to tailor the diagnostic and intervention phase to the individual person. To facilitate this process, we designed a flowchart for the diagnostic and intervention phase (Figure 1).

The diagnostic phase includes an anamnesis, physical examination, establishment of treatment goals, and determination of the treatment strategy. During the anamnesis, OA-related problems, comorbidity-related restrictions and contraindications for exercise therapy are identified. There- after, a clinical decision is made as to whether physical examination is possible, or whether the referring physician needs to be consulted because of contraindications for physical examination or the need for further medical information. With respect to the latter, test results of a maximum symptom-limited exercise test may be required (for example, for persons with heart failure) to establish an appropriate training intensity.

If there are no contraindications for physical examination, comorbidity-related examination is performed according to the protocols (e.g., foot examination in patients with type 2 diabetes). Subsequently, a decision is made as to whether there are contraindications or restrictions for exercise therapy. In case of a contraindication, referral to a physician is indicated. If there are comorbidity-related restrictions for exercise therapy, a comorbidity-adapted program is indicated. In this phase, the therapist also considers whether referral to professionals in other disciplines (e.g., a dietician, psychologist, or occupational therapist) is indicated.

With regard to the intervention phase, the basic intervention in persons with knee OA consists of regular exercise therapy, according to the Royal Dutch Society for Physical Therapy's guideline for physical therapy in patients with knee OA[15], which is similar to international guidelines[7,8]. Regular exercises for patients with OA comprise exercises aiming at improvement of muscle strength, aerobic capacity, flexibility, and ability to perform daily weight-bearing activities such as walking, stair climbing, and transfers (e.g., sitting down or standing up from a chair). Individual therapy is given two times per week for between 30 to 60 minutes per session. The training intensity is increased

Table 2. Patient characteristics and evaluation process evaluation of the treatment (n=11)

Patient number	Comorbid conditions	Sex	Age	Duration of knee complaints, years	K&L grade	BMI kg/m²	Adaptations to the treatment in patients with OA and comorbidity
1	Coronary disease, obesity, DM II	F	62	> 40	1	36	• Referred back to the cardiologist due to fluctuating blood pressure. • Postponement of strength and aerobic training until catheterization and fluctuations in blood pressure were under control through medication. • Low training intensity or limited repetitions in exercise or extended pauses during and between exercise due to angina pectoris (average Borg RPE score training intensity 12 [scale 6-20][50]). • There were no specific modifications to the treatment due to diabetes.
2	Heart failure, hypertension hand OA, hearing impairment	F	75	>30	2	21	• Referred back to general practitioner due to high blood pressure (196/105 mmHg). • Postponement of strength and aerobic training until the blood pressure medication was adjusted. • Referred back to the cardiologist due to patient's cardiac-related fear of exertion. • Occasional low training intensity or limited repetitions in exercise due to dyspnea (average Borg RPE score 12 [scale 6-20][50]). • Extended pauses during and between exercises. • Coaching on fear of exertion and improving knowledge of the heart disease and exercise options. • There were no specific modifications to the treatment due to hearing impairment.
3	DM II, obesity, hypertension	F	64	>12	2	53	• Referred back to general practitioner due to high blood pressure (196/100 mmHg). • Postponement of strength training and aerobic training until the blood pressure medication was adjusted. • Monitoring blood glucose levels before and after the training and in the evening (during the first two months of therapy). • Postponement of exercise training because of blood glucose level <5 mmol/L • Whole-body exercise instead of only exercise of the lower extremities due to decreased loadability of knee joint and surrounding connective tissue. • At the beginning of the program low training intensity and extended pauses during and between exercises due to decreased loadability (average Borg RPE score 12 [scale 6-20][50]). • Coaching on fear of exertion and improving knowledge of diabetes. • Reducing weight-bearing exercises. • Referred to a dietician.
4	Coronary disease, hypertension	M	51	2	1	30	• Referred back to general practitioner due to high blood pressure (180/110 mmHg). • Postponement of strength and aerobic training until the blood pressure medication was adjustment • Training intensity determined by Borg scale instead of the heart frequency due to use of beta blockers (average Borg RPE score 12 [scale 6-20][50]).
5	Coronary disease, COPD, Hypertension, obesity	F	59	6	-	38	• Improvement of knowledge of the use of medication combined with exertion. • Patient was already under treatment by a dietician (lost 16kg). • At the beginning of the program, low training intensity and extended pauses during and between exercise due to decreased loadability (average Borg RPE score 13 [scale 6-20][50]).

Table 2. Cont'd

Patient number	Comorbid conditions	Sex	Age	Durations of knee complaints	K&L grade	BMI kg/m²	Adaptations to the treatment in patients with OA and comorbidity
6	COPD, obesity, depression, non-specific LBP, hearing impairment	M	59	12	1	49	• Referred back to general practitioner due to decreased cardiovascular response to exercise. • Additional breathing exercises due to inadequate breathing pattern. • Whole-body exercises instead of only exercise of the lower extremities due to decreased loadability of the lower extremities. • Low training intensity or limited repetitions in exercise and extended pauses during and between exercises due to decreased loadability, dyspnea and fatigue (average Borg RPE score 15 [scale 6-20][59]) at the beginning of the program. • Low training intensity exercises in hot weather due to reduced thermoregulation. • Shortening the training session due to dyspnea and dizziness • Adaptation of starting position of exercises due to low back pain • Stimulation of positive attitudes towards physical activities and giving room to discuss feelings, due to the depression, • There were no specific modifications to the treatment due to hearing impairment.
7	Chronic pain, hypertension	F	46	10	2	27	• Use of a time-contingent approach, focussing on improvement of activities in daily life and not pain relief. Application of graded activity principles and information about pain, and coaching on coping with pain. • Limited possibilities to improve aerobe capacity due to hypertension medication.
8	Non-specific LBP	F	60	11	1	27	• Use of a time-contingent approach with a focus on improvement of activities in daily life and not on pain relief. Application of graded activity principles, information about pain, and coaching on coping with stress and fear of movement. • Adaptation of starting position of the exercises due to nonspecific low back pain.
9	Nonspecific Low back pain	M	59	6	3	28	• Reduction of the training intensity due to nonspecific low back pain • Adaptation of starting positions of the exercises due to nonspecific low back pain
10	Depression, Hypertension, DM II	M	62	11	4	28	• Extra attention to providing positive feedback, stimulation of positive attitudes towards physical activities, and giving time to discuss feelings, due to the depression. • No appointments scheduled early in the morning due to fatigue. • There were no specific modifications to the treatment due to hypertension and diabetes. • Prolonged period of low-frequency therapy sessions to encourage integration of exercises in daily life.
11	Low vision, Non-specific Low back pain	F	69	>30	4	27	• Changes in feedback from the therapist by means of using more manual guidance. • Changing the training environment, especially taking into account the lighting in the exercise hall. • There were no specific modifications to the treatment due to low back pain.

Note: - denotes missing data.
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM II, type 2 diabetes; F, female; K&L Kellgren and Lawrence[47]; M, male; OA, osteoarthritis.

from 40%–85% of the maximum oxygen uptake (VO_2max) or the heart rate reserve. The increase of training intensity is monitored by using the Borg RPE scale (6-20) or heart rate frequency. The eventually obtained training intensity depends on the condition of the patient. Participants are encouraged to perform exercises at home at least five times per week. The treatment ends when treatment goals are achieved or when no further improvement is feasible.

The regular OA exercises are adapted to the comorbidity by changes in the duration, frequency, intensity, and type (content) of exercise therapy. The exact adaptations depend on restrictions for exercise therapy identified by the therapist in the diagnostic phase (anamnesis and physical examination). The specific options for adaptations to OA exercises are listed in the protocols and summarized in Table 1.

Results from the field-testing

Fourteen participants were included in the study. Three participants dropped out, one because of ocular problems due to diabetes and two others because of comorbidities not included in this study (hemochromatosis and cancer). Drop-out was unrelated to treatment. Nine of the eleven remaining participants had two or more comorbidities (Table 2).

Table 2 provides results of the evaluation of the treatment process. The duration of the treatment ranged from 14 to 20 weeks. The normal duration of the treatment in persons with knee OA without comorbidity in our center is 12 weeks. There were no adverse events reported during the study.

In participants with comorbidities resulting in physiological impairments (coronary disease, heart failure, type 2 diabetes, COPD, and obesity; n= 6), four were referred back to the general practitioner or specialist because of a high or fluctuating blood pressure. In these cases, while medication was adjusted, aerobic and strength exercises were postponed during the first 4 to 6 weeks of treatment. The training intensity started at a low level and was gradually increased. Whole-body training or arm training was applied when loadability of the lower extremities was extremely low. This occurred mostly in participants with more than two comorbidities.

In participants with comorbidities resulting in behavioural impairments (chronic pain and nonspecific low back pain; n = 4), adaptations were made by using a combined

behavioural approach with regular OA exercises. In a time-contingent manner, the amount of physical activity was gradually increased combined with a gradual increase in the level of regular OA exercise, such as strengthening exercises of the lower limbs. Depression restricted the performance of OA exercises in two of the eleven participants. Adaptations were made by giving extra attention to providing positive feedback, stimulating a positive attitude toward physical activities, and gradually increasing the level of physical activity.

In one participant with low vision, environmental restrictions led to adaptations in training equipment, training conditions (e.g., lighting), and treatment location. No specific adaptations of the OA exercise program were needed in participants with hearing impairments (two of eleven participants).

With regard to the feasibility of the protocols, the physical therapists who tested the protocols found that they offered guidance in setting up a treatment plan/strategy, making clinical decisions, and adapting the treatment to the comorbid disease (Table 3). The following quote is from one of the physical therapists:

'By using the protocol I had more knowledge about the physical capabilities of the person with OA and this specific comorbidity. Because of this I was able to design a more adequate training program and to better estimate the training intensity. This enabled me to treat the patient more intensively than I would have done without the use of the protocol'.

All physical therapists indicated that the list of restrictions for exercise therapy was a conveniently arranged checklist for the diagnostic and treatment phases. The list was also helpful in the process of clinical decision making, especially when more than one comorbidity was present. If more than one comorbidity was present, more emphasis was placed on the protocol(s) for the comorbidity with the highest impact on physical functioning.

Importantly, the therapists agreed with the suggestion to increase feasibility by reducing the protocols to three main protocols. Protocol A concerned physiological adaptations (for persons with coronary artery disease, heart failure, hypertension, type 2 diabetes, obesity, and/or COPD). Protocol B concerned behavioural adaptations (for persons with chronic pain, nonspecific low back pain, and/or depression). Protocol C concerned environmental adaptations (for persons with visual and/or hearing impairments).

Three of eleven participants would have been excluded from treatment in the absence of the protocols. The therapists were less afraid to increase training intensity. They tailored the programs according to the individual's capacity, hereby preventing adverse events. The average duration of the intake consultation was 90 minutes per patient. The protocols were feasible in persons with mild (K&L grade 1) to severe (K&L grade 4) OA.

All participants were satisfied with the applicability of the protocols, as indicated by a mean score of 8 points (range: 7–10) on the NRS of satisfaction. None of the participants objected to the extended duration of the intake phase. Nine of eleven participants mentioned that the therapists appeared to have a good level of knowledge about their health condition(s), which gave them more confidence in performing exercises. The following quote is from one participant:

'I felt more con dent in performing exercises and was less afraid to get hypoglycemia during or after the training, because the therapist had more knowledge about my diseases and training possibilities. When I was treated in primary care for my knee complaints, I dropped out in an early phase of the treatment because my knee pain was getting worse due to the high training intensity at the beginning of the program. In addition, I was afraid when feeling an increase in my heart rate during the exercises and of becoming hypoglycemic. Therefore, I wasn't really motivated to do my exercises'.

Patient outcomes after treatment are presented in Table 4. On the WOMAC physical functioning scale, a statistically significant improvement ($P \leq 0.05$) was found, with an average increase of 18% above the baseline score. For the 6-minute walking test, the average increase was 13% above the base- line score ($P \leq 0.05$). There was also a statistically significant decrease in pain, as measured with the WOMAC pain subscale, where the average was 16% above the baseline score ($P \leq 0.05$). The main activity limitation (as ranked by each participant as being most important) on the Patient-Specific Functioning Scale questionnaire also showed a statistically significant improvement ($P \leq 0.05$). No

Table 3. Feasibility of the protocols

Topic	**Summary of therapists' answers**
Was it possible to integrate the protocols when multiple comorbidities were present? Did you follow one primary protocol if multiple comorbidities were present?	Integration of the protocols was possible. If more than one comorbidity was present, more emphasis was placed on the protocol for the comorbidity with the highest impact on physical functioning. This could change over time because of changes in health status.
Is it possible to reduce the 11 protocols to fewer protocols?	The 11 protocols can be reduced to three main protocols: a protocol for physiological related impairments, a protocol for behavioural related impairments and a protocol related to environmental impairments. Reducing the number of protocols is expected to increase the feasibility
Did the protocol help you in your clinical decision making process during in the diagnostic and treatment phases? If so, in what way(s)?	The protocol was helpful in clinical decision making and prevented exclusion from treatment due to lack of knowledge about the comorbidity or loadability of the patient. It was possible to tailor the exercise program to the individual capacity of the patient.
Did you encounter any obstacles when providing the treatment?	No specific obstacles were mentioned.
Do you have suggestions for improvements?	Reduce overlap in the protocols in the diagnostic and treatment phase if more comorbidities are present.
Topic	**Summary patients' answers**
Were the patients satisfied with the treatment?	Mean score on the NRS (0-10) was 8 points (range 7-10)
Were there any comorbidity-related problems during the treatment?	No specific problems were mentioned
Was the duration of the diagnostic phase (too) intensive for the patient?	None of the patients experienced problems with the extended duration of the intake phase. Patients were satisfied with the attention to their health conditions, which gave them more confidence in performing exercises.
Did the patients have any suggestions to improve the protocol?	One patient suggested to plan a standard appointment with a social worker or psychologist in the intake phase.

Table 4. Treatment outcome

Patient	WOMAC physical functioning (0-68)[a,29-31]		PSFL main problem[b,32]		Get Up and Go test,[33,34] seconds		6-minute walk test[35,36]		SF-36 Physical functioning (0-100)[c,37-41]		SF-36 General health perception (0-100)[c,37-41]		SF-36 Health change (0-100)[c,37-41]		HADS (0-21)[42,43]		WOMAC pain (0-20)[a,29-31]		Strength upper limb (Nm/kg)		GPE Scale (1-9)[46]
	To	T1	To	T1	To	T1	To	T1	To	T1	To	T1	To	T1	To	T1	To	T1	To	T1	T1
1	42	27	8	7	11.7	17.1	375	366	30	30	45	35	50	50	5	3	12	11	0.55	0.85	4
2	30	11	5	1	9.5	8.0	354	436	55	55	55	65	25	75	5	7	10	7	0.75	0.97	2
3	46	50	9	6	21.8	20.9	204	210	25	15	35	45	25	25	5	5	12	12	0.31	0.12	3
4	53	33	8	2	10.3	9.8	460	518.5	5	20	65	75	0	75	2	2	14	9	1.35	1.51	2
5	41	38	8	5	9.7	11.5	543	516	45	40	60	45	25	0	3	1	9	10	0.85	0.57	4
6	48	51	8	3	16.7	12.4	240	405	5	0	15	20	0	75	6	2	14	16	0.45	0.35	5
7	26	23	8	5	9.9	10.6	456	534	65	55	50	50	50	50	1	4	14	9	0.45	0.82	4
8	41	29	7	2	14.0	10.3	531	620	45	50	35	55	55	100	4	5	15	9	0.75	0.87	-
9	35	29	7	5	11.0	8.8	642	630	45	40	30	30	100	25	9	8	10	7	1.20	1.41	5
10	28	23	8	4	11.7	8.3	630	672	45	55	20	20	25	25	14	17	8	9	1.4	-	4
11	34	33	6	5	13.19	12.8	360	417	55	75	35	60	25	50	-	0	11	9	0.3	0.24	2
Total change score (SD)	-7.0 (8.3)		3.36 (1.6)		-0.82 (2.8)		48.14 (56.5)		1.3 (10.0)		5.0 (11.8)		15.45 (44.7)		0.0 (2,3)		-1.9 (2.7)		0.1 (0.18)		NA
P-value	0.026*		0.003*		0.386		0.033*		0.718		0.228		0.268		0.944		0.052*		0,114		NA

Notes: [a]lower score indicates better physical functioning and less pain, respectively; [b]lower score indicates less problems with the activity; [c]higher score indicates better physical functioning, general health perception, and health change, respectively; - denotes missing data. *p value≤ 0,05.

Abbreviations: GPE, global perceived effect; HADS, Hospital Anxiety and Depression Scale[42,43]; NA, not applicable; SF36; Short-Form Health survey[37-41]; SD, standard deviation; To, baseline measurement; T1, measurement directly after treatment; PSFS, Patient-Specific Functioning scale; WOMAC, Western Ontario and Mc Master Universities Osteoarthritis Index.

significant changes were found for the other measurements. With regard to the extent to which symptoms changed over the period of treatment (Global Perceived Effect scale), four patients indicated that they were much or moderately improved after treatment; four patients reported little improvement after the treatment; and two patients reported no change in symptoms after treatment.

Discussion

Comorbidity is highly prevalent in patients with knee OA. Nevertheless, no evidence-based recommendations are avail- able concerning comorbidity-adapted exercises in patients with knee OA. The present study concerns the development of comorbidity-adapted exercise protocols in patients with knee OA. The protocols were found to be feasible and helpful in clinical reasoning and adapting OA exercises.

To our knowledge, this is the first time that comorbidity- adapted protocols have been developed for exercise therapy in patients with OA of the knee and comorbidity. Evidence-based diagnostics and treatment strategies generally overlook comorbidity[13,14]. The interacting effects of diseases and their management require more complex and individualized care than simply the sum of separate guideline components.

Eleven comorbidity-adapted exercise protocols were developed for patients with knee OA and comorbidity. The protocols were found to provide guidance in clinical reasoning to direct both the diagnostic and treatment phases in persons with OA and complex, comorbidity-related health problems. The results of our field-testing revealed that the eleven protocols could be reduced to three main protocols due to overlap in diagnostics and/or treatment- related adaptations of the comorbidities and to improve user-friendliness. Protocol A concerned physiological adaptations (for persons with coronary artery disease, heart failure, hypertension, type 2 diabetes, obesity, and/ or COPD). Protocol B concerned behavioural adaptations (for persons with chronic pain, nonspecific low back pain, and/or depression). Protocol C concerned environmental adaptations (for persons with visual and/or hearing impairments). The protocols encourage physical therapists to think in advance about 1) how comorbidity compromises the regular application of exercise therapy by using the list of restrictions for exercise therapy of the comorbid disease and 2) how to adapt the exercise.

As expected, in participants with physiological impairments (e.g., coronary disease), the training intensity and frequency and type of exercises were adapted to the comorbidity. In participants with behavioural impairments (e.g., chronic pain), a combination of regular OA exercises with a behavioural approach was preferred, in which the level of physical activity was gradually increased in a time-contingent manner. In one participant with visual impairments, environmental adaptations were applied (e.g., adapting the lighting in the exercise hall). Furthermore, treatment had a significant beneficial effect on physical functioning and pain. An average increase of 18% on the

physical functioning subscale and a decrease of 16% on the pain subscale were found with WOMAC, which can be regarded as clinically important, relevant change[48]. The treatment was safe and, by using the protocols, more patients with OA and comorbidity could participate in the exercise therapy.

