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

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## Chapter I

# General introduction



## Osteoarthritis of the knee and hip

Osteoarthritis (OA), often referred to as degenerative arthritis, is the most common chronic joint disease in the world, mainly affecting middle-aged and older persons. Traditionally, OA has been considered a disease of articular cartilage, but we now know that OA affects the entire joint, including bone, cartilage, synovium, ligaments and muscles (**Figure 1**).<sup>1,2</sup> The disease most commonly affects the knee, hip and hand.<sup>2</sup> Musculoskeletal diseases, including knee and hip OA, are the second greatest cause of disability (i.e. impairments, activity limitations or participation restrictions) worldwide, as well as an economic burden on society.<sup>3,4</sup> Disability due to OA is rapidly increasing because of the ageing of the population and the growing epidemic of obesity, and will therefore have an even greater impact on society in the future.<sup>2,4</sup>

The exact pathogenesis of OA is unknown and varies from joint to joint. Briefly, OA results from a complex interplay of biochemical, biomechanical, genetic and metabolic factors that destabilize the process of interactive degradation and synthesis of articular cartilage, bone, and synovium.<sup>2,5</sup> Recent evidence shows that low-grade inflammation also plays a part in this process.<sup>2</sup>

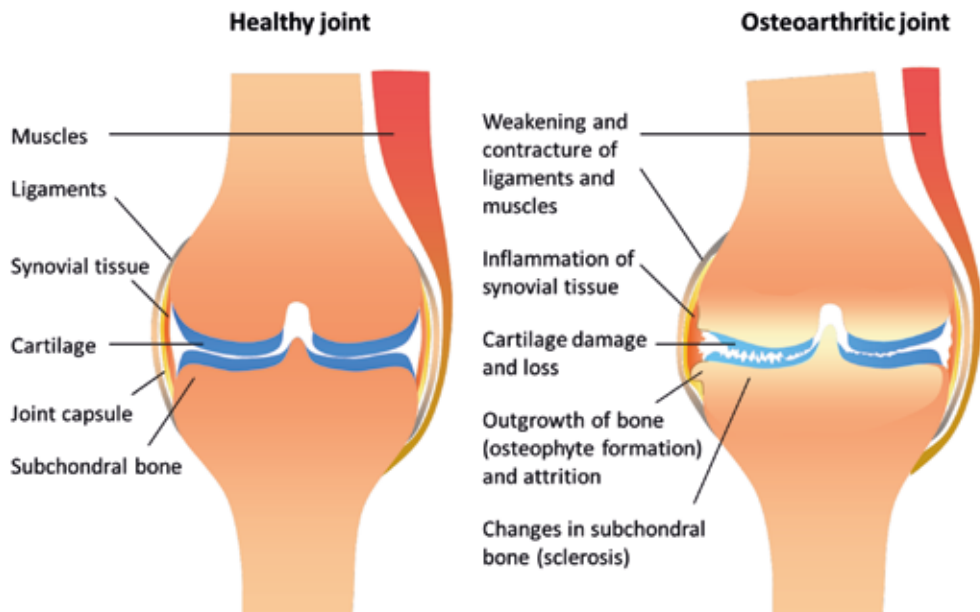


Figure 1. Schematic drawing of a healthy versus an osteoarthritic knee joint. © Floris Lafeber



## Epidemiology

The prevalence of knee and hip OA increases with age.<sup>6</sup> In the Netherlands, men are affected more often than women among those aged <55 years, whereas after age 60 women are more commonly affected.<sup>7</sup> In the population aged 45-70 years old, the age-category of the study population described in this thesis, knee and hip OA occur in around 28/1000 and 22/1000 women, and 27/1000 and 19/1000 men, respectively.<sup>7</sup> The prevalence in older persons is much higher. After age 65 knee and hip OA affect around 112/1000 and 90/1000 women, and 65/1000 and 48/1000 men, respectively.<sup>7</sup> These numbers are derived from general practice registrations. Because not all cases are registered, the real prevalence of knee and hip OA in the Dutch population is estimated to be 2-3.5 times higher.<sup>7</sup>

