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

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Chapter II

General discussion



The aim of this thesis was to examine, predict and explain the course of activity limitations in persons with early symptomatic OA of the knee or hip. To this aim, data from the Dutch CHECK study were used. Nine studies were performed which were described in the previous chapters. In this final chapter, we will discuss the main results of these studies and will provide suggestions for further research.

First, we will discuss the results of the studies on the course and prognosis of activity limitations. Second, we will discuss the studies on the validity of our theoretical model, which describes how behavioural and neuromuscular mechanisms lead to the development of activity limitations in persons with early symptomatic knee OA (**Figure 1**). Third, we will discuss the results of the studies on determinants and the diagnostic value of ROM measurements. Finally, we will end this discussion by providing implications for clinical practice.

Course, subgroups with distinct trajectories and prognostic factors of activity limitations

Course of activity limitations

In **chapters 2 and 3** the course of activity limitations was studied. We showed that, on average, in persons with early symptomatic knee or hip OA activity limitations develop very slow. After two years of follow-up, a small overall decrease in activity limitations was observed in both persons with knee symptoms and persons with hip symptoms.¹ In the CHECK study, participants were included based on knee or hip symptoms. Therefore, it is likely that there was a relatively high prevalence of symptoms at the time of inclusion. Because symptoms of OA are known to fluctuate,² it is possible that after 2 years some of these symptoms had improved resulting in a decrease in activity limitations.¹ After a longer follow-up of five years, we observed a small overall increase in activity limitations in both persons with knee symptoms³ and persons with hip symptoms (unpublished observations). This indicates that the average course of activity limitations slowly progresses over time.

Subgroups with distinct trajectories of activity limitations

Studying the average course of activity limitations is important, because it provides an impression of the overall impact of OA. However, because the knee and hip OA populations are heterogeneous and consist of different phenotypes or subgroups,⁴⁻⁶ from a theoretical perspective it seems suboptimal to describe the course of activity limitations using the average of the population.^{2,3} This conception is supported by the finding that both in early and in established OA the individual course of activity limitations is highly variable: some persons improve, others remain stable, and still others deteriorate.^{1,7} Therefore, in **chapter 3**, we examined the existence of homogeneous subgroups of persons with early symptomatic knee OA with distinct five-year trajectories of activity limitations.³ Three subgroups were identified: a 'good outcome' subgroup that developed or displayed slight activity limitations over time; a 'moderate outcome' subgroup that developed or displayed moderate activity limitations over time; and a 'poor outcome' subgroup that developed or displayed severe activity limitations over time.³ This subgroup classification resembles the classification in-

troduced by Sharma et al.⁸ in 2003, in that both the change over time and the level of activity limitations at baseline defined subgroups of persons with distinct trajectories of activity limitations. Our classification was derived from statistical analyses, whereas the classification of Sharma et al. was based on clinical reasoning. Sharma et al. justified their classification by arguing that in OA change may require a long time, and that therefore factors related to persistent high and low levels of activity limitations are of particular importance for the development of preventive and conservative interventions.⁸

The ‘poor outcome’ subgroup showed greater activity limitations at baseline and a greater worsening of activity limitations than the two other subgroups.³ This can be explained by a ‘horse-racing effect’, which is an analogy for the expected correlation between observed values and rates of change.⁹ Just as in a race between horses in which the faster horses are expected to be in front already halfway the race, persons whose activity limitations have been increasing faster than average previously are expected to have greater than average activity limitations at baseline and to continue to increase in activity limitations faster than average in the future.^{3,9} Apparently, very early in the disease a process has started that makes that some persons have a poor trajectory of activity limitations and others have not. When and how this process is started is not known, however, it is likely that pathophysiological, mechanical and psychological factors have a role in this process.¹⁰ Several mechanisms by which pain, low vitality and avoidance of activities may lead to activity limitations have been examined in chapters 4, 5, and 6 of this thesis and will be discussed further in this general discussion.