When taking comorbidity into account, adequate clinical reasoning is essential in order to deal with persons with a complex health status. Physical therapists need to be alert to changes in health conditions that may necessitate further adaptations of the exercises. Comorbidity may impose several different or even contradictory requirements for exercise. Physical therapists with experience in dealing with chronic conditions may have an advantage in clinical reasoning and in the adaption of exercise programs in accordance with the comorbidity. Physical therapists need to have an advanced understanding of complex system interrelationships regarding multiple morbidities. Therefore, therapists should receive specific training to increase their knowledge about various comorbidities and their effects on OA exercise therapy.

A number of remarks can be made about the usage and further development of the protocols. First, part of the results are based on personal opinions of three physical therapists working in a rehabilitation setting. To make the protocols broadly applicable, testing among various physical therapists practicing in different settings is needed. Second, the protocols were tested on eleven patients with knee OA and various comorbidities. To compare the effectiveness of the protocols to usual care, a randomized clinical trial should be performed.

Conclusion

Comorbidity-adapted exercise protocols for patients with knee OA were developed that can provide guidance in clinical reasoning with regard to diagnostics and treatment. To evaluate the effectiveness of treatment in line with our protocols, a randomized clinical trial should be performed.

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6

Chapter 7

Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: *a randomized controlled trial*

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Abstract

Objective. To evaluate the efficacy on physical functioning and safety of tailored exercise therapy in patients with knee osteoarthritis (KOA) and comorbidities.

Method. In a randomized controlled trial, 126 participants were included with a clinical diagnosis of KOA and at least one of the following target comorbidities: coronary disease, heart failure, type 2 diabetes, chronic obstructive pulmonary disease or obesity (body mass index ≥30kg/m^2), with severity score ≥2 on the Cumulative Illness Rating Scale. The intervention group received a 20-week, individualized, comorbidity-adapted exercise program consisting of aerobic and strength training. The control group received their current medical care for KOA and were placed on a waiting list for exercise therapy. Primary outcome measures were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale physical functioning and 6-minute walking test (6-MWT). Measurements were performed at baseline, after 20 weeks (post-treatment) and at 3 months post-treatment.

Results. Statistically significant physical functioning differences over time were found between the intervention and control group (WOMAC; B= -7.43, 95%CI -9.99 to -4.87, p <0.001 and 6-MWT; B= 34.16, 95%CI 17.68 to 50.64, p <0.001) in favor of the intervention group. At 3-months follow, the mean improvements in the intervention group were 33% on the WOMAC scale and 15% on the 6-MWT. These improvements are of clinical relevance. No serious adverse events occurred during the intervention.

Conclusion. This is the first study showing that tailored exercise therapy is efficacious in improving physical functioning and safe in patients with KOA and severe comorbidities. Dutch trial registration number: NTR3027

Introduction

Exercise therapy is a key intervention in the management of knee osteoarthritis (KOA) and recommended in international guidelines on KOA management[1,2]. It is an effective intervention to improve physical functioning and to reduce joint pain in patients with KOA[3]. However, the presence of comorbid diseases interferes with the application of exercise therapy[4], contributes to nonadherence[5], and may affect the outcome of exercise therapy.

Comorbidity is present in 68 to 85% of patients with osteoarthritis (OA)[6-8]. Frequently more than one comorbid disease is present[8]. Common comorbidities in KOA are cardiovascular diseases, type 2 diabetes, chronic obstructive pulmonary disease (COPD) and obesity[9]. 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 effect of exercise therapy in patients with KOA and severe comorbidity is not known. Patients with unstable medical conditions, precluding safe participation in an exercise program are excluded from clinical trials[10-13], because of the high risk of comorbidity induced adverse events. One study investigated the outcome of exercise therapy in a subgroup of patients with KOA and comorbidity compared to patients without comorbidity[14]. 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.

Guidelines on KOA do not provide guidance on tailoring exercise therapy to the presence of comorbidity[1,2,18,19]. In clinical practice, comorbidity is a frequent reason to exclude patients from exercise therapy[15]. 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[16,17].

We hypothesize that patients with severe comorbidity can exercise safely if certain precautions are taken and adequate adaptations to the exercise program are made. We have previously developed a treatment protocol to tailor exercise therapy for KOA to comorbid diseases[20]. The purpose of the present study was to evaluate the efficacy on physical functioning and safety of tailored exercise therapy in patients with KOA and comorbidity.

METHODS

Trial design

This was a single-blind, randomized controlled trial, conducted in a secondary outpatient rehabilitation center. Measurements were performed at baseline, at 10 weeks (midtreatment), 20 weeks (posttreatment) and 32 weeks (3-months posttreatment). The study was conducted in accordance with the Declaration of Helsinki principles[21]. The study protocol was approved by the Medical Ethical Review Board (Reade/Slotervaart Hospital; number 1148). All participants gave written informed consent. Dutch trial registration number: NTR3027.

Participants

Participants were recruited from December 2011 to January 2014 through regular referral by general health practitioners, rheumatologists, rehabilitation physicians and orthopedic surgeons, or from advertisements in local newspapers. Participant eligibility was assessed by a short online screening questionnaire, a telephone screening by the researcher (MdR), and subsequently by a rheumatologist and a rehabilitation physician. The final decision on in- or exclusion of a participant was made by the rehabilitation physician.

Inclusion criteria: 1) diagnosis of KOA according to the clinical criteria of the American College of Rheumatology[22]; 2) presence of at least one of the target comorbidities (coronary disease, heart failure, type 2 diabetes, COPD or obesity (Body Mass Index (BMI)≥ 30kg/m^2)), all diagnosed by a medical specialist, with severity score ≥2 for the comorbidity on the Cumulative Illness Rating Scale[23] (indicating that the comorbidity has an impact on daily activities and the patient was receiving regular care for the comorbid disease). Confirmation of the medical diagnosis was obtained by medical history taking and medication prescription. If there was any doubt about the diagnosis the medical specialist or general practitioner was consulted by the rehabilitation physician; and 3) the primary treatment goal was related to KOA (instead of comorbidity related). Exclusion criteria: 1) absolute contraindication for exercise therapy (e.g., myocardial infarction within last 3 months); 2) total knee arthroplasty (TKA) or planned TKA in near future; 3) participation in exercise therapy for KOA within the preceding three months; 4) insufficient comprehension of Dutch language; 5) psychological distress necessitating treatment; 6) dementia (Mini-Mental State Examination score >24); 7) significant physical limitations that would prohibit the participant from following exercise therapy; 8) expected to be lost for follow-up (e.g., because of a planned change of residency); and 9) refusal to sign informed consent.

Randomization, treatment allocation and blinding

Participants were randomly assigned to the intervention group or the control group by the web-based program MagMin24. This program uses a minimization algorithm based on the Pocock and Simon method25, balancing the comorbid diseases (coronary disease,

heart failure, diabetes type 2, COPD, BMI (BMI >30, BMI 30-35, BMI <35)) and pain severity (NRS score of 1-5, NRS score of 6-10). Comorbid diseases were weighted two, while pain severity was weighted one. Participants were randomized by an independent staff member who had no other involvement in the trial.

Randomization, treatment allocation and statistical analyses were performed blindly. The assessors (in total three) were blinded for treatment allocation. Participants and physiotherapists (PTs) were not blinded for treatment allocation.

Intervention

Exercise therapy. Exercise therapy comprised a 20-week individualized (tailored) KOA exercise program, with two sessions of 30 to 60 minutes a week under supervision of a PT. The exercise therapy provided in the present study was based on the protocol as developed by Knoop et al.[12] and consisted of muscle-strength training of the lower limb and aerobic training[1,2,12,19]. Flexibility and stability exercises of the lower limb were added on indication. See appendix 1 for an overview of the content of the exercise therapy. Comorbidity-related adaptations were made to the diagnostic phase and the intervention phase[20] (see appendix 2). In the diagnostic phase, comorbidity-related contraindications and restrictions were identified by history taking and physical examination in an extensive one–hour intake procedure. Absolute contraindications were defined as conditions that would lead to the immediate exclusion of the participant from exercise therapy (e.g., unstable angina). Restrictions (or relative contraindications) were defined as impairments which limit the application of exercise therapy (e.g., dyspnea in patients with COPD).

In the intervention phase, KOA exercises as described by Knoop et al[12] (see appendix 1) were adapted to the comorbid disease, taking into account restrictions. Exercise therapy was adapted by changing frequency, intensity, timing and type (FITT) factors of the exercises or by adding educational (e.g., providing comorbidity-related information on exercise therapy) or coaching strategies (e.g., coaching for reducing body weight or coaching for fear of exertion). Third, during every training session, comorbidity-related symptoms and clinical parameters were monitored, and exercise was adapted if required. The specific adaptations to the OA exercises were based on principles described in comorbidity-specific exercise guidelines (e.g., cardiac rehabilitation)[26] and were listed in the protocol[20] (see appendix 2). The training intensity was monitored with the Borg Rate of Perceived Exertion (RPE) scale 6-20[27] and on the heart rate reserve, if indicated[28]. In addition to the supervised exercise sessions, education on KOA was provided and participants were encouraged to perform exercises at home for at least five times a week.

Control intervention

Participants randomized to the control intervention received their current medical care for KOA and comorbid disease. They were placed on a waiting list for a period of 32 weeks, and thereafter the comorbidity adapted exercise intervention was offered.

Therapists

Exercise therapy was applied by seven qualified PTs with 3 to 25 years' work experience. The PTs were trained to work with the protocol and to provide treatment in accordance with the protocol. Booster sessions were provided every 12 weeks.

Participant characteristics

Baseline characteristics were obtained, i.e., age, sex, educational level, duration of knee symptoms, BMI, unilateral or bilateral KOA, Kellgren and Lawrence grade (K&L)[29], Cumulative Illness Rating Scale (CIRS)[23], use of pain medication, use of walking devices and mal-alignment of the knee.

Outcomes

Primary outcome measures. Physical functioning was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, Dutch translation) - subscale physical function[30] and the 6-minute walk test (6-MWT)[31]. An extended description of these measures is available in Appendix 3 (available on the onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract).

Secondary outcomes measures. Serious adverse events related to treatment and testing procedures were reported to the researcher by the treating PT or clinimetric assessors. Knee-pain severity during the last week was scored on a Numeric Rating Scale (NRS)[32] and with the pain subscale of the WOMAC[30]. Physical functioning was measured using self-reported physical function questionnaires (subscale of the 36-Item Short-Form Health Survey (SF-36)[33], Patient-Specific Functioning Scale (PSFS)[34], Walking Questionnaire (WQ35)[35], Climbing stairs Questionnaire (CSQ15)[36], Questionnaire Rising and Sitting down (R&SDQS39)[37]) and two physical performance tests (i.e., Get Up and Go test (GUG)[38] and time walking up-down stairs[39]). The LASA Physical Activity Questionnaire (LAPAQ) was used to assess the moderate-intensity physical activity[40]. Fatigue was assessed with the NRS scale. Isokinetic muscle strength and proprioceptive accuracy[41] were assessed as described in Appendix 3. Psychological functioning was assessed with the Hospital Anxiety and Depression Scale (HADS)[42]. The Evaluative Frailty Index for Physical activity (EFIP) was used to measure the level of frailty[43].

Global perceived effect (GPE) was assessed posttreatment (week 20) in the intervention group, on a 9-point Likert scale, and dichotomized as 'improved' (score 1-4) or 'not improved' (score 5-10)[44]. An extended description of the secondary outcome measurements is available in Appendix 3 (available on the onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract)

For knee-specific variables (K&L grade, muscle strength, proprioceptive accuracy) we used data from one knee per person (index knee). Index knees were determined by the clinical diagnosis of KOA according to ACR-criteria. In case of a clinical diagnosis of KOA in both knees, a knee was chosen at random.

Process outcome measures

PTs assessed patient-perceived training intensity on a Borg-scale[27] after each session, and pain severity (NRS)[32] during the preceding week once a week. In addition, PTs completed training diaries and registration forms to record specific adaptations to the exercise program (e.g., FITT factors and other adjustments to the exercise program).

Sample size

The a priori power calculation was based on the WOMAC physical function subscale with an expected effect size of 0.4 between intervention and control group at the 20-week follow-up, four time points of measurement (baseline and three follow-up moments), expected autocorrelation between the repetitions of 0.5, significance level of .05 and desired power of .80. Given these parameters a total sample size of 122 participants was needed. Allowing for a dropout rate of 20% during the study, we aimed to include 154 patients (i.e., 77 patients in each group). However, due to a low dropout rate of only 3% during the study we adjusted our sample size to 126 patients (i.e., 63 patients in each group).

Statistical analyses

Descriptive statistics for baseline participant characteristics were tabulated as mean (SD) or medians (IQR) or percentages if data did not have a normal distribution. All outcome measures were normally distributed, except for proprioceptive accuracy, GUG test, stairclimbing test, WQ35, R&SQ39, HADS and LAPAQ. A logarithmic transformation was applied for the non-normally distributed variables: by log10 (for proprioceptive accuracy, GUG test, stairclimbing test, HADS and LAPAQ) or square root (for WQ35, R&SQ39). Comorbidity-related adaptations to the exercise program were described in percentages.

Analyses were based on the intention-to-treat principle (ITT), in which data of all participants were analyzed according to group assignment. Generalized Estimating Equation (GEE) analysis was used to estimate the average group differences over time, and the group differences at the different time points. For the latter, time (treated as a categorical variable and represented by dummy variables) and the interaction between group and time were added to the model. Both analyses were adjusted for the baseline value of the outcome measure[45]. Prior to the regression analysis, the assumptions for linear regression were checked. An exchangeable correlation structure was used to account for the within-subject correlations. The between-group standardized mean difference (SMD) was calculated[46]. A sensitivity analysis was performed using the participants who fulfilled at least two-thirds of the training sessions *and* with adaptations of the exercise program for FITT factors. P values less than .05 were considered statistically significant. Analyses were performed with SPSS for Windows 22.0 software (SPSS, Chicago, IL).

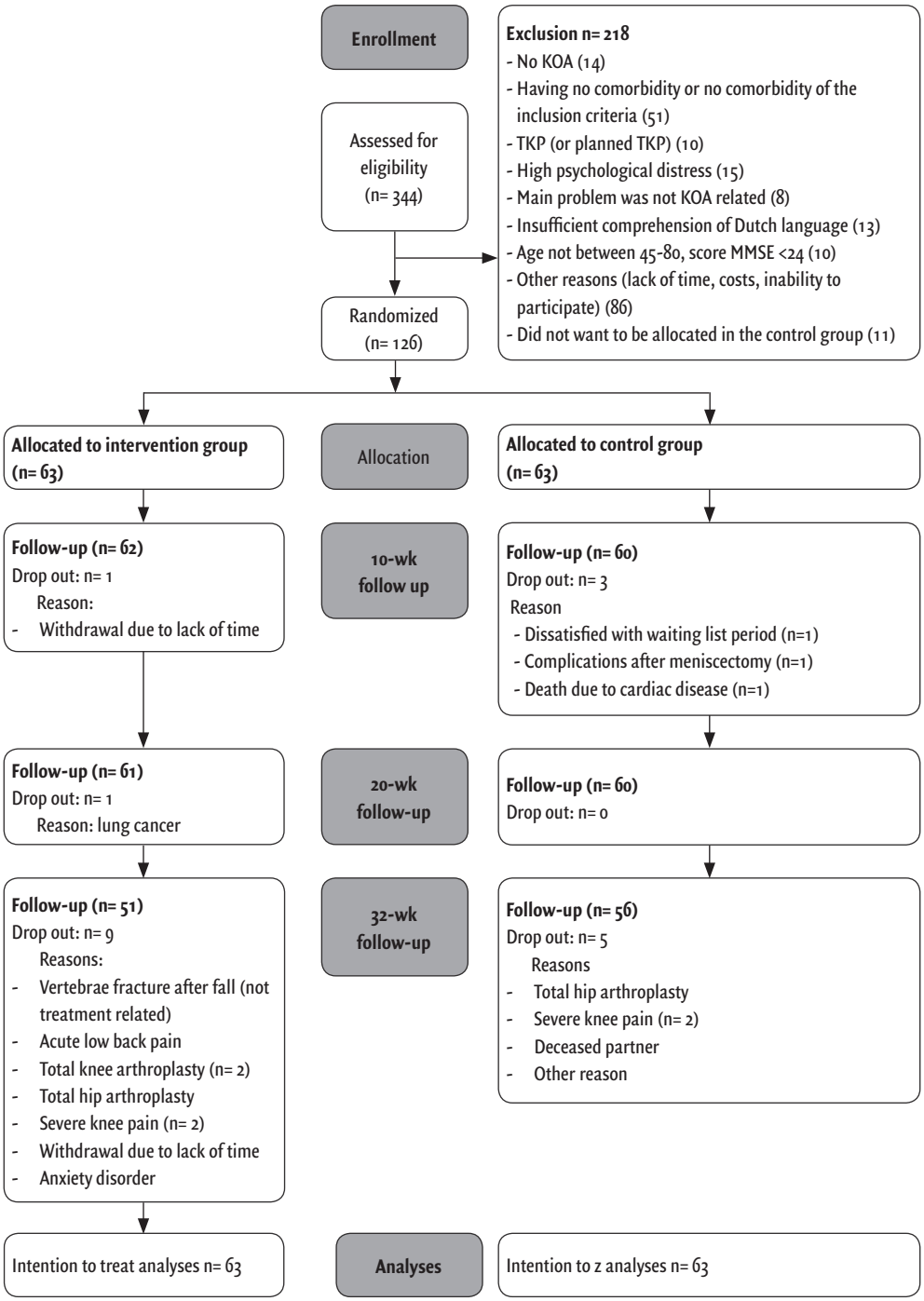

Figure 1. Flowchart

RESULTS

Participants

The participants' flow chart is presented in Figure 1. Out of the 344 potential participants, 218 (63%) were not eligible or did not wish to participate. In total, 126 participants were randomized and allocated to the intervention (n=63) or the control group (n=63). One participant of the intervention group and three participants of the control group were lost before the first follow-up measurement.

Baseline characteristics of the intervention and control groups are presented in Table 1. The groups were well balanced and similar on entry to the trial in terms of age, sex, BMI, K&L grade, comorbid diseases and outcome measures. Blinding for treatment allocation was successful. Group allocation was guessed correctly by the assessor in 64% of the participants (Cohen's kappa= 0.03 p value 0.4).

Compliance and co-interventions

Fifty-four (86%) of the 63 participants in the intervention group received ≥ two-thirds of the exercise sessions (≥27 out of 40 sessions). Of the nine participants who did not complete the program, two participants did not because of severe knee pain and seven participants due to other reasons (unrelated to the intervention). Nine (17%) of the participants performed the exercise program at a low training intensity (Borg scale ≤11), 40 participants (74%) reached a moderate training intensity (Borg scale 12-14) and five participants (9%) reached a high training intensity (Borg scale ≥15). On average, participants performed their home exercises four times a week (SD = 1.1) during the trial. In the intervention group, three participants received a corticosteroid injection for their knee symptoms; two of these participants subsequently received a total knee arthroplasty. In the control group two participants received a corticosteroid injection, one participant received a total knee arthroplasty and 11 participants received treatment from a PT (reason for consulting a PT is unknown).

Adaptations to the intervention

Comorbidity-related adaptations to the exercise program are described in Table 2. In addition to the general adaptations, FITT factors were tailored to the restrictions posed by the comorbid disease in 76% of the participants. In 96% of the participants, additional educational or coaching strategies were provided (e.g., coaching on body weight reduction in participants with obesity, or coaching on fear of exertion). For 80% of the participants, a combination of adjustment of FITT factors and education or coaching strategies was provided, while for 17% of the participants only educational or coaching strategies were provided.

