CHECKing activity limitations in persons with early osteoarthritis of the knee or hip

Course, prognosis and underlying mechanisms

Summary

Osteoarthritis (OA) is the most common chronic joint disease in the world, mainly affecting middle-aged and older persons. The disease progresses slowly over time, and activity limitations (i.e. difficulties an individual may have in executing activities such as walking and stair climbing) are considered one of its most important outcomes. Activity limitations are mainly studied in persons with established OA. In persons with early symptomatic OA, less is known about the course, prognosis and mechanisms explaining the development of activity limitations. As a result, many persons with knee or hip OA are insufficiently informed about their likely course of activity limitations, and are not adequately referred for treatment. The general aim of this thesis was to examine, predict and explain the course of activity limitations in patients with early symptomatic OA of the knee or hip.

Chapter 1 provided a general introduction on the research topics of this thesis. We described what is known about the course and prognosis of activity limitations in established OA, and introduced an integrated behavioural (i.e. the avoidance model) and neuromuscular model which is used to explain the development of activity limitations. In addition, we described the Cohort Hip and Cohort Knee (CHECK) study, a prospective multicentre cohort study on early symptomatic knee and hip OA, of which the research described in this thesis was part of. At the end of this chapter, we presented the aim and outline of this thesis.

Part 1 of this thesis was dedicated to describing the course and prognosis of activity limitations. This included the identification of homogeneous subgroups with distinct trajectories of activity limitations.

In **chapter 2** we aimed to predict the 2-year course of activity limitations in persons with early symptomatic OA of the knee or hip. To this aim, we used data of all 1,002 participants of the CHECK study. Activity limitations were measured with a self-report questionnaire. After two years of follow-up, a small overall decrease in activity limitations (i.e. improvement) was observed in both persons with knee symptoms and persons with hip symptoms. The inter-individual variation in change in activity limitations was large. Regression models were used to examine whether baseline variables predicted the 2-year course of activity limitations. In participants with knee symptoms, young age, non-Western ethnicity, bilateral hip pain, morning stiffness in the knee, high comorbidity count, high body-mass index (BMI), high bodily pain, poor general health perception, and pain coping strategy were found to predict a poor 2-year outcome of activity limitations. In participants with hip symptoms, few activity limitations at baseline, bilateral hip pain, morning stiffness in the knee, high comorbidity count, low active hip flexion, poor general health perception, and pain coping strategy were found to predict a poor 2-year outcome of activity limitations. We concluded that the 2-year course of activity limitations is highly variable between persons, and is to some extent already predictable at an early stage of knee and hip OA.

The knee OA population is heterogeneous, and is likely to consist of different phenotypes or subgroups. Therefore, in **chapter 3** we examined the existence of homogeneous subgroups with distinct trajectories of activity limitations in 697 CHECK participants with

early symptomatic knee OA. Activity limitations were measured yearly with a self-report questionnaire, resulting in 6 measurements over a period of 5 years. These 6 measurements were analysed using latent class growth analyses (LCGA). Three subgroups were identified: a 'good outcome' subgroup (n = 330) that developed or displayed slight activity limitations over time; a 'moderate outcome' subgroup (n = 257) that developed or displayed moderate activity limitations over time; and a 'poor outcome' subgroup (n = 110) that developed or displayed severe activity limitations over time. Multivariable regression analyses revealed that compared with the 'good outcome' subgroup, the 'moderate outcome' and 'poor outcome' subgroups were characterised by: younger age, higher BMI, greater pain, bony tenderness, reduced knee flexion, hip pain, osteophytosis, ≥ 3 comorbidities, lower vitality and avoidance of activities. These characteristics were consistent with existing knowledge on prognostic factors regarding activity limitations in persons with knee OA, which supported the validity of the identified subgroup classification.

Part 2 of this thesis was dedicated to the validation of a theoretical model that was developed to explain the development of activity limitations in persons with OA of the knee or hip.

In **chapter 4** we presented a cross-sectional study on the validity of the behavioural part of this model: the avoidance model. The avoidance model hypothesizes that pain-related avoidance of activities leads to muscle weakness and thereby activity limitations. Psychological distress (e.g., low vitality, depressed mood) is thought to strengthen the tendency to avoid activities. Two-year follow-up data of 151 CHECK participants with early symptomatic knee OA were analysed using structural equation modeling. Activity limitations were measured using both a self-report and performance-based measure. Pain and psychological distress were found to be associated with muscle weakness via avoidance of activities (mediation by avoidance). Avoidance of activities was found to be associated with activity limitations via muscle weakness (mediation by muscle weakness). In addition to these indirect associations, direct associations between pain, psychological distress, avoidance of activities, and muscle weakness or activity limitations were found. These results support the validity of the avoidance model in persons with early symptomatic knee OA. The direct associations indicate that in addition to avoidance of activities there are other mechanisms by which pain and psychological distress lead to activity limitations.

In **chapter 5** we presented a study in which we examined the cross-sectional and longitudinal associations between knee pain, low vitality, avoidance of activities and activity limitations. We used baseline, 2-year and 5-year follow-up data of 828 CHECK participants with early symptomatic knee OA. Knee pain, vitality, avoidance of activities and activity limitations were measured using self-report questionnaires. Autoregressive generalized estimating equations (GEE) and regression models were used to analyse the data. In longitudinal analyses, pain and vitality predicted a subsequent increase in avoidance of activities. In cross-sectional analyses, knee pain and lower vitality were found to be associated with higher levels of avoidance of activities at all time-points. In cross-sectional analyses, a higher level of avoidance of activities was found to be associated with greater activity limitations. In longitudinal analyses, this relationship was marginally significant. We concluded that already at an early stage of knee OA, knee pain and low vitality seem to lead to a subsequent increase in avoidance of activities. To establish the longitudinal relationship between avoidance of activities and activity limitations, alternative measurement

instruments (e.g. accelerometers and momentary assessments of pain, vitality and activity limitations) and a longer follow-up may be required.