We were the first to use latent class growth analysis (LCGA) to examine the existence of subgroups with distinct trajectories of activity limitations in persons with early symptomatic knee OA. To extend generalizability, our findings need to be externally validated in other samples. For this, prognostic studies with frequent measurements over a long follow-up period are needed. Similar to our study, participants should be included at onset of symptoms, or even earlier using population-based cohorts, to increase precision of the estimated trajectory subgroups.^{3,11} The Multicenter Osteoarthritis Study (MOST), the Osteoarthritis Initiative (OAI), and the Clinical Assessment Study Knee (CAS[K]) fulfil these conditions, and therefore seem suitable for external validation. Furthermore, instead of LCGA, growth mixture modelling could be used to identify trajectory subgroups. Growth mixture modelling is an extension of LCGA which, in addition to estimating mean trajectories for each subgroup, allows individual variation around these mean trajectories. Although LCGA has a slightly simpler interpretation by assuming that within each subgroups all individuals share the same trajectory, growth mixture modelling comes closer to reality by allowing inter-individual variation in trajectories within subgroups.¹²

Prognostic factors for activity limitations

In persons with early symptomatic knee OA, consistent evidence was found that younger age at onset of symptoms,^{1,3} higher BMI,^{1,3} ≥ 3 comorbidities,^{1,3} knee pain,^{3,13} hip pain,^{1,3} muscle weakness,¹⁴ reduced knee flexion range,^{1,3} bony tenderness,^{1,3} osteophytosis,^{3,13} low vitality,^{3,13} and avoidance of physical activities^{3,13} predict a poor outcome of activity limitations. In persons with early symptomatic hip OA, we found convincing evidence that bilateral hip pain, concomitant knee symptoms, ≥ 3 comorbidities, reduced hip flexion range, and poor general health perception predict a poor two-year outcome of activity limitations.¹



These prognostic factors are almost similar to prognostic factors identified in studies in established OA (Table 1).⁷⁻¹⁰ There are several mechanisms by which persons with knee or hip OA develop activity limitations; apparently these mechanisms are initiated early in the disease process and still play a role in established OA. As a result, nearly the same prognostic factors for activity limitations are identified in persons with early symptomatic OA as in persons with established OA.

Contrary to previous studies that found that older age predicted a poor outcome of activity limitations,^{8,15} we found that younger age predicted a poor outcome of activity limitations.^{1,3} This might be explained by the relatively young age of the CHECK population.

Table 1. Prognostic factors for a poor outcome of activity limitations in persons with osteoarthritis of the knee and hip

Prognostic factor	Evidence in knee osteoarthritis		Evidence in hip osteoarthritis	
	Established	Early symptomatic	Established	Early symptomatic
Impairments in body structures				
Bony tenderness ^{1,3}		+		
Radiographic features ^{3,10,13,84-86}	inconsistent	+		
Impairments in body functions				
Symptoms in multiple joints ^{1,3,87,88}	+	+		+
Knee pain ^{3,13,15,85,89,90}	+	+		
Hip pain ^{1,90}		+	+	+
Morning stiffness knee ^{1,88}	+			
Muscle weakness ^{14,30,85,88,90,91}	+	+	+	
Poor proprioception ^{51,92}	+			
Varus-valgus laxity ⁹²	+			
Reduced range of joint motion ^{1,3,90,93}	+	+	+	+
Activity limitations				
Greater activity limitations ^{1,3,93}	+	+		
Lower walking speed ^{84,93}	+			
Environmental factors				
Little social support ⁹²	+			
Personal factors				
Older age ^{10,15,85,89,90}	+			
Younger age ^{1,3}		+		
Low to middle education level ^{84,86,90,93}	+			
Non-Western ethnicity ^{84,86,89}	+			
Higher BMI ^{1,3,10,15,85,88,89}	+	+		
Comorbidity ^{1,3,10,15,84-86,90}	+	+	+	+
Avoidance of activities ^{3,13,89,90,94}	+	+		
Psychological distress ^{10,15,94,95}	+			
Fatigue / low vitality ^{3,13,96,96}	+	+		
Low self-efficacy ⁹²	+			
Poor general health perception ^{1,10,15,93}	+		+	+

Symptoms of OA at a relatively young age might be indicative of a more progressive disease course, with an associated poor outcome of activity limitations.¹