Table 1. Participants characteristics

	Intervention group (n=63) **mean ± SD**	**n (%)**	**Control group** (n=63) **mean ± SD**	**n (%)**
Demographics				
Age (years)	63.2 ± 8.4		63.9 ± 12.4	
Sex (female)		49 (77)		46 (73)
Educational level				
Primary level		12 (19.4)		12 (19)
Secondary level		29 (46.8)		32 (50.8)
College/university		21 (33.9)		19 (30.2)
Clinical variables				
Duration of knee symptoms, years	8.59 ± 8.6		9.4 ± 9.3	
BMI kg/m²	36.0 ± 6.8		35.0 ± 7.6	
Clinical diagnosis of KOA				
Unilateral		12 (19)		12 (19)
Bilateral		51 (81)		51 (81)
Radiographic severity of knee				
K/L grade 0/1		26 (41.3)		23 (36.5)
K/L grade 2		19 (30.2)		17 (27.6)
K/L grade 3		10 (15.9)		9 (14.3)
K/L grade 4		8 (12.7)		14 (22.2)
Total number of comorbidities (CIRS score ≥2) (range 0-12)				
1		31 (49.2)		24 (38.1)
2		17 (27.6)		21 (33.3)
≥3		15 (23.8)		18 (28.9)
Comorbidities of inclusion				
Cardiac diseases		24 (38)		21 (33)
Diabetes type 2		10 (15)		9 (14)
COPD		20 (31)		19 (30)
Obesity (BMI ≥30)		41 (65)		36 (57)
Use of pain medication (incl. NSAIDs)		50 (79.4)		48 (76.2)
Use of walking device		23 (36.5)		18 (28.6)
Mal-alignment of knee (≥5° varus or valgus)*		49 (77.8)		43 (68.3)
Physical Functioning				
WOMAC physical functioning (0-68)	35.1 ± 11.9		31.0 ± 12.3	
6-minute walking test (meters)	406.3 ± 107.6		406.4 ± 116.9	
SF 36 physical functioning (0-20)	18.4 ± 4.1		18.8 ± 4.1	
Get Up and Go test (sec) median (IQR)	12.1 (10.4; 14.5)		12.4 (10.4; 15.4)	
Stairclimbing test (sec) median (IQR)				
Ascend	7.5 (5.7; 11.4)		7.7 (6.3; 9.9)	
Descend	8.3 (6.0; 13.2)		8.5 (6.6; 12.5)	
LAPAQ total activity (moderate activity) median (IQR)	57.9 (23.6; 101.4)		45.7 (23.9; 64.3)	
Upper leg muscle strength (Nm/kg)*	0.65 ± 0.29		0.62 ± 0.34	
Pain				
NRS knee pain severity (0-10)	6.4 ± 1.8		5.9 ± 2.1	
WOMAC pain (0-20)	10.1 ± 3.4		9.4 ± 3.5	
Frailty				
EFIP (0-1)	0.3 ± 0.1		0.2 ± 0.1	
Psychological functioning				
HADS Depression and Anxiety (0-21)	11.3 ± 6.6		10.0 ± 6.8	

BMI Body Mass Index. CIRS Cumulative Illness Rating Scale. COPD Chronic Obstructive Pulmonary Disease. EFIP Evaluative Frailty Index for Physical activity. HADS Hospital Anxiety and Depression Scale. K&L Kellgren & Lawrence grade. LAPAQ LASA Physical Activity Questionnaire. NRS Numeric Rating Scale. NSAID Non-Steroidal Anti-Inflammatory Drugs. SD Standard Deviation. SF36 Short Form 36. WOMAC Western Ontario and Mc Master Universities Osteoarthritis Index. *data from the Index Knee.

Primary outcome

The WOMAC-pf and 6-MWT outcomes at week 10 (midtreatment), week 20 (directly posttreatment), and week 32 (3-months posttreatment) are illustrated in Figure 2. Significant differences over time between groups were found for WOMAC-pf (B= -7.43 (95%CI-9.99 to -4.87 p< 0.001)) and the 6-MWT (B= 34.16 (95%CI 17.68 to 50.64 p<0.001)) in favor of the intervention group (see table 3). At each time point, a significant difference between groups was found (see Appendix 4) (available on the onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). Directly posttreatment, between-group SMD for the intervention group was 0.9 and 0.6 for WOMAC-pf and 6-MWT, respectively. At three months posttreatment, between-group SMD was 1.0 and 0.7 for WOMAC-pf and 6-MWT, respectively.

Secondary outcomes

No serious adverse events occurred that could be attributed to the exercise therapy provided. We found a significant difference over time between groups in favor of the intervention group for pain and the majority of physical functioning measures (see Table 3), as well as for fatigue, muscle strength, physical activity and frailty (see Appendix 5) (available on

Table 2. Comorbidity-related adaptations to the exercise program

General comorbidity-related adaptations	**100%**
Extended intake procedure: identification of comorbidity related contraindication and restrictions for exercise therapy by history taken and physical examination	
Extended training program of 20 weeks (as opposed to 12 weeks which is regular in our center)	
During and after every training session therapists monitored symptoms and clinical parameters related to comorbidity and adapted the exercise program when required	
Exercise program: adaptations of FITT factors	**76%**
Frequency (number of repetition per exercise set)	15%
Intensity of exercises (exercise load)	76%
Time (duration of exercise session)	17%
Type of exercises	52%
Additions to exercise program	**96%**
Coaching on body weight reduction	76%
Coaching on fear of exertion	20%
Education related to the comorbid disease and exercise	69%
Other adaptations	
Consulting a medical specialist or GP about the comorbid disease (e.g., medication or high blood pressure or trainability of the patient)	24%
Monitoring blood glucose levels before and after the training and in the evening in patients with diabetes	7.4%
Postponement of the training session (e.g., high blood pressure, pain on the chest, dyspnea)	17%
Referred to a dietician	13%

FITT factors: Frequency, Intensity, Time, Type

the onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). No significant differences between groups were found for physical functioning measured with WQ35 and CTQ15 (see Table 3), proprioceptive accuracy, psychological functioning and BMI (see Appendix 5) (available on the onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). Ninety-seven percent of the participants in the intervention group reported improvement as a result of the intervention directly posttreatment, and 62.7% still reported improvement at 3-months follow-up (GPE scale).

Sensitivity analyses

The results on the primary outcome measures directly after treatment and at 3-months follow-up were similar when restricted to participants who received less than two-thirds of the training sessions and in whom specific adaptations to the exercise program included adjustments in FITT factors (data not shown). In addition, we performed a subgroup analysis only including patients with obesity (BMI ≥ 30kg/m^2). Similar results were found as compared to the results of the total group (data not shown).

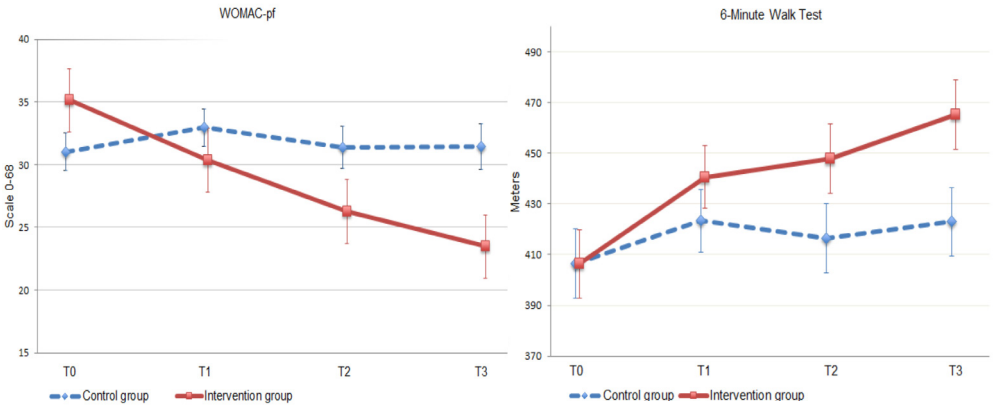

Figure 2. Mean and standard error of WOMAC-pf and 6-Minute Walk Test at baseline (T0), week 10 (T1 midtreatment), week 20 (T2 directly after treatment), and week 32 (T3 3-months posttreatment

Table 3. Outcome measures by group at different time-points (mean ± SD) and group differences over time (ITT)

	Baseline		10-wk FU		20-wk FU		32-wk FU		Group differences over time (10, 20, 32-wk FU) B (95% CI)*
	IG	CG	IG	CG	IG	CG	IG	CG	
Primary outcomes WOMAC-pf (0-68)	35.1 ± 11.9 n=63	31.0 ± 12.3 n=63	30.4 ± 11.6 n=60	32.9 ± 11.2 n=55	26.3 ± 12.7 n=59	31.4 ± 13.4 n=59	23.5 ± 13.1 n=51	31.4 ± 12.6 n=56	7.43 (-9.99, -4.87)‡
6-minute walk test (meters)	406.3 ± 107.6 n=63	406.4±116.9 n=63	440.6 ± 96.7 n=61	423.4± 115.5 n=53	448.0± 102.5 n=56	416.5± 116.9 n=58	465.3± 93.9 n=48	423.0± 114.8 n=55	34.16 (17.68, 50.64)‡
Secondary outcomes									
NRS pain week (0-10)	6.4 ± 1.8 n=63	5.9 ± 2.1 n=63	5.3 ± 1.9 n=60	5.7 ± 2.3 n=55	4.3 ± 2.0 n=59	5.8 ± 2.2 n=59	4.7 ± 1.9 n=51	6.2 ± 2.1 n=56	1.41 (-1.87, -0.95)‡
WOMAC pain (0-17)	10.1 ± 3.4 n=63	9.4 ± 3.5 n=63	8.4 ± 3.0 n=60	9.1 ± 3.6 n=55	6.9 ±3.4 n=59	8.8 ± 4.2 n=59	6.6 ± 3.6 n=51	8.6 ± 3.6 n=56	1.78 (-2,65, -0.91)‡
GUG (seconds)	13.6 ± 5.6 n=63	13.5 ± 5.5 n=63	12.0 ± 3.4 n=61	1 12.9 ± 4.3 n=55	11.9 ± 3.6 n=56	13.0± 4.4 n=58	11.4 ± 3.0 n=48	12.8± 3.7 n=55	-1.35 (-2.16, -0.55)‡#
Stair climbing up (seconds)	10.1 ± 6.9 n=63	9.2 ± 4.7 n=63	8.6 ± 6.7 n=61	11.4 ± 14.7 n=55	7.7 ± 4.3 n=55	8.7± 4.4 n=58	7.4 ± 3.8 n=47	10.0 ± 9.6 n=55	-2.41 (-4.40, -0.43)£#
Stair climbing down (seconds)	10.7 ± 7.2 n=63	11.0 ± 6.6 n=63	9.6 ± 8.0 n=61	11.6 ± 12.5 n=55	8.3 ± 4.4 n=55	9.8 ± 5.5 n=58	7.6 ± 3.8 n=47	9.7 ± 4.9 n=55	-1.64 (-3.18, -0.91)£#
SF36 subscale pf (score 0-20)	18.4 ± 4.1 n=63	18.8 ± 4.1 n=63	n/a	n/a	20.8 ± 4.5 n=59	18.9 ± 5.0 n=59	21.4 ± 4.5 n=50	18.9 ± 4.7 n= 55	2.19 (1.10, 3.28)‡
PSFL (performance of activities 0-10)**	6.7 ± 1.4 n=63	6.6 ± 1.3 n=63	n/a	n/a	4.2 ± 2.1 n=57	5.8 ± 1.7 n=58	4.1 ± 2.2 n=50	5.9 ± 1.8 n=55	1.59 (-2.19, -0.99)‡
WQ35 (walking, 0-100)	40.2 ± 23.3 n=61	39.76 ± 23.2 n=63	n/a	n/a	30.9 ± 25.2 n=59	38.4 ± 24.1 n=58	29.9 ± 25.4 n=51	34.9 ± 22.5 n=55	6.84 (-14.94, 1.26)∫#
CTQ15 (stairclimbing, 0-100)	51.4 ± 17.9 n=51	51.2 ± 16.7 n=56	n/a	n/a	42.7 ± 20.3 n=52	48.8 ± 18.2 n=50	40.3 ± 22.6 n=47	48.1 ± 18.1 n=46	6.10 (-13.41 , 1.21)∫
R&SQ39 (rising and sitting down, 0-100)	51.6 ± 27.2 n=56	45.5 ± 22.8 n=61	n/a	n/a	39.2 ± 26.1 n=55	45.9 ± 25.7 n=52	38.5 ± 26.7 n=48	43.8 ± 25.7 n=52	10.20 (-15.48, -4.92)‡#

CG. Control group. CI confidence interval. GUG Get up and Go. IG Intervention group. ITT Intention to treat. NRS Numeric Rating Scale. n/a not applicable. SD standard deviation. SF36 subscale pf Short Form 36 subscale physical functioning. PSFL Patient specific Functioning List. WOMAC-pf Western Ontario and Mc Master Universities Osteoarthritis Index, subscale physical functioning. *Adjusted for baseline value of outcome variable difference; # although outcome measure was not optimally distributed, analysis of non-transformed data reported, as this is more easily interpretable and yielded similar results as analysis with transformed data . ** average score of 3 activities that were most relevant and problematic for patient; £ p <.05; ‡ p <.001; ∫ p >.05. Overall, a lower score indicates an improvement in physical functioning or pain with exception of the 6-minute walk test and the subscale pf of the SF-36. For all other secondary outcome measures see appendix 3

Discussion

This is the first study showing that a tailored exercise program for patients with KOA and severe comorbidity is efficacious in improving physical functioning. Statistically significant improvements were found in the intervention group, compared to the control group, directly after treatment and at 3-months follow-up. With respect to physical functioning, the mean improvement in the intervention group was 11.6 points (33%) on the WOMAC-pf and 59 meters (15%) on the 6-MWT at 3-months follow-up. For pain, the mean improvement in the intervention group was 1.7 points (27%) on the NRS pain scale at 3-months follow-up. These improvements are of clinical relevance[47,48]. No treatment-related serious adverse events occurred and drop-out during the intervention was low, which suggests that our intervention is safe and feasible. However, we do realize that our sample size, although adequate for measuring the effectiveness of treatment, was small with respect to (serious) adverse events.

In comparison to other exercise trials in patients with knee osteoarthritis and comorbidity we included patients with more severe comorbidity[10,12,13,49]. Our study population had more activity limitations at baseline, had on average more pain and had lower muscle strength in comparison to the baseline characteristics of patients in other exercise trials[10,12,13,49]. We selected patients if they had a severity score ≥2 for the comorbidity on the Cumulative Illness Rating Scale[23], indicating that the comorbidity had an impact on daily activities and the patient was receiving regular care for the comorbid disease.

Remarkably, we found a large between-group effect size for self-reported physical functioning (SMD = 0.9) directly after ending treatment, and even further improvement during the following three months (SMD = 1.0). In a recently published Cochrane review, the magnitude of the treatment effect of exercise therapy on physical functioning in patients with KOA was found to be moderate (SMD = 0.5) (immediate posttreatment) to small (SMD = 0.15) (two to six months posttreatment)[3]. This suggests that tailoring exercise therapy to the comorbid disease is highly effective. The beneficial results of the present study can not only be attributed to the high volume and frequency of the exercise, but also to the several adjustments to the exercise program. First, in order to tailor exercise therapy to the individual patient, an extensive intake procedure was conducted. Second, therapists were encouraged to consult colleagues or medical specialists to discuss the medical condition of the patient, which provided them with the information needed to adapt the exercise program. Third, all patients were scheduled to receive an extended training program of 20 weeks (as opposed to 12 weeks which is regular in our center). Fourth, for more than two-thirds of the patients, exercises were adapted to the comorbid disease by changing FITT factors of the exercises. Fifth, in almost all patients, additional comorbidity-related education or coaching strategies were provided. Last, comorbidity-related symptoms were monitored during each training session, and exercise was adapted if required. We assume that all these factors contributed to exercise adherence in our treatment group.

Some methodological issues should be considered. First, patients in the control group received their current medical care for KOA and comorbid disease and were placed on a waiting list for exercise therapy. We included patients with a comorbidity severity score ≥2 on the CIRS indicating that the comorbidity has an impact on daily activities and the patient was receiving regular care for the comorbid disease. Because of an increased risk of comorbidity–related (serious) adverse events, it was considered unethical to provide regular exercise therapy without tailoring to the comorbid disease. Thus, the study contrast concerns tailored exercise therapy versus current medical care. Second, we included patients with various comorbidities. With the current sample size we cannot analyze the outcome of the exercise program in patients with specific comorbidities (except for patients with obesity in whom we observed similar results). Third, we performed an efficacy trial to evaluate the effect of tailored exercise. The treatment was provided in a secondary care setting where PTs have advanced skills in treating patients with complex health conditions and have close collaboration with rehabilitation physicians and rheumatologists. More research is needed to evaluate the effectiveness of the protocol in primary care. In addition, the effect of tailored exercise in other highly prevalent comorbid diseases in KOA (e.g., chronic pain or depression)[9,20,50] should be investigated. Fourth, a limitation of the present study is that we did not investigate the cost-effectiveness of the developed protocols to get insight if the costs outweigh the benefits on health-related outcomes, medication use, hospital care and outpatient care.

In conclusion, this is the first study showing that tailored exercise therapy is efficacious in improving physical functioning and is safe in patients with KOA and severe comorbidities. The results should encourage clinicians to consider exercise therapy as a treatment option for patients with KOA, even in the presence of comorbidity.