Major risk factors for the occurrence of knee OA include: increasing age, female sex, genetic susceptibility, high body-mass (obesity), joint overuse from occupational workload, strenuous exercise, knee misalignment, muscle weakness, and previous knee injury.<sup>1,2</sup> Risk factors for hip OA differ slightly from those for knee OA. Major risk factors for the occurrence of hip OA include: increasing age, genetic susceptibility (including congenital deformities), high body-mass (obesity), joint overuse from occupational workload, strenuous exercise, and previous hip injury.<sup>1,2</sup>

## Symptoms, radiographic features, diagnosis and treatment

OA cannot be cured and generally progresses slowly over time.<sup>2</sup> Main symptoms include pain, joint stiffness, reduced range of motion (ROM) of joints and loss of function.<sup>2</sup> Pain is the main reason for people to consult their general practitioner for OA.<sup>8</sup> In early OA pain is described as a predictable sharp or other pain, which is usually triggered by physical activity.<sup>8</sup> People with established OA describe pain as a constant aching or dull pain which is interspersed with short episodes of sudden intense pain.<sup>8</sup> Because pain is typically worst during and after weight-bearing activities, it often leads to avoidance of social and recreational activities.<sup>2,8</sup> Joint stiffness is also experienced as being distressing.<sup>8</sup> This stiffness is of short duration and particularly experienced in the evening, in the morning and after a period of inactivity.<sup>2</sup> Reduced range of motion in the knee or hip and loss of function leading to activity limitations are the other main symptoms accounting for general practitioner visits in people with OA.

When OA is advanced, changes within the joint are visible on x-rays, which show formation of new bone at the joint margins (i.e. osteophytes), narrowing of joint space, and sometimes changes in the subchondral bone (i.e. sclerosis) (**Figure 1**).<sup>1</sup> The diagnosis of OA is usually based on clinical examination and then confirmed by radiography, although radiographic confirmation is often not necessary.<sup>1,2</sup> Because of discrepancies between clinical symptoms and results of radiographic examination,<sup>9</sup> a distinction is made between clinical OA and radiographic OA. The two main systems used to classify OA are the clinical system of the American College of Rheumatology (ACR) and the radiographic system of Kellgren and Lawrence.<sup>10-12</sup> These main systems are summarized in **Table 1**.

At the onset of OA, treatment takes place in primary care and is aimed at patient education, reduction of pain and stiffness, and maintenance and improvement of physical function.<sup>2,13,14</sup> Additional long term treatment aims are prevention of further joint damage, maintenance of joint range of motion, and improvement of quality of

life.<sup>2,13,14</sup> There are three treatment modalities: a non-pharmacological modality (e.g. education, lifestyle advice, exercise therapy, dietary therapy), a pharmacological modality (e.g. paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of long-acting glucocorticoids), and a surgical modality (i.e. osteotomy, joint fusion, joint distraction, joint replacement). In the Netherlands, patients with OA are treated in primary care for approximately 7 years before they are referred to secondary care for orthopaedic surgery.<sup>15</sup>

## The Cohort Hip and Cohort Knee study (CHECK)

Health care providers recognize that the diagnosis of OA is often established at a late stage of the disease.<sup>2</sup> This is undesirable because the earlier a disease is diagnosed the more can be done to prevent progression. To diagnose OA at an early stage of the disease, the focus of OA research is shifting from disease management in persons with established OA to prevention in persons with early OA or at high risk of developing OA.<sup>17</sup> In the 2000s

**Table 1.** Clinical and radiographic criteria for osteoarthritis of the knee and hip

<b>Clinical criteria of the American College of Rheumatology</b>	
<i>Osteoarthritis of the knee</i> <sup>11</sup>	<i>Osteoarthritis of the hip</i> <sup>12</sup>
Knee pain and at least 3 of 6:	Hip pain and
- Age > 50 years	- Hip internal rotation < 15°
- Stiffness < 30 minutes	- Erythrocyte Sedimentation Rate (ESR) ≤ 45 mm/hour
- Crepitus	(if ESR not available, substitute hip flexion ≤ 115°)
- Bony tenderness	
- Bony enlargement	OR
- No palpable warmth	Hip pain and
	- Hip internal rotation ≥ 15°
	- Pain on hip internal rotation
	- Morning stiffness of the hip ≤ 60 minutes
	- Age > 50 years
<b>Radiographic criteria of Kellgren and Lawrence</b> <sup>10,16</sup>	
Grade 0	None
Grade 1	Doubtful narrowing of joint space and possible osteophytic lipping
Grade 2	Definite osteophytes and possible narrowing of joint space
Grade 3	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends



several longitudinal observational studies were initiated that focus on early OA or persons at high risk of developing OA. Examples are the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative in the United States of America,<sup>18,19</sup> the Knee and Hip Osteoarthritis Long-term Assessment (KHOALA) cohort in France,<sup>20</sup> and the Clinical Assessment Study Knee (CAS[K]) in the United Kingdom.<sup>21</sup> In the Netherlands, a cohort with early symptoms was formed between October 2002 and September 2005: the Cohort Hip and Cohort Knee (CHECK).<sup>19</sup>

The CHECK study is a prospective multicentre cohort study on early symptomatic knee and hip OA funded by the Dutch Arthritis Foundation. The aims of CHECK are: 1) to study the course of symptoms, activity limitations and joint damage; 2) to study mechanisms underlying the development of symptoms, activity limitations and joint damage; and 3) to identify markers for diagnosis and prognosis. The CHECK cohort consists of 1,002 individuals. Ten general and academic hospitals in the Netherlands participated. Inclusion criteria of the CHECK study are: being aged between 45 and 65 years; pain and/or stiffness in the hip and/or knee; and having had no consultation with a physician for these symptoms (or first consultation was within the 6 months immediately preceding inclusion). Participants of the CHECK study will be followed for 10 years in which clinical characteristics are measured every year using questionnaires and physical examination. In addition, radiographic and biochemical characteristics are measured regularly (at baseline and after 2, 5, 8 and 10 years of follow-up) using x-rays, blood samples, and urine samples. With the inclusion of persons at inception of symptoms and its frequent and extensive measurements, CHECK offers the opportunity to thoroughly study the development of activity limitations in persons with knee and hip OA.

## Activity limitations

The health status of persons with OA can be described using the International Classification of Functioning, Disability and Health of the World Health Organization.<sup>3</sup> In this classification system, activity limitations are defined as difficulties an individual may have in executing activities such as walking, stair climbing, rising up and sitting down.<sup>3</sup> Activity limitations are considered one of the three most important symptomatic outcome measures for OA together with pain and patient global assessment.<sup>22</sup> Health care providers and researchers often refer to activity limitations as the patient's functional status. In this context also the term physical functioning is used.

### Measurement

Activity limitations are measured with self-report questionnaires and performance-based tests. In a self-report questionnaire the person is asked to indicate his/her perceived level of difficulties in executing certain activities. The disease-specific Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and generic Short Form 36 Health Survey (SF-36) are recommended questionnaires to measure activity limitations in persons with knee and hip OA.<sup>23</sup> During a performance-based test the patient is asked to perform

one or more tasks (e.g. walking, stair-climbing, rising up from a chair) that are evaluated in a standardized manner using predefined criteria, such as timing or counting repetitions.<sup>24</sup>