In our study on the two-year course of activity limitations,¹ radiographic severity of knee OA was not found to predict a poor outcome of activity limitations, whereas in our study on the five-year course of activity limitations radiographic severity (i.e. osteophytosis) was found to be associated with a poor outcome of activity limitations.³ These conflicting findings can be explained by differences in measurements used for radiographic severity. In both studies, radiographic features were scored on posterioranterior, mediolateral and skyline radiographs according to Altman and Gold¹⁶ and Burnett et al.¹⁷ However, in the first study a summary score for radiographic severity, i.e. the Kellgren and Lawrence grade,¹⁸ was analysed, whereas in the second study more detailed measures of radiographic severity were analysed, i.e. joint space narrowing and osteophytosis. These findings emphasize the significance of the use of detailed measures, and confirm that if radiographic severity is scored and analysed in detail an association with symptoms can be found.¹⁹

So far, none of the developed prediction models can sufficiently discriminate between persons with a poor outcome and persons with a good outcome of activity limitations.¹ Therefore, prognostic factors for the course of activity limitations should be further studied, both in persons with knee OA and in persons with hip OA. In these prospective studies special attention should be paid to detailed, reliable and validated measures of prognostic factors that are routinely measured or easily implemented by physicians at an early stage of knee and hip OA.¹ Not only the prognostic value of factors assessed at baseline, but also the influence of variation in prognostic factors on activity limitations should be examined. Therefore, in addition to activity limitations, potential prognostic factors should be frequently measured over a long follow-up.

Explanation of activity limitations: evidence for our theoretical model (Figure 1)

The avoidance model

Based upon previous research on avoidance of pain-related activities in chronic pain,²⁰⁻²³ Dekker et al.²⁴ developed the avoidance model in knee and hip OA: a theoretical model explaining the associations between pain, psychological distress, avoidance of activities, muscle weakness and activity limitations (behavioural model in **Figure 1**).^{10,25,26} In **chapters 4, 5 and 6** we examined the validity of this avoidance model. First, we performed a cross-sectional study in which we examined all associations hypothesized by the model in persons with early symptomatic knee OA (**chapter 4**). We found: (1) that pain and psychological distress were partially associated with muscle weakness via avoidance of activities (mediation by avoidance); and (2) that avoidance of activities was partially associated with activity limitations via muscle weakness (mediation by muscle weakness).²⁷ The hypothesized underlying mechanism is that initial pain during physical activities leads to the expectation²⁸ that renewed activity results in more pain and consequently to avoidance of activities. Avoidance of activities results in physical deconditioning, most notably muscle weakness. Muscle weakness leads to an increase in activity limitations.^{10,25-27} In addition,



psychological distress (e.g. depressed mood, anxiety and low vitality) is hypothesized to strengthen the tendency to avoid activities and thereby to induce activity limitations.^{10,25,27} In agreement with other studies, we found that pain, psychological distress and avoidance of activities were also directly associated with activity limitations.²⁷ This indicates that besides the pathways described in the avoidance model, there are alternative pathways between pain, psychological distress, avoidance of activities and activity limitations. Pain, may for example lead to muscle weakness via poor voluntary effort,²⁹ and avoidance of activities may lead to activity limitations via low self-efficacy beliefs.²⁶ Our results support the validity of the avoidance model in persons with early symptomatic knee OA; however these results also indicate that avoidance of activities is not the only mechanism explaining activity limitations in persons with knee OA: it is one mechanism among other mechanisms.²⁷

In **chapter 5** we examined the average course of avoidance of activities, and cross-sectional and longitudinal associations between pain, vitality, avoidance of activities and activity limitations in persons with early symptomatic knee OA.¹³ On average, over a period of 5 years, avoidance of activities was found to be rather stable. This indicates that once