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Appendix 1. Regular exercises for knee osteoarthritis (OA)

General information

- Regular knee OA exercises, based on the protocol as developed by Knoop et al.[1].
- The training intensity is monitored with the Borg Rate of Perceived Exertion (RPE) scale 6-20[2].
- Supervised exercise therapy twice a week and home exercises for five days a week
- Education about OA disease, joint protection and risk factors for functional decline, and advice on self-management are provided.
- Exercise intensity and knee loading are gradually increased every week, to a maximal level that is possible for the patient. When exercise-induced knee pain persists during rest between exercise sets, or for more than one day after exercising, exercise intensity and/or knee loading is decreased in future sessions.
- Stability, flexibility or range of motion exercises of the lower limb are added on indication.
- Functional, patient tailored exercises targeting specific daily activities, which are indicated to be relevant and problematic by the patients themselves are added to the program
- Warming up 5-10 minutes
- Cooling down 5-10 minutes

Type	Intensity	Duration	Exercise (See below)
Aerobic exercise	50-80% of VO_2max/HRR/HRmax/maximal workload (moderate intensity) 30-<40% or VO_2max/HRR/HRmax/maximal workload (light intensity) is appropriate for individuals with arthritis who are deconditioned	Start with short bouts of 10 min (or less if needed), according individual's pain levels	1, 11, 15, 16, 17, 18, 19, 20
Endurance muscle strength exercise lower limb	40-60% of 1-RM	2-4 sets of 15-20 reps, with rest intervals of 2-3 min between each set of reps	1, 4, 6, 8 9, 11, 14, 16, 18, 20
Maximum muscle power training lower limb	60-80 % of 1RM	The selected resistance should permit the completion of 2-4 sets of 8-12 repetitions, or the number needed to induce muscle fatigue but not exhaustion), rest intervals of 2-3 min between each set of reps	4, 6, 8, 11, 14, 16, 20
Flexibility/range of motion exercises of the lower limb	Stretch to the point of feeling tightness or slight discomfort	2-4 repetitions, 2 or three times per week. Hold a static stretch 10-30 seconds	2, 3

Appendix 1. (cont'd)

Exercise

1. Exercise
2. warming up and cooling down on bicycle ergometer or rowing ergometer
3. stretching of mm. quadriceps femoris, mm. hamstring, m. iliopsoas, m. gastronemicus, m. soleus
4. isometrically contracting mm. quadriceps femoris while sitting on bench or floor with leg stretched
5. straight leg raising while sitting on bench/floor with leg stretched
6. flexion-extension of the unloaded knee (0-30° knee flexion) while standing in static stride position (weight loading in front knee)
7. squats (progress in angle of knee flexion up to 90°)
8. moving bodyweight from knee to knee, while standing in stride position
9. making a forward lunge step (0-30° up to 0-60° knee flexion)
10. making a forward lunge step under sideways knee load, by using a dynaband (0-30° up to 0-60° knee flexion)
11. making a forward lunge step ending in one leg standing position (0-30° knee flexion)
12. knee flexion –extension while standing on one leg on a step (non-standing foot dropping below step level, sideways)
13. one leg standing (0-30° knee flexion)
14. standing on a balance board, with two or one leg (0-30° knee flexion)
15. leg press workout
16. cycling work out
17. stepping workout
18. cross trainer work out
19. rowing workout
20. tread mill workout

Treatment goals (ICF-classification)

21. training of daily activities like walking on a flat or unstable surfaces, ascending/descending stairs, sitting down/rising up from a chair, or other activities that were reported to be relevant and problematic by patients at baseline
22. Treatment goals (ICF-classification)
23. b620: proprioceptive function (exercise 5, 6, 7, 8, 11, 12)
24. b710: mobility of joint functions (exercise 2, 3, 4, 7)
25. b715: stability of joint functions (exercise 5, 6, 7, 10, 11, 13, 14, 16, 17,19, 20)
26. b740: muscle endurance functions (exercise 1, 4, 6, 8, 10, 14, 15, 16, 18)
27. b760: control of voluntary movement functions (exercise 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20)
28. b410: heart functions (exercise 1, 15, 16, 17, 18, 19)
29. b445: respiration functions (exercise 1, 15, 17, 18,19)
30. d450: walking (exercise 19, 20)
31. b730: muscle power functions (exercise 6, 16, 14)
32. b740: muscle endurance functions
33. other daily activities, like stair ascending, stair descending, rising up from a chair, sitting down on chair, or other activities relevant and problematic for a patient (exercise 20)

ICF = International Classification of Functioning, Disability and Health

Appendix 2. Adaptations to the exercise program

General information

- The full protocol provides information regarding the comorbid disease (pathogenesis), medication use, medication use in relation to exercise, history taking, physical examination, and adaptation to the OA exercises. In this appendix we summarize the topics which are addressed.
- The protocol we previously developed, consists of a diagnostic phase and an intervention phase[1]. Each step in the protocol encourages clinical reasoning in order to tailor the diagnostic and intervention phase to the individual person.
  - The *diagnostic phase* (one hour intake procedure) includes an anamnesis, physical examination, establishment of treatment goals, and determination of the treatment strategy. During the anamnesis, OA-related problems, comorbidity-related restrictions and contraindications for exercise therapy are identified. Absolute contraindications are defined as conditions that would lead to the immediate exclusion of the participant from exercise therapy (e.g., unstable angina). Restrictions (or relative contraindications) are defined as impairments which limit the application of exercise therapy (e.g., dyspnea in patients with COPD)[2]. Thereafter, a clinical decision is made as to whether physical examination is possible, or whether the referring physician needs to be consulted because of contraindications for physical examination or the need for further medical information. If there are no contraindications for physical examination, comorbidity-related examination is performed according to the protocol. Subsequently, a decision is made as to whether there are contraindications or restrictions for exercise therapy. In case of a contraindication, referral to a physician is indicated. If there are comorbidity-related restrictions for exercise therapy, a comorbidity-adapted program is indicated. In this phase, the therapist also considers whether referral to professionals in other disciplines (e.g., a dietician) is indicated.
  - In the *intervention phase*, regular knee osteoarthritis exercises, based on the Dutch guideline[3] and described in detail by Knoop et al.[4] (see also appendix 1) are adapted to the comorbid disease, taking into account restrictions and contraindications due to the comorbid disease. Exercise therapy is adapted by changing frequency, intensity, timing and type of exercise or by adding educational (e.g., providing comorbidity-related information on exercise therapy) or coaching strategies (e.g., coaching for reducing body weight or coaching for fear of exertion)[1]. The exact adaptations depend on restrictions for exercise therapy identified by the therapist in the diagnostic phase (anamnesis and physical examination). In addition, during every training session, comorbidity-related symptoms and clinical parameters are monitored, and exercise is adapted if required. The specific options for adaptations to OA exercises are listed in the protocol.
- The adaptations to history taking, physical examination and the OA exercises are based on principles described in comorbidity-specific exercise guidelines[6-15] (e.g., cardiac rehabilitation[5]), ACSM guideline[16-18], medical guidelines[19] and expert opinion.
- Exercise therapy comprised a 20-week individualized (tailored) knee osteoarthritis exercise program, with two sessions of 30 to 60 minutes a week under supervision of a physical therapist.
- The full protocol is available from the first author. In a previous publication the development of the protocol is described[1].

Appendix 2. (cont'd)

Cardiac disease

History taking

- Medical diagnosis:
  Myocardial infarction, angina pectoris, heart failure, cardiac arrhythmias, mitral valve disease, other diseases
- Year of diagnosis
- Other medical diagnoses
- Relevant diagnostic and prognostic referral information on patient physical condition
- If present settings of Implantable cardiac defibrillator (ICD) (safe heart rate range for exercise) or pacemaker
- Is the patient's physical functioning affected by the cardiac disease?
- Is the patient's exercise capacity objectively reduced in relation to future functioning?
- Results of maximum or symptom limited exercise test
- Risk profile (e.g., smoking, alcohol use, physical inactivity, elevated blood cholesterol level, high blood pressure, overweight or obese, diabetes)
- All medication (type and dosage)
- Fear of exertion
- Knowledge of the disease and exercise options

Specification for heart failure:

- Details on the severity of the heart failure (expressed as left ventricular ejection fraction (LEVF) and New York Heart Association (NYHA) class and VO_2peak as a percentage of the predicted value)
- The remaining left ventricular function (ejection fraction), the severity of any valve disease, and the presence of ischemia and status of the coronary vessels, arrhythmias and conduction defects
- Presence or absence of an implantable cardioverter defibrillator (ICD) or (mostly biventricular) pacemaker (type, settings);
- Risk of decompensation
- Results of maximum or symptom-limited exercise test with gas analysis

Absolute contraindications for physical examination and participation in the training program include:

- Progressive increase in heart failure symptoms
- Severe ischemia of the cardiac muscle upon exertion
- Respiratory frequency of more than 30 breaths per minute
- Heart rate at rest >110 bpm, VO2 max, 10 mL/kg/minute; ventricular tachycardia upon increasing exertion
- Fever; acute systemic diseases
- Recent pulmonary embolism (<3 months ago) causing severe hemodynamic strain
- Thrombophlebitis; acute pericarditis or myocarditis
- Hemodynamically serious aortic stenosis or mitral valve stenosis
- Presence of unstable angina, for example, pain in the chest at rest or pain that does not react to specific medication
- NYHA functional classification class 4
- Myocardial infarction less than 3 months before the start of the training program
- Atrial fibrillation with rapid ventricular response at rest (>100 bpm)
- Weight gain of >2 kg within a few days, whether or not accompanied by increased dyspnea at rest is related to weight gain.

Physical examination

- Check relevant information: The patient's current physical condition, based on the maximum or symptom-limited exercise test (with gas analysis)
  (spiro-ergometry) and referral information provided by cardiologist
- Assess functional exercise capacity (Shuttle walk Test, Six Minute Walk Test) [20-23]
- Assess blood pressure (type OMRON M7) in rest and after the exercise test
- Are there any other factors that could affect the patient's ability to improve physical condition, such as:
  - Medication
  - Dyspnea or fatigue
- Fear of exertion

Appendix 2. (Cardiac disease cont'd)

Adaptations to the exercise program
General adaptations • Use the results of a maximum or symptom-limited exercise test to calculate the individual aerobic exercise intensity in patients with cardiac problems. (If the patient is using beta blockers, the exercises should be based on the results of the maximum or symptom-limited exercise test with beta blocker use). The optimized exercise zone can be calculated using the Karvonen formula, which calculates the exercise heart rate as a percentage of the heart rate reserve (the difference between the maximum heart rate and the heart rate at rest), added to the resting heart rate. Patients should start with 2 weeks of exercise at 40%–50% of their VO2 max then gradually raise the training intensity from 50% to 80% of their VO2 max or VO2 reserve. • Base the exercise intensity on a percentage of the maximum capacity expressed in watts or METs and/or a Borg RPE-scale (6–20)24 if the patient's heart rate does not rise sufficiently during the maximum or symptom-limited exercise test (see Load intensities expressed in various training load measures as reported by the American College of Sports Medicine, Pollock et al. 199025. • Continue monitoring and observing of the individual response of the patient and the way they tolerate the exercise load, and check whether the patient shows any signs of excessive strain. • Perform interval training for patients in poor physical condition instead of continuous aerobic training. • Perform dynamic instead of static strength exercise to prevent high blood pressure • Reduce the training intensity in warm climatic conditions.

Appendix 2. (Cardiac disease cont'd)

Exercise restrictions	Adaptations
Coronary disease	
• Pain in the chest during exercise	• Terminate exercise, ask patient to sit down in chair, wait for reduction of angina. If no reduction: ask if patient uses nitro spray, if yes: apply nitro spray. If no reduction, confer with medical specialist.
• Cardiac arrhythmias during exercise (high heart frequency disproportional to the level of exertion, irregular heart rate frequency, changes in known heart arrhythmias), abnormal changes in blood pressure during exercise during exercise (diastolic change ≥20 mmHg); reduction of systolic blood pressure during exercise (>10 mmHg), fainting; dizziness; vegetative reactions (e.g., excessive perspiring, pallor), shortness of breath disproportionate to exertion, abnormal fatigue disproportionate to exertion	• Terminate exercise, ask patient to sit down in chair and confer with medical specialist
• Insufficient knowledge of the disease and exercise options	• Provide information about disease and exercise options
• Fear of exertion	• Coaching to improve confidence in exercising; i.e., consider starting at lower exercise intensity and give positive rewarding feedback
Heart failure	• see coronary disease
• Known left ventricular ejection fraction of <30%	• Prolong the warming-up and cooling-down sessions to decrease the risk of cardiac decompensation. • Be careful with Valsalva Maneuvers, changing body position such as a supine to standing position because of reduced capacity to adapt blood pressure • Start at lower exercise intensity and consider high intensity interval training (HIIT). Avoid a rapid increase in the peripheral resistance training in patients with heart failure, as this increases the afterload strongly and the risk of decompensation. For improving muscle strength, start with 2 weeks on 30%–40% of 1RM and then gradually increase the resistance from 50% to 70%–80% of 1RM.
• Level 3 NYHA (New York heart Association Classification)	• Start with resistance training to reduce peripheral blood pressure and cardiac load before aerobic training
• Reduced recovery capacity	• Monitor recovery to normal ADL functioning within 3-4 hours after exercise. In case of reduced recovery, reduce training intensity

Appendix 2. (cont'd)

Diabetes type 2

History taking

- Medical diagnose
- Year of diagnose
- Other medical diagnoses
- Glycemic control:
  - Laboratory values (glucose, HbA1c)
  - Medication treatment diabetes (type and dosage):
  - Check if the used Glucose-Lowering Medications interact with the exercise
- Other medication (type and dosage):
- Risk profile (e.g., smoking, alcohol use, physical inactivity, elevated blood cholesterol level, high blood pressure, overweight or obese, Complications due to diabetes: cardiovascular, neurologic (peripheral and autonomic), nephrologic, retinal
- Additionally, maximal ergo spirometry testing with ECG monitoring should be done in patients less than 30 years or more than 40 years of age and with the presence of one of the following criteria: diabetes diagnosed more than 10 years previously, hypertension, cigarette smoking, dyslipidemia, retinopathy, or nephropathy. In the case of diagnosed or suspected coronary artery disease, peripheral arterial disease, cerebrovascular disease, autonomic neuropathy, or severe nephropathy (renal failure), such exercise testing also is indicated.
- Is the patient's physical functioning affected by diabetes?
- Knowledge of the disease and exercise options
- Fear of exertion
- Refer to physician when: development or worsening of hypertension, angina pectoris, heart rhythm disturbances, development or worsening of resting tachycardia, development or worsening of intermittent claudication, development or worsening of fasting hyperglycemia, frequent hypoglycemic episodes, development or worsening of wounds in lower extremities, cachexia, autonomic neuropathy, or development or worsening of vision disturbances

Absolute contraindications for participation in the training program include

n.a

Physical examination

- Evaluate of peripheral vascular status: assessment of pain, changes in extremity color, temperature, pulsations of peripheral arteries (dorsalis pedis, tibialis posterior). When a patient complains of having peripheral muscle pain that is provoked by walking and disappears during subsequent recovery, this complaint might indicate intermittent claudication.
- Check for presence of peripheral neuropathy: Test peripheral sensibility: monofilament (Semmes-Weinstein)[26]. During this assessment, use a 10-g monofilament for cutaneous pressure assessment, and a needle to assess pain sensation. Test vibratory sensitivity[8].
- Check for presence of autonomic neuropathy: Test heart rate in rest (resting (60–100 bpm) and exercise (rate and rhythm) heart rate), blood pressure and symptoms of orthostatic hypotension (a decrease in systolic blood pressure of greater than 30 mm Hg or a decrease in diastolic blood pressure of greater than 10 mm Hg when changing from a supine to standing position). A slowed heart rate recovery after exercise also is typically associated with autonomic neuropathy.
- Assess functional exercise capacity (Shuttle walk Test, Six Minute Walk Test) [20–23].
- Assess blood pressure (type OMRON M7) at start and end of exercise session (140/90 mm Hg). In the case of hypertension (blood pressure >140/90 mm Hg), heart rhythm disturbances, tachycardia (heart rate >100 bpm), and bradycardia (heart rate <60 bpm) with clinical symptoms, such patients should receive further attention and clinical examination.
- Are there any other factors that could affect the patient's ability to improve physical condition, such as:
  - Medication
  - Dyspnea or fatigue
  - Fear of exertion

Appendix 2. (Diabetes type 2 cont'd)

Adaptations to the exercise program

General adaptations

- Ensure adequate hydration and carbohydrate intake before exercise session.
- Check patients with type 2 diabetes regularly for wounds and sensory defects.
- Perform interval training for patients in poor physical condition instead of continuous aerobic training
- Fever: postpone exercise training until body temperature is restored
- Refer to physician in case of development or worsening of conditions that may be related to diabetes, such as hypertension, angina pectoris, heart rhythm disturbances, resting tachycardia, intermittent claudication, fasting hyperglycemia, frequent hypoglycemic episodes, wounds in lower extremities, cachexia, autonomic neuropathy, or vision disturbances.

Exercise restrictions	Adaptations
• Use of medication which increase in blood insulin level (insulin-dependent patients	• Monitor blood glucose levels before and after the exercise session and in the evening in case of insulin-dependent diabetes patients. Occurrence of induced hypoglycemia during exercise and up to 48 hours afterwards or 72 hours after intense strength training • Lower medication/insulin therapy in case of low blood glucose level (<4.2 mmol/L, <75 mg/dL) or symptoms of hypoglycemia before exercise training • Elevate carbohydrate intake in case of low blood glucose level (<5.5 mmol/L, 100 mg/dL) or symptoms of hypoglycemia before exercise training. Adjust training modalities (lower total exercise energy expenditure in case of low blood glucose level or symptoms of hypoglycemia; • Postpone exercise training in case of blood glucose values ≤5 and ≥15 mmol/L or signs of hypoglycaemia. Regulation of blood glucose level is necessary (use medication diary).
• Poorly regulated diabetes characterized by a high (>7%) HbA1c and or highly variable blood sugar levels (high or low) and frequent hypoglycemia	• Confer with the medical specialist (internist) about medication use (type, dosage) and exercise. Monitor blood glucose levels before and after the exercise session and in the evening. Be aware of signs of hypo/hyperglycemia and complications due to diabetes.
• Delayed recovery when injured	• Start with low exercise intensity and slowly increase
• Foot ulcer (as a result of peripheral neuropathy)	• Avoid weight bearing exercises when wounds at the feet are present.
• Sensory deficits (as a result of peripheral neuropathy)	• Refer for foot care if required.
• Retinopathy	• Be careful with exercises that require tactile feedback (e.g., balance) and consider providing exercises on machines (patients can have difficulties feeling where e.g., dumbbells are in his hands with the risk of dropping them).
• Nephropathy	• Avoid high-intensity training (>80% of maximum oxygen uptake [VO2max]) and Valsalva Maneuver
• Autonomic neuropathy with impaired cardiovascular response to exercise, response to dehydration, thermoregulation, postural hypotension, and /or decreased maximum aerobic activity	• Avoid hypertension (systolic blood pressure > 180 mm Hg) during exercise.
• Insufficient knowledge of the disease, medication and exercise	• Regularly check heart rate and blood pressure in rest and during exercise. The patient's heart rate may not rise or abate sufficiently during or after the training.
• Fear of exertion	• Provide information about disease and exercise options • Coaching to improve confidence in exercising; i.e., consider starting at lower exercise intensity and give positive rewarding feedback

Appendix 2. (cont'd)

COPD

History taking

- Medical diagnose

GOLD stadium: 1, 2, 3, 4

- Year of diagnose
- Other medical diagnoses
- Medication
- Results of maximum or symptom-limited exercise test with gas analysis
- Sensations of dyspnea at rest or during exercise
- Signs of impaired exercise capacity
- Is the patient's physical functioning affected by COPD?
- Signs of impaired mucus clearance
- Natural course of the symptoms and the disorder
- Recurrent respiratory infections with mucus retention
- Presence of factors that are influencing symptoms and their progression
- Fatigue
- Fear of exertion or fear of breathlessness

Absolute contraindications for participation in the training program include

- Pneumonia and exceptional loss of bodyweight (10% in the past half year or >5% in the past month).