In **chapter 6** we presented a systematic review of the scientific evidence for the validity of the avoidance model in persons with knee or hip OA. We conducted a literature search, assessed the methodological quality of the selected articles, and identified levels of evidence using a qualitative data synthesis. Sixty studies were included. In persons with knee OA, strong evidence was found that avoidance of activities is associated with activity limitations via muscle weakness (mediation by muscle weakness), and weak evidence was found that pain and psychological distress are associated with muscle weakness via avoidance of activities (mediation by avoidance). In hip OA, weak evidence was found for mediation by muscle weakness; and strong evidence was found for an association between muscle weakness and activity limitations. We concluded that for further validation of the avoidance model, more research is needed on the consecutive associations between pain or psychological distress, avoidance of activities and muscle weakness. In addition, more research is needed to confirm causal relationships.

The neuromuscular part of our theoretical model hypothesizes that the strength of the association between muscle weakness and activity limitations depends on the stability of the knee. In addition to muscle strength, proprioception (i.e. the conscious and/or unconscious perception of position and movement of an extremity or a joint in space) and varus-valgus laxity (i.e. the displacement or rotation of the tibia with respect to the femur in the varus-valgus direction) are thought to influence the stability of the knee. In **chapter 7** we assessed whether proprioception and varus-valgus laxity moderated (i.e. influenced the strength of) the association between muscle weakness and self-reported and performance-based activity limitations. We performed a cross-sectional study using two-year follow-up data of 151 CHECK participants with early symptomatic knee OA (the same sample as presented in chapter 4). The association between muscle weakness and activity limitations was found to be stronger in participants with poor proprioception than in participants with accurate proprioception (moderation by proprioception). Laxity was not found to moderate the association between muscle weakness and activity limitations. These results support the theory that in the absence of adequate proprioceptive input, muscle weakness affects a person's level of activity limitations to a greater degree than in the presence of adequate proprioceptive input. The hypothesis that the association between muscle weakness and activity limitations is stronger in OA patients with higher varus-valgus laxity was not confirmed in persons with early symptomatic knee OA.

In **chapter 8** we examined the same associations as in chapter 7 using a longitudinal design. We used 2-year and 5-year follow-up data of the same sample of 151 CHECK participants with knee symptoms. Although 3-year changes in muscle weakness and activity limitations were found to be very small, an increase in muscle weakness was found to be associated with an increase in performance-based activity limitations. Proprioception and varus-valgus laxity were not found to moderate the longitudinal association between muscle weakness and activity limitations. These results are a step forward in understanding the role of muscle weakness in the development of activity limitations. To establish causality, further well-designed experimental studies are indicated.

In addition to the behavioural and neuromuscular mechanisms described in our theoretical model there are other mechanisms leading to activity limitations in persons with knee and

hip OA. Reduced ROM of the joint is such a mechanism, and was studied in **part 3** of this thesis.

In **chapter 9** we explored the cross-sectional association between demographic, clinical, and articular factors and ROM in 598 CHECK participants with early symptomatic knee and/or hip OA. Active flexion of the knee, and internal rotation, external rotation, flexion, adduction, and abduction of the hip were assessed at baseline using a goniometer. Regression analyses showed that in participants with early symptomatic knee OA, higher BMI, pain, bony enlargement, crepitus, and osteophytosis were associated with lower knee flexion. In participants with early symptomatic hip OA, joint space narrowing (JSN) was found to be associated with lower ROM in all planes of motion. Male gender, higher BMI, pain, morning stiffness, osteophytosis, flattening of the femoral head, and femoral buttressing were found to be associated with lower hip ROM in two planes of motion. We concluded that male gender, higher BMI, pain, stiffness and features of articular degeneration are associated with lower knee and hip ROM in persons with early symptomatic knee or hip OA.

In **chapter 10** we examined the diagnostic accuracy of knee flexion, hip internal rotation, and hip flexion measurements for the presence of osteophytosis and JSN. We used the same data as in the study presented in chapter 9. In persons with early symptomatic hip OA, hip internal rotation < 24 C° was found to be the cut-off with the highest discriminative ability to distinguish between persons with and without radiographic features of OA. The current American College of Rheumatology (ACR) criterion of hip internal rotation < 15 C° increased the probability of the presence of osteophytosis or JSN from 25% to 58%. However, at this cut-off many participants with radiographic features were not identified (the percentage of false negatives was 21%). To reduce the number of OA patients that are not identified by the ACR criterion of hip internal rotation < 15 C°, we recommended to change this cut-off to internal rotation < 24 C° in persons with early symptomatic OA. For this cut-off the percentage of false negatives was 11%. The diagnostic accuracy of knee flexion and hip flexion measurements was found to be low. Additional research is needed to study the diagnostic accuracy of combinations of clinical tests or criteria for the presence of radiographic features in persons with early symptomatic knee or hip OA.

In **chapter 11** we discussed the main results of the studies presented in this thesis. We provided an overview of the obtained knowledge regarding the course and prognosis of activity limitations in persons with early symptomatic knee and hip OA, and discussed the evidence for the validity of our theoretical model. In addition, we provided suggestions for further research and implications for clinical practice.