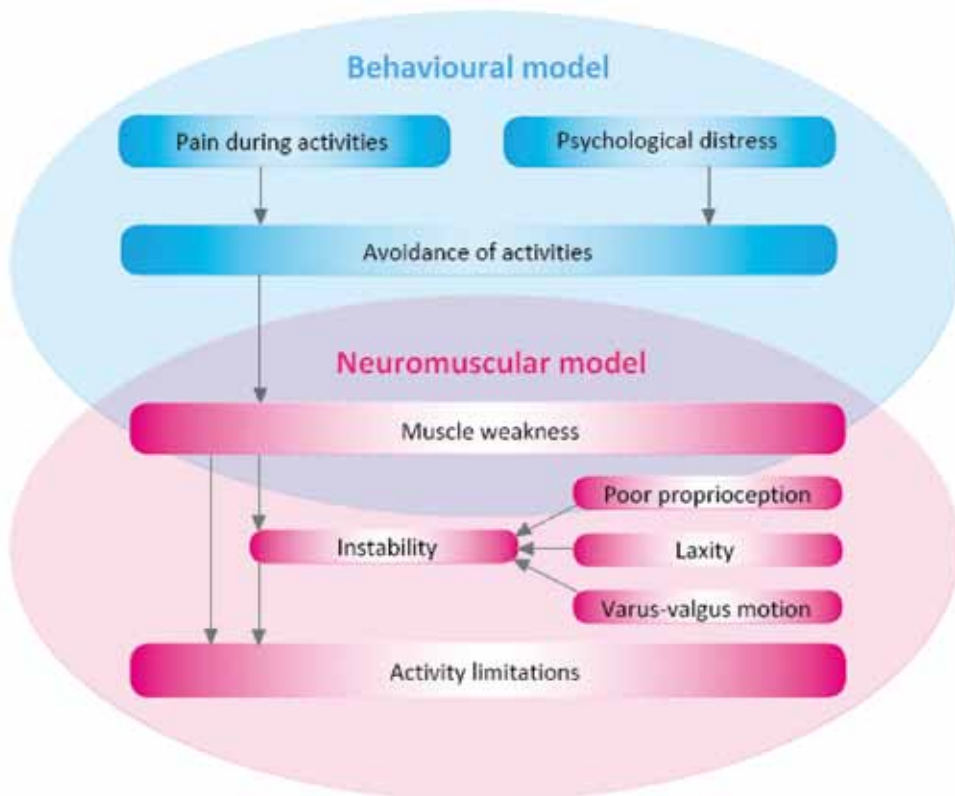


Figure 1. Integrated behavioural and neuromuscular model that is developed to explain the development of activity limitations in osteoarthritis of the knee and hip.¹⁰

one has adopted avoidance behaviour, there is a substantial chance that this behaviour persists. Knee pain and low vitality were found to be cross-sectionally associated with avoidance of activities. In addition, in longitudinal analysis, greater knee pain and lower vitality were found to predict a subsequent increase in avoidance of activities. Avoidance of activities was found to be cross-sectionally associated with activity limitations. In longitudinal analysis this relationship was marginally significant. Together, these results support the hypothesis that, already at an early stage of knee OA, knee pain and low vitality lead to an increase in avoidance of activities. The longitudinal relationship between avoidance of activities and activity limitations seems to exist, but should be further examined.

In **chapter 6**, we presented a systematic review in which we summarized the scientific evidence for the validity of the avoidance model.³⁰ In persons with knee OA, we found strong evidence that muscle weakness is associated with activity limitations, and that muscle weakness mediates the association between avoidance of activities and activity limitations. Muscle weakness may lead to activity limitations in two ways: directly, because muscle strength is needed for all activities of daily living;³¹ and indirectly via instability of the knee.^{10,32,33} A substantial part (9.1 to 18.1%) of the association between avoidance of activities and activity limitations was found to be mediated by muscle weakness.³⁰ One study, our own study presented in chapter 6,²⁷ provided weak evidence that avoidance of activities mediates the association between pain or psychological distress and muscle weakness or activity limitations. A substantial part ($\geq 15.3\%$) of the association between pain or psychological distress and muscle weakness was found to be mediated by avoidance of activities. In persons with hip OA, we found strong evidence that muscle weakness is associated with activity limitations. Because the stability of the hip joint is particularly provided by its shape, ligaments and joint capsule, in persons with hip OA, muscle weakness is believed to be a manifestation of general physical deconditioning, and is therefore directly associated with activity limitations.³⁰ In addition, we found weak evidence that muscle weakness mediates the association between avoidance of activities and activity limitations,³⁴ and that psychological distress is associated with avoidance of activities in persons with hip OA.³⁵ Especially fatigue was found to be associated with avoidance of activities.³⁰ In the avoidance model, fatigue is included in the component psychological distress. Because, fatigue seems to be particularly associated with avoidance of activities, it may be better to revise the avoidance model and treat fatigue or low vitality as a distinct concept.³⁰