Physical examination

- Check relevant information: The patient's current physical condition, based on the maximum or symptom-limited exercise test with gas analysis (spiro-ergometry) and referral information provided by pulmonologist. Typical items in the lung function assessment of these patients are elevated total lung capacity (> 110% of predicted value), functional residual capacity (> 150% of predicted value, reduced Tiffenau index (< 40%) and shape of the forced flow-volume curve.
- Assess functional exercise capacity (Shuttle walk Test, Six Minute Walk Test)[20-23]
- Assess blood pressure (type OMRON M7)
- Clinical inspection (dyspnea, leaning forward position, cyanosis, muscle atrophy, peripheral edema), chest wall configuration (hyperinflation, deformities), respiratory movement (respiratory rate, paradoxical thoracic-abdominal movement at rest and during exercise, accessory respiratory muscle activity, activity of abdominal muscles)
- Are there any other factors that could affect the patient's ability to improve physical condition, such as:
  - Medication
  - Dyspnea or fatigue
  - Fear of exertion or fear of breathlessness

Adaptations to the exercise program

General adaptations

- Use the results of symptom limited exercise test with gas analysis to calculate the individual aerobic exercise intensity.
- Start with interval training in patients with COPD with ventilation limitation or impaired oxygen transport in the lungs (hypoxemic [saturation <90%]/hypocapnic [$PaCO_2$> 55 mmHg] during exercising). Start endurance training if walking on 70% of maximum watts level for at least 10 minutes is possible.
- Use the Borg scale (0-10) to measure Dyspnea during exercise[27]. A dyspnea rating between 4 and 6 on a scale of 0-10 is the recommended exercise intensity.
- Check saturation level: O_2 saturation (SaO_2) should remain ≥90% during exercising (and should not fall by ≥4%).
- Be aware of poor nutritional status

Appendix 2. (COPD cont'd)

Exercise restrictions	Specific adaptations
• Peripheral muscle atrophy and weakness • Reduction of respiratory muscle function	• Pay extra attention to strength training • Add inspiratory muscle training (IMT) if respiratory muscle weakness is present (or consider referral to a specialized therapist for training of pulmonary impairments).
• Insufficient control of respiration and cough techniques	• Teach coughing/huffing/breathing exercise dependent on severity and causes of obstruction. Give advice and exercises targeting body position and breathing if hyperinflation is present. Breathing exercises aimed at reduction of (dynamic) hyperinflation and improvement of gas exchange: pursed lips breathing (PLB), slow and deep breathing, and active expiration.
• Present exacerbation of the disease	• Interval training, resistance training, or transcutaneous neuromuscular electrical stimulation can be used to immediately reactivate patients.
• Severe dyspnea	• Based on evaluation of the exercise limitations: Reduce training intensity or consider interval training and resistance training. It is recommended to use both upper limb and lower limb resistance weight training at an intensity of at least 60% to 80% of the one-repetition maximum. Two to 3 sets of 8 to 12 repetitions per muscle group are preferred. Consider breathing exercise and exercise targeting body position.
• Insufficient knowledge of the use of medication combined with exertion	• Provide information about disease and exercise options and medication use
• Fear of exertion/fear of breathlessness	• Coaching to improve confidence in exercising; i.e., consider starting at lower exercise intensity and give positive rewarding feedback • Coach the patient if there is presence of fear of exercising due to breathlessness.
Hypertension	
History taking	
• Medical diagnose • Year of diagnose • Medication • Blood pressure last time • Is the patient's physical functioning affected by hypertension?	
Contraindications for participation in the training program include	
• Resting systolic blood pressure of >180 mmHg or diastolic blood pressure of >115 mmHg. Refer to physician.	
Physical examination	
• Blood pressure assessment (type OMRON M7)	

Appendix 2. (Hypertension cont'd)

Adaptations to the exercise program	
General adaptations • Be aware that medication to lower blood pressure, like beta blockers, can reduce maximal exercise tolerance an attenuate heart rate response to exercise. • Beta blockers and diuretics may adversely affect thermoregulatory function • Check blood pressure-lowering medication with physician. If adequate but still hypertensive, low-to-moderate intensity strength straining should be performed instead of high-intensity strength training.	
Exercise restrictions	**Adaptations**
• Increased risk of high blood pressure, especially in case of left ventricular hypertrophy	• If the plan is to perform moderate (40% <60% VO_2R) to vigorous intensity (≥60% VO_2R) first refer for a symptom-limited exercise test
• Abnormal changes in blood pressure during exercise during exercise (diastolic change ≥20 mmHg); reduction of systolic blood pressure during exercise (>10 mmHg)	• Terminate exercise and refer to medical specialist
Obesity	
History taking	
• Medical diagnose • Year of diagnose • Other medical diagnoses • Body Weight • Duration of overweight or obesity • Is the patient's physical functioning affected by overweight or obesity? • Experience with body weight reduction/following a diet • Attitude and beliefs about food intake and diet • Food and nutrition related knowledge • Motivation to body weight reduction • Guidance needed to loose body weight (referral to a dietician)	
Contraindications for participation in the training program include	
n.a.	
Physical examination	
• Bodyweight (kg) • Height • Body Mass Index (BMI)= weight(kg)/height^2(m^2) Underweight = <18.5 Normal weight = 18.5–24.9 Overweight = 25–29.9 Obesity = BMI of 30 or greater • Assess blood pressure (type OMRON M7)	

Appendix 2. (Obesity cont'd)

Adaptations to the exercise program	
General adaptations • Stimulate weight reduction due to overweight or obesity and/or refer to a dietician	
Exercise restrictions	**Adaptations**
• Increased stress, pressure and pain in weight bearing joint	• Reduce weight-bearing exercises because of increase in knee joint pain, consider aquatic based exercise
• Shortness of breath	• Reduce training intensity, consider interval training
• Poor thermoregulation during exertion	• Reduce the training intensity in warm climatic conditions
• Fear of movement	• Coaching to improve confidence in exercising; i.e., consider starting at lower exercise intensity and give positive rewarding feedback
• Lack of motivation for weight reduction	• Provide information about weight loss and pain relief and exercise options. Stimulate and coach in weight reduction.

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Chapter 8

Exercise and comorbidity: *the i3-S strategy for developing comorbidity-related adaptations to exercise therapy*

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Abstract

Purpose. Exercise therapy is effective in a wide range of chronic diseases. Comorbid disease necessitates adaptations to exercise therapy. Guidance on how to develop such adaptations is currently not available. We present an innovative strategy for the development of comorbidity- related adaptations to exercise therapy in an index disease.
Methods. We previously developed comorbidity-related adaptations to exercise therapy in osteoarthritis. We now broaden this approach into a general strategy for the development of comorbidity-related adaptations to exercise therapy in an index disease.
Results. The i3-S strategy consists of four steps. The first three steps involve creating an inventory of comorbid disease, an inventory of contraindications and restrictions on exercise therapy, and an inventory of potential adaptations to exercise therapy. In the fourth step, this information is synthesized into guidance on comorbidity-related adaptations to exercise therapy in the index disease. The adaptations concern physiological, behavioural and environmental factors.
Conclusion. In view of the general effectiveness of exercise therapy and the high prevalence of comorbidity in older people, there is a great need for comorbidity-related adaptations to exercise therapy. We recommend to use and evaluate the i3-S strategy in future research.

Introduction

Exercise therapy is effective in a wide range of chronic diseases, with controlled studies showing consistent evidence that exercise therapy results in reduced morbidity, reduced symptoms and better functioning[1–3]. However, comorbid disease frequently leads to the exclusion of patients from treatment[4]. One example is comorbid diabetes, which leads to patients being excluded due to concerns related to hypoglycaemia. When patients with comorbid disease are referred, therapists often reduce the intensity of exercise to a level that is unlikely to be effective[5]. Because patients are inclined to do likewise, comorbid disease may result in non-adherence to exercise recommendations[6].

Patients with comorbid disease can exercise, provided that the exercise regimen is adequately adapted to the comorbidity. A patient with osteoarthritis of the knee and comorbid diabetes is allowed to exercise if their blood glucose level is monitored and the exercise is adapted accordingly. Current guidelines provide guidance on exercise therapy in the index disease (e.g., osteoarthritis as index disease, or diabetes as index disease). These guidelines fail to provide proper guidance on adaptations required because of the presence of comorbidity next to the index disease. For example, no adaptations because of diabetes were provided in a guideline on exercise therapy in osteoarthritis[7]. Conversely, no adaptations because of osteoarthritis were provided in a guideline on exercise therapy in diabetes[8,9]. General advice on exercise describes adaptations to the presence of disease, but does not describe how exercise in an index disease needs to be adapted to comorbidity (e.g., [10]).

We have previously developed comorbidity-related adaptations to exercise therapy in osteoarthritis of the knee[11,12]. We now broaden this approach into a general strategy for the development of comorbidity-related adaptations to exercise therapy in an index disease. Researchers and clinicians can use this strategy to develop comorbidity-related adaptations of exercise therapy in an index disease. We illustrate the strategy using our experience in developing comorbidity-related adaptations to exercise therapy for osteoarthritis of the knee as an example.

The i3-S strategy

The i3-S strategy consists of four steps – three inventories and a synthesis. The first three steps involve the gathering of relevant information and include creating an inventory of comorbid disease, an inventory of contraindications and restrictions on exercise therapy, and an inventory of potential adaptations to exercise therapy. In the fourth step, this information is synthesised into guidance on the adaptation of exercise therapy to comorbid disease (Figure 1).

Step 1 involves creating an inventory of relevant comorbid diseases: given a specific index disease, which comorbid diseases should be included? Criteria for selecting

comorbid diseases include comorbidity prevalence, comorbidity-related exercise risk and the impact of comorbidity on functioning. For example, we identified 11 diseases as relevant comorbidities in osteoarthritis of the knee: coronary artery disease, heart failure, hypertension, type 2 diabetes, obesity, chronic obstructive pulmonary disease (COPD), depression, chronic pain, low back pain and visual or hearing impairments[11,13].

Step 2 involves creating an inventory of comorbidity-related contraindications and restrictions on the application of exercise therapy in the index disease. Contraindications are conditions, which entirely preclude the application of exercise because the patient's safety cannot be guaranteed (e.g., chest pain before or during exercise in a patient with coronary artery disease). Restrictions are conditions, which limit the application of exercise therapy, necessitating adaptations to the therapeutic protocol (e.g., left ventricular ejection fraction of less than 30%). However, restrictions do not entirely preclude the application of exercise.

Contraindications and restrictions are derived from the literature on exercise therapy in patients with specific diseases. We created an inventory of contraindications and restrictions for exercise therapy in osteoarthritis of the knee[11], related to the 11 comorbid diseases identified in step 1. We began by reviewing the literature on exercise therapy in coronary artery disease to identify contraindications and restrictions related to coronary artery disease, followed by a similar process for type 2 diabetes and the remaining nine comorbid diseases.

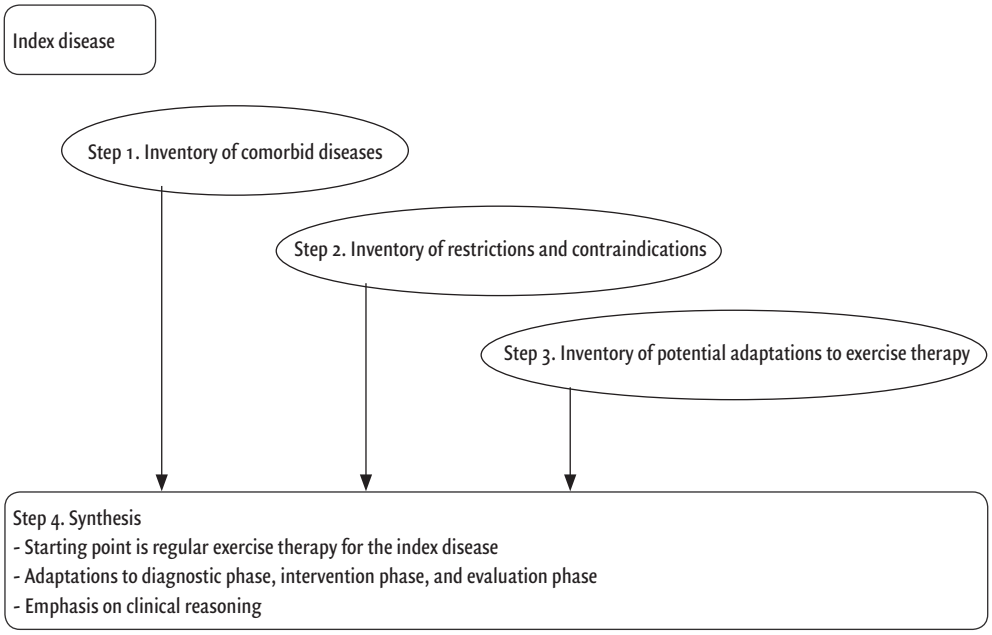

Figure 1. The i3-S strategy for developing comorbidity-related adaptations to exercise therapy.

Step 3 involves creating an inventory of potential adaptations to exercise therapy. These adaptations are derived from guidelines on regular exercise therapy in each comorbid disease (e.g., the guideline on exercise in COPD). In cases where no guideline is available, general guidelines on exercise (e.g., the American College of Sports Medicine guideline[10]), general medical guidelines on the treatment of the disease (e.g., guidelines for depression) and expert opinion provide relevant information on adaptations. From these sources of information, principles are derived on how to adapt regular exercise therapy for the index disease to restrictions associated with a specific comorbid disease. The adaptations concern the duration, frequency, intensity and type (content) of exercise therapy. In osteoarthritis of the knee, we created an inventory of potential adaptations related to coronary artery disease (e.g., adapted intensity of individual aerobic exercise), an inventory of potential adaptations related to diabetes (e.g., postponement of exercise when blood glucose is below or above specific cut-off values), and inventories of potential adaptations for all other comorbid diseases[12].

Step 4 involves the synthesis of the information obtained in the previous steps into guidance on the adaptation of exercise therapy to comorbid disease. Guidance on regular exercise therapy in the index disease is the starting point: this guidance is then adapted to the comorbid disease. For example, starting with the guideline on exercise therapy in osteoarthritis of the knee[14,15], we specified how the guideline should be adapted to comorbid disease[12].

In the diagnostic phase, comorbidity-related restrictions and contraindications for exercise therapy should be evaluated, the need for additional medical examination is evaluated, and comorbidity-adapted treatment goals are set, taking into account diagnostic findings related to both the index disease and the comorbid diseases. In the intervention phase, comorbidity-related adaptations to the duration, frequency, intensity and type (content) of exercise therapy are indicated. The exact adaptations depend on the restrictions on exercise therapy identified in the diagnostic phase. In the evaluation phase, treatment goals and the need for changes to the treatment plan are evaluated, with a specific emphasis on comorbidity.

Throughout the entire process, there is an emphasis on applying clinical reasoning (or professional reasoning) when developing exercise therapy that is appropriate for patients with a comorbidity[16,17]. Patients should be viewed in their entirety, with consideration of integrated body structures, functions and activities as a whole, rather than as separate organs. In the diagnostic phase, clinical reasoning may indicate the need for further medical examination to exclude contraindications. Similarly, clinical reasoning guides the selection of treatment goals, taking into account diagnostic findings related to both the index disease and the comorbid diseases. In the intervention phase, clinical reasoning is necessary when deciding on the specific exercise adaptations (duration, frequency, intensity and type of exercise) required for an individual patient. As comorbidity may impose several, sometimes even contradictory, requirements on exercise, clinical reasoning is essential when dealing with the range of exercise adaptations. An example is comorbid heart failure with osteoarthritis of the knee. While the osteoarthritis guideline

emphasises the need for strength training, due to heart failure a rapid increase in the level of peripheral resistance should be avoided, as this increases the afterload and risk of decompensation.

Physiological, behavioural and environmental adaptations

We initially developed 11 adapted exercise therapy protocols, in which regular evidence-based exercise therapy in osteoarthritis of the knee was tailored to each of the 11 comorbid diseases. However, during a pilot study, we found that these 11 protocols could be condensed to only three: a protocol for physiological exercise adaptations – related to coronary artery disease, heart failure, hypertension, type 2 diabetes, obesity and COPD; a protocol for behavioural exercise adaptations – related to chronic pain, non-specific low back pain and depression; and a protocol for environmental exercise adaptations – related to visual and hearing impairments[12]. A few examples include adjusted individual aerobic exercise intensity as a physiological exercise adaptation, a graded activity program as a behavioural exercise adaptation, and a larger font size of exercise instructions as an example of environmental adaptations. Although it is an open question whether categorisation into physiological, behavioural and environmental adaptations is applicable to index diseases other than osteoarthritis and to other comorbid diseases, this categorisation appears to be quite generalisable.

Perspective

In view of the general effectiveness of exercise therapy and the high prevalence of comorbidity in older people, there is a great need for a strategy for developing comorbidity-related adaptations to exercise therapy. We recommend to use and evaluate the i3-S strategy for the development of comorbidity-related adaptations to exercise therapy in an index disease in future research.

In a recent systematic review (see Appendix), we identified two other studies describing the development of comorbidity- adapted exercise, in patients with acute exacerbations of COPD[18] and in older adults living with HIV[19], in addition to our own study on patients with osteoarthritis of the knee[1]. All three studies described the development of specific comorbidity-related adaptations to exercise therapy, focusing on a specific index disease. None of these studies provided general guidance on how to develop comorbidity-related adaptations to exercise therapy in an index disease. A general strategy for developing such adaptations (i.e., the i3-S strategy) could facilitate future studies on the development of comorbidity-related adaptations to exercise therapy in an index disease. Remarkably, the other two studies used an approach which is rather similar to our original approach[12] (see Appendix). The similarity of the approach in these three studies suggests the usefulness of the general i3-S strategy. We believe the i3-S strategy will prove to be a useful approach for developing comorbidity-related adaptations to exercise therapy in index diseases.

The i3-S strategy structures the adaptation of regular exercise therapy for the index disease to co-existing comorbidity. In a patient with osteoarthritis of the knee (index disease), exercise is adapted to coexisting cardiac disease. Conversely, after a cardiac

event (index disease), exercise therapy is adapted to coexisting osteoarthritis of the knee. An obvious alternative would be to take a multi-morbidity approach, and to develop guidance on exercise therapy for patients with osteoarthritis and cardiac disease, and possibly other diseases as well. We strongly prefer the comorbidity approach used in the i3-S strategy, because (i) patients tend to present with specific symptoms, associated with a specific index disease, (ii) therapists tend to structure their treatment around the index disease, and (iii) this approach allows to preserve the detailed guidance on exercise for the index disease, and then add comorbidity-related adaptations. We recommend that the i3-S strategy should be used to develop adaptations of exercise therapy to comorbid disease.

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Appendix

Systematic review on strategies for the development of comorbidity-related adaptations to exercise therapy in an index disease

Aim

To identify and describe strategies for the development of comorbidity- related adaptations to exercise therapy in an index disease.

Methods

A protocol was developed with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[20].

Literature search

The literature was systematically searched from 1985 up to 3 May 2015, using the PubMed database, and using the following search strategy:
(''exercise'' [MeSH Terms] OR ''exercise'' [All Fields] OR ''exercise therapy'' [MeSH Terms] OR ''exercise therapy'' [All Fields] OR ''physical therapy modalities'' [MeSH Terms] OR ''physical therapy'' [All Fields] OR ''physiotherapy'' [All Fields] AND (''comorbidity'' [MeSH Terms] OR ''comorbidity'' [All Fields] OR comorbidities [All Fields] OR comorbid [All Fields] OR multimorbidity [All Fields] OR multimorbidities [All Fields] OR multimorbid [All Fields] OR coexisting [All Fields]) AND (''1985/01/01'' [PDAT]: ''2015/12/31'' [PDAT]) AND ''humans'' [MeSH Terms] AND English [lang]). The reference lists of all retrieved studies were also searched, as well as the authors' personal data base.

Inclusion criteria

Inclusion criteria for the present study were the following: (1) The study concerns exercise therapy in one or more specific index diseases; (2) the study describes a strategy or systematic approach towards the develop- ment of adaptations of exercise therapy in the index disease(s) to the presence of comorbidity; (3) the study was reported in the format of a full-text article; and (4) the study was published in English.

Data extraction

Data were extracted on the index disease, and on the strategy for the development of comorbidity-related adaptations to exercise therapy in the index disease, by means of a qualitative summary.

Data synthesis

A qualitative summary of the results.

