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. 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. 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\textsuperscript{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\textsuperscript{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\textsuperscript{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)\textsuperscript{21}, the Outcome Measures in Rheumatology (OMERACT)\textsuperscript{22}, or the OARSI clinical trial recommendations\textsuperscript{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)\textsuperscript{25}, the Multicenter Osteoarthritis Study (MOST cohort)\textsuperscript{26}, and the Cohort Hip & Cohort Knee (CHECK cohort)\textsuperscript{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\%)\textsuperscript{28} within the older worldwide population, compared with the prevalence of patients with hip OA (5 to 15\%)\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 $\sim 36 \text{ kg/m}^2$ 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.\textsuperscript{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\textsuperscript{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\textsuperscript{38,39} and meta-analyses\textsuperscript{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 HbA1c 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.

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. 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. 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. 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 adaptations 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.
# References


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