Together, there is quite some evidence for the validity of the avoidance model in persons with knee or hip OA.^{10,25-27,30,34} Also in other chronic pain populations, avoidance of activities has frequently been demonstrated to be an important factor accounting for activity limitations.³⁶⁻³⁸ However, there is still more research needed for further validation of the model, especially in hip OA. First, the consecutive associations between pain or psychological distress, avoidance of activities and muscle weakness have to be further examined. Second, because most studies on the validity of the avoidance model have a cross-sectional design,^{25-27,30} longitudinal and experimental studies are needed to enable causal inferences to be made. Further, focus should be on the use of reliable and valid measures of pain, psychological distress, avoidance of activities and activity limitations. In addition to pain coping questionnaires, studies should use accelerometry to objectively measure avoidance of activities because this method is not susceptible to response and recall bias.³⁹ In the measurements of pain and psychological distress, recall bias could be eliminated by using



momentary assessments during the accelerometer measurements.³⁹⁻⁴¹ In this time, in which more and more older adults are familiar with the use of electronic devices, use of accelerometers and event monitoring have potential to provide better evidence for the avoidance model. Because some persons with knee or hip OA stay physically active despite of pain,^{42,43} a final interesting subject for further research is overuse, the opposite of avoidance. For example, it is likely that non-obese persons with knee OA and relatively strong muscles (e.g. the 'strong muscle phenotype' identified by Knoop et al.⁶) tend to persist to be physically active despite of pain, whereas obese persons with knee OA and relatively weak muscles (i.e. the 'obese and weak muscles phenotype' identified by Knoop et al.⁶) are more inclined to avoid physical activities as a result of pain.

In the context of the larger literature regarding avoidance of activities,^{36,37} our findings emphasize that behavioural models are population specific.³⁸ We found strong evidence that muscle weakness mediates the association between avoidance of activities and activity limitations in persons with knee OA, whereas evidence in persons with low back pain and older adults suggests that muscle weakness does not substantially contribute to the association between behavioural variables and activity limitations.^{36,38}

The neuromuscular model

In **chapters 7 and 8** we examined the validity of the neuromuscular part of the integrated behavioural and neuromuscular model in persons with early symptomatic knee OA (neuromuscular model in **Figure 1**).^{10,32,44,45} In line with the results of our systematic review (chapter 6), we found an association between muscle weakness and activity limitations in both a cross-sectional (chapter 7) and a longitudinal (chapter 8) study.^{14,33} These findings support the hypothesis that muscle weakness contributes to the development of activity limitations in persons with knee OA.¹⁰ In addition, these findings are in line with the beneficial effect of exercise therapy on both muscle strength and activity limitations, as observed in randomized clinical trials.^{46,47}

In a cross-sectional study among 151 CHECK participants with knee symptoms (**chapter 7**), we found that the association between muscle weakness and activity limitations is stronger in persons with poor proprioception than in persons with adequate proprioception.³³ This finding confirms the results of a previous study of van der Esch et al.³² in persons with established knee OA, and strengthens the evidence for the theory that in the absence of adequate proprioceptive input, muscle weakness affects the level of activity limitations to a greater degree.^{32,33} Several mechanisms may explain the interaction between muscle weakness and proprioception. First, persons with knee OA and muscle weakness may have less muscle mass and fewer proprioceptors leading to impaired proprioceptive input.⁴⁸ Second, muscle weakness may lead to higher contraction levels during physical activity, and thereby reduced sensitivity of the muscle spindles, resulting in impaired proprioceptive input.^{48,49} Third, persons with weaker muscles may fatigue faster than persons with stronger muscles, leading to impaired proprioceptive input.⁴⁸ We also found a direct association between proprioception and activity limitations: persons with poor proprioception had greater activity limitations than persons with accurate proprioception.³³ This finding is in accordance with studies in established knee OA.^{32,49-54} Apparently, in persons with knee OA, poor proprioception affects activity limitations in two ways: directly, and indirectly by strengthening the association between muscle weakness and activity limitations.