Results

The search yielded 4342 unique references, which were screened on title and abstract. This resulted in 18 full text articles that were evaluated on eligibility. Three studies were included in the present systematic review (15 studies were rejected because they did not meet the selection criteria). The papers included in the present review described the development of comorbidity-adapted exercise in patients with acute exacerbations of chronic obstructive pulmonary disease[21], in older adults living with HIV[22], and in patients with osteoarthritis of the knee (our own study[23]).

Camp et al.[21,24] developed recommendations on exercise in acute exacerbations of chronic obstructive pulmonary disease (COPD). The authors conducted (i) systematic reviews on exercise in COPD, and 11 comorbid conditions (being older, heart failure, ischeamic heart disease, peripheral arterial disease, hypertension, obesity, osteoarthritis, osteoporosis, diabetes type 2, HIV and depression). The next step was (ii) a Delphi process which generated more detailed parameters for both exercise safety and effectiveness, and a corresponding clinical decision tool and patient guide. Further steps consist of (iii) a critical appraisal of the tool and guide by a focus group of health professionals, and (iv) a dissemination and implementation plan.

O'Brien et al.[22] conducted a knowledge synthesis combining two streams of evidence: (A) HIV-specific evidence addressing rehabilitation and ageing, and (B) evidence on the effectiveness of non-pharmacological rehabilitation interventions for comorbidities commonly experienced by older adults ageing with HIV. The recommendations were derived from literature, identified through systematic literature searches. The obtained evidence was synthesised, using a three-phase iterative process. This process involved (i) classification, assessing methodological quality, synthesis of the evidence and drafting the preliminary recommendations; (ii) interprofessional team review, grading the evidence, and revision of recommendations incorporating values and preferences; and (iii) external endorsement and final refinement.

Stream A resulted in overarching recommendations (e.g. ''Rehabilitation professionals should be prepared to provide care to older adults with HIV who present with complex comorbidities (. . .)'', (Supplement 2, p. 6). Stream B resulted in specific recommendations on rehabilitation, including recommendations on exercise in older adults with HIV, and eight categories of comorbidity, i.e. bone and joint disorders, cancer, stroke, cardiovascular disease, mental health challenges, cognitive impairments, Parkinson's disease, COPD and diabetes (e.g. ''Exercise-based cardiac rehabilitation should be recommended for older adults with HIV who have undergone a myocardial infarction (MI) (otherwise known as a heart attack) (or at risk of an MI) given evidence suggests exercise-based cardiac rehabilitation is effective in reducing cardiac deaths. The ideal frequency, intensity, time and type of exercise to maximize benefits are unclear''. (O'Brien et al.[22], Supplement 2, p. 43).

de Rooij et al.[23,25] developed comorbidity-adapted protocols for exercise therapy in osteoarthritis (OA) of the knee in five steps. (i) Comorbidities were selected that are

common, and have impact on pain or daily functioning. The following comorbidities were selected: cardiac diseases; hypertension; type 2 diabetes; obesity; COPD; low back pain; chronic pain; depression; and visual or hearing impairments. (ii) An inventory was made of restrictions and contraindications for exercise therapy in patients with OA of the knee and comorbidity, based on a systematic search of the literature. (iii) Guidelines on exercise therapy in each comorbidity were consulted, to derive potential adaptations to exercise therapy. These potential adaptations were incorporated into the guideline on exercise therapy for OA of the knee. (iv) Preliminary versions of the protocols were extensively discussed with clinical experts, and (v) the protocols were field-tested in a pilot study in patients with knee OA and the target comorbidities; feedback from therapists and patients was obtained, leading to further refinement of the protocols. One of these protocols is currently being evaluated in a randomised clinical trial.

Discussion

From these studies, the following characteristics of strategies for the development of comorbidity-related adaptations to exercise therapy in an index disease can be derived. (i) Specifying comorbidities of the index disease (step 1 in the i3-S strategy). All three studies explicitly stated which comorbidities were being studied[21-23]. (ii) An inventory of comorbidity-related restrictions and contraindications for exercise therapy in patients with the index disease (step 2). This is a unique characteristic of the approach of de Rooij et al.[23,25], which was not apparent in the other two studies. This step makes the important distinction between absolute contraindications (no exercise therapy allowed) and restrictions (adaptations to exercise therapy required). Furthermore, this step delineates exactly which restrictions need to be taken into account. It sets the agenda for step 3. (iii) Generating potential recommendations from the literature (step 3). All three studies[21-23] derived these recommendations from the literature and guidelines on interventions for specific comorbidities. Despite differences in the specific approach used, all three studies took basically the same approach: potential adaptations to exercise therapy in the index disease were derived from evidence on exercise therapy in the comorbid diseases (at that stage treated as index disease). For example: adaptations because of comorbid diabetes were derived from literature on exercise therapy in diabetes (as index disease). (iv) Developing specific recommendations on comorbidity-related adaptations to exercise therapy in an index disease (step 4). Expert knowledge and advise was obtained to develop specific recommendations. The studies used various approaches to elicit expert knowledge and advise (i.e. Delphi process, critical appraisal, interprofessional team review, external endorsement, extensive discussions with clinical experts and field-testing)[21-23]. All three studies emphasised the importance of obtaining expert knowledge and advise for the synthesis of the evidence and the development of specific recommendations.

None of these studies provided general guidance on how to develop comorbidity-related adaptations to exercise therapy in an index disease. All three studies described a specific approach towards developing comorbidity-related adaptations to exercise therapy, focusing on a specific index disease. A general strategy for developing such adaptations could facilitate future studies on the development of comorbidity-related adaptations to exercise therapy in an index disease.

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Chapter 9

General discussion

Discussion

The first part of this thesis provides insight into the course and predictors of pain and physical functioning in patients with osteoarthritis (OA) of the knee or hip. The second part describes the development and evaluation of comorbidity-adapted exercise therapy in patients with knee OA and comorbidity. In this chapter, the main results of the studies in this thesis are summarised and discussed. Furthermore, suggestions for future research are given.

Course and predictors of pain and physical functioning in knee or hip osteoarthritis
In **Chapters 2 and 3** we reviewed the scientific data on the course of pain and physical functioning in patients with knee or hip OA, and we gave an overview of predictive factors for deterioration in the course of pain and physical functioning. For patients with knee OA (**Chapter 2**), high heterogeneity across and within studies was found, indicating considerable differences between studies and between patients in the course of pain and physical functioning: some patients improve, some patients remain stable, while others deteriorate. Similar results were found in patients with hip OA (**Chapter 3**). These findings are consistent with the current trend of research. It has recently been hypothesized that the population of patients with OA actually consists of several homogeneous subgroups[1-3], each with a different clinical course of pain or physical functioning[4-7]. For example, in one analysis, after five years in the Cohort Hip & Cohort Knee (CHECK cohort), three subgroups with distinct trajectories in pain were identified in patients with early OA: patients with marginal, mild, or moderate pain[7]. Holla et al.[6] identified three subgroups with distinct trajectories of physical functioning in the same cohort of patients: patients who develop or display slight activity limitations over time (good outcome), patients who develop or display moderate activity limitations over time (moderate outcome), and patients who develop or display severe activity limitations over time (poor outcome). Describing the average course thus seems to be suboptimal. Identifying subgroups with different trajectories of pain or physical functioning seems to be more appropriate, and enables physicians to provide more tailored information about the prognosis of pain and physical functioning.

In **Chapter 2** we identified a number of prognostic factors that predict the course of pain or physical functioning of patients with *knee* OA. In comparison with a previous review on this topic[8], a larger number of high-quality studies were included in our review (39 compared with only one in the previous review). These studies provided strong evidence for a large number of predictors of deterioration in pain and physical functioning (see Figure 1). For other studied factors, the evidence found was weak, inconsistent, or inconclusive. Our findings have been partly confirmed by another recently published review on this topic. In a best evidence synthesis, Bastick et al.[9]

found strong or moderate evidence that comorbidity count, OA severity, and vitality are associated with clinical knee OA progression. However, there was also some discrepancy between the identified prognostic factors. For example, we found inconsistent evidence that BMI and age predict deterioration of pain or physical functioning, while Bastick et al.[9] found strong evidence that BMI and age predict clinical knee OA progression. This difference can be explained by the way the outcome was defined. Bastick et al.[9] used progression of symptomatic knee OA as the outcome measure, defined as an increase in pain, deterioration in physical function, or total joint replacement, while we used pain and physical functioning as separate clinical outcome measures. In our opinion it is preferable to separate these outcomes, as they measure different outcome domains.

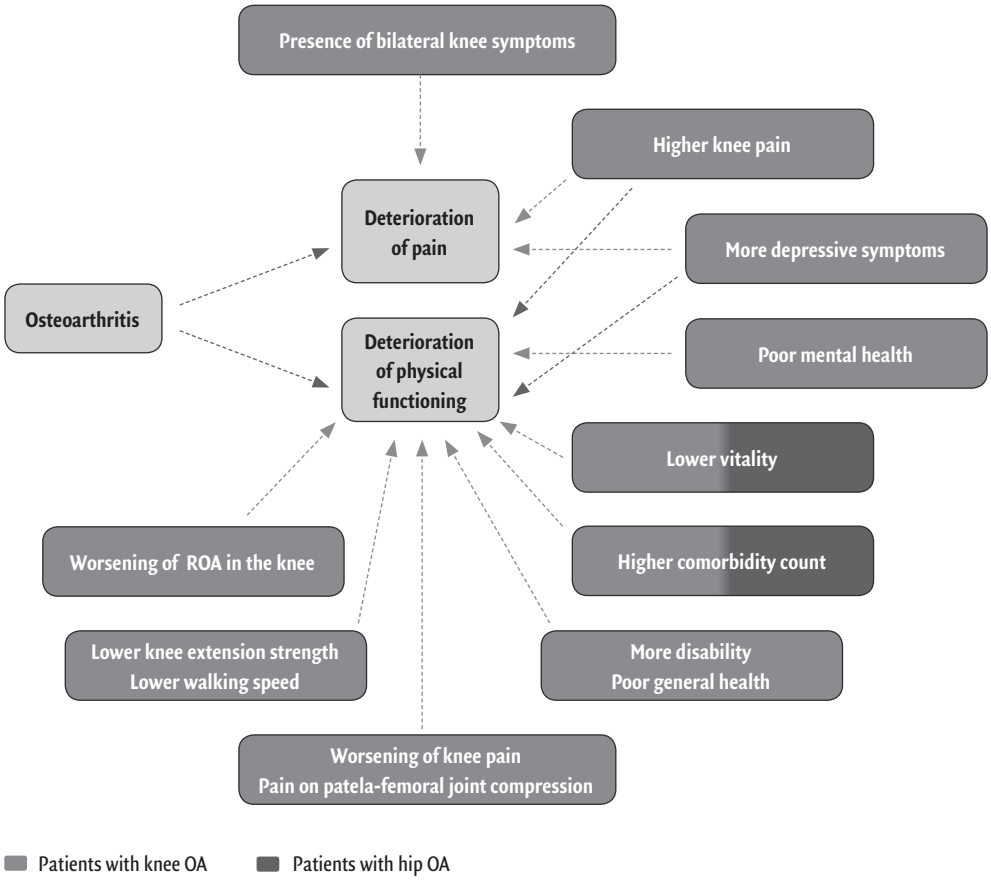

Figure 1. Summary of prognostic factors of deterioration in pain and physical functioning in patients with knee or hip osteoarthritis for which strong evidence was found. OA, osteoarthritis. ROA, Radiographic Osteoarthritis.

Knowledge of prognostic factors of deterioration of pain and physical functioning can contribute to the understanding of mechanisms and processes that cause deterioration. For example, muscle weakness has been found to be a predictor of deterioration in pain and physical functioning *and* has been found to be a causal factor in the development of activity limitations[10-18]. Another example is avoidance of activity, which has been found to be a predictor of deterioration in physical functioning in OA of the knee, *and* might be a causal factor in the development of activity limitations[19]. OA-related pain may cause persons to avoid activities such as walking. Avoidance of these activities reduces pain in the short term. In the long term, however, avoidance of activity contributes to a decrease in muscle strength and a deterioration of physical functioning[20]. A better understanding of these mechanisms and processes may lead to the development of therapeutic and preventive interventions.

A limitation of the present review is that, despite the large number of studies included in the qualitative analysis, different measurement scales and metrics were used to assess the outcome and predictor variables in the various studies. As a result, we could only perform a meta-analysis for a limited number of prognostic factors. More uniformity in the selection of outcome measures, potential predictor variables, instruments to measure these variables, and cut-off score is necessary to facilitate future meta-analyses and thereby provide stronger conclusions. Researchers should use recommended core sets of measurements to evaluate disease-specific and general outcomes in observational or trial studies such as the COMET (Core Outcome Measures in Effectiveness Trials)[21], the Outcome Measures in Rheumatology (OMERACT)[22], or the OARSI clinical trial recommendations[23,24]. Furthermore, collaboration of researchers in overlapping topics and data sharing is necessary. Nowadays, there are some longitudinal OA population cohorts of which datasets are available, for example, the Osteoarthritis Initiative (OAI cohort)[25], the Multicenter Osteoarthritis Study (MOST cohort)[26], and the Cohort Hip & Cohort Knee (CHECK cohort)[27]. Data sharing will contribute to enhanced statistical analyses, verification of individual findings, and reduction of publication bias.

In **Chapter 3** we identified strong evidence for a number of prognostic factors that predict the course of physical functioning in patients with *hip* OA (Figure 1). Weak, inconsistent, or inconclusive evidence was found for other studied factors. In comparison with the large number of studies included for assessing prognostic factors in patients with knee OA, in patients with hip OA we could only include two studies for assessing prognostic factors for deterioration of pain, and eight studies for deterioration of physical functioning. The difference in the amount of included studies between knee and hip OA can be explained by the higher prevalence of patients with knee OA (10 to 30%)[28] within the older worldwide population, compared with the prevalence of patients with hip OA (5 to 15%)[28-31]. In addition, clinical measurements of the knee are easier to perform and to standardize in clinical practice. Clearly, more research in patients with hip OA is needed to get more insight in the disease and the prognostic factors on the course of pain and physical functioning in these patients.

Development and evaluation of comorbidity-adapted exercise therapy in knee osteoarthritis

The development of the intervention was conducted in accordance with the Medical Research Council's (MRC) framework on complex intervention design[32,33]. The MRC framework addresses strategies for developing and evaluating complex interventions and proposes a phased approach. First, as part of the theoretical phase of the MRC framework, we identified prevalent comorbidities in patients with knee or hip OA (present in ≥5% of the patients) that affected pain and/or physical functioning (**Chapter 4**). The following comorbid diseases were identified: cardiac diseases, hypertension, type 2 diabetes, obesity, chronic obstructive pulmonary disease (COPD), depression, chronic pain, low back pain (LBP), visual or hearing impairments, and chronic cystitis. Second, and also part of the theoretical phase of the MRC framework, a literature search was carried out to identify restrictions and contraindications for exercise therapy for the various comorbid diseases (**Chapter 5**). Restrictions limit the application of exercise therapy, necessitating adaptations to the therapeutic protocol. If a contraindication is present, however, exercise therapy is not an option and the patient should be excluded from exercise therapy. Third, as part of the modelling phase of the MRC framework, for each selected comorbid disease a comorbidity-adapted exercise protocol was developed by consulting both exercise guidelines of the comorbid disease and experts on each comorbid disease (**Chapter 6**). Fourth, as part of the exploratory phase of the MRC framework, the protocol was tested in 11 patients with knee OA and comorbidity (**Chapter 6**). Field-testing showed that the protocols provided guidance in clinical decision making in both the diagnostic and the treatment phase. Because of overlap, the number of exercise protocols could be reduced to three: one requiring physiological adaptations (coronary disease, heart failure, hypertension, diabetes type 2, chronic obstructive pulmonary diseases, obesity), one requiring behavioural adaptations (chronic aspecific pain, nonspecific low back pain, depression), and one requiring environmental adaptations (visual or hearing impairments). Finally, as part of the randomized controlled trial phase of the MRC framework, the optimized protocol was tested in patients with knee OA and comorbidity requiring physiological adaptations (i.e., cardiac diseases, diabetes type 2, COPD, and obesity) (**Chapter 7**). The final phase of the MRC framework, the implementation phase, is not part of this thesis.

The results of the randomized controlled trial provided evidence that exercise therapy tailored to the comorbid disease was efficacious in reducing pain and improving physical functioning, and was safe for patients with knee OA and severe comorbidities (**Chapter 7**). Importantly, we found a large between-group effect for self-reported physical functioning (SMD = 0.9) directly after treatment, and even further improvement after three months (SMD = 1.0). This was noticeable because the effect of exercise therapy usually decreases after the intervention has ended[14]. We assume that the beneficial results of the present study can be attributed to several adjustments to the exercise program, which all contribute to an improved exercise adherence. Adherence by the patients to the treatment regimen is crucial for its success. Exercise adherence is influenced by

facilitators and barriers. In a recent systematic review, Dobson et al.[34] showed that many barriers to exercise adherence are related to beliefs about consequences and capabilities, whereas many facilitators are related to reinforcement strategies. The good exercise adherence in our trial might be explained by the use of different strategies, which are consistent with those proposed by Dobson et al.[34]: 1) the developed treatment was personalized; 2) physical therapists had a proactive role in facilitating exercise uptake and adherence; 3) personalized education was provided about beneficial consequences of the exercise, and reassurance about exercise capability, for example, changing negative beliefs about the severity of symptoms (e.g., symptoms of the comorbid disease, pain, fatigue, and disability) adversely impacting capability to exercise; 4) reinforcement strategies were used (e.g., endorsement from referring physicians, improvement in pain after exercise, and increased confidence in performing the exercise). Unfortunately, the follow-up duration of our trial was limited to three months posttreatment. To measure long-term exercise adherence, an additional follow-up of three to nine months would have been preferable.

Interestingly, we found no significant reduction of bodyweight after treatment in the intervention group. The mean BMI of the intervention group was ~ 36 kg/m^2 at baseline. During the intervention, obese and overweight participants were stimulated to lose weight, either supervised by a dietician or without supervision. A beneficial effect of weight reduction on clinical outcome measures has been demonstrated in patients with knee or hip OA. In a randomized controlled trial with overweight and obese adults with knee OA, Messier et al.[35] found that participants who lost 10% or more of bodyweight experienced improved function, reduced knee compressive force, lower systemic IL-6 concentrations (measure of inflammation), and less pain than those who lost <10% of bodyweight. An explanation for our finding of no reduction in weight might be that patients were recruited for participation in an OA exercise program and were not committed to losing weight. Only 13% of the patients of the intervention group wanted support from a dietician to lose weight during the treatment. Specific training of therapists in behavioural techniques based on social cognitive theory[36,37] and specific coaching/counselling of patients and goal setting in weight loss incentives might further improve the program we developed and its outcome. In addition, an integrated treatment in collaboration with other health care professionals, for example, dieticians or occupational therapists, could further improve treatment.

We found a greater improvement in pain, physical functioning, and health-related quality of life in the intervention group. It seems likely that the effects of the exercise program will not only affect knee-related outcomes, but also comorbidity-related outcomes. It is well documented that exercise is effective in a wide range of chronic diseases. For example, several reviews[38,39] and meta-analyses[40,41] report that increased physical exercise produces a significant improvement in glucose control in people with type 2 diabetes. In our trial we did not focus on comorbidity-related outcomes such as HbAc1 or blood pressure, but in future research these outcomes should be investigated too.