### Course and prognostic factors

Middle-aged and older persons with knee or hip OA are more likely to develop activity limitations than their contemporaries without OA.<sup>25,26</sup> In persons with knee and hip OA, activity limitations generally develop slowly over time.<sup>27,28</sup> However, there is considerable inter-individual variation: some persons gradually worsen, others remain stable, and still others improve.<sup>27,28</sup> Sociodemographic, clinical, radiographic and psychological factors partially explain this variability in the course of activity limitations. Known prognostic factors for a poor course of activity limitations in persons with knee OA are: older age,<sup>28-31</sup> non-Western ethnicity,<sup>31</sup> longer symptom duration,<sup>31</sup> higher body-mass index,<sup>28-30</sup> comorbidity,<sup>32</sup> greater knee pain intensity,<sup>28,29,31,32</sup> joint stiffness,<sup>30,31</sup> reduced ROM,<sup>31,32</sup> muscle weakness,<sup>28,31</sup> proprioceptive inaccuracy,<sup>28,31</sup> high varus-valgus laxity,<sup>28,31</sup> self-reported instability of the knee,<sup>31</sup> avoidance of physical activities,<sup>28,31</sup> psychological distress (i.e. depressed mood, anxiety, low vitality),<sup>28-31</sup> low self-efficacy,<sup>28,31</sup> little social support,<sup>28,31</sup> and poor general health perception.<sup>31</sup> In persons with hip OA, the course of activity limitations is less studied. Known risk factors for a poor course of activity limitations in persons with hip OA are: older age,<sup>31,32</sup> comorbidity,<sup>31,32</sup> greater hip pain intensity,<sup>31,32</sup> joint stiffness,<sup>31</sup> reduced ROM,<sup>32</sup> muscle weakness,<sup>31</sup> avoidance of activities,<sup>31</sup> poor cognitive functioning,<sup>32</sup> and poor general health perception.<sup>31</sup> However, these factors have been found in populations with established OA.<sup>31</sup> In persons with early symptomatic OA, prognostic factors for the course of activity limitations are less well studied. As a result, many patients are insufficiently informed about their likely course of activity limitations, and are not adequately referred for treatment.<sup>33,34</sup> Therefore, we investigated prognostic factors for the development of activity limitations in persons with early symptomatic knee and/or hip OA (**chapter 2**).

Sociodemographic, clinical, radiographic and psychological factors are not only used to predict the course of signs and symptoms of knee and hip OA, they are also used to classify the heterogeneous OA population into homogeneous phenotypes or subgroups.<sup>35,36</sup> It is likely that the course of activity limitations differs between these subgroups. However, so far, studies describing the course of activity limitations in persons with knee and/or hip OA usually present the average change score of activity limitations between two time-points. Because of the existence of subgroups,<sup>35,36</sup> this approach seems suboptimal.<sup>37</sup> Identification of subgroups with different trajectories of activity limitations seems more appropriate, and enables physicians to provide information which is more tailored to the individual patient. Therefore, we studied the existence of homogeneous subgroups with distinct trajectories of activity limitations in persons with early symptomatic knee OA (**chapter 3**).

### Explanation: theoretical model

To be clinically useful it should be known by means of which mechanisms risk factors cause activity limitations in persons with knee and hip OA. Underlying mechanisms can be examined using theoretical models. An integrated behavioural and neuromuscular model is used to examine the development of activity limitations in persons with knee OA (**Figure 2**).<sup>31</sup>





The behavioural part of this model is based upon previous research in chronic musculoskeletal pain,<sup>38-42</sup> and is referred to as the avoidance model.<sup>\*46-48</sup> According to the avoidance model in knee and hip OA, a person initially experiences pain during activities. This leads to the expectation that renewed physical activity results in more pain, and consequently to the avoidance of activities. In the short term, avoidance may have the desired effect of less pain, due to the decreased load on the affected joint. However, in the longer term, inactivity results in physical deconditioning, most notably muscle weakness. Muscle weakness leads to an increase in activity limitations.<sup>47,48</sup> In addition, psychological distress, defined as a broad range of aversive mood states including low vitality, nervousness and depressed mood, is thought to strengthen the tendency to avoid activities.<sup>27,47</sup> The association between avoidance of activities and activity limitations via muscle weakness (mediation by muscle weakness) has been examined in one cross-sectional study in persons with established knee OA.<sup>48</sup> The association between pain and muscle weakness via avoidance of activities (mediation by avoidance), and the role of psychological distress in the avoidance model have not yet been examined. Furthermore, although it is expected that the mechanisms described in the avoidance model apply to early OA, this has not been empirically proven. In early stage OA, in which patients experience pain during physical activity for the first time, the processes of mental and physical adaptation described in the model are thought to be initiated. Therefore, we examined the mediating role of both avoidance of activities and muscle weakness in the association between pain and activity limitations in persons with early symptomatic knee OA (**chapter 4**). In addition, we examined predictors and the outcome of avoidance of activities in a longitudinal study (**chapter 5**), and we synthesized the scientific evidence for the associations between all consecutive components of the avoidance model (**chapter 6**).