In **chapter 8**, we examined whether proprioception moderated the association between change in muscle strength and change in activity limitations, using 3-year follow-up data from the same CHECK sample.¹⁴ Proprioception was not found to moderate the longitudinal association between muscle strength and activity limitations. Possibly the course of muscle strength is too slow, or the moderating effect of proprioception is too small, to be established in a study with a small sample size and limited follow-up period of 3 years. We measured proprioception during a knee joint motion detection task in sitting position. However, in daily life proprioception is mainly needed during weight bearing activities. Therefore, for further research it is recommended to measure proprioception not only in sitting position, but also in a weight bearing position. This may yield a stronger association between poor proprioception and activity limitations.

In persons with early symptomatic knee OA, we could not confirm the theory that in persons with high joint laxity, muscle strength around the knee compensates for the loss of stability provided by the passive restraint system.⁴⁴ In contrast to previous studies in established knee OA,^{44,55} in our population with early symptomatic knee OA varus-valgus laxity did not influence the strength of the association between muscle weakness and activity limitations.^{14,33} Compared to these previous studies, our study population was younger, had less severe radiographic OA, greater muscle strength, greater varus-valgus laxity and less activity limitations.^{33,44,55} Possibly the association between muscle strength and activity limitations is only influenced by varus-valgus laxity in persons whose muscles are too weak to compensate sufficiently for the loss of stability provided by the passive restraint system.³³ The CHECK population with their relatively strong muscles, may have been able to actively stabilize their joints despite high varus-valgus laxity.³³ We found a negative association between varus-valgus laxity and activity limitations, indicating less activity limitations in participants with greater varus-valgus laxity. This finding is contrary to the findings of Sharma et al.⁵⁵ and van der Esch et al.⁴⁴ More research on varus-valgus laxity is needed to explain these contrasting results, because varus-valgus laxity is surprisingly little studied in persons with knee OA.

In summary, as hypothesized by the neuromuscular model, muscle weakness and poor proprioception were found to be associated with activity limitations in persons with early symptomatic knee OA.³³ The association between muscle weakness and activity limitations was stronger in persons with poor proprioception than in persons with adequate proprioception. This finding indicates that already in an early stage of knee OA, in the absence of adequate proprioceptive input, muscle weakness affects the level of activity limitations to a greater degree.^{32,33} The hypothesis that the association between muscle weakness and activity limitations is stronger in persons with higher varus-valgus laxity was not confirmed in early symptomatic knee OA. The associations between varus-valgus laxity, muscle weakness and activity limitations in the development of knee OA need further examination. In addition to muscle weakness, poor proprioception and varus-valgus laxity, the neuromuscular model hypothesizes that varus-valgus motion of the knee joint during walking contributes to instability of the knee, and thereby to activity limitations.^{10,45} The associations of varus-valgus motion during walking and knee instability with muscle weakness and activity limitations have not yet been examined in persons with early symptomatic knee OA, and should be addressed in further studies.



ROM measurements in early symptomatic knee and hip OA

As mentioned before, besides the mechanisms described in our theoretical model (**Figure 1**) there are other mechanisms leading to activity limitations in persons with knee and hip OA.^{10,27} Reduced range of motion (ROM) of the joint is such another mechanism.^{10,56} In the CHECK study, we found that participants with knee symptoms and a poor 5-year outcome of activity limitations had a reduced active knee flexion range compared to participants with a good 5-year outcome of activity limitations.³ In participants with hip symptoms, we found that reduced active hip flexion predicted a poor 2-year outcome of activity limitations.¹

Factors affecting ROM in knee and hip OA are surprisingly little studied.⁵⁶ Because ROM is associated with the development of activity limitations in knee and hip OA, and is considered as a clinical criterion for the classification of knee and hip OA, we decided to examine ROM more in depth.^{57,58} In **chapter 9**, we explored and tried to explain the association of sociodemographic, clinical, and articular factors with reduced ROM in CHECK participants with knee or hip symptoms.