Innovative strategy for developing comorbidity-adapted exercise therapy

In **Chapter 8** we presented an innovative strategy (i3-S strategy) for the development of comorbidity-related adaptations to exercise therapy in an index disease. This strategy is derived from our previous work on the development of comorbidity-related adaptations to exercise therapy in OA. We broadened this approach into a general strategy for a four-step development of comorbidity-related adaptations to exercise therapy in an index disease. The first three steps involve the creation of an inventory of comorbid disease(s), an inventory of contraindications and restrictions on exercise therapy, and an inventory of potential adaptations to exercise therapy. In the fourth step, this information is synthesized into guidance on comorbidity-related adaptations to exercise therapy in the index disease. The adaptations concern physiological, behavioural, and environmental factors[42].

The strategy structures the adaptation of regular exercise therapy for an index disease to the comorbidity. It assumes a comorbidity approach rather than a multi-morbidity approach. In a multi-morbidity approach someone has multiple disease conditions and no particular illness has the exclusive focus. We strongly prefer a comorbidity approach because in clinical practice patients tend to seek care for a specific problem and tend to present specific symptoms associated with a specific index disease. Furthermore, therapists tend to structure their treatment around an index disease and this approach allows us to both preserve the detailed guidance on exercise for the index disease and to add comorbidity-related adaptations. A multi-morbidity approach will be more appropriate if a patient is referred for a general exercise program, for example, to prevent frailty.

Clinical reasoning plays a major role in the i3-S strategy[43,44]. Patients should be viewed in their entirety, with consideration of integrated body structures, functions, and activities as a whole, rather than as separate functions. This implies that the treating health professional needs to be capable of advanced clinical reasoning and needs to have knowledge of the comorbid disease at issue. Especially with the increasing prevalence of chronic diseases, advanced clinical reasoning as well as skills of inter-professional collaboration will be important skills of health professional in order to properly treat patients with chronic diseases. Therefore, these topics should be a major component of the curriculum of health professions. Furthermore, to support feasibility of the comorbidity-adapted exercise protocols, it will be helpful to support clinical reasoning in daily practice, for example, by the use of computerized decision support by a web-based service that provides immediate feedback with information and advice when patient data are entered[45]. For example, in cardiac rehabilitation a web-based service, Cardiac Rehabilitation Decision Support System (CARDDS), is used to support clinical reasoning by physical therapists and nurses[46]. Future research should focus on the development of a reliable service and on the evaluation of how such a service may help in improving the quality of care in a user-friendly way.

Future directions for research and implementation

Based on the study findings in this thesis, the following directions for future research are suggested.

Because the course of pain and physical functioning is highly heterogeneous in patients with knee and hip OA, future research on subgroups is warranted to improve our understanding of the aetiology and pathogenesis of the disease and to develop targeted treatment for these specific subgroups.

Second, future studies are needed to evaluate the effectiveness and feasibility of tailored exercise therapy according to the developed protocol in other health care settings (e.g., primary care) and other highly prevalent comorbidities in OA (e.g., chronic pain or depression). Furthermore, the results should be replicated in studies with a longer follow-up.

Third, the cost-effectiveness of the developed protocols should be studied to find if the costs outweigh the benefits on health-related outcomes, medication use (comorbidity-related or analgesics), hospital care, and outpatient care. In addition, investigation of cost-effectiveness will provide important information for successful implementation of the protocol in a primary care setting.

Fourth, the long-term implementation (last phase of the MRC framework) was not part of this thesis. We intend to take this step in the future. One of the implementation strategies is training of primary care physical therapists through blended education (combination of an online course with face-to-face workshops) to increase knowledge about common comorbidities, and to improve clinical reasoning and skills to properly treat patients with knee or hip OA and comorbidity. Furthermore, facilitators and barriers for implementation and engagement of key stakeholders (e.g., insurance companies) will have to be mapped.

Lastly, given the general effectiveness of exercise therapy and the high prevalence of comorbidity in older people, there is an urgent need for comorbidity-related adaptations to exercise therapy. We believe that the i3-S strategy can be used to develop comorbidity-related adaptions to exercise therapy for other index diseases. However, the use and evaluation of the i3-S strategy in other chronic (index) diseases requires future research.

Conclusions

In summary, the following conclusions can be drawn from this thesis:

- At present, it is impossible to describe an average course of pain and physical functioning in patients with knee or hip OA, because of the high heterogeneity across studies and within study populations. Some patients seem to improve, some patients remain stable, while others deteriorate. These findings are consistent with the current trend of research in defining subgroups within the OA population.

- In patients with knee or hip OA, several factors were found to predict deterioration of pain or physical functioning. These factors include knee, clinical, health behaviour, and psychosocial factors. Knowledge about predictors of pain and physical functioning is important for both patients and clinicians. Based on this information, clinicians can identify patients who are at risk of future deterioration of pain and physical functioning.

- In patients with knee or hip OA, specific comorbidities were found to be associated with activity limitations and pain. These coexisting disorders need to be addressed in exercise therapy and rehabilitation.

- Restrictions and contraindications for exercise in patients with OA of the knee or hip and comorbidities were identified. This overview of restrictions and contraindications is helpful in decisions on the treatment of patients and has been instrumental in the development of a protocol for comorbidity-related adaptations in exercise therapy for patients with OA.

- Comorbidity-adapted exercise protocols for patients with knee OA were developed, providing guidance in clinical reasoning with regard to diagnostics and treatment. These protocols consist of physiological, behavioural, and environmental adaptations to exercise therapy.

- Tailored exercise therapy greatly improves physical functioning and pain and is also safe for patients with knee OA and severe comorbidity. The results should encourage clinicians to consider exercise therapy as a treatment option for patients with knee OA, even in the presence of severe comorbidity.

- We created a general strategy (i3-S strategy) to develop comorbidity-related adaptations to exercise therapy in an index disease. In this strategy, adaptations to exercise therapy for the index disease are developed in four steps, leading to guidance of therapists in the diagnostic and intervention phase of exercise therapy. Researchers and clinicians can use the i3-S strategy to develop comorbidity-related adaptations of exercise therapy in an index disease.

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Summary

Osteoarthritis (OA) is the most common rheumatic disease of the musculoskeletal system, and frequently affects the knee, hip, and hand joints. OA is the sixth primary cause of moderate-to-severe disability and the eighth cause of disease burden in Europe. The development of difficulties in performing daily activities is more pronounced in middle aged and older persons with OA than their contemporaries without this disease. However, the natural course of pain and physical functioning in OA of the knee or hip is highly individual and variable. Some patients improve, while others remain stable, or even deteriorate.

Exercise therapy is a key intervention in the management of patients with knee or hip OA. It is an effective intervention to reduce joint pain and to improve physical functioning in patients with knee or hip OA. Exercise therapy consists of muscle-strength training of the lower limb and aerobic training at a moderate to high training intensity. However, comorbidity is present in 68 to 85% of patients with OA. Comorbidity interferes with exercise therapy, contributes to non-adherence, and may affect the outcome of exercise therapy. 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. 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 unlikely to be effective, because of fear of aggravating symptoms of the comorbid disease. There are no guidelines for tailoring exercise to the presence of comorbidity. There is therefore a need for protocols with comorbidity-related adaptions that facilitate the application of exercise therapy and improve the outcome of exercise therapy in patients with knee or hip OA and severe comorbidity.

Chapter 1 provides a general introduction of the research topics of this thesis. The research described in this thesis has two objectives: First, to describe i) the course of pain and physical functioning in patients with knee and hip OA and ii) to give an overview of prognostic factors of pain and physical functioning by systematically summarizing the scientific literature (**Chapter 2, 3**), and second, to develop and evaluate a tailored exercise program for patients with knee OA and comorbidity (**Chapter 4-8**).

In **Chapter 2** the literature on the course of pain and physical functioning in patients with *knee OA* is systematically summarized and an overview is presented of prognostic factors that predict deterioration in pain and physical functioning. A meta-analysis and a qualitative data synthesis were performed. Of the 58 studies included, 39 were of high quality. High heterogeneity in the course of pain and physical functioning across studies and within study populations (as indicated by large standard deviations of change scores)

was found. Strong evidence was found for a number of prognostic factors predicting deterioration in pain (e.g., higher knee pain at baseline, bilateral knee symptoms, and depressive symptoms). Strong evidence was also found for a number of prognostic factors predicting deterioration in physical functioning (e.g., worsening in radiographic OA, worsening of knee pain, lower knee extension strength, lower walking speed, and higher comorbidity count). These factors are summarized in Figure 1 (see general discussion section). For several other studied factors, weak, inconsistent, or inconclusive evidence was found. Knowledge about predictors of pain and physical functioning is important for patients and clinicians. Based on this information, clinicians can identify patients who are at risk of deterioration of pain and physical functioning. More insight into predictors of the course of pain and physical functioning is the basis for improving and targeting treatment to specific subgroups of patients with knee OA.

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 deterioration in pain and physical functioning. A meta-analysis and a qualitative data synthesis were performed. Eleven out of the 15 included studies were of high quality. Because of high heterogeneity across studies and within study populations, no conclusions could be drawn with regard to the course of pain and physical functioning. Higher comorbidity count and lower vitality were found to predict deterioration of physical functioning (strong evidence) (see Figure 1). Clinical factors (higher comorbidity count and presence of knee OA), health behaviour factors (no supervised exercise and physical inactivity), and a socio-demographic factor (lower education) were found to predict deterioration of pain (weak evidence). For several other predictive factors, weak evidence was found (e.g., bilateral hip pain, increase in hip pain, bilateral knee pain, presence of knee OA). These findings may guide future research aimed at the identification of subgroups of patients with hip OA.

In **Chapter 4** the relationship between specific comorbid diseases, activity limitations, and pain in patients with OA of the hip or knee is described. A cross-sectional cohort study among 288 older adults (50–85 years of age) with OA of hip or knee was conducted. Subjects were recruited from three rehabilitation centres and two hospitals. The results of this study showed that 18 comorbidities occurred in >5% of the sample (e.g., chronic back pain, arthritis of the hands or feet, hypertension, asthma or COPD, diabetes, severe cardiac disorders, overweight or obesity, hearing or vision impairment and chronic cystitis). In addition, the results showed that the following comorbid diseases are associated with activity limitations: chronic back pain or hernia, arthritis of the hand or feet, and other chronic rheumatic diseases (all musculoskeletal disorders); diabetes and chronic cystitis (non-musculoskeletal disorders); hearing impairments in a face-to-face conversation, vision impairments in long distances, dizziness in combination with falling (all sensory impairments); and overweight and obesity. Comorbid diseases associated with pain were arthritis of the hand or feet and other chronic rheumatic diseases (musculoskeletal disorders), and diabetes (non-musculoskeletal disorder).

In **Chapter 5** restrictions and contraindications for exercise therapy are described for common comorbidities (cardiac diseases, hypertension, type 2 diabetes, obesity, chronic obstructive pulmonary disease (COPD), depression, chronic pain, low back pain (LBP), visual or hearing impairments, and chronic cystitis) in hip and knee OA patients. These were identified by performing a narrative review of the scientific literature. Restrictions limit the application of exercise therapy, necessitating adaptations to the therapeutic protocol. If a contraindication is present, however, exercise therapy is not an option and the patient should be excluded from exercise therapy. We found that cardiac diseases, hypertension, type 2 diabetes, COPD, and chronic cystitis are associated with restrictions resulting from physiological impairments. Conversely, LBP, chronic pain syndromes, and depression were associated with psychological and behavioural restrictions to exercise therapy. Visual and hearing impairments resulted predominantly in environmental restrictions to exercise. Obesity was associated with restrictions resulting from physiological and psychological impairments and behavioural barriers. In addition, several absolute contraindications exist and patient safety cannot be guaranteed when these are not taken into account during exercise therapy. This overview is helpful in decisions on the treatment of patients and will be instrumental in the development of a protocol for comorbidity-related adaptations in exercise therapy for OA patients.

Chapter 6 describes the development of adapted exercise protocols for patients with knee OA and comorbidity. Based on literature and expert opinion, comorbidity-adapted protocols were developed for highly prevalent comorbidities in OA. Field-testing showed that the protocols provided guidance in clinical decision making in both the diagnostic and the treatment phase. Because of overlap, the number of exercise protocols could be reduced to three: one requiring physiological adaptations (coronary disease, heart failure, hypertension, diabetes type 2, chronic obstructive pulmonary diseases, obesity), one requiring behavioural adaptations (chronic aspecific pain, nonspecific low back pain, depression), and one requiring environmental adaptations (visual or hearing impairments). Evaluation of patient outcomes after treatment showed significant ($P<0.05$) and clinically relevant improvements in pain and physical functioning. It was concluded that a randomized controlled trial should be performed to evaluate the effectiveness of treatment in line with our protocols.

In **Chapter 7** the results of a randomized controlled trial about the efficacy on physical functioning and safety of tailored exercise therapy in patients with knee OA and comorbidities are described. In this study, 126 participants with a clinical diagnosis of knee OA and at least one of the following target comorbidities were included: coronary disease, heart failure, type 2 diabetes, chronic obstructive pulmonary disease, or obesity (body mass index$\geq 30 kg/m^2$), with severity score ≥ 2 of the comorbidity on the Cumulative Illness Rating Scale. The intervention group received a 20-week, individualized, comorbidity-adapted exercise program consisting of aerobic and strength training. The control group received their current medical care for knee osteoarthritis and was placed on a waiting list for exercise therapy. The primary outcome measure was

physical functioning, measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale physical functioning and 6-minute walking test (6-MWT). Measurements were performed at baseline, at 20-weeks post-treatment, and at 3-months post-treatment. The results showed that tailored exercise therapy is efficacious in improving physical functioning and safe in patients with knee OA and severe comorbidities. The intervention group performed better on physical functioning over time. These differences were statistically significant. At 3-months follow-up, the mean improvement in the intervention group was 33% on the WOMAC scale and 15% on the 6-MWT. This improvement is of clinical relevance. No serious adverse events occurred during the intervention. The results should encourage clinicians to consider exercise therapy as a treatment option for patients with knee OA, even in the presence of severe comorbidity.

In **Chapter 8** an innovative strategy for the development of comorbidity-related adaptations to exercise therapy in an index disease is presented. This strategy is derived from our previous work developing comorbidity-related adaptations to exercise therapy in OA. We now broaden this approach into a general strategy for the development of comorbidity-related adaptations to exercise therapy in an index disease. The i3-S strategy consists of four steps. The first three steps involve creating inventories of 1) comorbid diseases, 2) contraindications and restrictions on exercise therapy, and 3) potential adaptations to exercise therapy. In the fourth step, this information is synthesized into guidance on comorbidity-related adaptations to exercise therapy in the index disease. The adaptations concern physiological, behavioural, and environmental factors. We recommend using and evaluating the i3-S strategy in future research.

Finally, in **Chapter 9** the main results of this thesis are summarized and discussed and directions for further research are provided.

Samenvatting

Artrose is één van de meest voorkomende reumatische aandoeningen van het bewegingsapparaat. Vaak zijn de knie-, heup- en/of handgewrichten aangedaan. Artrose van de knie en heup levert een belangrijke bijdrage aan het ontstaan van beperkingen in dagelijkse activiteiten, zoals lopen, traplopen en opstaan uit een stoel. Het natuurlijk beloop van pijn en fysiek functioneren bij mensen met knie- of heupartrose lijkt echter te variëren. Meer inzicht in het beloop van pijn en fysiek functioneren en factoren die het beloop voorspellen bij mensen met knie of heupartrose is daarom nodig.

Oefentherapie neemt een belangrijke plaats in bij de behandeling van knieartrose. Uit eerder onderzoek blijkt dat oefentherapie het fysiek functioneren verbetert en pijn in de gewrichten vermindert. Oefentherapie bij knieartrose bestaat uit krachttraining van de bovenbeenspieren, aërobe training en het trainen van dagelijkse activiteiten. Een matige tot hoge intensiteit van de training wordt aanbevolen. Echter, de overgrote meerderheid van de artrose patiënten (60-85%) heeft comorbiditeit, zoals hartproblematiek, diabetes of obesitas. Het effect van oefentherapie bij mensen met knieartrose en (ernstige) comorbiditeit is nog niet bekend, omdat deze mensen vaak worden uitgesloten van deelname aan wetenschappelijk onderzoek. In de klinische praktijk is het vaak lastig voor therapeuten om bij mensen met comorbiditeit de juiste trainingsintensiteit te bepalen. Zowel therapeuten als patiënten zijn geneigd de trainingsintensiteit te verlagen tot een niveau waarop het onwaarschijnlijk is dat het trainen effectief is. In bestaande artroserichtlijnen wordt geen advies gegeven over hoe oefentherapie aangepast kan worden aan comorbiditeit. Daarom is er behoefte aan het ontwikkelen en evalueren van een protocol voor oefentherapie voor patiënten met knieartrose en comorbiditeit, waarbij de fysiotherapeut ondersteund wordt in het aanpassen van de oefentherapie aan de comorbiditeit.

In **Hoofdstuk 1** wordt een algemene inleiding over de onderzoeksthema's van dit proefschrift gegeven. Het in dit proefschrift beschreven onderzoek heeft twee doelstellingen. Het eerste doel is tweeledig, namelijk het verkrijgen van i) inzicht in het beloop van pijn en fysiek functioneren bij mensen met knie- of heupartrose en ii) een overzicht van prognostische factoren die een achteruitgang in het beloop van pijn en fysiek functioneren voorspellen **(Hoofdstuk 2 en 3)**. Het tweede doel is het ontwikkelen en evalueren van een oefenprogramma op maat voor patiënten met knieartrose en comorbiditeit **(Hoofdstuk 4-8)**.

In **Hoofdstuk 2** worden de wetenschappelijke literatuur over het beloop van pijn en fysiek functioneren bij patiënten met *knieartrose*, en prognostische factoren voor dit beloop systematisch samengevat. Van de 58 studies die werden geïncludeerd, waren 39 studies van hoge kwaliteit. Met betrekking tot het beloop van pijn en fysiek func-

tioneren vonden we een hoge heterogeniteit tussen studies en binnen studiepopulaties. Hierdoor was het niet mogelijk om een conclusie te trekken over het beloop van pijn en fysiek functioneren. Met betrekking tot prognostische factoren voor het beloop van pijn vonden we sterk bewijs voor een aantal factoren die verergering van pijn voorspellen, bijvoorbeeld het hebben van meer kniepijn op baseline, aanwezigheid van knieklachten beiderzijds en depressieve symptomen. Ook vonden we sterk bewijs voor een aantal factoren die een achteruitgang in fysiek functioneren voorspellen, bijvoorbeeld toename van radiografische artrose, verergering van kniepijn, lagere spierkracht van de bovenbeen spieren, lagere loopsnelheid en de aanwezigheid van een hoger aantal comorbiditeiten. Voor andere voorspellende factoren vonden we slechts zwak, inconsistent of niet doorslaggevend bewijs.

In **Hoofdstuk 3** wordt de wetenschappelijke literatuur over het beloop en prognostische factoren die een achteruitgang in het beloop van pijn en fysiek functioneren voorspellen bij patiënten met *heupartrose* systematisch samengevat. In vergelijking met het hoge aantal geïncludeerde studies bij knieartrose (58 studies) konden we bij heupartrose beduidend minder studies includeren (15 studies). Elf van de 15 geïncludeerde studies waren van hoge kwaliteit. Vanwege de hoge heterogeniteit tussen de studies en binnen de studiepopulaties, konden we ook hier geen conclusie trekken over het beloop van de pijn en fysiek functioneren. Met betrekking tot prognostische factoren voor pijn vonden we zwak bewijs dat klinische patiëntkenmerken (de aanwezigheid van een groter aantal comorbiditeiten en de aanwezigheid van knieartrose), gezondheid gerelateerde factoren (niet uitvoeren van oefeningen en lichamelijke inactiviteit) en socio-demografische gegevens (lager onderwijs) voorspellend waren voor verslechtering van pijn. Achteruitgang van fysiek functioneren werd voorspeld door de aanwezigheid van een groter aantal comorbiditeiten en lagere vitaliteit (sterk bewijs). Voor een aantal andere voorspellende factoren werd zwak bewijs gevonden, bijvoorbeeld de aanwezigheid van bilaterale heuppijn, toename van pijn in de heup, kniepijn beiderzijds en de aanwezigheid van knieartrose).