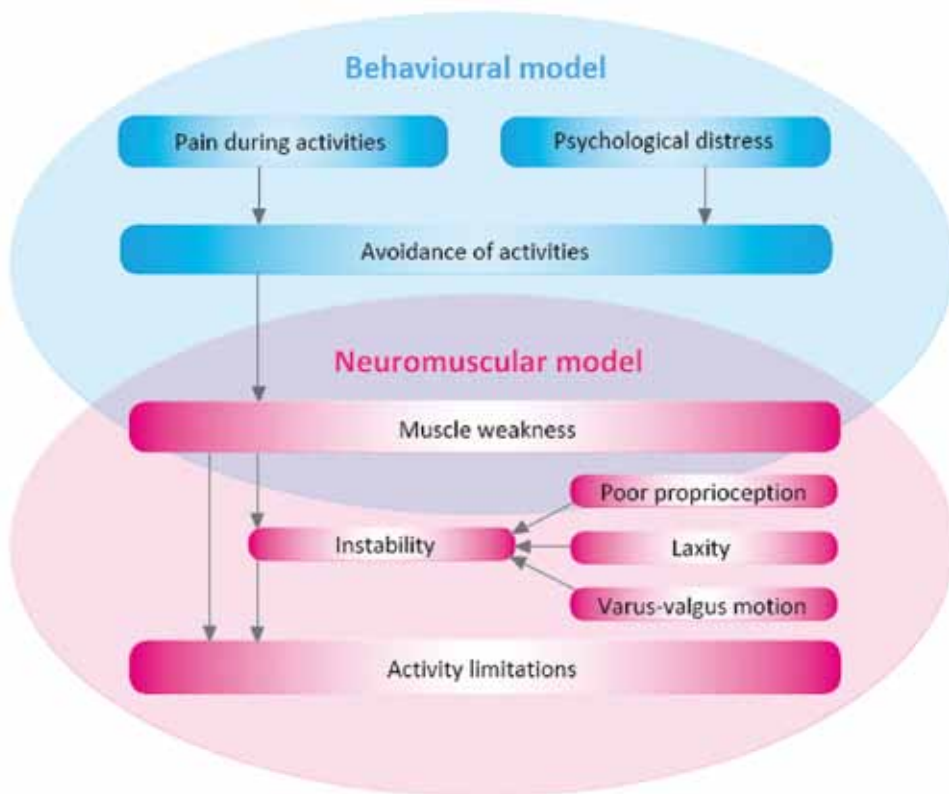
The neuromuscular part of the model hypothesizes that the strength of the association between muscle weakness and activity limitations is stronger in patients with instable knees compared to patients with stable knees.<sup>31</sup> The stability of the knee is influenced by proprioception (i.e. the conscious and/or unconscious perception of position and movement of an extremity or a joint in space), laxity (i.e. the displacement or rotation of the tibia with respect to the femur in the varus-valgus direction), and varus-valgus motion (i.e. the movement in the frontal plane during the weight acceptance and mid-stance phase of walking).<sup>31</sup> In cross-sectional studies in persons with established knee OA, it has been found that the association between muscle weakness and activity limitations is stronger in persons with poor proprioception (moderation by poor proprioception),<sup>49</sup> high varus-valgus laxity (moderation by varus-valgus laxity),<sup>50</sup> or high varus-valgus motion during walking (moderation by varus-valgus motion).<sup>51</sup> In persons with early symptomatic knee OA and in longitudinal studies these associations have not yet been examined. Therefore, we performed a cross-sectional (**chapter 7**) and a longitudinal

\* Another well-known model explaining the development of activity limitations in chronic musculoskeletal pain is the fear-avoidance model.<sup>40,43-45</sup> The avoidance model in knee and hip OA differs mainly from the fear-avoidance model in: i) the assumption that avoidance of activities is caused by expectations instead of fear; and ii) the inclusion of the component muscle weakness.<sup>31</sup>

(chapter 8) study in which we examined whether proprioception and varus-valgus laxity moderate the association between muscle weakness and activity limitations in persons with early symptomatic knee OA.