In persons with knee symptoms, we found that higher BMI, knee pain, crepitus, bony enlargement, and osteophytosis were independently associated with reduced active knee flexion. The association between higher BMI and reduced knee flexion can be explained by storage of fat around the joint which may limit the ROM. Pain may be associated with reduced active knee flexion via poor voluntary effort. Crepitus and bony enlargement result from irregularity of articular cartilage, osteophytosis and remodelling of the subchondral bone which may all lead to reduced ROM.⁵⁹ Osteophytosis may affect ROM by causing a mechanical block or irregularities in the joint surface.⁶⁰ In addition, osteophytosis may be a sign of disease progression which leads to rigidity of the joint capsule and thereby to reduced ROM.⁵⁶ Together crepitus, bony enlargement and osteophytosis support the assumption that articular deformation has a great impact on knee ROM.^{56,58}

In persons with hip symptoms, we found that male gender, higher BMI, hip pain, morning stiffness, osteophytosis, joint space narrowing (JSN), flattening of the femoral head and femoral buttressing were associated with reduced hip ROM.⁵⁶ Compared to women, men may have lower hip internal rotation and flexion because of differences in joint geometry and muscle mass: the pelvic region of the male body allows a smaller ROM than that of the female body, and men have greater muscle mass which may limit ROM.^{56,61} Pain and morning stiffness may be associated with reduced active hip ROM via poor voluntary effort or inflammation (morning stiffness is considered to be a clinical parameter for inflammation). Inflammation may lead to thickening of the synovial membrane and may thereby reduce ROM.⁶² The association between articular factors and reduced ROM may be explained by the same mechanisms as in knee OA (i.e. osteophytes may reduce ROM by forming a mechanical block; or disease progression may cause osteophytosis, JSN, irregularity in the joint surface, and rigidity of the joint capsule and thereby reduced ROM).⁵⁶ In persons with hip symptoms, internal rotation, flexion and abduction of the hip were found to be associated with superior JSN, whereas external rotation of the hip was found to be associated with medial JSN. Superior and medial OA are classified as different phenotypes of hip OA, thus possibly different phenotypes of OA develop reductions in ROM in different planes of motion.⁶³

Our study was cross-sectional and exploratory in design.⁵⁶ Additional longitudinal hypothesis-driven studies are needed to further examine factors affecting ROM in knee

and hip OA. Other factors that we did not measure but have the potential to affect active ROM include capsular contracture, muscle spasm, contracture of muscles and their overlying fascia, the shape of the hip joint (acetabulum, femoral neck, and head), muscle weakness, and reduced joint laxity.^{44,60,64-66} Minor variations in shape of the hip joint may lead to femoroacetabular impingement (i.e. abnormal contact between the femoral head-neck junction and the acetabulum), which in turn leads to reduced ROM.⁶⁴ In the CHECK study it has been shown that a cam-type deformity (i.e. extra bone formation in the anterolateral head-neck junction) is associated with reduced hip internal rotation and progression of radiographic severity.⁶⁴

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 in early symptomatic knee and hip OA.⁶⁷ In CHECK participants with hip symptoms, we found that reduced active internal rotation had diagnostic value for the presence of radiographic features. The diagnostic accuracy of knee and hip flexion measurements was low. Currently, hip internal rotation $< 15^\circ$ is one of the ACR criteria used for identifying persons with OA. The cut-off of $< 15^\circ$ is derived in persons with hip OA who were referred to a rheumatology clinic.⁶⁸ Because measures of diagnostic accuracy vary across different populations, this cut-off could be suboptimal for early diagnosis of OA.^{69,70} Therefore, we examined which cut-off for reduced hip internal rotation could best distinguish between persons with and persons without radiographic features of hip OA, and found that this was hip internal rotation $< 24^\circ$ which lies closely to the optimal cut-off defined by Birrell et al.⁷¹ of $< 23^\circ$. For the cut-off hip internal rotation $< 24^\circ$, the probability of the presence of osteophytosis or JSN increased from 25% to 58% with a positive test result and decreased to 22% with a negative result. When we used the current ACR criterion of hip internal rotation $< 15^\circ$, we found that many participants with radiographic features were not identified (the percentage of false negatives was 21%). For the cut-off of hip internal rotation $< 24^\circ$, the percentage of false negatives was much lower, namely 11%. Therefore, because at an early stage of the disease it is not desirable to exclude potential patients falsely from further diagnostics, we recommended to change the cut-off for reduced hip internal rotation from $< 15^\circ$ to $< 24^\circ$ in persons with early symptomatic OA.⁶⁷ In clinical practice, in addition to reduced ROM, other criteria are tested to identify persons with OA (e.g. age > 50 years, pain, morning stiffness, bony tenderness).⁷² We did not examine the probability of radiographic OA for combinations of criteria, which is more relevant for clinical practice. The diagnostic accuracy of combinations of classification criteria for knee and hip OA at an early stage of the disease should therefore be addressed in future studies.⁶⁷