Kennis over voorspellers van pijn en fysiek functioneren bij knie en heupartrose is belangrijk, omdat artsen hiermee patiënten kunnen identificeren die een hoger risico hebben op toekomstige achteruitgang van pijn en fysiek functioneren. Daarnaast vormt meer inzicht in voorspellers in het beloop van pijn en fysiek functioneren de basis voor het verbeteren en het ontwikkelen van doelgerichte behandelingen voor specifieke subgroepen van patiënten met knie- en heupartrose.

In **Hoofdstuk 4** worden de resultaten beschreven van een studie naar de relatie tussen specifieke comorbiditeiten, beperkingen in activiteiten, en pijn bij mensen met artrose van de knie of heup. Voor deze studie voerden we een cross-sectionele cohort studie uit onder 288 ouderen (50-85 jaar) met artrose van knie of heup. De proefpersonen werden gerekruteerd uit drie revalidatiecentra en twee ziekenhuizen. Uit de resultaten bleek dat onder andere de volgende comorbiditeiten bij meer dan 5% van de studie populatie voorkwamen: chronische lage rugklachten, artritis van de handen of voeten, andere reumatische aandoening, hypertensie, astma of COPD, sinusitis, diabetes, ern-

stige hartaandoeningen, obesitas, slechtziendheid en slechthorendheid en chronische blaasontsteking. Verder tonen de resultaten aan dat beperkingen in het dagelijks fysiek functioneren geassocieerd waren met de volgende comorbiditeiten: chronische rugpijn of hernia, artritis van de handen of voeten en andere chronische reumatische aandoeningen, diabetes, chronische cystitis, gehoorproblemen, slechtziendheid, duizeligheid in combinatie met een vallen, overgewicht en obesitas. Met pijn geassocieerde comorbiditeiten waren: artritis van de handen of voeten, andere chronische reumatische aandoeningen en diabetes.

In **Hoofdstuk 5** zijn op basis van bestaande wetenschappelijke literatuur restricties en contra-indicaties voor oefentherapie beschreven voor veel voorkomende comorbiditeiten bij patiënten met knie- of heupartrose. Bij aanwezigheid van restricties voor oefentherapie is oefentherapie wel mogelijk maar dient deze te worden aangepast, bijvoorbeeld in intensiteit, duur, aard of frequentie. Als er sprake is van een contra-indicatie voor oefentherapie, is oefentherapie niet mogelijk. We vonden dat hartaandoeningen, hypertensie, type 2 diabetes, COPD en chronische cystitis met name geassocieerd waren met fysiologische restricties voor oefentherapie, zoals restricties in frequentie, intensiteit, duur en/of type oefeningen. Chronisch lage rugpijn, chronische pijn en depressie waren met name geassocieerd met psychische en gedragsmatige restricties voor oefentherapie. Slechtziendheid en slechthorendheid resulteerde vooral in omgeving gebonden restricties voor oefentherapie. Obesitas was geassocieerd met zowel fysiologische als psychische en gedragsmatige restricties voor oefentherapie. De geïdentificeerde restricties en contra-indicaties voor oefentherapie gaven handvatten voor het ontwikkelen van een protocol met aanpassingen in de diagnostiek en behandeling voor patiënten met knie- of heupartrose en comorbiditeit.

In **Hoofdstuk 6** wordt de ontwikkeling van 11 protocollen voor oefentherapie bij patiënten met knieartrose en comorbiditeit beschreven. De protocollen zijn ontwikkeld op basis van literatuur en expert opinion. Vervolgens zijn deze protocollen getest in een pilotstudie. Uit de resultaten bleek dat fysiotherapeuten de protocollen als ondersteunend ervoeren in zowel de diagnostische, behandel- en evaluatiefase. Vanwege overlap tussen de protocollen werd het aantal protocollen teruggebracht tot drie hoofdprotocollen: één voor fysiologische aanpassingen (coronaire vaatziekten, hartfalen, hypertensie, diabetes type 2, chronische obstructieve longaandoeningen (COPD) en obesitas), één voor gedragsaanpassingen (chronische aspecifieke pijn, aspecifieke lage rugpijn en depressie) en één voor omgevingsgerelateerde aanpassingen (slechtziendheid en slechthorendheid). Bij evaluatie van de protocollen op patiëntuitkomsten (n=11) vonden we een statistisch significante en klinisch relevante verbetering in fysiek functioneren en pijn. Om een uitspraak te kunnen doen over de effectiviteit van de ontwikkelde protocollen hebben we vervolgens een gerandomiseerde en gecontroleerde studie uitgevoerd.

Hoofdstuk 7 beschrijft een gerandomiseerde en gecontroleerde studie waarin onderzocht is of aangepaste oefentherapie effectief is in het verbeteren van het fysiek functioneren bij patiënten met knieartrose en comorbiditeit, in vergelijking met een controle groep. In totaal werden 126 patiënten geïncludeerd. Deze patiënten hadden de klinische

diagnose knieartrose en ten minste één van de volgende comorbiditeiten: coronaire vaatziekten, hartfalen, type 2 diabetes, chronische obstructieve longziekte of obesitas (body mass index ≥ 30 kg/m^2), met ernst score ≥2 op de Cumulatief Illness Rating Scale. Gedurende 20 weken kreeg de interventiegroep een geïndividualiseerd oefenprogramma aangepast aan de comorbiditeit. De oefentherapie bestond uit krachttraining van de onderste extremiteit en aerobe training. De controlegroep ontving de huidige medische zorg voor knieartrose en de comorbiditeit en werd op een wachtlijst geplaatst voor oefentherapie. De primaire uitkomstmaat was fysiek functioneren, gemeten met de Western Ontario en McMaster Universities Artrose Index (WOMAC) subschaal fysiek functioneren en de 6-minuten wandeltest (6-MWT). Metingen werden uitgevoerd op baseline, na 20 weken (direct na de behandeling) en 3 maanden na afronding van de behandeling. De resultaten tonen aan dat een aangepast oefenprogramma effectief is in het verbeteren van het fysiek functioneren en pijn bij patiënten met knieartrose en ernstige comorbiditeit, in vergelijking met de controle groep. De interventiegroep verbeterde 33% op de WOMAC subschaal fysiek functioneren en 15% op de 6-MWT (drie maanden na het beëindigen van het programma). Dit zijn klinisch relevante verbeteringen. Bovendien is het oefenprogramma veilig gebleken; er werden geen ernstige bijwerkingen van de interventie gerapporteerd. De resultaten van deze studie laten zien dat oefentherapie, mits aangepast aan comorbiditeit, een belangrijke behandeloptie is voor patiënten met knieartrose en ernstige comorbiditeit.

In **Hoofdstuk 8** wordt een innovatieve strategie (i3-S strategie) gepresenteerd voor het ontwikkelen van comorbiditeit-gerelateerde aanpassingen aan oefentherapie voor een index ziekte. Deze strategie is afgeleid uit de stappen die gevolgd zijn voor het ontwikkelen van aanpassingen van oefentherapie bij mensen met knieartrose en comorbiditeit (zie hoofdstuk 4-7). Deze benadering is verbreed naar een algemene strategie voor de ontwikkeling van comorbiditeit gerelateerde aanpassingen voor oefentherapie voor een index ziekte. De i3-S strategie bestaat uit vier stappen. De eerste drie stappen omvatten het inventariseren van 1) comorbide ziekten, 2) contra-indicaties en restricties voor oefentherapie en 3) mogelijke aanpassingen aan oefentherapie vanwege de comorbiditeit. In de vierde stap wordt deze informatie samengevoegd in een advies over hoe de oefentherapie aangepast kan worden aan de comorbiditeit bij een bepaalde index ziekte. Hierbij staat het klinisch redeneren centraal. De aanpassingen hebben betrekking op fysiologische, gedrags- en omgevingsfactoren. Wij raden aan om het gebruik van de i3-S strategie in toekomstig onderzoek toe te passen.

In **Hoofdstuk 9** worden de belangrijkste resultaten van de beschreven studies bediscussieerd en worden suggesties gedaan voor verder onderzoek.

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About the author

Mariëtte de Rooij was born on March 19, 1976 in Est-Opijnen, The Netherlands. She completed her secondary school at the Koningin Wilhemina College in Culemborg in 1994, and after graduating she studied physical therapy at the Hogeschool van Amsterdam from 1994 to 1998. As a registered physical therapist she worked in a primary care centre 'Verheul en Weerman fysiotherapeuten' in Nieuw Vennep from 1998 to 2005. In 2005 she started working as a physical therapist at Reade, centre for rehabilitation and rheumatology (formerly Jan van Breemen Institute). Here she became interested in research. In 2006 she successfully completed a manual therapy specialization at the Stichting Opleiding Manuele Therapie (SOMT) in Amersfoort. In 2009, she started her PhD project under supervision of prof.dr. J. Dekker, in collaboration with the department of Rehabilitation Medicine at the VU University Medical Centre. During this period she successfully completed the Postgraduate Epidemiology Program at the EMGO-institute for Health and Care Research at the VU University Medical Centre. Since 2009 she combines her work as a researcher with her clinical work as a physical/manual therapist at Reade. Her future aim is to apply her knowledge and competencies to the interface between research and clinical practice. Her fields of interest are clinical epidemiology, musculoskeletal disorders, comorbidity, exercise therapy, physical therapy and rehabilitation.

List of publications

International journals

de Rooij M, van der Leeden M, van der Esch M, Cheung J, Häkkinen A, Haverkamp D, Roorda LD, Twisk J, Vollebregt J, Lems WF, Dekker J. Efficacy of tailored exercise therapy in patients with knee osteoarthritis and comorbidity: a randomized controlled trial. *Accepted for publication in Arthritis Care & Research (Hoboken), 2016*.

de Rooij M, van der Leeden M, Heymans MW, Holla JFM, Häkkinen A, Lems WF, Roorda LD, Veenhof C, Sanchez-Ramirez DC, de Vet HCW, Dekker J. Prognosis of pain and physical functioning in patients with knee osteoarthritis: systematic review and meta-analysis. *Arthritis Care & Research (Hoboken) 2016; 68:481-92*.

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Dekker J, **de Rooij M**, van der Leeden M. The i3-S strategy for developing comorbidity-related adaptations to exercise therapy. *Disability and Rehabilitation 2016; 38:905-9*.

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de Rooij M, van der Leeden M, Avezaat E, Häkkinen A, Klaver A, Maas T, Peter WF, Roorda LD, Lems WF, Dekker J. Development of comorbidity-adapted exercise protocols for patients with knee osteoarthritis. *Clinical Intervention in Aging 2014; 9:829-842*.

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Knoop J, van der Leeden M, Roorda LD, Thorstensson CA, van der Esch M, Peter WF, **de Rooij M**, Lems WF, Dekker J, Steultjens MPM. Knee joint stabilization therapy in patients

with osteoarthritis and knee and knee instability: subgroup-analyses in a randomized, controlled trial. *Journal of Rehabililatation Medicine 2014; 46:703-707.*

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de Rooij M, van der Leeden M, Lems WF, Roorda LD, Dekker J. Response to commentary on: 'Restrictions and contraindications for exercise therapy in patients with hip and knee osteoarthritis and comobrbidity: Exercise therapy in patients with osteoarthritis of the hip or knee: focus on comorbidity. *Physical Therapy Reviews 2013; 18:232-233.*

Beekman E, Mesters I, **de Rooij M**, de Vries N, Werkman M, Hulzebos E, van der Leeden M, Staal BJ, Dekker J, Nijhuis-van der Sanden R, de Bie RA. Therapeutic Consequences for Physical Therapy of Comorbidity highly prevalent in COPD: A Multi-case Study. *Journal of Allergy & Therapy 2013;(82):1-6.*

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Peter WF, Jansen MJ, Hurkmans EJ, Bloo H, Dekker J, Dilling RG, Hilberdink W, Kersten-Smit C, **de Rooij M,** Veenhof C, Vermeulen HM, de Vos RJ, Schoones JW, Vliet Vlieland TP; Guideline Steering Committee - Hip and Knee Osteoarthritis, "Physiotherapy in hip and knee osteoarthritis: development of a practice guideline concerning initial assessment, treatment and evaluation". *Acta Reumatol Port. 2011; 36:268-81.*

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de Rooij M, Steultjens MPM, van der Leeden M, Maas T, Roorda LD, Dekker J. Oefentherapie en comorbiditeit bij patiënten met heup- en/of knieartrose: ontwikkeling en evaluatie van een behandelprotocol. *Nederlands Tijdschrift van Fysiotherapie. 2010; 120:16-24.*

de Rooij M, van der Leeden M, Lems WF, Roorda LD, Dekker J. Het ontwikkelen en evalueren van behandelprotocollen bij patiënten met heup en/of knieartrose en comorbiditeit: COOA onderzoek. *Fysiopraxis 2013; (41) 43-46.*

van der Leeden M, de Rooij M, Dekker J. WOMAC – Het meten van ervaren pijn, stijfheid en beperkingen in activiteiten bij artrose van de knie en heup. *Fysiopraxis 2013; (12): 28-30.*

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Dekker J, Bossen D, Holla JFM, **de Rooij M**, Veenhof C**,** van der Leeden M. Chapter 25: *Psychological strategies in osteoarthritis of the knee or hip. Third edition. Oxford Textbook of Osteoarthritis and Crystal Arthropathy (accepted for publication 2016).*

de Rooij M, Lems WF, Marike van der Leeden, Dekker J. Chapter 10: Comorbidity, Obesity, and Exercise Therapy in Patients with Knee and Hip Osteoarthritis. Dekker J ed. In: *Exercise and physical functioning in osteoarthritis: medical, neuromuscular and behavioural perspectives. Springer; 2013.*

PhD Portfolio

Name PhD student: Mariëtte de Rooij
PhD period: Januari 2009 – September 2016

PhD Training	**Year**	**Workload (ECTS)**
Courses	2011	0.60
Good Clinical Practice, in company course, Reade	2011	1
Scientific writing in English, VU University, Amsterdam	2009	0.70
Scientific writing in English, in company course, Reade	2007	14.28
Methodology and statistics, Lectoraat HvA, in company course, Reade	2007-2013	60.00
Post-initial master Epidemiology		
- Epidemiology of diseases, Epidm		
- Systematic reviews: theory and practice, Epidm		
- Principles of epidemiological data analysis, Epidm		
- Linear regression analysis and analysis of variance, Epidm		
- Logistic regression analysis and analysis of survival data, Epidm		
- Epidemiological research: design and interpretation, Epidm		
Total European credit transfer system (ECTS)	**Equivalent**	**77 ECTS**
Congresses		
International	2016	3 days
OARSI[1], Amsterdam (the Netherlands). Poster presentation	2016	4 days
EULAR[2], London (United-Kingdom). Oral presentation	2015	4 days
EULAR[2], Rome (Italy). Poster presentation	2014	4 days
OARSI[1], Paris (France). Poster presentation (2x)	2014	4 days
EULAR[2], Paris (France). Participant	2013	4 days
EULAR[2], Madrid (Spain). Participant	2012	4 days
EULAR[2], Berlin (Germany). Workshop	2011	1 day
WCPT[3], Amsterdam. Participant	2010	3 days
EULAR[2], Copenhagen (Denmark). Participant	2008	4 days
EULAR[2], Paris. Poster presentation		
National	2016	4 hours
Masterclass Reade, Amsterdam. Oral presentation	2016	3 hours
Rehabilitation physician meeting, Amsterdam. Oral presentation	2016	2 hours
Orthopedic surgeons, Slotervaart Hospital, Amsterdam. Oral presentation	2015	1 day
KNGF[5] fysiocongres, Utrecht. Oral presentation	2015	1 day
NVR[4], Arnhem, Oral presentation	2015	1 day
Wetenschapsdag fysiotherapie WCF[6], Utrecht. Oral presentation		

Table (cont'd)

NVR[4], Arnhem. Poster presentation	2014	1 day
Rehabilitation physician meeting, Amsterdam. Oral presentation	2014	3 hours
General practioners meeting, Oral presentation	2013	1 day
KNGF[5] fysiocongres, Utrecht. Oral presentation	2013	1 day
Wetenschapsdag fysiotherapie WCF[6], Soesterberg. Oral presentation	2013	1 day
KNGF[5] fysiocongres, Maastricht. Oral presentation	2012	2 days
Reumanet, Amsterdam, Oral presentation	2012	3 hours
Onderzoek in beweging, Maastricht. Poster presentation	2012	1 day
Wetenschapsdag fysiotherapie WCF[6], Soesterberg. Oral presentation	2012	1 day
NVR[4], Arnhem. Oral prestation (2x)	2011	1 day
SWORA[7], Utrecht. Oral presentation	2011	3 hours
KNGF[5] fysiocongres, Amsterdam. Oral presentation (2x)	2010	1 day
NVR[4], Velthoven. Poster presentation	2007	1 day
Total European credit transfer system (ECTS)	**equivalent**	**14.6 ECTS**
Teaching activities		
Tutor for rehabilitation physician students, Reade, Amsterdam	2016	4 hours
Tutor for physical therapists, Bunnik	2016	1 day
Tutor for general practitioners, Reade, Amsterdam	2013	4 hours
Total European credit transfer system (ECTS)	**equivalent**	**1 ECTS**
	total	**93**

[1] Osteoarthritis Research Society International, [2] Annual congress European League Against Rheumatism, [3] World Congress Physical Therapy, [4] Jaarcongres Nederlandse Vereniging voor Reumatologie, [5] Jaarcongres Koninklijk Nederlands Genootschap voor Fysiotherapie, [6] Wetenschappelijk College Fysiotherapie, [7] Sociaal Wetenschappelijk Onderzoek bij Reumatische Aandoeningen.

Mariëtte de Rooij (1976) works as a physical therapist and researcher at Reade, centre for Rehabilitation & Rheumatology. Her future aim is to apply her knowledge and competencies to the interface between research and clinical practice. Her fields of interest are clinical epidemiology, musculoskeletal disorders, comorbidity, exercise therapy, physical therapy and rehabilitation.

This dissertation describes the development and evaluation of a tailored exercise program for patients with knee osteoarthritis and comorbidity. Exercise therapy is a key intervention in the management of patients with knee osteoarthritis. It is an effective intervention to reduce joint pain and to improve physical functioning. However, 68 to 85% of patients with knee osteoarthritis have one or more comorbid diseases. The presence of comorbidity interferes with exercise therapy, contributes to non-adherence, and may affect the outcome of exercise therapy. There are no guidelines for tailoring exercise to the presence of comorbidity. Therefore, comorbidity-adapted exercise protocols for patients with knee OA were developed and evaluated in a randomized controlled trial. The results showed that tailored exercise therapy greatly improved physical functioning, reduced pain and was also safe for patients with knee OA and severe comorbidity. These results should encourage clinicians to consider exercise therapy as a treatment option for patients with knee OA, even in the presence of severe comorbidity.