## Range of motion (ROM) of the knee and hip joint

Reduced ROM of the joint is thought to be a characteristic feature of OA. It is often measured during physical examination using a goniometer. The European League Against Rheumatism (EULAR) recommends to assess ROM of the knee because restricted movement should be indicative of knee OA.<sup>52</sup> The ACR has included reduced internal rotation and reduced flexion of the hip in the classification tree for hip OA, which is used for clinical diagnosis.<sup>12</sup> Furthermore, there is increasing evidence that reduced ROM contributes to the development of activity limitations in persons with knee and hip OA.<sup>28,31,53</sup> Higher age,<sup>54</sup> male gender,<sup>54</sup> higher BMI,<sup>55</sup> pain<sup>55,56</sup> and radiographic features<sup>57-60</sup> have been associated



**Figure 2.** Integrated behavioural and neuromuscular model that is developed to explain the development of activity limitations in osteoarthritis of the knee and hip.<sup>31</sup>



with reduced knee and hip ROM in elderly people or persons with OA. However, the number of studies examining predictors of ROM is limited, especially in early symptomatic OA. Because ROM measurements are used in the diagnostic process, it is important to examine which factors affect ROM. This is especially important in the early phase in which symptoms commence and the disease is diagnosed. Therefore, we explored the association of sociodemographic, clinical and articular factors with knee and hip ROM (**chapter 9**), and examined the diagnostic accuracy of ROM measurements for the presence of radiographic features of knee and hip OA (**chapter 10**).

## Aim and outline of this thesis

The research described in this thesis was part of the CHECK study. The overall aim 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, 5-year follow-up data from the CHECK cohort were used.

This thesis consists of three parts. **Part 1** describes the course of activity limitations and prognostic factors for an unfavourable course. **Chapter 2** presents a study aimed at prediction of the 2-year course of activity limitations in CHECK participants with early symptomatic knee and/or hip OA. To enhance the pragmatic applicability of the study results, the focus was on prognostic factors that are routinely measured or easily implemented by physicians at an early stage of the disease. **Chapter 3** reports a study aimed at the identification of homogeneous subgroups with distinct trajectories of activity limitations in CHECK participants with early symptomatic knee OA. In this study six measurements of activity limitations over 5 years of follow-up were used. After identification, the characteristics of the subgroups were described using baseline measurements of sociodemographic, clinical, radiographic, and psychological factors.

**Part 2** is dedicated to the explanation of how behavioural and neuromuscular factors lead to activity limitations in persons with early symptomatic knee OA. This is done using the theoretical model presented in **Figure 2**. The chapters 4 to 6 address the behavioural part of the model. **Chapter 4** describes a cross-sectional study in which we assessed the validity of the avoidance model. **Chapter 5** describes the 5-year course of avoidance of activities, and the longitudinal association of avoidance of activities with knee pain, vitality and activity limitations. In the systematic review presented in **chapter 6**, we summarized the scientific evidence from observational studies for the validity of the avoidance model in persons with knee and hip OA. Chapters 7 and 8 address the neuromuscular part of the model. **Chapter 7** reports a study in which we examined the validity of the neuromuscular model by studying whether proprioception and varus-valgus laxity moderate (i.e. strengthen) the association between muscle weakness and activity limitations. **Chapter 8** is about the longitudinal association between muscle weakness and activity limitations. We described the association of 3-year change in muscle strength with 3-year change in activity limitations, and examined whether this association was moderated by proprioception and varus-valgus laxity.

**Part 3** describes two studies on ROM of the knee and hip joint. **Chapter 9** presents a study in which we explored the association of sociodemographic, clinical and articular factors with ROM (i.e. active flexion of the knee and active internal rotation, external rotation,

flexion, adduction and abduction of the hip). **Chapter 10** addresses the diagnostic accuracy of active knee flexion, hip flexion and hip internal rotation measurements for the presence of radiographic features of OA.

Finally, in **chapter 11**, the results of the research presented in this thesis are summarized and discussed.

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