Implications for clinical practice

The research described in this thesis was observational in design and primarily aimed at obtaining a better understanding of the development of activity limitations in persons with early symptomatic knee and hip OA. Although our research was not intended to yield direct implications for clinical practice, it brought some knowledge and recommendations which are summarized here.



For clinicians it is important to be aware that the knee OA population consists of subgroups with differing prognoses regarding activity limitations.³ This will help them to better inform their patients. Currently, many persons with early symptomatic OA are insufficiently informed about their likely course of activity limitations, and are not referred for appropriate treatment.⁷³⁻⁷⁵ This is unfortunate, because developing activity limitations and losing independence is one of the main fears of persons with OA.⁷³

Exercise therapy is beneficial and recommended for persons with knee and hip OA, however only moderate effects on pain and activity limitations have been demonstrated.¹⁰ Some persons do not respond to exercise whereas others respond very well.¹⁰ This suggests that distinct homogeneous subgroups may benefit from different treatment strategies. In persons who are characterized by long-term avoidance of activities and psychological distress it seems beneficial to add a behavioural or psychological component to exercise therapy.⁷⁶ Combined exercise and behavioural treatment interventions have shown to have beneficial effects on pain, avoidance of activities, and activity limitations.^{10,76-82} However, combined exercise and behavioural treatment interventions have not always been demonstrated to be superior over exercise therapy alone.^{10,76,81,83} Therefore, to be of added value, interventions should be developed and tailored to specific subgroups using theoretical models as a guiding heuristic.^{10,38,76}

In persons with knee OA who are characterized by poor proprioception, it seems beneficial to offer an exercise intervention which targets not only muscle weakness but also other neuromuscular mechanisms leading to activity limitations such as poor proprioception.¹⁰ Exercise interventions in which besides functional and muscle strengthening exercises special attention is given to improvement of knee stability have shown to reduce pain and activity limitations.^{10,47} However, the inclusion of knee stabilisation exercises does not seem to have additional value compared to muscle strengthening and functional exercises alone.⁴⁷ One explanation is that joint stabilisation is already sufficiently trained during muscle strengthening and functional exercises. These findings point to the need for further theoretical work and the need to develop new interventions.^{38,47}

To reduce the number of persons with hip OA that are not identified by the ACR cut-off hip internal rotation $< 15^\circ$, early in the diagnostic process a cut-off of $< 24^\circ$ should be used. Individual hip flexion and knee flexion measurements seem to be of little diagnostic value for the presence of radiographic features of hip and knee OA.⁶⁷

Conclusion

In persons with knee and hip OA, activity limitations on average progress slowly over time. However, the individual course is highly variable. Based on the 5-year course of activity limitations the knee OA population can roughly be divided into three subgroups: a 'good outcome' subgroup that develops or displays slight activity limitations over time; a 'moderate outcome' subgroup that develops or displays moderate activity limitations over time; and a 'poor outcome' subgroup that develops or displays severe activity limitations over time.

Prognostic factors for activity limitations are highly similar for persons with early symptomatic knee or hip OA and persons with established knee or hip OA. These factors include clinical, radiographic, metabolic and psychological factors. So far, no prediction models

have been developed that can sufficiently discriminate between persons with a poor outcome of activity limitations and persons with a good outcome of activity limitations. Therefore, prognostic factors for the course of activity limitations should be further studied.

Behavioural and neuromuscular mechanisms partially explain the development of activity limitations in persons with early symptomatic knee OA. There is increasing evidence that pain and low vitality lead to subsequent avoidance of activities, and thereby to muscle weakness and activity limitations. In addition, poor proprioception seems to play a role in this process. Further longitudinal and experimental studies are needed to strengthen the evidence for the validity of these hypotheses.

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